FNM 2016
2nd Federation of Neurogastroenterology and Motility Meeting

August 25–28, 2016 • Hyatt Regency San Francisco • San Francisco, CA

This educational activity is jointly provided by ANMS and University of Kansas Medical Center Continuing Education.
The American Neurogastroenterology and Motility Society gratefully acknowledges the generous support of independent medical educational grants from the following companies:

**Benefactors**
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Salix Pharmaceuticals, Inc.

**Sponsors**
Allergan
Rome Foundation

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**FNM 2016 PLANNING COMMITTEES**

**FNM 2016 Host**
ANMS

**Scientific Meeting Planning Committee**
John Wiley, Chair
Guy Boeckxstaens
Nigel Bunnett
Sutep Gonlachanvit
Laurie Keefer
Hiroto Miwa
Michel Neunlist
Catia Sternini
José Tawil
G. Nicholas Verne
Justin Wu

**Young Investigator Forum**
Braden Kuo, Chair
Lin Chang
Beverley Greenwood-Van Meerveld
Shanthi Srinivasan

**Continuing Education Planning Committee**
Monya Floyd
Program Manager
Continuing Education & Professional Development
University of Kansas Medical Center
Jan Foecke, MS, RN, ONC
Assistant Dean for Community Affairs
Director of Nursing Continuing Education
University of Kansas School of Nursing

**Meeting Coordinator**
Lori Ennis
On behalf of the American Neurogastroenterology and Motility Society (ANMS), the host of this meeting, and our joint sponsors, the European Society of Neurogastroenterology and Motility (ESNM), Asian Neurogastroenterology and Motility Association (ANMA), Australasian Neurogastroenterology and Motility Association, Inc., (ANGMA), and Sociedad Latinoamericana de Neurogastroenterología (SLNG), we welcome you to the 2nd Federation of Neurogastroenterology and Motility Meeting.

The scientific meeting will address a broad range of cutting-edge research topics covering basic, translational, and clinical aspects of the brain–gut axis, neurogastroenterology, and motility. State-of-the-art presentations will cover the mechanisms of visceral pain, genetic and epigenetic approaches to diagnose functional bowel disorders, the role of gut microbiota, food sensitivities and intolerances, patient-reported outcomes, and biomedical informatics. Specific topics that will be covered include esophageal disorders, functional dyspepsia, gastroparesis, irritable bowel syndrome, chronic constipation, and fecal incontinence. In addition, participants will learn about current and novel therapeutic approaches for these conditions, including the role of acid suppressants, prokinetics, probiotics, dietary interventions, visceral analgesics, secretagogues, and other emerging therapies.

We welcome you to FNM 2016 in San Francisco, California and look forward to sharing this exciting meeting with you.

Scientific Planning Committee: John Wiley, Chair, Qasim Aziz, Guy Boeckxstaens, Nigel Bunnett, Sutep Gonlachanvit, Laurie Keefer, Hiroto Miwa, Michel Neunlist, Catia Sternini, José Tawil, G. Nicholas Verne, Justin Wu
Invited Speakers

Fernando Azpiroz, MD, PhD
University of Barcelona

Hans-Rudolf Berthoud, PhD
Pennington Biomedical Research Center

Khalil N. Bitar, PhD
Wake Forest University

L. Ashley Blackshaw, PhD
Queen Mary University of London

Guy E. Boeckxstaens, MD
KU Leuven

Darren Brenner, MD
Northwestern University Feinberg School of Medicine

Kirsteen Browning, PhD
Pennsylvania State University

Nigel W. Bunnett, PhD
Columbia University

Michael Camilleri, MD
Mayo Clinic

Lin Chang, MD
David Geffen School of Medicine at UCLA

Ji-Hong Chen, MD, PhD
Wuhan University

Isaac Chiu, PhD
Harvard Medical School

Carlo Croce, MD
The Ohio State University

Roberto De Giorgio, MD
University of Bologna

Evan S. Dellon, MD, MPH
University of North Carolina

Neelendu Dey, MD
Washington University

Carlo Di Lorenzo, MD
Nationwide Children’s Hospital

Sigrid Eisenbruch, PhD
University of Duisburg-Essen

Gianrico Farrugia, MD
Mayo Clinic

Jose Garza, MD
GI Care for Kids

Uday C. Ghoshal, MD
Sanjay Gandhi Postgraduate Institute of Medical Sciences

Sutep Gonlachanvit, MD
Chulalongkorn University

Beverley Greenwood-Van Meerveld, PhD
University of Oklahoma Health Sciences Center

Brian D. Gulbransen, PhD
Michigan State University

Gerry Higgins, MD, PhD
University of Michigan

Patrick A. Hughes, PhD
University of Adelaide

Laurie Keefer, PhD
Mount Sinai Health System

B U.K. Li
Medical College of Wisconsin

P. Kay Lund, PhD
National Institutes of Health

Sarkis K. Mazmanian, PhD
California Institute of Technology

Michel Neunlist, PhD
Inserm U913, University of Nantes

Vassilis Pachnis, MD, PhD
The Francis Crick Institute

Don W. Powell, MD
University of Texas Medical Branch

José M. Remes-Troche, MD
University of Veracruzana

Nathalie Rommel, PhD
KU Leuven

Kenton M. Sanders, PhD
University of Nevada, Reno School of Medicine

Miguel Saps, MD
Nationwide Children’s Hospital

Keith A. Sharkey, PhD
University of Calgary

Magnus Simrén, MD, PhD
University of Gothenburg

Terence Smith, PhD
University of Nevada, Reno School of Medicine

Stuart J. Spechler, MD
UT Southwestern Medical Center at Dallas

Jason K. Spence, PhD
University of Michigan

Vincenzo Stanghellini, MD
University of Bologna

Catia Sternini, MD
David Geffen School of Medicine at UCLA

Jan Tack, MD, PhD
KU Leuven

Nathalie Vergnolle, PhD
IRSD-Inserm U1220

G. Nicholas Verne, MD
Tulane University

Thomas D. Wang, MD, PhD
University of Michigan

Mamoru Watanabe, MD, PhD
Tokyo Medical and Dental University

John W. Wiley, MD
University of Michigan

Justin Wu, MD
Chinese University of Hong Kong

Heather M. Young, PhD
University of Melbourne

Young Investigator Awardees

ANMS is pleased to announce the recipients of the Young Investigator Award, a unique opportunity to interact with renowned faculty, and participate in a one-on-one mentoring program. The recipients are young investigators in the early stages of an independent career in basic and/or clinical investigation, and their scientific work received high priority scores on peer review. The Young Investigator Forum provides an opportunity for participants to get valuable experience in presenting their research, getting feedback from colleagues, and developing additional collaborator and mentor relationships within the neurogastroenterology community. Many previous awardees have gone on to become thought leaders in their respective areas of expertise.

Isola A. Brown
Michigan State University

Dustin A. Carlson
Northwestern University Feinberg School of Medicine

Peter L. Lu
Nationwide Children's Hospital

Sara Nullens
University of Antwerp

Joanne L. Ooi
Barts and The London School of Medicine and Dentistry

Ans Pauwels
KU Leuven

Francois Reichardt
Emory University

Eric D. Shah
University of Michigan

Sara R. Souza
Mayo Clinic

Estelle T. Spear
University of Vermont

Sandra Steensels
KU Leuven

Johanna E. Sundin
Gothenburg University

Elizabeth J. Videlock
David Geffen School of Medicine at UCLA

Candice Fung
University of Melbourne

Ali Zifan
University of California, San Diego
<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wednesday, August 24, 2016</td>
<td></td>
</tr>
<tr>
<td>3:00 pm – 6:00 pm</td>
<td><strong>Registration</strong> • Market Street Foyer</td>
</tr>
<tr>
<td>3:00 pm – 6:00 pm</td>
<td><strong>Exhibitor Set Up</strong> • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>5:30 pm – 9:00 pm</td>
<td><strong>Young Investigator Forum</strong> • Garden Room A • invitees only</td>
</tr>
<tr>
<td>Thursday, August 25, 2016</td>
<td></td>
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<tr>
<td>7:00 am – 5:00 pm</td>
<td><strong>Registration</strong> • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>7:30 am – 5:00 pm</td>
<td><strong>Young Investigator Forum</strong> • Garden Room A • invitees only</td>
</tr>
<tr>
<td>4:00 pm – 6:00 pm</td>
<td><strong>Poster Set Up</strong> • Pacific Concourse • All Friday posters #1–#158 must be up by 10 am Friday.</td>
</tr>
<tr>
<td>5:15 pm – 6:30 pm</td>
<td><strong>Welcome Reception</strong> • Waterfront, Atrium Level</td>
</tr>
<tr>
<td>6:45 pm – 8:30 pm</td>
<td><strong>Rome Symposium</strong> • Grand Ballroom</td>
</tr>
<tr>
<td>Friday August, 26, 2016</td>
<td></td>
</tr>
<tr>
<td>7:00 am – 5:00 pm</td>
<td><strong>Registration</strong> • Market Street Foyer</td>
</tr>
<tr>
<td>7:00 am – 7:45 am</td>
<td>Breakfast • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>4:00 pm – 6:00 pm</td>
<td><strong>Poster Set Up</strong> • Pacific Concourse • All Saturday posters #159–#318 must be up by 10 am Saturday.</td>
</tr>
<tr>
<td>6:30 am – 7:30 am</td>
<td>Breakfast Symposium • Treatment goals in GERD – Is it time for a paradigm shift? • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>7:45 am – 8:00 am</td>
<td><strong>Welcome</strong> • Grand Ballroom</td>
</tr>
<tr>
<td>8:00 am – 9:30 am</td>
<td>Plenary Session • Enteric Neuropathies</td>
</tr>
<tr>
<td>9:30 am – 10:00 am</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>10:00 am – 12:00 pm</td>
<td>Plenary Session • Stem Cells: Applications</td>
</tr>
<tr>
<td>12:00 pm – 2:30 pm</td>
<td><strong>Lunch</strong> • Poster Session • Pacific Concourse • #1–#158 • Presenters: Please remove posters by 3 pm</td>
</tr>
<tr>
<td>2:45 pm – 4:30 pm</td>
<td>Three Concurrent Sessions</td>
</tr>
<tr>
<td>2:45 pm – 4:30 pm</td>
<td>Microbiome • Grand Ballroom A</td>
</tr>
<tr>
<td>2:45 pm – 4:30 pm</td>
<td>Smooth Muscle, Glia, and ICC Interactions: Functional Roles in Health and Diseases • Grand Ballroom BC</td>
</tr>
<tr>
<td>2:45 pm – 4:30 pm</td>
<td>Esophageal Disorder • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>4:30 pm – 4:45 pm</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>4:45 pm – 6:15 pm</td>
<td>Three Concurrent Sessions</td>
</tr>
<tr>
<td>4:45 pm – 6:15 pm</td>
<td>Food Intolerances • Grand Ballroom A</td>
</tr>
<tr>
<td>4:45 pm – 6:15 pm</td>
<td>Clinical Phenotyping – Biomarkers • Grand Ballroom BC</td>
</tr>
<tr>
<td>4:45 pm – 6:15 pm</td>
<td>Developing Gut • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>6:20 pm – 6:45 pm</td>
<td><strong>ANMS Business Meeting</strong> • Grand Ballroom A</td>
</tr>
<tr>
<td>7:00 pm – 8:30 pm</td>
<td>Theme Symposium • Novel Mechanisms and Management of Abdominal Pain in Functional Bowel Disorders • Grand Ballroom BC • Light dinner included</td>
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</table>
### Saturday, August 27, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:00 am – 5:00 pm</td>
<td>Registration • Market Street Foyer</td>
</tr>
<tr>
<td>7:00 am – 8:00 am</td>
<td>Breakfast • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>8:00 am – 10:00 am</td>
<td>Three Concurrent Sessions</td>
</tr>
<tr>
<td>8:00 am – 10:00 am</td>
<td>Emerging Technologies to Study GI Luminal Function • Grand Ballroom A</td>
</tr>
<tr>
<td>8:00 am – 10:00 am</td>
<td>IBS and Visceral Pain: What’s New in Nociception • Grand Ballroom BC</td>
</tr>
<tr>
<td>8:00 am – 10:00 am</td>
<td>Pediatric Functional Disorders • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>10:00 am – 10:30 am</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>10:30 am – 12:00 pm</td>
<td>Three Concurrent Sessions</td>
</tr>
<tr>
<td>10:30 am – 12:00 pm</td>
<td>The Omics Revolution: Where are we headed? • Grand Ballroom A</td>
</tr>
<tr>
<td>10:30 am – 12:00 pm</td>
<td>Visceral Pain – Recent Developments and Future Directions • Grand Ballroom BC</td>
</tr>
<tr>
<td>10:30 am – 12:00 pm</td>
<td>Eosinophilic Esophagitis • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>12:00 pm – 1:30 pm</td>
<td>FNM Board Meeting • Boardroom B, Atrium Level • invitees only</td>
</tr>
<tr>
<td>12:00 pm – 2:30 pm</td>
<td>Lunch • Poster Session • Pacific Concourse • #159–#318 • Presenters: Please remove posters by 3 pm</td>
</tr>
<tr>
<td>2:45 pm – 4:05 pm</td>
<td>Three Concurrent Sessions</td>
</tr>
<tr>
<td>2:45 pm – 4:05 pm</td>
<td>Intestinal Disorders • Grand Ballroom A</td>
</tr>
<tr>
<td>2:45 pm – 4:05 pm</td>
<td>Brain–Gut Axis: Neuroimmune Mechanisms • Grand Ballroom BC</td>
</tr>
<tr>
<td>2:45 pm – 4:05 pm</td>
<td>Regulatory Mechanisms of Gut Chemosensing and Appetite • Bayview Rm, Bay Level</td>
</tr>
<tr>
<td>4:05 pm – 4:45 pm</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
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<tr>
<td>4:00 pm – 5:30 pm</td>
<td>Three Concurrent Sessions</td>
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<tr>
<td>4:00 pm – 5:30 pm</td>
<td>Anorectal Disorders • Grand Ballroom A</td>
</tr>
<tr>
<td>4:00 pm – 5:30 pm</td>
<td>The ENS: Neuroimmune Pathways • Grand Ballroom BC</td>
</tr>
<tr>
<td>4:00 pm – 5:30 pm</td>
<td>Gastric Disorders: Pathophysiology and Treatment • Bayview Room, Bay Level</td>
</tr>
<tr>
<td>7:00 pm – 9:30 pm</td>
<td>Reception • Banquet • Awards • Waterfront, Atrium Level • Banquet ticket required at door.</td>
</tr>
</tbody>
</table>

### Sunday, August 28, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:30 am – 10:00 am</td>
<td>Registration • Market Street Foyer</td>
</tr>
<tr>
<td>7:00 am – 8:00 am</td>
<td>Breakfast • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>8:00 am – 12:00 pm</td>
<td>Emerging Concepts • Grand Ballroom</td>
</tr>
<tr>
<td>8:00 am – 8:45 am</td>
<td>ANMS Oration • P. Kay Lund, National Institutes of Health</td>
</tr>
<tr>
<td></td>
<td>Intestinal stem cells in health and disease: Regulation by hormones, nutrients, and microbes</td>
</tr>
<tr>
<td>8:45 am – 10:05 am</td>
<td>Emerging Concepts</td>
</tr>
<tr>
<td>10:05 am – 10:30 am</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
</tr>
<tr>
<td>10:30 am – 12:00 pm</td>
<td>Emerging Concepts: Functional Bowel Disorders</td>
</tr>
<tr>
<td>12:00 pm</td>
<td>Adjourn</td>
</tr>
</tbody>
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Program Overview
The goal of the scientific meeting is to discuss recent scientific and clinical advances in the pathophysiology and treatment of common functional gastrointestinal and motility disorders. The objectives of the scientific meeting are to discuss evolving concepts in the understanding of the pathophysiology of visceral pain and motility disorders including irritable bowel syndrome, state-of-the-art methodological approaches in translational research studies used in chronic pain disorders, and the diagnosis and treatment of these conditions.

Multiple formats will be used including didactic lectures and original scientific abstract presentations. Information from society-based practice guidelines will also be covered.

Target Audience
This meeting is intended for primarily gastroenterologists, but also psychiatrists and other clinicians; physicians in training such as gastroenterology fellows, biochemists, molecular and cell biologists, physiologists, neurophysiologists, immunologists, pharmacologists, and behavioral psychologists, doctoral level researchers, and nurses involved in adult and pediatric GI and motility testing and research.

Objectives
The scientific program includes an excellent balance of topics relevant to the diagnosis and management of GI functional and neuromuscular disorders, and presentations that focus on future directions in the field. Particular attention was paid to include topics and speakers that will have a broad range of interest to an international audience including mechanisms and treatment of visceral hypersensitivity, the regulation of appetite and impact of bariatric surgery, complications of diabetes mellitus including gastroparesis, dietary factors in functional bowel disorders, and the role of the microbiome in a variety of gastrointestinal disorders.

- Discuss evolving concepts in the understanding of the pathophysiology of visceral pain and motility disorders including irritable bowel syndrome.
- Evaluate state-of-the-art methodologic approaches in translational research studies used in chronic pain disorders.
- Describe the diagnosis and treatment options available for motility disorders and other related conditions.
- Discuss the importance of recent basic science concepts in GI motility and how they apply to our understanding of clinical GI motility and functional bowel disorders.

Scientific Goal
The scientific meeting will address many cutting-edge research areas which range from clinical to translational and basic aspects of neurogastroenterology and functional GI disorders. Topics will include mechanisms of visceral pain, genetic and epigenetic approaches, role of the gut microbiota, food sensitivities and intolerances, mechanisms of visceral pain, genetic and epigenetic approaches, role of the gut microbiota, food sensitivities and intolerances, regulation of appetite and impact of bariatric surgery, complications of diabetes mellitus including gastroparesis, dietary factors in functional bowel disorders, and the role of the microbiome in a variety of gastrointestinal disorders.

- Discuss evolving concepts in the understanding of the pathophysiology of visceral pain and motility disorders including irritable bowel syndrome.
- Evaluate state-of-the-art methodologic approaches in translational research studies used in chronic pain disorders.
- Describe the diagnosis and treatment options available for motility disorders and other related conditions.
- Discuss the importance of recent basic science concepts in GI motility and how they apply to our understanding of clinical GI motility and functional bowel disorders.

Accreditation Statement
All participants are required to sign attendance rosters at the beginning of each day. A certificate of completion will be provided to all activity participants based on completion of the program evaluation, documentation of actual attendance time, meeting minimum attendance requirements specific to the activity, and payment in full. If you are not paid in full (check received before meeting), a link to complete evaluation and get your certificate will be emailed to you upon receipt of payment.

Physicians
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kansas Medical Center Office of Continuing Medical Education and American Neurogastroenterology and Motility Society. The University of Kansas Medical Center Office of Continuing Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

The KU Medical Center Office of Continuing Medical Education designates this live activity for a maximum of 22.75 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
Up to 22.5 contact hours will be awarded to all individuals based on documentation of actual attendance time, meeting minimum attendance requirements specific to the activity, and payment in full. University of Kansas School of Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

Disclosure of Relevant Financial Arrangements
As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME) and the American Nurses Credentialing Center (ANCC), the University of Kansas Medical Center Continuing Education & Professional Development must ensure that the health and well being of the public is more important than any economic interest, and that activity content is effective in improving practice, independent of commercial interests, and based on valid content. Individuals with control over the content of this activity are required to disclose to the learners any relevant financial relationships within the past 12 months with any proprietary entities producing, marketing, re-selling, or distributing healthcare goods or services related to the content of the activity (with the exemption of non-profit or governmental organizations and non-healthcare related companies). This includes any relevant financial arrangements involving their spouse/partner. Relevant financial relationships may include employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, etc. The intent of this disclosure is not to prevent an individual with a relevant financial relationship from being a planning committee member, a teacher, or an author of CME/CNE having control of, or responsibility for, the development, management, presentation, or evaluation of the CME/CNE activity, but rather to assist the provider in the identification and resolution of conflict of interest prior to the activity and to provide the learners with the information they need to determine whether these interests or relationships influenced the content of the activity.
The following presenters and planning committee members have disclosed relevant financial relationships with the following commercial entities producing healthcare goods or services related to the content of their presentations:

Darren Brenner, MD is on the speaker's bureau for Salix/Valeant Pharmaceuticals.
Nigel Bunnett, PhD receives consulting fees from Takeda Pharmaceuticals, Inc.
Michael Camilleri, MD performs contracted research for Rhythm, SK Life Science, and Ferring.
Lin Chang, MD receives consulting fees from AstraZeneca, Takeda Pharmaceuticals, Inc., Commonwealth Laboratories, QOL Medical, Synergy, and Ardeleyx.
Evan S. Dellon, MD, MPH receives consulting fees from the following: Banner Life Sciences, Receptors, Regeneron, and Roche. He is a contracted researcher for Meritage, Miraca Life Sciences, Receptors, Regeneron, and Shire.
Carlo Di Lorenzo, MD receives consulting fees from the following: QOL, Inc., Merck and Company, Inc., and Shire.
Jose Garza, MD is on the speaker's bureau for Abbott Laboratories.
Beverly Greenwood-Van Meerveld, PhD is a contracted researcher for GlaxoSmithKline.
Gerry Higgins, MD, PhD owns stock options in Assurex Health, Inc.
Patrick A. Hughes, MD is a contracted researcher for Ironwood.
Michel Neunlist, PhD receives research funding from Danone Research, Pileje, Amadette, and Lactalis-Bayer.
José M. Remes-Troche, MD is on the advisory boards of Allergan, Carnot and Sanfer. He receives consulting fees from: Alfa-Wasserman, Almirall, Commonwealth Labs, Takeda Mexico, Asofarma Mexico, and Sanfer. He is on the speaker's bureau for Alfa Wasserma, Takeda Mexico, Caront, Sanfer, and Almirall. He receives Research grants from Alfa Wasserma and Sanfer.
Nathalie Rommel, PhD has an ownership interest in AIM Analysis.
Stuart J. Spechler, MD receives consulting fees from Interpace Diagnostics and Ironwood.
Thomas D. Wang, MD, PhD is listed as an inventor on University of Michigan patents.
Momoru Watanabe, MD, PhD has research grants from all of the following: Asahi Kasei Kuraray Medical, AbbVie GK, Eisai, Mitsubishi Tanabe Pharma, Otsuka Pharma, Kyowa Hakko Kirin, Zeria Pharmaceutical, UCB Japan, JJMRO, Takeda, Daichi Sanyyo, Ono Pharmaceutical, GenCare Research Institute, and Astellas Pharma.
Justin Wu, MD receives consulting fees from: Abbott Labs, Takeda, AstraZeneca, Menarini, and Reckitt Benckiser.

The following presenters and planning committee members do not have any relevant financial relationships with any commercial entity producing healthcare goods or services related to the content of their presentations or related to the content of the activity:

Katharina Beck
Julie Iven
Hyo Jin Ryu
Francesca Bianco
Evelien Labeeuw
Eric Shah
Jessica Biesiekierski
Allen Lee
Stephen Shannon
Werend Boesmans
Zhiling Li
Sacha Sidani
Goede Bomsans
Casey Ligon
Estelle Spear
Maria Buckley
Peter Lu
Lincoln Stamp
Noemi Caballero
Maxime Mahe
Sandra Steensels
Florencia Carbone
Swapna Mahurkar-Joshi
Tiphaine Vanhaecke
Simona Carbone
Beate Niesler
Elizabeth Videlock
Dustin Carlson
Sara Nullens
Priya Vijayvargiya
Gianluca Cirpiani
Siobhain O’Mahony
Lixin Wang
Caroline Cobine
Olafur Palsson
Yang Yu
Emilie Duchalais
Tanis Patchartrakul
QiQi Zhou
Khalil El-Chammas
Ans Pauwels
Shi-Yi Zhou
Alison Goldin
Fatima Ramalhosa
Ali Zifan
Gera Govere
Meenakshi Rao

Resolution of Conflict of Interest
A conflict of interest, or a potential for bias, exists if an individual/entity in a position to benefit financially from the success of a continuing education activity is also in a position to influence its content, design, or implementation. For this continuing education activity, conflict of interest was resolved and successful resolution of conflict of interest will be validated through the implementation of the following mechanisms.

- Relevant financial relationships were disclosed and resolved prior to everyone’s participation in the planning, development, and implementation of this activity.
- Prior to participating in this activity, everyone in a position to influence its content, design or implementation received our terms and conditions regarding conflict of interest expectations and they agreed to comply.
- Speakers were selected based upon a review of their qualifications and an assessment of their ability to present the best available evidence accepted in health care practice.
- Clinical content was validated by a review of the activity for fair balance and bias, appropriate patient treatment recommendations, and whether scientific studies cited in the activity conform to standards accepted by the scientific community.
- Oversight will be maintained by monitoring the planning, development, and implementation of this continuing education activity.
- Disclosure of relevant financial relationships will be provided to the participants prior to the activity.
- Participants will evaluate the activity’s success in resolving conflict of interest and providing an activity free of bias.

Product Disclosures
Unless otherwise announced prior to the session, this activity does not include any information about off-label use of a product for a purpose other than that for which it was approved by the Food and Drug Administration (FDA).
Cairn Diagnostics
For many patients and physicians, the pathway to a definitive diagnosis can be complex, slow and frustrating. The mission of Cairn Diagnostics is to develop tests that eliminate complexity and create a safer, faster and clearer path to diagnosis.
Cairn’s FDA-approved 13C-Spirulina Gastric Emptying Breath Test (GEBT) offers a non-radioactive, non-invasive test for measuring the rate of solid phase gastric emptying in adults and is validated against the method of gastric scintigraphy.
The Cairn GEBT can be administered right in the physician’s office and does not require imaging equipment, specialized training or radioactive material. Results are easy to interpret, enabling rapid and accurate diagnosis of gastroparesis by avoiding the need for expensive, time-consuming referrals and scintigraphy.
For more information, visit www.cairndiagnostics.com

Crospon
Crospon’s EndoFLIP® system provides measurements of diameter and compliance within the esophagus and stomach to assist in assessment and surgical management of functional GI disorders. The EsoFLIP® dilation catheter incorporates the EndoFLIP® technology.

IM HealthScience (IMH)
IM HealthScience (IMH) was founded in 2012 by a group of senior pharmaceutical executives as a science driven and patient centric company whose mission is to research, develop and make available state of the art medical foods for gastrointestinal conditions such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD).
IMH is a family company rooted in the all too forgotten adage that the patient comes first and doing the right thing will always win out in the long term.
As a small, private organization, IMH is committed to putting patients before profits. IMH is also committed to bringing cutting edge life science and world class clinical research to the medical foods industry.

LABORIE
LABORIE takes great pride in improving patients’ lives through innovations in pelvic floor and gastroenterology diagnostic and treatment options. LABORIE’s GI product line includes Ambulatory Impedance-pH recorders for diagnosing GERD and advanced manometry solutions for esophageal and anorectal manometry studies.
For more information on LABORIE’s global product platform and educational course offerings please visit www.laborie.com.

Mederi Therapeutics
Mederi Therapeutics manufactures innovative radiofrequency (RF) therapies for GI disorders – Stretta for the treatment of GERD, and Secca for bowel incontinence. These safe, effective treatments fill the void between failed conservative therapies and invasive and expensive alternatives, like surgery or implants. Stretta and Secca use controlled, delivery of RF...
energy to the muscle at either end of the digestive tract, remodeling the muscle tissue, improving motility, symptoms and quality of life for chronic sufferers. Streata and Secca therapies are minimally invasive, outpatient, promote rapid recovery, and are now available in more than 35 countries. 800 Connecticut Ave, Suite 1E01, Norwalk, CT 06854 Tel: 203-930-9900, Website: www.mederi-inc.com

Medtronic
At Medtronic, we're committed to Innovating for Life by pushing the boundaries of medical technology and changing the way the world treats chronic disease. Our portfolio includes PillCam™ Capsule Endoscopy, Bravo™ pH Monitoring, MansoScan™ High Resolution Manometry, SmartPill™ Motility Monitoring, the Barrx™ RF Ablation System, bnx™ EUS Fine Needle Aspiration System, InterStim™ Sacral Neuromodulation System and Enterra® Gastric Electrical Stimulation System.

NeuroGASTRO 2017
NeuroGASTRO is a well-established European event that brings together leading experts and emerging young investigators actively involved in neurogastroenterology, digestive motility and functional gastrointestinal diseases from Europe and from all around the world to discuss cutting-edge research. The APC Microbiome Institute and University College Cork are delighted to welcome NeuroGASTRO 2017 to Cork, August 24–26, 2017. The APC Microbiome Institute is recognized as one of the leaders in the field of microbiome science. Cork is the international gateway to Ireland's Wild Atlantic Way with Cork International Airport serving over 50 international destinations. Cork also boasts the second largest natural harbour in the world and is the Food Capital of Ireland, home to the famed English Market and the best artisan food producers in the country. Don't just take our word for it — as Lonely Planet themselves said ‘Everything good about Ireland can be found in County Cork’.

Pelvalon
More than 20 million women in the U.S. suffer from loss of bowel control, sometimes called accidental bowel leakage (ABL) or fecal incontinence (FI). This debilitating condition can be caused by pregnancy, childbirth, nerve or muscle damage in the pelvic region, and gastrointestinal disorders such as irritable bowel syndrome (IBS). The Eclipse System is an innovative, non-surgical therapy that offers immediate results for women with this condition. Founded in 2010, Pelvalon’s groundbreaking technology originated from Stanford University’s Biodesign program, a collaboration between the schools of medicine and engineering. The Eclipse System has recently been made available via a limited commercial rollout in select centers of excellence in Illinois, Michigan, Alabama, California, and North Carolina.

Renew Medical
Renew Medical announces the US launch of the Renew® Insert, an innovative silicone rectal insert device now available by prescription for patients with Accidental Bowel Leakage (ABL), otherwise termed fecal incontinence. Renew Inserts are safe, easy-to-use and reduce ABL by 82% with high patient satisfaction.

Renew Inserts softly and comfortably fit the body and seal the rectum from the inside. Renew Inserts provide reliable and discreet internal protection that give your patients the confidence to live a normal and active life.

Rome Foundation
Rome Foundation is an independent not for profit 501(c)3 organization that supports activities to create scientific data to assist in the diagnosis and treatment of Functional GI Disorders. We seek to legitimize and update our knowledge of the Functional GI Disorders by bringing together scientists and clinicians to classify and critically appraise the science of gastrointestinal function and dysfunction. The Mission of the Rome Foundation is: To improve the lives of people with Functional GI Disorders.

The goals of the Rome Foundation are to: Promote clinical recognition and legitimization of FGIDs, Develop a scientific understanding of their pathophysiological mechanisms, and Optimize clinical management for patients with FGIDs

Salix Pharmaceuticals
For over 20 years, Salix Pharmaceuticals, a wholly-owned subsidiary of Valeant Pharmaceuticals International, Inc. has been committed to providing solutions for the management of many chronic and debilitating conditions. Salix currently markets products to U.S. healthcare providers in the areas of gastroenterology, hepatology, internal medicine, primary care, infectious disease, and allergy/immunology.

Sandhill Scientific
Sandhill Scientific continues to be a recognized global leader in GI diagnostics. Our long and rich history in the GI space has produced some of the innovations used today to help enhance the diagnostic yield of reflux and manometry. Since Sandhill introduced impedance/pH technology, it has set the standard for Total Reflux Monitoring. Our Ultima motility platform has the capability of connecting to High Resolution Impedance Manometry (HRIM®) and multiple configurations of High Resolution Anorectal Manometry (HRAM®) catheters. Zvu®, our new software platform and the latest innovation from Sandhill, enhances the user experience by providing the tools to allow quick, accurate analysis. The tie that binds all of this together is Sandhill University, which provides the most comprehensive training and education options to meet all of your clinical needs.

Torax Medical
Torax Medical develops and markets products designed to restore human sphincter function. Our technology platform, magnetic sphincter augmentation, uses attraction forces to augment weak or defective sphincter muscles to treat gastroesophageal reflux disease and fecal incontinence.
## Wednesday, August 24, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:30 pm–9:00 pm</td>
<td><strong>Young Investigator Forum</strong> • Garden Room A • Invitees only</td>
<td>Garden Room A</td>
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## Thursday, August 25, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>7:30 am–5:00 pm</td>
<td><strong>Young Investigator Forum</strong> • Garden Room A • Invitees only</td>
<td>Garden Room A</td>
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<tr>
<td>5:15–6:30 pm</td>
<td><strong>Welcome Reception</strong> • Waterfront, Atrium Level</td>
<td>Grand Ballroom</td>
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</table>
| 6:45–8:30 pm  | **Rome Symposium** • Grand Ballroom        |                           | **Rome IV Multidimensional Clinical Profile (MDCP): Augmenting Rome criteria to optimize patient-centered treatment**
|               |                                            |                           | **Moderator: Doug Drossman** • **Panelists: Lin Chang, Max Schmulson, Magnus Simrén, Jan Tack** |
|               |                                            |                           | **Introduction to the MDCP and presentation of MDCP functional GI cases:**
|               |                                            |                           | • Functional dyspepsia                        |
|               |                                            |                           | • IBS including coexistence with IBD or other functional GI disorders |
|               |                                            |                           | • Biliary and gallbladder                     |
|               |                                            |                           | • Esophageal                                  |
|               |                                            |                           | • Multicultural                              |
|               |                                            |                           | • Constipation and dyssynergic defecation     |

## Friday, August 26, 2016

<table>
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<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
<th>Details</th>
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</table>
| 6:30–7:30 am  | **Breakfast Symposium** • Bayview Room, Bay Level | Bayview Room, Bay Level   | **Treatment goals in GERD – Is it time for a paradigm shift?**
|               |                                            |                           | **Moderator: Ronnie Fass**                   |
| 7:45–8:00 am  | **Welcome & Opening Remarks**              |                           | John Wiley, University of Michigan; President, ANMS |
|               |                                            |                           |                                              |
|               | **Plenary Session • Enteric Neuropathies** | Grand Ballroom            | **Moderators: Brian Gulbransen, Pieter Vanden Berghe** |
| 8:00–8:30 am  | **Neuronal dysfunction: Clinical manifestations** |                           | Roberto De Giorgio, University of Bologna     |
| 8:30–8:45 am  | **Evidence for antibodies targeting the enteric nervous system in multiple sclerosis** |                           | *ET Spear, MM Haag, B Lavoie, A Applebee, C Teuscher, GM Mawe, Burlington, VT. University of Vermont* **YIF Participant** |
|               |                                            |                           | **Abstract 1**                               |
| 8:45–9:15 am  | **Neuronal degeneration: Basic mechanisms** |                           | Keith Sharkey, University of Calgary         |
| 9:15–9:30 am  | **Altered APOB48 expression can be a marker of severe panenteric dysmotility** |                           | *F Bianco, T Karunaratne, E Bonora, U Volta, G Barbara, P Clavenzani, M Seri, V Stanghellini, R De Giorgio, Bologna, Italy. University of Bologna* **Abstract 2** |
| 9:30–10:00 am | **Break • Visit Exhibits** • Grand Ballroom Foyer | Grand Ballroom Foyer      |                                              |
### Plenary Session • Stem Cells: Applications – Moderators: Ashley Blackshaw, Shanthish Srinivasan • Grand Ballroom

<table>
<thead>
<tr>
<th>Time</th>
<th>Presentation</th>
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</table>
| 10:00–10:30 am   | **Implementing in vitro models of the human gastrointestinal tract to study development and disease**  
                    Jason Spence, University of Michigan |
| 10:30–10:45 am   | **Coordinated activity of clonally-related enteric neurons**  
                    W Boesmans, R Lasrado, P Vanden Berghe, V Pachnis, Leuven, Belgium; London, UK. KU Leuven  
                    LBBB Participant |
| 10:45–11:15 am   | **Stem cell therapy for enteric neuropathies**  
                    Heather Young, University of Melbourne |
| 11:15–11:30 am   | **Functional enteric nervous system in human small intestine derived from pluripotent stem cells**  
                    MM Mahe, M Workman, S Trisno, H Poling, CL Watson, N Sundaram, P Aubert, M Neunlist, MA Helmraith, JM Wells, Cincinnati, OH; Nantes, France. Cincinnati Children’s Hospital  
                    Abstract 4 |
| 11:30 am–12:00 pm| Future applications of stem cells in the GI tract  
                    Mamoru Watanabe, Tokyo Medical and Dental University |
| 12:00–2:30 pm    | Lunch • Poster Session • Pacific Concourse • Posters #1 to #158 • Presenters: Please remove posters by 3:00 pm |

### 2:45–4:30 pm Concurrent Sessions

**Microbiome** • Grand Ballroom A  
Moderators: Purna Kashyap, Eammon Quigley

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<tr>
<th>Time</th>
<th>Presentation</th>
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| 2:45–3:10 pm     | **Envisioning how targeted manipulations of the gut microbiota could affect motility**  
                    Neelendu Dey, Washington University |
| 3:10–3:25 pm     | **High protein diet in diet-induced obesity rats promotes fat loss, sensitivity to CCK and induces shifts in gut microbial composition and limited modification of brain inflammatory signals**  
                    L Wang, J Jacobs, P-Q Yuan, V Wu, M Mulugeta, JR Reeve Jr, J R Pisegna, Y Taché, Los Angeles, California. David Geffen School of Medicine at UCLA  
                    Abstract 5 |
| 3:25–3:50 pm     | **Microbiota and chemoattractant receptors in the gut**  
                    Sarkis Mazmanian, California Institute of Technology |

**Smooth Muscle, Glia, and ICC Interactions: Functional Roles in Health and Diseases** • Grand Ballroom BC  
Moderators: Khalil Bitar, Nigel Bunnett

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<th>Time</th>
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| 2:45–3:10 pm     | **GI smooth muscle and interstitial cells: Novel insights in GI smooth muscle**  
                    Kenton Sanders, University of Nevada, Reno School of Medicine |
| 3:10–3:25 pm     | **No signaling in the circular smooth muscle layer of the murine proximal colon**  
                    K Beck, D Gronenberg, A Friebe, B Voussen-Lies, Wuerzburg, Germany. University of Wuerzburg  
                    Abstract 7 |
| 3:25–3:50 pm     | **Novel roles for enteric glia in health and chronic diseases**  
                    Michel Neunlist, Inserm U913, University of Nantes |

**Esophageal Disorders** • Bayview Room  
Moderators: Ronnie Fass, Ravinder Mittal

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<tr>
<th>Time</th>
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| 3:10–3:25 pm     | **Oropharyngeal dysphagia: Novel mechanisms**  
                    Nathalie Rommel, KU Leuven |
| 3:25–3:50 pm     | **A diagnostic classification scheme of esophageal motility using functional lumen imaging probe (FLIP) topography**  
                    DA Carlson, Z Lin, PJ Kahrilas, Z Listerick, M Tye, K Ritter, F Pons, JE Pandolfino, Chicago, IL; Amsterdam, The Netherlands. Northwestern University  
                    YIF Participant  
                    Abstract 9 |
| 3:10–3:25 pm     | **Mechanisms and management of PPI-resistant symptoms**  
                    Justin Wu, Chinese University of Hong Kong |
**Friday, August 26, 2016**

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<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Authors</th>
<th>Institution</th>
<th>Location</th>
<th>Abstract Number</th>
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<tbody>
<tr>
<td></td>
<td>Enteric glia play a sexually dimorphic role in the regulation of colonic motility but are not essential for epithelial maintenance</td>
<td>M Rao, D Rastelli, S Chiu, W Setlik, G Corfas, M Gershon, New York, NY; Ann Arbor, MI.</td>
<td>Columbia University</td>
<td>Grand Ballroom BC</td>
<td>Abstract 8</td>
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<tr>
<td></td>
<td>Moderate or high dose proton pump inhibition is associated with better delineation of PPI-REE diagnosis than low dose</td>
<td>AH Goldin, K Lo, M Hamilton, K Blatman, J Hornick, W Chan, Boston, MA. Brigham and Women's Hospital</td>
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<td>4:05–4:30 pm</td>
<td>Microbiome dysbiosis and metabolic disorders</td>
<td>Uday Ghoshal, Sanjay Gandhi Postgraduate Institute of Medical Sciences</td>
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<td>Control mechanisms of colonic motor patterns in animal models and patients with chronic constipation</td>
<td>Ji-Hong Chen, Wuhan University</td>
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<tr>
<td>4:30–4:45 pm</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
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<td>4:45–6:20 pm</td>
<td><strong>Concurrent Sessions</strong></td>
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<td><strong>Food Intolerances</strong> • Grand Ballroom A</td>
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<td></td>
<td>Prospective evaluation of serum 7αC4 and FGF19 to detect bile acid diarrhea in patients with IBS-diarrhea: Test sensitivity and intra-individual variation in replicate samples</td>
<td>P Vijayvargiya, J O’Neill, P Carlson, D Burton, M Camilleri, Rochester, MN. Mayo Clinic</td>
<td></td>
<td>Grand Ballroom BC</td>
<td>Abstract 14</td>
</tr>
<tr>
<td></td>
<td>Effects of exposure to GDNF, retinoic acid and/or 5-HT4 receptor agonists on the ability of enteric neurospheres to generate an enteric nervous system</td>
<td>LA Stamp, M Mohsenipour, AJ Bergner, HM Young, SJ McKeown, Parkville, VIC, Australia.</td>
<td>University of Melbourne</td>
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<td></td>
<td>What's new in achalasia?</td>
<td>Guy Boeckxstaens, KU Leuven</td>
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<tr>
<td>5:00-5:25 pm</td>
<td>What's in the future for FODMAPs (component analysis)?</td>
<td>Magnus Simrén, University of Gothenburg</td>
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<td></td>
<td>Genomic biomarkers in IBS: Diagnosis</td>
<td>Lin Chang, David Geffen School of Medicine at UCLA</td>
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<td>5:25–5:40 pm</td>
<td>Effect of intra-colonic administration of FODMAPs on colonic motility assessed with intraluminal colonic high resolution manometry (HRM) and gastrointestinal (GI) symptoms in healthy subjects</td>
<td>JR Biesiekierski, M Corsetti, T Vanuyltsel, I Demedts, J Tack, Leuven, Belgium.</td>
<td>KU Leuven</td>
<td>Grand Ballroom A</td>
<td>Abstract 12</td>
</tr>
<tr>
<td></td>
<td>Functional pathways associated with differentially expressed colonic mucosal microRNA and mRNA in irritable bowel syndrome</td>
<td>S Mahurkar-Joshi, E Videlock, D Iliopoulos, E Mayer, L Chang, Los Angeles, CA. David Geffen School of Medicine at UCLA</td>
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<td>Abstract 15</td>
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<tr>
<td></td>
<td>Rdh10 and retinoic acid signaling mediate ECM-composition and neural crest cell migration during colonization of the gut and in the pathogenesis of Hirschsprung disease</td>
<td>SR Shannon, NE Butler Tjaden, PA Trainor, Kansas City, Kansas; Kansas City, Missouri. University of Kansas Medical Center</td>
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<td>5:40–6:05 pm</td>
<td>Non-celiac gluten sensitivity (NCGS)</td>
<td>Sutep Gonlachanvit, Chulalongkorn University</td>
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<td>Emerging role of epigenetics and microRNA in IBS</td>
<td>G. Nicholas Verne, Tulane University</td>
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<td>Developmental immunology in the gut</td>
<td>Don Powell, University of Texas Medical Branch</td>
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**FNM 2016**

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### Friday, August 26, 2016

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<tr>
<th>Time</th>
<th>Event</th>
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</table>
| 6:05–6:20 pm | LPS mediated intestinal barrier dysfunction and visceral hypersensitivity in the IBS is prevented by low FODMAP diet  
S-Y Zhou, SL Eswaran, X Wu, WD Chey, C Owyang, Ann Arbor, MI. University of Michigan  
Abstract 13 |
|             | Differential colonic mucosal mRNA expression in IBS with constipation  
EJ Videlock, S Mahurkar-Joshi, I Karagiannidis, C Pothoulakis, D Iliopoulos, EA Mayer, L Chang, Los Angeles, CA. David Geffen School of Medicine at UCLA  
YIF Participant |  
Abstract 16 |
|             | Interaction between enteric glia and myeloid cells as critical players in intestinal immune homeostasis  
Abstract 19 |

6:20–6:45 pm | ANMS Business Meeting • Grand Ballroom A |

7:00–8:30 pm | **Theme Symposium • Grand Ballroom BC • Light dinner included**  
**Novel Mechanisms and Management of Abdominal Pain in Functional Bowel Disorders**  
Moderators: John Wiley, Gianrico Farrugia  
Novel pathophysiologic mechanisms to explain visceral hyperalgesia in functional bowel disorders  
Beverley Greenwood-Van Meerveld, University of Oklahoma Health Sciences Center  
Advances in strategies to identify novel biomarkers and targets to diagnose visceral hyperalgesia  
Michael Camilleri, Mayo Clinic  
New and emerging therapies for managing visceral hyperalgesia  
Lin Chang, David Geffen School of Medicine at UCLA  
Roundtable Discussion |

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### Saturday, August 27, 2016

<table>
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<tr>
<th>Time</th>
<th>Concurrent Sessions</th>
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| 8:00–10:00 am | Emerging Technologies to Study GI Luminal Function • Grand Ballroom A  
Moderators: Hiroto Miwa, P. Kay Lund  
Optogenetics: Applications in the gut  
Terence Smith, University of Nevada, Reno School of Medicine  
Microbes and pain: Neuronal sensing of bacteria  
Issac Chiu, Harvard Medical School  
Sacral nerve stimulation for treatment of constipation in children: Long-term outcomes, patient benefit, and parent satisfaction  
PL Lu, I Koppen, DK Orsagh-Yentis, K Leonhart, EJ Ambeba, KI Deans, PC Minneci, MA Benninga, D Yacob, C Di Lorenzo, Columbus, Ohio; Amsterdam, The Netherlands. Nationwide Children's Hospital  
YIF Participant  
Abstract 26 |
|              | IBS and Visceral Pain: What’s New in Nociception • Grand Ballroom BC  
Moderators: Patrick Hughes, Muriel LaRauche  
Neuronal circuitry analysis using live calcium imaging in the mouse colon  
ZL Li, MM Hao, W Boesmans, P Vanden Berghe, Leuven, Belgium. KU Leuven  
Bifidobacterium longum: A psychobiotic that attenuates stress-induced increases in salivary cortisol and anxiety, and alters EEG and neuro-cognitive performance in healthy volunteers  
AP Allen, W Hutch, YE Borre, PJ Kennedy, A Temko, E Gauthey, G Boylan, E Murphy, JF Cryan, TG Dinan, G Clarke, Cork, Ireland; Neuchâtel, Switzerland. University College Cork  
Abstract 23 |
|              | Pediatric Functional Disorders • Bayview  
Moderators: Samuel Nurko, Karla Vaz  
Functional bowel disorders: The role of early life events  
Miguel Saps, Nationwide Children’s Hospital  
Abstract 26 |
## Saturday, August 27, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Location</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>8:40–9:05 am</td>
<td>Imaging epithelial barrier dysfunction in situ: Laser endomicroscopy</td>
<td>Grand Ballroom BC</td>
<td>Thomas Wang, University of Michigan</td>
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<td>Sensitization of nociception: Molecular mechanisms</td>
<td>Grand Ballroom BC</td>
<td>Nigel Bunnett, Columbia University</td>
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<td>Functional abdominal pain in the pediatric population: Emerging concepts</td>
<td>Grand Ballroom BC</td>
<td>Carlo Di Lorenzo, Nationwide Children's Hospital</td>
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<tr>
<td>9:05–9:20 am</td>
<td>Visualization of pacemaker activity in intramucosal ICC in the internal anal sphincter</td>
<td>Grand Ballroom BC</td>
<td>CA Cobine, HJL Foulkes, KM Sanders, SA Baker, KD Keef, Reno, NV. University of Nevada, Reno School of Medicine (LBBB Participant)</td>
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<tr>
<td></td>
<td>COMT modulates nociception through TNF-α/MIR-155 pathways</td>
<td>Grand Ballroom BC</td>
<td>M Stakenborg, M van Winge, E Labeeuw, G Farro, M Hao, PJ Gomez-Pinilla, P Vanden Berghe, GE Boeckxstaens, G Matteoli (LBBB Participant)</td>
</tr>
<tr>
<td></td>
<td>A combination of dietary prebiotics and the probiotic LGG modulate behavioural and cognitive responses to early life stress</td>
<td>Grand Ballroom BC</td>
<td>SM O'Mahony, K-A McVey Neufeld, RV Wavoruntu, BM Berg, TG Dinan, JF Cryan, Cork, Ireland; Evansville, IN. University College Cork</td>
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<tr>
<td>9:20–9:45 am</td>
<td>Stress and gene transcription: Insights from the 4D Nucleome initiative</td>
<td>Grand Ballroom BC</td>
<td>John Wiley, University of Michigan</td>
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<td>Identification of novel mediators in IBS</td>
<td>Grand Ballroom BC</td>
<td>Ashley Blackshaw, Queen Mary University of London</td>
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<td>Functional diarrhea &amp; constipation in the pediatric population: Future directions</td>
<td>Grand Ballroom BC</td>
<td>Jose Garza, GI Care for Kids</td>
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<tr>
<td>9:45–10:00 am</td>
<td>Immune and stress factors in the distal colon alter vagal nerve activity</td>
<td>Grand Ballroom BC</td>
<td>MM Buckley, D O’Malley, Cork, Ireland. University College Cork (LBBB Participant)</td>
</tr>
<tr>
<td></td>
<td>Gender differences in serotonergic signaling are present in the duodenum in functional dyspepsia</td>
<td>Grand Ballroom BC</td>
<td>A Lee, B Lavoie, J Pan, J Kim, M Zenali, R Wilcox, P Callas, M Velez, P Moses, B Kuo, G Mawe, Burlington, VT; Ann Arbor, MI, University of Vermont; University of Michigan (LBBB Participant)</td>
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<td>Immunohistochemical analysis of pediatric achalasia; a case series</td>
<td>Grand Ballroom BC</td>
<td>KEI-Chammas, M Baker, A Kaul, Cincinnati, OH, Cincinnati Children's Hospital Medical Center (LBBB Participant)</td>
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<tr>
<td>10:00–10:30 am</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
<td>Grand Ballroom Foyer</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
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<td>10:30–11:50 am</td>
<td>Concurrent Sessions</td>
<td>Grand Ballroom Foyer</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
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<tr>
<td>10:30–10:55 am</td>
<td>The Omics Revolution: Where are we headed? • Grand Ballroom A</td>
<td>Grand Ballroom Foyer</td>
<td>Carlo Croce, The Ohio State University</td>
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<td>Visceral Pain – Recent Developments and Future Directions • Grand Ballroom BC</td>
<td>Grand Ballroom Foyer</td>
<td>Lin Chang, David Linden</td>
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<td>Eosinophilic Esophagitis • Bayview Room</td>
<td>Grand Ballroom Foyer</td>
<td>Evan Dellon, University of North Carolina</td>
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<tr>
<td>10:55–11:10 am</td>
<td>Transcriptome analysis reveals gene signatures in interstitial cells of Cajal</td>
<td>Grand Ballroom Foyer</td>
<td>S Ro, MY Lee, C Park, SE Ha, JP Park, R Fuchs, L Wei, B Jorgensen, D Redelman, SM Ward, KM Sanders, Reno, NV. University of Nevada, Reno School of Medicine (LBBB Participant)</td>
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<td>Modulation of resident macrophages in the muscularis externa by stimulation of enteric neurons</td>
<td>Grand Ballroom Foyer</td>
<td>J Iven, J Biesiekierski, I Depoortere, L Van Oudenhove, J Tack, Leuven, Belgium. KU Leuven (LBBB Participant)</td>
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<tr>
<td>11:10–11:35 am</td>
<td>Psychiatric pharmacogenomics: From clinical translation to discovery of novel CNS drug pathways</td>
<td>Grand Ballroom Foyer</td>
<td>Gerry Higgins, University of Michigan</td>
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<td>Behavioral strategies for managing GI pain</td>
<td>Grand Ballroom Foyer</td>
<td>Laurie Keefer, Mount Sinai Health System</td>
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<td>Eosinophilic esophagitis: Pathophysiology and diagnosis – novel insights</td>
<td>Grand Ballroom Foyer</td>
<td>Stuart Spechler, UT Southwestern Medical Center at Dallas</td>
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<td>12:00–1:30 pm</td>
<td>FNM Board Meeting • Boardroom B, Atrium Level • Invitees only</td>
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<td>12:00–2:30 pm</td>
<td>Lunch • Poster Session • Pacific Concourse • Posters #159 to #318 • Presenters: Please remove posters by 3:00 pm</td>
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<td>2:45–4:05 pm</td>
<td>Concurrent Sessions • Intestinal Disorders • Grand Ballroom A</td>
<td>Brain–Gut Axis: Neuroimmune Mechanisms • Grand Ballroom BC</td>
<td>Regulatory Mechanisms of Gut Chemosensing and Appetite • Bayview</td>
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<td>Pathophysiology, diagnosis and management of gas, bloating, and distention</td>
<td>Activation of the brain–gut axis: Role of stress-induced neuroimmune interactions</td>
<td>Brain–gut chemosensing: Bitter taste receptors as sensors of luminal content</td>
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<td>Fernando Azpiroz, University of Barcelona</td>
<td>Beverley Greenwood-Van Meerveld, University of Oklahoma Health Sciences Center</td>
<td>Catia Sternini, David Geffen School of Medicine at UCLA</td>
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<td>3:10–3:25 pm</td>
<td>Gastric gas dynamics in healthy humans • EN Caballero, I Marin, J Serra, Barcelona, Spain</td>
<td>The effect of prolonged abdominal sepsis on mesenteric nerve activity, dorsal root ganglia and the central nervous system in a murine model of cecal ligation and puncture induced sepsis</td>
<td>Lumenally-restricted TGRS agonists promote murine colonic motility</td>
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<td>YIF Participant</td>
<td>Monash University</td>
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<td>3:25–3:50 pm</td>
<td>Chronic intestinal pseudo-obstruction: Recent developments &amp; future directions</td>
<td>Integration of immune pathways: Role of the vagus</td>
<td>Bariatric surgery: What has it taught us about the regulation of appetite and body weight?</td>
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<td>Vincenzo Stanghellini, University of Bologna</td>
<td>Kirsteen Browning, Pennsylvania State University</td>
<td>Hans-Rudolf Berthoud, Pennington Biomedical Research Center</td>
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## Saturday, August 27, 2016

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<tr>
<th>Time</th>
<th>Concurrent Sessions</th>
<th>Abstract</th>
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<tr>
<td>3:50–4:05 pm</td>
<td>The central role of the intestinal microbiota in chronic intestinal pseudo-obstruction</td>
<td>S Sidani</td>
<td>G De Palma</td>
<td>M Pigrau</td>
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<td>S Lee, SM Collins, P Bercik, Hamilton, ON, Canada. McMaster University</td>
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<td>INOS inhibitor recovers the impaired sensitivity of mouse vagal afferents in diet-</td>
<td>Y Yu</td>
<td>SJ Park</td>
<td>MJ Beyak</td>
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<td>induced obesity</td>
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<td>Kingston,</td>
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<td>Y Queen's University</td>
<td>LBBB Participant</td>
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<td>Role of the gustatory signaling pathway in the metabolic reprogramming after Roux-</td>
<td>S Steensels</td>
<td>M Lannoo</td>
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<td>en-Y gastric bypass surgery in mice</td>
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<td>S Steensels, M Lannoo, T Thijs, B Avau, J Laermans, L Vancleave, R Farry, K Verbeke,</td>
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<td>I Depoortere, Leuven, Belgium. KU Leuven YIF Participant</td>
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<td>4:05–4:45 pm</td>
<td>Break • Visit Exhibits • Grand Ballroom Foyer</td>
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<td>4:45–6:05 pm</td>
<td>Concurrent Sessions</td>
<td>Anorectal Disorders • Grand Ballroom A</td>
<td>The ENS: Neuroimmune Pathways • Grand Ballroom BC</td>
<td>Gastric Disorders: Pathophysiology and Treatment • Bayview Room</td>
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<td>Moderators: Adil Bharucha, Satish Rao</td>
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<td>Emerging concepts in pathophysiology and diagnosis</td>
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<td>José Remes-Troche, University of Veracuzana</td>
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<td>5:10–5:25 pm</td>
<td>Does the type of dyssynergia influence the outcome of biofeedback therapy?</td>
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<td>T Patchartrakul, N Shaffer, A DeWitt, A Mack, SSC Rao, Augusta, GA. Augusta University</td>
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<td>Abstract 41</td>
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<td>5:25–5:50 pm</td>
<td>Fecal incontinence: Where are we headed in diagnosis and treatment?</td>
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<td>Darren Brenner, Northwestern University Feinberg School of Medicine</td>
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<td>5:50–6:05 pm</td>
<td>Balloon expulsion test in patients with fecal incontinence</td>
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<td>S Iqbal, P Koduru, G Ergun, EM Quigley, L Neshatian, Houston, TX. Houston Methodist</td>
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<td>Abstract 42</td>
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<td>7:00–9:30 pm</td>
<td>Reception • Banquet • Awards • Waterfront, Atrium Level • Note: Banquet ticket is</td>
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<tr>
<td>8:00–10:05 am</td>
<td>Emerging Concepts • Grand Ballroom</td>
<td>Moderators: G. Nicholas Verne, John Wiley</td>
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</table>
| 8:00–8:45 am      | ANMS Oration                                 | Intestinal stem cells in health and disease: Regulation by hormones, nutrients, and microbes  
P. Kay Lund, National Institutes of Health |
| 8:45–9:00 am      | Rome IV and Rome III functional dyspepsia in the US, Canada and United Kingdom | OS Palsson, M Simrén, MAL van Tilburg, AD Sperber, WE Whitehead, Chapel Hill, NC; Gothenburg, Sweden; Be'er Sheva, Israel University of North Carolina at Chapel Hill |
| 9:00–9:25 am      | Emerging tools to study enteric neuromuscular function | Brian Gulbransen, Michigan State University                                           |
| 9:25–9:40 am      | Colonic cancer cells adhere and migrate along enteric neurons via L1CAM and N-cadherin  
E Duchalais, C Guilluy, S Nedellec, H Boudin, L Van Landeghem, M Neunlist, Nantes, France. University of Nantes | Abstract 48                                                                        |
| 9:40–10:05 am     | What the future holds for tissue engineering in the GI tract  
Khalil Bitar, Wake Forest University |                                                                                   |
| 10:05–10:30 am    | Break • Visit Exhibits • Grand Ballroom Foyer |                                                                                   |
| 10:30 am–12:00 pm | Emerging Concepts: Functional Bowel Disorders • Grand Ballroom | Moderators: Beverley Greenwood-Van Meerveld, Emeran Mayer                              |
| 10:30–10:45 am    | Exploring the microstructure of the external anal sphincter using diffusion tensor based local and global fiber tractography  
A Zifan, M Ledgerwood-Lee, S Sinha, RK Mittal, San Diego, CA. University of California, San Diego | Abstract 49                                                                        |
| 10:45–11:10 am    | Functional bowel disorders: Emerging targets and treatments  
Michael Camilleri, Mayo Clinic |                                                                                   |
| 11:10–11:25 am    | Impaired gastric distribution of a meal is associated with impaired meal-induced intragastric pressure (IGP) drop and early satiation in functional dyspepsia (FD)  
| 11:25 am–12:00 pm | Functional bowel disorders: The road to personalized medicine  
Gianrico Farrugia, Mayo Clinic |                                                                                   |
| 12:00 pm          | Adjourn                                      |                                                                                   |
modelling and in vivo therapies are emerging. New stem cell strategies for in vitro cells, neural progenitor cells, and epithelial cells), gut-derived organoid synthetic and natural scaffolds as replacements to reconstruct the gut, be divided into acellular approaches such as decellularized matrices, of critical importance. New materials are emerging. Regeneration can proper functionality. Regeneration of the neuromuscular apparatus is each cell type that colonizes the tract. These properties are critical for the management of these patients.

Hans-Rudolf Berthoud, PhD
Pennington Biomedical Research Center

Bariatric surgery: What has it taught us about the regulation of appetite and body weight?
Bariatric surgeries produce lasting suppression of appetite and body weight. In addition, and mainly as a result of weight loss and the hypocaloric state, they drastically improve the diabetic state and reduce other comorbidities of obesity such as cardiovascular disease, sleep apnea and cancer. While attempts to lose weight through dieting largely fail because of strong counter-regulatory adaptive biological responses including increased appetite and decreased metabolism, these responses appear to be absent or neutralized after bariatric surgery. It appears that a newly defended level of body weight (set point) is reached after bariatric surgery. It is thus of considerable interest to reverse-engineer the molecular mechanisms determining body weight set point post bariatric surgery. Years of intensive research indicates that multiple signaling systems are involved. This view is supported by the many observational studies demonstrating structural, biochemical, and functional changes in the brain, adipose tissue, liver, muscle and the GI-tract itself. Much fewer interventional studies have directly tested specific mechanistic hypotheses, which will be discussed in this presentation.

Fernando Azpiroz, MD, PhD
University of Barcelona
Pathophysiology, diagnosis and management of gas, bloating & distention
Abdominal bloating, distension and flatulence are frequently reported in relation to flatulogenic meals, but the mechanism by which gas produces symptoms is not clear. In most cases the rate of gas production, as well as the volume of intestinal gas, are within the normal range. Visible abdominal distension seems a behavioral response, featuring a diaphragmatic contraction and descent with anterior wall protrusion, conceivably related to perception of symptoms the absence of excessive gas retention. Indeed, abdominal distension can be corrected by abdomino-phrenic EMG-guided biofeedback. Diets low in flatulogenic residues decrease gas production and improve symptoms, but in the long run such restrictive diets may have deleterious effects on intestinal microbiota. Other studies showed that prebiotics influence the composition of microbiota and have a beneficial effect of on gut symptoms. Proper pathophysiological diagnosis seems important for the management of these patients.

Khalil N. Bitar, PhD
Wake Forest University
What the future holds for tissue engineering in the GI tract
Tissue engineering and regenerative medicine aim to restore, repair, or regenerate the function of the tissues. Gastrointestinal tissue engineering is a challenging process given the specific phenotype and alignment of each cell type that colonizes the tract. These properties are critical for proper functionality. Regeneration of the neuromuscular apparatus is of critical importance. New materials are emerging. Regeneration can be divided into acellular approaches such as decellularized matrices, synthetic and natural scaffolds as replacements to reconstruct the gut, or cell-based approaches such as tissue specific cells (smooth muscle cells, neural progenitor cells, and epithelial cells), gut-derived organoid units, and stem cells (organ buds). New stem cell strategies for in vitro modelling and in vivo therapies are emerging.

Guy E. Boeckxstaens, MD
KU Leuven
What’s new in achalasia?
Achalasia is a primary esophageal motility disorder with an estimated annual incidence of 1 per 100,000 persons. It is characterized by absence of esophageal peristalsis and failure of the lower esophageal sphincter to relax upon swallowing, resulting in progressively severe dysphagia for solids and liquids, regurgitation, aspiration, chest pain and weight loss. Achalasia results from a loss of enteric neurons, most likely due to an auto-immune reaction. As achalasia cannot be cured, treatment is confined to disruption of the LES to improve bolus passage and thereby relieving symptoms. Treatment modalities available for this purpose include pneumatic dilation, laparoscopic Heller myotomy (LHM) and since recently peroral endoscopic myotomy (POEM). Current insight in pathophysiology, management and treatment options will be discussed in detail.

Darren Brenner, MD
Northwestern University Feinberg School of Medicine
Fecal incontinence: Where are we headed in diagnosis and treatment?
Fecal incontinence (FI) is a common and debilitating disorder significantly affecting quality of life. Defined as the recurrent uncon troll ed loss of stool, the prevalence of this disorder and its subtypes are highly variable. Studies have estimated that FI effects between 2.2–24% of the population with epidemiologic data suggesting that up to 70% of individuals do not report these symptoms to health care professionals. While many scientific tools are currently within our armamentarium (e.g. anorectal manometry, ultrasonography, electromyography, and nerve conductance testing), these data tell us that as physicians, our best diagnostic tool—our mouths—are being underused. Historically, this was due to our lack of understanding of the pathogenesis of FI and of effective therapeutic options. However, times have changed. While we continue to utilize

L. Ashley Blackshaw, PhD
Queen Mary University of London
Identification of novel mediators in IBS
IBS is a multifactorial disorder - in fact more than one disorder – possibly three or four based on symptom patterns and etiology. Therefore it is likely that different mechanisms and mediators underlie different symptom patterns. For example, immune products are implicated, and the nature of their involvement is becoming better understood. IBS-C is characterised by monocytes that produce less of the analgesic opioid beta-endorphin, and IBS-D is characterised by T-cells that produce more pro-inflammatory algesic cytokines like TNF alpha and interleukin 1-beta, but also produce more IL-10 in parallel. Microarray studies of IBS biopsies show changes in pathways of immune regulation that may explain some of these differences, and genome-wide association studies have uncovered candidates that we may or may not have predicted. For example, the ion channel TRPM8 was implicated after careful sifting of genomic data, which correlates with increased TRPM8 expression observed independently in IBS biopsies. Again, unexpectedly this is an immune-associated target rather than a neural target, demonstrating the need to investigate the etiology of IBS using a multi-system approach.

Khali N. Bitar, PhD
Wake Forest University
What the future holds for tissue engineering in the GI tract
Tissue engineering and regenerative medicine aim to restore, repair, or regenerate the function of the tissues. Gastrointestinal tissue engineering is a challenging process given the specific phenotype and alignment of each cell type that colonizes the tract. These properties are critical for proper functionality. Regeneration of the neuromuscular apparatus is of critical importance. New materials are emerging. Regeneration can be divided into acellular approaches such as decellularized matrices, synthetic and natural scaffolds as replacements to reconstruct the gut, or cell-based approaches such as tissue specific cells (smooth muscle cells, neural progenitor cells, and epithelial cells), gut-derived organoid units, and stem cells (organ buds). New stem cell strategies for in vitro modelling and in vivo therapies are emerging.

FNM 2016 INVITED SPEAKERS’ TALKS
diet modification, pharmacologic therapies, and physical therapy/biofeedback as first-line interventions due to their limited invasiveness and well-established safety profiles, newer devices and surgical procedures have been discovered. Unfortunately, current prognostic data is poor and newer more-invasive therapies are usually associated with higher risks. The next generation of clinical testing requires better standardization, head-to-head interventional trials, and should push us to determine the most appropriate interventions based on an individual’s primary symptoms.

Kirsteen Browning, PhD
Pennsylvania State University
Integration of immune pathways: Role of the vagus
The parasympathetic innervation to the upper gastrointestinal tract and pancreas are supplied by the vagus nerve. The sensory (afferent) vagus transduces and relays mechanical, chemical and osmotic signals from the viscera centrally, while the motor (efferent) vagus provides both excitatory and inhibitory control over gastric, intestinal and pancreatic functions. This talk will discuss the effects of cytokines and inflammatory mediators to activate peripheral and central vagal neurocircuits and the potential role this has in inflammation-associated gastrointestinal dysfunction. The actions of inflammation to induce neuroplasticity within vagal neurocircuits will also be discussed and its potential mechanistic role of both short- and long-term hypersensitivity and GI dysregulation.

Nigel W. Bunnett, PhD
Columbia University
Sensitization of nociception: Molecular mechanisms
Primary sensory neurons, which project nerve fibers to the intestinal wall and to the dorsal horn of the spinal cord, are the first cells in pathway to neurogenic inflammation and pain. The peripheral projections of these neurons are equipped with a large number of G protein-coupled receptors, tyrosine kinase receptors and transient receptor potential ion channels, which enable the detection of an extraordinary number of structurally diverse agents that are generated in tissues during injury and inflammation. Activated neurons release the neuropeptides substance P and calcitonin gene-related peptides in peripheral tissues, where they induce neurogenic inflammation, and in the spinal cord, where they activate second order spinal neurons that transmit information centrally. Many receptors sensitize nociceptors by regulating the activity and expression of ion channels, which can lead to exacerbated sensitivity and heightened nociception. New information about the mechanisms that control the activation and sensitization of nociceptors provides insights into chronic pain, with therapeutic implications.

Michael Camilleri, MD
Mayo Clinic
Functional bowel disorders: Emerging targets and treatments
The objectives are to review the following emerging treatments and targets in these disorders:
- Diets: FODMAP, NICE diet and gluten-free
- Glutamine
- Bile acid modulation for bowel dysfunction: diarrhea or constipation
- Ghrelin in gastroparesis and constipation
- Rifaximin: mechanism of action
- Drugs for constipation: 5-HT4 agonist, GC-agonist, NHE3 inhibitor
- Visceral pain: ebastine
- Mucosal expression targets

The field has interesting new mechanisms and targets and these should be enhanced by greater understanding of the intraluminal molecules, receptors and microbial flora in patients with diverse functional bowel disorders.

Lin Chang, MD
David Geffen School of Medicine at UCLA
Genomic biomarkers in IBS: Diagnosis
Increasing evidence supports a role of genetic factors in irritable bowel syndrome (IBS). Genomic studies conducted in IBS include twin and familial clustering of IBS, identification of candidate genes that are associated with the disease state, a quantitative trait (“endophenotype”), or response to treatment (i.e., pharmacogenomics study), and gene expression or epigenetic profiling in IBS vs. controls. Due to methodologic differences in twin studies, the genetic heritability has varied from 0 to 57% in these studies with a greater concordance between identical than fraternal twins. However, studies demonstrate that both genetic and environmental factors (e.g., social learning) contribute to familial clustering in IBS. IBS is likely a polygenic disorder determined by many common gene variants, each contributing very little of the variance of the clinical phenotype. However, a recent study found that a small subset of IBS patients had a genetic mutation that could account for a larger variance of the clinical phenotype. SCN5A mutations were found in 2.2% of IBS patients. SCN5A encodes for the α-subunit of the voltage-gated sodium channel NaV1.5 which can affect motility.

IBS has been associated with single nucleotide polymorphisms (SNPs) in candidate genes. Post-infection IBS (PI-IBS) has been associated with genes related to gut permeability (Cadherin-1, CDH1), immune response (Interleukin-6 (IL-6)) and response to bacterial DNA (Toll-like receptor 9 (TLR-9)), but these findings need to be validated in a larger cohort. The proinflammatory gene TNFSF15 SNP has been found to increase the risk of IBS in independent cohorts. A recent genome wide association study (GWAS) in 534 IBS cases and 4932 asymptomatic controls identified two genes KDELRE2 and GRID2IP. Findings were replicated in 8977 subjects.

SNPs in genes for CRF receptor 1(CRF-1R), bile acid receptor (TGR5, GPBAR1), cannabinoid receptors, a catechol-O-methyltransferase (COMT), and toll-like receptor (TLR9) have been associated with quantitative traits in IBS, including GI transit times, cardioautonomic tone, acoustic startle response, or morphologic brain imaging findings. Genetic polymorphisms have also been linked to differential treatment responses.

Studies measuring targeted gene expression in intestinal tissue samples in IBS patients and controls have primarily yielded inconsistent findings and are limited by small sample sizes. The first RNA sequencing study of the rectosigmoid mucosa was recently performed in a small number of IBS-D women and healthy women. Twenty-one genes were differentially expressed in IBS-D and ten genes with functions that were relevant to IBS-D pathophysiology (e.g., immune function, neurotransmitters, cytokines, ion channels) were confirmed by RT-PCR. Larger validation studies are needed.
IBS studies are starting to focus on the role of microRNAs, long non-coding RNAs (lncRNAs) and epigenetic modification of DNA since they modify gene expression. A recent study analyzed the entire methylome of peripheral blood mononuclear cells (PBMCs) in IBS patients and healthy controls identified disease specific DNA methylation signatures involved in oxidative stress and neuronal pathways. Confirmatory studies are needed and similar approaches in colonic tissue will hopefully reveal interesting insights into disease mechanism.

References:

Ji-Hong Chen, MD, PhD
Wuhan University
Control mechanisms of colonic motor patterns in animal models and patients with chronic constipation
High Resolution Colon Manometry using 36 or 84 channels, the latter covering the entire colon over 102 cm have revealed many characteristics of normal colonic motility in a total of 26 volunteers. We propose to incorporate Simultaneous Pressure Waves into the assessment of colonic motility since it is the most prominent pressure pattern that has propulsive contractions underlying it. This was proven using simultaneous HRCM with spatio temporal mapping of diameter changes in the proximal 3-taeniated rabbit colon. In humans, simultaneous pressure waves increase significantly after a meal, are associated with gas expulsion and anal sphincter relaxation. They can occur at high amplitude with a challenge with bisacodyl and are then associated with urge to defecate. Parallel studies on the rabbit and human have revealed features of motor patterns that are associated with haustra and hastral boundaries. Bisacodyl induced motor patterns occur mediated by the ENS or vagal afferent and efferent pathways. HRCM is giving us deep insight into mechanisms underlying colonic motility.

Isaac M. Chiu, PhD
Harvard Medical School
Microbes and pain: Neuronal sensing of bacteria
Nociceptor sensory neurons that mediate pain densely innervate barrier tissues including the gastrointestinal tract. Pain accompanies many types of bacterial infections. Until recently, it was thought that pain was secondary to immune activation. We have found that nociceptor neurons directly detect bacterial pathogens, and that this neural sensing is a major mechanism of pain production during infection. Nociceptor neurons detect bacterial N-formylated peptides and toxins, leading to calcium influx and action potential firing. These mechanisms mediate acute nociceptive behaviors, mechanical and thermal hyperalgesia in mice during infection. Following bacterial activation, nociceptors release neuropeptides including CGRP which modulate inflammation and host defense. Defining the specific molecular interactions between bacteria and the nervous system could lead to better treatments for pain in conditions such as irritable bowel syndrome and inflammatory bowel disease.

Carlo Croce, MD
The Ohio State University
Non-coding RNA diagnostics and therapeutics
MicroRNAs are components of pathways involved in cancer pathogenesis. This is the reason microRNAs are disregulated in all tumors. Dysregulation of microRNAs can be exploited for cancer diagnostics and prognostics, and to develop anti-cancer treatment.

Roberto De Giorgio, MD
University of Bologna
Neuronal dysfunction: Clinical manifestations
Abnormalities of the morpho-functional integrity of the innervation supplying the gut, the enteric nervous system (ENS), are labelled as enteric neuropathies. They are characterized by a severe impairment of gut function such as that detectable in chronic intestinal pseudo-obstruction (CIPO) or enteric dysmotility (ED). CIPO consists of periodic crisis of intestinal sub-occlusion due to a severe abnormality of gut motility. Some cases can be so severe that a volvulus can occur. The evolution of CIPO is towards a progressive dilatation with intestinal failure. ED patients may present with severe symptoms in the absence of intestinal sub-occlusion. CIPO and ED patients are being increasingly studied by full-thickness biopsy. A diagnosis of enteric neuropathy has been identified in most cases with evidence of degeneration and neuronal loss (20%–50%) hence the term ‘oligoneuronal hypoganglionosis’. In ~25% of patients an inflammatory, immune-mediated enteric (myenteric>submucosal) neuronal insult denotes a lymphocytic ganglionitis.

Evan S. Dellon, MD, MPH
University of North Carolina
Eosinophilic esophagitis: Future directions in treatment
Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated condition defined clinically by symptoms of esophageal dysfunction and pathologically by a marked eosinophilic infiltrate in the esophageal mucosa (≥15 eos/hpf) in the absence of other causes of local or systemic eosinophilia. The current first line treatments for EoE are either pharmacologic (ie swallowed topical steroids) or dietary (elimination of specific foods or food groups thought to cause EoE). This talk will briefly review these first line approaches, but will focus on future directions in treatment of EoE. Emerging medications include novel formulations of swallowed/topical steroids, biologics (including anti-IL-5, anti-IL-13, and anti-IL-4 antibodies), and small molecules that target components of the pathogenesis of EoE, the knowledge of which is expanding rapidly. This talk will also review new approaches to dietary therapy, including less restrictive empiric elimination diets.
Neelendu Dey, MD
Washington University

Envisioning how targeted manipulations of the gut microbiota could affect motility

Gut motility, a physiologic parameter critical for normal digestion and adequate nutrition, is affected by interactions between diet, the gut microbiota, host genetics, and the enteric nervous system. These interactions – and the global diversity in diet and composition of gut microbiota – are postulated to drive the variation in intestinal transit times between and within populations worldwide. The host-microbial dialogue at the interface between the intestinal lumen and the enteric nervous system involves metabolites modulated by bacteria, including bile acids, short-chain fatty acids, and neurotransmitters (e.g., serotonin). Gut microbes are implicated in irritable bowel syndrome (which can be post-infectious) and small intestinal bacterial overgrowth (in which bacterial bile acid deconjugation is associated with altered motility). A testable hypothesis is that microbial biotransformation of bile acids plays a causal role in shaping gut motility. Gnotobiotic mice colonized with human gut microbial communities of defined composition and fed human diets provide a way to test this hypothesis in a systematic manner. I will discuss how findings from preclinical models can refine our understanding of pertinent mechanisms in dysmotility and direct clinical studies of new diet- and microbiota-based diagnostic and therapeutic approaches. In the future, the work-up of patients with dysmotility disorders may entail analyses of the gut microbiota to guide the design and deployment of personalized therapies.

Carlo Di Lorenzo, MD
Nationwide Children’s Hospital

Functional abdominal pain in the pediatric population: Emerging concepts

Pain-predominant functional gastrointestinal disorders (FGID) are very common in children. School-based studies in Colombia and Sri Lanka found a prevalence FAP/IBS of 4.9% and 5.4%, respectively. IBS prevalence in children across the U.S. based on parental report ranges from 1.2% to 2.9%. More than 50% of new pediatric gastrointestinal clinic patients meet Rome 3 criteria for ≥1 FGID. New symptoms based diagnostic criteria have been proposed by the Rome committees. Current criteria have been improved, novel entities have proposed, new diagnostic algorithms have been recommended and the Multidimensional Clinical Profile (MDCP) has been introduced. Emerging pathophysiologic concepts that are likely to be relevant to treatment and outcome include alteration in intestinal permeability and microbiome and role of early life events and internalizing disorders. Finally, great progress has been made in testing the effectiveness of several treatments since Rome III was published. Most of the pediatric treatment studies of pain predominant FGID have involved children with FAP and IBS, making no differentiation between the two phenotypes. Current and emerging treatments of children with FBD can be divided in treatment targeting the gut, the brain, or the environment (parents) and they will be discussed in my presentation.

Sigrid Elsenbruch, PhD
University of Duisburg-Essen

Functional brain imaging: Where are we now & where are we headed?

Functional brain imaging has made a significant contribution to elucidating central mechanisms involved in the pathophysiology of chronic visceral pain in disorders of the brain-gut axis. In irritable bowel syndrome (IBS) and functional dyspepsia (FD), alterations in both resting state activity and in visceral pain-induced neural activation have been established, encompassing specific networks of interconnected brain regions. These differences in part reflect visceral hypersensitivity, and are shaped by psychological factors. These include psychiatric comorbidity, history of abuse and personality. Pain-related cognitions and emotions also demonstrably shape pain processing, as illustrated by conditioning and placebo paradigms. In the future, functional brain imaging studies in functional GI need to address connections between peripheral alterations, including changes in the microbiota and gut permeability, and changes at the level of the brain. Ideally, brain imaging findings should contribute to tailoring individual treatment approaches.

Gianrico Farrugia, MD
Mayo Clinic

Functional bowel disorders: The road to personalized medicine

The sequencing of the human genome gave rise to several “-omic” fields. The health-care promise of genomics has been throttled by a lack of understanding on which of the tens of thousands of variants predisposes to disease. Now, the increased robustness of available databases suggests this will change and will markedly affect the clinical practice for functional bowel diseases. Pharmacogenomics is a significant evolution from pharmacogenetics. Of all the “-omic” areas this has the most utility data and ability to impact patient care through existing mechanisms. The interaction between drugs commonly used in functional bowel diseases such as pain medications and tricyclics and genes such as CYP2D6 may help improve patient outcomes and reducing side effects. The emerging link between the intestinal microbiome and functional bowel diseases such as IBS suggests that this is a field of study with significant promise. Advances in epigenomics including the ability to analyze epigenomic and transcriptomic changes also offers significant promise for integrating the current diverse thought leadership positions on causes of functional bowel disease. Overall, precision, personalized, individualized medicine holds significant promise to transform our approach to both research and practice for functional bowel diseases.

Jose Garza, MD
GI Care for Kids

Functional diarrhea & constipation in the pediatric population: Future directions

The term functional constipation and functional diarrhea are used when no underlying organic cause can be identified for the symptoms. Constipation within childhood is a very common problem. Despite widespread use of laxatives by health professionals up to 25% of children continue with constipation beyond puberty. There is a paucity of data on pediatric constipation and even less in pediatric functional diarrhea. There is a substantial overlap in symptoms
between constipation and constipation predominant irritable bowel syndrome as well as between diarrhea and diarrhea predominant irritable bowel syndrome. Thus it is not surprising that treatment approaches for both disorders overlap, this presentation will focus on pathophysiology and pharmacological treatments that will hopefully change the management for children with functional constipation and diarrhea who do not respond to current available first line treatments.

**Udai C. Ghoshal, MD**  
Sanjay Gandhi Postgraduate Institute of Medical Sciences

**Microbiome dysbiosis and metabolic disorders**

Obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) are metabolic syndromes that are increasing in prevalence and are significant causes of morbidity and mortality worldwide. Conventionally, increased food intake and lack of exercise are considered to be the major mechanisms of these metabolic disorders; recently, the role of gut microbiota is being understood in the pathogenesis of these metabolic syndromes. Gut microbiota influences development of these metabolic syndromes by conserving extra energy from undigested foods, causing low grade inflammation and neuro-hormonal dysregulation. The major evidence of role of gut microbiota comes from animal studies, human case-control and interventional studies and mechanistic data. Increased expression of intestinal nutrient transporters, modified lipid and bile acid metabolism, production of short chain fatty acids that conserve energy from non-digestible dietary fibers are some of the major mechanisms how gut microbiota contributes to these metabolic syndromes. Gut microbiota may influence key metabolic pathways such as insulin signalling, incretin production and alteration of ileal brake altering peptide YY, neurotensin and glucagon like peptide through malabsorbed fat. Recent evidence from personalized dietary intervention in conjunction with gut microbiota studies uncovered how the same diet can have different glycemic indices in different subjects possibly due to variation in microbiota. Patients with untreated and surgically treated obesity and NAFLD have been shown to have small intestinal bacterial overgrowth, which is known to contribute to development of fatty liver. Endogenous alcohol production by bacteria may contribute to NAFLD in patients with SIBO. It is interesting to look at the possible ways to manipulate gut microbiota to prevent and treat these metabolic disorders.

**Sutep Gonlachanvit, MD**  
Chulalongkorn University

**Non-celiac gluten sensitivity (NCGS)**

A self care using gluten free diets (GFD) has been increasing in western people with no celiac disease (CD) or wheat allergy (WA). This follows by an increase concern on the condition called “NCGS” in medical community. NCGS has been proposed as a condition characterized by intestinal and extra-intestinal symptoms related to ingestion of gluten-containing diets (GCD), in the absence of celiac disease (CD) and wheat allergy (WA). The term “NCGS” may not be appropriated because not only CD and WA but also other mechanisms of GCD that can induced GI symptoms including high FODMAP effects, reaction to α-amylase/trypase inhibitors and other non-gluten proteins. It has been recommended that after excluding CD and WA, diagnosis of NCGS should include a double blind placebo-controlled (DBPC) gluten challenge test during GFD. However, DBPC studies of the effect of gluten ingestion on GI symptoms in non CD, non WA patients with or without IBS have inconclusive results. Recent studies suggested that GCD induced GI symptoms in most of non-CD and non-WA patients may be the effects of high FODMAP content. In conclusion, there is a group of non-CD, non-WA patients who have GI symptoms induced by wheat or GCD. However, apart from FODMAP, which component of GCD (gluten and/or others non-gluten proteins) plays role on this effect and should be eliminated from the GCD has not been well established.

**Beverley Greenwood-Van Meerveld, PhD**  
University of Oklahoma Health Sciences Center

**Activation of the brain–gut axis: Role of stress-induced neuroimmune interactions**

Irritable bowel syndrome (IBS) is a multifactorial disorder with symptoms that are worsened by adult stress and overlapping with other stress disorders including anxiety, post traumatic stress disorder and depression. The pathophysiology of IBS involves a dynamic interplay between the brain–gut axis with chronic stress activating abnormal central processing leading to HPA axis dysfunction, as well as autonomic nervous system and immune activation increasing intestinal permeability, visceral hypersensitivity, and abnormal motility and secretion. In my presentation I will discuss the experimental evidence supporting chronic stress as a mechanism for triggering the onset and exacerbation of IBS. The focus of the talk will be on the central glucocorticoid receptor (GR) and corticotrophin releasing factor (CRF)-mediated mechanisms within the central nucleus of the amygdala (CeA) that are activated by chronic stress to induce visceral and somatic hyperalgesia resembling that seen in a subset of IBS patients.

**Brian D. Gulbransen, PhD**  
Michigan State University

**Emerging tools to study enteric neuromuscular function**

Many of the basic tenants that govern enteric neuromuscular transmission were elucidated by studying the activity of enteric neurons and responses of smooth muscle cells. However, new data show that these processes are heavily influenced by non-neuronal cells. Understanding the contributions of non-neuronal cells in the transduction, modulation and transmission of signals from nerves to muscle has remained challenging and is the focus of several current debates. This presentation will focus on new tools to study the contributions of specific cells to neuromuscular transmission. These include advanced genetic models that permit the selective activation of cells, the manipulation of defined mechanisms and the study of cellular genomic composition. These tools will be discussed within the context of studies that address the roles of glial cells in neuromuscular transmission. The application of these tools to current studies holds great promise to gain novel insight into mechanisms that regulate gut motility in health and disease.
Psychiatric pharmacogenomics: From clinical translation to discovery of novel CNS drug pathways

Current pharmacogenomic tests used for medication optimization in psychiatry have demonstrated clinical utility and significant reductions in healthcare costs. This generation of SNP genotype-based pharmacogenomic tests are based largely on exome variants culled from the published scientific literature. However, the majority of pharmacogenomic GWAS SNPs impact enhancers, and the spatial organization and dynamics of the noncoding genome dictate gene regulatory pathways. We have focused on chromatin interactions and epigenomics to find pharmacodynamic pathways for CNS drugs that previously had no well-defined mechanism of action. We have mined the 4D pharmacoepigenome to define human CNS pathways for lithium, ketamine, and valproic acid (VPA). For example, VPA’s widespread transcriptional program in the human CNS involves induction of transcription factors responsible for neurogenesis, including NEUROD1 and TBRI, as well as activation of the npBAF complex active during CNS development. The birth of new neurons following VPA treatment in an animal model of traumatic brain injury is concomitant with functional recovery. The pharmacoepigenome represents a fertile domain for CNS drug discovery.

Patrick A. Hughes
University of Adelaide

Endogenous opioids and visceral pain

Visceral pain is a common symptom experienced in Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD). Opioids can be effective for treating acute pain and diarrhea, but chronic use is associated with significant side effects restricting their usefulness for treating IBS and IBD. Endogenous sources of opioids include the HPA axis and the nervous system, but recent advances have revealed immune cells also constitute an important source of opioids. Human and animal studies indicate immune derived opioids set the threshold to visceral pain in health and blocking this pathway sensitizes visceral afferent nerves to distension. Colitis increases opioid receptor expression on visceral afferent nerves, and also increases opioid secretion from immune cells. Further developing our understanding of how endogenous opioid pathways are altered in visceral pain states will potentially provide novel targets for the treatment of IBS and IBD.

Laurie Keefer, PhD
Mount Sinai Health System

Behavioral strategies for managing GI pain

Research from both animal and human studies have demonstrated that gastrointestinal pain is highly complex and stems from a combination of genetic, environmental and behavioral factors. Not only do these factors drive the onset and maintenance of pain symptoms, they can also influence response to treatment. Psychological factors in particular can amplify the experience of abdominal pain, particularly pain catastrophizing, attentional bias, inflexible coping, avoidance behavior and lack of perceived control. This talk will conceptualize pain from a fear-avoidance model and focus on how psychological contributors can be addressed through a range of behavioral therapies, including cognitive-behavior therapy, hypnotherapy and mindfulness-based approaches.

B U.K. Li, MD
Medical College of Wisconsin

Cyclic vomiting syndrome (CVS): Pathophysiology and treatment

CVS is a functional GI disorder characterized by recurrent episodes of intense nausea and vomiting and repeated Emergency Room visits for dehydration. Despite absence of a biomarker, it is increasingly recognized in children and adults based upon consensus diagnostic criteria (Rome IV, NASPGHAN, IHS). An ongoing ANMS-supported effort is establishing adult diagnostic and treatment guidelines.

Multiple co-morbid conditions (anxiety, depression) and many school or work absences contribute to a poor quality of life. Although the pathogenesis remains unknown, CVS appears to be a migraine variant and may also involve an altered HPA axis, autonomic dysfunction, and mitochondrial insufficiency. Cannabis-induced hyperemesis may be a form fruste of CVS triggered by prolonged, high-dose cannabis use.

Treatment remains empiric and treatment responses are heterogeneous. Treatment includes lifestyle modifications, prophylactic therapy especially tricyclic antidepressants, mitochondrial supplements, abortive medications given at the onset, and rescue IV therapy with a written hospital protocol.

P. Kay Lund, PhD
National Institutes of Health

Intestinal stem cells in health and disease: Regulation by hormones, nutrients, and microbes

Intestinal epithelial stem cells (IESC) are the drivers of continuous renewal and maintenance of the intestinal epithelium. IESC are give rise to progenitors that differentiate into multiple lineages including entero-endocrine cells, which are critical to metabolic homeostasis. This presentation will focus on a) current information about distinct IESC sub-types and reporter models to study IESC and EEC function, b) impact of injury and the insulin-IGF system on IESC and EEC, c) novel roles of the insulin receptor in normal and aberrant IESC function and d) impact of microbial colonization on IESC and EEC.

Sarkis K. Mazmanian, PhD
California Institute of Technology

Microbiota and chemoattractant receptors in the gut

The intestinal microbiota influences neurodevelopment, modulates behavior, and contributes to various neurological disorders. However, a link between gut bacteria and neurodegeneration remains unexplored. Synucleinopathies are neurodegenerative diseases characterized by aggregation of the protein α-synuclein (αSyn), often resulting in motor dysfunction, as exemplified by Parkinson’s disease (PD). Using mice that overexpress αSyn, we identify that the gut microbiota promotes motor deficits, increases microglia activation, and enhances αSyn pathology. Antibiotic treatment ameliorates, while microbial colonization promotes, pathophysiology in adult animals, suggesting disease arises from postnatal signaling between the gut and the brain. Indeed, oral administration of the microbial metabolites, short-chain fatty acids, to germ-free mice induces neuroinflammation and motor symptoms. Remarkably, colonization of αSyn- overexpressing mice with microbiota from PD patients enhances physical impairments compared to microbiota transplants from healthy human donors. These findings reveal that gut bacteria potentiate numerous Parkinsonian-like features in a mouse model, and suggest that alterations in the human microbiome represent a novel risk factor for PD.
**INVITED SPEAKERS’ TALKS**

**Michel Neunlist, PhD**
Inserm U913, University of Nantes

**Novel roles for enteric glia in health and chronic diseases**

Enteric glial cells (EGCs) are increasingly recognized as central regulators of gut homeostatic processes such as intestinal barrier functions, motility and immune functions. Glial regulation of gut functions are achieved either by modulating enteric neuronal functions or by directly acting at cellular components of the gut such as epithelial cells or immune cells. In this overview, we will present and summarize the latest knowledge gained in this expanding field such as developmental regulation of glial phenotype and functions, glial control of intestinal barrier and motor functions and immune cells. In addition, we will illustrate how during stress such as inflammation or during chronic diseases of the gut, such as inflammatory bowel diseases, or the brain, such as Parkinson’s disease, EGC phenotype and functions are altered and could contribute to diseases symptoms and evolution.

**Vassilis Pachnis, MD, PhD**
The Francis Crick Institute

**Emerging concepts in GI neurodevelopment**

The Enteric Nervous System (ENS) includes the intrinsic neuronal networks of the gut wall that regulate most aspects of gastrointestinal physiology. Despite being a key relay station along the Gut-Brain Axis, the ENS functions largely independently of the central nervous system to control complex gut motility patterns, secretory responses of the intestinal epithelium and blood supply to the gut wall. This is made possible by the generation of a vast number of enteric neurons (further subdivided into many neurochemical subtypes) and enteric glial cells (EGCs) that are assembled into functional neural circuits. Research in my laboratory focuses on understanding the genetic programmes and developmental rules that control the assembly of intestinal neuronal networks and explores the environmental factors (such as the microbiota) that regulate their function and homeostasis. We will present single-cell lineage tracing and transcriptomic studies which define the dynamic relationships of ENS lineages during development and determine their spatial organization in the adult gut.

**Don W. Powell, MD**
University of Texas Medical Branch

**Developmental immunology in the gut**

The major function of the immune system is to prevent or eradicate infection although its ability to enhance the eradication of cancer has been recently recognized. The development of the innate and adaptive immune system never ends, although three major periods of development and diseases can be recognized: 1) Embryological (pre-natal) development of hematopoietic stem cells in the yoke sac and embryonic/fetal liver which travel to the bone marrow and thymus and then to lymph nodes and spleen during which congenital immune diseases begin; 2) Post-natal development from birth to age three during which the gut microbiota, as altered by the route of birth, the introduction of food antigens (e.g., breast milk and grains or protein) or antibiotics may profoundly alter the developing immune system and promote future hypersensitivity or autoimmune diseases; 3) Adolescent and adult period in which the immune system responds to ever changing antigens from microorganisms, foods, xenobiotics or self with either eradication of infection and/or production of disease.

**José Remes-Troche, MD**
University of Veracruzana

**Emerging concepts in pathophysiology and diagnosis**

A good understanding of anorectal physiology is essential for the diagnosis and appropriate treatment of various anorectal disorders, such as fecal incontinence, constipation, and chronic anorectal pain. Newer techniques such as high-resolution and high-definition anorectal manometry, colonic manometry, wireless motility capsule, and magnetic resonance defecography can provide mechanistic insights. These techniques have been applied in healthy adults and in patients with constipation or fecal incontinence, anal fissure, perineal descent, chronic proctalgia, and Hirschsprung’s disease. Most of the studies have been conducted on adults, with only a few studies in pediatric populations. A more comprehensive characterization of motility patterns and coordinated activity may help to improve our understanding of the normal pathology and pathophysiology of anorectal disorders. Indications for investigations, steps in performing the tests, and interpretation of results are discussed.

**Nathalie Rommel, PhD**
KU Leuven

**Oropharyngeal dysphagia: Novel mechanisms**

Swallowing dysfunction or dysphagia has an important impact on the patient’s quality of life since it can lead to a range of significant consequences as aspiration pneumonia, malnutrition, dehydration and food impaction. Improving inefficient swallowing requires a detailed understanding of normal and abnormal deglutition through the use of adequate and objective assessment techniques.

In this talk we will discuss some novel mechanisms of oropharyngeal swallowing dysfunction using high resolution manometry impedance with video analysis. Combined pressure flow analysis with radiology can refine some aspects of the pathophysiology of oropharyngeal dysphagia previously described. If and how this leads to meaningful diagnostic information and assistance in the management of patients with pharyngeal dysphagia, will be presented in the talk.

**Kenton M. Sanders, PhD**
University of Nevada, Reno School of Medicine

**GI smooth muscle and interstitial cells: Novel insights in GI smooth muscle**

Gastrointestinal (GI) motility occurs from the coordinated contractions of the muscle layers of GI organs. Coordination of SMC contraction requires higher-level regulatory systems, such as interstitial cells, enteric neurons and hormonal influences. SMCs in GI organs are organized into electrical networks (syncytia) via gap junction coupling. SMCs are electrically coupled to interstitial cells of at least 2 classes: interstitial cells of Cajal (ICC) and fibroblast-like (PDGFRα+ cells). This greater syncytium is called the SIP syncytium. ICC generate electrical pacemaker activity (slow waves) that organizes phasic contractions fundamental for peristalsis and segmentation. Interstitial cells lie in close proximity to varicosities of enteric motor neurons and express receptors, 2nd messenger pathways and effector proteins that mediate, in concert with SMCs, responses to enteric neurotransmitters. PDGFRα+ cells mediate purinergic neurotransmission. The SIP syncytium occurs in human GI muscles in approximately the same anatomical niches and in close...
contact with enteric motor neurons. However, the functions of SIP cells in human GI motility have only been extrapolated from animal models at present.

**Miguel Saps, MD**  
**Nationwide Children's Hospital**

**Functional bowel disorders: The role of early life events**  
The early neonatal period is one of particular vulnerability. Adverse stimuli during this critical period may alter the development of nociceptive neuronal circuits which in turn may result in decreased pain thresholds later in life. Animal and human studies have shown that adverse events at times of developmental plasticity of the immature brain can have long-term consequences in sensory processing and gastrointestinal function. In children, infectious and non-infectious gastroduodenal and extraintestinal inflammation were shown to put children at risk of developing chronic abdominal pain and functional gastrointestinal disorders (FGIDs). Henoch-Schönlein purpura, urinary tract infections and acute gastroenteritis increase the risk of developing chronic abdominal pain and FGIDs later in childhood and in some cases probably into adulthood. Establishing the various factors that increase the risk of developing FGIDs and the protective factors that prevent some children from developing FGIDs may help develop prevention programs.

**Keith A. Sharkey, PhD**  
**University of Calgary**

**Neuronal degeneration: basic mechanisms**  
Loss of enteric neurons is associated with aging, systemic diseases such as diabetes mellitus, inflammatory diseases of the GI tract such as inflammatory bowel disease and myenteric ganglionitis and in other conditions. The mechanisms of neuronal degeneration vary between these conditions, though oxidative stress leading to apoptosis appears to be a central feature of many of them and nitrogentic neurons appear particularly susceptible to damage. The immunological targeting of enteric neurons by autoantibodies is a feature of achalasia and is being recognized in other conditions affecting GI motility. A novel mechanism underlying inflammation-induced enteric neuron death was recently reported. Here it was shown that inflammation causes enteric neuron death by activating a neuronal signaling complex comprised of P2X7 purinergic receptors, pannexin–1 channels, the Asc adaptor protein and caspases. Recent data show that activation of 5-HT4 receptors can protect against apoptotic cell death. This presentation will examine the molecular and cellular mechanisms of enteric neurodegeneration.

**Magnus Simrén, MD PhD**  
**University of Gothenburg**

**What’s in the future for FODMAPs (component analysis)?**  
Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are poorly absorbed in the small intestine and can pass unabsorbed to the colon, where they increase luminal water through osmotic activity and induce gas production due to fermentation by colonic bacteria. This in turn can cause luminal distension and lead to GI symptoms in susceptible individuals, and there are now several clinical trials supporting that reduction of FODMAPs is beneficial for IBS patients. However, based on the existing literature, several controversies / unresolved issues regarding the use of a low FODMAP diet to treat IBS patients still exist:

1. Is a low FODMAP diet superior to traditional IBS dietary advice?
2. Which group of IBS patient benefit the most from a low FODMAP diet?
3. Existing clinical trials have studied the effect of a low FODMAP diet during 3-4 weeks, but long-term management has not been studied.
4. Mechanistic studies suggest that the GI effects of the different FODMAP components differ, but the clinical relevance of this has not yet been established.
5. Are less restrictive FODMAP reduced diets based on knowledge about effects of the different FODMAP components the way forward?

**Terence Smith, PhD**  
**University of Nevada, Reno School of Medicine**

**Optogenetics: Applications in the Gut**  
The function of ENS neural networks and ICC (interstitial cells of Cajal) networks, and their role in the generation of complex motor behaviors in the gut is inherently difficult because of the large number of interacting different functional classes of neurons or ICC that can have emergent properties that can’t readily be predicted from recording from individual cells. Our goal is to utilize a number of cell-specific promoters to insert the genetically encoded Ca^{2+} indicator GCaMP3, which measures Ca^{2+} activity, in different functional classes of enteric neurons, glial cells and ICC: Wnt1-GCaMP3 (all enteric neurons and glia); nNOS-GCaMP3 (all nNOS neurons), ChAT-GCaMP3 (all cholinergic neurons), TPH2-GCaMP3 (5-HT neurons), GFAP-GCaMP3 and Kit-GCaMP3 (all ICC). GCaMP3 also preserves the morphology of cells. Furthermore, channel opsins (Channel Rhodopsin 2 (ChR2; Na^{+} channel) and Halorhodopsin (HR; Cl^{−} channel)) can also be expressed in specific cell types. Activation of ChR2 and HR with blue or yellow light respectively can cause depolarization (ChR2) or hyperpolarization (HR) of specific cells, allowing their activity during motor behaviors to be turned on or off at will. With these new tools an unprecedented level of information can be extracted from the myenteric plexus and submucous plexus and ICC networks since the activity in GCaMP3 labelled cells is usually so bright that it can be viewed in the undissected gut.

**Stuart J. Spechler, MD**  
**UT Southwestern Medical Center at Dallas**

**Eosinophilic esophagitis: Pathophysiology and diagnosis – novel insights**  
The pathogenesis of eosinophilic esophagitis (EoE) starts with a genetically-susceptible individual, for whom some food- or Aero-allergen activates the immune system, inducing a T helper (Th)2 response with the production of Th2 cytokines like interleukin (IL)-5, IL-13 and IL-4. IL-5 plays a key role in eosinophil production, activation, and recruitment. In the esophageal epithelium, IL-13 and IL-4 increase the production of eotaxin-3, a potent eosinophil chemoattractant that draws the activated eosinophils to the esophagus, where they release secretory products that mediate tissue damage, tissue remodeling and symptoms. This process can be interrupted by removing the inciting food allergen with an elimination diet, or with
Gastroparesis: What it is & what it isn't

Gastroparesis is defined as the presence of delayed gastric emptying in the absence of mechanical obstruction, and associated with symptoms of postprandial fullness, early satiety, nausea, vomiting and bloating. Gastroparesis is considered the end result of neuromuscular failure or excessive inhibitory influence, or both, on the components of the gastric emptying process. The concept of gastroparesis is popular in clinical gastroenterology practice, but there are major areas of uncertainty including the differentiation between functional dyspepsia with delayed gastric emptying and idiopathic gastroparesis, the poor relationship between delayed emptying and symptoms, and the therapeutic approach to gastroparesis patients. These uncertainties have questioned the validity of gastric emptying tests in clinical management and therapeutic trials.

Research over the last decade has assessed whether the available data justify the current concept of gastroparesis, as a separate disease entity, characterized by delayed gastric emptying as a key mechanism underlying symptom generation and driving therapeutic choices and outcomes. The majority of studies have failed to show specificity of the subgroup with delayed emptying compared to the broader patient group with epigastric symptoms in the absence of organic pathology or mechanically obstructing lesions. Delayed emptying is relatively poorly reproducible over time, does not correlate with symptom pattern, prognosis or complications, and does not predict outcome of prokinetic therapy. It does seem to predict lack of efficacy of tricyclic antidepressant therapy.

There is a need for a critical reappraisal of the gastroparesis concept, and clinicians need new guidance as to when to consider gastric emptying testing and how to use it in patient management. The use in poor improvements in therapeutic results. Rarity of the condition, uncertainties on its definition contribute to the lack of success of recent years. Multicentre, collaborative studies are warranted to move the field forward.

Catia Stermini, MD
David Geffen School of Medicine at UCLA
Brain–gut chemosensing: Bitter taste receptors as sensors of luminal content

Chemosensory processes in the gut are critical for digestion and absorption of nutrients and for neutralization and expulsion of harmful substances by activating sensory receptors on enteroendocrine (EEC) cells, and influence ingestive behavior through brain-gut axis signaling. Bitter taste receptors (T2Rs) detect the sense of bitterness that is regarded as a warning signal against threats. T2R activation leads to release of Ca²⁺ and peptides involved in gut chemosensing. In the gut, T2Rs are expressed by EEC cells and are upregulated by high fat diet, which alters gut microbiota and induces obesity. Gut T2Rs are correlated with different species of bacteria and bacteria products activate a GPCR cascade associated with T2R transduction in EEC cell lines. These findings support the hypothesis that intestinal T2Rs serve as regulators of luminal homeostasis and mediate host functional responses to changes in the gut microbiota by sensing bacterial products.

Jan Tack, MD, PhD
KU Leuven
Gastroparesis: What it is & what it isn't

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There is a need for a critical reappraisal of the gastroparesis concept, and clinicians need new guidance as to when to consider gastric emptying testing and how to use it in patient management. The use
of alternative approaches to gastric function testing, such as nutrient tolerance testing or measurement of gastric accommodation should be considered. The need for further therapeutic studies is more pressing than ever, taking into account recent discouraging outcomes of studies with prokinetics, devices and antidepressants.

Nathalie Vergnolle, PhD
IRSD, Inserm U-1220

Neuroimmune interactions in the gut

This paper will review the evidences that link the immune system and the extrinsic and intrinsic enteric nervous systems. The presence of immune cells in tissues from patients with functional disorders or irritable bowel syndrome will be evoked, as well as the activation status of immune cells in those patients. The impact of immune activation on gut sensorimotor functions and symptoms will be discussed as well as the impact of enteric neurons on immune cells.

G. Nicholas Verne, MD
Tulane University

Emerging role of epigenetics and miRNA in IBS

It has been increasingly appreciated that epigenetic change is a natural and regular occurrence that can manifest in the manner in which cells terminally differentiate or can have more damaging effects that can lead to the pathogenesis of human disease. There are currently 3 systems that initiate and sustain epigenetic change including DNA methylation, histone modification, and non-coding RNA such as miRNA. New studies are continuously uncovering the role of epigenetics in a variety of human diseases and disorders. MicroRNAs (miRNAs) are a class endogenously expressed RNAs 21-23 nucleotides long with a function distinct from but related to that of short interfering RNAs (siRNAs). Singlestranded miRNAs bind through partial sequence homology to the 3'-untranslated region (UTR) of target mRNAs and cause a block in translation or mRNA degradation. Over the past decade, miRNAs have emerged as regulators involved in gene expression of important processes, including development, differentiation, apoptosis and proliferation through imperfect pairing with target mRNAs of protein-coding genes. The regulation occurs through imperfect pairing with target mRNAs of protein coding genes and recent work has shown that miRNAs regulate gene expression by directing sequence-specific degradation of complementary mRNA molecules or by repressing translation. The underlying pathophysiology of certain gastrointestinal tract diseases and disorders such as IBS may be related to aberrantly expressed miRNAs or epigenetic mechanisms. Increased expression of miR-510 has been identified in IBS-D patients in which miR-510 targets HTR3E, a serotonin receptor gene. Upregulated miR-29a profiles have also been shown to be present in IBS-D patients along with decreased glutamine synthetase leading to increased intestinal permeability. Other investigators have identified elevated circulating levels of miR-150 and miR-342-3p in the blood of patients with irritable bowel syndrome. Both of these miRNAs are linked to inflammatory and pain pathways which are thought to be dysregulated in IBS. More recently, epigenetic regulation has been shown to modulate stress-induced visceral pain. Knock down of DNMT1 and EP300 in DRG neurons of rats reduced DNA methylation and histone acetylation that prevented stressed induced visceral pain. A more recent genome-wide DNA methylation profiling study in IBS patients revealed 133 differentially methylated positions. These genes were associated with glutathione metabolism related to oxidative stress and neuropeptide hormone activity. There are now emerging several possible working models in IBS that may be related to epigenetic mechanisms with either DNA methylation and/or altered miRNA signaling pathways. Future studies are needed to determine the role of epigenetics in the neurobiology of specific endophenotypes of IBS patients. These studies may then lead to more effective and targeted therapies than those currently available for IBS patients.

References


Thomas D. Wang, MD, PhD
University of Michigan

Imaging epithelial barrier dysfunction in situ: Laser endomicroscopy

The epithelium is a thin layer of tissue has dimensions of only a few hundred microns and provides an important barrier function. Biological processes can be visualized with sub-cellular resolution in vivo using optical sectioning if imaging instruments can be made sufficiently small in size and fast in speed. These instruments use the core of a single mode optical fiber to act as a “pinhole” and reject light scattered by tissue to produce images with breathtaking clarity. A flexible fiber is used to deliver and collect light. Current endomicroscopes are limited in imaging performance because they use simple scanning mechanisms that are either slow in speed and results in motion artifacts or bulky in dimension and require a proximal location with reduced image resolution. A fast compact scanner placed in the distal end of the endomicroscope can provide improved performance and flexibility for instrument control.

Mamoru Watanabe, MD, PhD
Tokyo Medical and Dental University

Future applications of stem cells in the GI tract

Recent studies have expanded our knowledge of stem cell biology in GI tract. In the series of our research, we developed a novel
culture method that maintains colonic stem cells \textit{in vitro}. Moreover, successful, long-term engraftment was observed even with the transplantation of organoids that were derived from a single colon stem cell after extensive \textit{in vitro} expansion in mice. We developed human colonic epithelial cell culture from normal and IBD patients. Our data for the first time demonstrate that adult tissue stem cell therapy \textit{in vitro} expansion and transplantation of stem cells in the GI tract could be an option for patients with severe epithelial injuries in the GI tract such as IBD in humans. New options for inducing mucosal healing in the GI tract by application of stem cells are currently under investigation by a 10-year grant from the Japan Agency for Medical Research and Development (AMED).

John W. Wiley, MD
University of Michigan

**Stress and gene transcription: Insights from the 4D Nucleome initiative**

Chronic stress is well known to be associated with exacerbation of IBS symptoms, including abdominal pain and impaired intestinal barrier function. Recent studies support a potentially pivotal role for epigenetic regulatory pathways in both central and peripheral pathways associated with chronic stress-related enhanced visceral pain (visceral hyperalgesia) and intestinal barrier dysfunction.

The combined application of next-generation bioinformatics tools and super-high resolution microscopy techniques have resulted in a renaissance in our understanding of how gene transcription is regulated which has significant implications regarding our understanding of the pathogenesis, pathophysiology and future treatment of IBS. For example, the NIH Roadmap Epigenome Consortium has identified a prominent role for noncoding promoter/enhancers as major determinants of phenotypic heterogeneity. Noncoding variants are more likely to be linked to common diseases than are coding variants, and they can account for the vast majority of heritability. Recent methodological advances suggest that enhancer-promoter interactions are encoded by complex genomic signatures on looping chromatin. The NIH 4D Nucleome initiative implicates an important role for noncoding promoter/enhancers as major determinants of phenotypic heterogeneity. Noncoding variants are more likely to be linked to common diseases than are coding variants, and they can account for the vast majority of heritability. Recent methodological advances suggest that enhancer-promoter interactions are encoded by complex genomic signatures on looping chromatin. The NIH 4D Nucleome initiative implicates an important role for noncoding promoter/enhancers as major determinants of phenotypic heterogeneity. Noncoding variants are more likely to be linked to common diseases than are coding variants, and they can account for the vast majority of heritability. Recent methodological advances suggest that enhancer-promoter interactions are encoded by complex genomic signatures on looping chromatin. The NIH 4D Nucleome initiative implicates an important role for noncoding promoter/enhancers as major determinants of phenotypic heterogeneity. Noncoding variants are more likely to be linked to common diseases than are coding variants, and they can account for the vast majority of heritability. Recent methodological advances suggest that enhancer-promoter interactions are encoded by complex genomic signatures on looping chromatin.

**References**


Justin Wu, MD
Chinese University of Hong Kong

**Mechanisms and management of PPI-resistant symptoms**

About 10–30% of GERD patients report symptoms that are resistant to PPI. Collectively known as refractory GERD, this entity represents a heterogeneous group of patients with various causes. Misdiagnosis of functional dyspepsia or belching disorder as GERD, poor compliance and improper doing time of PPI should be excluded before further investigation. Other putative mechanisms include weakly acidic or bile reflux, visceral hypersensitivity, acid pocket, esophageal spasm and delayed gastric emptying. Comorbidities such as anxiety, obstructive sleep apnea and concomitant functional gastrointestinal disorders are also contributing symptoms. Achalasia and eosinophilic esophagitis may present with PPI-resistant “GERD” symptoms. The choice of investigations, which include endoscopy with esophageal biopsy, esophageal manometry and reflux (pH, impedance and bile) monitoring, should be guided by thorough history taking.

Heather M. Young, PhD
University of Melbourne

**Stem cell therapy for enteric neuropathies**

Cell therapy offers the potential to treat gastrointestinal motility disorders caused by enteric neuropathies. We have previously shown that following transplantation into the colon of recipient mice, enteric neural progenitors isolated from the fetal and postnatal mouse bowel differentiate into a variety of neurochemical types of neurons. Here we used optogenetic and electrophysiological approaches to examine whether transplanted progenitors generate neurons that functionally innervate the colon. Neural progenitors expressing the light-sensitive ion channel, channelrhodopsin, were isolated from the fetal or postnatal bowel and transplanted into the colon of postnatal mice. Light stimulation resulted in excitatory and inhibitory junction potentials in colonic circular muscle with the same pharmacology as native motor neurons. Interneurons were also generated, but their pharmacological properties varied with the age of the donors from which progenitors were obtained. Our data demonstrate that transplanted progenitors generate different functional classes of neurons involved in the control of gut motility.

**INVITED SPEAKERS’ TALKS**
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1. Diagnosis of defecatory disorders with high resolution manometry  
   S Chakraborty, K Feuerhak, AE Bharucha, Rochester, MN. Mayo Clinic  
   Abstract 51

2. Dietary and related factors trigger and aggravate the bowel symptoms in patients with irritable bowel syndrome – a multicenter prospective survey in China  
   W Fan, X Fang, Dong Xu, P Wang, J Yu, J Wu, W Lin, Y Li, S Liu, J Zhang, L Zhu, Beijing; Jinan, Shandong; Wuhan, Hubei; Xian, Shaanxi; China. Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College  
   Abstract 52

3. Intolerance vs malabsorption: the role of fructose in functional gastrointestinal disorders  
   LA Harris, M Sharpe, JK DiBaise, AE Foxox-Orenstein, K Ruff, P Subramanian, MD Crowell, Scottsdale, AZ. Mayo Clinic  
   Abstract 53

4. Peptide tyrosine-tyrosine (PYY) enhances inhibitory effects of cholecystokinin (CCK) on gastric motility and food intake in rats  
   E Hosomi, N Yamaguchi, E Hosomi, M Ochiai, S Ro, K Takayama, K Yakabi, Leuven, Belgium. KU Leuven  
   Abstract 54

5. Dietary advice method for IBS: RCT of structural individual low FODMAP dietary advice (SILFD) vs. brief advice (BLFD)  
   LA Harris, A Juntrapirat, N Lakananurak, T Patcharatrakul, S Gonlachanvit, Bangkok, Thailand. Chulalongkorn University  
   Abstract 55

6. YH12852, a novel, potent and highly selective 5-HT4 agonist, improves delayed gastric emptying and restores feeding inhibition induced by acute restraint stress in rats  
   YS Kim, E-S Choi, HS Ryu, E Jeong, JT Sim, SY Ham, SC Choi, Iksan and Seoul, Korea. Wonkwang University Hospital  
   Abstract 56

7. Autonomic activity predicts weight stability 12 months after weight-loss program  
   M Mazurak, H. Sauer, K Weimer, E Loskutova, P Enck, S Zipfel, I Mack, Tübingen & Herborn Germany, University Tübingen; SymbioGruppe GmbH  
   Abstract 57

8. Caloric and non-caloric artificial sweeteners have dissociable effects on GI motility in healthy volunteers  
   AC Meyer-Gersbach, E De looose, J Biesiekierski, L Van Oudenhove, J Tack, Leuven, Belgium. KU Leuven  
   Abstract 58

9. Sex and age related differences in intestinal dysmotility in mice with high fat diet-induced type two diabetes  
   Y Nyavor, L Flesch, J Mcmillan, O Balembo, Moscow, ID. University of Idaho  
   Abstract 59

10. Sulfate-reducing bacteria completely converts hydrogen generated by fermentation to hydrogen sulfide  
    NL Ritz, MR Wilson, DM Lin, LL Barton, HC Lin, Albuquerque, NM. New Mexico VA Health Care System; University of New Mexico  
    Abstract 61
Brain Gut Axis in Health and Disease: Animal and Human Studies

21 Effect of oxidative stress and ageing on small intestine and colon
A Almuhammedi, D Grundy, Sheffield, UK. University of Sheffield
Abstract 71

22 Effect of physical and psychological symptoms on the quality of life of patients with diarrhea predominant irritable bowel syndrome
T Bai, J Cao, J Xia, Y Jiang, L Zhang, H Wang, J Song, W Qian, X Hou, Wuhan, China. Huazhong University of Science and Technology
Abstract 72

23 Gut permeability and inflammation in irritable bowel syndrome and inflammatory bowel disease: implications for pregnancy complications
Z Sabra, PJ Kennedy, GM Moloney, JF Cryan, TG Dinan, EMM Quigley, AS Khashan, LC Kenny, G Clarke, Cork, Ireland. University College Cork
Abstract 73

24 Leukocyte interactions with cerebral endothelial cells and brain changes in dextran sulfate sodium (DSS)-induced colitis in mice
Ni Cluny, K Dufé, L Griffin, QJ Pittman, MG Swain, KA Sharkey, Calgary, AB, Canada. University of Calgary
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25 Gastrointestinal transit in the stress model Wistar Kyoto rat compared with the Sprague Dawley strain.
JE Dalziel, S Bassett, W Young, NC Roy, Palmerston North, New Zealand. AgResearch.
Abstract 75

26 Transcutaneous cervical vagal nerve stimulation exerts an anti-TNF-α effect in healthy humans
AD Farmer, B Brock, AM Drewes, H Møller, M Pfeiffer-Jensen, Q Aziz, C Brock, London, UK. Wingate Institute of Neurogastroenterology
Abstract 76

27 Genetic and environmental alterations of the epithelial barrier function trigger HPA axis dysfunction and behavioral impairments in rodents
L Ferrier, M Rincel, O Inczefi, A Minni, V Bacquié, A Lepinay, L Xia, E Gaultier, JR Turner, S Layé, M Darnaudéry, V Théodorou, Bordeaux and Wingate Institute of Neurogastroenterology
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28 Neonatal bacterial infection leads to microbiota-gut-brain axis deficits in adulthood.
MG Garceau, EN Miller, M Kaur, Davis, CA. University of California, Davis. LBBB Participant
Abstract 78

29 Chronic oral administration of the guanylate cycloase-C agonist linaclotide attenuates colitis induced bladder afferent hyperactivity
L Grundy, S García-Caraballo, J Maddern, G Rychkov, G Hannig, C Kurtz, A Silos-Santiago, SM Brierley, Sahmri, Australia; Cambridge, MA. University of Adelaide LBBB Participant
Abstract 79

30 Investigating sex differences in neural correlates of visceral pain anticipation and processing during pain-related conditioning
A Icenhour, F Labrenz, N Theysohn, S Elsenbruch, Essen, Germany. University Hospital Essen
Abstract 80
1. **Parkinson's disease rat model**
   - Vagal neurons innervating the gastric muscularis externa in a Parkinson's disease rat model
   - By Z-Y Wang, H Lian, L Zhou, Y-M Zhang, L-F Zheng, J-X Zhu, Xinxian and Beijing, China. Xinxian Medical University

2. **Microbial translocation in IBS; relevance of sex, stress, and IBS subtype**
   - KR Weaver, NH Fournie, SK Abey, LB Sherwin, WA Henderson, Bethesda, MD; New York, NY; Columbia, MO. National Institute of Nursing Research, NIH, NYU College of Nursing

3. **Biomarkers for visceral hypersensitivity in patients with irritable bowel syndrome**
   - Z Mujagic; DMAE Jonkers, S Ludidi, D Keszthelyi, MA Hesselink, RN Kievit, JF Althof, ZZRM Weerts, JW Kruimel, FJ van Schooten, AAM Masclee, DMAE Jonkers, S Ludidi, D Keszthelyi, MA Hesselink, RN Kievit, JF Althof, ZZRM Weerts, JW Kruimel, FJ van Schooten, AAM Masclee

4. **Food-induced dopamine release in extra-striatal regions of the brain reward system predicts food intake in healthy humans**

5. **Sensations and colonic motor responses to a meal and to bisacodyl evaluated during high-resolution manometry (HRM) differ between laxative-refractory slow transit constipation with or without pain**

6. **Histological investigations into intestinal dysmotility in systemic sclerosis**
   - M den Braber-Ymker, JT Uijttenboogaart, M Lammens, ID Nagtegaal, JUijttenboogaart, M Lammens, ID Nagtegaal, KU Leuven

7. **Comparing quality of life indices in diabetics with constipation and normal or delayed colonic transit**
   - C Body, S Shroff, L Carter, N Shahnazav, M Harrison, K Dietz-Lind, E Huang, J Hanfelt, A Knezevic, S Srivinasa, J Christie, Atlanta, Georgia. Emory University School of Medicine

8. **Evaluating the relationship between hemoglobin A1c and gastric, small bowel, colonic, and whole gut transit**
   - C Body, S Shroff, L Carter, N Shahnazav, M Harrison, K Dietz-Lind, A Knezevic, S Srivinasa, J Christie, Atlanta, Georgia. Emory University School of Medicine

9. **The role of H_{2} test in irritable bowel syndrome. Analysis of 316 patients**
   - NS Carvalho, PIPC Carvalho, São Paulo, Brazil. Hospital Israelita Albert Einstein

10. **New-onset constipation in prospective first ischemic stroke cohort**

11. **Colonic motor dysfunction in laxative-refractory slow transit constipation is associated with neural dysfunction and infiltration of lba1-positive(+) cells in the submucosal plexus (SMP)**
    - C Cirillo, M Corsetti, T Vanuytsel, I Demedts, A Srinivasan, J Christie, Atlanta, Georgia.

12. **Factors that predict outcomes to prucalopride**
    - AD Farmer, S Khan, AI Bohan, Stoke on Trent, UK. University Hospitals of North Midlands
**Poster No. 61**
The puborectal continence reflex is not mediated by the pudendal nerve and seems to differ by age.

JE Jonker, MM Van Meegdenburg, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen

**Poster No. 62**
The puborectal continence reflex: The solid stool continence redefined

JE Jonker, PMA Broens, E Heineman, M Trzpis, Groningen, the Netherlands. University Medical Center Groningen

**Poster No. 63**
Visceral hypersensitivity remains stable over time in patients with IBS, but with individual fluctuations


**Poster No. 64**
Choice of rectal barostat protocol affects classification of sensory function and prediction of symptom severity in IBS


**Poster No. 65**
Risk factors among patients presenting with acute abdominal pain at a single center and prediction score of surgical emergencies

D Khemani, M Camilleri A Roldan, AD Nelson, S-Y Park, A Acosta, AR Zinsmeister, Rochester, MN. Mayo Clinic

**Poster No. 66**
Alteration of gastrointestinal motility and mast cell behavior in mice after DSS-induced colitis

M Kodani, H Fukui, T Tomita, T Oshima, J Watari, H Miwa, Nishinomiya, H Fukui, T Tomita, T Oshima, J Watari, H Miwa, Nishinomiya, Japan. Hyogo College of Medicine

**Poster No. 67**
Slow colonic transit is associated with increased risk of severe outcomes in patients with constipation

KJ Kim, BD Ye, JS Byeon, J Choe, SK Yang, SJ Myung, Seoul, Republic of Korea. University of Ulsan College of Medicine

**Poster No. 68**
Prediction of anorectal intussusception using high resolution anorectal manometry based on defecography in patients with chronic constipation

JS Lee, SM Choi, TH Lee, Y Jung, YK Cho, JS Park, SJ Hong, JP Han, SR Jeon, HG Kim, J-O Kim, Seoul and Bucheon, Republic of Korea. Soonchunhyang University College of Medicine

**Poster No. 69**
Dopamine regulates colonic mucus secretion via dopamine D5 receptor in rodents

Y Li, Y Zhang, LS Li, JX Zhu, Beijing, China. Capital Medical University

**Poster No. 70**
Solitary rectal ulcer syndrome as a sign of unrecognized Hirschspring's disease: Report of two cases

RJ Meinds, HPJ van der Doef, FAJA Bodewes, A Timmer, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen

**Poster No. 71**
Assessment of gas and liquid bolus movement using impedance manometry in rabbit colon

R Mohd Rosli, R Leibbrandt, T Omari, M Costa, N Spencer, L Wiklendt, PG Dinning, Adelaide, SA, Australia. Flinders University

**Poster No. 72**
Assessment of pelvic floor neuromuscular integrity by high-density surface electromyography

L Neshatian, Y Peng, C Zhang, R Khavari, T Boone, EM Quigley, Y Zhang, Houston, Texas. Houston Methodist Hospital

**Poster No. 73**
Adenosine receptors in inflammation on rat colon preparations. Are they involved in the anti-inflammatory action of the herbal drug STW 5

K Nieber, H Abdel-Aziz, O Kelber, Leipzig and Darmstadt, Germany. University Leipzig

**Poster No. 74**
Hyperactive motility responses occur in the distal colon following colonic surgery

G O’Grady, R Vather, A Lin, D Rowbotham, P Du, PG Dinning, IP Bissett, Auckland, New Zealand; Adelaide, SA, Australia. University of Auckland

**Poster No. 75**
Delayed colonic transit does not exclude evacuation disorder in patients with chronic constipation: experience based on 207 patients evaluated by a single gastroenterologist over 20 years

Y Zhang, LS Li, JX Zhu, Beijing, China. Capital Medical University

**Poster No. 76**
Barostat-assisted sensory training (BT) is superior to syringe-assisted training (ST) for rectal hypersensitivity

K Patcharatrakul, S Suksri, A Tanawatsuggasere, S Gonlachanvit, Bangkok, Thailand. Chulalongkorn University

**Poster No. 77**
Rectal sensation pattern in patients with fecal urgency and constipation

M Seo, S Joo, KW Jung, HJ Lee, SW Hwang, SH Park, D-H Yang, BD Ye, S-K Yang, SJ Myung, Seoul, Republic of Korea. University of Ulsan College of Medicine

**Poster No. 78**
Colonic fecal volume scoring systems for computerized tomography and their relationship to patients’ bowel habits

DO Prichard, D Ferguson, M Alsaahafi, R Scott, J Buckley, F Donnellan, LA Crosse, WI; Rochester, MN; Vancouver, BC. Mayo Clinic Health System; Mayo Clinic

**Poster No. 79**
The relationship between fecal volume identified by computerized tomography and patients’ bowel habits

DO Prichard, D Ferguson, M Alsaahafi, R Scott, J Buckley, F Donnellan, LA Crosse, WI; Rochester, MN; Vancouver, BC. Mayo Clinic Health System; Mayo Clinic

**Poster No. 80**
Anorectal manometry: Conventional vs. HRAM

L Quinlivan, L Barry, K Yousif, J McCarthy, M Buckley, Cork, Ireland. Mercy University Hospital

**Poster No. 81**
A new high-resolution anorectal manometry parameter based on three-dimensional integrated pressurized volume in both asymptomatic healthy individuals and patients with chronic constipation

M Seo, S Joo, KW Jung, HJ Lee, SW Hwang, SH Park, D-H Yang, BD Ye, S-K Yang, SJ Myung, Seoul, Korea. University of Ulsan College of Medicine
Poster No. 82
Symptoms compatible with functional bowel disorders in patients with ulcerative colitis in deep remission
M Simrén, B Jonefjäll, OS Palsson, WE Whitehead, H Törnblom, L Ohman, H Strid, Gothenburg, Sweden; Chapel Hill, NC. University of Gothenburg; University of North Carolina at Chapel Hill
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Poster No. 83
Increased fecal levels of granins in IBS patients; relationship to symptoms and intestinal inflammation?
J Sundin, S Bennet, B Le Nevé, M Stridsberg, H Törnblom, L Ohman, M Simrén, Gothenburg; Sweden Palaiseau, France; Uppsala, Sweden.
University of Gothenburg
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Diagnostic value of constipation in the Japanese population, using the Rome III criteria and definitions from the Japanese Society of Internal Medicine
T Tomita, A Tamura, F Toyoshima, M Kodani, Y Ohda, T Oshima, H Fukui, J Watari, H Miwa, Hyogo, Japan. Hyogo College of Medicine
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The outcomes of endo-anal ultrasound and three-dimensional high-resolution anorectal manometry do not predict fecal incontinence
MM van Meegdenburg, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen
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Pregnancy and labor, with or without episiotomy and obstetric laceration, are no risk factors for fecal incontinence
MM van Meegdenburg, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen
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Poster No. 87
Constipation in the general Dutch population: demographic risk factors and symptom patterns
SJ Verkuijl, RJ Meinds, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen
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Poster No. 88
Rectal filling sensations are not impaired in patients with increased rectal volumes
SJ Verkuijl, M Trzpis, PMA Broens, Groningen, the Netherlands. University Medical Center Groningen
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Poster No. 89
Effect of biofeedback therapy on anorectal physiological parameters among patients with fecal evacuation disorder
A Verma, A Misra, UC Ghoshal, Lucknow, India. Sanjay Gandhi Post Graduate Institute of Medical Sciences
Abstract 139

Poster No. 90
Efficacy, satisfaction and quality of life in patients with dyssynergic defecation biofeedback therapy: What are the number of sessions needed?
AS Villar-Chavez, E Coss-Adame, Mexico D.F. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Abstract 140

Poster No. 91
Diagnostic value of colonic transit time versus colonic manometry in patients with chronic constipation
L Vork, M van Avesaat, EA van Hoboken, D Keszhelyi, NF Rinisma, AA Mascele, Maastricht and Leiden, the Netherlands. Maastricht University Medical Center; Maastricht University
Abstract 141

Poster No. 92
Rome IV fecal incontinence prevalence and risk factors in the US, Canada and United Kingdom
OS Palsson, M Simrén, MAL van Tilburg, S Heymen, AD Sperber, WE Whitehead, Chapel Hill, NC; Gothenburg, Sweden; Be’er Sheva, Isreal. University of North Carolina at Chapel Hill
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Poster No. 93
Balloon evacuation test does not identify which patients respond to biofeedback for constipation; anorectal manometry or EMG, and structural evaluation are needed
WE Whitehead, G Chiarioni, O Palsson, S Heymen, M Simrén, Chapel Hill, NC; Verona, Italy; Gothenburg, Sweden. University of North Carolina at Chapel Hill
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Investigation of rhubarb induced mucus secretion and underlying mechanism in rat colon
J-X Zhu, J-D Xu, D Wu, L-S Li, Beijing, China. Capital Medical University
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Poster No. 95
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M Zakari, A Lembo, B Kuo, W Hirsch, K Staller, Boston, MA. Beth Israel Deaconess
Abstract 145

Poster No. 96
Quantitative analysis of diffusion tensor fiber tractography in the external sphincter muscle of anal incontinent patients
A Zifan, M Ledgerwood-Lee, S Sinha, M Reisert, K Mittal, San Diego, CA; Freiburg, Germany. University of California, San Diego
Abstract 146

Poster No. 97
Predicting anal sphincter dysfunction from high definition anorectal manometry using a robust automatic multivariable prediction model
A Zifan, M Ledgerwood-Lee, RK Mittal, San Diego, CA. University of California, San Diego
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Electrogastrography, Electrical Control, and Gut Electrical Stimulation

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Electrical vagal nerve stimulation prevents the development of acid induced esophageal hyperalgesia
AD Farmer, G Amersinghe, C Brock, A Drewes, AM Drewes, Q Aziz, London, UK. Queen Mary University of London
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Electrogastrography determines subtypes of gastroparesis responsive to pyloric balloon dilation: functional gastric outlet obstruction
MD Noar, PO Squires, Towson, MD; Pittsburgh, PA. Endoscopic Microsurgery Associates
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Enteric Neurons: Development and Degeneration, Enteric Neurobiology and Circuity

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Neurolgin-3 is located presynaptically in the myenteric plexus of the murine enteric nervous system
JC Bornstein, AJL Leembruggen, GO Seger, LJ Tatnell, EL Hill-Yardin, Parkville, Australia. University of Melbourne
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**FRIDAY, 12:00−2:30 PM**

### Poster No. 101
**The multi-electrode-array (MEA) approach is a suitable technology for in vitro pharmacological investigations on the enteric nervous system**  
*A Braun, M Grimm, T Hartmann, K-H Schäfer, H Rabe, Kaiserslautern and Saarbrücken, Germany. University of Applied Sciences Kaiserslautern*  
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### Poster No. 102
** Regulation of the antioxidant glutathione by enteric glia cells**  
*I Brown, B Gulbransen, East Lansing, MI. Michigan State University*  
**YIF Participant**  
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### Poster No. 103
**Vitamin a metabolism is required for vagal neural crest cell colonization of the gastrointestinal tract in the pathogenesis of Hirschsprung disease**  
*NE Butler Tjaden, LL Sandell, K Aoto, PA Trainor, Kansas City, MO; Kansas City, KS, Louisville, KY; Shizuoka, Japan. Kentucky Stowers Institute for Medical Research; University of Kansas Medical Center*  
**Abstract 153**

### Poster No. 104
**P2X7 receptor blockade attenuates effects in myenteric neurons following intestinal ischemia and reperfusion**  
*P Castelucci, K Palombit, CE Mendes, São Paulo, Brazil. University of São Paulo*  
**Abstract 154**

### Poster No. 105
**Tachykinin activation on enteric glia: A novel mechanism of enteric nervous system dysfunction in irritable bowel syndrome**  
*NM Delvalle-Dorta, GM Rivera-Lopez, BD Gulbransen, East Lansing MI; Humacao PR. Michigan State University*  
**Abstract 155**

### Poster No. 106
**Anti-enteric neuronal antibodies may be specific antibodies in sera of patients with irritable bowel syndrome**  
*W Fan, G Fei, Y Li, C Hu, X Li, H Xin, X Fang, Beijing, China. Chinese Academy of Medical Sciences*  
**Abstract 156**

### Poster No. 107
**Exposure to the antibiotic vancomycin modifies development of the enteric nervous system in early postnatal mice**  
*JPP Foong, P Unterweger, LY Hung, TC Savidge, JC Bornstein, Parkville, VIC, Australia; Houston TX. University of Melbourne*  
**LBBB Participant**  
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### Poster No. 108
**Mechanisms underlying cholera toxin-induced hypersecretion in mouse ileum**  
*C Fung, P Unterweger, K Koussoulas, AM Allen, JC Bornstein, JP Foong, Parkville, VIC, Australia. University of Melbourne*  
**YIF Participant**  
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### Poster No. 109
**VPAC1 activation reveals neuron-glial interactions in the submucosal plexus of mouse jejunum**  
*C Fung, C Cirillo, JC Bornstein, JP Foong, P Vanden Berghe, Parkville, VIC, Australia; Leuven, Belgium. University of Melbourne*  
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### Poster No. 110
**Expression of the precursor marker Sox2 in the myenteric plexus in the caecum of postnatal and adult mouse**  
*D Grundmann, E Loris, L Marx, E Wilms, L Aigner, S Couillard-Despres, C Reinhardt, K-H Schäfer, Kaiserslautern, Zweibrücken, and Mainz, Germany; Salzburg, Austria. University of Applied Sciences Kaiserslautern/Zweibrücken*  
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### Poster No. 111
**Development of innervation of the gastrointestinal mucosa by the enteric nervous system**  
*MM Hao, W Boesmans, P Vanden Berghe, Leuven, Belgium. KU Leuven*  
**LBBB Participant**  
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### Poster No. 112
**3D cultivation of enteric nervous system and smooth muscle cells as a first step towards an innervated artificial gut wall**  
*RR Khosanov, S Heumüller-Klug, E Wink, LM Wessel, CI Hagl, KH Schäfer, Mannheim and Zweibrücken, Germany. Medical Faculty Mannheim at Heidelberg University*  
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### Poster No. 113
**Structural changes of myenteric plexus in animal model of ulcerative colitis**  
*D Khochanskiy, O Makarova, S Buravkov, S. Kirukhin, Moscow, Russia. Research Institute of Human Morphology*  
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### Poster No. 115
**Enteric alpha-synuclein in relation to gastrointestinal dysfunction in Parkinson’s disease patients and neurologically intact subjects**  
*HJ Lee, KW Jung, SJ Chung, SM Hong, J Kim, JH Lee, SW Hwang, HS Ryu, MJ Kim, HS Lee, M Seo, SH Park, DH Yang, BD Ye, JS Byeon, J Choe, HY Jung, SK Yang, SJ Myung, Seoul, Republic of Korea. University of Ulsan College of Medicine*  
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**BGP-15 co-treatment protects against oxaliplatin-induced neuronal loss and alleviates gastrointestinal dysfunction**  
*RM McQuade, V Stojanovska, JC Sorensen, JC Bornstein, AC Petersen, E Rybalka, K Nurgali, Melbourne, Australia. Victoria University*  
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**Interleukin-7 is expressed by enteric glial cells**  
*P Naveilhan, T Durand, L Kermarrec, J Gonzales, M Neunlist, I Neveu, Nantes, France. Inserm UMR913*  
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**Canonical Wnt pathway regulates the neurogenic potential of enteric neural progenitor cells**  
*PH Neckel, K Seid, F Obermayr, L Just, Tübingen, Germany. University of Tübingen*  
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*H Rabe, L Schwarz, D Grundmann, M Weyland, K-H Schäfer, Kaiserslautern and Tübingen, Germany. Medical Faculty Mannheim at Heidelberg University*  
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**Western-diet induces nitriergic myenteric cell loss in the proximal colon and dysmotility in a TLR4 dependent mechanism**  
*F Reichardt, B Chassaing, BG Nezami, G Li, S Tabatabavakili, D Jones, AT Gewirtz, S Srinivasan, Atlanta, GA. Emory University, Atlanta VA Medical Center*  
**YIF Participant**  
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<td>M Rolli-Derkinderen, T Rousseau, E Baudu, C Pochard, M Neunlist, Nantes, France. Inserm, UMR913; Université Nantes; Centre Hospitalier Universitaire de Nantes.</td>
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<td>F Cosai, S Leuschner, M Barrenschee, C Lange, J Egberts, T Becker, M Böttner, T Wedel, Kiel, Germany. University of Kiel.</td>
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<td>M D’Amato, S Zhemakova, Bilbao, Spain; Stockholm, Sweden; Groningen, The Netherlands. BioCruces Health Research Institute; Karolinska Institutet.</td>
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<td>Psychological factors influence the overlap syndrome in functional gastrointestinal disorders and their effect on quality of life among firefighters</td>
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<td>Adult cyclic vomiting syndrome: What GI motility experts think regarding its diagnosis and management?</td>
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<td>Altered 5-HT4 receptor signalling in irritable bowel syndrome may be caused by impaired miRNA regulation</td>
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<td>E Shah, C Almario, B Spiegel, W Chey, Ann Arbor, MI; Los Angeles, CA.</td>
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<td>Gender differences in IBS: Separate pathophysiological background?</td>
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<td>Prevalence of joint hypermobility syndrome in patients with functional gastrointestinal disorders in an Asian tertiary gastroenterology unit</td>
<td>YT Wang, AML Ong, DMY Tan, CH Lim, CY Lee, HF Tan, P Ghosh, W Yeo, A Low, A Fikree, Q Aziz, Singapore; London, UK.</td>
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<td>C Wenzel, Y Zadvornova, T Dhindsa, T Venkatesan, Milwaukee, WI.</td>
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159 Manometric subtypes of ineffective esophageal motility
A Abdel Jalil, M Heistand, D Castell, Columbia, MO; Bern, Switzerland; Charleston, SC. University of Missouri

160 Cancelled

161 Amyl nitrite unresponsive esophageal outflow resistance
A Babaei, A Dodda, A Szabo, B Massey, Milwaukee, WI. Medical College of Wisconsin

162 Increasing BMI leads to increased incidence of GORD in a European Setting.
L Barry, L Quinlivan, T Murphy, M Buckley, Cork Ireland. Mercy University Hospital

163 The effect of head extension on pharyngeal and upper esophageal sphincter physiology using pressure flow analysis
S Bhuta, C Scheerens, A Gupte, SV Kiran, P Dhore, A Shukla, J Tack, T Omari, N Rommel, Mumbai, India; Adelaide, Australia; Leuven, Belgium. Seth G S Medical College and KEM Hospital

164 RNAseq analysis reveals dysregulated expression of novel genes in sporadic achalasia
F Bianca, E Bonora, M Lugaer, A Stanzani, Francesco Torresan, V Stanghellini, P Clavenzani, M Wouters, G Boeckstaens, S Mattioli, R De Giorgio, Bologna, Italy; Leuven, Belgium. University of Bologna

165 Increased bolus reflux on multichannel intraluminal impedance is an independent predictor of poor pulmonary outcomes over 1 year in patients with idiopathic pulmonary fibrosis
LF Borges, V Jagadeesan, H Goldberg, S Gavini, WK Lo, R Burakoff, N Feldman, W Chan, Boston, MA. Brigham and Women’s Hospital

166 Association between gas swallow during meals, gastric belching and supragastric belching
EN Caballero, C Julia, J Serra, Barcelona, Spain. University Hospital Germans Trias i Pujol

167 Decompensated achalasia: Clinical characteristics of patients hospitalized with achalasia
PR Caruana, MF Fina, KL Koch, Winston-Salem, NC. Wake Forest Baptist Medical Center

168 The laryngopharyngeal reflux by pharyngeal pH-impedanecmetry correlates with extra esophageal symptoms
PJP Carvalho, NS Carvalho, São Paulo, Brazil. Núcleo de Fisiologia do Hospital Israelita Albert Einstein

169 pH-metry X impedance-pH monitoring: Comparative study in the diagnostic of GERD in 535 patients
PJP Carvalho, RM Fernandez, NS Carvalho, São Paulo, Brazil. Núcleo de Fisiologia do Hospital Israelita Albert Einstein

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170 Defective esophagogastric junction morphology action is associated with GERD diagnosed by impedance pH or erosive esophagitis
YK Cho, CH Lim, M-G Choi, Seoul, Korea. The Catholic University of Korea

171 The diagnostic value of esophageal high resolution manometry parameters predicting GERD
YK Cho, CH Lim, JS Kim, JM Park, M-G Choi, Seoul, Korea. The Catholic University of Korea

172 Remifentanil induced changes in esophageal and esophagogastic junction (EGJ) bolus transport in healthy volunteers
C Cock, S Doeltgen, TI Omari, J Savilampi, Adelaide, Australia; Oerebro, Sweden. Flinders University

173 Esophageal neuromechanical states during solid bolus perception in healthy volunteers
C Cock, RE Leibrandt, PG Dinning, M Costa, L Wiklundt, M Schar, TI Omari, Adelaide, Australia. Flinders University

174 Reflux patterns and symptom occurrence as assessed by 24-h pH-impedance monitoring: Association between reflux impedance patterns
E Cos-Adame, AS Villar-Chavez, MA Valdovinos-Diaz, México D.F. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

175 High resolution manometry parameters to assess barrier function of the gastroesophageal junction and to identify patients with gastroesophageal reflux disease: A case-control study
N Freitas-Queiróz, D Jasper, M Hollenstein, B Misselwitz, P Layer, T Navarro-Rodriguez, M Fox, J Keller, São Paulo, Brazil; Hamburg, Germany; Zürich and Basel, Switzerland. University of São Paulo School of Medicine

176 Lack of association between esophageal spasm diagnosed on barium esophagram and esophageal spasm diagnosed on high-resolution esophageal manometry
KH Harer, S Dhalla, Baltimore, MD. Johns Hopkins University School of Medicine

177 Association of minor disorders of esophageal peristalsis with reflux and swallowed bolus clearance: comparison of Chicago Classification v2.0 with v3.0
R Hejazi, R Simons-Linares, KR. Devault, Jacksonville, FL; Chicago, IL. Mayo Clinic

178 Long-term outcomes of peroral endoscopic myotomy (POEM) in achalasia: experience from a single center
SJ Hong, JP Han, TH Lee, JS Lee, Bucheon, Korea. Soonchunhyang University College of Medicine

179 Down to the wire: the diagnostic yield of 48-hr wireless pH testing vs ph-multichannel intraluminal impedance in the evaluation of patients with refractory GERD symptoms
M Iyengar, P Solaimani, R Lee, J Samarasena, K Chang, B Smith, Long Beach, CA. University of California, Irvine
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T Kamiya, Y Kimura, M Shikano, T Mizoshita, E Kubota, S Tanida, H Kataoka, K Seno, T Joh, Nagoya, Aichi, Japan. Nagoya City University Graduate School of Medical Sciences

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L Vork, D Keszthelyi, NF Rinstra, R Farré, FJ Troost, M Elizalde, Z Helyes, AA Masdeee, JM Conchillo, Maastricht, The Netherlands; Leuven, Belgium; Madrid, Spain; Pécs, Hungary. Maastricht University Medical Center

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BJ Kim, CH Choi, JG Kim, SJ Kim, Seoul, Republic of Korea. Chung-Ang University College of Medicine

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JS Lee, HE Jung, TH Lee, JS Park, SJ Hong, JP Han, SR Jeon, HG Kim, J-O Kim, Seoul and Bucheon, Republic of Korea. Soonchunhyang University College of Medicine

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KJ Lee, JE Lee, CK Noh, Suwon, Korea. Ajou University School of Medicine

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201 Effect of buspirone in patients with ineffective esophageal motility
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206 Muscular thickness of lower esophageal sphincter and therapeutic outcomes in achalasia: a prospective study using high-frequency endoscopic ultrasound
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207 Predictors of partial vs. complete symptomatic response in patients with esophageal achalasia treated by per oral endoscopic myotomy (POEM)

208 Association of the HLA-DQB1-insertion in idiopathic achalasia and first genotype-phenotype (GxP) study using high-resolution manometry (HRM) data

209 Management of recurrent symptoms after peroral endoscopic myotomy in achalasia
A J Bredenoord, FB van Hoeij, FA Pocks, P Fockens, BAJ Bastiaansen, JE Pandolfino, JM Sternbach, T Rösch, AJPM Smout, Amsterdam, Netherlands; Chicago, IL; Hamburg, Germany. University of Amsterdam Abstract 259

210 Mucosal integrity and sensitivity to acid of the proximal esophagus in patients with gastroesophageal reflux disease
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216 Prucalopride improves symptoms and quality of life in a controlled cross-over trial in gastroparesis
F Carbone, A Rotondo, CN Andrews, L Holvoet, L Van Oudenhove, T Vanuytsel, R Bisschops, P Caenepeel, J Arts, A Papatheosopoulos, J Tack, Leuven, Belgium; Calgary, AB, Canada; Ioannina, Greece. KU Leuven Abstract 266

217 Validation of the Leuven postprandial distress scale (LPDS), a questionnaire for symptom assessment in patients suffering from functional dyspepsia/postprandial distress syndrome (FD-PDS)
F Carbone, A Vandenbergh, L Holvoet, L Van Oudenhove, M Jones, J Tack, Leuven, Belgium; Sydney, Australia. KU Leuven LBBB Participant Abstract 267

218 The effect of antidepressant mirtazapine on gastric accommodation, sensitivity to distention and nutrient tolerance in healthy subjects
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**Assessment of gastric motility and autonomic function in healthy volunteers and functional dyspepsia (FD) patients with or without the joint hypermobility syndrome (JHS)**
F Carbone, N Goelen, C Varon, S Van Huffel, A Fikree, Q Aziz, J Tack, Leuven, Belgium; London, UK. KU Leuven

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**The topography of nausea: location of chronic unexplained nausea may predict underlying mechanisms**
BT Cengia, P Stuart, KL Koch, Winston Salem, NC. Wake Forest Baptist Health

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**Proximal stomach is the most responsive site for motilin- and ghrelin-induced gastric contractions in Asian musk shrew stomach in vitro**
A Dudani, S Aizawa, A Mondal, T Sakai, I Sakata, Saitama and Okayama, Japan. Saitama University

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V Hammer, K Hammer, M Führer, J Hammer, Vienna, Austria. Medical University of Vienna

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R Hejazi, KR Devault, Jacksonville, FL. Mayo Clinic

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M Lazarou, K Feist, S Bühner, M Neunlist, A Bourreille, C Pehl, Michael Schemann. Freising and Vilsbiburg, Germany; Nantes, France. Technical University of Munich

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I Masuy, L Van Oudenhove, J Tack, JR Biesiekierski, Leuven, Belgium. KU Leuven

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A Mondal, K Koyama, T Mikami, I Sakata, T Sakai, Saitama, Japan. Saitama University

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241 Intestinal dysfunctions induced by intrauterine growth retardation are associated with altered autophagy in the enteric nervous system
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243 Pain modulation in youth with functional gastrointestinal disorders (FGID) may be normal: a role for baseline norepinephrine?
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244 Low bioenergetics in functional disorders parallel disability score
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245 Intravenous AAV injection targets the enteric nervous system in guinea pigs and non-human primates
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251 Lymphocytic intestinal leiomyositis associated with chronic intestinal pseudo-obstruction
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255 The Groningen defecation and fecal continence questionnaire: a comprehensive measure of anorectal functioning
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256 On the prevalence of constipation and fecal incontinence, and their co-occurrence, in the Netherlands
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258 Neuroplastic changes induce functional repercussions in the remaining ‘healthy’ bowel in Hirschsprung disease
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## Poster Sessions

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**Comorbid functional dyspepsia and psychological symptom severity are independently associated with higher gastrointestinal symptom scores after a combined nutrient and lactulose challenge test in IBS**
*Y Xiao, L Van Oudenhove, H Törnbloom, L Öhman, B Le Nevé, J Tack, M Simrén, Zurich, Switzerland; Gothenburg, Sweden; Palaiseau, France; Chapel Hill, NC. University Hospital Zurich*

### Poster No. 260
**Mechanisms of intestinal dysmotility in undernutrition**
*GA Preidis, RJ Shulman, ME Conner, Houston, TX. Baylor College of Medicine & Texas Children’s Hospital*

### Poster No. 261
**Paramagnetic labeled neural crest derived stem cells (NCSCs) can be tracked in the gastrointestinal tract after being transplanted**
*KH Schäfer, C Merscher, A Müller, A Braun, J Clasohm, D Grundmann, P Fries, G Schneider, A Bücker, Zweibrücken and Homburg, Germany. University of Applied Sciences Kaiserslautern*

### Poster No. 262
**Enteric neurospheres can be cryopreserved**
*KH Schäfer, S Heumüller-Klug, E Wink, CI Hagl, LM Wessel, Zweibrücken and Mannheim, Germany. University of Applied Sciences Kaiserslautern*

### Poster No. 263
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### Poster No. 264
**Constipation and fecal incontinence in children do not dissolve but exacerbate after transition to adulthood**
*MEW Timmerman, M Trzpis, PMA Broens, Groningen, the Netherlands. University of Groningen*

### Poster No. 265
**The Groningen pediatric DeFeC Questionnaire: Finally, defecation problems of children and adults can be compared**
*MEW Timmerman, M Trzpis, PMA Broens, Groningen, the Netherlands. University of Groningen*

### Poster No. 266
**The problem of constipation and fecal incontinence in children is underestimated and easily unrecognized**
*MEW Timmerman, M Trzpis, PMA Broens, Groningen, the Netherlands. University of Groningen*

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### Poster No. 268
**Fecal incontinence is not influenced by age and gender in the ‘healthy’ Dutch population**
*MM van Meegdenburg, M Trzpis, PMA Broens, Groningen, the Netherlands. University of Groningen*

### Poster No. 269
**Associations between hydrogen breath test and symptom responses during a combined nutrient and lactulose challenge in IBS patients and healthy controls**
*L Van Oudenhove, D Pohl, H Törnbloom, L Öhman, B Le Nevé, J Tack, M Simrén, Leuven, Belgium; Zurich and Gothenburg, Switzerland; Palaiseau, France, Chapel Hill. University of Leuven*

### Poster No. 270
**The correlation between dilated intercellular spaces (DIS) and pepsin in saliva of GERD patients**
*Y Xiao, Y Li, C Xie, M Chen, Guangzhou, China. Sun Yat-sen University*

### Poster No. 271
**Transition zone defects is correlated with incomplete bolus transit independent of the distal peristalsis break in GORD patients**
*Y Xiao, Y Li, C Xie, M Chen, Guangzhou, China. Sun Yat-sen University*

### Microbiome and Probiotics in GI Health and Disease

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*S Botschuijver, D Westing, SE Heinsbroek, WJ de Jonge, J Seppen, RM van den Wijngaard, Amsterdam, The Netherlands. Academic Medical Center*

### Poster No. 273
**Structural and functional alterations in the colon microbiome in a chronic stress rat model of irritable bowel syndrome**
*NH Fourie, D Wang, SK Abey, AL Creekmore, S Hong, JW Wiley, WA Henderson, Bethesda, MD; Ann Arbor, MI. National Institutes of Health, Department of Health and Human Services*

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*AV Golubeva, RM Martin, D Kandil, H Schellekens, NP Hyland, TG Dinan, JF Cryan, Cork, Ireland. University College Cork*

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*M Heitkemper, K Cain, R Burr, R Shulman, J Zia, C Han, M Jarrett, Seattle, WA; Houston, TX. University of Washington*

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*T Masaoka, Y Yamane, T Masaoka, M Nakashima, K Matsuoka, M Naganuma, T Kanai, Tokyo, Japan. Keio University School of Medicine*

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*A Shin, T James-Stevenson, Indianapolis, IN. Indiana University*

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*T Vanhoecke, PA Grohard, P Aubert, J Jaulin, J Chevalier, T Durand, H Boudin, P Naveilhan, A Ligneul, P Le Ruyet, M Neunlist, Nantes and Retiers, France. University of Nantes and Lactalis Research and Development*
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DH Rim, OY Lee, KN Lee, DW Jun, HL Lee, BC Yoon, HS Choi, Seoul, Republic of Korea. Hanyang University School of Medicine
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Evidence for antibodies targeting the enteric nervous system in multiple sclerosis
The University of Vermont, Burlington, VT, USA

Multiple sclerosis (MS) patients often experience constipation, but the etiology of this symptom is unknown. We hypothesize that constipation results as a form of collateral damage in response to autoantibodies generated at sites of inflammation in the central nervous system. To test this hypothesis, we tested whether mice with experimental autoimmune encephalomyelitis (EAE), which is known to have a strong autoimmune component, exhibit altered gastrointestinal (GI) motility and/or fecal composition. We also evaluated immunoreactivity to human MS serum samples in the myenteric plexus. EAE was induced in 8-week old, male SJL/J mice by injection of complete Freund’s adjuvant (CFA) with mouse spinal cord homogenate, control mice only received CFA. Whole GI transit time was determined by oral gavage of carmine red and calculating the latency for dye to appear in fecal pellets. Fecal water content was assessed by weighing fecal pellets before and after dehydration. Colonic motility was evaluated in vivo by inserting a glass bead 2 cm into the distal colon and recording the time to expulsion. The rate of whole GI transit was significantly longer in EAE mice (n = 8) vs controls (n = 8, p ≤ 0.05). Fecal water content was significantly lower in EAE (n = 6) compared to controls (n = 5, p ≤ 0.0001), and time until expulsion of a bead inserted into the colon was significantly longer in EAE (n = 10) than controls (n = 9, p ≤ 0.001). To determine whether constipation in MS could involve an autoimmune mechanism, we tested whether blood from MS patients contains antibodies directed against targets in ENS ganglia. We quantified ENS immunoreactivity by measuring intensity of fluorescence in guinea pig myenteric ganglia whole mount preparations stained with serum from MS patients (n = 39) and healthy controls (n = 20). Serum from MS patients yielded more robust immunoreactivity towards ENS ganglia than serum from control subjects (p ≤ 0.05). Serum from EAE mice also yielded ENS immunoreactivity. Structures labeled with MS and EAE serum included neurons, nerve processes, and/or glia. In summary, EAE causes delayed whole GI and colonic transit time and drier feces compared to control mice, all of which are consistent with a constipated state. Furthermore, ENS-targeted antibodies were detected in the serum of MS patients and EAE mice. Together, these findings support our hypothesis of an autoimmune role in MS-related constipation. Supported by a grant from the NMSS.

2 Altered APOB48 expression can be a marker of severe panenteric dysmotility
*Department of Medical and Surgical Sciences, DIMEC, University of Bologna, Italy and †Department of Veterinary Medical Sciences DIMEVET, University of Bologna, Italy

Introduction: Severe panenteric dysmotility, mainly in the clinical phenotype of chronic intestinal pseudo-obstruction (CIFO), is a severe gut dysmotility characterized by recurrent sub-obclusion episodes with no evidence of any mechanical obstruction. CIFO is a heterogeneous term as it can be applied to a variety of patients for whom a diagnostic biomarker is still unavailable. The diagnosis of CIFO would certainly benefit from the identification of a biomarker. We recently showed an altered expression of APOB in familial CIFO patients carrying a novel RAD21 mutation and in a few sporadic CIFO patients.

The aim of this study was to identify whether an altered APOB expression can be a possible biomarker for familial and/or sporadic CIFO by comparing CIFO patients to those with other conditions, e.g. Hirschsprung disease (HSCR), characterized by enteric neuron aganglionosis, irritable bowel syndrome (IBS) and motility unrelated disorders (e.g. celiac disease and non-celiac gluten sensitivity).

Aims & Methods: CIFO patients (n = 28, 18 F, age range: 17–67 years) and healthy controls (n = 10, 5 F, age range: 25–38) were used for western blot and quantitative immunohistochemistry. Sera from patients with motility unrelated disorders (n = 40 each group) served as disease controls.

Results: Sera from idiopathic CIFO patients showed an elevated expression of APOB48, compared to healthy controls and to sera from patients with HSCR, IBS, celiac disease as well as NCCS. Consistently, the APOB48 signal was markedly increased at tissue level in ileum biopsies of CIFO cases compared to healthy controls and IBS (32.9 ± 9.2% vs 7.2 ± 2.5% cases vs controls, p = 0.0012, Student’s t-test), 32.9 ± 9.2% vs 5.6 ± 1.5% CIFO cases vs IBS, p = 0.0008). Quantitative analysis performed in gut biopsies revealed also a significant reduction in the number of neuron specific enolase (NSE)-labeled myenteric ganglion cell bodies/ganglion in CIFO compared to control specimens (p = 0.0039).

Conclusion: APOB48 expression at serum and tissue level was homogeneously increased in sporadic CIFO highlighting a potential convergent mechanism on a gut-specific APOB isoform. The increased APOB48 can be exploited as possible biomarker to better differentiate CIFO from other diseases.

3 Coordinated activity of clonally-related enteric neurons
W. BOESMANS*, R. LASRADO*, P. VANDEN BERGH† and V. PACHNIS‡
*Lab for Enteric NeuroScience LENS, TARGID, KU Leuven, Belgium and †The Francis Crick Institute, Mill Hill Laboratory, London, UK

The enteric nervous system (ENS) is composed of integrated neuro-glial circuits that regulate gut function. Although decades of work have allowed the configuration of wiring diagrams explaining various forms of ENS output, the mechanisms underlying the assembly of enteric nerve circuits remain unclear. We have examined the connectivity of clonally-related enteric neurons and explored whether lineage-based rules contribute to functional circuit organization. To this end, we performed live Ca2+ imaging on Fluo-4 loaded adult myenteric plexus preparations from Sox10-CreERT2, R26R-Confetti mice carrying clonal cell clusters derived from single ENS progenitors labeled during embryogenesis (E12.5). Enteric neurons were stimulated by electric pulses transmitted via a focal electrode positioned on different interganglionic nerve strands linked to myenteric ganglia that contained...
identified clonally-related enteric neurons (RFP-labeled sister neurons). Our data indicate that pairs of sister neurons are more similar in their Ca$^{2+}$ response behavior as compared to pairs consisting of labeled and non-labeled cells. Furthermore, we observed that intraganglionic sister pairs were not different from interganglionic sister pairs in sharing similar Ca$^{2+}$ response patterns, and that their coordinated activity is irrespective of the stimulated intraganglionic nerve strand. Importantly, we find no difference between labeled and non-labeled enteric neurons in terms of their baseline intracellular Ca$^{2+}$ concentration or Ca$^{2+}$ transient amplitude elicited by trains of electrical pulses. Consistent with the reported involvement of other fast excitatory neurotransmitters in the mouse ENS and the possible contribution of antidromic activation in our experimental paradigm, we found that about half of the neurons activated by single pulse electrical stimulation respond via nicotinic synaptic inputs. Thus, although shared projection controls peristaltic movements, gastrointestinal blood flow and secretions and is involved in several functional gastrointestinal disorders. The molecular and cellular pathways of these ENS functions and control of GI functions remain elusive. In this context, the development of human intestine with an ENS represents a real opportunity to expand our knowledge into the effect of ENS on intestinal development and toward the understanding of pathophysiological processes leading functional gastrointestinal neuropathies.

Introduction: The enteric nervous system (ENS) controls peristaltic movements, gastrointestinal blood flow and secretions and is involved in several functional gastrointestinal disorders. The molecular and cellular pathways of these ENS functions and control of GI functions remain elusive. In this context, the development of human intestine with an ENS represents a real opportunity to expand our knowledge into the effect of ENS on intestinal development and toward the understanding of pathophysiological processes leading functional gastrointestinal neuropathies.

Microbiome

5 High protein diet in diet-induced obesity rats promotes fat loss, sensitivity to CCK and induces shifts in gut microbial composition and limited modification of brain inflammatory signals L. WANG, J. JACOBS, P.-Q. YUAN, W. WU, M. MULUGETA, J. R. REEVE JR., J. R. RISENGA and Y. TACHÉ
David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

High fat diets are known to induce disorders in glucose metabolism, CCK sensitivity, neuroinflammation and shifts in the composition of the gut microbiome in rodents and humans. A high protein diet (HPD) is an effective dietary intervention for management of obesity. The effects of a HPD on these disorders have not been previously investigated. To better define the role of HPD we employed Western diet (WD) with high fat and high sugar) induced obesity (DIO) rats that were switched to HPD for 6 weeks. Body composition was measured using rodent MRI, food intake and meal pattern by an automated feeding monitoring system, inflammatory mediators in the brain by quantitative PCR, and gut microbiome by 16S rRNA sequencing and analysis. Compared to rats on a normal diet (ND), DIO rats had a significant increase in body fat mass and weight by 73.4% and 9.3%, and a non-significant increase in lean mass [1.7%]. The DIO rats switched to HPD for 6 weeks had significant 15.7% decrease in fat mass, and 3.0% and 8.3% increase in body weight and lean mass. Food intake and meal pattern were not significantly changed by ip CCK-8S (1.8 and 5.2 nmol/ kg) in DIO rats on WD during the 1st hour of dark phase. In DIO rats switched to HPD, CCK-8S decreased the 1-h calorie intake at both doses by 37% and 49% via reducing the 1st meal size and increasing the latency to the 1st meal. Rats switched to HPD significantly improved blood glucose levels compared to DIO rats (98 ± 10 vs 111 ± 8 mg/dL). The DIO rats on WD and switched HPD had comparable microbial diversity, which was increased relative to rats on ND as measured by Chao1, phylogenetic diversity and Shannon index. UniFrac analysis demonstrated a shift in the microbiome composition in the HPD group compared to DIO rats remaining on WD. The HPD group had increased abundance of 114 OTUs and decreased 188 OTUs. Of those, Akkermansia muciniphila and an unclassified Clostridiales had a significant inverse and an unclassified RF99 and a Phascolarctobacterium positive correlation with fat mass after adjustment for diet. Expression of inflammatory cytokines was increased in the hypothyamus and dorsal medulla in DIO rats which were not significantly modified by switching to HPD. Both groups also had similarly decreased expression of CRP and mTOR in the hypothalamus and increased POMC and GLP-1 receptor in the medulla. In summary, HPD has beneficial effects in DIO rats by reducing body fat, blood glucose levels, and improving sensitivity to CCK. The reduction of fat mass by HPD is associated with extensive shifts in the intestinal microbiome with the expansion of Akkermansia as a potential mechanism by which a HPD induces weight loss.

*Inserm U913, IMAD, Nantes University and 1Lactalis Research and Development, Retiers

Background: Recent studies have highlighted the crucial role of intestinal microbiota in promoting postnatal maturation of the intestinal barrier [IB] and modulating behavior. Therefore, probiotics may be useful in reducing IB-allergy-associated dysfunction and anxiety-like behavior. We characterized the impact of oral administration of Lactobacillus fermentum CECT 5716 (LF) on the IB function, identified molecular targets and investigated whether LF modulated anxiety-related behavior of rat pups.

Methods: Newborn rats received by gavage, from postnatal day (PND) 7 to 10 or PND7 to 21, either LF (10^9 CFU/100 g body weight/day) or water (controls). Gut paracellular permeability (PP) was measured in vivo and ex vivo. LF effects were also characterized on the IB function in response to stressors (maternal separation (MS), water avoidance stress (WAS)). Relative expression levels of tight junction proteins were analyzed by Western blot. Anxiety-like behavior was assessed using an elevated plus maze (EPM).

Results: After 15 days of LF administration, PP was decreased by 20% in vivo (n = 25, p < 0.01) with no change in total transit time. At PND21, after 2 h of WAS, in vivo PP was increased in controls (+72%, n = 6, p < 0.001) but not in the LF group (+32%, n = 6, p > 0.05). At PND10, after 4 h of MS, in vivo PP was
increased in controls (+48%, n = 9, p < 0.05) but not in the LF group (+18%, n = 9, p > 0.05). In addition, ex vivo IP in ileal and jejunal segments of pups subjected to WAS decreased markedly in the LF group as compared to controls (−33%, p < 0.0001, −18% p < 0.05, n = 18). Furthermore rats subjected to WAS demonstrated increased expression of ZO-2 (+106%, p < 0.05), JAM-A (+66%, p < 0.05) and cingulin (+64%, p < 0.05) but no change in occludin, ZO-1, claudin-1-2-3 expression in LF group as compared to controls (n = 18). Interestingly, LF-treated pups exhibited increased activity and exploration in EPM (e.g. open arm head entries p < 0.001, stretching p < 0.01, rearing p < 0.05) with no change in corticosterone serum levels.

Conclusion: These results show the ability of Lactobacillus fermentum CECT 5716, daily and orally administered to rat pups, to strengthen the IB not only in basal conditions but also in response to stress. LF functionally targets the small intestine by modulating the expression of specific tight junction proteins. Interestingly, LF increases exploratory behavior. The use of this probiotic may provide a new approach in the prevention and treatment of functional intestinal abnormalities and associated behavioral comorbidities.

Smooth Muscle, Glia and ICC Interactions: Functional Roles in Health and Diseases

No signaling in the circular smooth muscle layer of the murine proximal colon

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Gastrointestinal (GI) motility is the result of complex coordination of excitation and inhibition of the smooth muscle syncytium. NO is an important inhibitory neurotransmitter which is involved in the regulation of GI motility. In the colon, NO-sensitive guanylate cyclase (NO-GC) is expressed in several cell types such as smooth muscle cells (SMC) and interstitial cells of Cajal (ICC). We have previously demonstrated distinct functions of NO-GC in SMC and ICC in the longitudinal muscle layer of mouse colon. Here, basal neuronal released NO interacts with the pacemaker activity in ICC, whereas elevated endogenous NO concentrations most act via NO-GC in SMC where it suppresses spontaneous contractions. This study focuses on the role of NO-GC in the circular muscle layer of the murine proximal colon. In isometric force studies the motility patterns of colonic circular muscle were recorded from global NO-GC knockout (GCKO) and cell-specific knockout mice lacking NO-GC specifically in SMC or ICC. Measurement of spontaneous contractions in the circular smooth muscle revealed three different patterns. We recorded continuous small high frequency contractions, which were interrupted by bigger ‘intermediate contractions’, as well as periodic ‘giant contractions’ which are characterized by a strong tonic contraction with superimposed ‘ripples’. An increased number of ‘giant contractions’ was detected in the GCKO compared to the WT colon. Inhibitors of the NO/cGMP signaling cascade induced a tonic contraction in WT and ICC-GCKO. Vice versa, application of NO led to tonic relaxation in WT and ICC-GCKO but not in GCKO and SMC-GCKO colon. Moreover, ‘giant contractions’ were abolished in all genotypes except for GCKO colon. Tetrodotoxin inhibited giant contractions in all genotypes but evoked a regular contraction pattern with increased amplitude and number of intermediate contractions. In the circular muscle layer, basal NO-GC regulates smooth muscle tone and thus, regulates the frequency of ‘giant contractions’. Relaxation of the muscle layer is mediated exclusively by NO-GC in SMC. In contrast, previous studies with the longitudinal muscle layer revealed NO-GC not to be involved in modulation of smooth muscle tone, thus, indicating a differential function of NO-GC in circular and longitudinal muscle layer.

Enteric glia play a sexually dimorphic role in the regulation of colonic motility but are not essential for epithelial maintenance

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**University of Michigan, Ann Arbor, MI, USA

Glia outnumber neurons by several fold in the enteric nervous system and form an extensive network throughout the bowel. Ablation studies targeting cells expressing glial fibrillary acidic protein (GFAP) to investigate enteric glial function in vivo, have suggested that glia are essential for the regulation of epithelial barrier function, epithelial proliferation, neuronal maintenance, and gastrointestinal (GI) motility. GFAP expression, however, is limited to a subset of enteric glia, in contrast, virtually all enteric glia express proteolipid protein 1 (PLP1). To assess the role of enteric glia in GI function, we utilized the PLP1 promoter to drive expression of diphtheria toxin subunit A (DTA) in young adult mice. Induction of DTA expression in PLP1-expressing cells caused the loss of at least 75% of 51000 glia throughout the intestine within 7 days. Glia were depleted both inside and outside ganglia; moreover, electron microscopy revealed empty lacunae in lieu of the glial somata and processes that normally surround neurons and neurite bundles. Surprisingly, ablation of PLP1 instead of GFAP+ cells did not lead to intestinal inflammation, furthermore, epithelial proliferation, barrier function, and neuronal numbers remained intact. Prior observations on the effects of ablating enteric glia may thus have been the result of inadvertently targeting non-glial cells. Acute loss of PLP1+ enteric glia by induction of DTA expression, however, did compromise GI motility and this effect was sexually dimorphic. Glial ablation accelerated total GI transit time in female but not in male mice. Gastric emptying and small intestinal transit were unchanged, suggesting that altered colonic motility was responsible for the sex-dependent difference in total GI transit time. To investigate the role of glia in ENS-mediated colonic motility, peristaltic reflexes were studied ex vivo in the colons of control and glial-ablated mice. This analysis revealed that PLP1+ enteric glia are essential for the regulation of colonic migrating motor contraction (CMMC) frequency in female mice. Ablation of enteric glia doubled CMMC frequency in the female colon but not in colons of male littermates. These data show that enteric glia play a sexually dimorphic role in the regulation of colonic motility but are not essential for maintenance of intestinal epithelial barrier integrity, epithelial cell proliferation, or prevention of inflammation.

Esophageal Disorders

A diagnostic classification scheme of esophageal motility using functional lumen imaging probe (FLIP) topography

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†Academic Medical Center, Amsterdam, The Netherlands

Background: Esophagogastroduodenal junction (EGJ) distensibility and secondary peristalsis can be assessed with the functional lumen imaging probe (FLIP) during sedated upper endoscopy. We aimed to develop and describe a classification scheme of esophageal motility based on parameters generated with a novel analysis paradigm: FLIP topography.

Methods: 100 patients (ages 19-82, 50 female) present with dysphagia that underwent upper endoscopy with a 16-cm FLIP and high-resolution manometry (HRM) were included. HRMs were analyzed according to the Chicago Classification of esophageal motility disorders. A customized MATLAB program generated FLIP topography plots of diameter by axial position over time. EGJ-distensibility index (DI) was measured by dividing the narrowest ECL cross-sectional area by the median intra-bag pressure at a 60-mL distension volume. Esophageal contractions were identified by noting periods of reduced diameter and contractility patterns including repetitive antegrade contractions
Food Intolerances

11 Vagus nerve stimulation dampens Th2-mediated food allergy

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Background: The cholinergic anti-inflammatory pathway (CAIP) via the vagus nerve has emerged as an important modulator of the intestinal innate immune system. To what extent the CAIP also affects the adaptive immune response remains unclear. Thus, we investigated the effect of vagus nerve stimulation (VNS) in a typical Th2-mediated intestinal disorder such as food allergy.

Methods: Balb/C mice were sensitized with ovalbumin (OVA; day 0 and 14) followed by intragastric challenges with OVA every other day, from day 28 onwards. Prior to the first challenge, mice received VNS (5 min, 5 Hz, 1 mA) or sham stimulation. Mice were sacrificed 1 h after the 3rd OVA challenge and cytokine gene expression and lamina propria (LP) immune cells were analyzed by qPCR and flow cytometry, respectively. Mast cell degranulation was assessed by measuring mouse mast cell protease 1 (MMP-1) in the serum. Data shown as mean ± SEM, p < 0.05 is considered statistically significant, unpaired t-test or Mann-Whitney U-test was performed.

Results: VNS-treated mice showed significantly lower expression in the duodenum of the Th2 cytokines IL-4, IL-5 and IL-13 and of IL-6 compared to sham-treated mice (see Table). Furthermore, VNS significantly reduced serum MMCP-1 after the 2nd (Sham 2934 ± 545 ng/mL vs VNS 1556 ± 296, n = 8, p = 0.04) and 3rd (Sham 5758 ± 1315 ng/mL vs VNS 2352 ± 329, n = 8, p = 0.03) intragastric challenge with OVA. Finally, VNS significantly reduced the % and number of neutrophils in the LP (Sham 2.4 ± 0.4% vs VNS 1.1 ± 0.2%, p = 0.008), and Sham 3.3 × 10^6 ± 6.4 × 10^3 vs VNS 1.8 × 10^6 ± 5.8 × 10^3, p = 0.03, n = 8, but not lamina propria (LP) eosinophils.

Conclusion: Our data show that VNS reduces intestinal inflammation and dampens mast cell activation in a murine model of food allergy. This indicates that VNS not only modulates the innate but also the adaptive immune system. Further insight in the underlying mechanism could ultimately lead to new targets and novel therapeutic approaches to treat or improve food allergy.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sham (n = 8)</th>
<th>VNS (n = 8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>2017 ± 768</td>
<td>452 ± 115</td>
<td>0.03</td>
</tr>
<tr>
<td>IL-5</td>
<td>15.0 ± 4.0</td>
<td>2.0 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-13</td>
<td>5.8 ± 1.4</td>
<td>2.8 ± 0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>IL-6</td>
<td>68 ± 24</td>
<td>16 ± 4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abstract 11.
scale (VAS) every 15 min. Number of pan-colonic presurr-turations (PCP, Corsetti 2015) and of long distance low-amplitude propagating sequences (LDPS, Dinning 2014) were evaluated. VAS score and HRM data (mean ± SD) were analysed using mixed models and Student’s t-test respectively.

Results: Over time, sensations of abdominal gas, abdominal discomfort, desire to evacuate gas and desire to defecate were significantly increased with the FO (p < 0.05), but not water. FO (and not fructose) significantly increased sensations of abdominal gas (p = 0.014), abdominal discomfort (p = 0.036) and desire to defecate (p = 0.002) when compared to water. During the pre-prandial period the number of both LDPSs and PCPs did not differ between the three solutions. Postprandially, the number of LDPSs was significantly higher during FO compared to fructose (42 ± 28 vs 22 ± 13, p = 0.04), whilst number of PCPs did not differ between the three solutions (39 ± 59 vs 27 ± 24 vs 28 ± 38).

Conclusion: These findings show that FO may exert similar effects in the colon by a combination of sensitivity effects and colonic motor pattern changes, whereas the effects fructose are more sensory related.

13 LPS mediated intestinal barrier dysfunction and visceral hypersensitivity in the IBS is prevented by low FODMAP diet
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Intestinal barrier dysfunction and visceral hypersensitivity (VH) are common among IBS patients. Diet has a profound effect on the gut microbiome and a low FODMAPs (fermentable oligo-, di-, and mono-saccharides and polyols) diet (LFD) appears to improve IBS symptoms by unclear mechanisms. Lipopolysaccharide (LPS) from bacteria cell wall causes mucosal inflammation and impaired barrier function. We hypothesize that LPS from gut dysbiosis mediates intestinal barrier function and VH, and can be prevented by LFD. To test this hypothesis, we obtained fecal samples from 10 healthy controls (HC) and 10 symptomatic IBS-D patients before and after 4 week LFD. Four wk LFD resulted in significant improvement of IBS symptoms. Fecal LPS measurements showed the endotoxin was -2-fold higher among IBS-D patients compared to HC (13 EU/g vs 8.3 EU/g, p < 0.05) and LFD normalized the fecal LPS to a level similar to that of HC. To evaluate VH, fecal supernatant (FS; 0.5 mL) from IBS-D patients and HC were administered intracolonically (IC) to naive rats and visceral motor response (VMR) to colorectal distension (CRD) were performed 3 h after substantum administration. IC administration of FS from IBS-D patients caused a three to fourfold increase in VMR to CRD at 20, 40, 60 and 80 mmHg. No abnormal increases in VMR were observed in rats receiving FS from patients after 4 week LFD HC. Administration of a potent LPS antagonist LPS-BS (100 µg/kg IC) prevented the development of VH caused by IC LPS IC. The endotoxin inside human colonoids to test the permeability of the epithelium. Human colonoids were injected with a fluorescence dye FITC and images were obtained at different time points. When exposed to FS from HC the colonoids retained 69% of FITC at 12 h. FS from IBS-D reduced the retention of FITC 4.32% (p < 0.05). This abnormality was prevented by co-administration of LPS- RS. In contrast, FS from IBS-D patients following 4 week LFD did not impair mucosa barrier function. Separately, we showed that IC administration of LPS increased mast cell immunostaining in colon mucosa and histamine release in vitro. The effects of LPS to induce VH and activation of mast cell in vivo were prevented by the mast cell stabilizer cromolyn (30 mg/kg). In conclusion, in IBS-D increased fecal LPS from dysbiosis induces barrier dysfunction allowing access of endotoxins in mucosa to activate mast cells. LFD altered gut dysbiosis and normalized LPS restoring mucosal integity and abolishing VH, resulting in IBS symptoms improvement.

Clinical Phenotyping – Biomarkers

14 Prospective evaluation of serum 7αC4 and FGF19 to detect bile acid diarrhea in patients with IBS-diarrhea: test sensitivity and intra-individual variation in replicate samples
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Background: Based on 48-h stool testing, ~32% of IBS-diarrhea (IBS-D) patients have bile acid (BA) diarrhea. Serum 7αC4 (C4) is a direct (reflecting hepatocytic BA synthesis) and FGF19 (ideal hormone that provides negative feedback on hepatocytic BA synthesis) an indirect serum marker of BA diarrhea.

Objective: To analyze the reproducibility over time in repeat fasting C4 and FGF19 values and prospectively determine prevalence of BA diarrhea among IBS-D patients.

Methods: We prospectively identified 80 IBS-D patients based on Rome III criteria and obtained fasting blood samples to perform C4 and FGF19 tests. Among these patients, 71 had previous serum C4 values and 26 had previous FGF19 values. We used prior normal values (C4 >31 ng/mL; FGF19 >79 pg/mL) to identify the proportion of the 80 current patients with evidence of elevated serum C4. We performed Wilcoxon rank sum test and Spearman correlation to appraise the values at two different times.

Results: Among the 80 patients with IBS-D, serum C4 levels were 20 ± 15.7 ng/mL (SD), and 16% had elevated serum C4 (>31 ng/mL). As previously demonstrated, there was a significant reciprocal relationship between serum C4 and FGF19 (Rs = –0.288, p = 0.015). The serum FGF19 levels were 121.9 ± 79.9 pg/mL (SD), and 34% had reduced serum FGF19. 11.6% of patients had abnormal results on both tests. In the patients with replicate serum measurements, 6/31 (19%) had elevated C4 values. There were significant differences between replicate C4 values (p = 0.000), however, there was a significant correlation of serum C4 at two different times (Rs=0.613, p = 0.0001). Conversely, there were no differences between FGF19 values at the two time points (p = 0.923), but no significant correlations between replicate FGF19 measurements (Rs = 0.073, p = 0.716).

Conclusions: Among 80 patients with IBS-D, 16% had elevated serum C4 and 34% had reduced FGF19 levels; there was significant negative correlation between fasting FGF19 and C4 levels. Based on serum C4 repeat testing, 19% of patients with IBS-D have persistent evidence of BA diarrhea, a proportion similar to previous reports based on fecal BA testing. FGF19 values were more consistent over time and may be a more sensitive screening test for BA diarrhea. Further analysis of sensitivity and specificity relative to the gold standard (48 h fecal BA excretion or [13C]octanoate retention) is warranted.

15 Functional pathways associated with differentially expressed colonic mucosal microRNA and mRNA in irritable bowel syndrome
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Background: Irritable bowel syndrome (IBS) is a stress-sensitive disorder characterized by chronic abdominal pain and diarrhea and/or constipation. Peripheral mechanisms contributing to visceral hypersensitivity, altered gut secretion and motility are incompletely understood. MicroRNAs (miRNAs) are small RNAs capable of regulating mRNA levels. MiRNA-mRNA functional pathways have recently been identified in a water avoidance stress (WAS) rat model of IBS (Bradesi et al., Plos One 2015).

Aim: To institute an integrative pathway analysis approach of differentially expressed miRNA-mRNA target pairs in the colon mucosa in IBS compared to healthy controls (HC).

Methods: Female and male Rome III + IBS and age and sex matched HCs underwent sigmoidoscopy with sigmoid colon biopsies, from which total RNA was extracted. MiRNAs were measured using nCounter miRNA assay from NanoString. Gene expression (mRNA) was measured using ArrayStar microarrays in a subset of IBS patients and HCs. Differential expression was identified using Student’s t-tests. A p-value <0.05 was considered significant. Validated miRNA targets were obtained from miRtarBase (a database for experimentally validated miRNA-target interactions). PathwayGene Ontology (GO) terms were determined using Enrichr (a gene-list enrichment analysis tool).

Results: 29 IBS (55 % F, mean age 34 years, 14 IBS-D and 15 IBS-C) and 15 HCs (47% F, mean age 34 years) participated. Sixteen miRNAs were significantly different between IBS and HCs (p < 0.05). In the subset of 20 IBS patients (10 IBS-D, 10 IBS-C) and 10 HCs (50% F in both groups), there were 2075 differentially expressed miRNAs (p < 0.05). Of these, we identified 308 that overlapped with validated targets of differentially expressed miRNAs and 187 miRNA-mRNA pairs that were deregulated in opposite directions (i.e., high miRNA-low mRNA and low miRNA-high mRNA.)
Conclusions: Using an integrative approach, we identified deregulation of validated mRNA targets of differentially expressed mRNAs in the colonic mucosa associated with GDNF, and in both enteric and nociceptive pathways. Janus kinase (JAK) and Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathways have been associated with neuroinflammation and neuropathic pain and found to be upregulated in lumbar spine in WAS rats with visceral hypersensitivity. Similarly, fibrobast growth factor receptor (FGFR) signaling mediates axon-glial interaction in the peripheral sensory pain pathways. Nerve growth factor (NGF) signaling has been implicated in visceral sensitivity via expression of NGF and its receptor (tyrosine kinase, TrkA) in neuronal and non-neuronal tissues of the gut. These findings provide new potential pathophysiologic insights and potential drug development targets in IBS.

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Differential colonic mucosal mRNA expression in IBS with constipation
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Background: Studies evaluating mucosal mRNA expression associated with irritable bowel syndrome with constipation (IBS-C) are few and sample sizes are small.

Aims: To evaluate mucosal mRNA expression in IBS-C patients vs healthy controls (HCs) and confirm differentially expressed genes in our sample to publically available microarray data.

Methods: 10 Rome III + IBS-C patients and 10 age and sex matched HCs underwent sigmoidoscopy with sigmoid biopsies, from which total RNA was extracted. Gene expression (mRNA) was measured using ArrayStar (Agilent platform) microarrays. Differential expression was identified using the limma package in R. A Benjamin-Hochberg-adjusted p-value <0.05 was considered significant. Two publically available microarray (Affymetrix) analyses of sigmoid biopsies collected by Aerssons et al. (E-TABM-176, 15 IBS-C and 25 HCs) and rectal biopsies from Swan et al. (GSE36701, 18 IBS-C and 21 HCs) were accessed and analyzed with the affy datasets. Figure 1 shows a heatmap of these hierarchically clustered.

Results: In our dataset, 1149 unique mRNAs were differentially expressed between IBS-C and HCs. There were 17 mRNA that were differentially expressed (in the same direction) in our sample as well as in both external datasets. PCP2 was found to be upregulated in the mucosa of both IBS-C and healthy controls, and downregulated in IBS-C patients with IBS and HCs. An unadjusted p-value threshold of <0.05 was used for significance threshold for matching genes in the external data-sets.

Conclusions: Analysis of publically available gene expression data is useful in identifying mRNAs that are differentially expressed in IBS-C in different samples. Several of these genes have potential relevance functions. PVR1, also known as nectin-1, is a protein in the adherens junction of epithelial cells. It was shown to be downregulated by miR-199a-5p which has been associated with increased permeability in the bladder and gut. PCDH6 and CENP are also cell-adhesion molecules. ST3GAL3 is involved in pre-NTCH signaling, and TLXNL is upregulated by lipopolysaccharide. These genes are among those that will be further evaluated with targeted replication.

Developing Gut

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Effects of exposure to GDNF, retinoic acid and/or 5-HT4 receptor agonists on the ability of enteric neurospheres to generate an enteric nervous system
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Cell therapy has the potential to treat enteric neuropathies. Previous studies have shown that enteric neural progenitors can be isolated from the bowel of infant and adult humans and laboratory animals, and following transplantation into the bowel of rodents, they migrate and differentiate into functional neurons. Although patient-derived cells offer key clinical advantages as a source of stem/progenitors for transplantation, patient-derived stem cells may be defective in their ability to migrate and/or generate sufficient enteric neurons. Moreover, the distance that transplanted stem cells need to migrate in humans is significantly greater than has been demonstrated in animal models. It is therefore highly likely that patient-derived cells will require manipulation prior to transplantation into the bowel. We examined whether exposure to GDNF, retinoic acid and/or 5-HT4 receptor agonists enhanced the ability of enteric neurospheres to generate an enteric nervous system (ENS) in aneural embryonic gut explants in vitro, and in the colon of postnatal mouse in vivo. Neural progenitors were isolated from the gut of E14.5 mice and neurospheres generated. Enteric neurospheres exposed to 50 ng/ml GDNF were significantly larger in volume, and contained significantly more cells, than controls. Neurospheres were grown in the presence of GDNF and/or 5-HT4 receptor agonist (RA), and then co-cultured with explants of aneural gut. Progenitors in neurospheres exposed to GDNF, but not RA, migrated significantly further along gut explants than progenitors from control neurospheres. Exposure of the co-cultures to the 5-HT4 agonist, R567506, did not significantly increase the distance migrated by progenitors. We then transplanted control neurospheres, or neurospheres grown in the presence of 50 ng/ml GDNF, into the colon of postnatal recipient mice. The recipient colon was examined 4 weeks later. The area occupied by graft-derived cells and nerve fibers and the number of graft-derived neurons were higher in recipients containing neurospheres that had been exposed to GDNF. We conclude that exposure of enteric neurospheres to GDNF prior to transplantation into the colon in vivo promotes migration, neuronal differentiation and nerve fiber extension.

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Rdh10 and retinoic acid signaling mediate ECM-composition and neural crest cell migration during colonization of the gut and in the pathogenesis of hirschspring disease
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Vagal neural crest cells are a migratory stem and progenitor cell population that give rise to the neurons and glia of the enteric nervous system (ENS) in the
Emerging Technologies to Study GI Luminal Function

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Neuronal circuitry analysis using live calcium imaging in the mouse colon

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Background: Different regions of the gut exhibit specific motility patterns regulated by the enteric nervous system (ENS). Currently, little is known about how ENS circuits are differentially organized to generate these regionally distinct motility patterns.

Aim: To explore whether calcium imaging of the ENS can uncover differences in neuronal circuits between the proximal and distal colon.

Methods: Live Ca²⁺ imaging was performed on myenteric plexus preparations from adult Wt1-Cre;R26-GCaMP3 mice, where all enteric neurons express the genetically-encoded Ca²⁺ indicator, GCaMP3. To simultaneously record intracellular Ca²⁺ changes of many neurons in different ganglia, we used a low magnification lens (6×) to maximize the field of view (600 μm × 600 μm) while maintaining single cell resolution. Focal electrical stimulation was applied (300 μs, 20 Hz, 2 s) and responses in individual neurons analyzed. Immunohistochemistry and Dil labeling were used to compare differences in the neurochemical phenotype and projections of myenteric neurons.

Results: Analysis of the proportion of ChAT+ and nNOS+ myenteric neurons showed that there was a greater proportion of nitricergic neurons in the distal colon compared to the proximal colon (39 ± 2% vs 33 ± 2%, p = 0.05). In addition, Dil labeling revealed that in the distal colon, the projections of myenteric neurons were more numerous and extended further along the longitudinal axis. In the proximal colon, application of the nicotinic receptor antagonist, hexamethonium (200 μM), significantly decreased the electrically-evoked Ca²⁺ transients in the majority of neurons compared to time controls. Interestingly, inhibition of nNOS using L-NAMe (100 μM) also reduced the Ca²⁺ transients in a large proportion of neurons. Moreover, it induced Ca²⁺ rises in a vast amount of cells not active in preceding control conditions. In both regions, hexamethonium completely abolished Ca²⁺ responses in a population of neurons. This proportion was larger in the distal compared to the proximal colon (34 ± 11% vs 15 ± 6%, p < 0.05). L-NAMe did not produce any significant effect on electrically-evoked responses in the distal colon.

Conclusions: While our experiments indicate that both the morphology and neurochemical content of myenteric ganglia varies between different regions of the colon, Ca²⁺ imaging reveals only subtle differences at the functional level. Our future investigations aim at understanding how these subtle differences translate to regionally defined motility patterns.

Methods: Immune labeling was performed to study the interaction between EGCs and immune cells in murine gut. To study the possible anti-inflammatory effect of EGC-secreted factors, primary murine EGCs were co-cultured with MFs. After co-culture with EGCs, the phenotype of MFs was analyzed by gene expression. To analyze the contribution of enteric glia in vivo during intestinal inflammation, EGCs were FACS sorted from control or mice subjected to dextran sodium sulfate (DSS) colitis and gene expression was analyzed.

Results: Immunohistochemical analysis revealed that EGCs are in close contact with MFs both in the muscularis externa and in the lamina propria. Interestingly, glial-secreted molecules were able to decrease expression of pro-inflammatory cytokines such as IL-12 and IL-6 in MFs in response to LPS stimulation, while IL-10 was increased. Moreover, typical anti-inflammatory MF markers, such as MRC-1, Lyve-1 and Stab-1, were increased in MFs stimulated with EGC supernatant. In vivo during colitis, EGCs express high level of CX3CR1L, a chemokine that typically attracts monocytes, as well as genes involved in the synthesis of the tolerogenic molecule retinoic acid (i.e. RALDH4).

Conclusion: In the current study we provide anatomical, in vitro and in vivo evidence suggesting that EGCs exert immunomodulatory effects on intestinal antigen presenting cells. Taken together, our data indicate that interaction between enteric glia and the intestinal immune system might be crucial to maintain immune homeostasis and prevent immune-mediated diseases such as IBD.
IBS and Visceral Pain: What’s New in Nociception

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Bifidobacterium longum: A psychobiotic that attenuates stress-induced increases in salivary cortisol and anxiety, and alters EEG and neurocognitive performance in healthy volunteers

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Background: Psychobiotics - live microorganisms with a potential mental health benefit - represent a novel approach for managing stress, via precise targeting of the microbiome-gut-brain axis. Preclinical studies have identified B. longum as a putative psychobiotic with an impact on stress-related behaviours, physiology and cognitive performance. We hypothesised that these effects could be translated to human volunteers.

Methods: This research received approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Healthy male volunteers aged 18–40 (N = 22) consumed B. longum or placebo daily for 4 weeks each in a repeated-measures design. Participants completed study visits at baseline, post-placebo and post-probiotic. The socially evaluated cold pressor test (SECPST) was employed to induce acute stress, and stress was assessed using self-reported anxiety (STAI) and salivary cortisol. Daily stress was assessed via validated online questionnaires. Cognitive performance was assessed using the CANTAB platform and neurocognitive activity via resting electroencephalography (EEG).

Results: Following B. longum, SECPST-induced increases in cortisol output and subjective anxiety were attenuated. Self-reported daily stress was lowered during psychobiotic consumption. There was an improvement over placebo in visuospatial memory performance in paired associate learning following B. longum consumption. Consistent with improved memory performance, resting EEG indicated that mobility at Fz was higher following B. longum consumption compared to baseline and placebo.

Conclusions: B. longum is associated with attenuated responses to acute stress, a modest improvement in cognitive performance and altered resting EEG. Further studies are warranted to evaluate the benefits of this putative psychobiotic in relevant stress-related conditions.

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COMT modulates nociception through TNF-α/miR-155 pathways

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Introduction: Irritable bowel syndrome (IBS) is a common GI disorder that is characterized by heightened peripheral and central nociceptive pain processing mechanisms. In addition to visceral pain, some IBS patients may also exhibit somatic symptoms suggesting both peripheral and central hyperalgesic dysfunction, possibly from nociceptive input from the CNS or enteric nervous system. Genetic variations in the Catechol-0-Methyltransferase (COMT) gene has been associated with altered perception of nociceptive stimuli in chronic pain conditions such as fibromyalgia, migraine headaches, and temporomandibular joint and muscle pain.

Aim: The aim of this study was to evaluate the downstream target genes for COMT that drive central and peripheral nociception. We hypothesized that COMT modulates TNF-α through regulation of miR-155.

Methods: The water avoidance stress (WA) model was used for 1 h each day for 10 consecutive days to induce visceral nociception in both COMT+/− [n = 10] and wild type mice [n = 10]. EMG recordings of the external oblique abdominal muscles were performed to measure the VMB following colorectal distension. The mice were sacrificed and a miRNA microarray and Fluorescence in situ RNA hybridization (FISH) were performed on colon-specific DRGs from the mice. Cluster analysis was performed to determine expression of specific miRNAs that were either significantly decreased or increased in COMT+/− vs wild type mice.

Results: Significantly increased expression of miR-155 was present in COMT+/− DRGs [p < 0.001]. Increased colonic-miR-155 also was found in COMT+/− mice [p < 0.01]. There was significantly increased visceral nociception following WA stress in COMT+/− compared wild type mice [p < 0.01]. Pearson correlation analysis revealed a tight correlation between visceral nociception and COMT expression following WA stress [r = 0.72, p < 0.001]. Pearson correlation demonstrated that TNF-α expression in colon-specific DRGs’s was tightly correlated with visceral nociception [r = 0.77, p < 0.001] in mice following WA stress.

Conclusions: COMT may be one of the key factors that modulates TNF-α via miR-155. There may be a potential feedback mechanism between TNF-α and COMT expression. Therefore, COMT may regulate nociceptive pathways in patients with chronic functional disorders such as IBS.

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Gender differences in serotonergic signaling are present in the duodenum in functional dyspepsia

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Introduction: Functional dyspepsia (FD) is a common, disabling condition that is poorly understood.
Pediatric Functional Disorders

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Sacral nerve stimulation for treatment of constipation in children: Long-term outcomes, patient benefit, and parent satisfaction

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Background: Studies suggest that sacral nerve stimulation (SNS) may be an effective treatment for children with constipation, but long-term outcomes have not been described.

Objective: To evaluate the long-term efficacy of SNS for children with constipation and to describe patient benefit and satisfaction.

Methods: Using a prospective patient registry, we identified patients ≥ 21 years who initiated SNS ≥ 2 years ago for constipation. We compared medication usage, PedsQL GI Symptom Scale (GSS), Fecal Incontinence Quality of Life Scale (FIQL), and Fecal Incontinence Severity Index (FISI) at baseline and follow-up. We also administered the Glasgow Children’s Benefit Inventory (GCBI) and a parent satisfaction questionnaire by phone. Wilcoxon signed-rank test and McNemar’s test were used for comparison.

Results: We included 25 children (52% M, mean 14.0 years; 17 had functional constipation, 6 had anorectal malformation, 1 had Hirschsprung’s disease, 1 had tethered cord. In addition to constipation, 18 had fecal incontinence and 16 had urinary symptoms. 13 (52%) were using antegrade continence enemas (ACE) at baseline. Use of laxatives and ACE had decreased at follow-up. Of the 13 using ACE, 8 underwent closure of the appendicostomy/cecostomy and the remaining 5 had decreased ACE frequency at follow-up. GSS, most FQIL domains, and FISI were significantly improved at follow-up. 16 parents (64%) completed the GCBI and parent satisfaction questionnaire after a mean of 2.5 years. Median GCBI was 42.7 (IQR 23.4–77.1) and 15 (94%) reported GCBI scores >0, indicating positive health-related benefit. 14 (88%) would proceed with SNS if given the opportunity to remeasure their disease. All would recommend SNS to patients with similar symptoms. 6 (24%) had complications requiring surgery, including 4 requiring SNS replacement.

Conclusion: SNS is a promising treatment for children with constipation. In our cohort, SNS led to continued symptomatic improvement in children with constipation 2 years after treatment initiation. Despite a 24% complication rate requiring additional surgery, nearly all parents reported health-related benefit and would recommend SNS to others.

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A combination of dietary prebiotics and the probiotic LGG modulate behavioural and cognitive responses to early life stress

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Background: Maternal separation (MS) of rat pups is a robust and reliable model of early life adverse events that induces long-term alterations to behavior and brain neurochemistry. These changes are particularly apparent with respect to the microbilia-gut-brain axis.

Methods: Since dietary factors are known to impact the gut microbiota, this study assessed the impact of consuming prebiotics polydextrose (PDX) and galactooligosaccharide (GOS) with or without the probiotic *Lactobacillus rhamnosus* GG (LGG) on cognition, social- and anxiety-related behaviors in rodents. Rats were separated from their mothers between postnatal days (p) 21–12 as described in O’Mahony et al., 2009. Both MS and MS rats [N = 5–9 each] were fed control or probiotic diet (7 g/kg PDX-GOS) with or without LGG (108 cfu/mL) in drinking water from p21 throughout behavioral testing to p100.

Results: No differences in body weight or food intake was noted across diets. However, the open field test revealed that MS rats traveled a shorter distance with reduced velocity compared to the NS rats (p < 0.05). The effects or early life stress were ameliorated by probiotic feeding (p < 0.01) and LGG (p < 0.01), but intriguingly not when combined. MS rats displayed deficits in spatial memory in the Morris water maze (p < 0.05) while rats fed probiotic in addition to LGG showed a reversal of this impairment (p = 0.05). All diets reduced Glucocorticoid Receptor (GR) mRNA levels in non-stressed rats, however LGG was only diet to increase levels in stressed rats (p < 0.05) (A). Combination of probiotic with LGG ameliorated the MS-induced up-regulation of hippocampal GABA A2 receptor mRNA (p < 0.05).

Conclusions: These results demonstrate that both prebiotics and LGG ameliorate early life stress-induced changes in adult behavior and when combined can improve memory performance. These results aid to further our understanding of the effects of dietary manipulation on the microbilia-gut-brain axis in an animal model of early life stress.

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Immunohistochemical analysis of pediatric achalasia: A case series

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Background: Histopathologic patterns among achalasia subtypes have been described in adult patients and help to understand the pathophysiology of achalasia. This has not been reported in the pediatric population. The purpose of this study was to examine histopathologic patterns of achalasia in pediatric patients.

Methods: High resolution esophageal manometry tracings were reviewed to categorize the achalasia subtype (Chicago Classification) from children who had deep biopsies from the lower esophageal sphincter (LES) obtained during laparoscopic myotomy. Histologic evaluation of formalin-fixed samples was performed using H&E stain as well as immunohistochemistry using antibodies to neuronal elements [calretinin, PGP9.5, GLUT-1], inhibitory neurotransmitters [VIP and nNOS], interstitial cells of Cajal (CD117), inflammatory cells [CD3], glia (S-100) and smooth muscle (alpha-actin).

Key Results: Five pediatric patients with achalasia who had biopsies were identified and included, one patient had Allgrove’s syndrome. Three patients had type II achalasia and two patients had type III achalasia. Biopsies from these patients were studied and compared to those from a control (autopsy) who had no significantly amongst the three groups. TPH-1 and SERT RNA levels were comparable amongst the three groups. However, TPH-1 and SERT RNA levels were significantly decreased in female EPS patients compared to controls (p < 0.05). TPH-1 and SERT levels in female PDS and male EPS patients were similar to controls.

Conclusions: This data indicates that there may be gender differences in serotonergic signaling with regard to the duodenal mucosa in FD, specifically in female subjects with EPS. This was not seen in female PDS subjects or male FD subjects. Further studies are needed to confirm these findings given the small sample size. The project was supported by a grant from the ANMS to AL.
The Omics Revolution: Where are We headed?

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Transcriptome analysis reveals gene signatures in interstitial cells of Cajal
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Transcriptome reveals essential clues of the molecular mechanisms in cellular functions and biological processes. Transcriptomics is a rapidly growing field in mechanistic studies of cellular functions and biological processes. Transcriptomics is a rapidly growing field in mechanistic studies of cellular functions and biological processes. Transcriptomics is a rapidly growing field in mechanistic studies of cellular functions and biological processes. Transcriptomics is a rapidly growing field in mechanistic studies of cellular functions and biological processes.

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A functional variant in the alternative serotonin transporter gene SLC6A4 promoter P2 has a potential impact on irritable bowel syndrome
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The serotonin reuptake transporter (SERT) gene SLC6A4 represents one of the most promising candidate regions involved in the aetiology of irritable bowel syndrome (IBS). SERT is responsible for the reuptake of serotonin from the synaptic cleft into the presynaptic neuron and the intestinal space into enterocytes. To date, two distinct promoters of SLC6A4 have been described: P1 and P2. The short allele of the haplotype polymorphism 5-HTTLPR has been found to be associated with IBS in various studies. In addition, its association with depression and anxiety is well established supporting the biopsychosocial model of IBS. The alternative promoter P2 predominantly drives expression in the gastrointestinal tract. For unravelling the role of P2 in IBS development, we have performed sequencing analysis of the promoter region P2 in a discovery sample from the UK consisting of 98 patients with diarrhoea (IBS-D), 100 patients with constipation (IBS-C) and 92 control individuals. This revealed several single nucleotide polymorphisms (SNPs) within the respective promoter region to be associated with IBS. Interestingly, haplotype analysis uncovered all SNPs to be in strong LD (>0.9) among each other and to be incorporated in two main haplotypes. The tagging SNP rs2020938 (tagSNP) was determined for validation of the association finding in additional case control samples. The tagSNP rs2020938 has so far been found to be associated in three case control samples: in the initial screening collective from the UK, an US American (197 IBS, 95 controls) and a Greek sample (161 IBS, 143 controls). Currently, additional case control collectives from partners in the COST Action BM1106 GENIEUR (The Genes in Irritable Bowel Syndrome Research Network Europe, www.GENIEUR.eu) are being tested for association (1950 IBS, 2580 controls). Functional follow-up of the risk/protective haplotypes in luciferase reporter assays in the two neuronal cell lines SH-SY5Y and IMR-32, as well as the gastrointestinal cell lines Caco2 and Colo 320 and the standard embryonic kidney cells HEK293 showed that the risk haplotype leads to enhanced luciferase activity corresponding to increased expression compared to the protective haplotype. Our hypothesis is that the protective allele of rs2020938 in P2 might lead to decreased expression levels and the risk allele to the opposite effect. Studies are currently ongoing comparing expression in different subregions of the gut, including jejunum, ileum and colon to confirm our findings. We will report on latest replication and expression data.

Visceral Pain - Recent Developments and Future Directions

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Intragastric bitter tastant decreases hedonic food intake and affects brain activity in homeostatic and hedonic regions
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Introduction: Intragastric administration of bitter tastants decreases hunger ratings in the fasted state. This indicates a potential role for bitter agonists in the regulation of appetite and food intake, potentially via interference with gut-brain signals to regions involved in homeostatic (brainstem, hypothalamus) and hedonic (mesolimbic reward system) control of feeding.

Aim: To study the effect of intragastric administration of the bitter tastant Quinine Hydrochloride (QHC1) on brain activity in homeostatic and hedonic regions and to test the hypothesis of lower hunger and prospective food consumption (PFC) ratings, and lower hedonic food intake after QHC1 administration compared to saline.

Methods: Fifteen healthy women were studied after an overnight fast. Brain activity before and up to 50 min

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after infusion of QHCl (10 mg/kg) or saline (placebo) was recorded using functional magnetic resonance imaging (fMRI), while hunger and PFC scores were assessed every 10 min using Visual Analogue Scales. Hedonic food intake was measured immediately after scanning using an ad libitum chocolate milkshake drink test. MRI preprocessing and analysis was conducted using SPM12. Brain responses over time to QHCl vs saline infusion were compared in a priori defined regions of interest (ROI) at a voxel-level threshold of p FWEcorrected < 0.05 combined with an extent threshold of k > 25 voxels. Similarly, the infusion-by-time interaction effect was tested on hunger and PFC scores with mixed models. Hedonic food intake was compared between infusions using a one-tailed paired t-test.

Results: Compared to saline, intragastric infusion of QHCl significantly increased neural activity in 5 different clusters within the ROIs, with local maxima in the putamen, insula, caudate, amygdala, anterior cingulate cortex, medial prefrontal cortex, medial orbitofrontal cortex and hippocampus. A decrease of neural activity was observed in the brainstem. Significantly lower PFC scores were observed after QHCl administration compared to placebo (p = 0.02), but no significant differences were observed for hunger scores (p = 0.34). Milkshake intake was significantly lower after QHCl administration, compared to saline (p = 0.04, Cohen’s d = 0.50).

Conclusion: Intragastric administration of the bitter tastant QHCl suppressed prospective food consumption ratings, significantly altered activity in homeostatic and hedonic brain regions and decreased hedonic food intake.

A2  Mindfulness improves brain structure in irritable bowel syndrome (IBS)
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Background: IBS is a brain-gut disorder characterized by recurrent abdominal pain, altered bowel habits, and stress-related symptoms. Mindfulness-based stress reduction (MBSR) is an intervention that reduces symptom severity in IBS, possibly due to improvements in brain function. We hypothesized that MBSR treatment of IBS would lead to positive changes in brain microstructure measurable with diffusion tensor imaging (DTI).

Aim: To assess changes in brain structure in IBS after 2 months of mindfulness training.

Methods: We studied 39 Ileum III positive IBS subjects (30 females, mean age 31.9 ± 8.8 years), who underwent MBSR with eight weekly 2-h group sessions, one 4-h retreat, and daily 30-min meditation at home. We scanned subjects on Siemens Trio 3T scanner with DTI and T1 anatomical protocols prior to and after the intervention. Indices included [i] mean diffusivity (MD) which increases with loss of structural integrity, [ii] axial, [iii] radial diffusivity (AD and RD) which increase with axonal and myelin disruption respectively, and [iv] fractional anisotropy (FA) which reflects fiber integrity. We performed whole-brain analysis and a priori assessments of 8 ROI’s previously shown to be affected in IBS with paired t-tests in SPM12 software, allowing for subject variation in baseline.

Results: Whole-brain analysis with family-wise error correction revealed decreased AD in bilateral white matter and basal ganglia including nucleus accumbens, putamen, and caudate nucleus (left: t = 0.04, t = 5.7, right: t = 0.08, t = 5.8). No other indices changed at the whole brain level. Regionally, right insula diffusivity decreased (MD: t = 0.06, t = 3.5, AD: p = 0.03, t = 3.8, RD: p = 0.05, t = 3.6, posterior: MD: p = 0.04, t = 3.5, RD: p = 0.04, t = 3.5) and FA increased (anterior: p = 0.02, t = 3.9, posterior: p = 0.02, t = 3.8). The left cingulate gyrus showed decrease in MD (anterior: t = 0.05, t = 3.7, middle: t = 0.01, t = 4.4). Left parahippocampal gyrus FA increased (p = 0.03, t = 3.8), and left thalamus AD decreased (p = 0.06, t = 3.96). No changes appeared in bilateral amygdala and hippocampus, right anterior and middle cingulate gyrus, and right parahippocampal gyrus.

Conclusions: The structural changes in nucleus accumbens, basal ganglia, insula, cingulate cortex, and white matter suggest improved connectivity in salience circuitry, potentially due to enhanced axonal integrity from increased myelin or axon diameter. Two months of MBSR improves brain structure, especially axon integrity in relevant regions, in IBS patients.

Eosinophilic Esophagitis 33

Modulation of resident macrophages in the muscularis externa by stimulation of enteric neurons
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Background: Neuroimmune mechanisms contribute to the maintenance of intestinal immune homeostasis. We showed that electrical stimulation (ES) of the vagus nerve and administration of prucalopride reduced muscularis inflammation and improved intestinal transit in a murine model of postoperative ileus, most likely by dampening the activation of resident muscular macrophages (MF). As the vagus nerve is not directly interacting with these MF but synapses with the enteric nervous system, we hypothesize that the resident MF are modulated by enteric neurons (EN).

Methods: MF activation was assessed by responses to ATP (100 μM) in situ live imaging of the muscularis externa of adult C57Bl/6 GFP/WT C57Bl/6 mice. Responses are represented as mean difference in ΔF/ΔT [ΔF/ΔT] before and after ES (20 Hz, 5 min) or prucalopride ([150 μM] application. To study the effect of EN on MF phenotype skewing, bone marrow derived macrophages were cultured overnight in the presence/absence of supernatant (SN) of EN cultures [14d,v, containing 80 ± 3% ChaT+ neurons] or co-cultured with freshly isolated myenteric plexus (MP) ganglia (n = 300). Subsequently, MF were stimulated with lipopolyssacharide (100 mg/mL) for 12 h and cytokine release in the SN was assessed. Results are represented as mean ± SEM. One-way ANOVA with Tukey’s multiple comparisons test was applied for statistical analysis. Alpha value=0.05 was considered statistically significant.

Results: Activation of MFs by ATP was significantly reduced by ES (ΔF/ΔT: −1.042 ± 0.168, n = 57 MFs/5 mice) and prucalopride treatment (ΔF/ΔT: −1.042 ± 0.2233, n = 87/4 compared to Krebs’ solution [ΔF/ΔT: −0.0357 ± 0.1925, n = 100/7]). In the presence of TTX, ES failed to significantly reduce MF activation (ΔF/ΔT: −0.5431 ± 0.1297, n = 69/3) compared to Krebs’ solution, indicating the involvement of neurons.

In addition, MF cultured in the presence of SN of EN or co-cultured with MP ganglia released more IL-10 (835 ± 34 pg/mL and 1016 ± 24 pg/mL resp.) compared to MF cultured in unconditioned medium (287 ± 23 pg/mL and 777 ± 46 pg/mL resp.). No difference in TNF-α was detected [EN: 3071 ± 77 pg/mL vs unconditioned: 3247 ± 276 pg/mL and MP ganglia: 1089 ± 70 pg/mL vs 1376 ± 11 pg/mL].

Conclusion: Our data show that activation of ENs dampens ATP-induced MF activation and induces a shift towards a more tolerogenic phenotype. These data indicate a neuromodulatory role for the enteric nervous system most likely contributing to the tolerogenic phenotype of resident muscularis MFs.
nesting (LN) and [iv] following (30 days) an acute colitis induced by 2,4,6-trinitrobenzene sulfonyl acid (TNBS), 50 mg/kg, termed post-inflammatory [PI]. Visceral hypersensitivity was measured via a visceromotor response [VMR] to graded pressures (0–60 mmHg) of isobaric colorectal distension (CRD). Changes in VMR to CRD were analyzed by two-way repeated measures analysis of variance followed by a Bonferroni post-test. 

Results: In comparison to untreated controls, AA, WAS, LN and PI exposure increased the VMR to CRD. In all four experimental paradigms, following treatment with GSK101, there was a significant (p < 0.05) inhibition of visceral hypersensitivity [AA: 40 mmHg; 50%, LN: 40 mmHg; 85%, PI: 40 mmHg; 36%, 60 mmHg; 34%].

Conclusions: To our knowledge, this is the first study demonstrating that targeting the RET kinase pathway may serve as a novel approach for treating chronic pain disorders such as IBS, and provides new insight into the etiology of visceral nociception.

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Intestinal Disorders

Gastric gas dynamics in healthy humans

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Introduction: A wide range of gas volumes can enter into the stomach during meals. In addition to gas emptying to the small intestine, distension of the stomach triggers the belching reflex to prevent symptomatic gas retention. However, the normal ways of transit and evacuation of free gastric gas have been poorly investigated. Our aim was to study the dynamics of free gastric gas in healthy subjects, and the correlation between gas retention, rectal and oral gas evacuation.

Methods: In 24 healthy volunteers without gastrointestinal symptoms [14 women and 10 men, age-range 21–33 years], 1500 mL of a mixture of non-absorbable gases was infused into the stomach, 5-cm caudal to the lower margin of the LES. In groups of 6 volunteers the following gas infusion rates were tested: 0 mL/min [sham infusion], 25 mL/min, 50 mL/min and 100 mL/min. In the subjects receiving sham infusion, 400 mL/min of gas were infused at the end of the study until belching occurred. Belching, by an esophageal multilumen impedance manometry catheter, and rectal gas evacuation, via a rectal tube connected to a barostat, were continuously recorded for 90 min.

Results: Infusion of gas at 400 mL/min induced belching in all subjects at a lower infused volume [703 ± 132 mL] than the infused volume associated with first belching at the lower infusion rates [1300 ± 148 mL, pooled data of infusion at 25–100 mL/min]. Overall, there was a negative correlation between rectal gas evacuation and belching [r = -0.66, p = 0.05].

Conclusion: In healthy subjects, gastric gas is rapidly emptied to the small bowel and propelled to the rectum preventing gas retention and gastric distension. Only when gas arrives to the stomach at a very high rate the belching reflex, acting as a reserve defense mechanism, is activated and oral venting of gas occurs.

The central role of the intestinal microbiota in chronic intestinal pseudo-obstruction

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Background: Chronic Intestinal Pseudo-Obstruction (CIPO) is a severe disorder of gastrointestinal (GI) motility leading to clinical features of intestinal obstruction without mechanical occlusion. The intestinal microbiota is an important stimulator and regulator of gut motility. We hypothesized that patients with CIPO have dysbiosis, which may contribute to clinical features of the disease.

Aims: (1) To characterize the gut microbiota of patients with CIPO. (2) To determine whether this microbiota is responsible for clinical features typical of CIPO using a gnotobiotic mouse model. (3) As proof of principle, to evaluate whether fecal transplantation improves symptoms of CIPO.

Methods: The fecal microbiota of 3 patients with CIPO (1 female, median age 38.6 ± 11 years) and 3 healthy volunteers (2 females, median age 39.5 ± 9 years) was analyzed using 16s rRNA based illumina sequencing. Stool samples from 1 patient with CIPO and 1 healthy control were used to colonize germ-free NSH Swiss mice (n = 8 mice per donor) by oral gavage. GI transit was determined at 2 weeks using a validated in vivo videofluoroscopic technique. Cecum and stomach size, and maximal bowel diameter, were determined using abdominal CT scan. Fecal transplantation was performed in a CIPO patient by jejunal infusion.

Results: The fecal microbiota of patients with CIPO exhibited marked dysbiosis. There was a large predominance of Proteobacteria species, especially of the Enterobacteriaceae class. In contrast, healthy volunteers showed a predominance of Firmicutes and Bacteroidetes. Bacterial richness and diversity were lower in patients with CIPO. The fecal microbiota profiles of gnotobiotic mice resembled that of human donors. Additionally, mice transplanted with microbiota from the CIPO patient had a significantly slower GI transit than those transplanted with healthy control microbiota [mean transit score 1 ± 2 vs 12 ± 5, p < 0.001]. Furthermore, mice colonized with CIPO microbiota had a larger cecum size [2.39 ± 0.32 cm³ vs 1.56 ± 0.22 cm³, p < 0.001] and a higher maximal bowel diameter [3.3 ± 0.2 mm vs 2.9 ± 0.2, p < 0.001] compared to mice colonized with healthy microbiota. Finally, fecal transplantation of a healthy donor stool into a CIPO patient led to a rapid improvement in symptoms, functional status and overall quality of life.

Conclusion: The fecal microbiota of patients with CIPO is altered and contributes to clinical features of the disease in a mouse model. Fecal transplantation may be an effective treatment for patients with CIPO.

Brain-Gut Axis: Neuroimmune Mechanisms

The effect of prolonged abdominal sepsis on mesenteric nerve activity, dorsal root ganglia and the central nervous system in a murine model of cecal ligation and puncture induced sepsis

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Background: Ileus together with mucosal barrier dysfunction maintains sepsis by facilitating bacterial translocation. Intestinal afferent nerves transmit inflammatory signals to the brain. Direct exposure of afferent nerves to LPS results in increased afferent activity, but the effect of a polymicrobial sepsis on neuronal activity remains unknown. We aimed to study jejunal afferent nerve activity following cecal ligation and puncture (CLP), the gold standard animal model in sepsis research. The status of the central nervous system (CNS) and dorsal root ganglia (DRG) were studied by means of PET/CT imaging and PCR.

Methods: Sepsis was induced in OF1 mice by CLP. Sham-operated animals served as controls. Mice were sacrificed 48 h following CLP and a 3 cm jejunal segment was dissected and placed in a recording
chamber. The mesenteric afferent nerve bundle was isolated and nerve discharge was recorded using a suction electrode. Ramp distensions up to 60 mmHg were performed, and single-unit analysis was performed. For the PET/CT acquisition all mice were fasted overnight, after which they received an i.v. injection of 18.5 MBq [18F]FGD 30 min before the PET scan. A volume of interest [VOI] analysis (PMODv3.3) was done by calculating the standard uptake value corrected for glucose levels per brain region. These images were then used as input for a voxel-based analysis (SPM8). After sacrifice the lumbar DRGs (L1-L6) were isolated for RT-PCR of cFos, CGRP, NMDA, TRPA1, TRPV1 and opioid receptors.

Results: Afferent discharge at higher distension pressures was significantly attenuated following CLP due to a decreased activity of wide dynamic range (WDR) and high threshold [HT] fibers. The VOI based analysis showed a significant global decrease in [18F]FDG uptake (p < 0.0001) in septic mice compared to sham. SPM revealed that the most significant clusters with decreased [18F]FDG uptake (p < 0.001) were the amygdala, left and right cortex, striatum and olfactory area. PCR of DRGs showed a significant increase in the neuronal activation marker cFos in septic mice, as well as increased expression of TRPA1 and NMDA receptors and decreased expression of the δ-opioid receptor.

Conclusion: Polymicrobial abdominal sepsis desensitizes mesenteric afferent nerves at higher pressures via decreased HT and WDR afferent activity and significantly reduced metabolic activity in all brain regions, most notably in cortex, amygdala and striatum, regions involved in the processing of visceral pain. Analysis of lumbar DRGs revealed increased neuronal activation markers as well as a decrease in δ-opioid receptor mRNA level in septic CLP-mice.

38 iNOS inhibitor recovers the impaired sensitivity of mouse vagal afferents in diet-induced obesity

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Our previous studies have demonstrated impaired vagal afferent sensitivity to satiety mediators and distention of the gut in high fat fed obese mouse (Daly et al., 2011). Studies on iNOS (inducible nitric oxide synthase) knockout mice have suggested that iNOS-derived NO may play a role in the pathophysiology of obesity-induced metabolic dysfunctions (Noronha et al., 2005). Thus, this study aimed to examine the involvement of iNOS in obesity-related impairment of vagal nerve sensitivity. Nodose ganglion and jejunum were obtained from high (60%) and low (10%) fat fed male C57/B6J mice. NO was measured using a Nitrate/Nitrite fluorometric assay kit. Membrane excitability of nodose neurons was assessed by whole cell patch clamp. Afferent discharge was recorded from jejunal mesenteric nerves. In comparison with lean mice, NO concentration in nodose culture supernatant from obese mice was significantly increased (p < 0.001, N=6, unpaired t-test) and pre-treatment with L-NIL (10 μM) reversed this change (p < 0.001, N=6, unpaired t-test). Excitability of nodose neurons was significantly increased by pre-incubation with L-NIL (10 μM), as evidenced by decreased rheobase [67.0 ± 5.9 vs 112.1 ± 14.6 μA, p < 0.05, N=10, unpaired t-test] and increased action potentials at twice rheobase [2.2 ± 0.4 vs 1.4 ± 0.1, p < 0.05]. In line with these observations, afferent response to satiety mediators cholecystokinin [CCK, 100 μM] was significantly increased by bath-applied L-NIL (30 μM, 71.8 ± 9.9 vs 60.6 ± 12.7, p < 0.05, N=7, paired t-test) and afferent response to ramp distention was significantly augmented by intraperitoneal injection of L-NIL [10 mg/kg, p < 0.05, N=9, two-way ANOVA]. Single unit analysis revealed that this increase in afferent sensitivity was mainly contributed by low threshold afferents. All experiments were duplicated in low fat fed mice and no significant change was seen. These data suggest that iNOS may be the key molecule in the obesity-induced impairment of vagal nerve sensitivity and thus a potential therapeutic target for obesity-related dysfunctions.

39 Lumenally-restricted TGR5 agonists promote murine colonic motility

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Bile acids (BA), secreted from the gall bladder into the small intestine, assist in digestion and absorption of fats. The majority are reabsorbed at the terminal ileum. Increased BA delivery to the colon may enhance transit in pathophysiological conditions, conversely bile acid transport inhibitors that prevent reuptake at the ileum may be a treatment option for chronic constipation. The BA receptor, TGR5, may have a role in these prokinetic effects. However, actions at the muscularis vs the mucosa may by opposing. Therefore the potential of systemically exposed vs lumenally-restricted TGR5 agonists should be investigated as therapeutics for conditions such as constipation. We analysed the ability of synthetic agonists to activate TGR5 compared with the BA, deoxycholic acid (DCA). We measured cAMP production in HEK293 cells stably expressing human TGR5. DCA caused a concentration dependent accumulation of cAMP ([C50 = 210 nM]) as did the synthetic small molecule agonist CBT086 (EC50 = 0.19 nM) and its non-absorbable version 15C ([C50 = 1.4 nM]). TGR5 agonists inhibited electrically-evoked contractions of the mouse colon. Although this action is anti-prokinetic, we used this assay to access the potency of TGR5 agonists in mouse tissue. Contractions in segments of the distal colon were inhibited by CBT086 and 15C, where CBT086 had greatest potency ([C50: CBT086 = 720 nM, 15C = 1067 nM, N = 4]). Bath addition of DCA (100 μM) inhibited propulsive contractions in whole segments of colon. However, intraluminal application had minimal effects. At 5 nM, intraluminal application of DCA increased the length propulsive contractions travelled along the colon by 14%. This is within the range of concentrations of BA found within stool water of patients with ileal malabsorption (1–15 mM). Intraluminal application of CBT086 and 15C (100 μM) were more effective at altering propulsive motility than DCA. Compared with its own vehicle control, propulsive contractions travelled 25 ± 4% with intraluminal application of CBT086 (p < 0.01, N = 8) and 17 ± 4% further with 15C (p < 0.01, N = 6). Although TGR5 activation has prokinetic effects in the mouse colon, these are limited to lumenal application of agonists. Lumenally-restricted agonists may be a useful avenue for the development of therapies for digestive diseases.

40 Role of the gustatory signaling pathway in the metabolic reprogramming after Roux-en-Y gastric bypass surgery in mice

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*GIDRU, Kingston General Hospital; Queen’s University, Kingston, ON, Canada; †Taste receptors coupled to the gustatory G-protein, gustducin, on endocrine cells play an important role in gut hormone release. During Roux-en-Y gastric bypass (RYGB) surgery nutrients are rerouted to more distal regions of the gut. We hypothesize that this may have important effects on the chemosensory mechanisms controlling gut hormone release and hence energy – and glucose homeostasis.

Methods: We studied the role of the gustatory signaling pathway in the metabolic improvements after RYGB surgery in wild-type (WT) and s-gustducin−/− (s-gust−/−) mice. After 12 weeks on a western diet, mice were randomized to RYGB or sham (pair fed) surgery and sacrificed 7 weeks after surgery, 15 min after a nutrientdrink® gavage.

Results: After RYGB surgery, body weight loss was more pronounced in WT mice and was partially due to reduced food intake in WT but not in s-gust−/− mice. The decreased food intake played a major role in the improved glucose tolerance and insulin resistance after RYGB surgery in WT mice, while s-gust−/− mice were protected against the diabetogenic effect of the diet. Nutrient refeeding induced morphological changes in the foregut of WT, but not of s-gust−/− mice. This was accompanied by an increased jejunal L-cell count and a decreased expression of the differentiation marker neuroginin 3 in WT mice. The mRNA levels of the protein sensor [GLP1R] and the glucose transporters [SGLT1, GLUT2] in the limb exposed to nutrient excess were increased in s-gust−/− mice, but not in WT mice. The increase in plasma PYY but not GLP-1 levels was genotype-dependent and more pronounced in s-gust−/− mice. In the distal gut, RYGB surgery changed bacterial fermentation in the cecum of s-gust−/− mice, which showed increased butyrate and propionate levels compared to WT mice. This resulted in decreased mRNA levels of the short chain fatty acid receptor, Ffar2, in
the colon of α-gust−/− mice, while FFAR3 mRNA levels were decreased in both genotypes. RYGB surgery improved colonic permeability independent of the genotype.

Conclusion: Nutrient sensing plays a role in the effects of RYGB surgery on body weight loss, glucose homeostasis, gut morphology, L-cell differentiation, nutrient sensor expression, PYY levels, and bacterial fermentation. The effects on plasma GLP-1 levels and colonic permeability were gustducin independent. Supported by IWT Flanders.

Anorectal Disorders

41 Does the type of dyssynergia influence the outcome of biofeedback therapy?
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Dyssynergic defecation (DD) causes chronic constipation in 40% of patients. At least 4 subtypes of DD patterns have been described. Whether these types influence outcome of biofeedback therapy (BT) is unknown.

Methods: Patients with DD (ROME III), unresponsive to medical treatment were enrolled in 2 prospective BT trials, 6 biweekly sessions without sensory training or 3 months home BT. Responders were defined as a normalization of dyssynergia pattern after 3 months of BT.

Results: 172 patients (134F, age 41 ± 14 years) were enrolled, 22.1% dropped out. Baseline demographics, constipation symptoms, and bowel satisfaction score were similar between 4 types. After BT, type I, II and IV had higher response rate than type III. All except type III had significant manometric parameters improvement and decreased balloon expulsion time after BT (p < 0.05). Type III had significantly higher baseline rectal sensory thresholds (p < 0.05) compared to other types. All subtypes had significantly improved of bowel satisfaction scores (p < 0.05).

Conclusions: Dyssynergia subtypes influence BT outcome, type I, II and IV are more favorable. They help therapist to tailor the treatment program. Poor outcome in type III may be due to rectal hyposensitivity.

42 Balloon expulsion test in patients with fecal incontinence
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Background: High resolution anorectal manometry is routinely used in evaluation of patients with fecal incontinence (FI). The utility of Balloon Expulsion Testing (BET) in evaluation of these patients with FI is not well-defined.

Objectives: To study the relationship between anal pressure profiles and balloon expulsion in patients with fecal incontinence.

Methods: 56 patients with FI (44 female) and mean age of 60 ± 13 years (mean ± SD) were identified. Anorectal function was assessed by both high resolution anorectal manometry and BET. BET was evaluated by ability to evacuate a 50 cc water filled balloon on a commode. Manometric parameters are expressed as mean ± SD and compared between groups using Student’s t-test.

Results: A total of 53.5% of all patients with FI failed BET. Average age in both groups was comparable (61 ± 13 vs 60 ± 14 years, p = 0.88). Length of the anal sphincter was longer in the patients who failed BET (3.2 ± 1 vs 2.7 ± 0.7 cm, p = 0.03). Low maximal resting pressures were identified in 55% of all patients in this cohort (69 ± 33 mmHg). Although lower than normal, mean and maximal resting anal pressures were significantly higher among incontinent patients who failed BET as compared to those who did not; 71 ± 31 and 81 ± 36 vs 50 ± 233 and 56 ± 24.5 mmHg, p = 0.002 and p = 0.003, respectively. Maximal anal squeeze pressures were low in 86% of all patients with FI (121 ± 59 mmHg). Maximal anal squeeze was also significantly higher in patients who failed BET (138.5 ± 68 vs 101.3 ± 40 mmHg, p = 0.007). Both residual anal pressures and anal relaxation rate, during bear down maneuvers, were similar in both groups. However, rectal pressures were significantly less in patients who failed BET (48.3 ± 32 vs 69.7 ± 39, p = 0.01). Compared to gender-specific normal values for pressure parameters, maximal anal pressures were decreased in 59% of females (66 ± 32 mmHg) and 41.6% of males (81 ± 36 mmHg) at rest and 86% of females (109 ± 53 mmHg) and 83% of males (163 ± 63 mmHg) during squeeze. Anal residual pressures were elevated in 54.5% of women (57.9 ± 27 mmHg) and 58% of men (98 ± 39 mmHg) during bear down manoeuver. Rectal pressures were low in 16% of women (56 ± 36 mmHg) as compared to 33% of men (67 ± 42 mmHg).

Conclusions: More than half of those with fecal incontinence were unable to evacuate a 50 mL water-filled balloon, mainly as a result of elevated anal residual pressures during simulated defecation, despite low resting and squeeze anal pressures. These results highlight the importance of coordinated anorectal function, and not just sphincter pressures, in maintaining continence.

The ENS: Neuroimmune Pathways

43 How prenatal synthetic glucocorticoids administration impacts the ENS in Wistar rats?
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Synthetic glucocorticoids are routinely administered to pregnant women at risk of premature labor. The effects of this administration has been studied both in humans and in rodents, since the exposure to prenatal and early adverse events cause persistent alterations in the central nervous system. Despite the greatly improved survival of preterm babies with prenatal dexamethasone administration, little is known about possible adverse effects of this treatment in the enteric nervous system (ENS). We previously showed that Wistar rats exposed prenatally to dexamethasone, as animal model of intrauterine synthetic glucocorticoid exposure (iuGC), have shorter small intestine, slower transit and lower serotonin levels compared with controls. To further investigate these effects, both duodenum-jejunum junction and proximal colon motility were assessed using video-imaging and construction of spatiotemporal maps in 1 month old male rats. Moreover, in order to understand if particular subpopulations of myenteric neurons were affected by prenatal dexamethasone exposure, we used immunohistochemistry to count numbers of neurons expressing Hu, numbers of neurons expressing neuronal nitric oxide synthase (nNOS) and numbers of neurons expressing calbindin or calretinin. We found a
44 Evaluating the safety and efficacy of eluxadoline for treating diarrhea-predominant irritable bowel syndrome: A Meta-analysis

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Background: Eluxadoline is an opioid receptor agonist/antagonist recently approved by the FDA for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). We evaluated the safety and efficacy of eluxadoline in treating IBS-D based on controlled clinical trial data. Methods: We searched the literature (PubMed and Cochrane database) and abstract books since 2005 from ACCG, DDW, and UEGW to identify relevant randomized placebo-controlled trials. Study eligibility was independently evaluated by ES and MP. Consistent with recent FDA methodology, data were pooled based on similarities in population characteristics and trial design. Our primary endpoints were (i) number needed to harm (NNH) of adverse event (AE)-related study withdrawal, representing the patient-centered binary decision of whether continuing therapy is worth the potential benefit, and (ii) number needed to treat (NNT) based on the IBS-D FDA responder endpoint. We assessed NNH related to AE of constipation and serious AE incidence. Relative risk (RR) was calculated with 95% confidence intervals.

Results: Three randomized double blind Phase II and III registered trials of eluxadoline were included representing 519 patients on therapy. The NNNT was 12.7 (RR = 1.5, 95% CI: 1.3–1.8) based on the FDA responder endpoint. The pooled rate of study withdrawal due to AE was 8.0% on therapy and 4.4% on placebo, resulting in a statistically significant number needed to harm (NNH = 28.3, RR = 1.9, 95% CI: 1.4–2.6). The excess incidence of constipation was 4.5%, resulting in a NNH of 23.6 (RR = 2.9, 95% CI: 1.9–4.4). Regarding serious AE, the rate of pancreatitis on eluxadoline was 0.7% in phase II evaluation and 0.4% in pooled analysis (with no pancreatitis on placebo), though not all phase III trials excluded patients with specific additional risk factors of pancreatitis.

Conclusions: Eluxadoline is efficacious in treating IBS-D, though constipation is not uncommon and may hamper the observed benefit of eluxadoline based on its mechanism of action. There were eight cases of pancreatitis in clinical trial patients randomized to eluxadoline therapy.
Emerging Concepts

47 Rome IV and Rome III functional dyspepsia in the US, Canada and United Kingdom
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Background/Aims: Rome IV criteria for functional dyspepsia (FD) are similar to Rome III except they do away with several qualifiers for diagnosing the Epigastric Pain Syndrome (EPS) variant. It is unknown how the new criteria affect FD population prevalence and demographic distribution: This was investigated by using data from a large three-country internet survey.

Methods: The survey included the Rome IV Diagnostic Questionnaire for Adults, Rome III FD diagnostic questions, demographics and health history, and was completed by a community sample of individuals aged 18+ in the US, UK and Canada (1000 in each country). Quota-based sampling was used to ensure equal proportion of sex (50%/50%) and age groups (40% aged 18-39, 40% aged 40-64, 20% aged 65+) across countries, and control education distributions (40% maximum college graduates). Age and gender proportions were adjusted with census weights to obtain national FD prevalence estimates.

Results: 5931 response sets were judged valid for analysis (49.2% female, mean age = 47.4, range 18-92, 1949 US, 1994 UK, 1988 Canada). Sex and age group proportions were equivalent between countries since sampling was quota-based. Raw and census-weighted (in parentheses) FD prevalence by Rome IV vs Rome III criteria was 11.9% (12.7%) vs 9.4% (10.0%) in the US, 8.4% (8.7%) vs 7.2% (7.3%) in Canada, and 7.6% (7.7%) vs 5.9% (6.0%) in the UK. FD prevalence was higher with Rome IV vs Rome III criteria in the total sample (raw prevalence 9.3% vs 7.5%, p = 0.0001). The US had higher (p = 0.05) Rome III FD rate than UK and Canada, and higher Rome IV FD rate than the UK. In the total sample, women had higher FD rates than men (Rome IV: 11.3% vs 7.3%, p = 0.0001; Rome III: 9.9% vs 5.1%, p = 0.0001), and individuals aged 65+ had lower FD rates than younger ones (Rome IV: 5.4% vs 10.8%, p < 0.0001; Rome III: 4.8 vs 8.2, p = 0.0001). Of Rome IV FD cases, 61.5% classified as Postprandial Distress Syndrome (PDS), 17.6% as EPS and 20.9% as both. With Rome III criteria, 77% of FD cases classified as PDS, only 0.5% as EPS (due to the multiple symptom exclusions required), and 22.5% as neither.

Conclusions: Rome IV FD rates range from 7.7% to 12.7% and Rome III FD rates from 6.0% to 10.0% in the nations sampled. FD is more prevalent in the US than Canada or UK, is female predominant, and less common in older individuals. EPS is a more common FD subtype in Rome IV vs Rome III due to eased diagnostic restrictions.

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48 Colonic cancer cells adhere and migrate along enteric neurons via L1CAM and N-Cadherin
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Introduction: Enteric neurons are part of the colorectal cancer (CRC) microenvironment as attested by the observation of ‘perineural invasion’, defined as cancer cell nest surrounding enterochromaffin cells in myenteric plexus. Others actors of tumor microenvironment such as endothelial or immune cells interact with tumor cells via direct (cell/cell contact) and indirect (paracrine crosstalk) interactions that play a central role in the tumor growth and dissemination. Into CRC perineural invasion, the nature of interactions between CRC cells and enteric neurons remains unknown.

Aims: We hypothesized that interactions between CRC cells and EN involve physical adhesion. The aims of the study are to determine whether TEC adhere on EN and whether this physical interaction impact TEC properties.

Methods: TEC (Caco-2 cells GFP+) or primary culture of TEC isolated from human CRC were dropped on primary culture of rat ENS (pcrENS; including EN, smooth muscle and epithelial cells) were counted and observed using confocal microscopy. Caco-2 cells GFP+ were cocultured under 12 h with pcrENS infected with a lentivirus expressing GFP and observed by video-imaging in order to evaluate TEC migration along neuronal vs mesenchymal cellular structures. The molecular complexes implicated in the adhesion of TEC on EN were identified using a proteomic approach. Blocking antibodies targeting the neuronal adhesion molecule previously identified were added in pcrENS medium before dropping TEC for adhesion and migration analysis.

Results: The density of adhering Caco-2 was significantly larger in pcrENS with EN as compared to pcrENS without EN (p = 0.01). Moreover, 1 h after adding TEC in pcrENS, 80 ± 2% of TEC were juxtaposed to EN structures whereas EN structures area only represented 29 ± 10% of the total area of pcrENS (p = 0.01). Confocal microscopy analysis confirmed the direct interactions, i.e cellular contact, between Caco-2 and EN, both in pcrENS and in human submucosal plexus. TEC juxtaposed to EN migrated significantly further and faster than TEC not juxtaposed to mesenchymal structures (p = 0.01). Western-Blot analysis of adhesion complex isolated according to our novel proteomic approach identified L1CAM and N-Cadherin also present in pcrENS. With blocking antibodies anti-L1CAM and anti-N-Cadherin, the proportion of TEC juxtaposed to EN at the end of adhesion tests and the distance to origin covered by TEC adhered on EN significantly decreased (p = 4 and 20 respectively).

Conclusion: Our data demonstrates that TEC from CRC adhere and migrate along EN via L1CAM and N-Cadherin. This study defined the ENs as a new way of propagation in CRC. A better understanding of the cellular mechanisms and the molecules implicated would help to identify new therapeutic approach to inhibit CRC progression.

49 Exploring the microstructure of the external anal sphincter using diffusion tensor based local and global fiber tractography
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Background: There remains debate as to the true morphology of the external anal sphincter (EAS) muscle complex. However, if the morphology of the EAS muscle is not a circular, the results could have significant implications for episiotomy practice as both birth and overlapping sphincteroplasty as surgical treatment in fecal incontinent patients. Diffusion-based tractography offers an enormous potential for the study of human EAS microanatomy. We use both local and global tractography for the first time, to study the microstructure of the EAS.

Method: A spin echo-based echo planar diffusion-weighted sequence with spatial spectral fat saturation, minimum possible echo time of 45-50 ms, repetition time of 4500-6500 ms, 20-cm field of view, 3-mm slice thickness, 0.4-mm spacing, and 8 averages was used, having a b-value of 400 s/mm² to obtain a higher SNR. Studies were done in 8 healthy asymptomatic nulliparous women, producing 30-34 slices in the axial and perpendicularly planes to the anal canal axis. Fiber tractography was constructed in the DT image via FiberTools.

Results: Both, local and global tractography method reveal the string purge morphology of the EAS. The local tractography focuses only on a single tract, reconstructing a fiber step by step, by following the voxelwise information and successively adding segments to the fiber, which prevents them in following complex fiber configurations such as crossings or kissings. In light of the above, it might indicate the presence of looping fibers, as inherently deterministic tractography methods are not able to resolve intra voxel crossings/kissings due to the tensor ellipsoid assumptions. Global tracking was the only method capable of reconstructing the full extent of the fiber crossing pathways, compared to the deterministic algorithm which performed less adequately.

Conclusions: If a detailed depiction of the EAS fiber anatomy is intended then the computationally time-consuming global tracking should be preferred, as it tries to reconstruct all fibers simultaneously, searching for a global optimum. Although it is critical to remember that the reliability of tractography algorithms as a tool for tissue assessment is dependent on factors such as anatomic deviation and compression, intracellular and extracellular edema, tissue infiltration by tumors, fiber degeneration, and inflammation.

50 Impaired gastric distribution of a meal is associated with impaired meal-induced intragastric pressure (IGP) drop and early satiation in functional dyspepsia (FD)
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IGP measurement using high resolution manometry (HRM) during intragastric inflation of a nutrient drink
Rectal and anal pressures are greater in ‘UP’ than LL position. Anal relaxation evaluated with ‘New’ position measured with the ‘New’ technique revealed significant improvement post-biofeedback. Conclusion: Rectal and anal pressures are greater in ‘UP’ than LL position. Anal relaxation evaluated with ‘New’ but not ‘Med’ improved after biofeedback therapy.
Dietary and related factors trigger and aggravate the bowel symptoms in patients with irritable bowel syndrome—a multicenter prospective survey in China

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Objective: To investigate the relationship between bowel symptoms onset and dietary and related factors, using a modified 6-scale score of IBSQOL significantly in patients with irritable bowel syndrome (IBS).

Methods: Four centers recruited IBS patients who met Rome III diagnostic criteria. Patients were administered CRF of IBS symptoms and dietary factors by the investigators, and the nutritional status and QOL were evaluated by Mini Nutritional Assessment (MNA) and SF-36.

Results: A total of 392 IBS patients were recruited, 32 cases with incomplete information were eliminated and 360 cases were enrolled in final analysis, including 191 males and 169 females, with age of 44.0 ± 12.0 years, BMI of 22.5 ± 3.3, the average duration is 4.9 ± 5.8 years. Of 88.3% patients are IBS with diarrhea. The illness conditions are stable for 67.5% patients, and 30% became worsening in the past 3 months. In list of 26 dietary and 6 related factors, the most easily (refers as sometimes and often) triggered and aggravating IBS symptoms are cold food [74.5%], uncooked food [64.7%], spicy food [61.1%], greasy food [52.8%], alcohol [52.7%], and dining out [51.0%], followed by travelling, fruits, carbohydrate beverages, milk and products, leftovers, and eating too much [45.4–33.9%]. In addition, catching cold [66.5%], climate change [54.0%], anxiety [42.6%], depression [40.0%], poor sleep [39.3%] are also triggers for bowel symptoms. Selected avoidance of triggering foods or factors, 20.5–73.9% patients might achieve symptoms relief. Patients also adopted methods to alleviate their bowel symptoms while onset, the efficacy of fasting, improving diet and nutritional status and QOL were significantly in patients with food intake for 1 after the injection. Some rats were given IP injection. The amounts of the mixture of food and glass beads was given into the stomach with polyethylene tube and then PYY or CCK was IP injected. In some experiment, CCK was IP injected followed by PYY injection and the interaction with CCK and PYY on gastric emptying was examined. The combination of CCK 10 nmol/kg and PYY 100 pmol/kg amplified the suppression of gastric emptying and food intake. (5). The combination of CCK 10 nmol/kg and PYY 100 pmol/kg dose-dependently inhibited gastric emptying (control:CCK 1 nmol/kg, CCK 10 nmol/kg, 87.9 ± 2.5:73.6 ± 3.2:62.6 ± 6.6, p = 0.01) (2) CCK 10 nmol/kg significantly inhibited food intake for 1 after the injection (control: CCK for 1 h, 1.6 ± 0.3:4.3 ± 0.2, p = 0.001) (3) PYY (0.5–10 μg/kg) biphasically inhibited gastric emptying (control PYY: 1 μg/kg, PYY 10 μg/kg, 80.9 ± 2.4:41.8 ± 4:08.1 ± 5.4, p = 0.01) (4) PYY 1 μg/kg significantly inhibited food intake for 1 h after the injection (control PYY 30 ± 0.4:1.8 ± 0.2, p = 0.001). However, PYY 10 μg/kg did not inhibit food intake. (5) The combination of CCK 10 nmol/kg and PYY 10 μg/kg inhibited gastric emptying more than CCK alone (significant) or PYY alone (not significant), (control:CCK+PYY:CCK-PYY 87.9 ± 2.5:65.6 ± 6.6:5.4 ± 5.4:47.4 ± 5.0, p = 0.01) PYY and CCK additively inhibited food intake when PYY was injected 20 min later from CCK injection (control:CCK+PYY:CCK-PYY 7.9 ± 1.0:5.4 ± 0.5:5.3 ± 0.4:3.9 ± 0.3 g).

Conclusion: PYY and CCK inhibits gastric emptying and food intake. The combination of PYY with CCK amplified the suppression of gastric emptying and food intake each other. The result suggests that the sequencing secretion of CCK and PYY might strengthen the inhibition of food intake that is important for adjusting energy intake.
Dietary advice method for IBS: ret of structural individual low FODMAP dietary advice (SILFD) vs brief advice (BLFD)

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Implementation of low FODMAP diet for IBS patients has not been well explored.

Aims: To compare the effect of SILFD vs BLFD in out-patient clinic.

Methods: IBS (ROME III) patients were randomized to receive SILFD (n = 30) or BLFD (n = 32) for 4 weeks. The SILFD was a 30 min advice which included (i) analyzing the 1 week food diary, (ii) identifying high FODMAP diets, (iii) avoiding high FODMAP foods, items advice, and (iv) discuss with the patients to replace high FODMAP items with low FODMAP items from our FODMAP handbook which contained common low FODMAP diet menu in our country. The BLFD was a 5 min dietary advice which included avoiding of large meals, reducing fruits, vegetables, and gas producing foods, such as beans and garlic intake. Food diaries were recorded during a week before and during the 4th week after dietary advice. H2 breath samples were collected for 4 h after taking patients own food before and at the end of study. Responders were defined as ≥30% decrease in the average of daily worst abdominal pain or abdominal discomfort during the 4th week compared to baseline.

Results: 63 patients (47 F, age 51 ± 14 years) completed the studies. Baseline characteristics, symptom severity, number of high FODMAP items intake, and H2 breath production were similar between SILFD and BLFD. After SILFD, 18(60%) patients were fulfilled responder criteria whereas 9 (28%) patients responded after BLFD (p = 0.01). Global IBS symptoms and bloating severity scores were significantly improved, number of high FODMAP items intake and post-prandial H2 breath production were significantly decreased compared to baseline after SILFD (p < 0.05) but not after BLFD (p = 0.05).

Conclusions: Structural individual low FODMAP dietary advice for IBS treatment in out-patient setting and should be advocated as standard service in IBS clinic.

YH12852, a novel, potent and highly selective 5-HT4 agonist, improves delayed gastric emptying and restores feeding inhibition induced by acute restraint stress in rats

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Background: Acute restraint stress [ARS] induces delayed gastric emptying (GE) and inhibition of food intake in rats. These effects can be reversed or prevented by treatment with 5-HT4 receptor agonists. YH12852 exhibits high affinity and selectivity for human recombinant 5-HT4A receptors, and in vivo animal studies have demonstrated a potent prokinetic effect in the upper and lower GI tract. The aim of this study was to investigate the effect of YH12852 on delayed GE and feeding inhibition induced by ARS in rats.

Methods: Male Wistar rats were divided into the following three groups: non-stressed/vehicle, stressed/vehicle, and stressed/YH12852 groups. The effects of YH12852 at single oral doses of 0.3, 0.6, 1.0, 2.0 or 3.0 mg/kg on GE (rat = 10-12 in YH12852 group, n = 19 in vehicle groups) and food intake (rat = 15-18/group) were separately evaluated in two studies, while an additional study was conducted to confirm the mechanism of YH12852 on GE rates by pretreatment of a 5-HT4 antagonist (GR113808) 15 min prior to vehicle or YH12852 administration. 24-h fasted rats received YH12852 or vehicle 50 min prior to food intake [1.5 g]. Following a 10-min period of food intake, the rats were restrained for 60 min and then euthanized to assess GE. To evaluate the effect of ARS on food intake, 24-h fasted rats received YH12852 or vehicle by oral gavage and were then restrained for 60 min. Immediately following the cessation of restraint, pre-weighed food was provided and the quantity consumed was measured at 1 and 2 h-time points.

Results: ARS significantly reduced GE rates and food intake: YH12852 dose-dependently recovered GE rates to 94.6-107.9% from 89.7% in the Stressed/Vehicle group. The improvement in GE by YH12852 treatment was completely abolished by pretreatment with GR113808 10 mg/kg. In parallel, YH12852 at doses of 1 and 2 mg/kg enhanced food intake to 93.2% and 78.1% of the non-stressed/vehicle group. Conclusion: YH12852 reverses stress-induced delayed GE and feeding inhibition. These results suggest that YH12852 has complementary therapeutic potential to fulfill unmet medical needs for patients with functional dyspepsia, gastroparesis, and overlap syndrome of functional dyspepsia and functional constipation/irritable bowel syndrome with constipation.

Correlation between HRV and changes in weight after weight-loss program

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Successful weight reduction in childhood obesity is often regarded as an important factor for the weight stability in adulthood. Previous results have shown that a 6-8 weeks weight reduction program in a specialized rehabilitation clinic which consisting of nutritional education, physical activity, and psychological support led to successful weight loss in children with obesity. Here we present data on the relationship between autonomic activity, psychological parameters and weight stability at 6 and 12 months after the end of the program.

Methods: Children with obesity (all female) between 9 and 17 years were recruited during their inpatient stay at Children Rehabilitation Hospital, Wangen i.A., Germany (Sauer et al. 2014). They were investigated twice – upon admission (T1) and prior to their discharge from the clinic (T2). Upon both occasions, heart rate variability (HRV) was measured during rest condition and during a mental stress test, and blood pressure (BP) and psychometric data, including data regarding their stress vulnerability (SSKI-8) were collected. Six and twelve months after discharge children were contacted again in order to obtain information regarding their weight. To relate changes in body weight after discharge to the weight loss program, differences of all parameter between T1 and T2 investigations were computed. We performed a series of regression analyses to investigate relationship between HRV indices, blood pressure and stress coping with body weight.

Results: We collected body weight data from 29 children at 6 months and from 31 children at 12 months after the end of the program. For the 6 month follow-up, we found that changes in low frequency power (LF) during mental stress test at T2 together with changes in stress vulnerability at T2 significantly predicted weight dynamics (F = 3.704, p = 0.038) – higher baroreflex activity (arousal) at T2 was associated with weight re-gain. Change in high frequency power (HF) of the HRV upon rest condition alone (F = 8.159, p = 0.008) or together with stress vulnerability (F = 4.051, p = 0.028) were significantly associated with changes in 12 months – increased stress vulnerability and vagal tone supported weight re-gain.

Conclusion: Changes of HRV indices during weight-loss has a predictive value for future weight dynamics. Mediation analyses with other physiologic and psychological indices may elucidate the underlying mechanisms.

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migrating motor complex (MMC) signal hunger feelings. The mechanisms underlying interruption of the MMC by specific sweet tastants has not been studied yet. It is conceivable that this requires sweet taste receptor activation and accompanying changes in the release of satiation hormones.

**Aim:** To determine the effect of caloric and non-caloric sweeteners on GI motility and peptide secretion as well as on subjective hunger feelings in healthy volunteers.

**Methods:** The study was conducted as a randomized, single-blind, cross-over trial. A total of 12 healthy volunteers were included. Participants were registered for the duration of one complete MMC followed by the intragastric administration of 250 mL tap water (control), or equisweet caloric (50 g glucose, 25 g fructose) and non-caloric sweeteners (220 mg ascesulfame-K) dissolved in 250 mL tap water. Measurement was continued until at least one subsequent phase III occurred. Recording of antroduodenal intraluminal pressures was performed using a Manoscan™ high resolution manometry catheter. Blood samples were collected for determination of GI hormones. Visual analogue scales were used to rate the subjective sensation of hunger and satiation.

**Results:** Intragastric administration of glucose and fructose significantly reduced antral motility compared to placebo and ascesulfame-K (glucose: p = 0.004 and p = 0.012, respectively) and fructose: p = 0.016, respectively). Antral motility after ascesulfame-K administration did not differ significantly from placebo (p = 0.75). Plasma glucose levels were significantly increased after glucose and fructose (p = 0.001 and p = 0.006, respectively). Ascesulfame-K had no effect on plasma glucose. Hunger scores showed a trend (p = 0.064) to differ over the course of time between the different conditions. The course of satiation scores differed significantly (p < 0.0001) between the 4 conditions. Post-hoc analysis showed a significant (p = 0.0048) difference between glucose and ascesulfame-K with a slower decrease in satiation scores after glucose compared to ascesulfame-K administration.

**Conclusion:** Caloric and non-caloric sweeteners have dissociable effects on gastrointestinal motility and satiation scores. We hypothesize that these changes are due to differences in gastrointestinal peptide secretion.

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61 Sulfate-reducing bacteria completely converts hydrogen generated by fermentation to hydrogen sulfide

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Microbial fermentation in the gut generates hydrogen (H₂) which is subsequently consumed by sulfate-reducing bacteria (SRB) and converted to hydrogen sulfide (H₂S) or by methanogens to methane (CH₄). The absence of H₂ and CH₄ excretion is commonly interpreted in clinical breath testing as an absence of fermentation (non-excreters). Whether or not this finding could be explained by complete conversion of H₂ gas to H₂S is not known as commercial gas chromatographs do not routinely measure H₂S.

**Aim:** In this study, we tested the hypothesis that SRB can convert H₂ generated by fermentation to H₂S.

**Method:** Live bacterial cultures of H2 producer Bac teroides thetaiotaomicron (B. thetaiotaomicron) and H₂ consumer Desulfuromonas vulgaris (D. vulgaris) were used in this in vitro study. Bacteria were suspended in Hungate anaerobic culture tubes containing a solution of lactulose (0.01 M) and phosphate buffered saline flushed with nitrogen, and incubated at 37°C. Groups (n = 4/group) tested were B. thetaiotaomicron (1 × 10⁸), D. vulgaris (1 × 10⁹), and combined D. vulgaris + B. thetaiotaomicron. Gas from the tubes was sampled at 120 min and analyzed for H₂, CH₄, and H₂S using gas chromatographs (Quinton SC, Oralchrom). Data were compared using two-way ANOVA.

**Results:** B. thetaiotaomicron produced the most H₂ (19.48 ± 1.34 ppm, p < 0.001) compared to D. vulgaris (0 ± 0 ppm) and combined B. thetaiotaomicron + D. vulgaris (0 ± 0 ppm). Combined B. thetaiotaomicron + D. vulgaris produced the most H₂S (0.82 ± 1.5 ppm, p < 0.001) followed by D. vulgaris (3.46 ± 0.28 ppm, p < 0.001) then B. thetaiotaomicron (0.19 ± 0.03 ppm). Low levels of CH₄ was detected in B. thetaiotaomicron (0.4 ± 0.8) and combined B. thetaiotaomicron + D. vulgaris (0.08 ± 0.07) but no CH₄ was found in D. vulgaris (0 ± 0).

**Conclusion:** Sulfate-reducing bacteria completely converts hydrogen generated by fermentation to hydrogen sulfide.

This study is supported in part by the Winkler Bacterial Overgrowth Fund.
Dietary FODMAP restriction alters faecal fermentation in patients with irritable bowel syndrome (IBS). We investigated whether this diet alters microbial fermentation, a process that may be involved in IBS symptom generation.

Methods: Patients with IBS were included consecutively to participate in a 4-week FODMAP restricted diet. IBS symptoms were evaluated by using the IBS severity scoring system (IBS-SSS). Total chain fatty acids (SCFAs) were analysed in faecal samples before and after the dietary intervention, both at baseline and after in vitro fermentation for 24 h.

Results: Sixty-three patients completed the study. Following the dietary intervention, IBS-SSS scores improved significantly (p < 0.001). Total SCFA levels were reduced in faecal samples analysed both at baseline (p < 0.005) and after in vitro fermentation for 24 h (p < 0.018). Following diet, baseline levels of acetate (p = 0.003) and n-butyric acids (p = 0.009) decreased, whereas 24 h levels of i-butyric (p = 0.003) and i-valeric acids (p = 0.008) increased. Faecal SCFA levels and IBS symptom scores were not correlated.

Conclusion: Dietary FODMAP restriction markedly modulated faecal fermentation in patients with IBS. Saccharolytic fermentation decreased, while proteolytic fermentation increased, apparently independent of symptoms.

Stress enhances suppressive effects of cholecystokinin on food intake and gastric emptying in rats

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Background/Aims: Dietary restriction of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may relieve symptoms in patients with irritable bowel syndrome (IBS). We investigated whether this diet alters microbial fermentation, a process that may be involved in IBS symptom generation.

Methods: Patients with IBS were included consecutively to participate in a 4-week FODMAP restricted diet. IBS symptoms were evaluated by using the IBS severity scoring system (IBS-SSS). Short-chain fatty acids (SCFAs) were analysed in faecal samples before and after the dietary intervention, both at baseline and after in vitro fermentation for 24 h.

Results: Sixty-three patients completed the study. Following the dietary intervention, IBS-SSS scores improved significantly (p < 0.001). Total SCFA levels were reduced in faecal samples analysed both at baseline (p < 0.005) and after in vitro fermentation for 24 h (p < 0.018). Following diet, baseline levels of acetate (p = 0.003) and n-butyric acids (p = 0.009) decreased, whereas 24 h levels of i-butyric (p = 0.003) and i-valeric acids (p = 0.008) increased. Faecal SCFA levels and IBS symptom scores were not correlated.

Conclusion: Dietary FODMAP restriction markedly modulated faecal fermentation in patients with IBS. Saccharolytic fermentation decreased, while proteolytic fermentation increased, apparently independent of symptoms.

Brain mechanisms underlying the effect of motilin receptor agonist erythromycin on hunger feelings in healthy volunteers

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Introduction: We have previously shown that infusion of 40 mg of the motilin receptor agonist, erythromycin (EM), induces peaks in fasting hunger ratings, accompanied by a premature phase III of the migrating motor complex. It is likely that the sensation of hunger during motilin receptor stimulation results from changes in brain activity in regions involved in the regulation of appetite and satiety.

Aim: To explore the brain responses to intravenous EM infusion and its influence on hunger feelings and hedonic food intake in healthy volunteers.

Methods: Fourteen healthy right-handed women were recruited for this counterbalanced 2 visit study. On each visit day, subjects were given a 275 kcal standard breakfast after an overnight fast. Hundred-and-five minutes after breakfast, an intravenous cannula was inserted into a forearm vein, 10 min later subjects entered the magnetic resonance (MR) scanner for a 10 min adaptation period after which MR images were acquired for 50 min. Ten minutes after the start of scanning, 40 mg EM or saline were intravenously infused over 20 min [rate: 2 mg/min]. Hunger ratings (visual analogue scale) were obtained during scanning. After scanning, subjects drank chocolate milkshake ad libitum as a measure of hedonic eating. Preprocessing and analysis were performed in SPM12. The effect of EM vs saline infusion on brain responses in a priori defined regions of interest (ROIs) was assessed using one-way ANOVA, with time (1 min bins) as within-subject factor, at a voxel-level threshold of pvox<0.05 combined with an extent threshold of k=10. The ROIs consisted of brain regions involved in homeostatic and hedonic control of feeding.

Results: EM infusion decreased anterior insula (bilateral), left amygdala, and left putamen. In contrast, activation of Pons, right caudate, midbrain, and left pallidum were observed during EM infusion. The effects reached a peak 35 min after the start of infusion. In addition, hunger ratings [increase from baseline] and milkshake intake were both significantly higher after EM compared to saline (p = 0.010 and p = 0.044, respectively, paired Student’s t-test, one-tailed), further confirming the peak in hunger ratings coincided with the peak in the brain responses.

Conclusion: Intravenous infusion of the motilin agonist EM affects hunger ratings, hedonic food intake and activity in brain regions related to homeostatic and hedonic control of appetite and feeding.

The feasibility, usability and perceived clinical utility of traditional paper food and symptom journals for patients with irritable bowel syndrome

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Background: Paper food and gastrointestinal (GI) symptom journals are used in clinical practice to help patients with irritable bowel syndrome (IBS) determine potential trigger foods. The primary aim of this study was to evaluate the feasibility, usability, and perceived clinical utility of such journals as a data collection tool. Secondary aims were to evaluate its impact on GI symptoms and to introduce a method for analyzing journal data.

Methods: Participants (N = 17, 18–70 years old) were asked to record 3 sets of 3-day food and GI symptom journals over a 15-day period. They were asked to record all food/drink consumed in a meal and peak GI symptoms (abdominal pain, bloating, diarrhea, constipation) since the prior meal entry on a scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Feasibility was evaluated by journal completion rates, symptom logging compliance, and tracking fatigability. Perceived feasibility, usability, and clinical utility were assessed by customized evaluation and exit interview. To assess the impact on GI symptoms, IBS Symptom Severity Scale (IBS-SSS) scores were compared pre and post-logging. For each participant’s journal, regression analyses were conducted to examine relationships between key meal nutrients and subsequent GI symptoms.

Results: Most participants were female (N = 14, 82%) and Caucasian (N = 13, 72%) with a mean age of 35 years (SD = 12). Journal completion rates were 100% with no observed tracking fatigability. 6 participants (35%) were non-compliant with symptom logging. Most participants perceived paper journaling of food and GI symptoms as feasible, usable, and clinical useful. The

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Biliary, Pancreatic and Small Intestinal Physiology, Pathophysiology, and Clinical Disorders

67 Development of a mixed triglyceride breath test in an Irish hospital setting
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Introduction: Pancreatic exocrine insufficiency (PEI) is thought to be an under recognised clinical problem. Several non-invasive tests are available to assess pancreatic function, most commonly faecal elastase is used in the hospital setting. This test has limitations however & is thought not to be useful in mild-to-moderate pancreatic exocrine insufficiency. In cases of mild pancreatic exocrine insufficiency studies have shown faecal elastase to have a sensitivity ranging from 0% to 47%. We looked at patients on long term Somatostatin analogue therapy (6 months) as it has been suggested that these patients may suffer from unrecognised PEI as these agents mimic the Somatostatin action which is inhibitory to pancreatic hormones.

Methods: 6 patients (4 male) on Somatostatin analogue treatment underwent a 13C Mixed Triglyceride Breath Test (13C-MTGBT). All patients received a standardized high-lipid [16 g of fat] test meal, which consisted of 100 g of toast with 17 g of butter and the recommended dose of 200 mg pure powder of the mixed triglyceride (1,3-diaseyl-2 octanoyl glycerol). The meal was ingested within 10 min with 200 mL water. We collected breath samples before ingestion of the test meal and every 15 min for a 6-h period. We determined the 13C/12C isotope ratio in the subject’s breath by using isotope-ratio-mass-spectrometry. Our results were expressed as delta values and expressed as % cumulative 13C – exhalation.

Results: It has been shown that cumulative 13C exhalation recovery over 6 h of 29% of dose administered is the best parameter for evaluation of 13C-MTGBT when compared to the gold standard secretin test. We found 2 patients (33%) with abnormal 13C-MTGBT with %cum 13C exhalation <29% GI symptoms were common among the group with 66% of patients reporting diarrhoea, 50% steatorrhea, 66% a frequent urgency to defecate, 50% reported bloating and 66% reported abdominal pain.

Conclusions: This limited study demonstrated the first experience of 13C-MTGBT. Further studies need to be undertaken to assess the usefulness of this indirect method of detection of PEI. Also the long period of breath sampling involved is a limitation in a routine clinical setting, studies looking at the possibility of shortening the study without compromising the sensitivity would be worthwhile.

68 Evaluating the effect of lubiprostone on small bowel transit time as measured by Smartpill® in a predominantly African-American population of patients with diabetes mellitus with constipation: A randomized, double-blind, placebo-controlled trial
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Introduction: Constipation is the most common GI symptom in patients with diabetes mellitus (DM). Many patients with chronic constipation have prolonged small bowel transit times (SBTT) and some diabetics have also been studied to have prolonged SBTT. Lubiprostone’s effect on SBTT in healthy patients as measured by video capsule endoscopy is unclear due to conflicting data. However, lubiprostone has recently been studied to improve colonic transit time as measured by Smartpill® in diabetics with constipation.

Methods: Diabetic patients with chronic idiopathic constipation (CIC) as defined by Rome III criteria were recruited from outpatient clinics at a tertiary care center and a Veterans Administration Hospital as part of a larger study. Demographics and baseline stool patterns were obtained. Baseline SBTT was evaluated utilizing the Smartpill® motility capsule. Patients were randomised in a double-blind fashion to 48 μg/day lubiprostone or placebo for 8 weeks. A follow-up Smartpill® was performed after 4 weeks of therapy.

Results: 76 patients (mean age 56.8 ± 8.9 years, 65.8% Females) were enrolled and 42 patients completed the Smartpill® portions of the study. There were no significant differences between the two groups’ demographics or baseline data. Following 4 weeks of therapy, neither patients in the lubiprostone group [5.13 ± 1.58 vs 6.08 ± 1.974 h, p = 0.47] nor the placebo group [5.85 ± 2.32 vs 4.9 ± 1.08 h, p = 0.34] experienced a significant change in SBTT from baseline. The change in SBTT from baseline in the treatment group was not significantly different than the change in SBTT from baseline in the placebo group [0.95 ± 2.68 vs –0.96 ± 2.01 h, p = 0.25]. There were no serious adverse events in either group.

Discussion: This study suggests lubiprostone has no significant effect on SBTT in patients with DM and CIC.

Discussion: Paper journaling of food and GI symptoms for a limited time period was feasible and usable for IBS patients. The majority perceived journaling as clinically useful. Journaling alone did not appear to affect GI symptoms, at least immediately post-logging. Findings from this study support the anecdote that food trigger(s) and associated GI symptom(s) vary for each individual.

69 Clinical predictors of small intestinal bacterial overgrowth (SIBO) by duodenal aspirate culture
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Background: Small intestinal bacterial overgrowth (SIBO) occurs when the relatively sterile small bowel contains >10^4 cfu/mL bacteria. Associations between SIBO and several gastrointestinal conditions have been reported, but there remains inconsistency with some risk factors (e.g. irritable bowel syndrome [IBS], proton pump inhibitors [PPI]). A study in 2005 did not find IBS associated with SIBO or PPI use. However, our institution’s microbiology reporting methods have since changed, now including non-enteric flora, and we speculated that risk factors for SIBO may have changed as well.

Aims: To estimate the proportion of patients (pts) with SIBO among pts who had duodenal aspirate and identify clinical predictors of a positive aspirate with new microbiologic reporting.

Methods: A retrospective chart review was done for pts who underwent a quantitative duodenal aspirate culture. 870 pts provided research authorization 1/1/2014–12/31/2014. Among these, 287 charts were randomly selected. Data on indication for testing, clinical diagnoses, symptoms, medications, and aspirate test results were collected from the medical record. Results were defined as (i) positive: bacteria >100 000 or aerobic gram negative bacteria >100 000, (ii) intermediate: aerobic gram negative bacteria >100 000 or anaerobic bacteria <100 000, or (iii) negative: no growth or only yeast >1000. The associations between aspirate results and diagnoses, symptoms, and medications were assessed using ordinal logistic regression (OR [95%CI]) adjusting for age and gender.

Results: 88 (13%) of 287 did not have aspirates performed leaving 249 subjects for the analysis. Mean age was 51.4 years (SD 16.7) and 166 (67%) were female. Underlying diagnoses included: IBS (12%), gastric surgery (6%), celiac sprue (11%), and diabetes mellitus (15%). The most common symptoms were bloating (88%), abdominal pain (81%). Overall, 97 (32%) had a positive result, 79 (32%) had an intermediate result, and 73 (29%) had a negative result. Variables associated with a positive result were: increasing age (p < 0.001, OR = 1.53 per 10 years [1.25–1.88]) and active PPI use (p = 0.016, OR = 2.52 [1.26–5.05]). Variables not significantly associated with a positive result included gender, IBS-status, or other GI diagnoses including gastric surgery. The only variable associated with intermediate growth was increasing age (p = 0.019, OR = 1.28 per 10 years [1.04–1.57]).

Conclusion: Greater than 1/3 of patients who underwent duodenal aspirate had findings consistent with a diagnosis of SIBO. Increasing age and active PPI use were
associated with a positive duodenal aspirate. This is the largest retrospective study to show an association between SIBO and PPI use as ascertained by duodenal aspirate.

70 The positivity to glucose breath test in patients with hysterecroyy, gastroscopy and cholecystectomy J. M. LEE, C. N. PARK, D. B. KIM, W. C. CHUNG and K-M. LEE Department of Internal Medicine, St. Vincent’s Hospital, The Catholic University of Korea, Seoul, Korea

Background/Aims: Small intestinal bacterial overgrowth (SIBO) could be associated with abdominal surgery. We investigated the prevalence of positive results and characteristics of glucose breath test (GBT) in patients who underwent abdominal surgery as gastroscopy, cholecystectomy, and hysterectomy.

Methods: 171 patients with surgery (50 hysterecroyy, 14 gastroscopy, 107 cholecystectomy), 665 patients diagnosed as functional gastrointestinal disease (FGID) and 30 controls, evaluated for SIBO undergoing GBT, were reviewed. After administration of substrate for GBT, the baseline H\textsubscript{2} or CH\textsubscript{4}, by >15 parts per million (ppm), or increase in H\textsubscript{2} or CH\textsubscript{4}, of <12 ppm above baseline level within 60 min were considered the positivitics to GBT for hydrogen (H\textsubscript{2}) [GBT (H\textsubscript{2})+] or methane (CH\textsubscript{4}) [GBT (CH\textsubscript{4})+].

Results: The GBT+ were significantly different among surgical patients (31.9%), FGID patients (31.9%), or controls (13.4%, \( p < 0.01 \)). Among patients, 65 (80.0%), 4 (2.5%), and 6 (3.5%) of surgical patients, and 150 (22.6%), 30 (4.5%), and 32 (4.8%) of FGID patients were in the GBT (H\textsubscript{2})+, (CH\textsubscript{4})+, and (mixed) groups, respectively (\( p < 0.01 \)). Gastroscopy group had a significant higher preference than hysterectomy group or cholecystectomy group in the GBT+ (71.4% vs 42.0%, or vs 41.1%) and GBT (H\textsubscript{2})+ (64.3% vs 32.0%, or vs 37.4%, \( p < 0.01 \)). During GBT, total H\textsubscript{2} were significantly higher in gastroscopy group, whereas total CH\textsubscript{4} were significantly lower in cholecystectomy group than those in other groups, respectively.

Conclusion: SIBO producing H\textsubscript{2} is common in abdominal surgical patients. The different pathogenesis for GBT+ might be possible according to types of abdominal surgery.

Brain Gut Axis in Health and Disease: Animal and Human Studies

71 Effect of oxidative stress and ageing on small intestine and colon A. ALMUHAMMADI and D. GRUNDY Department of Biomedical Science, University of Sheffield, UK

Background: Oxidative stress appears to be involved in many gastrointestinal diseases and may contribute to gut dysfunction in ageing. How diverse regions of the gut react to, and handle, elevated level of ROS is unclear. Here, we investigated the effect of oxidants on sensory signalling in the small intestine and colon of young (3-months) and aged (22-months) mice. We hypothesised that there would be regional differences between jejunum and colon in susceptible to stress and ageing.

Methods: Sensory nerve recordings were conducted in vitro from jejunum and colon of male C57BL/6J mice. Data are presented as mean ± SEM, \( n = 6 \). Statistical analysis was performed using t-test and ANOVA [two-way] as appropriate, \( p < 0.05 \). DNA and RNA were extracted from epithelial cells for molecular analysis, \( n = 3 \). RNA was used to determine differential gene expression in jejunum and colon of young and aged mice by microarray analysis. Oxidative DNA damage (8-OHdG) was used as a marker for oxidative stress.

Results: Ramp distension of the intestine evoked an activation of low (LT), wide dynamic range (WDR) and high threshold (HT) mechanosensitive afferent fibres. Baseline nerve activity remained unchanged in jejunum and colon between young and aged group. Nerve firing in response to distension was attenuated with age only in colon, especially in WDR & HT components between 30 and 60 mmH\textsubscript{2} (\( p = 0.05 \)). To examine the regional difference in response to oxidative stress, the mitochondrial inhibitor Antimycin A (20 \textmu M) was applied intracellularly to jejunum and colon. Response to oxidant was found only in colon of young and aged mice. Nerve firing in response to distension was enhanced by antimycin A (20 \textmu M), mainly WDR & HT. Likewise, baseline activity increased (14.43 ± 4.3 vs 23.08 ± 5.7 spike/s) \( p = 0.02 \). Higher levels of 8-OHdG were detected only in aged colon, \( p < 0.05 \). Microarray analysis of jejunum and aged epithelium showed higher expression of genes related to antioxidant mechanism (e.g. Fabp1, Apoa4) in the jejenum while genes implicated in the generation of oxidants (e.g. Nox1, Hoa) were more expressed in colon (≥20-fold). In aged colon, a marked reduction (≥−2.2) in the expression of Apa12a (involved in mitochondrial function) was detected.

Conclusion: Our data suggest that colon responds to oxidative stress less efficiently than the small intestine. Difference in response could be due to differential expression in genes involved in oxidants generation and antioxidiant mechanism. The ability of small intestine to handle stress seems to be conserved during ageing. In aged mice, the most marked effects of ageing were observed in the colon.

72 Effect of physical and psychological symptoms on the quality of life of patients with diarrhoea predominant irritable bowel syndrome T. BAI, J. CAO, J. XIA, Y. JIANG, L. WANG, J. SONG, W. QIAN and X. HOU Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubet, China

Objective: Improvement of symptoms and quality of life of the patients with diarrhoea predominant irritable bowel syndrome (D-IBS) is an important target in the treatment of disease. This study intended to clarify the relationship between different aspects of quality of life in patients with D-IBS, and to provide reference for individual management of D-IBS.

Methods: 100 patients with D-IBS diagnosed in the department of digestive medicine, Wuhan Union Hospital, were included in this study. Face to face survey of each patient was performed for data collection. Data includes: general data of patients, severity of patients’ symptoms, quality of life, SAS self rating scale. The quality of life was evaluated in eight dimensions: physiological function, physiological function, body pain, general health, vitality, social function, emotional function and mental health. The score of anxiety was negatively correlated with the vitality, mental health and overall health score. Depression score was negatively correlated with physical function, emotional function, social function and mental health score.

Conclusion: Anxiety and depression on D-IBS was independently associated with the quality of life of patients. After controlling for confounding factors, severity of somatic symptoms of D-IBS was negatively related with physical function, bodily pain, general health, social function, emotional function and mental health score. We can improve the physical symptoms and psychological symptoms of D-IBS patients from different aspects to improve the quality of life of patients.


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Background: Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are gastrointestinal disorders that are very prevalent in women of reproductive age. Both conditions are associated with an increased risk for adverse outcomes from pregnancy but the biological

severity of somatic symptoms was related to the quality of life, and the emotional and physiological functions were greatly affected. A multiple linear regression model showed that severe physical symptoms score was negatively related to physical function, physical pain, general health, social function, emotional function and mental health score. The score of anxiety was negatively correlated with the vitality, mental health and overall health score. Depression score was negatively correlated with physical function, emotional function, social function and mental health score.

Conclusion: Anxiety and depression on D-IBS was independently associated with the quality of life of patients. After controlling for confounding factors, severity of somatic symptoms of D-IBS was negatively related with physical function, bodily pain, general health, social function, emotional role and mental health. We can improve the physical symptoms and psychological symptoms of D-IBS patients from different aspects to improve the quality of life of patients.
basis of this risk is poorly understood. This study is based on the hypothesis that both non-pregnant women with IBS or with IBD who are in remission may share a common deficit in intestinal permeability leading to chronic low grade inflammation which may subsequently lead to complications during pregnancy. This hypothesis was assessed using lipopolysaccharide-binding protein (LBP) as a circulating marker of intestinal permeability.

Methods: This study was conducted on 29 non-pregnant healthy controls, 33 IBS subjects, and 16 IBD subjects in remission. Plasma levels of LBP were assayed using a commercially available immunoassay. Plasma levels of IL-8 were measured using an electrochemiluminescence-based assay. Tryptophan and kynurenine pathway metabolites were measured using HPLC.

Results: LBP was significantly elevated in IBD patients compared to controls (p < 0.05). This was associated with increased concentrations of TNF-α (p < 0.05) and altered tryptophan metabolism (p < 0.001). Although not significantly different from controls, IBS subjects displayed an intermediate physiological signature between healthy controls and IBD.

Conclusion: Women with IBD in remission and IBS share a graded biological scar indicative of increased gut permeability and an associated pro-inflammatory profile that impacts on tryptophan metabolism. This may have implications for the mechanism underpinning the pregnancy complications associated with both gastrointestinal disorders but it is currently unknown whether these biological features are further exacerbated during gestation. Future studies are thus required to understand how these biomarkers alter during pregnancy and the associated implications for fetal neurodevelopment.

Leukocyte interactions with cerebral endothelial cells and brain changes in dextran sulfate sodium (DSS)-induced colitis in mice

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Systemic inflammatory diseases, such as inflammatory bowel disease (IBD), are associated with the manifestation of centrally-mediated behavioral comorbidities such as anxiety, depression and fatigue. The communication pathways between the periphery and the central nervous system that are established in systemic inflammatory and lead to altered brain function are not well understood. We tested the hypothesis that altered immune signaling to the brain is associated with behavioral abnormalities in colitis. We used DSS-induced colitis in mice as a model of IBD. Colitis was induced in male C57BL/6 mice by the addition of 2.5% DSS to their drinking water from day 0 to 5, followed by tap water for 2 further days. Age-matched control mice drank only water. Studies were carried out on day 7, at the peak of colitis. We investigated behavioral changes using the elevated plus maze (EPM). We used immunohistochemistry and intravital microscopy to investigate microglial activation in the brain and leukocyte recruitment at the cerebral vasculature, respectively. Following DSS treatment, mice showed clinical and macroscopic signs of colitis. In the EPM, mice with colitis displayed anxiety-associated behaviors, spending a greater percentage of time in the closed arms (80.6 ± 2.5%) and less time in the open arms (64.4 ± 1.8%), compared to control mice (63.8 ± 2.2% and 20.5 ± 2.4%, respectively). Iba1 staining in the brain showed that microglia were activated in DSS-treated mice. There was an increase in leukocyte rolling (10.9 ± 4.0 cells/min/100 μm) and adhesion (2.6 ± 0.7 cells/100 μm) in cerebral venules of DSS mice, compared to controls (0.4 ± 0.4 cells/min/100 μm and 0.11 ± 0.11 cells/100 μm). These data suggest that at the peak of inflammation in DSS-induced colitis, there are behavioral changes in the mouse indicative of an anxiety-like phenotype. This is accompanied by microglial activation in the brain, and associated with increased immune cell interactions with the cerebral vasculature. Brain immune mechanisms are therefore a feature of this model of colitis and may contribute to the behavioral changes that we observe.

75 Gastrointestinal transit in the stress model Wistar Kyoto rat compared with the Sprague Dawley strain

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Background: The Wistar Kyoto (WKY) strain of rat is sensitive to stress and considered a model for anxiety and depression. Altered intestinal morphology suggests that gastrointestinal (GI) transit may be altered, as occurs in intestinal stress-associated functional disorders. To investigate whether strain differences exist, we compared the gastrointestinal transit of WKY and Sprague Dawley (SD) rats.

Methods: To determine whether transit of solid content is altered between different strains and in different regions along the GI-tract, transit of metallic beads [with 15% barium] was tracked over 12 h by high resolution X-ray imaging. Stomach emptying was monitored at 4 h and transit in the small and large intestine at 9 and 12 h, respectively. Procedures were carried out under brief isoflurane anesthesia. A rating scale was used to classify GIT bead location in vivo (p = 12).

Results: At 4 h, 77% of beads were retained in the stomach of WKY animals compared with only 35% retention for SD animals. At 9 h, small intestine transit was decreased by 36% in WKY compared with SDs, and at 12 h large intestine transit was decreased by 21% in WKY compared with SDs (p < 0.05). Interestingly, excluding those retained in the stomach at 9 h, transplanting beads had moved 89% further through the small intestine over 4–9 h for WKY compared with SDs (p = 0.05).

Conclusions: Our findings demonstrate impaired stomach emptying, yet rapid small intestine transit, in non-stress induced WKY rats compared with SD animals. This was unexpected and reveals that the slower GI transit in WKY can be largely attributed to delayed stomach emptying. These observations suggest that WKY rats may be also be considered an appropriate model for functional gastric disorders.

76 Transcutaneous cervical vagal nerve stimulation exerts an anti-TNF-a effect in healthy humans

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Introduction: The vagus nerve is the main neural substrate of the parasympathetic nervous system and has a pivotal role in modulating inflammation through the cholinergic anti-inflammatory pathway, via inhibition of the production of pro-inflammatory cytokines at the level of the spleen and the intestinal mucosa. Animal studies have demonstrated that in vagotomised mice, electrical vagal nerve stimulation (VNS), applied distal to the severson, ameliorates the pro-inflammatory cytokine response to lipopolysaccharide. The cervical vagus nerve is located directly under the skin, making it a suitable target for transcutaneous non-invasive VNS (n-VNS). In this pilot study, we sought to evaluate the effect of non-n-VNS on pro-inflammatory cytokines and cardiometrically derived autonomic parameters in humans.

Methods: In healthy volunteers, heart rate, blood pressure and validated sympathetic, cardiac sympathetic index and vagal, cardiac vagal tone (CVT), indices were measured directly before, and 24 h after, 2 min of n-VNS applied bilaterally. Venous blood was also drawn and assayed for pro-inflammatory cytokines (tumour necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6)) directly prior to, and 24 h after n-VNS.

Results: 20 healthy volunteers (13 females, median age 34 years, range 23–55) all tolerated the n-VNS. Table 1 details the changes in the recorded parameters. There was no change in heart rate or blood pressure. There was a negative correlation between change in CVT and change TNF-a (r = −0.45, p < 0.05).

Conclusions: These results, for the first time in humans, provide preliminary evidence for an anti-TNF in response to n-VNS, potentially mediated by an increase cardiac vagal tone. These data, warrant further investigation in immune mediated inflammatory disorders.
A high proportion of IBS patients also suffer from urological symptoms characteristic of interstitial cystitis. A mouse model (C57BL/6) of neonatal bacterial infection with enteropathogenic \textit{Escherichia coli} (EPEC) has demonstrated that neonatally infected mice exhibit bladder afferent sensitization and altered cystometry. 

In conclusion, our study brings new data on the mechanisms underlying these sex differences along the brain-gut axis. The anticipation and experience of visceral pain stimuli was assessed in a pain-related conditioning paradigm. The anticipation and experience of visceral pain stimuli was assessed in a pain-related conditioning paradigm. The anticipation and experience of visceral pain stimuli was assessed in a pain-related conditioning paradigm.
81 Contribution of conditioning to neural correlates of nocebo effects in visceral pain
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Background: The complex experience of pain is subject to dynamic modification by centrally-mediated psychological factors, impressively demonstrated by phenomena such as nocebo hyperalgesia. Despite indubitable clinical relevance, existing studies addressing neural mechanisms of nocebo effects have mainly induced negative expectations through verbal suggestions, while the role of classical conditioning is essentially unknown, especially in the field of visceral pain. The aim of this functional magnetic resonance imaging (fMRI) study was to investigate the contribution of conditioning to neural correlates of nocebo hyperalgesia in a visceral pain model.

Methods: Twenty healthy volunteers underwent classical conditioning, during which individually-calibrated rectal distensions of high intensity were repeatedly preceded by one visual cue (CSHigh), while a second visual cue (CSLow) was always followed by low intensity distensions. In a subsequent test phase, only distensions of low intensity were delivered, preceded by either CSHigh or CSLow. When preceded by CSHigh, low intensity distensions were hypothesized to evoke enhanced neural responses in regions of pain processing and modulation. Pain intensity ratings served as behavioral measures of nocebo hyperalgesia.

Results: During test phase, CSHigh evoked enhanced neural responses in fronto-limbic structures, caudate and thalamus. Increased distension-induced neural activation was observed in somatosensory cortex, prefrontal and thalamus. Increased distension-induced neural responses in fronto-limbic structures, caudate and thalamus showed increased sensitivity to the presence or absence of a nocebo cue.

Conclusion: Differential neural activation during distension processing suggests that classical conditioning amplifies pain-related activation in brain regions modulating cognitive, emotional and sensory dimensions of pain with remarkably similar responses during pain anticipation. Behavioral findings indicate a dissociation between central pain amplification and cognitive evaluation. Abnormalities in brain networks mediating cognitive and affective dimensions of pain could favor the development of associations between past events and painful episodes, which could play a role in the maintenance of chronic pain in patients with visceral pain syndromes.

82 Effects of a high FODMAP diet on visceral sensitivity: involvement of advanced glycation end products and colonic mast cells
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Introduction: In a clinical setting, a low-FODMAP diet can successfully reduce symptoms of IBS. However, the mechanism of action of this diet is poorly understood. We hypothesize that production of aldehydes such as methylglyoxal linked to the fermentation of certain FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) can directly or indirectly lead to an increase in IBS symptoms. Methylglyoxal is a glycating agent able to play a key role in the formation of Advanced Glycation End products (AGEs), which are pro-inflammatory. In addition, mast cells, and specifically their proximity to nerve endings in the colon, have been strongly implicated in IBS. We used lactose, a disaccharide member of FODMAPs, in an animal model to evaluate the effects of a chronic oral administration of lactose on both gut sensitivity and permeability. We also aimed to evaluate the involvement of AGEs and the mucosal mast cell population in the effects induced by this chronic lactose intervention.

Materials and methods: C57Bl/6 mice were treated daily with an oral gavage of saline or saline solution containing 5 mg of lactose and/or 5 mg of pyridoxamine (an inhibitor of glycation reactions) for 3 weeks. Then, visceral sensitivity was measured using electromyography and total intestinal permeability was assessed by measurement of free FITC in the blood after oral administration. Colonic samples were obtained and analyzed by immunohistochimistry (αAGEs and sMMCPI: (mouse mast cell protease 1)).

Results: Chronic lactose treatment led to visceral hypersensitivity and increase in intestinal paracellular permeability. Both of these effects were prevented by co-treatment with pyridoxamine. In addition, the treatment led to increased concentrations of AGEs and increased mast cell counts in colonic mucosa, which was prevented by co-treatment with pyridoxamine.

Conclusion: Chronic oral treatment with lactose leads to both an increase in visceral sensitivity and gut permeability in mice. These effects are mediated by production of glycating agents in the colon which are directly or indirectly involved in colonic mucosal hyperglycation. These findings support the hypothesis that glycating agents produced during fermentation of certain FODMAPs can be responsible for IBS symptom generation, and indicate an alternative understanding of the efficacy of the low-FODMAP diet for IBS patients.

Introduction: Preliminary evidence indicates that (i) IBS symptom severity is associated with a specific gut microbial signature (Tap et al., 2015) and (ii) microbial structure, measured by 16s ribosomal RNA methods has correlates within the brain in IBS (Laboro et al., 2015). We hypothesized that in IBS subjects, gut microbial signatures show correlations with structural and functional measures of brain sensorimotor and interoceptive regions, as well as with physiological and behavioral measures.

Methods: 16s ribosomal RNA gene sequencing was performed on stool samples collected from 65 adult IBS patients (46 F, 19 M) who also underwent structural and functional brain imaging studies and a thorough pathophysiological examination as part of a larger parent study (ClinicalTrials.gov NCT01252550). The properties of hypothesized brain regions in large-scale functional networks were quantified with local centrality measures indexing a region’s contribution to the network’s structural integrity and information flow. Tripartite network analysis was performed for integrative analysis. The nodes of the network were the bacterial genera comprising the IBS severity signature, psychophysiological data and the morphometry and functional network metrics characterizing insula, somatosensory cortex, basal ganglia, and thalamus. The edges (or links) between nodes were based on significant correlations (p < 0.05) between nodes.

Results: There were several significant interactions between the relative abundance of Bacteroides (Bacteroides, Parabacteroides, Alistipes) and Firmicutes associated genera (Clostridium sensu stricto, Clostridium XIVa, Clostridium XIVb, Oscillibacter, Clostridium XVIII) with psychological (oral transit times) and behavioral (self-reports of sensitivity, urgency, pain and discomfort during rectal distension, and pain rating during the lactulose challenge) measures, and the morphometry and functional connectivity (centrality) of insula and sensorimotor region. Key findings include: (i) increased abundance of Clostridium IV was associated with decreased surface area of the posterior insula and this reduction was associated with decreased oral transit times. (ii) Increased abundance of Clostridium XIVa and Clostridium XIVb were associated with increased pain reports during the lactulose challenge and this was associated with a reduced morphometry in a somatosensory region, the left central sulcus.

Conclusions: Several bacterial genera were associated with the morphometry and the connectedness (centrality) of insular-and somatomotor cortical regions, basal ganglia, and the thalamus, confirming earlier results obtained in a different sample. Furthermore, tripartite network analysis provides a whole brain perspective involving gut microbiota brain interactions in IBS pathophysiology.

83 The guanylate cyclase-C (GC-C) agonist linaclootide decreases colonic hypersensitivity following unpredictable early life stress in a rodent model
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84 Tripartite network analysis links symptoms to the gut microbe brain axis in irritable bowel syndrome
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30 ORAL PRESENTATIONS
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Background: Female patients diagnosed with irritable bowel syndrome (IBS) are 2–4 times more likely to report instances of early-life stress (ELS). Using an odors attachment learning (OAL) paradigm of ELS, we previously established a female-specific rat model of adult visceral hypersensitivity. The goal of this study was to investigate the effect of linaclootide, a GC-C agonist that relieves abdominal pain and constipation in patients with IBS-C, on colonic hypersensitivity in adult female rats following unpredictable neonatal ELS.

Methods: Neonatal female rat pups (n = 43) received 11 trials of conditioning on post-natal days (PN) 8–12. Unpredictable OAL pups received a 5 mA shock 2 min after odor presentation. Odor-only control pups received a 30-s odor presentation with no shock. Home-cage female control rats reared in the animal facility served as controls. From PN 84–90 rats received an oral dose of linaclootide (3 mg/kg/day) or vehicle. Two hours after the last dose of linaclootide, colonic sensitivity was assessed via a visceromotor response (VMR) to graded pressures (0, 20, 40, 60 mmHg) of isobaric colorectal distension (CRD). Changes in VMR to CRD were analyzed by two-way repeated measures analysis of variance followed by a Bonferroni post-test. p < 0.05 was considered statistically significant.

Results: Adult female rats exposed to unpredictable ELS (n = 15) exhibited colonic hypersensitivity in adulthood compared to odor-only (n = 15) or home-cage controls (n = 18). Linaclootide had no effect on colonic sensitivity in adult home-cage control rats. Similarly, linaclootide did not alter the VMR to CRD in adult rats previously exposed to odor only as neonates. In contrast, linaclootide significantly reduced colonic hypersensitivity CRD response to the level of CRD response seen in odor-only or home-cage controls.

Conclusions: We have shown that linaclootide significantly inhibits visceral hypersensitivity in adult female rats previously exposed to unpredictable early-life stress. This study highlights a pivotal role of GC-C mediated mechanisms in visceral pain processing and advances our understanding of the mechanisms of stress-induced visceral hypersensitivity. Research funding was provided by Ironwood Pharmaceuticals.

Distribution of monoamine oxidase in human colon and its alteration in 6-hydroxydopamine-induced Parkinson’s disease rats


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Background: Monoamine oxidase (MAO), a major metabolite enzyme of monoamine neurotransmitters, has two isoforms, MAO-A and MAO-B. They are widely distributed in the central nervous system and gastrointestinal tract (GIT), and play important roles in the monoamine breakdown and neural protection. Parkinson’s disease (PD), a neurodegenerative disease, always manifests GIT problems and monoamine system disorder. In our previous study, rats microinjected with 6-hydroxydopamine into bilateral substantia nigra (6-OHDA rats) exhibited constipation and enteric monoamine neurotransmitters alteration. However, it is not clear whether the two isoforms of MAO are distributed in the colon or any alteration of their expression in the 6-OHDA rats.

Methods: Immunofluorescence and western blot were used to investigate the distribution and expression of MAO. Fluorescent detection was delivered to measure MAO activity, and the content of monoamine neurotransmitters and their metabolite were evaluated through HPLC/MS.

Results: Both MAO-A and MAO-B were abundantly distributed in the colonic mucosa and muscular layer in both human and rat. It is worth emphasizing that MAO-B-immunoreactivities (IRs) were markedly observed in the enteric nervous system. It is not only co-localized with NF-IRs neurons (NF: neurofilament, a neuronal marker), but also GFAP-IRs glial cells (GFAP: glial fibrillary acidic protein, a glial cell marker). Further, in the colon of 6-OHDA rats, the MAO-B protein was increased (control: 0.62 ± 0.11, 6-OHDA: 0.99 ± 0.12, n = 6, p < 0.05) without alteration of the MAO-A, and colonic dopamine content was enhanced without change of serotonin (5-HT) and noradrenaline. However, the content of 5 HIAA (the metabolite of 5-HT) was significantly decreased (control: 301 ± 64 ng/g tissue, 6-OHDA: 114 ± 42 ng/g tissue, n = 6, p < 0.05), and the MAO activity manifested a decrease tendency (control: 3.10 ± 0.77 μM/g tissue, 6-OHDA: 1.14 ± 0.15 μM/g tissue, n = 5, p < 0.06).

Conclusions: MAO-A and MAO-B are abundantly distributed in the colon of human and rat. Besides the enteric neurons, MAO-B is also distributed in the enteric glial cells which play a key role in the development, function and protection of enteric neuron. The increased MAO-B expression and decreased MAO activity in 6-OHDA rats might be associated with the enteric monoamines disorder and GI dysfunction. Funded by the NSFC, 81170443 and 81370482.

86 Fecal biomarkers of gut inflammation and intestinal barrier dysfunction in Parkinson’s disease


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Background: Parkinson’s disease (PD) is characterized by alpha-synucleinopathy at all levels of the brain-gut axis including the enteric nervous system (ENS). Lesions in the ENS may be associated with gut inflammation, increased intestinal permeability and dysmotility contributing to the pathogenesis of PD and gastrointestinal manifestations.

Aims: To evaluate fecal calprotectin as a biomarker of gut inflammation and fecal zonulin as a biomarker of intestinal barrier dysfunction in patients with PD.

Methods: Ten consecutive patients with PD (mean age 65, 5 F, 5 M) and 10 healthy controls (mean age 58, 8 F, 2 M) participated in the study. The quantitative evaluation of calprotectin and zonulin in stool samples was performed by ready-to-use sandwich ELISA tests. Additionally, patients filled out a short questionnaire concerning gastrointestinal symptoms. The Kruskal–Wallis test was used for the comparison of differences between the groups.

Results: A mean duration of PD in the studied group was 8 years (range 3–20 years). None of the patients was diagnosed with inflammatory bowel disease. The PD patients reported constipation (40%), alternating bowel movement pattern (40%), or normal bowel habit (20%) and in addition, abdominal pain (20%) and distension (50%). The increased levels of calprotectin and zonulin in stool samples were found in 60% and 40% of the PD patients, respectively. Fecal calprotectin level was within the normal range in all the controls, while zonulin level was slightly elevated only in one out of 10 control subjects. The biomarker levels are presented as median and the lower quartile (25q) – upper quartile (75q). The fecal calprotectin level (μg/g) was significantly higher in PD patients than in the controls: 134.6 (89.1–145.5) vs 24.8 (18.0–27.9), p = 0.0025. The fecal zonulin level (ng/mL) was also higher in PD patients compared to the controls, but the p value did not reach statistical significance: 105.5 (63.5–166.0) vs 54.5 (44.0–73.0), p = 0.0588.

Conclusions: Gastrointestinal symptoms are frequently reported by PD patients. The signs of gut inflammation and increased intestinal permeability are present in a remarkable number of PD patients. This is the first study using stool ELISA tests which confirmed the gut immune system activation and changes in the intestinal epithelial barrier integrity observed in PD patients.

87 Modulation of visceral sensitivity by supernatants of Staphylococcus aureus

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Background: The gastrointestinal epithelium constitutes an important barrier to prevent bacterial infection from commensal microorganisms. Under pathological conditions, this barrier is weakened and bacteria, in particular pathogens, may interact with target cells residing in the mucosa. Immune cells are thought to recognize these intruders but recent findings suggest that sensory neurons play a direct role during the early recognition stage (Chiu et al., 2013). Here we test the hypothesis that soluble factors released from Staphylococcus aureus can directly interact with sensory neurones in mouse small intestine.

Methods: Sensory nerve activity was recorded ex vivo from distal intestinal segments of adult C57BL/6 mice. Supernatants from virulent JE2 Staphylococcus aureus (SSA) were prepared and bath-applied at up to 20% in Krebs buffer for 90 min during which the intestine was distended every 15 min (0–30 minHg). Baseline firing and distension-induced increase of baseline firing (fold change) were quantified. In vitro cytotoxicity assays using Trypan Blue were performed on primary dorsal root ganglia neurones (DRG), bone marrow-derived mast cells (BMMC) and HEK cells.

Results: Bath application of SSAs from overnight cultures caused an initial transient excitation of intestinal sensory nerves. Prolonged application resulted in a decrease of baseline firing from 49.06 ± 2.4 spikes/s to 1.92 ± 1.5 spikes/s (p = 0.004, N = 7). In addition, the distension-induced increase of nerve activity (>7 fold compared to baseline) was significantly reduced from 85.47 ± 17.46 spikes/s to 2.13 ± 1.5 spikes/s (p = 0.011, N = 7). In vitro experiments using primary DRGs, BMMC and HEK cells were conducted to measure cytotoxicity of SSA. Cell viability was compromised in all three cell types after 30 min incubation with SSA. Quantification of cell death indicated that
Classifying IBS from cortical thickness patterns

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Background: Our core network in the irritible bowel syndrome (IBS) brain is the salience network, responding to subjective salience of stimulus or the expectation of stimulus. In our study we use powerful machine learning classification methods to analyze cortical thickness in key nodes of this network.

Material and method: Two successive 3D T1-weighted MRI acquisitions from 15 IBS patients and 15 healthy controls (HC) were recorded on a GE Sigma 3.0T MR scanner and segmented with FreeSurfer. Mean cortical thickness values from 6 × 2 anatomical regions (left and right hemisphere) in the salience network were extracted and analyzed in R with a two-layer neural network classifier, predicting HC vs IBS. For training the network we used a hold-out method including 75% of the total sample with resampling and cross validation (10-fold, repeated 10 times). For the assessment of classification performance and possible generalization abilities, we repeated the hold-out method 50 times, each with random sampling of 46 observations used for training and with the remaining 14 observations (7 HC, 7 IBS) used for testing.

Results: The 50 hold-out experiments gave the following results: mean classification accuracy 0.687 (SD 0.125), mean sensitivity 0.643 (SD 0.178), mean specificity 0.716 (SD 0.118). Very similar performance measures were confirmed using a Random Forest classifier.

Discussion/conclusion: Patients with IBS seems to have structural brain signatures differing from healthy controls in terms of cortical thickness patterns within the salience network. The finding of such patterns, making it possible to discriminate between the IBS brain and the HC brain with a sensitivity/specificity of about 64% / 75% is highly interesting, both diagnostically and mechanistically. In our following up we will use both diffusion tensor MRI data and resting state fMRI recordings to further explore characteristics of the structural and functional connectivity within the salience network of these IBS patients, and also increase our sample size.
projecting motoneurons were observed in the caudal and rostral parts of the DMV, and neurons with D1- and CHAT-immunoreactivity (IR) were widely colocalized in the DMV. Many TH-IR fibers were observed around the D1- and D2-IR neurons. Moreover, decreased D2 and enhanced D3 expression in the DMV was observed in 6-hydroxydopamine (6-OHDA) rats that were treated with a bilateral microinjection of 6-OHDA in the SN.

**Conclusions:** The results indicate that dopamine receptors are involved in the functional modulation of DMV neurons innervating the gastric muscular externa, while altered expression of dopamine receptors in the DMV may contribute to the gastroparesis observed in PD.

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**Microbial translocation in IBS: relevance of sex, stress, and IBS subtype**

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Irritable bowel syndrome (IBS), a common disorder of the gastrointestinal tract, is multifactorial in etiology and a challenge to effectively treat. IBS is often comorbid with psychological and other pain-related disorders, and is more prevalent in the female sex. Symptomatology in IBS has been attributed, in part, to intestinal barrier dysfunction and a dysregulated stress response system. The purpose of this investigation was to explore patterns and associations of microbial translocation in patients with IBS. Ninety-one participants (age 27.9± 7.78 years, 45 males) were included. Participants with IBS were diag- 

**Biomarkers for visceral hypersensitivity in patients with irritable bowel syndrome**

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**Background:** Up to 60% of patients with Irritable Bowel Syndrome (IBS) have increased visceral perception. Intestinal inflammation, neuroendocrine activity and intraluminal metabolic processes may contribute to the development of visceral hypersensitivity. Previously, we found that markers that are indicative for these biological processes are altered in IBS patients compared to healthy controls. We hypothesize that normo- and hypersensitive IBS patients significantly differ in biomarker levels.

**Aim:** To get more insight in biological processes associated with altered visceral perception, several faecal and plasma markers were measured in normosensitive (IBS-NORM) and hypersensitive IBS patients (IBS-HYP).

**Methods:** IBS patients underwent a rectal barostat to assess visceral perception to pain and based on the outcome were classified as IBS-NORM or IBS-HYP. Callo- 

**Results:** Food cues are generally believed to be dopaminergic in nature, but evidence supporting this hypothesis in humans is limited and inconsistent.

**Aim:** To assess in vivo dopamine (DA) release in both striatal and extra-striatal brain regions in response to food cues and establish whether DA release is associated with gut peptide levels (motilin, ghrelin) and hedonic food intake.

**Methods:** Twelve healthy females (BMI = 22.1 ± 2.0 kg/m²) underwent a dynamic Pos- 

**Results:** Food cues (high-calorie images) were shown after intravenous administration of 183.3 ± 7.0 MBq of the highly selec- 

**Conclusion:** Food cues induce significant DA release in extra-striatal regions of the reward system (orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and insula (all p < 0.02) and increased motilin (p = 0.03) but not ghrelin levels (p = 0.24). Moreover, food-induced DA release in OFC subregions, right insula and bilateral ACC predicted the amount of consumed milkshake (all R² > 0.30, p < 0.02). DA-release in OFC subregions was also positively associated with ghrelin and inversely associated with motilin levels during presentation of food cues (all R² > 0.15, p < 0.088). Finally, motilin (R² = 0.30, p = 0.002) but not ghrelin levels (R² = 0.37, p = 0.08) predicted the amount of consumed milkshake.
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Anorectal manometry characteristics of constipated fibromyalgia patients in relationship to self-reported abdominal symptom severity

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Background: Altered bowel habits, rectal hypersensitiv-
ity (RH), pelvic floor dysfunction (PFD), and abdominal
discomfort symptoms are frequently reported in
fibromyalgia (FM). Limited information exists to func-
tional anorectal features assessed by anorectal manom-
etry (ARM) in constipated FM pts relative to abdominal
symptom severity.

Objective: Determine if constipat ed FM pts with mod-
erate to severe (M-S) abdominal discomfort are more
likely to have RH and PFD compared to constipated FM
pts with absent to mild (A-M) abdominal discomfort.

Methods: Retrospective analysis of FM pts (<18 yoa)
referred for ARM and Balloon Expulsion Testing (BET)
in January 2010 to February 2016. Data included (age,
gender, race, and BMI), anal sphincter pressures, rectal
sensation, anal sphincter response during defecation,
and BET results. Abdominal symptoms were assessed by
the abdominal domain score (ADS) on the Personal
Assessment of Constipation Symptom questionnaire
(PAC-SYM): pain, bloating, cramping, and discomfort.
Pts dichotomized by ADS into a score ≤8 (A-M abdom-
inal symptoms) vs pts with a score >8 (A-M abdominal
symptoms). RH defined by a Threshold Volume (TV) of
≤58 and an Urge Volume ≤90. Failure of anal sphincter
relaxation during simulated defecation was considered
abnormal. Abnormal BET defined as the inability to pass
a 50 mL water balloon in <60 s. Statistical analysis was
performed using linear regression, chi-squared test and
independent t-tests. P-values <0.05 were considered
statistically significant.

Results: 196 constipated FM pts referred for ARM
and BET were analyzed (mean age 52.0 years, 95% female,
85% Caucasian, mean BMI 29.4). Majority (135 pts,
69%) of FM pts had a higher mean PAC-SYM ADS: 11.6
vs 4.5, p = 0.001. Younger age was associated with
higher mean internal anal sphincter pressure 80.45
vs 79.35 mmHg. Hypotensive BET were associated with
greater abdominal symptom severity in FM pts (mean
scores of pts ≤60 yoa vs pts >60 yoa: 9.9 vs 8, p = 0.006).
The proportion of RH was similar in constipated FM pts
with greater and lower ADS (TV = 34.3 vs 27.9%,
Urg = 58.5% vs 36.1%). FM pts with a greater ADS
were more likely than those with a lower ADS to have
an abnormal BET (44.4% vs 25.0%, p = 0.01) and elicited
higher mean internal anal sphincter pressure (65.5 mmHg
vs 54.3 mmHg, p = 0.04).

Conclusion: Constipated FM pts with higher PAC-SYM
ADS elicited no differences in ARM characteristics and
RH. Higher prevalence of an abnormal BET for consti-
pat ed FM pts with moderate to very severe abdominal
symptoms may have resulted from underlying structural
abnormality. Further investigation to understand defec-
atory disorders in constipated pts with FM are
warranted.

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HRAM highlights the prevalence of defecatory
dys synergy

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Introduction: Defecatory Disorders are a common
problem in the community, the advent of HRAM not
only allows for measurement of anorectal sphincter
function but also allows for a better understanding of the
dynamic processes of defecation. Biofeedback has been
identified as an appropriate treatment in those who
suffer from defecatory disorders, HRAM may allow for
better selection of patients for this intervention.

Methods: We retrospectively reviewed HRAM tracings
of 29 consecutive patients attending our C1 Function
Laboratory between October 2015 and January 2016.
Patterns of simulated defecation were analysed and
classified as per Rao classification of dysynergic defec-
tory.

Results: Faecal Incontinence 23 of the 29 (79.4%)
patients had symptoms of Faecal Incontinence (FI)
79.3%. Mean ano-rectal resting pressure
75.7 ± 27.47 mmHg. 17% of FI patients were reported
with hypotensive resting pressure. Mean ano-rectal
squeeze pressure 131.84 ± 46.6 mmHg. Hypotensive
Squeeze was reported in 46% of those with FI. HRAM
pressure topography plots of simulated defecation were
reviewed and were assigned a Rao classification.
C ons tipation: 6 of 29 (20.6%) patients presented
with constipation (66% female). Mean ano-rectal
resting pressure 80.45 ± 17.18 mmHg. All patients with
constipation were reported to have no ano-rectal rest-
ing pressure. Mean ano-rectal squeeze pressure
173.3 ± 55.65 mmHg.

Conclusion: 89.6% of patients presenting with faecal
incontinence show evidence dysynergic defecation.
100% patients presenting with constipation show evi-
dence of dysynergic defecation. Disordered defecation
is a common finding among patients presenting with
either Faecal Incontinence or Constipation. These
patients may benefit from embarking on a biofeedback
programme.

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Abdominal radiographs – appropriately used in the
management of functional constipation in children?

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Abdominal radiographs (KUB) are frequently used to
assess stool burden when managing pediatric constipa-
tion, despite evidence that the radiographic findings
donot correlate with clinical symptoms or severity of
fetal retention and despite recent guidelines which
recommend obtaining KUBs only in children in whom
fetal impaction is suspected but in whom physical
examination is unreliable or not possible.

Aim: This study aims to discern the reasons for
obtaining KUBs and how they are used in the diagnosis
and management of pediatric constipation.

Method: 25 Pediatric Gastroenterologists and Nurses
were surveyed on a total of 71 patients who were seen
for known or suspected functional constipation and the
evaluation of which included obtaining a KUB. Physi-
cians were given a questionnaire after the visit and
asked about their plans of management before and after
viewing the KUB. Multiple answers were permitted for each
question. Plan of management before and after viewing KUB:
69% of physicians had a treatment plan in mind before
obtaining KUB including clean out at home [99%] or
implementing [2.8%], adding an osmotic [12.7%] or stim-
ulant laxative [11.3%], demonstrating stool burden to the
families [11.3%], no changes [8.5%], increasing osmotic
[5.6%] or stimulant laxative [1.4%], or decreasing

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Serum mucosal cytokine profiles do not discriminate between health and IBS, but increased levels of pro-inflammatory cytokines correlate with longer oral transit time and reduced psychological well-being.

Methods: Serum from 144 IBS patients and 42 healthy controls was analyzed for mRNA expression. Multivariate discrimination analysis evaluated global sigmoid colon biopsies were analyzed for mRNA levels of IFN-γ, IL-10, IL-8, IL-6, TNF, IL-12, IFN-β, and TNF by MSD ORAL PRESENTATIONS 35

Results: FOXP3 (2.5 × 10⁻⁴ [1.8 × 10⁻⁴ to 3.5 × 10⁻⁴]), 3.1 × 10⁻⁴ [2.2 × 10⁻⁴ to 3.7 × 10⁻⁴] p = 0.07 tended to be decreased in IBS patients. Within both the full study cohort and IBS patients alone, serum level of IL-12p70 was positively associated with looser stool pattern while subjects with more wide-spread somatic symptoms had increased serum levels of IL-6 (p = 0.2, p = 0.01), IL-8 (p = 0.18, p = 0.01) and TNF (p = 0.15, p = 0.04). While neither IBS bowel habit subgroups nor patients with IBS symptoms with sudden onset following possible gastroenteritis were associated with distinct cytokine profiles, a small cluster of clinically similar IBS patients with comparatively elevated immune markers was identified.

Conclusion: Global cytokine profiles did not discriminate IBS patients from healthy subjects but a higher variability in cytokine profiles was found in IBS patients. Positive association of inflammatory cytokines with some clinical symptoms suggests that immune activation may be of importance in a subset of IBS patients.

Background: The most common gastrointestinal [GI] symptom in patients with diabetes mellitus [DM] is constipation. Studies have shown a direct relationship between constipation symptoms and delayed colonic transit as well as impaired colonic contractions. However, there is little data evaluating the correlation between the severity of subjective constipation and objective evidence of colonic dysfunction.

Methods: Retrospective analysis of patients with DM and Rome III criteria defined chronic idiopathic constipation with controlled and uncontrolled diabetes as well as the gastrointestinal, small bowel, and whole gut transit time for each of these groups. There is no statistically significant difference in GI transit times between patients with controlled vs uncontrolled diabetes (p > 0.05). However, there is a trend toward longer transit times in those with lower AIc: mean gastric transit (4.6 vs 7.8 h, p = 0.14) and mean whole gut transit [6.4 vs 5.7 h, p = 0.17] in those with controlled vs uncontrolled diabetes, respectively.

Discussion: This study did not find a statistically significant relationship between AIC and gastric, small bowel, colonic, or whole gut transit. It is possible that daily glycemic control is more likely to affect GI transit. Additionally, given that AIc reflects the average blood sugar over the prior 3 months, a normal AIc may not reflect previous neurological damage from uncontrolled diabetes.

The role of H2 Test in irritable bowel syndrome.
Analysis of 316 patients
N. S. CARVALHO and P. J. P. C. CARVALHO

Introduction: Patients with bowel habit alterations, abdominal distension and pain are frequently diagnosed with irritable bowel syndrome. These symptoms are common in patients with bacterial overgrowth and carbohydrate intolerance.

Objective: The objective of this study is to evaluate the prevalence of such alterations in patients diagnosed with IBS according to the Roma III protocol, who did not show any improvements through clinical treatment.

Method: In period between 09/01/2014 and 09/01/2015, out of the 316 patients from the Núcleo de Fisiologia Gastrointestinal do Hospital Israelita Albert Einstein, 176 were females and 140 males of an age average of 38.9 were included in the study. All patients underwent to...
Medicine, Seoul, Korea and Research Institute, Ewha Womans University School of Medicine, Seoul, Korea. *Department of Internal Medicine, Ewha Medical Research Institute, Ewha Womans University School of Medicine, Seoul, Korea. J. Y. CHOI, T.-J. SONG, T.-J. KIM, C. M. MOON, S.-E. KIM, K.-N. SHIM and S.-I. JUNG.**

Background: The prevalence of constipation in patients with stroke is comparatively high, and constipation at acute phase might relate with a poor short-term outcome. However, limited studies have been available to show the association of constipation and long-term stroke outcome. This study was aimed to access the incidence of constipation after first stroke and its impact on long-term outcome.

Methods: This study was conducted in prospective stroke cohort of 840 patients admitted with stroke unit between 2012 and 2014. The patients who had a previous history of stroke or transient ischemic attack (n = 648) and first vascular stroke (n = 73) were excluded. We compared the prevalence of constipation in 120 patients with stroke with 453 controls who had past history of stroke or transient ischemic attack (n = 43%). The prevalence of constipation was significantly higher than that in hypertensive controls (47.1 vs 23.4%, p = 0.001). The crude incidence of new-onset constipation after first stroke was 24.5% at 1 year post-stroke. The frequent constipation symptoms were hard stool (100%) and, abdominal discomfort, pain and healthy subjects (HS). Constipation symptoms were also common among patients with ischemic stroke. New onset constipation after first stroke does not seem to be significantly related with poor neurological outcome, but has a negative impact on the patient's QOL.

Results: The test for H2 exhalation in the air was positive in 116 patients (43%), out of whom 42 were positive for bacterial overgrowth (36%), 64 were positive for lactose intolerance (40%) and 30 were positive for fructose intolerance (7%).

Conclusion: The results confirm the high prevalence of bacterial overgrowth and carbohydrate intolerance in patients with refractory symptoms to the clinical treatment of IBS.

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Colonic motor dysfunction in laxative-refractory slow transit constipation is associated with neural dysfunction and infiltration of Iba1-positive(+) cells in the submucosal plexus (SMP) C. CIRILLO, M. CORSETTI†, T. VANUYTSEL*, I. DEMEDTS*, A. S. DESMET*, L. VANCLEEF†, T. THIJN*, A. D’HOORE†, I. DEPOORTERE*, P. VANDEN BERGHE* and J TACK†

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The pathogenesis of chronic constipation is still unknown but alterations of the neuromuscular structures controlling colonic motility have been implicated. As integrated analyses are lacking, our aim was to study in patients with laxative-refractory slow transit constipation: (i) colonic motility, using high resolution manometry (HRM), and (ii) enteric nerve function, using live imaging in the SMP.

Methods: Consecutive patients with laxative-refractory slow transit constipation (S100+), 24 refractory slow-transit constipation patients (43 ± 13 years) were studied. Pan-colonic pressures were recorded for 3 h before and 2 h after a meal, and for 1 h after intra-colonic bisacodyl (10 mg). Abdominal discomfort, abdominal gas, desire to evacuate gas, desire to defecate and urgency to defecate were evaluated by means of 100 mm visual analogue scale (VAS) every 15 min. Number of pan-colonic pressures (PCPs), LAPS, (De Schryver 2002) and high-amplitude propagating sequences (HAPSS, De Schryver 2002) were evaluated. A normal response to bisacodyl was identified by the occurrence of at least one high-amplitude propagating sequence (HAPSS, De Schryver 2002). SMP was isolated and calcium (Ca2+) imaging used to examine the response to high-K+ or ATP, activating respectively neurons and glial cells (Cirillo 2012). Post-hoc immunohistochemistry was performed to identify neurons (HuCD) and glial cells (S100(+)10). Data (mean ± SD) were compared to those obtained in 10 healthy subjects (HS, 30 ± 11 years, 5 females).

Results: 11 women with refractory slow-transit constipation (43 ± 13 years) were studied. Pan-colonic pressures and retrograde sequences significantly increased after a meal in HS (p = 0.01) but not in patients. Bisacodyl response was absent in 3 patients and abnormal (repetitive ducal or pan-colonic pressures and atypical HAPSSs) in 3 others. Ca2+ responses (AF5/Fs to high-K+ were decreased in SMP neurons of patients (right colon: 0.62 ± 0.53, left colon: 0.73 ± 0.51) as compared to HS (right colon: 1.32 ± 0.18, left colon: 1.25 ± 0.08, all p < 0.01) and to those without pain (p < 0.01). The response to bisacodyl was normal in all patients with pain and in 2/8 (25%) of those without pain (p = 0.01, Fisher's test). VAS scores for discomfort differed significantly between patients with pain as compared to both patients without pain and healthy subjects (p < 0.003). HRM in adults, aim was to evaluate the sensations and colonic motor response to a meal and to bisacodyl in patients with laxatives-refractory slow transit constipation with or without pain M. CORSETTI*, A. THYS†, T. VANUYTSEL*, I. DEMEDTS*, E. DELOOSE*, A. WOLTHUIS*, A. D’HOORE† and J TACK†

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In clinical practice colon manometry is recommended to exclude colonic inertia (no response to meal and to drug, i.e. bisacodyl) in patients with laxatives-refractory slow transit constipation (Bharucha 2013). As to date, this technique is not widespread. The aim was to study the prevalence of colonic motor dysfunction, associated with structural and functional alterations and infiltration of Iba1(+) cells in the SMP.

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Sensations and colonic motor responses to a meal and to bisacodyl evaluated during high-resolution manometry (HRM) differs between laxatives-refractory slow transit constipation with or without pain M. CORSETTI, A. THYS†, T. VANUYTSEL*, I. DEMEDTS*, E. DELOOSE*, A. WOLTHUIS*, A. D’HOORE† and J TACK†

"TARGID, KU Leuven, Belgium and 1Department of Abdominal Surgery, KU Leuven, Belgium.

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Methods: Consecutive patients with laxative-refractory slow transit constipation (S100+), 24 refractory slow-transit constipation patients (43 ± 13 years) were studied. Pan-colonic pressures were recorded for 3 h before and 2 h after a meal, and for 1 h after intra-colonic bisacodyl (10 mg). Abdominal discomfort, abdominal gas, desire to evacuate gas, desire to defecate and urgency to defecate were evaluated by means of 100 mm visual analogue scale (VAS) every 15 min. Number of pan-colonic pressures (PCPs), LAPSs (De Schryver 2002) and high-amplitude propagating sequences (HAPSSs, De Schryver 2002) were evaluated. A normal response to bisacodyl was identified by the occurrence of at least one high-amplitude propagating sequence (HAPSS, De Schryver 2002). SMP was isolated and calcium (Ca2+) imaging used to examine the response to high-K+ or ATP, activating respectively neurons and glial cells (Cirillo 2012). Post-hoc immunohistochemistry was performed to identify neurons (HuCD) and glial cells (S100(+)10). Data (mean ± SD) were compared to those obtained in 10 healthy subjects (HS, 30 ± 11 years, 5 females).

Results: 24 refractory slow transit constipation patients (43 ± 13 years, 22 females) were studied, 15 of these also referred pain or discomfort. The number of PCPs was significantly lower in patients without pain as compared to HS (respectively, 19 ± 21 vs 49 ± 40, p = 0.01), while it did not differ in patients with pain (60 ± 41). The number of LAPs did not differ in patients with pain (88 ± 46), but was significantly lower in patients without pain as compared to HS (6 ± 10 vs 52 ± 39, p < 0.001). PCPs significantly increased after a meal in HS and in patients with (p = 0.01) but not in those without pain (p = 0.20). Retrograde LAPs increased significantly after the meal in HS (p < 0.01) but not in the two groups of patients (all p > 0.25). The response to bisacodyl was normal in all patients with pain and in 2/8 (25%) of those without pain (p = 0.01, Fisher's test). VAS scores for discomfort differed significantly between patients with pain as compared to both patients without pain and healthy subjects (p < 0.003). HRM in adults, aim was to evaluate the sensations and colonic motor response to a meal and to bisacodyl in patients with laxatives-refractory slow transit constipation with or without pain M. CORSETTI*, A. THYS†, T. VANUYTSEL*, I. DEMEDTS*, E. DELOOSE*, A. WOLTHUIS*, A. D’HOORE† and J TACK†

"TARGID, KU Leuven, Belgium and 1Department of Abdominal Surgery, KU Leuven, Belgium.

In clinical practice colon manometry is recommended to exclude colonic inertia (no response to meal and to drug, i.e. bisacodyl) in patients with laxatives-refractory slow transit constipation (Bharucha 2013). As to date, this technique is not widespread.
The antagonist profile of ibodutant at the tachykininNK2 receptor in the human colon. Functional studies were performed using fresh human colonic muscle strips mounted along the circular muscle orientation in organ baths. Contractile responses to NKA and the selective NK2 receptor agonist Lys5, MeLeu4, Nle7-[NKA(4-10)] were recorded in the presence of ibodutant (0.01, 0.1 and 1 µM) to determine its antagonist properties.

Results: The NK2 receptor immunoreactivity is strongly expressed across all muscle layers, as well as blood vessels. Negligible NK2 immunoreactive staining was seen on myenteric and submucosal ganglia. There were no obvious differences in cellular distributions between genders. Ibodutant showed a property of competitive antagonism and caused a rightward shift of agonist concentration curves. Interestingly, ibodutant displayed a significantly higher degree of antagonism against NKA in females, pKB = 8.38 (95% CI: 7.75–10.35, n = 9), than in males, pKB = 7.80 (7.26–9.45, n = 8, p < 0.05). However, the gender discrepancy for ibodutant did not exist when against Lys5, MeLeu4, Nle7-[NKA(4-10)]. pKB = 7.76 (7.41–8.41, n = 9) for females and pKB = 7.80 (7.36–8.73, n = 7) for males.

Conclusion: The antagonistic ability of ibodutant appeared agonist-dependent in females, indicating that the NK2 receptor is of ligand bias property, which involves ligand-dependent conformations. This may underlie the gender-related effectiveness of ibodutant in the treatment of IBS.


**109 Factors that predict outcomes to prucalopride**

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**Introduction:** Chronic idiopathic constipation (CIC) is a prevalent disorder with traditional management focussing on lifestyle measures and laxatives. Prucalopride, a selective 5-HT3 receptor agonist, has efficacy in treatment of CIC. However, factors that predict clinical response are incompletely understood.

**Aims:** To identification of baseline factors, either physiological or psychological, that may predict positive clinical outcomes in patients taking prucalopride for CIC in a secondary care clinic.

**Methods:** A single centre, prospective open label trial was undertaken in consecutive patients with CIC, defined as less than 2 spontaneous complete bowel movements (SCBM) per week, who were commenced on prucalopride from November 2011-October 2015. Validated questionnaires were used to assess the severity of symptoms (patient assessment of constipation symptoms (PAC-SYM)), somatic symptoms (patient health questionnaire-12 (PHQ-12-SYM)), anxiety/ depression and the personality traits of neuroticism and extraversion (big five inventory-neuroticism or extraversion scale (BFI-N and BFI-E)). Patients were excluded if they did not wish to complete the questionnaires. Other investigations, such as colonic transit studies (CTS), were undertaken as clinically appropriate. At follow up, clinical response was defined as the proportion of patients achieving 3 or more SCBM per week.

**Results:** 70 patients (68 female, mean age 48 years, range 18–83) had a mean SCBM per week of 1.7 (range 0.5–2). At mean follow up of 5.1 weeks (range 4–8) 32/70 (45.7%) patients achieved clinical response. 9/70 (12.8%) did not tolerate treatment due to side effects. In an intention to treat analysis, SCBM per week increased from 1.7 to 3.2 (p = 0.01) with PAC-SYM scores reducing from 27.5 to 19 (p < 0.001). Logistic regression analysis demonstrated that PHQ-12-SYM, anxiety and neuroticism were independently associated with clinical response (odds ratio 1.1–1.3, p = 0.005) and BFI-N [odds ratio 1.8, 95% confidence interval 1.2–3.2, p = 0.01] were associated with clinical response.

**Conclusions:** These data suggest that the clinical efficacy of prucalopride could be enhanced by targeting patients who are more neurotic and higher somatic symptoms. The personality trait of neuroticism has been associated with differential expression of the serotonin transporter which could explain this association. Nevertheless, the underlying mechanisms for this association and warrant further investigation.

**Falal Incontinence: are structural and functional studies of the anorectum indicative of symptomatic pathology?**

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**Introduction:** Faecal incontinence can result from an array of complex, multifactorial pathological processes. Disruption to the normal structure and function of the anal sphincter mechanism would be expected to cause dysfunction, yet there are many patients with sphincter injuries who maintain continence. Conversely, there are incontinent patients who are found to have an intact sphincter and preserved anorectal function. This study intended to explore the associations between structure, function, and symptom severity using anorectal laboratory measures and symptom scores collected routinely in the investigation of faecal incontinence.

**Methods:** All adult patients who presented to the Flinders Medical Centre anorectal laboratory for investigation of faecal incontinence between January 1998 and December 2015 were collated for the analysis. Investigation included endoanul ultrasound, anorectal manometry, rectal sensation, rectorhinal inhibitory reflex, pudendal nerve latency, and completed a Wexner symptom score for incontinence. Patients with a previ-ous history of trauma, anorectal or perineal surgery, anorectal pathology, or radiotherapy to the pelvis and anorectum were excluded (n = 256). Multivariate analyses were undertaken to explore correlations between structure, function, and symptom severity.

**Results:** 853 patients were included in the analysis. 45.9% of the cohort had an intact anal sphincter on sonography. Of those with an intact sphincter, 59.9% had normal resting pressures, 31.5% had normal squeeze pressures, 58.1% had normal pudendal nerve latencies, and 72.0% had normal rectal sensation. The Wexner score correlated poorly with laboratory measures generally; there was a weak correlation only between maximal squeeze pressure (Pearson’s r = 0.181, p = 0.001) and a Wexner score >9. In patients with both an intact sphincter and normal manometric measures, 14.3% reported Wexner scores >9.

**Conclusions:** Subjective symptom severity scores, including the Wexner score, are widely used in studies to assess usefulness of any treatment arm. On the basis of symptoms alone, anatomical and physiological
Conclusions: 

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Background & aims: We have recently found that conscious and unconscious contractions of the puborectal muscle are required for fecal continence and that unconscious contraction is mediated by the puborectal continence reflex. In this study we aimed to investigate whether the puborectal continence reflex is regulated by the same nerve pathway as conscious contraction of the puborectal muscle. Furthermore, we aimed to find whether conscious and unconscious contractions of the puborectal muscle are influenced by each other, by age and by gender.

Methods: We included all adult patients who underwent anorectal function tests between 2010 and 2014 at the UMCG (n = 283). In total, 189 patients were excluded, because of possible generalized nerve damage or operations in the pelvic region, after which 94 patients remained. The patients underwent the anorectal sensitivity test, to measure anal electrosensitivity, the anorectal pressure test, to measure conscious contraction and the balloon retention test, to measure unconscious contraction.

Results: We found no correlation between unconscious contraction and anal electrosensitivity (p = 0.811). In contrast, we found a correlation between conscious contraction and anal electrosensitivity (p = 0.012). Furthermore, there was no correlation between conscious and unconscious contraction (p = 0.634). Age had no influence on unconscious, nor on conscious contraction of the puborectal muscle (p = 0.080 and p = 0.344, respectively). Gender had no influence on unconscious contraction (p = 0.673). However, gender did have a significant influence on conscious contraction (p = 0.001), since men had a significantly stronger conscious contraction.

Conclusions: We conclude that the nerve pathway responsible for the puborectal continence reflex is different than the one responsible for conscious contraction of the puborectal muscle. In addition, conscious and unconscious contractions work independently of each other. The puborectal continence reflex and conscious contraction of the puborectal muscle seem to support fecal continence during aging.

The puborectal continence reflex: the solid stool continence reflex

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Background: Fecal continence is maintained by voluntary contraction of the anal sphincter and puborectal muscle. Recently, we showed that the anal-external sphincter continence reflex also regulates fecal continence. Current knowledge does not explain why some patients with severe sphincter defects are nevertheless continent, nor do we know what mechanisms underlie liquid and solid stool continence. We aimed to investigate the presence of additional mechanisms that control fecal continence.

Methods: The anorectal pressure test, to measure conscious contraction, balloon retention test, to measure unconscious contraction for solid stool and rectal infusion test, to measure unconscious contraction for liquid stool were performed in 23 healthy subjects. We measured the time and strength of voluntary and involuntary contractions of the puborectal muscle generated to maintain fecal continence.

Results: The strength of maximal voluntary contraction of the puborectal muscle was significantly weaker and the duration of contraction was shorter than maximal involuntary contraction of the puborectal muscle (70 mmHg vs 150 mmHg, p < 0.001 and 1.5 vs 5.8 min, p < 0.001). The mean pressure of involuntary puborectal muscle contraction during solid stool was significantly higher than during liquid stool measurement (75 mmHg vs 30 mmHg, p = 0.001).

Conclusions: We found an additional regulatory mechanism - we call it the puborectal continence reflex - which controls fecal continence by involuntary contraction of the puborectal muscle. This reflex is activated to maintain solid rather than liquid fecal continence. It seems to be initiated by dilatation at the level of the puborectal muscle. Presumably, the puborectal continence reflex protects patients with serious anal sphincter dysfunctions against full fecal incontinence.

Visceral hypersensitivity remains stable over time in patients with IBS, but with individual fluctuations

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Background & Aims: Visceral hypersensitivity in IBS, measured with a rectal barostat, has been suggested to be a phenomenon that is abolished due to habituation at repeated investigations (Naliboff 2006). We aimed to investigate the stability of rectal sensitivity in patients with IBS who had undergone a previous rectal barostat study (index investigation) and also assess variations in symptom pattern and severity in relation to rectal sensory function.

Method: IBS patients, who had previously been investigated with a rectal barostat, were included. All patients underwent a second rectal barostat study using the same protocol as the index investigation (isobaric phasic distensions, 30 s duration, 30 s rest, 5 mmHg increments). Thresholds for first sensation, urge to defecate, discomfort, and pain were determined during the distensions. Visceral hypersensitivity was defined as a pain threshold <31 mmHg (5th percentile healthy controls).

Symptoms were characterized by use of questionnaires; GI Symptom Rating Scale-IBS (GSRS-IBS), Hospital Anxiety and Depression Scale, Visceral sensitivity index (VSI), and Symptom Checklist-90-Revised.

Results: We included 27 subjects (17, mean age at index investigation 41 [21–61] years). The second investigation was done 8–12 years later. Pressure sensory thresholds were unchanged comparing the index study with the new one, perception (7.8 [new] vs 8.9 [old] mmHg, p = 0.09), urge to defecate (13.5 vs 15.9 mmHg, p = 0.1), discomfort (22.7 vs 24.9 mmHg, p = 0.4), and pain (36.9 vs 37.9 mmHg, p = 0.7). At the index, 8/27 patients had visceral hypersensitivity of which 4 were now reclassified normosensitive, and 7 from normo- to hypersensitive at the new investigation, meaning that 11/27 patients were hypersensitive at follow-up. Nine patients had increased pain thresholds (3–28 mmHg) at the new investigation, and 17 had decreased (<17 mmHg). Total CSRS-IBS score and the individual symptoms remained unchanged, and no association between change in GI symptom severity and change in perception thresholds were seen (p > 0.05). There were no differences in anxiety or depression (p > 0.05 for both) or somatization (p > 0.05) at follow-up. However, GI specific anxiety was lower at the time of the new investigation (VSI, 31 vs 26 p = 0.04).

Conclusions: Visceral hypersensitivity and GI symptoms were stable at the group-level over 8–12 years in this cohort of IBS patients, even though individual fluctuations were noted. Our findings contradict previous findings in this area indicating that visceral hypersensitivity is an unstable trait in IBS patients.

Choice of rectal barostat protocol affects classification of sensory function and prediction of symptom severity in IBS

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Background: Rectal barostat studies are widely used to assess visceral sensory function in patients with irritable bowel syndrome (IBS). This study compares two protocols and their ability to distinguish between patients and healthy controls, and if the sensitivity measures associate differently with GI symptom severity.

Methods: Cohort 1 included 469 patients with IBS (38.5 ± 12.5 mean ± SD years, 279 females) and 35 healthy controls (36 ± 11 years, 27 females), cohort 2 included 153 patients with IBS (34 ± 12 years, 105 females) and 66 healthy controls (41.5 ± 9 years, 41 females). IBS symptoms were characterized by use of IBS-SSS and CSRS-IBS questionnaires. Cohort 1 underwent a rectal barostat study with isobaric phasic distensions (30 s duration, 30 s rest; 5 mmHg increments, Posserud et al. 2007). Sensory thresholds and the perceived intensity of unpleasantness and pain were determined during the distensions. Cohort 2 underwent a rectal barostat study with ramp inflation for sensory thresholds (4 mmHg steps, 1 min/step) followed by random phasic distensions (12, 24, 36, 48 mmHg) for intensity of gas, urge, discomfort and pain (Cremonini et al. 2005). The fifth percentile for pain thresholds in healthy controls was used as cutoff for defining hyper-sensitivity in both cohorts.

Results: IBS patients in cohort 1 had lower thresholds for first sensation and pain (p < 0.001 for both) compared with cohort 2. However, the perceived intensity of pain was higher at the lowest comparable pressure levels in cohort 2 (p < 0.001 for all) and differed from their controls (p < 0.05). There was also a significant difference in the proportion of patients classified as having hypersensitivity in cohort 1 vs 2, for pain 43% vs 7%, urge to defecate 23.5% vs 7.5%, discomfort 47.5% vs 15%, and altered rectal perception for at least one sensory threshold 60% vs 19% (p < 0.001 for all).

Overall, the protocol used in cohort 1 showed a better
Background: ZINSMEISTER NELSON, S.-Y. PARK, A. ACOSTA and A. R. in patients where ramp test using isobaric phasic distensions perceived less pain Conclusion: IBS patients evaluated with a rectal barostat 0.15, 0.74; p = 0.007) were retrieved. After a median follow-up of 4.8 years, 10 patients had undergone constipation-related surgery. The median time to surgery was 1.2 years. The 5-year surgery-free survival probability was 99.3%. All patients who underwent surgery showed slow colonic transit, and they had a more prolonged total colon transit time compared with the non-surgery group [median 63 h vs 37 h, p = 0.002]. Twenty-nine patients had been newly diagnosed with idiopathic PD, and the median time to diagnosis was 4.8 years. The cumulative probabilities of developing PD were 1.0% at 5 years, and 2.6% at 10 years. Old age and slow colonic transit were associated with the risk of PD. Only five patients were newly diagnosed with colorectal cancer during follow-up. Conclusions: Slow colonic transit is associated with increased risk of surgery and future PD in patients with constipation. 117 Slow colonic transit is associated with increased risk of severe outcomes in patients with constipation. H. J. LEE*, K. W. JUNG*, M. J. KIM*, H. S. LEE*, M. SEO, S. W. HWANG*, S. H. PARK*, D. H. YANG*, K. J. KIM*, B. D. YE*, J. S. BYEON†, J. CHOE*, S. K. YANG* and S. J. MYUNG* "Health Screening and Promotion Center, Asan Medical Center, University of Ulsan college of Medicine, Seoul, Korea and Department of Gastroenterology, Asan Medical Center. University of Ulsan College of Medicine, Seoul, Korea Background: The risk of potential severe outcome of constipation is still unclear. We aimed to investigate the subsequent risk of constipation-related surgery, Parkinson's disease (PD), and colorectal cancer in constipated patients and their association with the clinical subgroups of constipation. Methods: We evaluated the results for 2694 constipated patients who underwent both anorectal manometry and a colon transit study between 2000 and 2010 at the Asan Medical Center, a tertiary university hospital. Patients who had prior history of colorectal cancer or colorectal surgery, and patients with any organic disease of the colon, PD, cerebrovascular disease, and any psychiatric disorders were excluded. Slow colonic transit was diagnosed, using radiopaque markers method, when the total colon transit time was more than 48 h, or more than 16 h in the right or left colon. The cumulative probability of developing each outcome from the diagnosis of constipation was calculated using the Kaplan-Meier method. Results: The records of a total of 2165 constipated patients [M : F = 716 : 1449, median age = 54 years] were retrieved. After a median follow-up of 4.8 years, 10 patients had undergone constipation-related surgery. The median time to surgery was 1.2 years. The 5-year surgery-free survival probability was 99.3%. All patients who underwent surgery showed slow colonic transit, and they had a more prolonged total colon transit time compared with the non-surgery group [median 63 h vs 37 h, p = 0.002]. Twenty-nine patients had been newly diagnosed with idiopathic PD, and the median time to diagnosis was 4.8 years. The cumulative probabilities of developing PD were 1.0% at 5 years, and 2.6% at 10 years. Old age and slow colonic transit were associated with the risk of PD. Only five patients were newly diagnosed with colorectal cancer during follow-up. Conclusions: Slow colonic transit is associated with increased risk of surgery and future PD in patients with constipation.
Dopamine regulates colonic mucus secretion via dopamine D5 receptor in rodents

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Background: The major component of colonic mucus is mucin 2 (MUC2), produced by colonic mucous cells. It plays an important role in intestinal mucosal protection, and is regulated by the autonomic nervous system and bioactive molecules. Dopamine as an important biotic amine is involved in the regulation of gastrointestinal motility and electrolyte transport. DA receptors are distributed in the colonic mucosa, but whether DA has effects on the mucus release remains unknown. This study aims to detect the location of DA receptors in the colonic mucosa and the role in the mucus secretion.

Methods: In the last 5 years, among patients with chronic constipation who underwent HRARM and BD both at the same period, 20 patients with INTU (16 female, age 60.7 ± 12.4, mean ± SD) by BD randomly extracted, and we analyzed characteristics of the attempted defecation using a pressure topography of HRARM in these patients. Additionally 30 (21 female, age 56.3 ± 13.3) patients with/without INTU were randomly extracted, and two investigators (CSM, LJS) tried to diagnose the presence of INTU by HRARM based on above characteristics. Diagnostic yield and concordance rate between two investigators were calculated based on the result of BD.

Results: The characteristics of INTU using HRARM are upward and/or downward displacement of high pressure band with/without short-segment pressurizations. Based on this criteria, detection rate of INTU by investigators are 70% and 64%. Diagnostic yields by each investigator are 53% and 63% sensitivity, 82% specificities, 83% and 86% positive predictive value and 50% and 56% negative predictive value respectively. Agreement between the two investigators is moderate concordance (κ = 0.595, p = 0.001). The main reasons of underdiagnosis by HRARM were concomitant DD and/or rectocele.

Conclusions: INTU could be identified using HRARM with good specificity and moderate degree of inter-observer concordance in patients with chronic constipation. HRARM may have a role in the diagnosis of the INTU without defecography.

120 Solitary rectal ulcer syndrome as a sign of unrecognized Hirschsprung's disease: report of two cases

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Background: Late diagnosed Hirschsprung’s disease (HSCR) patients often suffer from longstanding gastrointestinal complaints, such as chronic constipation and abdominal distension. Little is known, however, about patients presenting with solitary rectal ulcer syndrome as a sign of unrecognized HSCR. We aim to bring to attention patients who present themselves with solitary rectal ulcer syndrome that might be associated with unrecognized HSCR.

Methods: We describe the medical history of two male patients with recurrent solitary rectal ulcer syndrome and with a late diagnoses of HSCR.

Results: The first patient suffered from episodes of iron deficiency anaemia, rectal bleeding, and constipation throughout childhood. Repeated colonoscopy showed a recurrent solitary rectal ulcer, which responded poorly to treatment. Because of the poor response a resection of the sigmoid was performed. Microscopical analysis of the resected tissue revealed a surprising hypoganglionic, matching a transition zone seen in HSCR. The second patient also suffered from gastrointestinal complaints and recurrent solitary rectal ulcer syndrome throughout childhood. Because his medical history resembled the first case described above, the patient was also suspected of having an unrecognized HSCR. Indeed, rectal suction biopsies were performed and confirmed the diagnosis of HSCR, when the patient was 14 years old. Both patients underwent an anorectal manometry, which showed an absence of the rectoanal inhibitory reflex, supporting the diagnosis of HSCR.

Conclusions: Based on the medical history of the two patients, we think that solitary rectal ulcer syndrome should be considered as a possible presenting symptom of long-standing, and unrecognized, HSCR. We therefore emphasize the importance of anorectal manometry and possibly rectal suction biopsies, as part of the standard diagnostic work-up of patients with solitary rectal ulcer syndrome.
Background: Puborectalis and external anal sphincter muscles play important roles in maintaining continence. Electromyography (EMG) provides useful information on the neuromuscular integrity. A high-density (64 channels) intra-rectal probe was placed in the subjects' rectum. The probes are approved. A high-density surface electromyography probe in the assessment of anorectal neuromuscular integrity. Assessment of pelvic floor neuromuscular integrity by high-density surface electromyography was previously limited as for its invasive nature and surface EMG lacks accuracy.

Methods: Ten healthy females were recruited, with IRB approval. A high-density (64 channels) intra-rectal probe was placed in the subjects' rectum. The probes are equipped with an 8 × 8 high-density electrode grid which allows the EMG motor unit action potential (MUAP) detection and innervation zone mapping on the anorectal canal surface. The subjects were asked to perform 10 short (1 s) contractions followed by 10 long (3 s) contractions with 5 s rests between two consecutive contractions. The EMG signals were collected using the Relafix system (Twente Medical Systems International, Enschede, The Netherlands). After EMG acquisition, the MUAP decomposition was performed on the total 64-channel anorectal EMG signal using the K-means Clustering and Convolution Kernel Compensation algorithm.

Results: EMG recordings from two subjects were excluded due to large movement artifacts. EMG signals from puborectalis, pubococcygeus and the external anal sphincter muscles were identified by registering the electrode positions. Excellent Intra-class correlations were found between two sessions (R > 0.90). MUAPs were detected at different depths of the EMG grid. EMG decomposition was successfully performed with innervation zones visually inspected for each MUAP of each subject. The propagations of each MUAP were estimated after van Gieson staining. All four adenine receptor subtypes were expressed in untreated colon preparations. Activation of A1, A2B, and A3 receptor with specific agonists decreased the acetylcholine release (ACH, 10 µM)-induced contractions, while activation of A2B receptor enhanced it. After incubation with TNBS morphological damages in colonic mucosa and muscle walls were detectable followed by reduced ACh-contractions. The TNBS-mediated decrease of ACh-contractions as well as the morphological damages is partially normalised by co-incubation of TNBS with CGS 21680 (10 µM) and/or with PSB 1115 (100 µM). These results are in accordance with ligand binding studies indicating that STW 5 but not STW 6 interact with the A2AR and decreased the TNBS gene expression and release. Anti-inflammatory mechanisms and cell protective actions of STW 5 are partly due to the interaction with adenine receptors. The results give a clear-cut cut correlation with symptom improvements in clinical trials and thereby highlight the relevance of STW 5 as a therapeutic approach in IBS.

Conclusions: In this study, we successfully decomposed the MUAP propagations of the puborectalis and external anal sphincter muscles through the proposed high-density EMG probe and obtained their innervation zone positions. This technique could characterize the nature and level of injury in patients with fecal incontinence and further serve as a guide for sphincter repair or sacral nerve stimulation.

Hyperlaxity motility responses occur in the distal colon following colonic surgery

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Background: Ileus is common after colonic surgery. It is generally assumed that quiescence of colonic motility in this post-operative period hinders the passage of flatus and bowel motions, however this assumption has not been formally tested. This study defined the distal colonic response to bowel surgery using high-resolution (HR) colonic manometry.

Methods: Patients undergoing elective right hemicolectomy underwent HR colonic manometry using a fiber-optic catheter (36 sensors at 1 cm intervals). The catheter was placed endoscopically into the distal ileum and rectum prior to surgery. Manometry recordings were taken pre- and post-operatively. Movements were quantified by frequency, amplitude, extent and velocity, and data were statistically compared across the three recording periods.

Results: Data comprised recordings from five patients. In all patients, a marked increase in distal colonic motility occurred from pre-operative (mean 19.7% active duration) to intraoperative (47.4%) to 18 h post-operative periods (89.1%; p < 0.001). Cyclic motor patterns occurring at 2.5–4 cycles/min were dominant, with a declining frequency gradient from rectum to descending colon. Post-operative pressure events also showed a greater extent of propagation compared to those recorded pre-operatively (mean 7.5 ± 2.7 vs 5.8 ± 1.7 cm, p < 0.001) and greater amplitude (34 ± 23 vs 23 ± 15 mmHg, p < 0.001), while propagation velocity was unchanged (p > 0.4).

Conclusions: A marked and sustained hyperactive motility response occurs in the distal colon after right colonic surgery. It is likely that a neurally-mediated surgical stress response results in excessive expression of intrinsic cyclic motor patterns, with colonic pacemakers operating over a series of frequency plateaus. Traditional notions of colonic ileus in the immediate post-operative period must be revised.

Delayed colonic transit does not exclude evacuation disorder in patients with chronic constipation: experience based on 207 patients evaluated by a single gastroenterologist over 20 years

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Background: After exclusion of structural diseases, chronic constipation (CC) may be normal transit (NTC), slow transit (STC) or rectal evacuation disorders (ED). Aims: To evaluate: (i) clinical features and anorectal function in patients with objective slow colonic transit (CT), (ii) differences of CT according to the presence or absence of ED, (iii) gender-based differences in transit in patients with slow CT. Methods: Among the 1558 patients evaluated by a single gastroenterologist from 1994 to 2015 at a tertiary medical center, 207 [155 females, mean age 41.3 ± 15.3 years (SD)] had slow CT by scintigraphy (colonic geometric center, GC24 < 1.7 or GC48 < 3.0). ED was identified on anorectal manometry: resting anal pressure > 90 mmHg, balloon expulsion requiring > 200 g weight, evacuation gest (EG), colonic filling (CF), overall CT (GC24 and GC48) and ascending colon half-emptying time (AC; t1/2). Effects of ED and gender on colonic transit were assessed by Mann–Whitney rank sum test.

Results: Among 207 patients, there were 113 with ED (ED+ve) and 94 patients without ED (by test [68] or clinical [111] findings). There was no significant difference in overall CT (GC24, GC48, and AC t1/2) or gastric emptying (GE), between those with ED+ve or without ED (ED-ve). Conversely, there were significant differences in gender by the 207 patients with slow CT: GE 2 h (p < 0.001), GE 4 h (p = 0.001), CF 6 h (p < 0.001), GC24 (p < 0.001), GC48 (p = 0.004), AC t1/2 (p < 0.001).

Conclusions: Physicians should always consider the presence of ED in patients with CC. In patients with CC and objectively slow CT, females had slower gastric, small bowel, and colonic transit than males.
Barostat-assisted sensory training (BT) is superior to ADAME

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Rectal hyposensitivity (RH) is seen in 30–40% of patients with constipation and incontinence. Improving RH can restore bowel function but whether sensory training is effective is unknown.

Aim: To determine the efficacy of BT vs ST in patients with RH and compare their clinical utility in a RCT.

Methods: Patients with RH (first sensation, desire, or urge to defecate thresholds ≥2 SD of controls) and with chronic constipation or fecal incontinence were randomized to receive up to 6 biweekly sessions of BT or ST. BT was performed with a 10 cm compliant balloon, connected to a barostat (G&J Electronics Inc., Canada); phasic inflations/deflations were performed in 2 mmHg steps, inflated to 40–60 mL; (iii) rectal hyposensitivity type II: low S2 and/or S3 with normal S2 to S3 gap and normal S2 to S3 gap with normal S2, S3 ≥36%); GI symptoms other than FU and prevalence of each abnormal rectal sensation pattern were similar between patients with and without FU (p = 0.05).

Conclusion: Abnormal rectal sensation in patients with fecal urgency can be rectal hypersensitivity or normal rectal sensory threshold but narrow gap between desire to defecate and urgency threshold. Larger study including study on rectal compliance is needed to find the pathophysiology of urgency symptom in chronic constipation.

Colonial fecal volume scoring systems for computerized tomography and their relationship to patients’ bowel habits

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Introduction: Feces are visualized on all abdominal computerized tomography (CT) examinations. The relationships between fecal volume and distribution and people’s bowel habits is unclear. Potentially, data pertinent to a clinical evaluation is being underutilized.

Methods: Adult patients (n = 48, median age 64, IQR 51–71) undergoing abdominal CT were prospectively invited to complete a detailed gastrointestinal symptom questionnaire based on Rome 3 criteria. Fecal volume was scored by a radiologist blinded to the questionnaire results. Scoring systems were modified from the pediatric scoring systems for abdominal X-rays used by Barr [1989], Starreveld [1990], Rheedyn [1995] and Leech [1999]. Exclusion criteria included emergency imaging, bowel preparation in the last 4 weeks, colorectal inflammation, cancer or strictures, perianal sepsis, previous colonic surgery or inflammatory bowel disease.

Results: The median Bristol Stool Scale consistency was 4 (IQR 3–4), median bowel motion (BM) frequency was 5–10 motions per week and median time since last BM was 2 h (IQR 1–12). BM frequency did not correlate (Spearman’s Rho) with fecal scores. Both stool consistency and time since last BM correlated with total colonic fecal volume and recto-sigmoid (RS) fecal volume in the Leech and Barr scoring systems.

Conclusions: Moderate correlation exists between CT fecal volume scores, stool consistency and the time since last BM. Within the Leech and Barr systems total fecal score on planar CT images correlates more strongly with stool consistency and RS fecal volume correlates more strongly with time since last BM.
The relationship between fecal volume identified by computerized tomography and patients’ bowel habits

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1 Mayo Clinic Health System, La Crosse, WI, USA, 2Mayo Clinic, Rochester, MN, USA

Introduction: The relationship between bowel function and fecal volume identified on computerized tomography (CT) is unknown. This research investigated (i) whether physicians utilize abdominal CT in their clinical assessment of patient’s bowel function and (ii) the relationship between an individual’s bowel habit and the fecal volume and distribution identified by CT.

Methods: Physicians in the Divisions of Gastroenterology, Colorectal or General Surgery, Emergency Medicine, Geriatrics and Genital Internal Medicine were invited to participate in an online survey. Separately, adult patients undergoing abdominal CT were prospectively invited to complete a detailed gastrointestinal symptom questionnaire based on Rome III criteria. Exclusion criteria included emergency imaging, bowel preparation within 4 weeks, active colonic inflammation, colon or rectal cancer, perianal sepsis, colonic strictures, previous colonic surgery or inflammatory bowel disease. Fecal volume was determined by a radiologist blinded to the questionnaire results using the method proposed by Barr et al. (1979).

Results: Physician survey response rate was 31% (38/125). Of these, 69% had used fecal volume seen on CT when evaluating acute symptoms and 38% when evaluating chronic bowel habit. 19% had requested a CT to evaluate a patient’s bowel habit. 28% believed there was evidence correlating fecal volume seen on CT and a patient’s bowel habit. Patient participation rate was 19% (49/261, median age 64 years [IQR 51–71]). Total fecal volume on coronal CT imaging correlated moderately with fecal consistency (Bristol stool scale, ρ = 0.50, p < 0.001) but not bowel motion frequency (ρ = 0.25, p = 0.09). Fecal volume in the rectum correlated with time since last bowel motion (ρ = 0.43, p < 0.01). Fecal volume was different between patients with and without functional constipation (p = 0.55). Fecal volume did not correlate with bloating (p = 0.73), distension (p = 0.57), postprandial fullness (p = 0.77), nausea (p = 0.07) or vomiting (p = 0.85).

Conclusion: Two-thirds of physician respondents have utilized fecal volume data from CT scans to support patient evaluations. While CT colonic fecal volume correlates with stool consistency there is no association with bowel motion frequency, functional constipation or upper gastrointestinal symptoms. Fecal volume seen in the rectum correlates with interval since last bowel motion. These findings require validation in a larger cohort.

A new high-resolution anorectal manometry parameter based on three-dimensional integrated pressurized volume in both asymptomatic healthy individuals and patients with chronic constipation


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Background: Anorectal manometry with the push maneuver aims at its conventional parameters based on linear waves has a limitation in predicting balloon expulsion (BE) test results. We previously reported that integrated pressurized volume (IPV), based on the spatiotemporal plot of high-resolution anorectal manometry (HRAM), was significantly correlated with the BE test results in asymptomatic healthy individuals. However, its clinical application in a large number of constipated patients has not been investigated. We aimed to demonstrate the correlation between IPV and BE test results in both healthy individuals and patients with chronic constipation.

Methods: From September 2011 to July of 2013, a total of 230 male subjects, consisting of 26 asymptomatic healthy individuals and 204 patients with chronic constipation as defined by the Rome III criteria, were prospectively enrolled in this study. All of the enrolled subjects underwent HRAM and BE test. Delayed BE test was defined as a requirement of more than 1 min to expel the balloon. HRAM profiles were converted into ASCII files and analyzed using a MATLAB program to calculate the three-dimensional IPV by multiplying the amplitude, distance, and time during push maneuver. Receiver operating characteristic (ROC) curve analysis was used to select the significant parameters. Partial least square regression (PLSR) was conducted to find a novel numerical equation for the prediction of BE test results based on IPV parameters.

Results: Among 230 subjects, 137 (59.6%) showed early BE and the remaining 93 (40.4%) showed delayed BE. The ROC curve analysis demonstrated that the IPV ratio between the upper 1 cm and the lower 4 cm of anal canal was a better parameter at predicting BE test results (area under the curve [AUC]: 0.74, 95% confidence interval [CI]: 0.67–0.80, p = 0.01) than the conventional anorectal parameters including defecation index (AUC: 0.60, 95% CI: 0.52–0.68, p = 0.01) and rectoanal gradient (AUC: 0.60, 95% CI: 0.52–0.67, p = 0.01). The PLSR model by using linear combination of novel IPV parameters provided an AUC of 0.80 with a sensitivity of 80.0% 95% CI: 0.74–0.86, p < 0.01, specificity of 70.1%, PPV of 64.4%, and NPV of 83.5%.

Conclusions: The novel IPV method during the push maneuver showed a more significant correlation with the BE results than conventional parameters that are based on the linear waves of anorectal manometry even in a large number of constipated patients. Moreover, the combination of IPV parameters by using PLSR method appears to be promising in the prediction of the results of BE tests.

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Symptoms compatible with IBS are common in patients with ulcerative colitis (UC) in remission, but previous studies have not excluded mild inflammatory changes as a cause of the symptoms. Moreover, nothing is known about the prevalence of symptoms compatible with other functional bowel disorders (FBD) than IBS in UC in deep remission, and the overall burden of these symptoms.

**Methods:** In a cross-sectional study, patients with UC (n = 291) were divided into active disease or deep remission. They completed the Rome III FBD module to define presence of symptoms compatible with FBD, and questionnaires to measure psychological distress, stress, GI symptom severity, somatic symptoms, quality of life, and general fatigue.

**Results:** Active UC was present in 159 patients (55%). Of the 132 patients (45%) in deep remission, 37% fulfilled Rome III criteria for a FBD, 18% IBS (11% IBS-M, 4% IBS-C, 3% IBS-D), 12% functional bloating, 4% functional diarrhea, and 3% functional constipation. M, 4% IBS-C, 3% IBS-D, 12% functional bloating, 4% functional diarrhea, and 3% functional constipation.

**Conclusion:** IBS patients who fulfilled diagnostic criteria for a FBD other than IBS and patients with no FBD. Age, disease duration of UC patients in deep remission a substantial proportion reported some subthreshold symptoms compatible with FBD, and only 18% of patients with UC in deep remission reported no symptoms compatible with FBD (~1 day/month). Compared with UC patients in deep remission with symptoms compatible with other FBDs than IBS, or with no FBD, patients who fulfilled diagnostic criteria for IBS reported more severe psychological distress (p < 0.0001), somatic symptoms (p < 0.0001), and general fatigue (p = 0.004), as well as reduced quality of life (p < 0.0001), and they tended to have higher levels of perceived stress (p = 0.06). None of those factors differed between patients who met diagnostic criteria for a FBD other than IBS and patients with no FBD. Age, disease duration, I-light treatment or high-sensitive CRP did not differ between the groups. Overall GI symptom severity was highest in patients with symptoms compatible with IBS (p = 0.0001 vs the other groups), and intermediate in patients who fulfilled criteria for one of the other FBDs (p = 0.05 vs the no FBD group).

**Conclusion:** Symptoms compatible with FBDs in general, and not only IBS, are common in patients with UC in deep remission. However, the overall disease burden seems to be greater in patients with symptoms compatible with IBS than with the other FBDs. These observations are of importance when managing patients with IBD to avoid escalating anti-inflammatory treatment, and instead focus on other treatment options to help these patients to manage their symptoms.

**134 Increased fecal levels of granins in IBS patients: relationship to symptoms and intestinal inflammation?**

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**Background:** We have previously shown increased levels of fecal chromogranins (Cg) and secretogranins (Sg) in IBS patients [1]. However, the consequences and cause of increased luminal levels of granins in IBS are still undefined. Therefore, this study aimed to determine fecal granin levels in IBS patients and evaluate potential relationships between granin levels, immune activation and IBS symptoms.

**Method:** Levels of CGA, CgR, SgI, SgII and calprotectin were analyzed with ELISA in fecal samples from IBS patients (n = 148) and healthy subjects (n = 43). mRNA expression of IL-8, IL-10, TNF and FOXP3 in mucosal biopsies from the sigmoid colon were determined by qRT-PCR. IBS symptom severity and psychological distress were evaluated with the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) and the Hospital Anxiety and Depression Scale (HADS), respectively.

**Results:** IBS patients demonstrated significantly higher CgA levels (8.1 (3.3–17.4) pmol/mL) compared to healthy subjects (7.4 (2.9–9.0), p < 0.02) pmol/mL. The level of SgII in IBS patients (0.8 (0.1–3.6), 2.0 (0.8–4.8), pmol/mL were significantly increased compared to healthy subjects (0.1 (0.0–0.2), p < 0.01) pmol/mL and 0.7 (0.4–2.4), p < 0.01) pmol/mL. There was a positive correlation between GI symptom severity (GSRS-IBS) and the levels of CgA (r = 0.22, p < 0.001). General psychological distress measured by HADs was positively correlated to both CgA (r = 0.24) and CgR (r = 0.34, both p < 0.05). No association between granin levels and immune activity could be detected.

**Conclusion:** This study confirms increased levels of CGA, CgR and SgII in fecal samples of IBS patients compared to healthy controls. Further, the increased levels of granins were correlated to IBS severity and psychological distress. However, no correlation between increased luminal granins and mucosal immune activation could be found.


**135 The outcomes of endo-anal ultrasound and three-dimensional high-resolution anorectal manometry do not predict fecal incontinence?**

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**Background:** Because fecal incontinence (FI) is often associated with anal sphincter defects, patients suffering from FI are frequently screened for anal sphincter defects. Currently, the gold standard for diagnosing anal sphincter damage is endo-anal ultrasound (EUS).

Another diagnostic tool that can be used to visualize functional sphincter defects is three-dimensional high-resolution anorectal manometry (3D-HRARM). There is, however, controversy whether 3D-HRARM is as reliable as EUS in diagnosing anal sphincter defects in patients with FI.

**Aim:** We aimed to compare the diagnostic value of EUS and 3D-HRARM in association with FI.

**Methods:** We, retrospectively, included all patients older than 17, who had undergone EUS and 3D-HRARM for fecal incontinence, between July 2010 and February 2015 (N = 42). During 3D-HRARM, the presence of anal sphincter defects was examined in rest and during external anal sphincter contraction. All patients underwent a rectal infusion test and balloon expulsion test to determine whether they suffered from fecal incontinence for liquid and/or solid stool.

**Results:** No correlation was found between anal sphincter defects detected by EUS and continence for liquid or solid stool. There was also no correlation found between anal sphincter defects in rest diagnosed with 3D-HRARM and continence for liquid or solid stool. We did find a significant negative correlation between anal sphincter defects during contraction, diagnosed with 3D-HRARM, and continence for solid stool (r = -0.392, p = 0.011). Further analyses, showed that only 2 (11%) of the 18 patients, with a sphincter defect during contraction diagnosed with 3D-HRARM, suffered from fecal incontinence for solid stool, while 11 (48%) of the 23 patients without a sphincter defect during contraction did suffer from fecal incontinence for solid stool.

**Conclusions:** Although EUS can demonstrate the presence of anal sphincter damage and 3D-HRARM can demonstrate the presence of functional anal sphincter...
defects, their outcomes are not correlated with fecal incontinence for liquid or solid stool. So, neither EUS nor ID-HRAM can be used as a reliable test to predict fecal incontinence.

136 Pregnancy and labor, with or without episiotomy and obstetric laceration, are no risk factors for fecal incontinence

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Background: It has been assumed that pregnancy and vaginal delivery are associated with the development of fecal incontinence (FI). However, if pregnancy and labor were risk factors for FI, women would suffer from FI more often than men and the FI prevalence after deliveries would increase.

Aim: We aimed to determine whether pregnancy and labor are associated with FI.

Methods: We studied a cross-section of the female Dutch population (N = 680). All respondents completed the Groningen Defecation & Fecal Contience questionnaire. We excluded women that suffered from chronic diseases or had surgery that could have negatively influenced fecal continence (n = 112), after which 568 women remained for analyses. We defined FI as recurrent uncontrolled loss of liquid or solid stool at least once a month during the past 6 months.

Results: Of the 568 women, 308 (54%) were parous, of which 274 (88%) had vaginal delivery only, 21 (7%) had caesarean section only, and 16 (5%) had vaginal delivery and caesarean section. Although parous women were older than nulliparous women (52.9 vs 41.2, p = 0.001), the prevalence of FI did not differ between both groups (n = 17, 5.5% vs n = 14, 5.4%, respectively). Of the 308 parous women, 107 (35%) had episiotomy, 87 (12%) had obstetric laceration, and 46 (15%) had both. Furthermore, 64 (21%) of the women underwent an assisted vaginal delivery (i.e. use of forceps or vacuum). Simple logistic regression analyses showed that there was no correlation between FI and, delivery, including vaginal delivery, and caesarean section. Also no correlation was found between FI and birth weight of the newborn, duration of pushing, obstetric laceration, episiotomy, and the use of instruments during vaginal delivery.

Conclusions: Pregnancy and labor, obstetric lacerations, episiotomy, use of instruments, and high-birthweight seem to be no risk factors for developing FI.

137 Constipation in the general Dutch population: demographic risk factors and symptom patterns

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Background: The prevalence of constipation differs between demographic groups. Females, for example, suffer from constipation more often than males. Objective: We aimed to examine whether the prevalence and constipation-associated symptom patterns differ between various demographic groups. Secondary, we aimed to explore if obstetric history is a possible risk factor of constipation.

Methods: In this cross-sectional study, the Groningen Defecation and Fecal Contience questionnaire was answered by a representative group of the general Dutch population. Respondents using medication and/or having disorders that are known to be related to constipation were excluded. This way we obtained a ‘healthy’ study population (n = 891). Constipation was defined according to the Rome III criteria.

Results: The prevalence of constipation in the ‘healthy’ population was 21.5%. Using multivariate regression analysis, we found that females, adults younger than 38 years, and urban residents independently had a significantly higher prevalence constipation (p < 0.001, p = 0.003 and p = 0.033, respectively). Educational level and body mass index did not influence the likelihood of constipation. Constipated females experienced incomplete defecation and abdominal bloating significantly more often than males (p = 0.018 and p = 0.004). Adults younger than 54 years reported incomplete defecation and anal and abdominal pain more frequently than older respondents (p = 0.008, p = 0.011 and p = 0.43, respectively). Lastly, obstetric history did not influence the likelihood of constipation.

Conclusion: Gender, age, and residency type independently influenced the likelihood of constipation. Moreover, the pattern of constipation-associated complaints varied between genders and age groups, indicating that these groups might experience different types and severity of constipation.

138 Rectal filling sensations are not impaired in patients with increased rectal volumes

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Background: Increased rectal volumes and impaired rectal sensation upon mechanical rectal balloon distension, i.e. rectal hypoesthesia are often associated with patients with constipation.

Objective: In this study we aim to show that rectal filling sensation is not impaired in patients with increased rectal volumes.

Methods: In this retrospective, observational study, we reviewed the medical records of adult patients, who had undergone anorectal manometry because of defecation problems between 24 March 2010 and 20 January 2015. Patients with a history of (congenital) disorder and/or surgery with a possible influence on the anorectal function were excluded. Finally, 114 patients were eligible for analysis. Rectal volumes and pressures were determined during balloon retention test at the following rectal filling sensation levels: constant sensation level, urge sensation level and maximal tolerable volume.

Results: The distribution of the rectal volumes of all patients showed a great variance at the different rectal sensation levels, while the rectal pressures were comparable. No correlation was found between rectal volume and rectal pressure at constant and urge sensation level (r = 0.176 and r = 0.037 respectively). We also analyzed the distribution of rectal pressures in three subgroups of equal size (n = 38), which were formed based on the rectal volumes observed at constant and urge sensation level. The medians of the rectal pressures at constant sensation in patients with low (10–80 mL), medium (80–150 mL) and increased rectal volumes (155–550 mL) were 37 mmHg, 43 mmHg and 41 mmHg, respectively, and did not differ significantly (p = 0.109). The medians of the rectal pressures at urge sensation in patients with low (45–140 mL), medium (145–255 mL) and increased rectal volumes (270–660 mL), were 48 mmHg, 48 mmHg and 49 mmHg, respectively, and did not differ significantly (p = 0.478).

Conclusions: Since changes of rectal pressure are known to be the trigger for the rectal filling sensation and we show that the rectal pressures measured at different rectal sensation levels are similar in patients with small, medium and enlarged rectal volumes, our study indicates that patients with increased rectal volumes do not need to experience impaired rectal sensation. Thus, the currently postulated association between increased rectal volume and hypoesthesia in patients with defecation problems seems to be inappropriate.

139 Effect of biofeedback therapy on anorectal physiological parameters among patients with fecal evacuation disorder

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Introduction: Fecal evacuation disorders (FED) are common among patients with chronic constipation presenting to tertiary care centers. Though biofeedback therapy is effective in relieving symptoms in these patients, there is limited data on improvement in physiological parameters after such treatment. Therefore, we evaluated efficacy of biofeedback in improving anorectal physiological parameters among patients with FED.

Methods: Consecutive patients with FED (diagnosed in symptomatic patients based on defecography, balloon expulsion test [BET] and anorectal manometry) referred to Gastrointestinal Pathophysiology and Motility Laboratory of a large university hospital from August 2012 to July 2015 were included. Anorectal manometry parameters such as basal and squeeze pressures, residual sphincter pressure during attempted defecation and balloon expulsion test parameters were evaluated before and after biofeedback therapy (two sessions per day for 2 weeks).

Results: Of 41 patients (median age 44 y, range 19–76, 30 [71%] male), defecography and BET and was abnormal in 30/34 (70%) and 34/40 (85%) respectively. Pre and post-biofeedback manometric parameters (median and range) were as follows: basal pressure 78 (52–128) vs 64 (53–102), p = 0.04, squeeze pressure 142 (75–248) vs 140 (81–246), p = 0.9, residual anal sphincter pressure during attempted defecation 109 (52–148) vs 83 (37–122), p = 0.02, weight needed to expel intra-rectal balloon during BET 500 (0–700) vs 200 (0–700), p = 0.01. Dysstergia and BET got corrected in 22/34 (65%) and 12/30 (40%) patients after biofeedback.

Conclusions: Successful biofeedback therapy improves anorectal physiological parameters.
Efficacy, satisfaction and quality of life in patients with dyssynergic defecation biofeedback therapy: What are the number of sessions needed?

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Background: Patients with functional constipation and dyssynergic defecation (DD) remain symptomatic despite lifestyle changes and optimal medical treatment. Biofeedback therapy (BFT) is the first line therapy for DD patients and usually provided for six sessions.

Aim: To assess the efficacy, satisfaction and quality of life after BFT in patients with DD at third and sixth sessions.

Methods: We enrolled consecutive patients referred for BFT to our GI motility lab between October 2014 to February 2016. All patients underwent six sessions and were evaluated at baseline, third and sixth sessions. We analyzed age, sex, BMI, anorectal manometry values, dyssynergic pattern, rectal sensitivity, level of satisfaction by a visual analog scale (VAS), number of complete spontaneous bowel movements (CSBM >50% increase from baseline), Bristol scale, use of laxatives and normalization of defeation pattern. Data are presented as percentage or median (range) and compared using Kruskal-Wallis or Wilcoxon tests.

Results: We enrolled 23 consecutive patients [19 females, mean age 53 years [range 42-66] mean body mass index 26.7 kg/m² [range 22.7-39]]. At baseline, more prevalent type of dyssynergia was type I in 18 (78%) patients, 39% had rectal hypersensitivity, 83% did not eje the ballon. At the third session, there was an increase in 74% for CSBM, level of satisfaction in 65%, a decreased in use of laxatives in 61% and a normal defeation pattern in 74%. At the sixth session, there was an increase in 70% for CSBM, level of satisfaction in 63%, a decreased in the use of laxatives in 70% and a normal defeation pattern in 83%. Compared to baseline, third and sixth sessions were associated with similar improvements in VAS, Bristol scale, CSBM and Rectoanal Index (p < 0.05). Use of laxatives improved only at sixth session (p < 0.05). Interestingly, there was not more cumulative improvement in CSBM and Rectoanal between third and sixth sessions (p > 0.05). While VAS, Bristol scale and use of laxatives continue to improve between sessions (p < 0.05).

Conclusions: BFT significantly improve patients with DD at third and sixth sessions. Although there are some differences between both sessions, most patients improve after third session. We think that some patients could have a short active BFT and decrease health-related costs.

Diagnostic value of colonic transit time versus colonic manometry in patients with chronic constipation

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Introduction: Colonic manometry (CM) may be helpful in constipated patients to further delineate colonic motility. However, CM is an invasive, demanding procedure associated with discomfort and is only available in specialized motility centers. Colonic transit time (CTT) as measured with radio-opaque markers is a less invasive procedure but co not known whether this method might be helpful in determining in which patients CM is indicated. Aim was to assess the diagnostic value of CTT compared to 24-h colonic manometry in patients with chronic constipation.

Methods: Prospectively collected data from patients undergoing both a CTT as well as 24-h CM in our tertiary referral center were reviewed. Healthy volun- teers were studied to obtain control values. CTT was measured using radio-opaque markers (X ray at day 4). A catheter with 6 solid-state pressure sensors was pos- tioned endoscopically and clipped to the mucosa in order to perform 24-h ambulatory CM. CM was defined as normal when \geq three high-amplitude propagating contractions (HAPCs), i.e. propagating waves with amplitude \geq 80 mmHg over at least three sensors, were identified. Results are shown as means ± SD and propor- tions and were compared using independent-samples t-test and chi-squared test.

Results: Data of 71 patients [62 women, 44.6 ± 14.7 years] and 12 healthy controls [10 women, 47 ± 14.4 years] were evaluated. Slow colonic transit (SCT) was based on CTT. Mean number of HAPCs per 24 h was significantly lower in patients showing SCT on CTT compared to patients with normal colonic transit and controls [1.9 ± 2.3 ± 4.8 ± 1.6 and 5.25 ± 3.0, p < 0.001 and p < 0.001 respectively]. In total, 59 patients showed SCT on CTT, of which 40 (67.8%) showed abnormal CM. All 12 patients with normal colonic transit at CTT had normal CM. Therefore, the negative predictive value (NPV) of CTT for colonic dysmotility was found to be 100%, with a negative likelihood ratio (LR-) of 0.

Conclusion: In the evaluation of patients with chronic constipation for colonic motility disorders, a normal CTT excludes colonic dysmotility at CM, whereas abnormal CTT is a strong indicator for colonic dysmotility at CM. Colonic transit studies are helpful in selecting patients with chronic constipation for colonic manometry.

Rome IV fecal incontinence prevalence and risk factors in the US, Canada and United Kingdom

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The utility of anorectal manometry (ARM) and pelvic floor EMG for diagnosing functional defecation disorder and selecting patients for biofeedback treatment has been challenged. Our aim was to determine whether patients with different causes of difficult defecation are equally responsive.

Methods: Included were 132 patients with an abnormal balloon evacuation test (BET >2 min) and fewer than 3 complete spontaneous bowel movements per week (CSBM). A nurse who was unaware of the diagnostic test results provided all patients with 5 biofeedback training sessions designed to teach relaxation of pelvic floor muscles simultaneous with contraction of abdominal wall muscles when evacuating. Primary outcomes were self-ratings of improvement in constipation symptoms on a 7-point scale (‘markedly worse’ to ‘markedly better’), and changes in CSBMS.

Results: [1] Digital rectal examination, ARM, pelvic floor EMG, and defecography led to classifying 33 as obstructed defecation (OD), 20 as dyssynergic defecation only (DD), paradoxical contraction or inability to relax pelvic floor muscles when attempting to defecate), 10 as inadequate rectal propulsion only (IRF, rectal pressure <45 mmHg when attempting to defecate), and 67 as combined DD and IRF (DD/IRF). [2] OD patients

Balloon evacuation test does not identify which patients respond to biofeedback for constipation, anorectal manometry or EMG, and structural evaluation are needed

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Investigation of rhubarb induced mucus secretion and underlying mechanism in rat colon J.-D. XU, D. WU, L.-S. LI and J.-X. ZHU Department of Physiology in School of Basic Medical Science, Capital Medical University, Beijing, China

Background and aim: Rhubarb has been used as a traditional herb for thousands years, since its detoxification and laxative. It has not been reported that whether rhubarb could promote mucus secretion on the rat colon. Our earlier findings show that Rhubarb can activate the role of mast cells degranulation, including histamine, leukotrienes, a variety of inflammatory cytokines and so on. And goblet cells express different histamine receptors. The aim of the present investigation is to explore whether rhubarb participates into the matter of the promotion of mucus secretion via the effect of mast cells.

Methods: Immunofluorescence was used to investigate the distribution of mast cells and histamine receptors. Western blotting was used to quantify content of chymase in mast cells. Specifically, mucus secretion was stained by AB/PAS. ELISA was used to detect the contents of histamine in the feces under the administration of different doses of rhubarb. In order to observe the effect of rhubarb on mucus secretion, the perfusion system was performed and Bradford protein was evaluated according to its assay kit.

Results: The results indicated that there were abundant HR1 and HR1 in the colon of rats. The content of chymase in mast cell was enhanced in different concentration of rhubarb respective, the content of chymase in 3 g/kg group is increasing about 128.57% (p < 0.05, n = 11) compared to control group, the 6 g/kg group about 285.71% (p < 0.001, n = 10) and 9 g/kg group about 123.91% (p < 0.05, n = 9). The content of histamine was also increased in dose-dependent manner, from 12.88 ± 2.63 ng/mL to 20.6 ± 5.699 ng/mL and 28.92 ± 11.70 ng/mL at the different groups (p > 0.05, n = 8). But pretreatment with the stabilizer of mast cell, ketotifen at the dose of 1 mg/kg, the content of histamine were decreased as the control group. It was found that rhubarb could stimulate the goblet cell secreting the mucus via the histamine receptors on the surface of the goblet cells, which was decreasing with ketotifen. We have also get the same results on the feces number and its water content, the feces number of control group was 33.68 ± 10.68 (n = 8), 40.22 ± 7.68 (n = 9) in 3 g/kg group, 60.25 ± 4.95 (n = 8) in 6 g/kg group and 63.13 ± 11.62 (n = 8) in 9 g/kg group in 24 h respectively, while the feces number was significant reduced in the ketotifen group (p < 0.05, n = 11). All the same changing tendency was also observed in the water content.

Conclusions: The present study demonstrated that rhubarb is able to stimulate rat colonic mucin secretion and enhance feces number and water content, which is predominantly mediated by histamine released from mast cell. This work was supported by the National Natural Science Foundation of China (81274173 JD Xu), Beijing Natural Science Foundation Program (71220107).

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Quantitative analysis of diffusion tensor fiber tractography in the external sphincter muscle of anal incontinent patients A. ZHIAN*, M. LEDGERWOOD-LEE†, S. SINHA*, M. REISERT† and R. K. MITTAL†

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Background: The anal sphincter complex, comprised of anatomically overlapping internal anal sphincter (IAS), external anal sphincter (EAS) & puborectalis muscle (PRM) play an important role in the anal continence (AI) mechanism. Little data exists on the EAS fiber microarchitecture, and its relationship to anatomical disruption.

Goal: The main goal here is to develop a quantitative approach using deterministic fiber tractography analysis of the EAS muscle.

Methods: A total of 16 subjects were recruited with informed consent, 8 healthy subjects and 8 patients with symptoms of anal incontinence. The microstructure of the EAS muscle was analyzed from the diffusion tensor images (DTI) from a 3-T MRI scanner using spin-echo, echo-planar imaging sequence. Fiber tractography was constructed in the DT image via FiberTools using a deterministic Fiber Assignment by Continuous Tracking (FACT) algorithm and a probabilistic method based on an extended Monte Carlo Random Walk with fractional anisotropy (FA) threshold set at 0.08 and angle threshold at >70°. Region of interest (ROI) was defined to cover the EAS complex for analysis. The mean length and standard deviation of tracked muscle bundles was measured for comparison between healthy subjects and AI patients.

Results: The length of tracked muscle bundles was numerically shorter in the FI patients, however the difference was not statistically significant (p = 0.23) in AI patients compared with healthy subjects (healthy: 20.07 ± 14.30 mm, AI: 16.61 ± 5.92 mm). Moreover, there was no statistical significance in the density of fibers tracts (p = 0.27).

Discussions: Quantitative analysis of deterministic fiber tractography results did not found statistically significant differences between the two studied groups when it came to fiber length and density. It should be noted however that care should be taken when it comes to analyzing complex structures such as the EAS muscle with deterministic fiber tracking methods because this algorithm usually fail to resolve complex fiber organizations (e.g. fiber crossings/kissing). Furthermore, fibrosis in the EAS muscle as may happen in the AI patients can also result in shorter muscle fiber length because of early termination of the fiber propagation due to hindrance to water diffusion motion from presence of extracellular matrix a consequence of muscle fibrosis.

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Predicting anal sphincter dysfunction from high definition anorectal manometry using a robust automatic multivariable prediction model A. ZHAN*, M. LEDGERWOOD-LEE† and R. K. MITTAL†

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Background: Three-dimensional high-definition anorectal manometry (3D-HDAM) is a novel technique to assess anal sphincter function. There is no consensus
Electrogastrography, Electrical Control, and Gut Electrical Stimulation

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Electrical vagal nerve stimulation prevents the development of acid induced esophageal hyperalgesia

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Introduction: Accumulating evidence suggests that the vagus nerve exerts an anti-nociceptive effect in the viscera. Visceral pain hypersensitivity is a key pathophysiological facet of a number of common disorders including gastro-esophageal reflux disease (GERD) and irritable bowel syndrome (IBS). We have previously demonstrated that physiologically increasing vagal tone, with deep breathing, prevents the development of acid induced esophageal pain hypersensitivity.

Aims: To determine whether electrical stimulation of the auricular branch of the vagus nerve influences the development of hypersensitivity in a validated model of acid induced esophageal pain.

Methods: Forty asymptomatic healthy subjects (11 male, mean age 30 years, range 21–42) were recruited and were randomized in a blinded crossover design to receive either transcutaneous auricular electrical vagal nerve stimulation (VNS; pulse width: 250 μs) during acid stimulation (VNS: pulse width: 250 μs on, 30 μs off), or sham stimulation, during acid stimulation (VNS: pulse width: 250 μs on, 30 μs off). Subjects were randomized in a blinded crossover design to receive either transcutaneous auricular electrical vagal nerve stimulation (VNS; pulse width: 250 μs) during acid stimulation (VNS: pulse width: 250 μs on, 30 μs off), or sham stimulation, during acid stimulation.

Results: VNS increased cardiac vagal tone (31.6 ± 58.7% vs –9.6 ± 20.6, p = 0.02) in comparison to sham stimulation. VNS did not influence cardiac sympathetic index (–5.8 ± 41.7% vs 17.7 ± 84, p = 0.35). Mixed effects linear regression, controlling for age and gender, demonstrated that VNS prevented the development of acid-induced esophageal hypersensitivity in comparison to sham stimulation (coefficient 15.4 ± 9.5, 95% confidence interval 8.8–22.2, p = 0.003).

Conclusions: The development of esophageal hyperalgesia is prevented by electrically stimulating the auricular branch of the vagus nerve. This study provides further evidence of the anti-nociceptive role of the parasympathetic nervous system. Further work is warranted in patients groups, such as those with recalcitrant GERD or IBS.

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Electrogastrography determines subtypes of gastroparesis responsive to pyloric balloon dilation: functional gastric outlet obstruction

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Background: The etiology of gastroparesis is varied and often poorly understood. Pyloric balloon dilation has been used with variable results in treating gastroparesis. Gastroparesis due to structural mechanical outlet obstruction has previously been observed to have prominent high amplitude 3 cycle per minute (3CPM) regular electrogastrography (EGG) patterns. Structural outlet obstruction treated by balloon dilation frequently results in gastric emptying and symptomatic improvement. Prominent elevated 3CPM activity has also been noted in the absence of mechanical obstruction and has been recognized as functional outlet obstruction. The aim of this study was to determine if there were specific EGG characteristics that predict improvements in symptomatology and gastric emptying after pyloric balloon dilation in gastroparesis patients with non-structural or functional gastric outlet obstruction.

Methods: Thirty-one patients with gastroparesis and dyspeptic symptoms underwent EGG with water load test, solid phase nuclear gastric emptying study, and standardized dyspepsia survey before and 6 months after 2-min pyloric dilation with a 20 mm through-the-scope balloon.

Results: A joint model based on EGG 3CPM activity was developed to diagnose and predict gastric emptying improvement after pyloric balloon dilation. Sensitivity and specificity of identifying improvements in gastric emptying after dilation were 96.15% and 75.00%, respectively with 93.33% of patients correctly classified. After dilation, 3CPM activity decreased significantly in high-3CPM subset (p < 0.0005), while normal-3CPM patients showed no significant change in activity at any time point (p > 0.05) except 10 min, at which 3CPM activity increased significantly (p = 0.0278). Patients with high-3CPM activity demonstrated significant post-dilation improvement in gastric emptying at 120 min (p < 0.0001) in contrast to no significant improvement in patients with normal-3CPM activity (p = 0.2358). Patients with high-3CPM activity also demonstrated significant improvements in symptoms post dilation including: upper abdominal discomfort, discomfort worsened by eating, early satiety, fullness, nausea, and bloating (p < 0.0001) in contrast to no significant improvement in any symptom in the normal 3CPM activity subset (p > 0.05).

Conclusions: [1] Electrogastrography is able to diagnose non-structural or functional pyloric outlet obstruction associated with gastroparesis. [2] EGG diagnosis of functional pyloric outlet obstruction predicts successful resolution of gastroparesis and symptoms in response to balloon dilation of the pylorus vs patients with normal EGG studies and gastroparesis. [3] EGG may play a significant role in accurately diagnosing subtypes of gastroparesis that will respond to specific therapy.
Enteric Neurons: Development and Degeneration, Enteric Neurobiology and Circuity

Neuroligin-3 is located presynaptically in the myenteric plexus of the murine enteric nervous system. Affecting the neurotransmitter acetylcholine (ACh) and Channel Systems, Reutlingen, Germany) to examine the logical and pharmacological investigations. Here we examined neuronal oxidized glutathione (GSSG) content increased <p><i>0.05). The neuronal GSSG/GSH ratio did not increase during an in situ model of neuroinflammation with the P2X7R antagonists RITA. Inhibition of glial GSSG synthesis with BSO decreased myenteric neuron density (p < 0.01) but did not potentiate P2X7R mediated neuron loss or alter the GSSG/GSH ratio in surviving neurons. Our data suggests a novel neuroprotective role for enteric glia as inhibition of the GSH-producing glial enzyme GCL is sufficient to drive enteric neurodegeneration in the absence of other pathological stimuli.

Regulation of the antioxidant glutathione by enteric glia cells

Enteric glia are a unique type of peripheral neuroglia that regulate the health and activity of neurons in the enteric nervous system (ENS). Enteric inflammation significantly alters glial phenotype and the transformation of enteric glia is thought to contribute to enteric neuropathies. Yet, how this happens is unclear. We recently discovered that the activation of enteric glia by neuron danger cues drives neurodegeneration via mechanisms that involve oxidative stress (Brown et al, 2016). Yet other data show that the ablation of glia leads to neuroregeneration and altered gastrointestinal (GI) motility patterns (Aubé et al, 2006, Abd et al, 2010). This suggests that glia can contribute to neurodegeneration through several mechanisms including active signaling and a loss of glial neuroprotective factors such as reduced glutathione (GSH). Here, we test the hypotheses that enteric glia are the primary source of GSH in the ENS and that changes in glial GSH content and/or production contribute to neurodegeneration during inflammation. We measured cellular content of reduced/oxidized glutathione (GSH/GSSG) using antibodies against free GSH/GSSG. We measured neuronal survival and localized GSH synthesis proteins using immunohistochemistry and inhibited GSH synthesis using Buthionine Sulfoximine (BSO), an inhibitor of the GSH synthesis enzyme glutamate-cysteine ligase (GCL). We induced enteric glia injury using 2,4-dinitrobenzoic acid (DNBS) and in situ using the P2X7 receptor (P2X7R) agonist RITA. GCL, the first and rate limiting GSH synthesis enzyme that produces γ-glutamylcysteine, is primarily expressed in enteric glia. Meanwhile, glutathione synthetase, the second GSH synthesis enzyme that converts γ-glutamylcysteine and glycine to GSH, is primarily localized to enteric neurons. The localization of GSH synthesis proteins was not altered during DNBS colitis in mice. However, neuronal oxidized glutathione (GSSG) content increased (p < 0.001) with no corresponding change in neuronal reduced glutathione (GSH). These changes increased the ratio of oxidized/reduced glutathione (GSSG/GSH) in neurons (p < 0.05). The neuronal GSSG/GSH ratio did not increase during an in situ model of neuroinflammation with the P2X7R antagonist RITA. Inhibition of glial GSSG synthesis with BSO decreased myenteric neuron density (p < 0.01) but did not potentiate P2X7R mediated neuron loss or alter the GSH/GSSG ratio in surviving neurons. Our data suggests a novel neuroprotective role for enteric glia as inhibition of the GSH-producing glial enzyme GCL is sufficient to drive enteric neurodegeneration in the absence of other pathological stimuli.

Vitamin a metabolism is required for vagal neural crest cell colonization of the gastrointestinal tract in the pathogenesis of hirschsprung disease

Rdh10 dehydrogenase 10 (RDH10) oxidizes vitamin A to its active metabolite, retinoic acid (RA). Insufficient or excess RA can result in congenital abnormalities, such as Hirschsprung disease (HSCR). In HSCR, neurons are absent from variable lengths of the gastrointestinal tract leading to megacolon and/or the failure to pass meconium. HSCR occurs in 1/5000 live births, and typically requires surgical resection of the aganglionic bowel. Enteric neurons are derived from neural crest cells (NCC), hence HSCR is associated with incomplete NCC development or colonization of the gastrointestinal tract. Rdh10mutant mouse embryos exhibit colonic aganglionosis in association with decreased retinoid signaling. We hypothesize that RDH10 is necessary for vagal NCC migration and enteric nervous system (ENS) formation. Organ explant culture and in vitro retinal supplementation define a temporal requirement for RA in ENS development between E7.5- E9.5. Tamoxifen-inducible deletion of Rdh10 at E6.5- E7.5 confirms this early retinal role, while later Rdh10 deletion suggests retinal independence for continued enteric NCC colonization. Furthermore, removing Rdh10 from NCCs shows no gross or ENS-specific neuronal defects, suggesting RDH10 is not intrinsically required in enteric NCCs for proper colonization of the gut, but rather is necessary as a paracrine signal in the vagal NCC microenvironment. Currently we are examining RDH10 regulated microenvironmental signals for their roles in governing NCC migration and colonization of the gut. Potential candidates include GDNF and extracellular matrix proteins. These novel models of HSCR will improve our understanding of RA contribution to intestinal development and may lead to innovative non-surgical treatments to reduce the morbidity and mortality of this congenital disease.
acetyl transferase (ChAT). Also, we analyzed the neuropeptide synthase (NOS), neurofilament (NF) and choline acetyl transferase (ChAT). In the present work, we have analyzed the effects of the BBG on the P2X7 receptor and rats ileum myenteric plexus following I/R.

Methods: The ileal artery was occluded for 45 min with an atrumatic vascular clamp. In the I/R 24 h group (n = 5), BBG (50 mg/kg) or saline (sal), vehicle, n = 5 was given subcutaneous 1 h after ischemia. In the I/R 14 day group (n = 5), BBG was given once daily for the next 5 days. Myenteric neurons were evaluated for immunoreactivity against the P2X7 receptor, nitric oxide synthase (NOS), neurofilament (NF) and choline acetyl transferase (ChAT). Also, we analyzed the neurons in intestine layers, protein expression of P2X7 receptor and intestinal motility.

Results: The density of the (neurons/cm²) P2X7-IR, NOS-IR, NF-IR and ChAT-IR neurons was decreased by 28%, 36%, 40% and 18%, respectively, in I/R 24 h sal group, and was reduced by 19%, 21%, 23%, 13%, respectively in BBG50 and BBG100 I/R 24 h groups (p < 0.05). The density of P2X7-IR, NOS-IR, NF-IR and ChAT-IR neurons were reduced by 22%, 45%, 34% and 38% in I/R 14 sal group, respectively, and in the BBG50 and BBG100 I/R 14d groups were reduced by 15%, 33%, 26%, 17%, respectively (p < 0.05). There was a decrease in the area of the cell body profile in neuronal classes in the I/R groups and recovery profile area of the I/R BBG-50 and I/R BBG-100 groups. In ischemic groups, there was an increase in the expression of the P2X7 receptor and in the numbers of neurotrophs in intestine layers, and the intestinal motility was decreased. In the BBG 24 and BBG14 days, the groups of neurotrophs, P2X7 receptor protein expression and intestinal motility were recovered.

Conclusion: We concluded that I/R affected morphologically and functionally the intestine and that the effects of the I/R were influenced by use of the BBG antagonist, demonstrating a possible neuroprotection and participation of P2X7 receptor in enteric neurons in ischemia.

156 Anti-enteric neuronal antibodies may be specific antibodies in sera of patients with irritable bowel syndrome

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Background and Aim: Studies indicated that the positive rate of anti-enteric neuronal antibodies (AENA) in sera of patients with irritable bowel syndrome (IBS) was significantly higher than that of healthy controls or non-IBS FGIDs patients. The aims of this study are to compare the positive rates of AENA in IBS and disorders involving colon and healthy subjects (HS), as well as to explore the specificity of AENA from IBS sera in immunoreactivity (IR) to enteric and central neurons.

Methods: IBS patients met Rome III criteria were enrolled. Control groups included HS and patients with slow transit constipation (STC), intestinal pseudo-obstruction (IPO), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Small intestinal and cerebellar tissue of mouse (Euroimmune Lübeck, Germany) were used as substrates in indirect immunofluorescence to test anti-neuronal antibodies in sera. IR results were interpreted by two investigators in blinded manner, which were read as negative, mild, moderate and intensive IR. The positive sera for AENA were defined as sera with moderate and intensive IR in intestinal substrates, and positive sera for IR with cerebral neurons were defined as those with moderate or intensive IR in cerebral substrates. All sera were also tested for antinuclear antibody (ANA) by indirect immunofluorescence.

Results: A total of 293 IBS patients with median age of 40.0 (18.0) were enrolled including 177 male and 116 female patients. The median course of disease was 6 years. The percentage of IBS with diarrhea, IBS with constipation and mixed IBS were 95.4%, 2.4% and 3.1%, respectively. The positive rate of AENA in IBS group was 43.7%, and there was no significant difference between ANA-positive and ANA-negative subgroup of IBS (49.2% vs 42.2%, p = 0.319). The positive rate of AENA in IBS patients was significantly higher than that in HS group (43.7% vs 7.0%, p < 0.001), and also in STFC, IBD and IOP patients. About 14% sera from IBS patients showed positive IR with cerebral neurons, which was significantly lower than that in IBD, ANA-positive SLE and ANA-negative RA groups (47.0%, 75.0% and 45.0%, respectively, p < 0.05).

Conclusions: Compared with HS and other functional bowel disorder, dysmotility or inflammatory bowel disorders, the positive rate of AENA in sera of Chinese IBS patients was markedly higher, meanwhile, the positive rate of IR with cerebral neuron was much lower than that of autoimmune diseases. These evidences indicate that AENA in sera of IBS patients may have specific effects on enteric neurons and it might account for important pathophysiology of IBS. Support by grant 2014DFA31850
of vancomycin-fed pups had a significantly lower myenteric neuron density (control: 0.12 ± 0.01 mm²; vancomycin: 0.09 ± 0.003 mm², n = 8–9, p < 0.01), but there was no difference in the neuron density in the duodenum (n = 8–9, p = 0.8). Moreover, there was a lower proportion of nNOS and a larger proportion of calbindin-expressing neurons in the colon (control: nNOS 36.8 ± 1.3%, calbindin 19.5 ± 1.9%, vancomycin: nNOS 38.5 ± 1.5%, calbindin 25.8 ± 1.6%, n = 8–9, p < 0.05) but not duodenum [n = 8–9, nNOS = 0.4, calbindin = 0.8], of vancomycin-fed pups. Therefore, neonatal exposure to vancomycin alters development of enteric neurons and motility patterns in the colon, but not the duodenum.

158 Mechanisms underlying cholera toxin-induced hypersecretion in mouse ileum C. FUNG, P. UNTERWEGGER, R. KOUSSOUMAS, A. M. ALLEN, J. C. BORNSTEIN and J. P. FOONG* University of Melbourne, Parkville, Victoria, Australia

Cholera-induced hypersecretion causes severe dehydration and death if left untreated. It is well established that cholera toxin (CT) exerts some of its effects via the enteric nervous system (ENS), but the circuitry involved is unclear. To investigate this, we incubated mouse ileal loops with CT (12.5 μg/mL or saline [control] for 3.5 h in vivo), then examined the tissue in vitro. Ileal segments from R26-GrCaMP3 and C57BL6 mice were examined in Ussing chambers to measure CT secretion and to label for activity-dependent markers c-Fos and pCREB. Ileal tissues from Wnt1-Cre;R26-GrCaMP3 mice, which express a calcium indicator in the ENS, were used for calcium imaging to assess circuit excitability. Recorded cells were identified by post-bac immunohistochemistry. Basal secretion was higher in CT-treated full thickness preparations compared to control (p < 0.0001, n = 10–11 animals) but responses to neural stimulation with veratridine (Na⁺ channel activator, 1–30 μM) and DMPP (nicotinic agonist, 1–30 μM) were unchanged. In the submucosal plexus, CT did not induce c-Fos, but increased the proportion of neurons (marked by the pan-neuronal marker, Hu) that expressed pCREB (66.3% vs 10.8 ± 5.1%, respectively, p < 0.01, n = 3). More submucosal neurons were spontaneously active in CT-incubated tissues (32/160 neurons) than controls (4/145 neurons), and these were primarily cholinergic (choline acetyltransferase²) neurons. The amplitudes of DMPP (10 μM, n = 3) and electrically-evoked (single pulse and train of 20 pulses, n = 41 calcium transients were also increased in cholinergic submucosal neurons (p < 0.05). In the myenteric plexus, CT increased c-Fos expression in neurons compared to controls (28.2 ± 2.5% vs 5.9 ± 1.6% Hu neurons, p < 0.01, n = 5), 62.6 ± 5.1% of c-Fos neurons were neural nitric oxide synthase+/nNOS¹ and 30.3 ± 1.1% were calbindin². However, fewer myenteric neurons were spontaneously active in CT-incubated tissues (2/251 neurons) than controls [21/ 279 neurons]. Amplitudes of calcium responses to DMPP (10 μM, n = 3–4) and single pulse stimulation (p < 4.6) were also reduced in myenteric neurons (p < 0.05), but responses to trains of 20 pulses were increased in nNOS neurons (p < 0.05, n = 4–6). Collectively, we showed that specific subsets of submucosal and myenteric neurons were differentially affected by CT. Further, CT increased basal secretion at least partly by increasing excitability and spontaneous activity in cholinergic submucosal neurons.

VPAC1 activation reveals neuron-glia interactions in the submucosal plexus of mouse jejunum C. FUNG*, C. CIRILLO, J. C. BORNSTEIN*, J. P. FOONG* and P. VANDEN BERGHE* Department of Pathology and Structural Biology, University of Melbourne, Parkville, Victoria, Australia and Institute for Cell Science, Deakin University, Geelong, Victoria, Australia.

Enteric glia interact with neurons to actively regulate intestinal function. ATP is a key signaling molecule, but neuron-glia signaling mechanisms are largely unknown. We examined whether vasoactive intestinal peptide (VIP) is involved in enteric neuron-glia interaction, as in the central nervous system neurally-released VIP exerts neuroprotective effects by activating astrocytes. In the enteric nervous system this is also neuroprotective and promotes epithelial barrier integrity – two functions associated with glia. We investigated the role of VIP using calcium imaging on jejunal submucosal plexus and mucosa preparations from Wnt1-Cre;R26-GrCaMP3 mice where enteric neurons and glia express a fluorescent calcium indicator. Agonists for the VIP receptor subtypes, VPAC1 and VPAC2, were applied to submucosal ganglia by pressure ejection and antagonists were superfused. VPAC1 expression in the submucosal plexus was examined using immunofluorescence. VPAC1-immunoreactivity was found in cholinergic (choline acetyltransferase) neurons and nerve fibers (peripherin¹), but not on glia (glial fibrillary acidic protein). The VPAC1 agonist (K15, R16, L27VIP[1–7]) 100 μM] evoked intracellular calcium transients in neurons and glia – the glial response was tetetodtoxin (TTX)-insensitive (1 μM, n = 5) but was inhibited by PPADS (100 nM, n = 6, p < 0.05). The P2Y1 selective antagonist (MRS2179, 10 μM, n = 4) also reduced the glial response (p < 0.05), but not the neural response. The P2Y1 agonist 2MeSADP (100 μM) selectively evoked calcium rises in glia, some of which also responded to the VPAC1 agonist albeit with a longer latency [4.5 s vs 18.2 s, respectively, n = 5] The VPAC2 agonist R-813 (100 nM, n = 3) did not evoke responses in neurons or glia. VIP [100 μM] primarily induced TTX-sensitive neuronal responses, but the number of responding glia increased in the presence of TTX (p = 8.6 ± 0.05) and in the presence of the VPAC2 antagonist PG9-465 (1 μM, n = 7, p < 0.01). The VPAC1 antagonist PG9-249 (1 μM, n = 11) reduced VIP-evoked neural responses without affecting glia (p < 0.05). VPAC1-activation stimulates a neuron-glia interaction that involves purinergic P2Y1 signaling, is TTX-insensitive, and may be antagonized by VPAC2-activation. Our data reveal a component of an enteric niche that can be regulated by VIP via a balanced activation of VPAC1 and VPAC2-mediated pathways.

160 Expression of the precursor marker Sox2 in the myenteric plexus in the caecum of postnatal and adult mouse D. GRUNDMANN*, E. LORIS*, L. MARX*, E. WILMS*, L. AGNEIS*, S. COUILLARD-DESPRES*, C. REINHARDT² and K.-H. SCHÄFER² *ENS Group, University of Applied Sciences Kaiserslautern/Zweibrücken, Germany, ²Center for Thorbism and Hemostasis CTH, Johannes Gutenberg-University, Mainz, Germany and ³Spinal Cord Injury and Tissue Regeneration Center Salzburg SCTi-TrCS, Paracelsus Medical University Salzburg, Austria

The enteric nervous system originates from the enteric neural crest stem cells at embryonic stage but also from Schwann cell precursors, which colonize the intestine at later embryonic stages and differentiate into neurons after birth. The expression of Sox2 was currently described in glial cells and progenitors in the midgut after birth. In this study, the Sox2 expression in the myenteric plexus of the mouse caecum was investigated. The caecum is an important site of fermentation and harbors a huge number and variety of microbes. These permanent environmental stimuli should be mirrored in the phenotype of the neurons, glial cells and their progenitors. The Sox2 expression was revealed in combination with glial and neuronal markers by immunofluorescence stainings at the postnatal and adult stage in normal mice. Moreover, germfree mice were used in order to investigate the impact of the microbiota upon the Sox2 expression. As expected the expression of Sox2 was predominantly found in glial cells that expressed S100 or GFAP. Moreover, there were also Sox2 expressing cells in the myenteric plexus with a neuronal marker in normal mice. In germfree mice, the Sox2 cells were present in both postnatal and adult mice. Roughly 80% of the glia contained Sox2 cells at both ages. The Sox2 cells were also present in adult germfree mice. In conclusion, Sox2 is expressed in both enteric glia and neurons in the caecum after birth. Most probably Sox2 is not associated with self-renewal in postmitotic enteric neurons and exerts other functions such as cell survival. The Sox2 expression in neurons depends not on the presence of the intestinal microbiota.
layer showed a strong spontaneous activity when it was cultured with myenteric cells. The presented study is a first step towards a fully organized artificial gut wall with all necessary cell types implemented.

163 Structural changes of myenteric plexus in animal model of ulcerative colitis

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The myenteric plexus and interstitial cells of Cajal play a prominent role in motor and to a lesser extent secretory function of gastro-intestinal tract. They are affected in inflammatory bowel diseases, including ulcerative colitis and Crohn’s disease. Changes in myenteric neuron or ganglia numbers are well described in colitis. However, alterations in size and geometry of myenteric ganglia, interconnecting nerve tracks and intramuscular fibers are not sufficiently characterized.

Aims: To quantify the morphological changes of the myenteric plexus in the distal colon using a murine model of acute ulcerative colitis.

Methods: Adult male C57Bl/6 mice were used. Acute colitis was induced by 5% aqueous solution of dextran sulfate sodium (50 kDa, AppliChem). A whole mount of muscular layer with the myenteric plexus from the distal colon was marked with the polyclonal antibody against JBl-subulin (ab8207, Abcam), pan-neuronal marker, the polyclonal antibody against 2-kil (ab112177, Abcam), marker for cells of Cajal and stained with the nuclear dye DAPI (ProLong Gold antifade, Life Technologies). Digital images were obtained with Zeiss laser scanning confocal system and analyzed with the ImageJ (JAI) image processing software.

Results: The administration of dextran sodium sulfate caused acute inflammation of the colon with extensive mucosal ulceration. In both groups of mice myenteric neurons formed an interconnected net with no clear boundary between discrete ganglia. In the ulcerative colitis there was a decrease in perimeter to area ratio and mean thickness of myenteric ganglia and interganglionic space. The area occupied by the myenteric plexus was unchanged. There was no significant difference in total cell and neuron number within ganglia between two groups, although there was a decrease in net intersections per plexus area in colitis. The overall number of cells of Cajal, associated with the myenteric plexus was unchanged. The intramuscular fibers were unchanged.

Conclusion: The inflammatory shortening of the colon partially compensated the loss of ganglionic area by thinning the myenteric plexus. These changes may indicate an axonal damage in colitis which in turn may result in impaired colonic motor and secretory function.

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Background: The presence of α-synuclein in the enteric nervous system (ENS) has been demonstrated in Parkinson’s disease (PD), and has recently been reported to be expressed in neurologically intact subjects. However, the functional impact of α-synuclein in the ENS remains unknown, and no studies have shown a causative link between this pathological abnormality and the corresponding gastrointestinal dysfunction.

Therefore, our study aimed to evaluate the association between the presence of α-synuclein and gastrointestinal dysfunction in the human stomach and colon of PD and neurologically intact subjects.

Methods: A total of 35 PD patients and 52 neurologically intact subjects were enrolled in this study. Endoscopic biopsies were performed during the course of an esophagogastroduodenoscopy and/or colonoscopy, and then immunohistochemical staining was performed for α-synuclein. All of the subjects completed the validated Rome III questionnaire for the assessment of gastrointestinal symptoms. The association between gastrointestinal symptoms and the α-synuclein pathology in gastrointestinal mucosa was evaluated.

Results: No significant association was found between the α-synuclein in the stomach and colon mucosa and gastrointestinal symptoms including constipation, dyspepsia symptoms and abdominal discomfort or pain, regardless of whether the subjects had clinical PD or not (p > 0.05).

Conclusions: The presence of α-synuclein in the gastrointestinal mucosal nerve fiber appears not to be associated with gastrointestinal dysfunction. Our present study suggests that the deposition of α-synuclein in the ENS is not reflected by functional impairment of the affected segment of the gut.

This study was supported by a grant of the Korea Healthcare Technology R D Project, Ministry of Health & Welfare, Republic of Korea (no. HI14C2206, HI06C0868 and HI15C3078), and the Bio & Medical Technology Development Program of the National Research Foundation [NRF] funded by the Korean government (MEST) (no. 2011-0019632).
cause of dose reduction and delay presenting a constant challenge in the efficient and tolerable treatment of cancer. Oxaliplatin (OXL), a third generation platinum-based chemotherapeutic is specifically associated with high rates of GI dysfunction. The mechanismsunderpinning these side-effects is yet to be elucidated, however OXL administration has been found to result in significant enteric neuronal loss associated with long-term GI dysmotility. In this study we investigated the effects of OXL on myenteric neurons and GI function and present evidence of the neuroprotective effect of a novel PARP-1 inhibitor, BGP-15.

Methods: Balb/c mice (6–8w), received intraperitoneal OXL (3 mg/kg/d) with or without BGP-15 (15 mg/kg/d) for 14 days. GI transit was analysed in vivo prior to and at 3, 7 and 14 days post-treatment via serial x-ray imaging using contrast agent BaSO4. Following 14 days of OXL+BGP-15 (n = 10/group), colons were collected for assessment of ex vivo colonic motility, circular muscle tone, neuronal mitochondrial superoxide (O^-2) and immunohistochemical analysis of myenteric neurons.

Results: Chronic OXL administration induced a decrease in mitochondrial O^-2 as well as nitrosylation of proteins, release of cytochrome c and neuronal apoptosis in the myenteric plexus. OXL administration altered the response of circular muscles to the NO donor, Sodium Nitroprusside which correlated with a significant delays to overall GI transit and reduced colonic motor activity. Co-administration of OXL with BGP-15 protected against myenteric neuronal loss, significantly reduced mitochondrial O^-2, alleviated delays in GI transit and restored colonic motor patterns.

Conclusions: This study is the first to examine the effects of OXL+BPG-15 co-administration on GI function and enteric neuronal survival. Our results indicate that co-administration of BGP15 protects against OXL-induced neuronal loss whilst improving colonic motility and overall GI transit. These results suggest that BGP-15 may be a potential treatment for relieving GI side-effects associated with OXL therapy.

168 Canonical Wnt pathway regulates the neurogenic potential of enteric neural progenitor cells

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Within the last 15 years there has been a growing realization of a role for the canonical Wnt pathway in the colon. This pathway has been shown to be involved in the expansion of neural progenitors in vitro and vivo. Canonical Wnt signaling increases the proliferation of differentiated neural progenitors and leads to a higher yield of differentiated neurons in vivo, both in humans and mouse models. Additionally, we identified the expression of signaling components of the Wnt pathway in human gut sections, like Frizzled-4. Further this marker can be used for FACs-based isolation of neural progenitors from human tunica muscularis, that give rise to enteric neurons in culture. These results contribute to a better understanding of the molecular mechanisms regulating the postnatal enteric neuronal progenitor cell pool. Ongoing and future work will elucidate the impact of Canonical Wnt activation on enteric progenitors in vivo as well as the cellular partners involved in progenitor homeostasis in the living animal and human specimen.

170 Understanding mechanisms of rectal prolapse in the mouse model of spontaneous chronic colitis: damage to the muscles and nerves

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Introduction: Patients with symptomatic rectal prolapse often suffer from constipation, incomplete rectal evacuation, excessive straining at stool, fecal incontinence, anal pain and rectal ulcers. The aetiology underlying rectal prolapse is unclear and has been linked to advanced age, chronic constipation/diarrhoea, increased abdominal pressure, and prior hysterectomy. The Winnie mice have chronic inflammatory disease with severe mucosal damage, goblet cell loss, thickening of muscle and mucosal layers, and display symptoms of diarrhoea (not watery), ulcerations, rectal bleeding and pain similar to those in human IBD. However, only about 25% of Winnie mice develop rectal prolapse. The reason why not all Winnie mice develop prolapse is unknown. Enteric nervous system (ENS) is the key regulator of intestinal motility and abnormalities of the ENS are associated with gastrointestinal motility disorders. However, studies on changes in intestinal...
innervation in humans and animal models with rectal prolapse are extremely scarce.

**Method:** In this study we investigated changes in the total number of myenteric and subpopulations of inhibitory motor neurons and evaluated changes in the density of sensory afferents, sympathetic and parasympathetic fibers in the rectum colon of *Winnie* mice with \( n = 21 \) and without rectal prolapse \( n = 21 \) using immunohistochemistry and confocal microscopy. Functional changes in the rectum were studied using force transducers \( n = 6 \) (group).

**Result:** The results of this study demonstrated that rectal prolapse in *Winnie* mice is associated with enhanced levels of inflammation, gross morphological damage and muscular hypertrophy of the rectum. Animals with prolapse had more severe damage to the rectal innervation compared to *Winnie* mice without prolapse. This includes more severe neuronal loss in the myenteric plexus, loss of nNOS-immunoreactive (IR) neurons which has not been observed in non-prolapsed mice, and more severe loss of VACHT IR fibers. Both *Winnie* mice with and without prolapse had comparable levels of noradrenergic and sensory fiber loss in the rectum. These changes in the ENS correlated with changes in the rectal colon contractile activity in mice with prolapse.

**Conclusion:** This is the first study providing evidence that damage and death of enteric neurons including nitrergic neurons in myenteric ganglia as well as the loss of cholinergic nerve fibers are important factors in structural and functional changes in the rectum of mice with rectal prolapse.

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Withdrawn.

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Glial PGE2 production induced by inflammation regulates glial response to ATP.

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Enteric glial cells (EGC) are essential to intestinal epithelial barrier (IEB) homeostasis. In healthy intestines, EGC reduce IEB permeability and promote mucosal healing. In inflammatory bowel disease (IBD) such as Crohn’s Disease (CD) and Ulcerative Colitis (UC), both EGC phenotype and IEB functions are altered, but putative involvement of EGC in IBD pathogenesis remains unknown. If the astrocyte reactivity is well studied, the reaction of EGC to chronic inflammation is not well documented. We investigated whether EGC impact on IEB permeability was altered in an inflammatory environment and in EGC from IBD patients. Rat EGC as well as human EGC from control, CD and UC patients were stimulated with the cytomix TI (TNFalpha/ILbeta, 1 ng/mL) for 1 or 4 days. Reactive EGC phenotype where characterized and reactive EGC functional impact on IEB permeability was studied in *vitro* using human intestinal epithelial cells (IEC) in a non-contact co-culture model, or in *vivo* by grafting the treated rat EGC in colon wall of Sprague Dawley rats. Rat and human control EGC induced a significant reduction of IEB paracellular permeability after TI treatment when compared with untreated or LPS treated EGC. LPS or TI treatment had no significant effects on IEC alone. In *vivo* colon wall grafting with control EGC did not modify the permeability whereas colon wall grafting with EGC preconditioned by TI significantly reduced the permeability when compared to control animals. Human EGC from control or UC patients treated with TI induced a decrease in IEB permeability too, but EGC from CD patients did not. This work is not only the first evidence showing that reactive EGC can have beneficial effects upon IEB permeability, but also shows that EGC from CD but not UC patients have lost these reactivity. This could define EGC as active players in CD pathogenesis.

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Prenatal development of the myenteric plexus at the human ileocaecal junction

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Background: The neural crest cells derived enteric nervous system (ENS) is the complex division of autonomic nervous system which can function independently. Paucity of existing literature on the development of MP (myenteric plexus) at human ileocaecal junction

control and an increased reactivity. In addition our work suggests that PGE2 glial production could participate in the differences observed between CD and UC patho-
logical features.
Innovations of ICJ may help in reconstruction of the ICJ from fetal ICJ from 9 to 33WG. The knowledge of the neuron density towards the tip of the ICJ may help in reconstruction of the ICJ for better model of ileal contents and to prevent retrograde flow of caecal content into the ileum.

Conclusion: This study represents a morphometric analysis of the development of innervation of human foetal ICJ from 9 to 33WG. The knowledge of the innervations of ICJ may help in reconstruction of the ICJ for better model of ileal contents and to prevent retrograde flow of caecal content into the ileum.

Platinum accumulation and changes in mitochondrial function of the longitudinal muscle and myenteric plexus following oxaliplatin administration

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Introduction: Oxaliplatin (OXL) is a platinum (Pt)-based anti-cancer agent that causes chronic neurotoxicities and gastrointestinal (GI) side-effects that compromise treatment. We hypothesised that Pt accumulation in the longitudinal muscle-myenteric plexus (LMMP) causes cell damage/death that may be implicated in GI dysfunction. We investigated: (i) concentration of Pt and copper (Cu) in nuclear and mitochondrial fractions of the LMMP; (ii) expression of the Cu transporter 1 (CTR1) receptor involved in Pt drug influx; (iii) expression of damage-associated molecular patterns (DAMPs); calreticulin and high-mobility group protein box 1 (HMGB1)); and (iv) mitochondrial function of LMMP cells.

Methods: Balb/c mice received i.p. injections of OXL (4 mg/kg/day) or sterile water tri-weekly for 2 weeks. At the end of the treatment mice were culled and the LMMP was harvested for Pt and Cu mapping using laser ablation inductively coupled plasma mass spectrometry, and dissociated to isolate the nuclear and mitochondrial fractions to quantify Pt and Cu using atomic absorption spectrophotometry. The expression of CTR1 and DAMPs in myenteric neurons was investigated immunohistochemically. Mitochondrial and anaerobic functions of LMMP cells were assessed via extracellular flux analysis.

Results: A significant amount of Pt was found in the nuclear and mitochondrial fractions of the LMMP following OXL, but not vehicle treatment. No changes to Cu concentration was observed but CTR1 expression was reduced in myenteric neurons following OXL (p < 0.01), but not vehicle treatment. Cytoplasmic translocation and nuclear overexpression of calreticulin (p < 0.05) and HMGB1 (p < 0.01) was found in myenteric neurons following OXL but not vehicle treatment. OXL depressed mitochondrial basal respiration and anaerobic potential as indicated by reduced oxidative and anaerobic metabolic potential (all p < 0.05) when compared to vehicle-treated.

Conclusions: Pt from OXL accumulates within the LMMP, induces the hallmark presentation of DAMPs indicative of cell damage, and depresses mitochondrial function. These data implicate damage to the LMMP by OXL in the pathobiophysics of chronic GI dysfunction and side-effects associated with this agent.

Postsynaptic proteins are vital components of postsynaptic densities, but little is known about the expression of postsynaptic proteins in the enteric nervous system. PSD-93 [chapsyn-110/SAP90] is a member of membrane-associated proteins (MAGUK) postsynaptic protein family. In the central nervous system, PSD-93 interacts with several postsynaptic molecules including neurelin, SHANKs and particularly neuronal nitric oxide synthase (nNOS), but little is known about its expression and role in the enteric nervous system. We conducted a systematic investigation of the expression of PSD-93 in the myenteric plexus of mouse colon.

Introduction: Oxaliplatin (OXL) is a platinum (Pt)-based anti-cancer agent that causes chronic neurotoxicities and gastrointestinal (GI) side-effects that compromise treatment. We hypothesised that Pt accumulation in the longitudinal muscle-myenteric plexus (LMMP) causes cell damage/death that may be implicated in GI dysfunction. We investigated: (i) concentration of Pt and copper (Cu) in nuclear and mitochondrial fractions of the LMMP; (ii) expression of the Cu transporter 1 (CTR1) receptor involved in Pt drug influx; (iii) expression of damage-associated molecular patterns (DAMPs); calreticulin and high-mobility group protein box 1 (HMGB1)); and (iv) mitochondrial function of LMMP cells.

Methods: Balb/c mice received i.p. injections of OXL (4 mg/kg/day) or sterile water tri-weekly for 2 weeks. At the end of the treatment mice were culled and the LMMP was harvested for Pt and Cu mapping using laser ablation inductively coupled plasma mass spectrometry, and dissociated to isolate the nuclear and mitochondrial fractions to quantify Pt and Cu using atomic absorption spectrophotometry. The expression of CTR1 and DAMPs in myenteric neurons was investigated immunohistochemically. Mitochondrial and anaerobic functions of LMMP cells were assessed via extracellular flux analysis.

Results: A significant amount of Pt was found in the nuclear and mitochondrial fractions of the LMMP following OXL, but not vehicle treatment. No changes to Cu concentration was observed but CTR1 expression was reduced in myenteric neurons following OXL (p < 0.01), but not vehicle treatment. Cytoplasmic translocation and nuclear overexpression of calreticulin (p < 0.05) and HMGB1 (p < 0.01) was found in myenteric neurons following OXL but not vehicle treatment. OXL depressed mitochondrial basal respiration and anaerobic potential as indicated by reduced oxidative and anaerobic metabolic potential (all p < 0.05) when compared to vehicle-treated.

Conclusions: Pt from OXL accumulates within the LMMP, induces the hallmark presentation of DAMPs indicative of cell damage, and depresses mitochondrial function. These data implicate damage to the LMMP by OXL in the pathobiophysics of chronic GI dysfunction and side-effects associated with this agent.

Postsynaptic proteins are vital components of postsynaptic densities, but little is known about the expression of postsynaptic proteins in the enteric nervous system. PSD-93 [chapsyn-110/SAP90] is a member of membrane-associated proteins (MAGUK) postsynaptic protein family. In the central nervous system, PSD-93 interacts with several postsynaptic molecules including neurelin, SHANKs and particularly neuronal nitric oxide synthase (nNOS), but little is known about its expression and role in the enteric nervous system. We conducted a systematic investigation of the expression of PSD-93 in the myenteric plexus of mouse colon.

Standard triple labeling immunohistochemical studies were conducted on adult c57B16 colon myenteric plexus whole mounts. Potential colocalization of PSD-93 with the pan-neuronal marker, Hu, and enteric neuronal subtype markers including nitric oxide synthase (nNOS), choline acetyltransferase (ChAT) and calretinin (CaR), which labels a subset of ChAT neurons, were examined. Ten confocal micrographs (LSM550, 40x objective) were obtained from each preparation and immunoreactive cells were counted using ImageJ software. Immunoreactivity for PSD-93 was predominantly observed in the cytoplasm of neuronal cell bodies and in some dendritic and axonal processes. No differences were observed in proportions of PSD93 positive neurons in proximal, mid and distal colon. In the distal colon, PSD-93 was expressed in 71 ± 3% [n = 8 mice] of the total number of Hu-neurons. PSD-93 was expressed 61 ± 6% [n = 3] of nNOS+, 68 ± 8% [n = 2] of ChAT+ and 56 ± 4% [n = 3] of CaR+ neurons. Of the PSD-93 immunoreactive neurons counted, 56 ± 3% [n = 3], 45 ± 4% [n = 2] and 34 ± 2% [n = 3] were positive for nNOS, ChAT and CaR, respectively. Overall, PSD-93 was in multiple subtypes of myenteric neurons, but many neurons lacked this protein, while some PSD-93 neurons lacked both nNOS and ChAT.

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Previously, we have identified NDRG4 promoter CpG island methylation as a promising biomarker for the early detection of colorectal cancer (CRC, Melotte et al. INCI, 2009). The biomarker potential has been confirmed independently by other groups and NDRG4 is currently included in an FDA approved multi target stool DNA test (Cologuard is currently included in an FDA approved multi target stool DNA test (Cologuard)), which is able to accurately detect CRC and advanced precancerous lesions [5]. Surprisingly, given its connection to CRC, the expression pattern and functional role of NDRG4 in the gastro-intestinal (GI) tract has not yet been investigated. In this study we used immunohistochemistry to visualize the whole-body expression of NDRG4, with a focus on the GI tract in mouse and human. Additionally, whole-mount preparations of mouse intestine were labeled with antibodies against NDRG4, the glial fibrillary acidic protein (GFAP), the pan-neuronal marker HuCD, neuronal nitric oxide synthase (nNOS) and Calretinin. Immunofluorescent read-outs were evaluated using confocal microscopy. We discovered that NDRG4 immunoreactivity in the intestine is restricted to the enteric nervous system, in both mouse and man. More precisely, NDRG4 labeled cell bodies inside ganglia of the myenteric (Auerbach’s) and submucosal (Meissner’s) plexus. Furthermore, the nerve fibers connecting the ganglia in both plexus, and innervating the muscularis mucosae and externa showed NDRG4 reactivity. Using whole-mount mucosal intestinal preparations, we observed that NDRG4 was only expressed in neurons, as NDRG4 positive cells were always labeled for the pan-neuronal marker HuCD, but never colocalized with the glial cell marker GFAP. NDRG4 expression was found in a subset of Calretinin positive neurons but was virtually absent in the nNOS expressing population. The specific neuronal expression of NDRG4 was observed in most of the other murine organs tested (e.g., heart, lungs, skin, liver). In the central nervous system, NDRG4 is predominantly expressed in various neurons of the cerebrum and Purkinje cells of the cerebellum, which has previously been described. We conclude that within the intestine NDRG4 is exclusively expressed by enteric nerves and that it can be used for identifying neuronal structures in the gastrointestinal tract. How the expression pattern of NDRG4 associates with its potential as a biomarker for early CRC detection and its function in the gut, is subject for future investigation.

Epidemiology, Genetics, Cross-Cultural and Psychosocial Factors in Functional GI Disorders in Adults


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Summary: Studies on systematic assessment of ROME III diagnostic questionnaire were limited. This study aims to assess the clinical value of ROME III questionnaire for Functional Gastrointestinal Disorders (FGIDs) in Chinese and to evaluate diagnostic significance of endoscopy and ultrasound in FGIDs.

Methods: Patients with gastrointestinal symptoms who attended the out-patient department of 2 hospitals in Hubei, China were recruited. Adult patients without red flag were empirically diagnosed with FGIDs and were included for analysis. Upper and/or lower gastrointestinal endoscopy were performed depending on their symptoms. All participants underwent abdominal ultrasound. We collected the demographic data, and used ROME III questionnaire for symptom assessment. Final diagnosis was based on questionnaire and examinations outcomes. Data of both the symptom questionnaire and the examinations carried out were analyzed.

Results: 69.3% (443/639) patients were finally diagnosed FGIDs. As for the differential diagnosis from organic diseases, the sensitivity and specificity for ROME III questionnaire were 88.3% and 45.9% respectively with good consistency (κ = 0.57). As for different location of FGIDs, PPV of questionnaires were 68.2% [30/44], 72.7% [197/271] and 90.1% [164/182] respectively for FGIDs in esophagus, gastro-duodenum and intestine. Among the patients diagnosed FGIDs by questionnaires, positive rate of endoscopy and ultrasound were higher in patients with upper gastrointestinal tract symptoms than those with lower gastrointestinal tract symptoms. In the 497 patients diagnosed FGIDs by questionnaires, 2 (0.4%) got cancer and 22 (4.4%) got precancerous diseases. The possibility of misdiagnosis was related with age rather than gender. Patients older than 34.5 with upper gastrointestinal symptoms and those older than 47.5 with lower gastrointestinal symptoms were more likely to be misdiagnosed as having FGIDs.

Conclusion: ROME III questionnaire is a valuable diagnostic tool especially for screening FGIDs. However, the diagnostic efficacy varies with the location of symptoms in Chinese. For further diagnosis and exclusion of organic diseases, endoscopy and ultrasound still have irreplaceable value.
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Marijuana users do not have increased healthcare utilization after an NHANES study

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Background: Legalization of marijuana has led to its widespread use in the US for multiple conditions such as pain, nausea and vomiting, anxiety and also recre-ational purposes over the past few years. However, the impact of marijuana use on health and health care utilization remains unclear. In fact, chronic cannabis use has been linked to cyclic vomiting and resultant hospitalizations. We thus sought to determine the impact of marijuana use on health care utilization including outpatient healthcare visits and hospital admissions in a large sample of the US population.

Methods: We queried the US National Health and Nutrition Examination Survey (NHANES), 2011–2012 and identified adults, 18–59 years of age, who used marijuana. We performed a univariate and multivariate analysis to determine if marijuana use or frequency of use affected health care utilization (outpatient health-care visits and hospital admissions). Variables with a p-value ≤0.2 on univariate analysis were included in the multivariate analysis.

Results: Of 174 159 864 US adults, 53% stated that they used marijuana, 35% denied marijuana use and the remaining 12% did not respond to the question. Marijuana users were more likely to be Caucasian (71%), male (56%) and have a history of smoking (39%), alcohol use (20%) or polysubstance abuse (33%). Number of outpatient healthcare visits (visit to doctor’s office or emergency room over the past year) were similar in both marijuana users and non-users (adjusted OR 1.03, 95% CI: 0.73–1.46, p = 0.8). Similarly, marijuana use was not associated with increased hospital admissions compared to nonusers (adjusted OR 0.85, 95% CI: 0.56–1.28, p = 0.4). Frequency of marijuana use also did not affect health care utilization. On comparison of marijuana users smoking ≥38 pipes/day versus those smoking 1–2 pipes/day, there was no significant difference in outpatient healthcare visits (adjusted OR 1.27, 95% CI: 0.72–2.25, p = 0.39) or hospital admission (adjusted OR 1.35, 95% CI: 0.72–2.48, p = 0.31).

Conclusions: This study finds that marijuana use is not associated with increased health care utilization contrary to popular belief. These findings cannot be used to support the use of marijuana given its multiple adverse effects. Rather, this study provides the basis to examine the impact of marijuana on health care utilization in the future, given the projected increase in marijuana use in the US.

Involvement of enteric glial cells in diverticular disease

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Background: Diverticular disease (DD) is associated with intestinal motility dysfunctions, enteric neuropathy and down-regulation of neurotrophic factors such as GDNF. Enteric glial cells (EGC) are important regulators of intestinal motility and this function was recently shown to be mediated by EGC-specific expression of the gap junction protein Connexin 43 (Cx43). However, whether the EGC population is altered in DD remains unclear.

Material and Methods: Expression of the glial markers S100β, GFAP, Sox10 and of Cx43 was measured by qPCR in the tunica muscularis and in isolated myen-teric ganglionic tissue from the sigmoid colon of patients with DD and controls. Expression of S100β, GFAP and Cx43 in the myenteric plexus of patients with DD and controls was further assessed using immunohistochemistry and the impact of GDNF on the expres-sion of glial markers and of Cx43 was analyzed in primary rat myenteric nerve cell cultures.

Results: No major changes in mRNA expression were observed for the analyzed glial markers in vitro. S100β and GFAP immunoreactivity was not altered in patients with DD, whereas Cx43 immunoreactivity was decreased in 5 out of 15 patients with DD in comparison to controls. Expression of Cx43 was further increased after treatment with GDNF in vitro, whereas GDNF had no impact on S100β, GFAP or Sox10 expression.

Conclusions: The preliminary results do not support previous studies showing decreased S100β expression in patients with DD and suggest that DD is associated with only limited alterations of the EGC network as compared to enteric neurons. Furthermore, our study indicates that Cx43 expression is regulated by GDNF, and Cx43 downregulation might contribute to the pathology of DD in a subset of patients. Further experiments are required to fully characterize the potential implication of EGC in DD.

The genetics of irritable bowel syndrome in 800,000 Europeans: the bellgyenes initiative

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A hereditary component of irritable bowel syndrome (IBS) has been demonstrated in family and twin studies. However, genetic studies in IBS so far have been mainly limited to candidate genes in small sample sets of cases and controls, and no unequivocal IBS risk locus has been identified. The only exception is represented by the TNFSF15 gene we originally reported associated with risk of IBS in Sweden and USA [PMID 21636646], and which has later shown similar effects in independent cohorts from UK and Canada [PMID’s 24041540 and 22684480]. Because of its high prevalence, we recently proposed the use of population-based cohorts for genetic studies of IBS. Existing genotypic and phenotypic information may be exploited to discover IBS genes with a considerable impact in a single size and homogeneity [PMID 23826979]. Using data from questionnaires and the Rome criteria, we conducted the first genome-wide association study (GWAS) of IBS in a Swedish general population sample, and replicated findings in 6 inde-pendent EU/USA case-control cohorts [PMID 25248455]. Hence, population-based cohorts provide excellent opportunities to study the genetic architecture of IBS and related gastrointestinal symptoms. The bellgyenes initiative is a transnational project recently approved by the European Biobanking and Biomedical Resources Research Infrastructure – Large Prospective Cohorts (bbmri-lpc), aiming to study IBS and genotype in a target population exceeding 800,000 Europeans.

Through GWAS studies and their meta-analyses, we will make use of genotype data in relation to a series of IBS definitions, based on questionnaire data [Rome Criteria], self-reported conditions, and ICD10 diagnoses from electronic medical/healthcare records. The bellgyenes initiative will contribute pathophysiological understanding that can help explain the etiology of IBS, inform molecular reclassifications of the disease, and ultimately aid the development of new therapeutic strategies. The strategic pipeline of data access and use, current state of the art, and preliminary results from the analysis of 25 000 individuals will be discussed.
Psychosocial features of irritable bowel syndrome in the study of health in Pomerania (SHIP)  

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Conclusion: People in Northeast Germany fulfilling IBS cohorts in Germany and elsewhere. Thus, this survey criteria show similar characteristics as patients from IBS GRABE and H. M. OHLER study of health in Pomerania (SHIP) 187

Results: When Rome-III criteria for IBS were applied to the other regions of Germany (11.5%), we expected approximately 589 returned a postal questionnaire, asking for sociographic data, clinical symptoms, comorbid conditions, medication intake, and health care behavior related to constipation. Among them, 245 reported some somatic diagnoses, and another 120 regular medication intake. They were compared to individuals without comorbid condition and presumed functional constipation (n = 215). We also used the Rome criteria for IBS-C and functional constipation to evaluate the specificity of the criteria.

Methods: Of 1087 individuals with constipation identified during a telephone survey, 589 returned a postal questionnaire, and high health and social status (both p < 0.001) but similar general life satisfaction (n.s.). Their quality-of-life was lower for the physical (p < 0.001) but not for the mental health domain (n.s.) (SF12), while among those with functional constipation, the mental health domain distinguished IBS-C individuals from those with functional constipation but without pain (p < 0.001). Specificity of the Rome-III diagnostic criteria was 52.6% for IBS-C and 45.7% for Functional Constipation.

Conclusion: In an unselected population sample with constipated individuals, those with a comorbid condition outnumber those with functional constipation but without pain (< 0.001). Specificity of the Rome-III diagnostic criteria was 52.6% for IBS-C and 45.7% for Functional Constipation.

Comorbidity in chronic constipation  
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Background: Comorbidity in chronic constipation has rarely been investigated, despite the fact that constipation can occur as one symptom in a number of neurological, systemic and other non-intestinal and intestinal disorders.

Methods: Of 1087 individuals with constipation identified during a telephone survey, 589 returned a postal questionnaire, asking for sociographic data, clinical symptoms, comorbid conditions, medication intake, and health care behavior related to constipation. Among them, 245 reported some somatic diagnoses, and another 120 regular medication intake. They were compared to individuals without comorbid condition and presumed functional constipation (n = 215). We also used the Rome criteria for IBS-C and functional constipation to evaluate the specificity of the criteria.

Results: Individuals reporting a somatic comorbid condition and/or regular medication had a similar sex distribution (n.s.) but were significantly older than those with functional constipation (62.7 ± 15.8 and 43.7 ± 15.5 years, resp., p = 0.001), and had lower health and social status (both p < 0.001), but similar general life satisfaction (n.s.). Their quality-of-life was lower for the physical (p < 0.001) but not for the mental health domain (n.s.) (SF12), while among those with functional constipation, the mental health domain distinguished IBS-C individuals from those with functional constipation but without pain (p < 0.001). Specificity of the Rome-III diagnostic criteria was 52.6% for IBS-C and 45.7% for Functional Constipation.

Conclusion: In an unselected population sample with constipated individuals, those with a comorbid condition outnumber those with functional constipation but without pain (< 0.001). Specificity of the Rome-III diagnostic criteria was 52.6% for IBS-C and 45.7% for Functional Constipation.

Psychological factors influence the overlap syndrome in functional gastrointestinal disorders (FGIDs) among middle aged women in South Korea  
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Objective: The purpose of this study was to investigate the psychological factors influence the overlap syndrome in FGIDs and their effect on quality of life among middle aged women in South Korea.

Methods: This study examined data collected from 627 middle aged women. After selecting FGIDs according to the Rome II diagnostic criteria, we measured psychological factors by self-reported questionnaire. Depression and anxiety were identified using the Patient Center for Epidemiologic Studies Depression scale (CES-D) and Beck Anxiety Inventory (RAI). Negative cognition and cognitive triad were identified using the Automatic Thoughts Questionnaire-Negative (ATQ-N) and the Cognitive Triad Inventory (CTI). Resilience and quality of life were identified using the Connor-Davidson Resilience Scale (CD-RISC) and World Health Organization Quality of Life scale abbreviated version (WHOQOL-BREF). The scores for depression, anxiety, QOL, and negative cognition were analyzed. The correlation between psychological factors and QOL was also analyzed and performed a hierarchical regression analysis.

Results: Overlap syndrome had the highest CES-D (16.66 ± 11.79, p ≤ 0.001), BAI (17.46 ± 16.7, p ≤ 0.001), and ATQ-N score (53.61 ± 20.88, p ≤ 0.001) followed by non-overlap syndrome and healthy control. Healthy controls had the highest WHOQOL-BREF score (77.69 ± 13.5, p < 0.001). According to the WHOQOL-BREF, depression, anxiety, negative cognition, cognitive triad and resilience were significantly correlated with QOL in overlap syndrome of FGIDs. After the stepwise selection, the final model explained 61.8% of the CI variance, and contained three significant variables: resilience (β = 0.443, p < 0.001), negative cognition (β = -0.234, p = 0.006), and cognitive triad (β = -0.280, p = 0.007).

Conclusion: These results indicate that psychological factors are associated with overlap syndrome of FGIDs. Acknowledging this common comorbidity may facilitate recognition and treatment, and opens new questions as to the pathways and mechanisms of the association.
Background: Depression and somatization are important symptom determinants in patients with gastroesophageal reflux disease (GERD). We aim to investigate the relationship between psychological distress and response to proton pump inhibitors (PPI).

Methods: A total of 50 subjects with mild to moderate GERD symptoms without NSAIDs history [Male: Female = 19: 31, 47.8 ± 16.1 years] were prospectively enrolled and diagnosed with non-erosive reflux disease (NERD, n = 34) and erosive reflux disease (ERD, n = 16) by upper endoscopy. All subjects completed demographic profiles and PHQ-9 and PHQ-15 questionnaires for depression and somatization, respectively. Subjects then received daily PPI (dexlansoprazole 30 mg and 60 mg for NERD and ERD, respectively) therapy for 4 weeks. PPI therapy response was evaluated at 2nd and 4th week using symptom questionnaire including frequency and severity of acid regurgitation, heart burn and epigastric fullness.

Results: The rate of complete (≥80%) satisfactory (79–50%), partial (<50%) and refractory responses at 2nd week were 46%, 27%, 19% and 8%, respectively. And final response rates at 4th week were 62%, 24%, 10% and 4%, respectively. There was no statistical difference in respects to sex, endoscopic finding and BMI between complete (≥80%) vs incomplete (<80%), or satisfactory (≥50%) vs unsatisfactory (<50%) groups. PHQ-9 score, PHQ-15 score, total PHQ score, depression (PHQ-9 ≥10) and somatization (PHQ-15 ≥10) were also not statistically different between these groups. In addition, there was no difference between ERD and NERD group for above parameters and response rate to PPI. Although combined fullness could not affect on response rate to PPI, patients with fullness showed statistically higher PHQ-15 score, somatization and female predominance compared to patients without fullness.

Conclusions: Depression and somatization seems to have no effect on response rate to PPI treatment in patients with mild to moderate GERD symptoms. Epigastric fullness is related to somatization and gender difference.

Irritable bowel syndrome ten years after acute Giardia lamblia infection: A controlled prospective cohort study

Background: Serotonin (5-HT), as a main neurotransmitter of the gut-brain axis, plays a key role in the pathophysiology of irritable bowel syndrome (IBS). Although serotonin pathway genes in IBS have been widely studied extensively, the findings remain inconsistent.

Aims: To assess the association of six polymorphisms of serotonin-related genes with different subtypes of IBS.

Methods: Ninety five IBS patients selected according to the Rome II criteria (mean age ±SD: 49 ± 14, range: 18–73 years, gender: 81 F, 14 M) participated in the study. Six polymorphisms were genotyped: (i) the 44 bp insertion/deletion polymorphism in the promoter region (5-HTTLPR) of serotonin transporter gene (SLC6A4), (ii) the 5-HT1A receptor gene (HTR1A) C102T polymorphism (rs6295), (iii) the 5-HT2A receptor gene (HTR2A) C102T polymorphism (rs6313), (iv) the 5-HT2C receptor gene (HTR2C) cys25ser polymorphism (rs6318), and (v) the tryptophan hydroxylase-1 gene (TPH1) A218C polymorphism (rs45703). The 5-HTTLPR polymorphism was determined using PCR-based method. Single nucleotide polymorphisms were detected by minisequencing method. Differences in the genotypic distribution of the studied polymorphisms between different IBS subtypes were analyzed using chi-squared test. All tests were two-tailed with 0.05 level of significance.

Results: According to the bowel habit, the IBS patients were divided into three subgroups including 32% of patients with constipation (IBS-C), 32% of patients with diarrhea (IBS-D), and 36% of patients with mixed bowel habits (IBS-M). No statistically significant differences in the genotypic distribution of the studied polymorphisms between different IBS subtypes were found (p-values >0.05). An additional analysis in which two subgroups of the patients were compared: IBS constipated subjects vs IBS non-constipated subjects (including both IBS-D and IBS-M). The 5-HTTLPR polymorphism also did not reveal any significant association with the polymorphisms distribution (p-values >0.05).

Conclusions: Our results do not provide any evidence for the association between the serotonin-related gene variants with different stool characteristics in IBS patients.
Psychological stress increases placebo and nocebo effects on urge-to-defecate induced by rectal distensions

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Background: The placebo effect constitutes a prominent example of psychological influences on clinical symptoms. Within gastroenterology, the neurological mechanisms and clinical relevance of placebo effects are well-characterized in the context of visceral pain and hyperalgesia in IBS. Nocebo effects remain understudied, and urge-to-defecate, a symptom of broader clinical relevance, has not been studied in the context of placebo research. Therefore, the first aim was to test placebo and nocebo effects on urge-to-defecate, induced by different treatment expectations. The second aim was to test effects of psychological stress on placebo and nocebo effects on urge-to-defecate induced by rectal distensions with a barostat.

Methods: In 120 healthy volunteers (60 women, 60 men), urge-to-defecate in response to individually calibrated distensions were measured with visual analogue scales (VAS) at baseline. Participants were then randomized to a psychological stress condition (public speaking stress, N = 60) or a control condition (easy cognitive task, N = 60). Subsequently, a second randomization was achieved among groups receiving positive verbal instructions (placebo, N = 40), negative verbal instructions (nocebo, N = 40) or neutral instructions (control, N = 40) regarding an intravenous treatment with a substance that in reality was only saline. In a test session, the same distensions were repeated, and changes in VAS were compared between groups using ANOVA and post-hoc tests. Stress effects were quantified by state anxiety, cardiovascular measures and salivary cortisol.

Results: Perceived urge-to-defecate was significantly influenced by the placebo and nocebo instructions across groups (main effect of condition: p < 0.001). Stress led to significant increases in state anxiety (p < 0.001), heart rate (p = 0.035), systolic blood pressure (p < 0.001) and cortisol levels (p < 0.001). An interaction between instruction and condition was observed (p = 0.033). Compared to the control condition, stress increased the magnitude of both placebo and nocebo effects on urge-to-defecate.

Conclusion: Urge-to-defecate is modifiable by expectancies as key mechanisms of placebo and nocebo responses in healthy individuals. Both placebo and nocebo effects are modulated by psychological stress. These findings have broad implications for many clinical conditions in gastroenterology and call for an integration of psychological concepts into interventions.

196 Psychological factors influence the overlap syndrome in functional gastrointestinal disorders and their effect on quality of life among firefighters

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Objectives: The purpose of this study was to investigate the psychological factors influence the overlap syndrome in functional gastrointestinal disorders (FGIDs) and their effect on quality of life among firefighters in South Korea.

Methods: Within a cross-sectional survey, 1140 firefighters completed validated questionnaires regarding FGIDs including gastroesophageal reflux disease (GERD), functional dyspepsia (FD), irritable bowel syndrome (IBS) and functional constipation (FC) by at least once a week of typical reflux symptoms and Rome III criteria. Depression symptoms and anxiety were identified using the Patient Centered Epidemiologic Studies Depression scale (CES-D) and Beck Anxiety Inventory (BAI). Negative cognition and cognitive triad were identified using the Automatic Thoughts Questionnaire–Negative (ATQ-N) and the Cognitive Triad Inventory (CTI). Resilience and quality of life were identified using the Connor-Davidson Resilience Scale (CD-RISC) and World Health Organization Quality of Life scale abbreviated version (WHOQOL-BREF).

Results: The overlap syndrome was observed in 76 subjects (12.1%) and each two-way combination of the overlap syndrome was present in overlaps between GERD and IBS were found in 32 subjects (10.7%), GERD and IBS in 22 subjects (21.1%), GERD and FC in 14 subjects (13.4%), FD and IBS in 19 subjects (18.2%), FD and FC in 17 subjects (16.6%). Overlap syndrome had the highest CES-D (F = 16.66, p < 0.001, η² = 0.056), BAI (F = 48.72, p < 0.001, η² = 0.135), and ATQ-N score (F = 15.86, p < 0.001, η² = 0.049) followed by non-overlap syndrome and healthy control. Healthy controls had the highest WHOQOL-BREF score (F = 38.25, p < 0.001, η² = 0.098). According to the WHOQOL-BREF, depressions symptoms, anxiety, negative cognition, cognitive triad and resilience were significantly correlated with QOL in overlap syndrome of FGIDs. After the stepwise selection, the final model explained 61.8% of the CI variance.

Conclusion: These results indicate that psychological factors such as negative automatic thought and resilience are associated with overlap syndrome of FGIDs. Acknowledging this common comorbidity may facilitate recognition and treatment, and opens new questions as to the pathways and mechanisms of the association.
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Adult cyclic vomiting syndrome: What GI motility experts think regarding its diagnosis and management? M. HALL, N. SHANKAR, M. BASHASHATTI and I. SAROSIEK

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Background: Cyclic vomiting syndrome (CVS) in adults is a chronic, functional gastrointestinal disorder with episodes of relentless vomiting and abdominal pain separated by relatively symptoms-free intervals. The aim of our project was to collect opinions of GI motility experts about their perception of the challenges in diagnosis, management, and treatment of CVS.

Methods: A survey with 31 members of ANMS was sent in February 2015.

Results: Forty-five experts responded to our survey. More than 73.3% believed that CVS is under-diagnosed and is not adequately managed. 77.3% considered the management as a challenge. 20% predicted less favorable prognosis for most patients. The primary diagnosis for patients who had initially received a diagnosis other than CVS was usually nonspecific with 26.6%-revaling around migraine, psychiatric disorders, or drug seeking behavior, etc., gastroparesis in 24.4%, and dyspepsia in 19.8%.

Conclusion: A 12-months delay in the final diagnosis of CVS based on 61% of all answers, and at least 6 months delay based on 39% of the responses. 57.7% of experts consider cannabis-induced hyperemesis syndrome as a part of CV vs Based on 88.8% of opinions, migraine headaches largely coincide with CVS, while diabetes mellitus is not a key finding. Marijuana cessation when applicable (40%), tricyclic antidepressants (15.5%), anti-emetics (13.3%) and stress reduction (11.1%) were the most important treatments recommended for CVS. More than 80% of the participants, insufficient management of CVS, results in moderate to severe job or workplace disruptions. 95.5% of responders believe that future evidence-based research should place priority on CVS management and pathophysiology of this GI motility disorder.

Conclusions: The lack of objective data for diagnosing adult CVS, insufficient training of non-neurogastroenterologists in recognizing this entity, and the misattribution of CVS symptoms to neurological, psychiatric, and behavioral disorders result in significant delay in clinical care of CVS patients, as well as sub-optimal management. All of these factors contribute to a significant burden on patients and their families, community and the health care system by this increasingly prevalent entity.

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Differences in lower and upper GI symptoms between individuals with irritable bowel syndrome with constipation and chronic functional constipation E. SHAH*, C. ALMARIO†, B. SPIEGEL‡ and W. CHEY*

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Introduction: Patients with irritable bowel syndrome with constipation (IBS-C) and chronic functional constipation (FC, also known as chronic idiopathic constipation) share many of the same bowel symptoms. We evaluated the distribution of gastrointestinal symptoms among individuals with these disorders in a nationwide sample.

Methods: Individuals meeting Rome III criteria for IBS-C or FC were identified using an NHI PROMIS® questionnaire administered via a novel health app called MyGetHealth. US adults (at least 18 years) identified from an incentivized, opt-in list from a contract research company (Cint) completed the survey (Survey commissioned by Ironwood Pharmaceuticals, Inc.). Participants contributed demographic and gastrointestinal symptom-specific information within the prior 7 days to the dataset. Analysis of symptom distribution using odds ratios (OR) were conducted for IBS-C relative to FC individuals. Regression analysis was used to adjust for demographic variables.

Results: A total of 1009 adults completed the survey and met criteria for IBS-C or FC (275 with IBS-C & 734 with FC). Demographics were similar for both groups with the exception of higher university education, likelihood of being married, and household income among individuals with FC. Adjusting for demographic differences, constipation severity by PROMIS score was worse among individuals with IBS-C vs FC (75.5 ± 21.8 vs 69.5 ± 23.9, p < 0.005). Not surprisingly, the IBS-C cohort reported more frequent & severe abdominal pain than the FC group (76.2 ± 20.1 vs 67.3 ± 26.0, p < 0.001). The IBS-C group also reported more frequent and more severe bloating than FC (77.2 ± 21.7 vs 65.2 ± 27.4, p < 0.001). Differences in upper GI symptoms were also observed. The IBS-C and FC groups had similar prevalence of dysphagia, heartburn and nausea. However, those with IBS-C had more severe heartburn by PROMIS scores than the FC group (68.1 ± 26.4 vs 57.9 ± 27.4, p = 0.002).

Conclusions: In addition to greater levels of constipation and abdominal pain, individuals with IBS-C reported more severe and more frequent bloating than those with FC. Upper GI symptoms are common in both groups but those with IBS-C reported more severe heartburn. These observations raise interesting questions about the pathogenesis and optimal treatments for IBS-C and FC.
L. B. SHERWIN

fulfill this large and unmet gap in curriculum. Training programs should devote resources to
educating non-responders may not be offering GI motility
limited by sampling bias and likely overestimated train-
fellows to perform motility testing. Our results are
therapy;
breath testing, wireless motility capsule, and biofeedback
training is more focused on esophageal testing with
Curriculum minimum standards. Also, GI motility
Conclusions: Sixty-four of 165 GI fellowship programs
interpreted motility tests in 59 programs (92.2%).
observed motility tests in 57 programs (89.0%), and
training derived from the GI Core Curriculum. Trainees
programs met the minimum standards for motility
programs. Twenty-five (39.1%) of responding fellowship
Differing prevalence and disease characteristics of
irritable bowel syndrome between Hispanics, non-
 whites and blacks

W. SZETO

Background: Patients with motility disorders account for
many 50% of GI practice, necessitating the need for
subspecialty training. However, the availability of GI
motility testing, trainee exposure, and nature of training
are unknown. We aimed to assess the breadth and depth of
GI motility tests and training available as well as if
programs met GI Core Curriculum requirements through
a brief survey.
Methods: A survey questionnaire of 14 items was sent to
assess the size of program (number of faculty/fellows),
whether GI motility training is offered, which motility
testing trainees are exposed to, and trainees’ level of
participation – performance/observance/interpretation.
Achievement of minimum standards was defined as
fellow training in esophageal manometry, pH impede-
dance, anorectal manometry, and biofeedback therapy.
Results: Sixty-four of 165 GI fellowship programs
(38.8%) responded to the survey. Only three programs
reported not providing any GI motility training to their
fellows. Of 64 programs, trainees were exposed to
esophageal manometry in 61 (95.3%) programs, pH
impedance in 58 (90.6%) programs, anorectal manome-
try in 43 (66.2%) programs, breath testing in 36 (56.3%)
programs, wireless motility capsule testing in 37
(57.8%) programs, and biofeedback therapy in 26 (40.6%)
programs. Twenty-five (39.1%) of responding fellowship
programs met the minimum standards for motility
training derived from the GI Core Curriculum. Trainees
performed motility tests in 16 programs (25.0%),
observed motility tests in 57 programs (89.0%), and
interpreted motility tests in 59 programs (92.2%).
Conclusions: This survey shows a significant dearth of GI
motility training in the United States with only 39.1% of
responding GI fellowship programs meeting the GI Core
Curriculum minimum standards. Also, GI motility
training is more focused on esophageal testing with
limited training in other areas (anorectal manometry,
breath testing, wireless motility capsule, and biofeedback
therapy; p = 0.05). Only 25% of fellowship programs train
fellows to perform motility testing. Our results are
limited by sampling bias and likely overestimated train-
ing, as non-responders may not be offering GI motility
training. Training programs should devote resources to
fulfill this large and unmet gap in curriculum.

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The influence of catastrophizing on psychosocial and
functional outcomes in irritable bowel syndrome
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and §National Institutes of Health, Bethesda, MD, USA

Background: Catastrophizing is a cognitive process
characterized by a propensity to concentrate on and
magnify the value of an actual or anticipated painful
stimulus and negatively assesses one’s ability to cope.
Catastrophizing is an important predictor of pain-related
outcomes. A cornerstone symptom of irritable bowel
syndrome [IBS] is abdominal pain or discomfort. Also,
individuals with IBS have been reported to have a
tendency to catastrophize. In a sample of individuals
who suffer from IBS we hypothesized those individuals
who catastrophize would have worse outcomes as
compared to those who do not catastrophize (non-
catastrophizers).

Methods: One-hundred and one adults with IBS (79% female,
mean age 42 years, 97% white) were recruited from
outpatient clinics and data were collected through self-
report measures. Catastrophizing was measured with
the catastrophizing subscale of the Coping Strategies
Questionnaire [CSQ]; Illness representations were mea-
sured with The Revised Illness Perception Question-
naire [IPQ-R]; psychological distress was measured with
the Brief Symptom Inventory 18 [BSI-18] and health-
related quality of life was measured using the Irritable
Bowel Syndrome-Quality of Life Measure [IBS-QOL].
Descriptive statistics and correlations were used to
describe participants and the associations of the vari-
ables of interest.

Results: Overall, participants reported poor HRQOL
(M = 63.32, range 0–100). Individuals that catastro-
phized differed significantly on IBS-QOL from non-
catastrophizers (M = 59.04 vs non-catastrophizers
M = 85.74; p < 0.001), BSI-18 (M = 16.23 vs non-cata-
strophizers M = 3; p < 0.001) and IPQ-R, specifically
the consequences (M = 20.29 vs non-catastrophizers
M = 15.26; p < 0.001) and emotional representations
(M = 18.99 vs non-catastrophizers M = 14; p < 0.001).
Catastrophizing was positively correlated with the
consequences (r = 0.54, p < 0.01) and emotional repre-
sentations (r = 0.65, p < 0.01) and negatively correlated
with HRQOL (r = –0.76, p < 0.01).

Conclusion: The findings indicated that participants
who catastrophized reported worsened psychosocial and
functional outcomes. Thus, catastrophizing may be an
important factor to address in optimizing health out-
comes in individuals with IBS. In addition, illness
perceptions were strongly related to catastrophizing and
HRQOL assessment and integration of illness percep-
tions as well as catastrophizing into the management of
individuals who suffer with IBS may maximize the
health outcomes.

Table 1 Baseline Characteristics of 17 590 Patients with IBS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NHW</th>
<th>Black</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15 489</td>
<td>1045</td>
<td>1106</td>
</tr>
<tr>
<td>Age (mean, year)</td>
<td>62.17 ± 18.11 (p &lt; 0.01)</td>
<td>51.64 ± 16.71 (p &lt; 0.01)</td>
<td>56.57 ± 19.46 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Female gender [%]</td>
<td>83</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>Government insurance [%]</td>
<td>65 (p &lt; 0.01)</td>
<td>56 (p &lt; 0.01)</td>
<td>61 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Commercial insurance [%]</td>
<td>30</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Self pay [%]</td>
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Polyorphism in IL-6, IL-10 cytokine genes and serum MIF level in irritable bowel disease

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Background: Irritable bowel syndrome [IBS] is a multi-factorial functional gastrointestinal disorder. Numbers of pathophysiological mechanisms have been proposed, including abnormalities of motility, visceral hypersensitivity, and even alterations due to bacterial fermentation inside the gut. Cytokine productions are under genetic control and are involved in regulation of immune and inflammatory response. Interleukin 6 (IL 6), Interleukin 10 (IL 10) polymorphism and Macrophage Migration Inhibitory factor (MIF) serum level is an important pro-inflammatory cytokine and plays a critical role in immune and inflammatory responses. MIF, IL 10 and IL 6 levels may be related to the pathogenesis and induction of inflammation.

Aim: To evaluate the role of cytokines IL-6 and IL-10 gene polymorphism and serum MIF level in IBS patients.

Method and Materials: A total of 188 subjects [127 IBS and 61 Healthy controls] were enrolled for the study fulfilling inclusion and exclusion criteria. Blood samples were obtained after informed consent for serum separation. Enzyme linked immune sorbent assay (ELISA) was performed using commercial Laboratory kit for human MIF according to manufacturers instruction. PCR for IL 10 (–1082, –819, –592) followed by restriction digestion using enzyme MnlI, RsaI and MaeIII was done. For IL-6 PCR was done using double set of primers. The products obtained were analysed on % agarose gel. A p value of less than 0.05 was considered significant. Statistical analysis was conducted using by SPSS 16.0.

Results: In case of IL-10-1082 both IBS and HC showed dominance of AA genotype having 57.1% and 62%. For IL-10-819 maximum number of IBS patients 39% and 50% of healthy controls showed CC genotype. In case of IL-10-592 majority of IBS patients i.e. 64.3% and 25% HC showed AA genotype. IL-6 was found equal in IBS patients i.e. 67% and 75% in HC were high producer GC genotype. MIF level in IBS patients was also found significantly elevated (p = 0.0006) having mean SD 4.96 ± 3.19 (Z score p = 0.19) which was not related to healthy control.

Conclusion: Low production of anti-inflammatory cytokines IL-10 seen in patients of IBS. High production of IL-6 we found in IBS patients and HC. High level of MIF supports the claim that inflammation could be an effective factor in the pathogenesis of disease.

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Gender differences in IBS: Separate pathophysiological background?

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Introduction: The prevalence of IBS as well as the clinical presentation differ between males and females. However, studies on gender differences with regard to potential pathophysiological factors in IBS are lacking. Our aim was to explore whether differences exist in pathophysiological mechanisms and their representative factors between female and male IBS patients.

Methods: Clinical, demographic data, stool and plasma samples were available for a subgroup of IBS and control subjects (HC) participating in the Maastricht-IBS cohort. A set of fecal and serological markers associated with and representing various underlying mechanisms were analyzed with respect to gender differences: i.e. fecal chromogranin A (enteroendocrine cells), human beta defensin 2, (antimicrobial peptide) calprotectin (inflammation), short-chain fatty acids (SCFAs, colonic metabolism), plasma citrulline (intestinal mass) and cytokines. Furthermore, demographic variables, a 14-day symptom diary, the Gastrointestinal Symptom Rating Scale (GSRS), quality of life, and depression scores were assessed in the 2 weeks before blood sample collection.

Results: Female IBS patients showed significantly higher discomfort scores and more impaired physical QoL compared to male IBS patients (p < 0.05). Furthermore, significantly lower total SCFA and citrulline concentrations were found in female compared to male IBS patients (all p < 0.05), but not in HC. In a linear regression analysis, only BMI showed a significant association with the total SCFA concentrations not affected by gender difference. No gender differences were observed with respect to the other biomarkers or variables.

Conclusion: We have shown that discomfort scores are higher and fecal SCFA concentrations are decreased in female vs male IBS patients. Differences in intestinal microbiota composition and colonic metabolism may underlie these gender differences in IBS and deserve further evaluation.

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Prevalence of joint hypermobility syndrome in patients with functional gastrointestinal disorders in and Asian tertiary gastrointestinal unit

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Introduction: The underlying mechanism of functional gastrointestinal disorders (FGID) is incompletely understood. Recently a high incidence of joint hypermobility syndrome (JHS) was reported in a group of FGID patients in the United Kingdom. The prevalence of JHS in other FGID population is unknown. Our aim is to determine the prevalence of JHS among FGID patients in an Asian population.

Method: Case control study design was used. FGID patients who fulfilled the ROME III criteria for either Irritable bowel syndrome (IBS) or functional dyspepsia (FD) were recruited from the outpatient gastroenterology unit of a teaching hospital in Singapore. The control cases were patients attending the clinic with other diagnoses. IHS was diagnosed based on the Revised Brighton Criteria and joint measurements were performed by blinded assessors. Symptom severity was assessed with Gastrointestinal Symptom Rating Scale (GSRS) and Quality of life with EQ-SD. In a subset of FGID patients (n = 27), gastrointestinal transit time (GTT) was measured using wireless motility capsules and small intestinal bacterial overgrowth with glucose hydrogen breath test (HBT).

Results: 130 FGID patients and 79 controls were recruited between 1st January 2014 and 20th January 2016. There were more females in FGID (69%) vs Control (32%), p = 0.0001. The FGID group was younger (Median age 46 vs 54, p = 0.0001), race distribution was similar, the predominant race in both groups was Chinese (FGID 88% vs Control 96%). JHS is more prevalent in the FGID group (13%), there was no JHS among the controls (p = 0.001). Diagnoses among JHS patients were FD (JHS 14% vs non JHS 39%, p = 0.035), IBS (29% vs 25%, p = 0.81) and Overlap (57% vs 36%, p = 0.16). 14% of JHS patients reported severe pain (GSRS ≥ 7) vs none in JHS (non-significant). Quality of life was similar between the 2 groups. GTT was abnormally slow in 66% (2/3) of JHS vs 55% (1/3) of non-JHS, p = 0.69 in non-JHS. 33% (1/3) JHS vs 21% (2/9) of non-JHS had positive HBT.

Conclusion: JHS is more prevalent among FGID patients in a predominant Chinese cohort in an Asian tertiary gastroenterology unit.
Conclusion: There are 2 distinct manometric subtypes of patients (52%) compared to IEM-A (22%; in IEM-P than IEM-A (3.5% acid exposure in upright position was significantly higher reflux study done. The average percentage of esophageal acid control (pH 95% CI: 20 – 619). 146/231 patients had an ambulatory study was defined by: excess total number of reflux episodes (>48/24 h), abnormal esophageal acid exposure (>6% in upright position and/or ≥2% in recumbent off treatment with proton pump inhibitor (PPI), or pH ≥5.5 and/or ≥0.5 on PPI, or symptom index ≥50%. Results: 195 (84%) patients were identified with IEM-A and 86 (16%) with IEM-P. There was a striking gender difference with 19 males having IEM-P (53%) and 67 with IEM-A (34%), p = 0.038. The mean age of IEM-P patients [59.6 years, 95% confidence interval (CI) 55.9–63.3] was significantly greater than that of IEM-A [55.5 years, 95% CI 54.6–57.4, p = 0.047]. The mean lower esophageal sphincter (LES) resting pressure was significantly lower in IEM-P (20.8 mmHg, 95% CI: 16.0–25.4) compared to IEM-A (29 mmHg, 95% CI: 27.0–31.3, p = 0.002). There was no difference in bolus transit or manometric presence of hiatus hernia between the two groups. In subgroup analysis, 41 patients had dysphagia as main presenting symptom, 33 had IEM-A (17%) and 8 had IEM-P (22%, p = 0.27). Mean DCI for liquid swallows was significantly lower in IEM-P (111 mmHg cm) compared to IEM-A (421, p = 0.047, 95% CI: 20–619). 146/231 patients had an ambulatory reflux study done. The average percentage of esophageal acid exposure in upright position was significantly higher in IEM-P than IEM-A (3.5% vs 1.7%, p = 0.04). Postgastric acid control [pH >4] was more prevalent among IEM-P patients (52%) compared to IEM-A (23%, p = 0.04). Conclusion: There are 2 distinct manometric subtypes of IEM, IEM-P with an older male predominance, weaker LES, and a trend to more advanced reflux disease, and worse response to PPI therapy, a more advanced manifestation than IEM-A. However, the question if there are different etiologies underlying the two subtypes remains to be answered.

Comparative study between endoscopic pneumatic dilation versus laparoscopic Heller’s Myotomy in idiopathic achalasia patients

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Introduction: Achalasia is an incurable primary motor disorder of the esophagus. The best treatment modality for achalasia is still controversial. This study compared the outcome and complications and improvement in quality of life between Endoscopic Pneumatic Dilation (EPD) vs Laparoscopic Heller’s Myotomy (LHM) for the management of patients with idiopathic achalasia. Methods: This randomized controlled prospective study was carried out in IMS, BHU, including patients who were diagnosed with achalasia cardia. Patients who were fulfilled inclusion and exclusion criteria were enrolled in study after written informed consent. A total of 112 patients of dysphagia were evaluated by HRM, of these 90 patient were diagnosed with achalasia and 65 (30 male and 35 female) were further analyzed for outcome and rest were lost to follow-up. Patients were classified into two groups: Group 1 [33 patients] Endoscopic Pneumatic Dilation (EPD), whereas Group 2 [32 patients] with Laparoscopic Heller’s Myotomy (LHM). Patients were evaluated pre-treatment and follow-up on 3 months, 6 months, 1 year and 2 years postoperatively. The results were compared for Heartburn was significantly high in LHM group (p = 0.001). Significant improvement of HRQOL was observed by SF 36 questionnaire and disease specific AE Compared to the general US population. Extra-intestinal conditions such as anxiety and depression are major drivers of poor quality of life in CVS. These findings support the need for a biopsychosocial model of care in these patients, with particular emphasis on treatment of comorbid conditions such as anxiety, depression and pain.

Esophageal Physiology, Pathophysiology, and Clinical Disorders

Manometric subtypes of ineffective esophageal motility

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University of Colorado, Boulder, CO, Bern, Switzerland, and Charleston, SC

Background: Ineffective esophageal motility (IEM) is characterized by well-defined manometric criteria. However, much variation exists within the diagnosis. Some patients exhibit exactly the required 5 low amplitude swallows to make the diagnosis but with intermittent normal swallows. Other patients show consistently ineffective swallows with total absence of any normal swallow. Hypothesis: There are two different manometric subtypes of IEM, IEM Alternans (IEM-A) and IEM Persistent (IEM-P). Methods: 231 IEM patients were identified. IEM was defined by high-resolution manometry criteria with distal contractile integral (DCI) >450 mmHg cm in ≥50% of test swallows. Reflux testing was performed with ambulatory impedance-pH monitoring. Abnormal study was defined by: excess total number of reflux episodes (≥48/24 h), abnormal esophageal acid exposure (≥6% in upright position and/or ≥2% in recumbent off treatment with proton pump inhibitor (PPI), or ≥5.5% and/or ≥0.5 on PPI, or symptom index ≥50%. Results: 195 (84%) patients were identified with IEM-A and 86 (16%) with IEM-P. There was a striking gender difference with 19 males having IEM-P (53%) and 67 with IEM-A (34%), p = 0.038. The mean age of IEM-P patients [59.6 years, 95% confidence interval (CI) 55.9–63.3] was significantly greater than that of IEM-A [55.5 years, 95% CI 54.6–57.4, p = 0.047]. The mean lower esophageal sphincter (LES) resting pressure was significantly lower in IEM-P (20.8 mmHg, 95% CI: 16.0–25.4) compared to IEM-A (29 mmHg, 95% CI: 27.0–31.3, p = 0.002). There was no difference in bolus transit or manometric presence of hiatal hernia between the two groups. In subgroup analysis, 41 patients had dysphagia as main presenting symptom, 33 had IEM-A (17%) and 8 had IEM-P (22%, p = 0.27). Mean DCI for liquid swallows was significantly lower in IEM-P (111 mmHg cm) compared to IEM-A (421, p = 0.047, 95% CI: 20–619). 146/231 patients had an ambulatory reflux study done. The average percentage of esophageal acid exposure in upright position was significantly higher in IEM-P than IEM-A (3.5% vs 1.7%, p = 0.04). Postgastric acid control [pH >4] was more prevalent among IEM-P patients (52%) compared to IEM-A (23%, p = 0.04). Conclusion: There are 2 distinct manometric subtypes of IEM, IEM-P with an older male predominance, weaker LES, and a trend to more advanced reflux disease, and worse response to PPI therapy, a more advanced manifestation than IEM-A. However, the question if there are different etiologies underlying the two subtypes remains to be answered.

Comparative study between endoscopic pneumatic dilation versus laparoscopic Heller’s Myotomy in idiopathic achalasia patients

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Aml nitrate unresponsive esophageal outflow resistance

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Background: The diagnostic classification of esophageal outflow resistance [OR] is characterized by elevated deglutitive esophageal peristalsis, abnormal peristalsis, and total acid exposure % and symptom sensitivity index (SSI) and Symptom association probability (SAP) for Heartburn was significantly high in LHM group (p = 0.001). Significant improvement of HRQOL was observed by SF 36 questionnaire and disease specific AE Compared to the general US population. Extra-intestinal conditions such as anxiety and depression are major drivers of poor quality of life in CVS. These findings support the need for a biopsychosocial model of care in these patients, with particular emphasis on treatment of comorbid conditions such as anxiety, depression and pain.

Method: We reviewed our esophageal high-resolution manometry database to identify studies where AN was given to assess possible EOR. Patients with history of surgery and chronic opioid intake were excluded. ECG pressure, along with integrated relaxation pressure (IRP) before and after AN administration were recorded. Patients were considered to have EOR unresponsive to AN when the difference between ECG pressure following deglutitive relaxation and AN induced relaxation was >9 mmHg. Manometric and clinical characteristics in this group were compared to those in patients with normal esophageal motility (N = 10) and achalasia (N = 22).
Results: The normal motility subjects had normal deglutitive EGI pressures that were similar to those after AN-induced EGI relaxation. The achalasia patients had significant additional AN-induced relaxation beyond relaxation observed during wet swallow (i.e. relaxation gain). A total of 10 EOR patients (8F, 64 ± 13 years) were identified who did not show relaxant response to AN (Figure A). Their IRP remained significantly higher than both control and achalasia patients after AN administration (Figure B). None of the AN-unresponsive EOR patients had distal esophageal stricture/mir in esophagogastrroduodenoscopy while seven showed hiatal hernia.

Six EOR patients were morbidly obese (BMI=42±5.4) and had history of obstructive sleep apnea (OSA). All three groups showed persistent rhythmic inspiratory EGI pressure augmentations during AN-induced LES inhibition similar to baseline period (Figure C) however, amplitude of crural contractions in EOR patients (37 ± 19 mmHg) was higher than control and achalasia patients (17 ± 8 mmHg and 12 ± 10 mmHg respectively, p < 0.05).

Conclusions: A subgroup of EOR patients show a failed EGI relaxation response to AN, indicating that restricted flow across EGI is not a result of LES smooth muscle dysfunction. Instead, the etiology may be related to altered anatomy and/or increased contractile activity of the crural diaphragm. The distinction is important to avoid misguided intervention in this group.

Introduciton: Gastro-oesophageal reflex disease (GORD) is a prevalent disease worldwide particularly in the developed world. It’s increased prevalence may be attributed to the increase of obesity in the general population. 60% of the Irish population have been classified as either overweight or obese in 2015. We aim to identify how many patients seeking diagnostics from a busy GI lab are overweight and obese and if this is likely to significantly influence their DeMeester score and number of reflux events with the aid of combined pH & impedance monitoring.

Methods: BMI data of 122 consecutive patients undergoing HRUM and 24 h Impedance pH between 09/15 and 01/16 was evaluated. The study consisted of 72 females (59%) and 50 males (41%). 5 patients out of the 122 did not have full studies and so were excluded. 117 studies were completed successfully. We applied chi-squared tests of dependence to evaluate the relationships between being overweight and obese and [1] abnormal acid reflux exposure with a raised DeMeester score and [2] abnormal number of reflux episodes by using impedance measurements.

Results: 37/117 (32%) patients were classified normal weight of these 23 were female. 51/117 (44%), 249 patients were classified overweight. 25/117 (21%) patients were classified as obese. 19F, 65% patients were either overweight or obese, 57% of these were female. There was a statistically significant (p < 0.05) relationships between both increased DeMeester score and number of reflux events in those presenting to our laboratory who are classified as being overweight and obese.

Conclusion: Our study demonstrates a significant association between physiologically gastro-oesophageal reflux and BMI.

213 The effect of head extension on pharyngeal and upper esophageal sphincter physiology using pressure flow analysis
S. BHATIA*, C. SCHEERENS, A. GUPTA*, S. V. KIRAN*, P. DHORE+, A. SHUKLA*, J. TACK, T. OMARE† and N. ROMMEL†
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Background: The optimal neck position for safe swallowing is a neutral or flexed chin down position as these positions decrease the laryngeal inlet. However, Indians are accustomed to swallowing fluids with the neck in the extended position. The aim of this study was to measure the physiological effects of neck extension on pharyngo-oesophageal function.

Methods: Measurements were performed using a 36 pressure and 12 impedance solid-state manometry-impedance catheter (Medtronic) in subjects who were sitting and supine. Five liquid swallows were performed (20 s apart) in each of three neck positions: 0° (neutral), 60° and 90°. Pressure and impedance data from 390 swallows were analysed using Matlab-based pressure-flow analysis software (AIMplor T Omani). Statistical analysis: Data are presented as mean (SEM). After normality test, metrics of two neck extensions were compared to head neutral position using repeated measure analysis with post hoc t-test/Wilcoxon signed rank test with Bonferroni correction (α = 0.05, p < 0.05, *p < 0.01, **p < 0.001).

Results: Thirteen Indian healthy subjects (age 32.8 [10.9] years, 8 M), able to swallow liquids in a neck-extended position, were included and none developed signs of aspiration during the study. Pressure-flow markers of pharyngeal propulsion timing, bolus presence and intrabolus pressure were unaffected by neck extension. However, UES basal pressure, UES integrated relaxation pressure, pharyngeal contractility and UES contractility (post relaxation) were all increased with neck extension.

Conclusion: The results show that in healthy controls, the UES is the region most affected by neck extension, where altered biomechanics leads greater pressure generation.

214 RNAseq analysis reveals dysregulated expression of novel genes in sporadic achalasia
F. BIANCO*, E. BONORA†, M. LUCARESI‡, A. STANZANI*, F. TORRESA†, V. STANGHELLINI†, P. CAVENZAN†, M. WOTTERS‡, G. BOECKSTAEN‡, S. MATTIOLO* and R. DE GIORGIO‡
*Department of Veterinary Medical Sciences DIMEVET, University of Bologna, Italy, †Department of Medical and Surgical Sciences, DIMEC, University of Bologna, Italy and ‡Department of Clinical and Experimental Medicine, Leuven, KU Leuven, Belgium

Objective: Esophageal achalasia is a rare motility disorder characterized by myenteric neuronal and interstitial cell abnormalities leading to deranged absent peristalsis and lack of relaxation of the lower esophageal sphincter.

Conclusion: Our study demonstrates a significant association between physiologically gastro-oesophageal reflux and BMI.

213 The effect of head extension on pharyngeal and upper esophageal sphincter physiology using pressure flow analysis
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Objective: Esophageal achalasia is a rare motility disorder characterized by myenteric neuronal and interstitial cell abnormalities leading to deranged absent peristalsis and lack of relaxation of the lower esophageal sphincter.
sphincter. The mechanisms contributing to neuro-ICC changes in achalasia are only partially understood. Thus, the aim of this study was to identify novel genetic features occurring in patients with achalasia.

Methods: 16 (7 F, age range: 26–72 years) clinically, radiologically and manometrically characterized patients with sporadic achalasia were included. A group of 9 (2F, age range: 30–67 years) subjects undergoing surgery for eosporic achalasia served as controls. Tissue RNA extracted from biopsies of cases and controls was used for library preparation and sequencing on HiScan SQ. Data analysis was performed with the ‘edgeR’ option of R-Biocountin. Gene expression was validated by real-time qRT-PCR, western blotting and immunohistochemistry.

Results: Quantitative transcriptional evaluation and cluster analysis revealed 115 differentially expressed genes, with a p = 10^{-7}. Nine genes with a p < 10^{-4} were chosen for validation and further analysis by qRT-PCR. Among the genes not previously associated to the achalasia phenotype in human samples CYR61, CTGF, KIT, DUSP5, EGFr were downregulated, whereas AKAP6 and INNP4B were upregulated in patients vs controls. Compared to controls immunohistochemical analysis revealed a clear increase in AKAP6 and INNP4B immunostaining, whereas KIT immunolabelling resulted downregulated. Based on previous evidence that INNP4B regulates Akt pathway we used western blot to show that phospho-Akt isoforms, (p-Akt(Thr308), p-Akt(Ser473)), were significantly reduced in achalasia patients vs controls.

Conclusions: The identified dysregulated genes, including the overexpression of INNP4B, a regulator of the Akt pathway, indicates a novel altered signalling pathway with implications in the neuro-ICC changes underlying achalasia. Our findings may provide a molecular basis for a better definition of subsets of achalasia patients.

215 Increased bolus reflux on multichannel intraluminal impedance is an independent predictor of poor pulmonary outcomes over 1 year in patients with idiopathic pulmonary fibrosis L. F. BORGES, V. JAGADESSAN*, H. GOLDBERG*, S. GAVIN*, W. K. LOT*, R. BURAKOFF*, N. FELDMAN* and W. CHAN*
*Division of Gastroenterology, Brigham and Women’s Hospital, Boston, MA, USA and 1Division of Pulmonary Medicine, Brigham and Women’s Hospital, Boston, MA, USA

Background: Gastroesophageal reflux (GER) may be a driver of pathogenesis in idiopathic pulmonary fibrosis (IPF), and may contribute to disease pathways. Understanding the longitudinal relationships between GER and IPF may help define the role of GER in IPF, and identify patients for further management.

Aim: To evaluate the association between objective GER measures on multichannel intraluminal impedance and pH study (MII-pH) and development of poor pulmonary outcomes in an IPF cohort.

Methods: This was a retrospective cohort study of adults with IPF who underwent pre-lung transplant evaluation with MII-pH off proton pump inhibitors (PPI) from 6/2008 to 11/2014. Patients with prior fundoplication were excluded. Subjects were followed for 1 year from time of MII-pH for poor outcomes, defined by hospitalization for respiratory exacerbation or death. Associations between baseline GER and measures on MII-pH and poor outcomes within 1 year were evaluated using Student’s t- or Fisher-exact test for univariate analyses and forward stepwise logistic regression for multivariate analyses.

Results: Twenty-one of 59 patients were hospitalised within 1 year were evaluated using Student’s t- or Fisher-exact test for univariate analyses and forward stepwise logistic regression for multivariate analyses. Time-to-event Cox regression and Kaplan-Meier analyses were performed with censoring at anti-reflux surgery, lung transplant, or last clinic follow-up, whichever was earliest.

Results: 75 subjects [mean age = 60.4 years, 65% male] met criteria for inclusion. On univariate analyses, increased bolus exposure time (BET) on MII-pH was associated with higher incidence of 1 year poor pulmonary outcomes (OR 4.46, p = 0.01). Increased BET remained an independent predictor for poor pulmonary outcome on multivariate analysis (OR 4.05, p = 0.03) after controlling for age, gender, BMI, smoking, baseline lung disease severity, and PPI use. On time-to-event analysis, increased BET was predictive of decreased time to poor pulmonary outcome after controlling for potential confounders [HR 3.49, p = 0.02]. Positive trends were found between increased BET and both 1-year mortality (OR 1.92, p = 0.52) and decreased time to death (HR 1.45, P = 0.068).

Conclusion: Increased BET on MII-pH is an independent predictor of poor pulmonary outcome over 1 year in IPF patients. GER likely plays a role in IPF pathogenesis in some patients. Routine MII-pH should be considered to identify candidates for aggressive anti-reflux therapy in the management of IPF.
The laryngopharyngeal reflux by pharyngeal pH-impedancemetry correlates with extra esophageal symptoms

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NUFIG - Núcleo de Fisiologia do Hospital Israelita Albert Einstein – São Paulo, Brazil

**Introduction:** The gastroesophageal reflux disease can be characterized by esophageal and extramucosal symptoms. The extramucosal manifestations may occur when the reverse movement of gastric contents (acid and non-acid) reaches the areas above the esophagus’ superior sphincter’s protection areas, also known as Laryngopharyngeal reflux (LPR), which leads to symptoms related to the larynx and hypopharynx. The pH and impedance probe with pharyngeal sensor is capable of registering the ascending gastric reflux content up to the pharynx, differentiating it into acid, non-acid and gas and it is currently the most acceptable method to document LPR.

**Objective:** To confirm the LPR clinical diagnosis through pharyngeal pH-impedancemetry and correlate the result of acid and non-acid LPR with typical and atypical symptoms.

**Methods and Materials:** It was a prospective study, in which patients referred to possible GERD investigation with extramucosal manifestations were submitted to pH-impedancemetry at the Nucleo de Fisiologia do Trato Gastrointestinal do Hospital Israelita Albert Einstein, whose protocol was to use a n. 56 probe which has a pharyngeal sensor. During the study, the reflux occurrence identified by the Ph-impedancemetry was investigated and characterized into acid (pH < 4), non-acid (< 4) or non-acid (pH > 4), registered 5 cm above the inferior sphincter, and 1 cm above the superior one.

**Results:** A total of 31 patients, 15 male and 16 female, of an average age of 46, under the suspicion of GERD and with extramucosal symptoms followed the proposed protocol. They underwent the pH-impedancemetry test with a pharyngeal probe with sensor. Of the 31 patients, 15 presented ascending reflux up to the pharynx, 7 of whom showed relation between the symptoms and the LPR episode and 4 of the ones who had related symptoms, also displayed typical symptoms. 8 Out of the 15 patients who had ascending reflux up to the pharynx had predominantly non-acid reflux.

**Discussion:** The use new technology, a pharyngeal impedance-pH monitoring and correlate the result of acid and non-acid LPR with typical and atypical symptoms. The monitoring of the oropharynx through Ph-impedancemetry has allowed us to more accurately identify patients with LPR and further studies are necessary to better analyze the ideal criteria for the diagnosis.

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**Table 1 Reflux and Impedance parameters according to EGJ morphology**

<table>
<thead>
<tr>
<th></th>
<th>Type I EGJ</th>
<th>Type II EGJ</th>
<th>Type III EGJ</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid reflux (% time)</td>
<td>0.3 (0.0.75)</td>
<td>0.5 (0.2-1.1)</td>
<td>0.5 (0.1-1.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonacid reflux (% time)</td>
<td>0.4 (0.2-0.6)</td>
<td>0.5 (0.9)</td>
<td>0.4 (0.2-0.7)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total reflux (% time)</td>
<td>0.8 (0.5-1.3)</td>
<td>1.2 (0.8-1.9)</td>
<td>1.1 (0.7-1.6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table 1 Comparison of HRM parameters according to GERD diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>GERD</th>
<th>Non GERD</th>
<th>Healthy volunteers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal LES pressure</td>
<td>20.0 ± 7.4</td>
<td>24.5 ± 10.3</td>
<td>25.4 ± 8.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DCI</td>
<td>1044 ± 770.9</td>
<td>1513 ± 1059</td>
<td>1103 ± 732</td>
<td>N.S.</td>
</tr>
<tr>
<td>EGJ CI</td>
<td>29.7 ± 25.5</td>
<td>54.5 ± 31.8</td>
<td>59.7 ± 32.55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Type III EGJ morphology</td>
<td>18/46 (39%)</td>
<td>22/91 (23%)</td>
<td>3/23 (8%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* p-value between GERD vs asymptomatic volunteers. Abstract 221

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**The diagnostic value of esophageal high resolution manometry parameters predicting GERD**


The Catholic University of Korea, Department of Internal Medicine, Seoul, Korea

**Background/Goals:** Esophageal manometry is usually done before esophageal pH testing. It is not known whether the detailed information of high-resolution manometry [HRM] can predict GERD. We aimed to determine to which extent HRM findings can predict GERD.

**Methods:** We compared HRM parameters in 137 patients suspected with GERD symptoms and 23 healthy subjects and the predictive value of HRM for the diagnosis of GERD was explored.

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**Abstract 221**

The diagnostic value of esophageal high resolution manometry parameters predicting GERD

**Y. K. CHO, C. H. LIM and M.-G. CHOI**

The Catholic University of Korea, Department of Internal Medicine, Seoul, Korea

**Background/Aims:** High-resolution manometry (HRM) provides information about on esophagogastric junctional (EGJ) morphology, distinguishing three different subtypes. We aimed to evaluate the relation between EGJ morphology with impedance pH and endoscopic findings in patients with suspected GERD.

**Methods:** We reviewed the data of HRM and impedance pH testing off-therapy done in suspected GERD patients from 2011 to 2015. EG was classified as: Type I, no separation between the lower esophageal sphincter (LES) and crural diaphragm (CDI), Type II, minimal separation (≤ 2 cm), Type III, > 2 cm separation. We compared EG morphology with impedance pH parameters and erosive esophagitis.

**Results:** We enrolled 137 patients (50 + 9 years, 66 male) and identified 84 (61%) type I, 13 (9%) type II, and 40 (29%) type III EG morphology. Median (interquartile range) DeMeester score was higher in the order of Type III (6.25 [4.4-14.4]) compared with Type II (2.7 [0.9-4.5, p = 0.03]) and Type I 0.75 (0.8-6.2) (p = 0.046). Type III EG patients had higher [%] time of acid, nonacid and total reflux, compared with type I EG patients [Table 1].

The percentage of erosive esophagitis, positive impedance pH test and abnormal esophageal acid exposure was higher in type III EG compared with others (27.5% vs 14.4%, p < 0.05, 35% vs 16.4%, p < 0.05, 25% vs 12.4%, p < 0.05) but symptom positivity was not different.

**Conclusions:** Defective EGJ morphology is associated with positive impedance pH and erosive esophagitis.
Results: 137 patients were diagnosed as 25 erosive esophagitis, 21 non erosive esophagitis (pathologic acid exposure or positive symptom association), 37 functional heartburn and 54 non-GERD by endoscopy and impedance pH test. GERD patients had a significantly lower distal contractile integral (DCI), basal LES pressure and esophagogastric junction - contractile integral (EGJ-CI) than healthy controls or non-GERD patients. GERD patients more often had defective EGJ morphology than healthy subjects (39% vs 8%, p = 0.05; Table 1). On multivariate logistic regression analysis, both esophagogastric junction contractility (EGJ-CI, OR1.039, 95% CI 1.021–1.057, p = 0.01) and DCI (OR 1.001, CI 1.000–1.001, p < 0.01) were independent predictors of GERD. The sensitivity and specificity of these findings were highest in EGJ-CI (AUC 0.76 [0.645–0.88, p = 0.01, sensitivity 58%, specificity 99%), but the other parameter had low AUC (0.55–0.66) in ROC curve.

Conclusions: EGJ-CI and DCI were significant HRM parameters predicting GERD, but the predictive values are low.

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Remifentanil induced changes in esophageal and esophagogastric junction (EGJ) bolus transport in healthy volunteers

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Introduction: Administration of remifentanil, a mu-opioid receptor agonist, is associated with subjective dysphagia and an objective increase in aspiration risk. We assessed bolus transit through the esophagus and esophagogastric junction (EGJ) following remifentanil administration.

Methods: Data from eleven healthy young participants (23 ± 3 years, 7M) were studied using high-resolution impedance manometry (Manoscan™, Medtronic). Data were analyzed for esophageal pressure topography, esophageal pressure flow analysis, and EGJ bolus presence (BPT) and flow time (BFT) using custom Matlab™ analyses. Paired t-tests were performed with a p-value of <0.05 regarded as significant.

Results: EGJ bolus presence [71 ± 0.5 vs 51 ± 0.5 s, p = 0.001] and bolus flow time [5.0 ± 0.4 vs 3.0 ± 0.3 s, p = 0.001] at the EGJ decreased 30 min following remifentanil administration, with no observed changes in IRP4. Distal latency [7.5 ± 0.2 vs 5.2 ± 0.4 s, p = 0.001] and distal esophageal distention contraction latency [4.7 ± 0.2 vs 3.5 ± 0.1 s, p < 0.001] were both reduced following remifentanil administration. There was no evidence of increased esophageal bolus residue by impedance criteria.

Conclusion: Remifentanil decreased descending inhibition leading to rapid peristaltic propagation, while bolus transport through the distal esophagus and EGJ remained intact in healthy volunteers.

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Esophageal neuromechanical states during solid bolus perception in healthy volunteers

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†Department of Gastroenterology of Surgery, Flinders University, Australia and ‡Department of Human Physiology, Flinders University, Australia

Introduction: The ability to predict neuromechanical states of the esophageal wall provides a framework for understanding the neurogenic and passive factors underpinning the generation of esophageal symptoms [Leibbrandt et al 2016, Front. Syst. Neurosci.]. This study aimed to correlate our recent description of esophageal neuromechanical states with solid bolus perception in asymptomatic healthy volunteers.

Methods: High-resolution impedance manometry [MMS, Unisensor] was conducted in fourteen healthy volunteers (8M, 30 ± 5 years), seven each with and without bolus perception (visual analogue scale) during solid low. Data were exported and analyzed via Matlab™ for characterization of neuromechanical states, and compared between perceived and non-perceived swallows, with p-value < 0.05 considered significant.

Results: Neuromechanical analyses were consistent with bolus presence in the transition zone (TZ) during the majority, but not all perceived swallows. Specifically, there was evidence of states not routinely observed in healthy swallowing: increased passive isometric pressure increase - IPP (4% vs <1%), passive isometric pressure decrease - IPD (6% vs 1%), and distended quiescence - DQ (21% vs 7%) in the TZ during perceived swallow. Differences of a lesser magnitude were present in the distal esophagus.

Conclusions: There was evidence of esophageal bolus retention and analyses of mechanical states show evidence of the esophagus contracting onto retained bolus in healthy subjects with bolus perception. Further studies of neuromechanical states in relation to perception are needed in patient groups.

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Reflux patterns and symptom occurrence as assessed by 24-h pH-impedance monitoring: association between reflux impedance patterns

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Background: Multichannel Intraluminal impedance pH (MII-pH) is helpful in determining the association between reflux and symptoms. Better categorization of reflux events may be helpful in explaining symptom correlation. Transient lower esophageal sphincter relaxation (TLESR) has been proposed as the main pathophysiological factor for gastroesophageal reflux disease (GERD). However, the role of this mechanism has not been fully elucidated.

Aim: To assess reflux patterns on 24-h MII-pH and its association with symptoms occurrence.

Methods: We prospectively enrolled GERD patients with either partial response or refractory to proton pump inhibitors (PPI) who underwent 24-h MII-pH off PPI therapy from July to December 2015. We describe twelve dominant MII-pH patterns: swallowed-induced reflux (acid, non-acid reflux, proximal and distal extent of reflux), isolated liquid reflux (acid, non-acid reflux, proximal and distal extent of reflux) and gastric belching (acid, non-acid reflux, proximal and distal extent of reflux) and patients were classified in two groups: acid reflux (AR), acid esophageal exposure [AET] >4.2% of time and symptom correlation and functional heartburn (FH; AET <4.2%, negative symptoms correlation).

Results: We enrolled 50 consecutive patients (29 females, mean age 44.5 years [range 38.8–57.2] mean body mass index [BMI] 25.2 kg/m² [range 22.5–27.8], 25 patients in the AR group and 25 patients in the FH group. Mean AET in the AR group was 7.4% [5.3–9.4%] vs 0.3% [0.1–0.9%] in FH group (p = 0.0001). A total of 2435 reflux events were identified, only 634 (26%) were associated with symptoms [96.4% into AR group vs 3.6% in FH group, p = 0.0001]. Distribution of symptom correlation according MII-pH patterns was as follows: 149 swallowed-induced reflux-distal acid [24.5%], 155 isolated liquid Reflux-proximal acid [24.4%], 85 swallowed-induced reflux-proximal acid [13.4%], 47 isolated liquid Reflux-proximal non-acid [7.4%]. In the AR group, swallowed-induced reflux-distal acid more

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frequently presented with symptoms (23.5%) vs isolated liquid reflux-distal acid (8%), p = 0.012). Symptoms associated with reflux were predominantly acidic regardless of pH patterns.

Conclusions: We found that swallowed-induced reflux is similar in prevalence and correlates as frequent with symptoms as compared with isolated reflux. We did not find more symptom correlation with proximal reflux and gas (belching). Further studies are needed to assess the role of TLESR and MI-pH pattern to better define reflux pathophysiology.

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High resolution manometry parameters to assess barrier function of the gastro-esophageal junction and to identify patients with gastro-esophageal reflux disease: a case-control study

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Objectives: Existing manometric measurements of the esophagogastric junction (EGJ) barrier function are suboptimal. This study tested the performance of novel, high-resolution manometry (HRM) parameters of EGJ function in the assessment of patients with suspected gastro-esophageal reflux disease (GERD).

Methods: Patients with reflux symptoms and healthy controls (HC) underwent HREM with ten water swallows and 24-h, ambulatory pH multichannel impedance measurements. EGJ morphology, lower esophageal sphincter pressure integral (LES-P), EGJ-contractile integral (EGI-CI) were compared with ‘stableEGJ-CI’ a novel parameter summarizing EGJ barrier function during the entire HRM protocol. Interaction with peristaltic function assessed by distal contractile integral (DCI) was evaluated. Esophageal acid exposure ≥4.2%/24 h assessed using pH-Refux pos and V-Refux pos subjects compared with HC and patients without GERD. Stable-EGJ-CI was also the single best parameter for prediction of pathological reflux (optimal cut-off 47 mmHg cm, ROC AUC 0.736, p = 0.0001). Only stable-EGJ-CI was consistently lower in A-Refux-pos and V-Refux-pos pos subjects compared with HC and patients without GERD. Stable-EGJ-CI was consistently lower in A-Refux-pos and V-Refux-pos pos subjects compared to HC and patients without GERD. Stable-EGJ-CI was also the single best parameter for prediction of pathological reflux (optimal cut-off 47 mmHg cm, ROC AUC 0.736, p = 0.0001). This cut-off value, approximately 1 SD below the mean normal value, showed modest sensitivity 52% and PPV 46%, but good specificity 85% and NPV 88%.

Conclusion: Novel HRM metrics predicted the presence of GERD on pH-impedance studies better than standard measurements. Stable-EGJ-CI, a metric that summarizes EGJ barrier function over time, had the best performance characteristics. Pathological reflux was unlikely if this metric was within the upper two-thirds of the normal range.

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Lack of association between esophageal spasm diagnosed on barium esophagram and esophageal spasm diagnosed on high-resolution esophageal manometry

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Background: High-resolution esophageal manometry (HREM) is the gold standard test to evaluate esophageal spasm, however, esophageal spasm is also commonly diagnosed via barium esophagram. It is unknown if spasm diagnosed on barium esophagram is associated with spasm diagnosed on HREM.

Aim: To evaluate if esophageal spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed via the gold standard test, HREM.

Patients and Methods: We conducted a retrospective study of 212 adult patients who underwent HREM evaluation at a single tertiary care center between 11/11/2011 and 10/31/2012 and had a barium esophagram performed within 6 months of the HREM date. Patients with prior esophageal surgery were excluded. The association of esophageal spasm diagnosed on barium esophagram with spasm diagnosed on esophageal manometry was measured by the odds ratio comparing the presence or absence of esophageal spasm on barium esophagram with the presence or absence of spasm diagnosed via gold standard HREM.

Results: Of the 212 patients, 41(19%) were diagnosed with esophageal spasm on HREM and 100 (47%) were diagnosed with spasm on barium esophagram. The median number of days between studies was 29 days. Of the 100 patients diagnosed with spasm on barium esophagram, only 24(24%) were also diagnosed with spasm on esophageal manometry. Barium esophagram demonstrated a sensitivity of 41.46% and specificity of 55.56% for esophageal spasm diagnosis when compared to the gold standard HREM. Multivariable logistic regression demonstrated an OR 1.92 [95% CI[0.92-3.98], p = 0.08] for the diagnosis of esophageal spasm, after adjustment for age, gender, indication, and number of days between tests.

Conclusions: Esophageal spasm diagnosed on barium esophagram did not demonstrate a statistically significant association with spasm diagnosed via gold standard HREM. The lack of association may be explained by the intermittent nature of esophageal spasm, however, the unexpectedly low percentage of patients with spasm on barium esophagram who were also diagnosed with spasm on HREM suggests spasm diagnosed via esophageal spasm after barium does not always represent true esophageal spasm as defined by manometric criteria. The question is then raised if these lower amplitude contractions visualized on barium esophagram are indicative of a hypercontractile disorder that may escalate into esophageal spasm.

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Association of minor disorders of esophageal peristalsis with reflux and swallowed bolus clearance: comparison of Chicago Classification v2.0 with v3.0

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Background: Minor disorders of peristalsis including ineffective esophageal motility (IEM) and fragmented peristalsis are commonly seen in patients with gastroesophageal reflux disease (GERD). Adopting Chicago classification (CC) v3.0 has eliminated some of minor abnormalities of peristalsis which are now considered normal. The aim of this study is to determine how the change from Chicago v2 to v3 impacts the relationship between these minor disorders and both swallowed bolus and refluxate clearance.

Methods: In a retrospective study, HRIM and 24-h multichannel impedance-pH (MI-pH) monitoring were assessed in 100 patients with GERD between January 2014 and September 2015. HRIM was assessed using both CC v3.0 and v2.0. Esophageal clearance function evaluated by impedance measured complete bolus transit (CBT), reflux bolus clearance time and mean distal acid clearance time. Acid exposure time (AET) was also calculated.

Results: Demographic characteristics were: mean age 55 ± 14 (SD) years, 69/100 male, 93% Caucasian and BMI 27.6 ± 5.3. Patients were not on reflux medication during the study. No patient with hiatal hernia was included. Baseline measures of HRIM were: IRP 10.9 ± 6.5 mmHg, DCI 1695 ± 1335 mmHg cm, DL 7.1 ± 2.06 s. Abnormal motility patterns were observed in 65% and 83% of patients assessed by CC v2.0 & v3.0, respectively (Table). Complete bolus transit (CBT) was not achieved in 63% of patients. Analysis of CBT based on motility pattern showed that weak peristalsis with large breaks (WPLBs) and failed peristalsis (CC v2.0) was significantly associated with not achieving CBT (p < 0.05), as was the case for fragmented peristalsis (CC v3.0, p < 0.05). Pathological AET was observed in 71 patients with mean AET of 11.6% (range 6.3–34.7%) and the reminder showed a normal pH profile (mean AET 2.8%, range 0.6-4.3%). Subsequent analysis of AET in IEM and normal motility subgroups showed significant increases in AET in IEM [10.8 ± 4.8 vs 3.2 ± 1.9, p < 0.05]. Similar analysis showed increased AET in failed peristalsis and WPLBs subgroups compared to normal motility based on CC v2.0 [9.7 ± 3.8 vs 3.6 ± 2.1, p < 0.05 and 8.8 ± 3.5 vs 3.6 ± 2.1, p < 0.05, respectively].

Conclusions: GERD patients with IEM and failed peristalsis have increased pathological AET. Bolus clearance function is impaired in patient with WPLBs and failed peristalsis (CC v2.0) as well as fragmented peristalsis in CC v3.0. Further studies with focus on erosive & non-erosive GERD and the role of inflammation on HRM and MI-pH measures are recommended. Distribution of contraction pattern abnormality assessed by Chicago classification v2.0 and v3.0 and presence of CBT of 100 patients with GERD

<table>
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<th>Integrity of contraction</th>
<th>Patients (%)</th>
<th>CBT (%)</th>
<th>No CBT (%)</th>
<th>p-value</th>
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<td>45</td>
<td>95</td>
<td>5</td>
<td>&lt;0.05</td>
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<td>14</td>
<td>22</td>
<td>78</td>
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<td>&lt;0.05</td>
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</table>

Abstract 227
Long-term outcomes of peroral endoscopic myotomy (POEM) in achalasia: experience from a single center

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Background/Aims: Peroral endoscopic myotomy (POEM) was introduced as an alternative treatment for achalasia patients. The aim of this study was to evaluate the long-term outcomes of POEM in achalasia patients.

Methods: This is a retrospective analysis at a tertiary referral center. A total of 14 achalasia patients underwent POEM between August 2012 and January 2013. There were 9 patients with type I, 1 patient with type II, and 2 patients with type III achalasia were included. The patients received periodic follow-up over 3 years. The main outcomes were Eckardt score, changes of parameters on esophageal manometry, and development of reflux esophagitis.

Results: The length of myotomy was 8.4 ± 2.6 cm. All patients showed a significant improvement in Eckardt score after POEM during median follow-up of 39.5 months [6.5 ± 2.7 vs 0 ± 0.5, p < 0.001]. There were no significant decrease in IPR and LES pressure, respectively (p = 0.001 and p = 0.002). Over 3 years, no symptom recurred occurred.

Conclusion: Long-term outcome of POEM for achalasia are excellent. In the future, large scale studies are needed to confirm this result.

New bolus transit parameter in high-resolution impedance manometry: validation with simultaneous barium esophagography

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Background: High-resolution impedance manometry (HRIM) is used to detect and differentiate between complete vs incomplete bolus transit. The three-dimensional volume (3-D) of inverted impedance (VII) was developed to measure the remnant impedance volume between each swallow. However, its clinical usefulness and value has not been completely evaluated. Barium esophagography (BE) has been used to determine bolus transit in esophageal motor disorders. Here, we aimed to investigate the absolute measurement of bolus transit based on the 3-D volume of inverted impedance and its clinical meaning by assessing its relationship with simultaneous BE.

Methods: This was a cross sectional study of refractory GERD patients who underwent either pH-MII or Wi-pH off of PPI. Groups were evaluated for pathologic T-RE by a 20- or 30-mmHg isobaric contour was significantly correlated regardless of the length of the TZ or time lapse.

Conclusions: The newly developed VII method appears to have a close relationship with the currently using BE despite different protocols.

Persistent and troublesome reflux symptoms despite proton pump inhibitors therapy cause disorder of mental health, sleep, anxiety and depression in Japanese patients with gastroesophageal reflux disease

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Background: Some gastroesophageal reflux disease (GERD) patients experience persistent reflux symptoms despite proton pump inhibitor (PPI) therapy and they reduce health-related quality of life (HRQOL). The aim of this study is to evaluate the relationship between efficacy of PPI and HRQOL, and to evaluate predictive factors affecting response to PPI, in Japanese GERD patients receiving PPI therapy.

Methods: We asked a questionnaire of the gastroesophageal reflux disease questionnaire (GERD Q), 8-item Short Form health Survey (SF-8), Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS) before and after PPI therapy. Using GerD Q, we classified them in well controlled patients to PPI therapy [responders] and not well controlled patients [partial responders]. Using SF-8, PSQI, and HADS, we evaluated HRQOL of responders and partial responders.

Results: Sixty-nine patients [47.6%] were partial responders. Partial responders had significantly lower scores in five of eight subscales and in mental health component summary in SF-8 than those of responders. Partial responders had significantly higher scores of PSQI and HADS including anxiety and depression than those of responders. Non-erative reflux disease and double PPI dose were predictive factors of partial responders.

Conclusion: Persistent reflux symptoms despite PPI therapy caused mental health disorder, sleep disorder, psychological distress in Japanese GERD patients.
Exploring the role of the esophageal mucosal barrier in non-erosive reflux disease: a comprehensive analysis
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Background: In the absence of visible mucosal damage in patients with non-erosive reflux disease (NERD), it is hypothesized that alteration in the esophageal mucosal barrier and/or esophageal afferent function are involved in the pathogenesis of NERD. Aim of the present study was to perform a comprehensive analysis of the mucosal barrier function in NERD patients in comparison to patients with active erosive esophagitis (EE) and healthy volunteers (HV). A second aim was to explore the gene transcription of TRPV1 (a key molecule involved in nociceptive signalling) in relation to the mucosal barrier function and heartburn symptoms.

Methods: In this prospective study, 10 NERD patients, 11 patients with active erosive esophagitis (grade A–C) and 10 healthy volunteers were included. Esophageal biopsies from macroscopically normal mucosa were obtained at 5 cm above the gastroesophageal junction for (i) ex vivo analyses (Ussing chamber) of transepithelial electrical resistance and permeability, (ii) evaluation of intercellular space diameter with transmission electron microscopy and (iii) gene transcription of tight junction proteins and TRPV1.

Results: No differences in transepithelial electrical resistance (TEER), permeability or intercellular space diameter were found between NERD patients and healthy volunteers, whereas TEER was significantly lower and the intercellular space diameter was larger in patients with erosive esophagitis. TRPV1 gene transcription was not significantly different between EE, NERD and controls.

Conclusions: NERD patients do not exhibit a clear impaired mucosal barrier function and mucosal TRPV1 transcription is not significantly altered. Therefore, further research is warranted for elucidating the role of mucosal nerve sensitivity and central pain processing mechanisms in NERD.

Clinical impact of lower esophageal sphincter function on the symptom assessment of non-erosive reflux disease
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Background/aim: Although high resolution manometry (HRM) is considered for the accurate interpretation of esophageal motility disorders, study about the diagnostic validity of pressure tomography using head-to-head comparison with conventional line tracing is lacking. Our aim is to investigate the difference of inter-observer variation and accuracy of esophageal motility disorders between pressure tomography and line tracing manometry.

Methods: Six experts and eight trainee from three university hospitals participated in the study. All raters analyzed forty patients esophageal manometry images with high resolution pressure tomography (HRPT) format at first and images with six pressure-sensored conventional line tomography (CLT) format a week later. Motility disorders were categorized into three groups according to Chicago classification v.3.0, group I (EGJ relaxation abnormality), group II (major esophageal body peristaltic abnormality) and group III (normal EGJ relaxation: with minor abnormal or normal body peristalsis). Inter-observer variation (IOV), exact diagnostic accuracy and correct identification of esophageal motility disorders (group I and II) were analyzed.

Results: IOV of HRPT were excellent in category I (p = 0.859 and 0.853, respectively) and good in category II (p = 0.677 and 0.741, respectively) and moderate in group III (p = 0.527 and 0.588, respectively) among both experts and trainee groups. IOV of CLT were also good to excellent in category I (p = 0.794 and 0.858, respectively) and II (p = 0.844 and 0.940, respectively) and good in category III (p = 0.639 and 0.702, respectively) among both experts and trainee groups. Exact diagnostic accuracy was significantly correlated with number of manometric interpretation experience (p = 0.001), interpretation with CLT format (p = 0.001) and category I motility disorders (p = 0.001). Correct identification of major esophageal motility disorders was higher in HRPT than CLT (OR: 1.517, p = 0.003) among all raters.

Conclusions: IOV of HRPT for major motility disorders was comparable to that of CLT. HRPT was superior to CLT for correct identification of major motility disorders.

Comparison of the free swallow test in patients with non-erosive reflux disease
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Background/Aims: Our aim was to evaluate FW integrated relaxation pressure (IRP) compared with single swallow (SS) IRP during esophageal high resolution manometry (HRM) in sitting position based on timed esophageal manometry (TE) in patients with achalasia.

Methods: Forty two patients with achalasia (20 female, 54.6 ± 16.8 years) were performed FS provocation test during HRM (Sierra Scientific Instruments, Given Imaging, Los Angeles, CA) regardless of treatment. All of them received TE (0, 1, 2, 5 min) at the same day. For FS test, one free swallow of 200 mL of water within 30 s was administered using a straw.

Results: Six patients failed to FS because of overload, and exclude for analyses. SS IRP was significantly correlated with % barium retention by dimension at 5 min in TE (R = 0.404, p < 0.05). FW IRP is significantly correlated with % barium retention by dimension at 5 min (R = 0.395, p < 0.05) and % barium height at 5 min (R = 0.387, p < 0.05) in TE. FS/SS IRP ratio was not correlated with parameters of TE. We select two groups as Group A (n = 7) if more than 50% barium by dimension are retained at 5 min in timed esophageal manometry and Group B (n = 35) when retained barium dimension less than 50%. Only one patient showed IRP <15 in SS and FW both in Group A. Group A showed significantly high FS IRPs than Group B [median 58.1 mmHg (IQR 16.3–65.0) vs 13.4 mmHg (7.0–22.8), p < 0.05] and tended to high SS IRPs than Group B [32.8 mmHg (17.3–55.4) vs 12.5 mmHg (8.7–25.6), p < 0.05]. There was no difference in FS/SS IRP ratio between two groups (1.16 ± 1.4 vs 0.98 ± 0.85). In patients with over 1 FS IRP ratio, height of barium column is tended to high than that of the patients with under 1 in FS/SS IRP ratio (29.6 ± 4.1 cm vs 8.8 ± 2.5 cm, p = 0.004).
Conclusions: SS and FW IRPs were both sensitive to detect EGJ outflow obstruction in patients with achalasia. FW test might be more sensitive to SS test, but further study will be needed to elucidate the clinical significance of FW test in achalasia.

236 The usefulness of baseline impedance level measurement for the diagnosis of gastroesophageal reflux disease in endoscopy-negative patients with esophageal or supraesophageal symptoms

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Background/Aims: Baseline impedance measurement can be used to evaluate changes in the integrity of the esophageal mucosa. Distal baseline impedance levels (BILs) in GERD patients are known to be markedly lower than those in healthy volunteers. The aims of this study were (i) to evaluate whether BILs are related to various reflux events or acid-related parameters in endoscopy-negative patients with esophageal or supraesophageal symptoms, and (ii) to determine whether the specific baseline impedance value could be used in the diagnosis of GERD.

Methods: Consecutive endoscopy-negative patients with esophageal or supraesophageal symptoms who underwent multichannel intraluminal impedance pH monitoring from March 2013 to March 2015 were included in this study. The mean BILs measured 6 times with 3 h intervals during the selected time period (10 min) in the distal (4 cm and 5 cm above the LES) and proximal (15 cm and 17 cm above the LES) sites were used. The subjects with distal acid exposure time ≥4.2% were classified as the acid reflux group. The subjects with bolus exposure time >1.4%, who did not meet the criteria for the acid reflux group, were classified as the nonacid reflux group. The other subjects were classified into the hypersensitive esophagus group who showed positive symptom association with reflux episodes and the non-GERD group who showed no symptom correlation with reflux episodes, respectively.

Results: The mean proximal BILs did not significantly differ in the 4 groups including the acid reflux group (n=21), the nonacid reflux group (n=26), the hypersensitive esophagus group (n=37), and the non-GERD group (n=43). The mean distal BIL in the acid reflux group were significantly lower, compared with the other groups [136.1 ± 478.9 vs 210.3 ± 683.5 VS 2532.7 ± 700.7 vs 2359.5 ± 747.9, p < 0.001, ANOVA with LSD post-hoc comparisons]. The mean distal BILs did not significantly differ in the 3 groups including the nonacid reflux group, the hypersensitive esophagus group, and the non-GERD group. There was no significant difference in the mean proximal BIL between the GERD (the acid reflux group, nonacid reflux group, and hypersensitive esophagus group) and non-GERD groups. The mean distal BIL in the GERD group was significantly lower than that in the non-GERD group [1972.0 ± 843.3 vs 2359.5 ± 747.9, p = 0.017, Student’s t-test]. In the ROC curve, the value of 1700 Ω showed 83.1% sensitivity and 76.2% specificity for the diagnosis of the acid reflux group, and 86.0% sensitivity and 61.0% specificity for the diagnosis of the GERD group.

Conclusions: Reduced BILs are associated with GER, especially acid reflux. The measurement of BILs in the distal esophagus may be useful in the diagnosis of GERD in endoscopy-negative patients with esophageal and supraesophageal symptoms.

237 The effect of acute auditory and visual stress on esophageal motor function and reflux parameters in healthy volunteers

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Background/Aims: Stress has been recognized as a precipitating factor of gastrointestinal symptoms in patients with functional GI disorders. The effect of acute stress on esophageal motor function and gastroesophageal reflux is not clearly demonstrated. We aimed to investigate the effect of acute auditory and visual stress on esophageal motor function and reflux parameters in healthy volunteers.

Methods: A total of 10 (M:F = 8:2; median age 34 (31-37) years-old, experiment 1) and 8 healthy volunteers (M:F = 6:2; median age 35 (29-42) years-old, experiment 2) who had no recurrent gastrointestinal symptoms and no esophagitis on endoscopy participated in this study. Eligible volunteers were randomized in the order of experiments. They underwent esophageal high resolution manometry with 10 wet swallows (experiment 1) and esophageal impedance-pH monitoring (experiment 2) under either real stress or sham stress. Stress scores were measured using VAS.

Results: The sum of stress scores measured 2 times at an interval of 10 min after the start of the experiment was significantly greater under real stress, compared with sham stress (experiment 1: 1.9 ± 2.1 vs 3.2 ± 0.9, p < 0.001, experiment 2: 2.9 ± 1.9 vs 5.5 ± 1.6, p<0.001). The percentages of weak, failed, hypercontractile, rapid, and premature contractions was not significantly altered during real stress and sham stress, compared with those measured without stress. There were no significant changes in the mean LES resting pressure and distal contractile integral during real stress and sham stress. Contractile front velocity was significantly decreased [4.2 ± 0.9 cm/s vs 4.9 ± 1.6, p = 0.003] and distal latency was significantly increased [7.6 ± 1.0 s vs 6.4 ± 0.6, p = 0.002] during real stress. Those alterations were not observed during sham stress. In the esophageal impedance-pH study, all reflux percent time, longest episode of acid exposure, % time with pH<4, median bolus clearance time, and reflux episodes of proximal extent were not significantly altered during real stress and sham stress, compared with those measured without stress.

Conclusions: Acute auditory and visual stress can significantly affect esophageal body motility. However, it appears to be too weak to induce abnormal motor patterns or alter the reflux parameters.

238 Composite pH predicts chronic proton pump inhibitors use in patients with suspected laryngopharyngeal reflux

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Background: Overdiagnosis of laryngopharyngeal reflux (LPR) is common due to lack of objective biomarkers. Composite pH incorporating both pharyngeal and esophageal acid refluxes may be a useful marker based on the ‘reflux’ and ‘reflex’ pathophysiological mechanisms.

Aim: We investigated whether composite pH can predict chronic proton pump inhibitor (PPI) users for LPR, with or without concomitant typical reflux symptoms (CTRS).

Methods: Patients with LPR in a tertiary center undergoing 24-h esophageal pH test, followed by a 12-week esomeprazole (40 mg, twice daily) treatment, were followed up under routine clinical care for the PPI dosage prescribed on a need basis. Positive composite pH was defined as the presence of (i) excessive pharyngeal acid reflux, and/or (ii) excessive distal esophageal acid reflux. Chronic PPI use was defined as ≥120 tablets of PPI dosage prescribed at the second year.

Results: Out of 129 LPR patients received esomeprazole treatment, 100 (77.5%) were followed to the second year, including 63 with CTRS and 37 without CTRS. The baseline CTRS did not predict PPI use, 46% (29/63 with CTRS) vs 28% (11/37 without CTRS), p = 0.16. Instead, positive composite pH and response to PPI therapy predicted PPI users with an odds ratio of 6.2 (2.0-19.2) and 3.6 (1.3-10.2) for patients with CTRS, and 6.1 (1.1-34.2) and 5.0 (1.1-23.8) without CTRS, respectively. Positive composite pH also predicted PPI users at years 1-6 in both groups.

Conclusions: The composite pH may predict chronic PPI users in patients with suspected LPR, implying a diagnostic value.

239 A novel method for quantitative analysis of functional lumen imaging probe (FLIP) data obtained with a 16-cm balloon on the esophagus

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Background: Major challenges with the FLIP data obtained with a 16-cm balloon on the esophagus are associated with esophageal contraction and movement artifacts. This study aimed to develop a quantitative analysis method for FLIP data obtained with a 16-cm balloon.

Methods: Ten healthy controls and 10 patients with esophagopharyngeal esophagitis (EoE) were evaluated during endoscopy using a modified FLIP device with 17 ring electrodes spaced 1 cm apart and a solid-state pressure transducer positioned through the EGI and distal 10 cm of the esophageal body. Sixteen channels of the esophageal diameter and one channel of intrabag pressure data were simultaneously obtained during stepwise bag distension with 5-mL increments from 0 to 60 mL and analyzed by a customized MATLAB program with
five functions: (i) identifying the EGI-midline by searching for minimal diameter values on the distal six planimetry channels and reconfiguring the data array from this landmark, (ii) applying a median filter to intrabag pressure data to minimize vascular and respiratory artifact and deriving a steady pressure value from between-contraction recording segments during each distension volume, (iii) calculating maximal diameters achieved for each distension volume and then finding the smallest of these maximal diameters during each distension volume, (iv) modeling the narrowest diameter of the esophageal body-pressure relationship with a polynomial regression technique to derive the distension slope (DS) of the best-fit line and curve fitting to ascertain restrictive diameter plateau (RDP), and (v) creating a maximal diameter spatial variation plot for the pressure at 40 mmHg to determine the minimal diameter and area under the curve (AUC) on the esophageal body.

Results: Mean values of the RDP [patients 16 vs controls 21 mm, p < 0.01], the best fit line slope for the RDP-pressure relationship (0.19 vs 0.06 mm/mmHg, p < 0.05), minimal diameter (15 vs 20 mm, p < 0.01) and mean AUC [176 vs 222 mm³, p < 0.05] for distension pressure at 40 mmHg on the esophageal body in patients with EoE were significantly lower than those in healthy subjects and the mean intrabag pressure to reach the RDP in EoE patients (36 vs 51 mmHg) were higher than those in normal controls.

Conclusions: The proposed novel analysis method could improve the quantitative analysis of FLIP data obtained with a 16-cm balloon and showed significant differences in RDP, minimal diameter and AUC values for the pressure at 40 mmHg on the esophagus body between healthy controls and EoE patients.

240 Changes in the pattern of response to a 200 mL rapid drink challenge test are associated to treatment success in achalasia
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Introduction: Evaluation of treatment success in achalasia is mainly based on clinical symptom response and radiological examination, but in some patients with partial response, decision of retreatment can be difficult in the clinical setting. We have recently described 3 patterns of response to a 200 mL rapid drink test during high resolution esophageal manometry: a normal hypotensive pattern characteristic of healthy subjects and minor motility disorders, a non obstructive brief hypotensive pattern observed in major motility disorders, and an obstructive pattern that is characteristic of patients with untreated achalasia (Marin et al. 2016, Neurogastroenterol Motil). The aim of the present study was to evaluate if successful treatment of achalasia reverts the obstructive pattern of achalasia to a non-obstructive or normal pattern.

Methods: We prospectively studied 7 healthy subjects, as controls, and 7 consecutive patients that were diagnosed of achalasia and treated with endoscopic dilatation or Heller myotomy. In each patient we performed a 200 mL rapid drink test before treatment and 2-3 months after treatment, using high resolution esophageal manometry. Dysphagia before and after treatment was scored using the Eckardt scale. Pressure responses of the esophageal body during the drink challenge test were analyzed and each patient was allocated to a specific pattern of pressure response according to previously described criteria.

Results: All healthy subjects had a normal hypotensive pattern during the drink challenge test, whereas all patients had an obstructive pattern before treatment, with 8 ± 5 pressurizations, 63 ± 9% of time with a pressure above 20 mmHg and a pressure gradient across EGI of 20 ± 4 mmHg (p < 0.05 vs 0 pressurizations, 0 ± 0% of time pressure >20 mmHg, and 2.6 ± 1.4 mmHg pressure gradient across UEG in healthy controls). Treatment of achalasia was followed by an improvement of the dysphagia score from 4.0 ± 2 before treatment to 1.4 ± 0.6 after treatment (p < 0.05), that was associated to a return to a non-obstructive pressure pattern in response to the rapid drink challenge test in all patients but one. The number of pressurizations decreased to 2 ± 1, only 12 ± 11% of time the pressure of the esophageal body was above 20 mmHg, and the pressure gradient across UEG decreased to 6 ± 4 mmHg (p < 0.05 vs before treatment for all).

Conclusion: Evaluation of changes in specific patterns of response to a 200 mL rapid drink test can be a useful tool to objectively evaluate the responses to treatment in patients with achalasia, and could guide therapeutic decision in patients with poor symptomatic response.

241 Achalasia subtypes based on clinical symptoms, radiographic findings and stasis scores
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Background: Three subtypes of achalasia are defined with high-resolution esophageal manometry (HREM): subtype I shows no pressurization with swallows, II has increased isobaric pan-esophageal pressure, and III has distal esophageal spastic non-isobaric contractions. Many patients have symptoms for years prior to diagnosis with HREM: dysphagia to solids and liquids, regurgitation, and chest pain. Studies describing the subtypes based on clinical symptoms, radiological findings and stasis scores are limited.

Aim: We wanted to determine if the three subtypes could be differentiated based on symptoms, radiologic findings and stasis scores.

Methods: Patients undergoing HREM received a questionnaire for symptoms and previous treatments. The questions asked about presence of symptoms and severity based on a 1-4 scale with descriptions mild, moderate, severe and very severe. Frequency was based on categorizations of episodes with every meal, at least once a day, several times a week and several times a month, or rarely. Pre-HREM barium swallow tests were evaluated for maximum esophageal diameter. All data including HREM subtype classifications were compared and analyzed using SPSS 22.0 with chi squared test, ANOVA and Pearson’s test.

Results: 108 patients with HREM diagnosis of achalasia (I n = 8, II n = 84, III n = 16) from 1/2012 to 6/2015 were included. Gender distribution was similar among subtypes. Patient age was younger for subtype I (38 ± 16 years), compared to II (55 ± 17 years) and III (63 ± 17 years, p < 0.01). Esophageal symptoms did not differ between subtypes regarding frequency and severity of nausea, chest pain, coughing and heartburn. However, patients reported a higher severity of vomiting in subtype I compared to II and III (2.8 ± 1.4 vs 1.4 ± 1.4 vs 1.2 ± 1.2, p = 0.03). A significant difference in esophageal dilation radiologically was seen between subtype II and III (38 ± 1.4 vs 24 ± 7.2 mm, p = 0.02), but no difference was seen in comparison to subtype I (31.8 ± 12.2 mm, p>NS). The stasis scores were similar among the subtypes (5.8 ± 1.7 vs 6.5 ± 2.2 vs 4.8 ± 2.5, p = NS).

Conclusions: Achalasia subtype II was the most common subtype among our center cohort. Although esophageal symptoms were similar among the subtypes, subtype I did have increased severity of vomiting. The maximum diameter of the esophagus in subtype II was significantly higher than subtype III. Overall, clinical symptoms, radiologic findings and stasis scores are insufficient to distinguish among the achalasia subtypes making HREM fundamental for assessing achalasia and its subtypes.

242 Influence of esophagectomy on the gastroesophageal reflux in patients with esophageal cancer
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Background/Aims: The present study aimed to assess the influence of esophagectomy with gastric transposition on the gastroesophageal reflux (GER) and gastric acidity in patients with esophageal cancer.

Methods: Forty-five esophageal cancer patients who underwent 24-h impedance-pH monitoring after esophagectomy were retrospectively analyzed. We used a solid state esophageal pH probe in which esophageal pH sensor was placed 1.5 cm distal to the upper esophageal sphincter and gastric pH sensor is located 15 cm distal to esophageal pH channel. 24-h impedance-pH monitoring data and other clinical data including anastomosis site stricture and pneumonia were collected. We defined pathologic reflux with reference to known normative data. Stricture was defined when intervention such as bougienage or balloon dilatation was required to relieve dysphagia.

Results: Esophageal and gastric mean pH was 5.65 ± 1.35 and 3.29 ± 1.65, respectively. Percent time of acidic pH (>4) was 5.2 ± 10.5% in the esophagus and 72.2 ± 31.9% in the stomach. Esophageal pathologic acid reflux was noticed in 28.9%, 17.8%, and 33.3% during total, upright, and recumbent time, respectively. Esophageal pathologic bolus reflux was noticed in 86.7%, 80%, and 64.4% during total, upright, and recumbent time, respectively. Gastric acidity increased with time after esophagectomy. Esophageal acid exposure time correlated with intragastric pH. However, esophageal pathologic acid reflux was not associated with anastomosis site stricture and pneumonia. Conclusions: GER frequently occurs after esophagectomy. Strict life-style modification and acid suppression seems necessary to manage GER in patients undergoing esophagectomy.

243 Endoscopic risk factors and a predictive model for acid reflux in patients with reflux symptoms
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Background/Aims: In practice 24-h multichannel intraluminal impedance-pH monitoring (24-h MII-pH) is often required for diagnosis in patients with presumably non-erosive esophageal reflux disease (NERD). However, 24-h MII-pH is uncomfortable and is not widely available, limiting its practical feasibility. Thus we aimed to establish a predictive model for acid reflux using endoscopic findings.

Methods: Between June 2011 and February 2015, 494 patients who underwent 24-h MII-pH monitoring for reflux symptoms without erosive esophagitis were included in this study. All endoscopic images were reviewed for grading hiatal hernia (HH), gastroesophageal flap valve (GEVF), esophageal metaplasia, and chronic atrophic gastritis (CAG). We defined pathologic acid exposure (PAE) as intrathoracic pH of <4 for more than 4.2% of the recording time. The association between endoscopic parameters and PAE was evaluated and a predictive model for PAE was established using the identified risk factors.

Results: Multivariate analysis revealed that PAE was associated with hiatal hernia (HR = 0.001) and was inversely associated with CAG (HR = 0.005). A mathematical predictive model was established using these factors after internal validation, and the area under the receiver operating characteristic curve of the model was 0.705 (95% confidence interval, 0.619 – 0.790). The cut-off value of 0.10 had a sensitivity of 72.1%, a specificity of 64% of cases had a chief complaint of dysphagia.

Conclusion: Endoscopic parameters can be used to predict acid reflux symptoms in patients with non-erosive reflux disease (NERD). The proposed model is a novel tool to predict NERD in clinical practice.

245 Symptomatic esophageal motor dysfunction: how should we investigate these patients?
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Background: Esophagogastroduodenoscopy was introduced by the Chicago Classification and is increasingly found on high-resolution manometry (HRM). However, there is no consensus on how to further investigate EGOO as there is little data on its clinical relevance, especially if symptomatic. The aim of our study was to identify (i) the modality of investigations chosen for symptomatic EGOO and their subsequent pathological diagnostic yield, and (ii) if clinical features and HRM parameters can differentiate a pathological EGOO from an insignificant EGOO.

Methods: Retrospective analysis of clinical details and HRM parameters of patients who underwent HRM at our centre between February 2012 and October 2014 was conducted, and patients with symptomatic EGOO selected. HRM parameters were analysed using the Chicago 2 classification. Upper GI endoscopy was performed for all patients prior to HRM, with normal findings in all. We defined pathological EGOO as a diagnosis that resulted in a change in management or outcome for the patient. Statistical analysis via t-test and chi-squared test for quantitative and categorical variables respectively was done.

Results: Symptomatic EGOO is common and found in 22/116 (19.0%) of our patients undergoing HRM. Majority (16/22, 77.3%) of patients were deemed to have an insignificant EGOO after further investigations. Of these, 12/16 (75%) had spontaneous resolution of their symptoms on follow up. 6/22 (27%) were deemed pathological after further investigations. CT scans (2/16, 12.5%) were the most popular investigations chosen but barium swallows (8/10, 80%) had the best yield for a pathological diagnosis, while other modalities were not helpful. The 6 pathological EGOO diagnoses included 3 achalasia variants, 1 infiltrative metastatic breast cancer, 1 eosinophilic esophagitis and 1 esophageal spasm.

Conclusion: EGOO is common and may be pathological although most patients will have an insignificant EGOO. Further investigations are warranted and barium swallows are useful in these patients. Clinical symptoms and HRM parameters are not useful to distinguish patients with pathological EGOO from insignificant EGOO.
Background: Achalasia is a relatively rare primary oesophageal motor disorder characterised by absent peristalsis and failure of relaxation of the lower oesophageal sphincter (LOS). The mainstays of treatment are pneumatic dilatation and surgical myotomy with reported 2-year success rates of 85–95%. With time, the diagnostic uncertainty regarding the precise mechanism(s) of dysphagia and consideration of re-treatment targeted at the LOS, but in some patients dysphagia may be multifactorial and may not be improved by attempting to further lower LOS pressure. We aimed to evaluate the GI physiological findings of patients seen in our tertiary referral unit to investigate recurrence of dysphagia post-treatment.

Methods: We interrogated our database for patients undergoing high resolution oesophageal manometry (24-h reflux studies due to dysphagia post-treatment for achalasia between July 2009 and February 2016. We recorded achalasia subtype, LOS relaxation pressure (known as integrated relaxation pressure, or IRP), and reflux study results if performed.

Results: 101 patients with recurrent dysphagia who had previously been treated for achalasia (52 male, age range 11–83 years, median 45 years) were identified. 98 had high resolution oesophageal manometry performed. 20 patients had 24-h reflux studies for concomitant heartburn and/or regurgitation. 41 had undergone surgical myotomy, 54 previously underwent dilatation, and 6 had no response to botox injection. 50 patients were treated with POEM, 54 previously underwent dilatation, and 6 patients had 24-h reflux studies for concomitant heartburn/GERD.

Conclusion: Nuclear IL-33 is up-regulated in NERD patients. Up-regulated IL-33 expression in lower esophageal mucosa of NERD patients may contribute to the generation of symptoms.

249 Obesity is associated with higher symptom burden but fewer motor diagnoses on esophageal high resolution manometry (HRM)

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Background: The influence of body mass index (BMI) on oesophageal motor diagnoses according to the oesophageal manometry (OM) in patients with obesity. The success of per-oral myotomy in patients with achalasia?

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247 Oesophageal physiology findings in 98 patients with recurrent dysphagia post-achalasia treatment: retest before re-treating

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Background: Achalasia is a relatively rare primary oesophageal motor disorder characterised by absent peristalsis and failure of relaxation of the lower oesophageal sphincter (LOS). The mainstays of treatment are pneumatic dilatation and surgical myotomy with reported 2-year success rates of 85–95%. With time, the diagnostic uncertainty regarding the precise mechanism(s) of dysphagia and consideration of re-treatment targeted at the LOS, but in some patients dysphagia may be multifactorial and may not be improved by attempting to further lower LOS pressure. We aimed to evaluate the GI physiological findings of patients seen in our tertiary referral unit to investigate recurrence of dysphagia post-treatment.

Methods: We interrogated our database for patients undergoing high resolution oesophageal manometry ± 24-h reflux studies due to dysphagia post-treatment for achalasia between July 2009 and February 2016. We recorded achalasia subtype, LOS relaxation pressure (known as integrated relaxation pressure, or IRP), and reflux study results if performed.

Results: 101 patients with recurrent dysphagia who had previously been treated for achalasia (52 male, age range 11–83 years, median 45 years) were identified. 98 had high resolution oesophageal manometry performed. 20 patients had 24-h reflux studies for concomitant heartburn and/or regurgitation. 41 had undergone surgical myotomy, 54 previously underwent dilatation, and 6 had no response to botox injection. 50 patients were treated with POEM, 54 previously underwent dilatation, and 6 patients had 24-h reflux studies for concomitant heartburn/GERD.

Conclusion: Nuclear IL-33 is up-regulated in NERD patients. Up-regulated IL-33 expression in lower esophageal mucosa of NERD patients may contribute to the generation of symptoms.
contractions were premature in 5 patients (3 type II, 1 type III, 1 EGI-OEI). POEM was successful (Richard score ≤3) in 42 patients (89%) at 3 months (100% in type I achalasia and EGI-OEI, 91% in type II and 88% in type III, p = 0.011). No factor (age, baseline symptom severity, ECI resting pressure, IRP before and after POEM, post POEM esophageal contractions, PEP during 5–mL water swallow or MWS, esophageo-gastric pressure gradient during MWS, POEM failure at 3 months, Dysphagia, regurgitation and chest pain were reported by 49%, 27% and 22% of patients respectively 3 months after POEM. Patients with regurgitation had a lower ECI resting pressure before POEM (12 vs 26 mmHg, p = 0.03) and a higher post POEM esophageo-gastric pressure gradient during MWS (4.7 vs 0.2 mmHg, p = 0.03) compared to those without regurgitation. No parameter was associated with dysphagia or chest pain.

Conclusion: While POEM is associated with significant changes of esophageal function as assessed with HRM, no manometric parameter but achalasia subtype was predictable of 3-month outcome. Further data are required to confirm that post POEM esophago-gastric pressure gradient during MWS might be associated with regurgitation.

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Body mass index is associated with erosive esophagitis: a retrospective cohort study

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Background/Aims: Obesity has been recognized as a risk factor for GERD and several studies demonstrated a positive association between the body mass index (BMI) and GERD symptoms. However, literatures on whether BMI is related to the erosive esophagitis are scant. This study aimed to investigate the effect of BMI change on the erosive esophagitis.

Methods: A retrospective cohort study was performed to assess the natural course of erosive esophagitis according to the changes in BMI. A total of 1126 cases of erosive esophagitis were included in this study. The degree of erosive esophagitis was measured by esophageogastroendoscopy and serially checked during the follow up period of 5 years. A Cox proportional hazards model was used to investigate the hazard ratios (HR).

Results: Patients with decreased BMI were associated with resolution of erosive esophagitis compared to patients with increased BMI (Hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.01–1.36). Even after adjusting for sex, age, smoking, alcohol consumption, and fatty liver status, the association between the BMI and erosive esophagitis was not attenuated (HR 1.18, 95% CI 1.02–1.38).

Conclusions: Resolution of erosive esophagitis is potentially associated with the decrease in BMI and BMI was independently associated with erosive esophagitis.

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Esophageal dystomyoty in postural orthostatic tachycardia syndrome patients

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Background: Postural orthostatic tachycardia syndrome (POTS) is a disorder characterized by defects in autonomic dysfunction. It is often associated with gastrointestinal and esophageal symptoms but have not been well characterized.

Aim: We sought to characterize the symptoms and manometric findings in our POTS population.

Methods: In a retrospective observation study design, consecutive patients [pts] between 2014 and 2015 with POTS undergoing high resolution manometry (HRM) were included. Pts who did not have an autonomic reflex study (ARS) or HRM were excluded. HRM was performed with a solid state catheter with 36 circumferential pressure sensors spaced 1-cm apart. Esophageal pressure topography plots of 10 single 5 mL liquid swallows were reviewed. Bolus transit was assessed for studies that included impedance measurements.

Results: We included 131 dysphagia patients (57M, 35 vs 15 years) underwent HRM using a 36P16Z catheter. Test boluses of 5–10 mL liquid, 5–10 mL semisolid, and 2–4 cm² solid were administered orally. Perception of bolus passage was evaluated with each swallow using a validated 6-point categorical scale.

Conclusions: The results from this large patient cohort confirm pilot results, concluding that PFA metrics, which are altered in relation to bolus consistency, have added value as they link with patients’ perception. Combining the PFI with the IR in a PFA-matrix shows that our patients with dysphagia who have predominately abnormal bolus clearance can be distinguished from patients with abnormal bolus flow resistance.

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as >20% swallows abnormal. Lower esophageal sphincter was defined as hypotensive if resting mean LES was <15 mmHg. Demographics, motility findings and presenting symptoms were collected from electronic medical record. Statistical analysis using frequencies was employed.

Results: 16 patients met inclusion criteria. 94% (15/16) were female with mean age 35(range 18–64). 75% (12/16) had dysphagia. Other esophageal presenting complaints were chest pain (2/16) and acid-reflux-like symptoms (2/16). Esophageal symptoms were most commonly associated with constipation 69% (11/16). Other associated symptoms included bloating (7/16) and eructation (5/16). Only 25% (4/16) patients had delayed gastric emptying and 12.5% (2/16) delayed small bowel emptying. One patient was on narcotic analgesics. ARS was sent in 75% (12/16) with either weak or failed peristalsis.

Conclusions: Esophageal symptoms are not uncommon in POTS pts, who are predominantly female. The most common symptom is dysphagia which was associated with acid reflux, chest pain, bloating or constipation.

Background: In subjects who present with upper gastrointestinal symptoms: a case series

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Background: Patients with achalasia usually have a thicker muscle at the lower esophageal sphincter (LES), which may impair the esophageo-gastric junction (EGJ) distensibility and affect the treatment outcomes. We hypothesize that muscular features of LES, as determined by high-frequency endoscopic ultrasound (EUS), may affect the efficacy of current treatment modalities aiming to disrupt or weaken the LES.

Methods: During 2010-2015, consecutive adult patients with suspected achalasia were prospectively enrolled in the National Taiwan University Hospital. All subjects underwent a comprehensive diagnostic work-up, including symptom evaluation, blood biochemistry, timed barium esophagogram (TBE), esophageal manometry and pH studies. During EUS session, the LES thickness, including the internal circular muscle (ICM) and outer longitudinal muscle (OLM), were measured with a 12-MHz ultrasonic miniprobe. After treatment with graded pneumatic dilatation (PD), laparoscopic or endoscopic myotomy, all patients were followed up with Eckardt score and TBE. After 12 months thereafter, Treatment failures were defined as an Eckardt score greater than 3 or an improvement in height less than 50% in follow-up TBE.

Results: Three patients were found to have pseudoachalasia (2 had malignancies at the EGJ and 1 had EGJ outflow obstruction on high resolution manometry) and globus sensation. During a mean follow-up of 19 months (4–36 months), 6 patients (46.2%) in the two myotomy groups and 7 patients (50.0%) in the PD group had treatment failure, while 3 patients were lost to follow-up. For patients who underwent PD as the initial treatment, patients with long-term recurrence had significantly greater thickness of OLM (1.9 ± 0.4 vs 1.1 ± 0.5 mm, p = 0.035) but not ICM (2.2 ± 0.3 vs 2.0 ± 0.9 mm, p = 0.780) at LES. Using a cutoff of 1.3 mm, thicker OLM was associated with a significantly lower long-term remission rate to PD than the thinner LES (36.4% ± 100%, p = 0.013).

Conclusions: The above-mentioned data and previous studies support the importance of TBE for the initial assessment of the likelihood of symptom improvement. Although TBE of the LES cannot replace modern techniques to guide treatment decision-making, it is a useful and inexpensive tool to assess the likelihood of symptom improvement after PD. It may also be valuable in screening for pseudoachalasia and predicting treatment success with PD.
258 Association of the HLA-DQB1-insertion in idiopathic achalasia and first genotype-phenotype (GxP) study using high-resolution manometry (HRM) data
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Background: Achalasia is a rare esophageal motility disorder characterized by impaired relaxation of the lower esophageal sphincter and disturbed peristalsis of the distal esophagus, thus blocking the myenteric plexus. Achalasia can be classified according to the Chicago classification which is based on HRM into three different types: I = 100% failed peristalsis, II = panesophageal pressurization with ≥20% of swallows, III = spastic contraction with ≥20% of swallows. Exact pathogenesis of achalasia is unknown, it is a multifactorial disorder including genetic and environmental factors. The strongest genetic risk variant identified so far represents a SNP rs28688207, which leads to an 8-amino-acid insertion in the HLA-DQβ1 protein that together with HLA-DQA1 forms HLA-DQ receptor placed on the surface of antigen-presenting cells.

Aims and methods: The aim of our study was to replicate the role of rs28688207 in achalasia pathogenesis in a sample from the Czech Republic (203 patients, 220 controls). In addition, we performed a CoxP study to test whether rs28688207 is disease-associated to a particular HRM-subtype of achalasia. For this analysis we used a cohort of patients from the Czech Republic and Germany. From a total of 164 cases, 41 were type I, 109 type II and 14 type III.

Results: Genotyping of rs28688207 in the case-control sample yielded a strong achalasia-association (p = 1.22 × 10–4). The insertion in HLA-DQβ1 was present in 9.1% of patients and in 2.7% of controls, which corresponds with the frequency seen in other countries in Central Europe. The CoxP study revealed that rs28688207 is most prevalent in HRM-type I achalasia (12.2%) compared to type II (9.6%) and type III (3.6%), although this was not statistically significant (p = 0.458).

Conclusions: The study provides further evidence that the 8-amino-acid insertion in HLA-DQβ1 plays a pivotal role in achalasia pathophysiology. The insertion is most frequent in HRM-type I achalasia. Despite the clear trend of increasing frequency of the insertion from type III to type I achalasia, this was not significant, which might be due to a small sample size of patients with HRM-type I and III.

259 Management of recurrent symptoms after peroral endoscopic myotomy in achalasia
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Background: Peroral endoscopic myotomy (POEM) rapidly gains ground as treatment for achalasia. Although POEM is a safe and effective treatment, a subset of patients have persistent or recurrent symptoms after POEM. It is currently not known how these patients can be managed best. This study aimed to investigate the efficacy of different treatments for achalasia patients after failed POEM.

Methods: POEM was performed on 418 achalasia patients at three tertiary care hospitals between 2011 and 2015. A review of prospectively collected data was conducted. All achalasia patients with significant persistent or recurrent symptom after POEM, defined as an Eckardt symptom score >3, were included. Retreatment success was defined as Eckardt ≤5 persisting for at least 6 months.

Results: 43 patients (14 females, mean age 42 years) had persistent or recurrent symptoms after POEM, of which 34 patients (79%) received on or more retratements after POEM. The other eight patients started a modified diet or refused treatment. Laparoscopic Heller myotomy was effective in 53% of patients, re-POEM in 67% of patients and pneumatic dilatation (PD) up to 35 mm in 22% of patients. When PD 35 mm was not effective, PD 40 mm also was not effective. No complications of retratements occurred. Patients that failed on retreatment after POEM were more often male patients (14/17), as compared to cases with good outcome of retreatment (3/17), p = 0.038.

Conclusions: Re-POEM and LHM are the most effective treatments after POEM failure while the efficacy of retreatment with proemidations is poor. Failure of retreatment occurred more often in male patients.

260 Mucosal integrity and sensitivity to acid of the proximal esophagus in patients with gastroesophageal reflux disease
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Background: Reflux episodes that extend to the proximal esophagus are more likely to be perceived. Our hypothesis is that the enhanced sensitivity of the proximal esophagus is related to more pronounced impairment of mucosal integrity in this part of the esophagus. We aimed to assess acid sensitivity and mucosal integrity of the proximal and distal esophageal segments separately in patients with gastroesophageal reflux disease (GERD) and to investigate the relationship between these parameters.

Methods: We included patients with heartburn and evidence of GERD on ambulatory pH-impedance measurement. After PPI washout, an esophageal hydrochloric acid perfusion test measuring segmental acid sensitivity proximally and distally in the esophagus (3 and 18 cm above the Z-line) and an upper endoscopy with biopsies at both levels were performed. During endoscopy, electrical tissue impedance spectroscopy was performed at the two levels and biopsies were taken from macroscopically unaffected mucosa. Biopsies were used to measure dilution of intercellular spaces with transmission electron microscopy as a morphological measure of impaired integrity and to investigate transepithelial electrical resistance and transepithelial fluorescein permeability in Ussing Chambers as a functional measure of mucosal integrity. Results: We included 12 CD and FD patients (mean age 48 years, range 28–65, M/F: 4/7). Lag time to heartburn perception was shorter after proximal acid perfusion (mean [95% CI] 0.8 min [0.16–1.44]) than after distal acid perfusion (mean [95% CI] 2.4 min [2.2–4.8]), log rank P = 0.01. In vivo extracellular tissue impedance was lower in the distal esophagus (mean [95% CI] 4914 Ω.m (3206–8705)) compared to the proximal esophagus (8926 Ω.m (5805–14 069)), p < 0.01. Transepithelial fluorescein permeability was higher in the distal than the proximal segment (median 2051 nmol/cm²/h and 368 nmol/cm²/h), p = 0.05.

Conclusion: The proximal segment of the esophagus in GERD patients off PPI is more rapidly sensitive to acid perfusion, while the distal esophagus shows a more pronounced impairment of mucosal integrity. These findings show that the enhanced sensitivity to acid in the proximal esophagus is not explained by increased mucosal permeability.

261 The magnitude of gastric accommodation determines the number of transient lower esophageal sphincter relaxations in health
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Background: Several studies reported on the high symptomatic overlap between gastro-esophageal reflux disease (GERD) and functional dyspepsia (FD). Impaired gastric accommodation (GAC) is a well-established mechanism underlying symptom generation in FD and has been suggested to provide a plausable mechanism of overlap between GERD and FD symptoms. Aim: To study the relationship between GAC, transient lower esophageal sphincter relaxations (TLESRs) and reflux events in healthy volunteers (HV) and patients with overlapping GERD and FD symptoms.

Methods: Twenty HV (10 m, 23 years [range 19–46]) with no prior history of digestive disease and 9 patients with both GERD and FD symptoms (2 m, 34 years [range 20-54]) underwent combined high resolution impedance and manometry (HRM) monitoring, with the catheter placed into the stomach. Recordings were made 30 min before and 60 min after a high carbohydrated and high fat solid meal (1000 kcal). Medical Measurement System (MMS) software was used for
Gastric Physiology, Pathophysiology, and Clinical Disorders

265 Gastric Enterovirus infection: A possible cause of gastroparesis

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Background: Gastroparesis (GP) is a debilitating GI disorder with high morbidity, severely impacting patients’ quality of life. The most common etiology is idiopathic (40%), which occurs mainly in young or middle-aged women, followed by diabetes-related (30%). Idiopathic GP (IGP) may acutely present after viral-like GI illness, thus speculation that IGP may result from a viral cause. The aim of this study is to present gastric Enterovirus (EV) infection as a possible cause of IGP.

Methods: Eleven patients referred to our tertiary-care motility center with a diagnosis of GP underwent extensive workup to exclude known causes of GP including endocrine and autoimmune etiologies, and if negative, were diagnosed with IGP. Gastric biopsies from patients who had history of flu-like symptoms or gastrenteritis prior to the onset of GP symptoms were sent for viral immunoperoxidase testing to assess for gastric EV infection (EVMED Research, Lomita, California).

Results: Of the 11 patients who had EV testing performed, 9 (82%) were found to be EV positive on gastric biopsies. Seven (78%) were female with a mean age of 48 years. Data on presenting symptoms, extra-intestinal
Prucalopride improves symptoms and quality of life in a controlled cross-over trial in gastroparesis

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Background: Gastroparesis is a chronic gastrointestinal disorder characterized by delayed gastric emptying without mechanical obstruction, and clinical symptoms such as post-prandial fullness, early satiety, bloating, nausea and vomiting. Prokinetics are considered the preferred treatment for gastroparesis, but evidence of their efficacy is lacking. Prucalopride, a selective 5-hydroxytryptamine 4 receptor (5-HT4R) agonist used in the treatment of constipation, was shown to enhance gastric emptying rate.

Aim: In a single-center double-blind, randomized, placebo-controlled cross-over study we evaluated the efficacy of prucalopride in improving gastric emptying, symptoms and quality of life in gastroparesis.

Methods: 34 gastroparesis patients (28 idiopathic, mean age 43.5 ± 2.3, 8 men) underwent a 13C-octanoic acid nutrient drink (ND; 1.5 kcal/mL). GA sensorimotor function were observed. After 3 weeks of placebo, no changes in gastric emptying were detected. Our study was conducted in healthy volunteers (HV). In a single-blind parallel-group study HVs underwent an intragastric infusion of ND until maximal nutrient delivery (one subject withdrew due to nausea). The ND was scored every 5 min.

Results: 60 patients (38% females, 38 ± 16 years) were enrolled and showed ≥90% questionnaire compliance. Factor analysis identified 3 cardinal LPDS items (early satiety, postprandial fullness, upper abdominal bloating), whose mean intensities generate weekly LPDS scores (0-4). Known-groups analysis based on low or high OSS scores showed large effect size differences in weekly LPDS scores (Cohen’s d = 2.16). High cross-sectional correlations (r > 0.57) between LPDS scores and relevant anchors were found at baseline, indicating good convergent validity. Internal consistency of the LPDS score was good with high inter-item correlations (0.67–0.76), and test-retest reliability (r = 0.85). A range of symptom change during the trial was sufficiently varied including improved as well as unchanged and worsened patients. Changes in LPDS scores were highly convergent with changes in OTE, OSS, PAGISYM (all r > 0.52). MCID analysis showed consistency for all anchors. Stability of the findings was confirmed by similar results when analyzing the first 20 or 40 patients.

Conclusions: The LPDS diary is a sensitive and reliable PRO instrument to assess severity of PDS symptoms.

266 The effect of antidepressant mirtazapine on gastric accommodation, sensitivity to distention and nutrient tolerance in healthy subjects

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Disturbances of gastric motor function have been implicated in the pathogenesis of functional dyspepsia meal-related symptoms such as early satiation and postprandial fullness, and hence, motility modifying agents are usually considered for its treatment. Mirtazapine, an antidepressant with affinity for 5-HT and histamine receptors, was recently shown to improve symptoms and nutrient tolerance in FD patients with weight loss. Our aim was to evaluate the effect of mirtazapine on gastric sensorimotor function in healthy volunteers (HV). In a single-blind parallel-group study HVs underwent an intragastric pressure measurement (ICP) with high resolution manometry and a barostat study on separate days before and after 3 weeks of placebo or mirtazapine (15 mg). Isobaric distensions with stepwise increments of 2 mmHg and scoring of intensities of gastric sensations (0–6; pain) were used to determine gastric compliance and sensitivity. Gastric accommodation (GA) measured by the barostat was quantified as the difference [delta] in intra-balloon volume before and after ingestion of 200 mL of a nutrient drink (ND, 1.5 kcal/mL). GA measured by ICP was quantified as the drop of ICP from baseline during the intragastric infusion of ND until maximal satiation. During all tests, epigastric symptoms were scored every 5 min.

Results: 30 HVs (15 placebo; 24.9 ± 1.0 years old, 15 mirtazapine; 23.9 ± 0.8 years old) were recruited for the study. After 3 weeks of placebo, no changes in gastric sensorimotor function were observed. After 3 weeks of mirtazapine, a significant increase in body weight had occurred (67.8 ± 3.7 to 69.1 ± 3.7 kg, p < 0.01). Analysis of the mean change in pressure and area under the curve (AUC) for each digestive phase showed a significant increase in gastric accommodation and sensitivity (all p < 0.05), upper abdominal bloating (p > 0.05) and belching (p < 0.05). Consistently, the ICP drop during meal ingestion was significantly suppressed after mirtazapine treatment (AUIC = −43.3 ± 4.5 vs. −28.3 ± 3.1 mmHg, p < 0.005). Conclusion: Mirtazapine does not induce changes in gastric sensorimotor function that could explain its beneficial effects on FD symptoms and nutrient tolerance. The occurrence of weight gain and decreased meal-induced symptoms in spite of a suppressed meal-induced ICP drop, point towards a central mode of action.
Assessment of gastric motility and autonomic function in healthy volunteers and functional dyspepsia (FD) patients with or without the joint hypermobility syndrome (JHS)

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FD is defined as the presence of epigastric symptoms in the absence of underlying organic disease. Recently, the connection between JHS and FD, a connective tissue disorder with multi-systemic involvement and a high prevalence of dysautonomia, has been highlighted. Our aim is to study the impact of the presence of JHS on dyspeptic symptoms, gastric motor function, nutrient tolerance, autonomic response to a meal in FD with and without JHS. The intragastric pressure (IGP) was assessed by means of high resolution manometry in healthy volunteers (HV) and FD patients during the intragastric infusion (60 ml/min) of a nutrient drink (ND, 1.5 kcal/ml) until maximal satiation. The presence of JHS was evaluated by the Brighton classification. Sympathetic (LF) and parasympathetic (HF) modulation was assessed by analysis of Heart Rate Variability (HRV) derived from simultaneous ECG monitoring, computed for before, during, and after the meal.

Results: 63 FD patients (78±5, 41±2 years) and 15 HVs (53±7, 27±2 years) participated. Based on Brighton criteria, 61% of the FD patients and only 1% HV had JHS. FD with JHS reported higher prevalence of early satiation (71% vs 42%), and lower prevalence of nausea (48% vs 67%) and belching (52% vs 83%) compared to patients without JHS (p<0.05). In FD the IGP drop and nutrient tolerance were impaired compared to HVs (AUC HVs: 19.6±2.9 mmHg and FD: −16.1±2.2 mmHg, p=0.37), ingested calories HVs: 984±108 kcal vs FD:741±78 kcal, p=0.08). No difference in IGP drop was observed between JHS and No-JHS patients (p>0.05). JHS patients tended to tolerate higher ND volumes compared to no-JHS (JHS: 832±109 kcal and no-JHS: 590±86 kcal, p=0.14). HRV STD was decreased in FD compared to HVs before (p=0.03), during (p=0.06) and after the meal (p=0.06). After the meal, the HF dropped significantly in HVs (0.03) but not in FD. At the current sample size (N=14) no differences in autonomic tone were observed between JHS and no-JHS patients.

Conclusion: FD-FD patients have a suppressed IGP drop and lower nutrient tolerance, associated with lower vagal tone. JHS co-exists in a large subgroup, which is characterized by early satiation, but no significant differences in IGP, nutrient tolerance or autonomic function compared to the group without JHS were found.

Proximal stomach is the most responsive site for motilin- and ghrelin-induced gastric contractions in Asian musk shrew stomach in vitro

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Background and Aim: During the interdigestive state, motilin and ghrelin are released to regulate and initiate the phase III contractions of migrating motor complex (MMC). Previously, we observed that motilin and ghrelin synergistically induced gastric contraction in vitro and in vivo. These coordinated cyclic motor patterns originate from the stomach and propagate downward in the alimentary canal. On the basis of this, we hypothesized that certain regions in the stomach are more responsive to motilin and ghrelin, and strong gastric contractions are propagated from such responsive sites. Therefore, we aimed to find the active responsive site for motilin- and ghrelin-induced gastric contractions in the stomach.

Methods: We examined motilin- and/or ghrelin-induced gastric contractile patterns in different parts of the shrew stomach using an organ bath system. Treatment with tetrodotoxin and atropine was carried out to determine the involvement of the neural pathway. We performed q-PCR analysis to measure the mRNA expression of the motilin receptor, GPR38. We also examined the distribution of ghrelin-producing cells and GHSR mRNA expression in different parts of the shrew stomach using immunohistochemistry and RT-qPCR, respectively.

Results: The in vitro study revealed, only the proximal corpus induced gastric contraction even at a motilin concentration of 10−10 M, while strong contractions were induced at a motilin concentration of 10−7 M in all the other parts of the stomach. Ghrelin (10−11–10−7 M) with pretreatment of a low dose of motilin (10−10 M) induced gastric contraction in a dose-dependent manner only in the fundus and proximal corpus but not in the distal corpus and antrum. These contractions were mediated by the cholinergic neural pathway in the myenteric plexus. GPR38 mRNA expression was higher in the proximal corpus than in the other segments. Ghrelin cell density and GHSR mRNA expression were also higher in the fundus and proximal corpus than in other parts.

Conclusions: These results suggest that the motilin and ghrelin reactivity is not consistent throughout the stomach. The fundus and proximal corpus are most sensitive and responsive to motilin- and ghrelin-induced synergistic gastric contractions suggesting that the proximal stomach is the most active site for the onset of MMC contraction.

Type 1 diabetic patients with peripheral neuropathy have pan-enteric prolongation of transit times and heightened cecal fermentation

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Objectives: The objective of this study was to explore whether type 1 diabetic patients with established sensorimotor neuropathy (DSN)-D) have demonstrable segmental and pan-enteric dysmotility in comparison to matched healthy controls, and to investigate the co-relations between gastrointestinal (GI) function, degree of DSN and clinical symptoms.

Methods: 41 patients with DSN (36 male, mean age 51 years, range 35-71) and 41 healthy controls (36 male, mean age 51 years, range 28-78) underwent a standardised wireless motility capsule test. Vibration thresholds, Michigan Neuropathy Screening Instrument (MNSI) and Patient Assessment of Upper Gastrointestinal Symptom Index were recorded in patients.

Results: In comparison to healthy controls, patients had prolonged gastric emptying ([80 ± 3.86 vs 70 ± 45 min, p = 0.005]), small bowel transit ([80 ± 108 vs 231 ± 63 min p = 0.0007]), colonic transit ([2010 (interquartile range (IQR) 1134-2766 vs 1048 (IQR 881.5-1599) min, p = 0.0004) and whole gut transit time ([7270 (IQR 1575-3866) vs 1442 (IQR 1261-2041) min, p = 0.0001]). In patients there was an increased pH-drop...
across the ilaeocal valve [–1.8 ± 0.4 vs –1.1 ± 0.5 pH, p = 0.0001], which was associated with prolonged colonic transit [p = 0.4, p = 0.01]. Multivariable regression, controlling for age, gender, disease duration and glycemic control, did not demonstrate an association between transit times or GI symptoms. Vibration thresholds and MSNI were associated with prolonged gastric emptying (p = 0.03 and p = 0.002, respectively).

Conclusions: Pan-enteric GI prolongation of transit times and heightened colonic fermentation is present in patients in a manner independent of disease duration and glycemic control. Further work is warranted to examine the longitudinal nature of these findings.

Capsaicin ingestion improves symptoms in chemosensitive patients with functional dyspepsia

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Background: Half of the patients with functional dyspepsia (FD) are chemosensitive as demonstrated by the oral capsaicin capsule test. Repeated oral application of capsaicin may reduce upper GI symptoms in FD (Bortolotti et al., APT 2002).

Aims: To assess whether a 4-week trial with oral capsaicin improves symptoms of FD in chemosensitive and non-chemosensitive patients.

Methods: N = 59 patients performed an oral capsaicin capsule test (0.75 mg capsaicin capsule ingested after an overnight fast). Thereafter they recorded their daily symptoms on a standard questionnaire during a 1-week run in period and during 4 weeks while they swallowed 0.25 mg capsaicin tid. Questionnaires assessed the severity of several upper GI symptoms on a graded scale (0 = no problem, 6 = interference considerably with daily activities). An overall weekly score was calculated by summing the daily symptoms. Data are given as mean ± SEM, p < 0.05 was considered significant.

Results: 32 patients [84%] tested capsaicin positive (caps pos = chemosensitive), 27 [46%] tested caps negative. 14 patients did not finish the study, mainly because of pain without relief and/or increased in the management of caps pos (p < 0.05). 45 patients completed the study, (22 caps pos, 23 caps neg). Baseline overall symptom scores were not significantly different in caps pos (9.4 ± 4.1) and caps neg patients (7.1 ± 3.8). After 4 weeks capsaicin ingestion overall symptom scores were significantly reduced as compared to baseline in caps pos patients [5.7 ± 4.9, p < 0.05], but not in caps neg patients (NS). Epigastic pain [p = 0.01], epigastric fullness [p < 0.01] and postprandial satiation [p < 0.05] improved in caps pos patients already at week 3 only in caps pos FD, epigastric bloating did not improve (NS).

Conclusion: Cchestosensitive FD patients benefit from a 4-week capsaicin trial, based on a reduction of epigastric pain, fullness and postprandial satiation. A high drop out rate was mainly based on pain induced by capsaicin in the first 2 weeks of treatment in capsaicin positive patients.

275 Pattern of gastric emptying in adult patients following lung transplantation

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Background: Lung transplantation is a lifesaving procedure for patients with severe lung disease. Gastronestinal (GI) complications, particularly gastroesophageal reflux and esophageal dysmotility are common and may negatively influence long-term outcome. The prevalence and significance of gastric emptying disturbances in this population are incompletely described.

Methods: We performed a retrospective study of 37 adults who underwent lung or heart/lung transplantation between 2001 and 2012 at Mayo Clinic, Jacksonville, Florida in which a 4-h radionuclide gastric emptying study (GES) was available. Gastric emptying was measured by a standardized scintigraphic method involving a low fat (2%) isoce white meal of 250 kcal, with anterior and posterior gastric imaging in the standing position obtained at 0, 1, 2, 4 h after meal ingestion. Rapid GE was defined as <50% isoce retention at 1st h and/or <30% at 2nd h and delayed GE as >10% at 4 h. All GES were performed in outpatient setting with the patient taking the least amount of medications, which could potentially affect gastric emptying.

Results: Thirty seven patients were analyzed: 23 females, 14 males, mean age 55 ± 12 years [range: 26–72 years]. Ectologies for lung transplantation were idiopathic pulmonary fibrosis (41%), emphysema (37%), severe pulmonary hypertension (13%) and cystic fibrosis (9%). Fifty percent underwent single and 37% double lung transplant. Thirteen percent had heart/lung transplant. Fifteen patients [42%] met criteria for delayed GES, 21 [57%] had normal GES and 1 [3%] had rapid GE. Of those who had delayed GES, reflux symptoms, in addition to typical gastroesophageal reflux symptoms were present in 55% compared to 28% in normal GES (p < 0.05). There was no difference in age, gender and etiology of transplant in the different GES groups.

Conclusion: In lung transplantation patients, GES is commonly delayed and associated with an increased risk of reflux symptoms. Further work is needed to determine ectologies (pre-existing lung disease, intraoperative vernal nerve injury, immunosuppression and other etiologies) and to determine the effect upon medium and long-term outcomes.

276 Activation of guinea pig enteric neurons by serum from patients with Crohn’s disease

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Background: It is well established that neuronal activity in the enteric nervous system (ENS) is modulated by mediators released from tissue resident non-neuronal cells. Ganglia of the enteric nervous system are close to blood vessels and there is a potential that blood borne factors influence neuronal excitability.

Methods: We therefore applied serum from patients with Crohn’s disease (CD, n = 6), collagen induced arthritis (CIA) and healthy control (HC, n = 6) on guinea pig submucous neurons and analysed their spike discharge with voltage-sensitive dye (Di-8-ANEPPS) recording in 4 submucous plexus preparations (50 ganglia, 574 neurons).

Results: Application of HC-serum caused a small activation consisting of a fast onset spike discharge. Application of serum from CD active or CD remission caused a fast onset spike discharge at 4.5 ± 1.2 Hz or 4.3 ± 1.6 Hz, respectively. This was significantly larger [p = 0.005, p = 0.006] than the rather small spike rate increase evoked by HC serum (1.5 ± 1.5 Hz). Interestingly, the % of neurons responding to the serum was higher for CD-active [67%–20] compared to CD-remission [36%–5, p = 0.010] or to HC [25%±16, p = 0.002]. The overall neuronal activity in the ganglia was best represented by the neuroindex, which is the product of percentage of responding neurons and their spike frequency. The mean values were 2.9 ± 0.4, 1.9 ± 0.9 and 0.5 ± 0.5 ± Hz for CD active, CD remission and HC, respectively, and were significantly different between the three groups (p < 0.05).

Conclusions: We demonstrated substantial excitatory effects of serum from CD patients on enteric neurons. Importantly the activation was strongest for CD-active patient serum. This highlights the importance of serum factors for the excitability of enteric neurons. Strikingly, the nerve activation is less in CD-remission indicating that there is fluctuation in nerve activation with the disease stage and the symptom severity.

277 Effect of FODMAPS on gastric accommodation, upper GI motility and symptom generation in health and in IBS

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Introduction: There is accumulating evidence for the benefit of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) in the management of irritable bowel syndrome (IBS) symptoms. Whether FODMAPs alter the upper GI response to nutrients, including gastric accommodation (GA), and whether this contributes to symptom generation, remains to be assessed.

Aims & Methods: The objectives were to assess the impact of different FODMAPs on the intragastric pressure (IGP) response to nutrient ingestion (which reflects GA), meal-induced satiation and symptom generation. A high resolution manometry and infusion catheter were positioned in the proximal stomach of healthy volunteers and IBS patients. After a stabilization period of at least 60 min, fructans [25g/L] or glucose [100 g/L] were intragastrically infused at 60 ml/min until maximal satiation (0-5 scale), 3 days to 1 week apart in a single-blind randomised cross-over order. IGP was presented as change from baseline (mean ± SEM). Epigastric and GI symptom intensities were rated on 100 mm VAS before infusion, and then every 15 min up to 3 h. Data were analysed using linear mixed models.

Results: Twenty healthy volunteers (HV), 19–32 years, 10 men, 18–44 BMI) and 16 IBS patients (18–55 years, 4 men, 18–32 BMI) were included. Nutrient volume tolerance did not differ significantly between nutrients and between groups. However, during fructan infusion, GA response was significantly inhibited in HV.
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Changes of duodenal pH are important for the occurrence of strong gastric contraction by the release of motilin in the Suncus murinus

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Background: Motilin, a 22-amino acid polypeptide, is considered to mediate gastric phase III contraction of the fasting migrating motor complex (MMC). However, the initiation factors involved in the occurrence of MMC remain unclear. Therefore, this study aimed to elucidate the possible causes or factors that regulate the occurrence of the fasting gastric contractions by using Suncus murinus, a motilin- and ghrelin-producing mammal.

Methods: We examined the effect of intraduodenal alkalization, acidification, luminal pressure, and the involvement of the vagus nerve in the regulation of gastric contractions in fasted anesthetized S. murinus. To measure the gastric contractions, a strain gauge force transducer was implanted on the serosa of the suncus stomach.

Results: A bolus intravenous [iv] injection of motilin (300 ng/kg) evoked phase III-like gastric contractions and was considered as the positive control. Intraduodenal bolus infusion of saline with different pHs [6, 7, and 8] and volumes (0.5, 1, 2, 0.5 mL) showed different gastric contractile patterns. We observed that intraduodenal infusion of 2 mL saline, pH 6, evoked maximum gastric contraction, and the motility index [MI %] showed similar results when compared to the positive control. Interestingly, the infusion of 2 mL saline, pH 6, into the duodenum did not cause gastric contractions. The intraduodenal alkaline pH-induced gastric contraction was almost completely abolished by the intravenous administration of MA 2029 (motilin receptor antagonist) and D-Lys-GHRP6 (ghrelin receptor antagonist). Additionally, vagotomy had no effect on this intraduodenal alkaline pH-induced gastric contraction. Moreover, lowering duodenal pH (pH 2) also evoked gastric contraction about 30 min after bolus intraduodenal infusion, and this effect was eliminated by administering MA 2029 and D-Lys-GHRP6. In addition, iv infusion of SHF (10 μg/kg) also showed similar phase II- and phase III-like contractile patterns in the anesthetized suncus.

Conclusion: These results suggest that change in the duodenal pH to alkaline condition is an essential factor for stimulating the endogenous release of motilin and governs the fasting MMC in a vagus-independent manner. We hypothesize that duodenal acidic pH may trigger duodenal bicarbonate release and increase the alkaline pH to mediate phase III contractions, and SHF may play an important role as an intermediate molecule in the underlying mechanism.
in slow wave dysrhythmias that impact recovery. In this study, high-resolution (HR) electrical mapping was applied to define the electrophysiologic consequences of SG.

**Methods:** Patients undergoing SG (n = 5) or revisional gastric bypass after SG (n = 1) underwent intra-operative gastric mapping using laparoscopically-placed HR arrays (128 electrodes, 4 mm spacing). Slow wave profiles were compared before and after SG. In addition, a series of weaner pig studies were conducted (n = 4), in which HR mapping was performed before and after SG, followed by gastric pacing (4 mA, pulse-width 400 ms, period 20 s) to mimic normal pacesetting of the sleeve remnant.

**Results:** At baseline, slow waves showed normal ante-grade propagation (mean frequency 3.1 cycles/min, velocity 2.8 mm/s). In all patients, SG resulted in immediate onset of ectopic pacemaking with retrograde propagation at high velocity (8–20 mm/s, p < 0.001 vs controls), and/or quiescent regions. In one patient with chronic nausea, food intolerance and sleeve remnant dysmotility 5 months after SG, mapping revealed a stable ectopic pacemaker operating in the antrum, with retrograde propagation (2.7 cycles/min, 12.6 mm/s, p < 0.001 vs baseline data). The porcine studies showed that gastric pacing could restore antegrade slow wave activity and overcome SG-induced ectopic pacemaking.

**Conclusions:** Ectopic pacemaking and dysrhythmic conduction occur after SG, and can be associated with long-term dysmotility of the remnant stomach. Ectopic pacemaking could contribute to acute or chronic post-operative symptoms such as food intolerance, nausea, vomiting and reflux, and can be treated with gastric pacing.

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**Postprandial intragastric pH levels are elevated for significantly longer on reflux monitoring in patients with confirmed gastroparesis**


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**Background/Aims:** Among gastroenterology patients, complaints of postprandial retrosternal/epigastric discomfort and delayed gastric emptying times on breath test, who also had undergone 24-h reflux monitoring off PPI. Another group of symptomatic patients with normal gastric emptying times on breath test, who also had reflux monitoring, were identified as controls. We interrogated reflux monitoring traces for baseline fasted pH, then measured time taken for intragastric pH to return to baseline from the end of self-reported mealtimes. Median times for return of postprandial intragastric pH to baseline were compared between groups.

**Results:** 80 eligible patients with gastroparesis (54 female, age range 18–84 years, median 42 years) were identified and compared with 20 subjects with normal gastric emptying times (12 female, age range 14–70 years, median 42 years). Median baseline fasting intragastric pH in both groups was 1.3. The median duration for postprandial intragastric pH to return to baseline for the gastroparesis group was 118 min (95% CI: 109–153 min) compared to 42.5 min in controls (95% CI: 36–68 min). The difference between the two groups was extremely significant (two-tailed p < 0.0001).

**Discussion:** Intragastric pH is elevated for longer periods postprandially in patients with gastroparesis. The intragastric pH data readily captured on reflux monitoring shows promise as an alternative modality for identifying gastroparesis. A prospective study where 13C-octanoic acid breath testing using standardised meals is performed with concurrent reflux monitoring is currently underway at our unit.

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**Upper gastrointestinal dysmotility and vagal dysfunction after ablation therapy for atrial fibrillation: a single institution study of 13 patients**

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**Background:** Following ablation therapy for cardiac arrhythmias, patients may develop upper gastrointestinal symptoms. The vagus nerve is in close proximity to atria and is potentially affected by the transmission of the electrical energy required to ablate abnormal electrical conducting tissue in the heart.

**Aims:** Our aims were to review Mayo Clinic medical records to identify patients with upper gastrointestinal disorders following ablation therapy for atrial fibrillation and to appraise evidence suggestive of injury to the vagus nerve.

**Methods:** We identified all patients who underwent a catheter ablation for atrial fibrillation between January 1, 2009 and December 1, 2015 by including a primary diagnosis code for atrial fibrillation (ICD-9-CM diagnosis code 427.31) and a Current Procedural Terminology for radio frequency ablation. We identified vagal dysfunction by electrocardiogram tracing showing at least 10 QRS complexes, and we sought evidence of sinus node dysfunction after application of phosphate-buffered saline (PBS, as control group), PE 400 µg and sustained-release PE 400 µg into sphincter muscle using a hollow microinocle. Anal pressure of sober rats was monitored after administration of drugs as function of time using Solenette Urodynamic systems.

**Results:** Topical administration of PE 400 µg and sustained-release PE using hollow microinocles increased the mean resting anal pressure significantly compared with negative control (p < 0.05, n = 5 respectively). The peak resting anal pressure between two groups, simple and sustained-release PE injection was not different (p > 0.05, n = 5). However, time interval for peak resting pressure for sustained-release PE injection was significantly longer than that for simple PE injection (p < 0.05, n = 5).

**Conclusion:** Hollow microinocle-sustained release PE system induced significant contraction of internal anal sphincter at least 12 h after injection. (Experiments are still under way)

Figure 1. Image of hollow microinocle for fecal incontinence [length < 1 mm, inner diameter: 350 µm, inner diameter: 200 µm].

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**Local transdermal delivery of sustained-release phenylephrine using hollow microinocles as a treatment of fecal incontinence**

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**Abstract 285**

**Background/Aims:** Our previous study presented that locally targeted delivery of phenylephrine (PE) to perianal muscles using hollow microinocle [Fig. 1] could increase resting anal sphincter pressure without complications [Control Release 2015, 207: 1–6]. The next step in our research is to demonstrate that local delivery of sustained-release PE using hollow microinocle system can induce elevation of anal sphincter tone with durable effects and biological safety.

**Methods:** Sustained release formula of PE was made of 25% Pluronic F-127, 1% HPMC and PE 400 µg (24 h sustained release formula). After administering sustained-release PE using a hollow microinocle into muscle, drug distribution around anus was investigated using fluorescent dye (Rhodamine B) and IVIS [in vivo imaging system]. The increase in rat anal pressure was investigated using analysis of phosphate-buffered saline (PBS, as control group), PE 400 µg and sustained-release PE 400 µg into sphincter muscle using a hollow microinocle. Anal pressure of sober rats was monitored after administration of drugs as function of time using Solenette Urodynamic systems.

**Results:** Topical administration of PE 400 µg and sustained-release PE using hollow microinocles increased the mean resting anal pressure significantly compared with negative control (p < 0.05, n = 5 respectively). The peak resting anal pressure between two groups, simple and sustained-release PE injection was not different (p > 0.05, n = 5). However, time interval for peak resting pressure for sustained-release PE injection was significantly longer than that for simple PE injection (p < 0.05, n = 5).

**Conclusion:** Hollow microinocle-sustained release PE system induced significant contraction of internal anal sphincter at least 12 h after injection. (Experiments are still under way)

Figure 1. Image of hollow microinocle for fecal incontinence [length < 1 mm, inner diameter: 350 µm, inner diameter: 200 µm].

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atrial fibrillation. Conservative management is therefore unrelated to potential vagal dysfunction (2 achalasia, 1 elevated LES pressure (47.9 mmHg), 1 ineffective esophageal motility, and 1 accelerated gastric emptying. In 3/13 patients, the symptoms appeared unrelated to potential vagal dysfunction (2 achalasia, 1 systemic amyloidosis).

Conclusion: Vagal dysfunction may occur after radio frequency ablation for atrial fibrillation, but the vast majority of patients do not experience long-standing symptoms, and the vagal dysfunction may spontaneously resolve. Conservative management is therefore recommended for upper GI symptoms post-RFA for atrial fibrillation.

285 Manometry features of pylorospasm—a case study

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Introduction: Pylorospasm should be considered in the differential diagnosis of recurrent emesis in children with an otherwise unremarkable evaluation. Pylorospasm can lead to chronic, intermittent vomiting in both children and adults, and may be hard to differentiate from other causes with traditional testing such as ultrasonography. Antroduodenal manometry is helpful in establishing the diagnosis.

Methods: A 5-year-old male with chronic, severe, episodic vomiting and a previously unremarkable workup was followed at Children’s Hospital Los Angeles. He underwent a 6-h antroduodenal manometry study with a conventional water perfused manometry system for evaluation of a possible gastric or intestinal motility disorder.

Results: Antroduodenal manometry showed a pattern of high amplitude phasic contractions in the antral/pyloric region (>300 mmHg) occurring in intermittent clusters, which were associated with nausea. These high amplitude phasic contractions were reproducible with erythromycin provocation and correlated with his clinical symptoms.

Summary: Antroduodenal manometry can be used to assess peristalsis in the upper gastrointestinal tract. The characteristic contractile features of the antral and pyloric regions can be studied over time and evaluated in relation to symptoms. For these reasons, antroduodenal manometry is useful in differentiating pylorospasm from other causes of chronic vomiting and may help guide treatment decisions.

286 Abdominal pain in gastroparesis: use of serum trypsin to identify chronic pancreatitis

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Abdominal pain in patients with gastroparesis (GP) is poorly understood. Patients with chronic pancreatitis (CP) have abdominal pain and can also have delayed gastric emptying. No studies have examined the prevalence of CP in patients with GP. The serum trypsin assay is unique among pancreatic function tests in being a noninvasive serum test. Using low serum trypsin level as a biomarker, we hoped to identify GP patients with abdominal pain from CP. The aims of this study were to: (i) Assess the prevalence of low trypsin levels in patients with GP, (ii) Determine if lower trypsin levels are associated with a specific type of abdominal pain quality.

Methods: Patients seen for GP filled out 3 questionnaires including demographic and medical information, PAGI-SYM grading symptoms of GP, and a questionnaire rating overall, constant, and episodic abdominal pain as absent (0), mild (1), moderate (2), severe (3). Serum trypsin performed by radioimmunoassay assay.

Results: 56 patients were enrolled in this study. 47/56 patients (83.9%) had abdominal pain. 16/56 total patients (28.6%) and 14/47 patients with abdominal pain (29.8%) had low trypsin levels (<20 ng/mL). Trypsin levels tended to be lower in patients with abdominal pain (30.2 ± 15.3 [SD]/ng/mL) compared to patients with no abdominal pain [39.8 ± 22.9 ng/mL; p = 0.12]. Abdominal pain scores were similar in the low trypsin group compared to the normal trypsin group for overall pain (2.2 ± 1.1 vs 2.1 ± 1.1), constant pain (1.3 ± 1.3 vs 1.8 ± 1.3), and episodic pain (1.9 ± 1.3 vs 2.0 ± 1.3). There were no significant correlations between the trypsin levels and abdominal pain in the total 56 patients for overall pain (r = 0.019; p = 0.16), constant pain (r = 0.20; p = 0.05), and episodic pain (r = 0.19; p = 0.15). Of the 16 patients with low trypsin levels, 14 patients reported abdominal pain as a symptom. In 12 patients, the pain was worse after eating a meal, and in 5, the abdominal pain radiated to the back.

Conclusions: Low trypsin levels, used as a biomarker for CP, were present in 30% of GP patients with abdominal pain. Clinical characteristics of abdominal pain were similar in the low serum trypsin level group of patients compared to patients with normal serum trypsin levels. Thus, low serum trypsin levels suggesting CP were seen in a number of patients with GP and abdominal pain, which could not be differentiated from the normal trypsin group based on symptoms alone.

287 The profile of pro-inflammatory and anti-inflammatory cytokines in patients with gastroparesis

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Background: Gastroparesis (GP) affecting up to 10 million individuals in the United States is characterized by the presence of chronic symptoms accompanied by delayed emptying of the stomach, in the absence of any obstruction. Studies have shown a potential shift from M2 anti-inflammatory to M1 pro-inflammatory macrophage phenotype in diabetic GP. Interleukin (IL)-1 induces GP in rats and IL-10 reverses the delayed transit and improves the pathophysiology in diabetic mice with GP. The cytokine profile of patients with GP has not been well elucidated. In this study, we investigate the plasma cytokine status of patients with GP.

Methods: Plasma samples were collected from 15 diabetics without GP (DM), 15 diabetic gastroparetics (DM-GP), 12 idiopathic gastroparetics (ID-GP) and 25 healthy controls recruited consecutively from our clinics. Study subjects were female with no allergic, autoimmune or infectious diseases and were not on immunosuppressant, antibiotic or nonsteroidal anti-inflammatory drugs. The plasma cytokine levels were measured using multiplexed immunobead assay. Normality of data was tested by D’Agostino-Pearson omnibus test. Data were analyzed using one-way analysis of variance or Kruskal-Wallis followed by appropriate post hoc tests.

Results: Patients’ mean ages were 65 ± 58.3, 60.5 and 57.1 years in DM, DM-GP, ID-GP and controls, respectively (p < 0.05). The mean body mass index was 29.7 and was similar among the groups. In DM-GP, monoocyte chemoattractant protein (MCP)-1 which is involved in the polarization of M2 macrophages and IL-18, a modulator of T-helper-1 response, were significantly increased by ~43% and ~99%, respectively. These changes were not observed in ID-GP. The pro-inflammatory IL-1β tended to decrease in the DM, DM-GP and ID-GP. This trend reached significance in DM-GP vs control. IL-6 decreased in DM-GP and ID-GP, but not in DM patients. The analysis of anti-inflammatory cytokines revealed decrease in IL-10 by ~74% in DM-GP and by ~91% in ID-GP. IL-1RA was decreased by ~49%, only in the ID-GP group. The levels of transforming growth factor-β1 were similar in the studied groups.

Conclusions: GP is associated with an imbalance in plasma cytokines. Specifically in DM-GP, IL-18 and MCP-1 were increased and IL-10 was decreased consistent with the pro-inflammatory phenotype and a shift from M2 to M1. Future studies should focus on whether manipulating cytokines including IL-10 therapy could be considered as a potential therapeutic option in GP.
Table 1 Comparison of FD and IBS

<table>
<thead>
<tr>
<th>Percentage</th>
<th>women</th>
<th>Mean BMI (SD)</th>
<th>Median age [min-max]</th>
<th>Mean proximal frontal diameter 0 min [cm]</th>
<th>Mean proximal sagittal area 0 min [cm²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD [n = 94]</td>
<td>80%</td>
<td>22.1 (4.1)</td>
<td>27.5 [36.0]</td>
<td>26.5</td>
<td>4.5</td>
</tr>
<tr>
<td>IBS [n = 88]</td>
<td>72%</td>
<td>23.8 (4.6)</td>
<td>36.0 [40.5]</td>
<td>29.3</td>
<td>5.3</td>
</tr>
<tr>
<td>p</td>
<td>0.264</td>
<td>0.038</td>
<td>0.008</td>
<td>0.001</td>
<td>0.003</td>
</tr>
</tbody>
</table>

FD = functional dyspepsia; IBS = irritable bowel syndrome

Results: As presented in Table 1, patients with FD had significantly lower frontal diameter and sagittal area of the proximal stomach than patients with IBS, both immediate postchilally and 10 min postchilally (p = 0.005) indicating impaired accommodation. There were no significant differences in the antral area or antral emptying fractions.

Conclusion: In this study, patients with FD were generally younger and leaner than patients with IBS, but the female:male ratio was similar in both groups. Patients with FD had impaired gastric accommodation to a liquid meal compared to patients with IBS, but gastric emptying was equal between the groups.

Table (continued)

<table>
<thead>
<tr>
<th>Table 1 Comparison of FD and IBS (continued)</th>
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<tbody>
<tr>
<td>Mean proximal frontal diameter 10 min [cm]</td>
</tr>
<tr>
<td>FD [n = 94]</td>
</tr>
<tr>
<td>IBS [n = 88]</td>
</tr>
<tr>
<td>p</td>
</tr>
<tr>
<td>22.4</td>
</tr>
<tr>
<td>25.5</td>
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<tr>
<td>&lt;0.001</td>
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</table>

GI Motility and Functional GI Disorders in Children and Adolescents

Reference


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Prenatal nicotine exposure impairs gastric emptying, glucose metabolism and growth in newborn rat pups

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Background: Nicotine exposure delays gastric emptying and results in metabolic derangement in adults. The effects of prenatal nicotine exposure (PNE) on motility in neonates have not been explored.


Methods: The Animal Review Committee at the University of Mississippi Medical Center approved the protocol. Starting 2 weeks before mating, nulliparous female rats (200-250 g) were randomly assigned to receive daily subcutaneous injections of nicotine bitartrate (1 mg/kg/day) or vehicle (saline). Maternal injections were continued until weaning (postnatal 21 days). Weight and caloric intake were compared between groups. Glucose metabolism was evaluated using the Insulin Tolerance Test (ITT). Gastric Emptying (GE) was evaluated using the Evac’s Blue method.

Results: PNE rats (n = 4) weighed less than controls (n = 4) at 3 months post-natal age (PNE 35.8 ± 16 g vs control 40.2 ± 9 g, p < 0.05). PNE rats consumed less feed (PNE 16.24 ± 0.13 g/day vs control 18.14 ± 0.21 g/day, p < 0.05) and fewer calories than controls (PNE 48.53 ± 0.57 kcal/day vs 54.43 ± 0.63 kcal/day, p < 0.05). Glucose metabolism was impaired in PNE rats (n = 4) compared to controls (n = 4) by ITT (see table). GE was slower in PNE rats (n = 5) compared to controls (n = 5, 30 min Retention: PNE GE 89% vs control GE 72%, p < 0.05).

Discussion: The model used in this study mimics fetal and neonatal exposure from a smoking mother on breast-feeding. These findings suggest PNE plays a role in growth, metabolism and motility in rat pups. The effects were observed several weeks after weaning, therefore, PNE continues to affect offspring in an indirect fashion.

Abstract 288

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Abstract 289

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NEUROGASTROENTEROL. MOTIL. 2016, 8, SUPPLEMENT 1, 5-108
Intestinal dysfunctions induced by intrauterine growth retardation are associated with altered autophagy in the enteric nervous system.

**Objective:** The intra uterine growth retardation (IUGR) is characterized by a low birth body weight (<2.5 kg) and represents 4% of births. IUGR has long term consequences on health in adulthood, with an elevated risk to develop metabolic diseases and hypertension. In this study, we examined whether IUGR alters gastrointestinal (GI) and enteric nervous system (ENS) functions during life.

**Methods:** Pregnant rat dams were fed with a normal protein diet (20% protein, control group) or with an isocaloric low protein diet (8% protein, IUGR group) until weaning. The study was performed on the progeny at post-natal day 35 (PN35). Digestive functions (motility and permeability) and their response to a stress, the water avoidance stress (WAS), were analyzed in vivo and ex vivo. Changes in ENS phenotype were evaluated in whole mounts and in primary culture of ENS from control or IUGR group.

**Results:** No difference was observed between control and IUGR rats for motility and permeability under basal conditions both in vivo and ex vivo. By contrast, following WAS, paracellular permeability in the distal colon was increased in control but not in IUGR group. Similarly, following WAS, fecal pellet output was increased in control but not in IUGR group. Analysis of ENS revealed a reduction of nitricergic neurons in the ileum of RCIU rats compared to control animals. In addition, autophagy, a key cellular pathway during stress condition, was decreased in the nitricergic, but not cholinergic, neurons in the distal colon of IUGR rats. Moreover, using a coculture system of enteric neurons and glia, we found that IUGR neurons were less resistant than control neurons to cell death induced by glia deprivation. In this model, pharmacological blockade of autophagy indicated that survival of IUGR neurons critically required autophagy while control neurons did not.

**Conclusions:** Our study suggests that early life stress, such as IUGR, can alter the capacity of the GI tract to respond to an environmental stress later in life, in part via alterations of ENS functions. These ENS dysfunction might involve impaired autophagic pathways.

**Funding:** INSERM, Region Pays de la Loire (Parimad), Fondation LCL, Fondation Sainte-Dige.

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294 Low bioenergetics in functional disorders parallel disability score

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**Background:** We hypothesized that patients with functional disorders (FD e.g. chronic migraine, functional gastrointestinal disorders, chronic fatigue syndrome, etc.) show impaired mitochondrial bioenergetics.

**Methods:** We compared blood from youth with an FD with carefully screened healthy controls (HC) with no functional disorder or chronic medical condition. The Oxygen Consumption Rate and Extracellular Acidification Rate (ECAR) measurements utilized the Seahorse, XP96 Extracellular Flux Analyzer (North Billerica, MA), in unbuffered/serum free RPMI assay media supplemented with 1 mM pyruvate. Peripheral Blood Mononuclear Cells (PBMCs) were seeded in a PS V7 cell culture plate at a density of 3.5 x 10⁵ cells per well, then placed in a non-CO₂ incubator for 1 h. Oligomycin (1 µg/mL), Carbonyl cyanide-4-phenyl-hydrazone (FCCP, 1 µM) and Antimycin A (10 µM) determined the mitochondrial parameters. A Mann-Whitney test compared skewed variables, and Fisher’s exact test dichotomous variables. Regression correlated with DNIC activation, suggesting that norepinephrine levels directly regulate pain modulation. Supported by a Digestive Disease Center grant and Advancing Healthier Wisconsin 5520298.

295 Pain modulation in youth with functional gastrointestinal disorders (FGID) may be normal: a role for baseline norepinephrine?

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**Background:** Children with FGID report pain compared to HC but pain complaints outside the gastrointestinal tract, suggesting abdominal pain Neuronal Control (DNIC). Catecholamines impact pain modulation in animals and are a logical target of investigation in humans.

**Hypothesis:** DNIC is reduced in children with FGID and correlates with functional disability. The DNIC response reflects circulating norepinephrine levels.

**Methods:** In this prospective IRB approved study, we compared DNIC (Chalaye et al.) in ascending and descending immersion of the arm to the shoulder in 12 °C cold water, with a 45 min rest in between. Each of 4 segments (fingers, wrist, forearm and shoulder) was immersed for 2 min in cold water with a rest period of 5 min between segments, and pain reported by the subject on a 10-point numeric rating scale every 15 s during the immersion. DNIC is calculated by subtracting finger and wrist immersion during the ascending period (DNIC not activated) from the same report during the descending period (full DNIC activation). Blood was obtained through an IV at baseline, at end of ascending, prior to descending and after descending is complete. Functional Disability Inventory (FDI) measured functional disability.

**Results:** We enrolled 11 subjects with FGID (1 male, mean age 15.1 years, range 13–17 years). FDI ranged from 4 to 28 with a median of 22 points [±SEM: N=1]. DNIC could not be calculated in 2 subjects because they reported no significant pain (<2 in NRS) when immersing their hand in cold water. The other 10 FGID subjects had a normal DNIC activation of a median of 8 points with a range of 2.8–10. Catecholamines and present DNIC were available in 7 subjects. In those subjects, DNIC activation correlated highly with baseline norepinephrine value (r = 0.97, p = 0.01). The FDI did not correlate norepinephrine (r = 0.36, p = 0.42).

**Conclusions:** DNIC is preserved in youth with FGID. Basal norepinephrine levels are lower than healthy controls, suggesting that norepinephrine levels directly regulate pain modulation.

Supported by a Digestive Disease Center grant and Advancing Healthier Wisconsin 5520298.

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**Timing of symptoms during fructose breath hydrogen test in fructose-sensitive children with chronic abdominal pain**

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**Background:** Carbohydrate malabsorption can cause symptoms such as pain, nausea, bloating, passing of gas, and diarrhea in sensitive patients. Fructose malabsorption can be determined with the fructose breath hydrogen test (BHT).

**Aim:** We evaluated the development of symptoms over time in children with fructose sensitivity.

**Methods:** 60 consecutive patients (age: 10-15 years, 28 male, 32 female) with chronic abdominal symptoms received a fructose BHT for clinical suspicion of carbohydrate-induced gastrointestinal symptoms. Symptoms during the BHT were assessed regularly up to 9 h after commencement of the test in Frankel’s Faces Pain Scale (0 = no symptom, 5 extreme symptom). 21 patients (13 m, 8 f) turned out to be fructose sensitive, as one or more symptoms increased significantly (2 points or more).

**Results:** Mean ± SEM are reported, p < 0.05 was considered significant.

- 23 subjects displayed fructose malabsorption, of whom 11 developed symptoms. 10 subjects had symptoms without increase in breath H2. 21 patients (13 m, 8 f) turned out to be fructose sensitive. Before fructose ingestion abdominal pain scores were low in both fructose sensitive patients (0.60 ± 0.2) and non-sensitive patients (0.87 ± 0.2). In the fructose sensitive group, pain scores stayed low for the following 120 min (NS vs baseline) but increased significantly at 150 min (1.33 ± 0.3, p < 0.05 vs baseline). Pain resolved thereafter and did not recur. In contrast, nausea developed 30 min after baseline and continued until 120 min, increased bloating was present between 120 and 150 min and urge to pass flatus was noticed 3-6 h after fructose ingestion. Diarrhea did not develop in the fructose sensitive patients within the 9 h observation period.

**Conclusion:** After fructose ingestion various symptoms arise at different points in time in a pediatric population with chronic abdominal pain. Both the result of the H2 test as well as the distinct timing patterns of symptoms suggest that not all symptoms may be associated with fructose malabsorption but that other mechanisms might be also responsible for the development of some symptoms.
Distribution of dystrophin and utrophin in gastric wall of a patient with duchenne muscular dystrophy and gastrocolonic dysmotility

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Background: Duchenne muscular dystrophy (DMD) represents the severest of heritable dystrophies. Superior supportive therupeties have prolonged survival, however clinical presentation are encountering additional symptoms and flexes in these older DMD children, particularly gastric dysmotility. Little is known regarding the distribution of dystrophin and its autosomal homologue utrophin within gastric musculature, or whether dystrophin is decreased/ lacking in these layers in the context of DMD.

Materials and Methods: Immunohistochemistry (IHC) was performed on fresh-frozen samples from our DMD patient a 17-year-old male with cyclic vomiting since age 15, documented delayed gastric emptying, and abnormal swallowing, as well as multiple frozen non-pathologic gastric biopsy specimens from normal patients. Antibodies targeting dystrophin (C. N termini), utrophin (N terminus), and spectrin were employed. Normal skeletal muscle served as control.

Results: In contrast to normal gastric samples showing dense staining for dystrophin in both smooth muscle layers (muscularis mucosa and propria), autopsied procured gastric samples from our DMD patient showed weak to absent staining by dystrophin IHC. Dystrophin was likewise weak/absent in smooth muscle layers of small and large bowel, and peripheral and esophageal skeletal muscle (spectrin positivity retained). Interestingly, utrophin was detected in muscularis mucosae but not muscular propria of normal stomach samples. In our DMD patient samples, utrophin was retained in the muscularis mucosa, but aberrant staining was not detected in muscularis propria smooth muscle. In con- tradistinction, utrophin-positive fibers were present in both our patient’s peripheral and esophageal skeletal muscle.

Conclusion: Additional studies will be required to determine whether DMD-related gastric dysmotility is directly related to this loss of dystrophin in gastric smooth muscle, or if other neuromuscular elements involved in functional motility are alternatively compromised.

An unusual congenital colonic neuromusculopathy in an infant with total colonic dysmotility

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Background: Calretinin (CAl) is being increasingly used as an immunohistochemical marker for the histopathological diagnosis of human intestinal neuropathies.

Case Report: An 8 month old Arabic girl, born to consanguineous parents, presented with a history of delayed passage of meconium after birth and abdominal distension. Daily rectal irrigations helped decompress her abdomen, but she had no spontaneous bowel movements. Other than mild developmental (gross motor) delay, she had a normal physical examination. Full thickness rectal biopsy was hypoganglionic with reduced Calretinin (CAl) + terminal nerves and normal ACFase activity, not suggestive of Hirschsprung disease. Contrast enema at 8 months showed a capacacious colon with poor spontaneous evacuation. Colanic manometry lacked high amplitude propagated contractions (HAPC), even after bisacodyl stimulation. Antro-duodenal manometry was normal. She did well for 8 months after an ileostomy but repeat colonic manometry remained abnormal. After subtotal colectomy with takedown of ileostomy, bowel function is normal. We compared histology and immunohistochemistry of circumferential strips of her resected colon from ascending to sigmoid region to a control colon using antibodies to neuronal elements (calretinin, FGF9, GAP43, Glut-1), interstitial cells of Cajal (CD117) and sympathetic. The mucosa appeared normal throughout. The muscularis propria showed patchy atrophic changes. The submu- cosal and myenteric plexi in ascending colon showed reduced number of ganglion cells and non-uniform reduction in prevalence of CAl+ nerves in the lamina propria that tended to normalize in the distal colon when compared with the control specimen. The gan- glion cells were often small, some pyknotic, some displaced, some immature and some apoptotic. There were skip areas in the submucosal and myenteric plexuses where there were no ganglion cells or hyper- trophic nerves identified along the entire length of the colon. Quantitative studies are in progress.

Conclusion: We describe an unusual congenital colonic neuromuscular abnormality in an infant with total colonic dysmotility.
small bowel manometry in a child with chronic intestinal pseudo-obstruction.

302 High-resolution solid-state colonic manometry in children with intractable functional constipation

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†Pediatric Gastroenterology and Nutrition, Nationwide Children’s Hospital, Columbus, OH, USA,
‡Human Physiology, Flanders University, Adelaide, SA, Australia and §Gastroenterology & Surgery, Flanders Medical Centre, Adelaide, SA, Australia

Background: Our aim was to quantify colonic motor patterns in children with FC using solid-state high-resolution colonic manometry (HRCM) and to compare these results with previously published data from constipated children and healthy adults. Methods: Retrospective analysis of all children with FC who underwent HRCM at our tertiary children’s hospital (Columbus, OH, USA). A solid-state catheter with 36 sensors (at 3 cm intervals) was placed in a prepared colon with the aid of colonoscopy or intervention radiology via the anus (retrograde) or through a cecotomy (anteGRADE). Recordings included 2 h before and after a meal, followed by 1 h of recording after infusion of bisacodyl through the central lumen of the catheter. These data were compared with, (i) 18 children [median age 15 years, 2 male] with intractable FC studied in Amsterdam, the Netherlands (water-perfused manometry, 36 channels, at 1.5 cm intervals), and, (ii) 12 healthy adults [median age 51 years, 5 male] studied in Adelaide, Australia (fiber-optic manometry, 72 sensors at 1 cm intervals). The dominant frequencies of contractile activity were quantified for pre- and post-prandial recordings. All recordings were examined for the presence of high amplitude propagating contractions (HAPCs).

Results: 18 children [median age 11.5 years] from Columbus were analyzed. While contractile activity was recorded in all of these children, the 2-4 cycle per minute contractions that dominate colonic motility recordings in healthy adults was diminished. This was particularly evident after a meal and also observed in the children studied in Amsterdam. Prior to bisacodyl, HAPCs were identified in 5 children before the meal and in 5 children after the meal. After bisacodyl, HAPCs were present in 14 children (median number of HAPCs: 6) and these were initiated at a median duration of 9 min (IQR 5–28 min) after bisacodyl infusion. The post-bisacodyl HAPCs were similar in characteristics to the spontaneous HAPCs.

Conclusion: As the colonic meal response is likely to be mediated via extrinsic neural input, these data support the hypothesis that an extrinsic neuropathy exists in patients with intractable FC. Our results also show that sex, catheter type and minor protocol differences do not influence this outcome.

303 Antroduodenal manometry abnormalities in adolescents with functional gastrointestinal disorders associated with joint hypermobility syndrome [JHS]

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*Medical College of Wisconsin, Milwaukee, WI, USA and †Equal contribution of first two authors.

Background: Gastrointestinal (GI) complaints are often debilitating in patients with JHS. Upper GI manometric patterns are not well characterized in children with JHS. We aim to describe antroduodenal motility (ADM) patterns in children with functional gastrointestinal disorders (FGIDs) and co-morbid JHS.

Methods: Retrospective review of 10 adolescents with FGIDs, seen in a tertiary Neurogastroenterology clinic. JHS was classified as a Beighton score ≥4. All patients underwent high-resolution ADM with a 36-sensor HR catheter (distal 4 sensors spaced 5 cm and rest 1 cm apart) placed beyond the ligament of Treitz. Study protocol: fasting 3 h, post-Erythromycin (1 mg/kg) 1 h and post-prandial 2 h (≥400 kcal meal). Enteric neuropathy characterized by: (i) absence of phase-III migrating motor complex (MMC), (ii) non-propagating/retrogade propagating MMC, (iii) ≥1 MMC/h, (iv) non-propagating bursts of high-amplitude (≥20 mmHg), prolonged (>2 min) contractions in small bowel, (v) sustained (>30 min), poorly coordinated phasic activity in isolated bowel segment, (vi) prolonged (>3 min) tonic increase in basal tone (≥30 mmHg) during MMC/fasting, (vii) inability to convert to fed pattern 2 h post meal, or (viii) return of MMC within 60 min of meal. Enteric neuropathy described as generalized low-amplitude contractions (<20 mmHg). Post-prandial hypomotility characterized visually by lack of sustained antroduodenal contrac- trility ≤60 min post-meal or ≥15 min segments and rumination syndrome by classic R-waves.

Results: All subjects were female; mean age 16 (range 11–18) years. All met criteria for JHS (mean Beighton score ≥5). 9/10 had MMC activity in fasting or post-erythromycin stimulation. 7/10 subjects met ≥ criteria for an enteric neuropathy. Of these, 20% of subjects had disorganized or non-propagating MMC, 30% non-propagating bursts of high-amplitude contractions in small bowel and 40% tonic increase in basal pressure. 90% of patients showed post-prandial hypomotony, which correlated with a history of gastroparesis in majority. 30% of subjects had rumination syndrome.

Conclusion: Mechanisms underlying GI symptoms in patients with JHS are unknown. In this cohort of adolescents with FGIDs and JHS, there is a high prevalence of motility abnormalities suggestive of gastroparesis and an enteric neuropathy.

304 Association of constipation and delayed gastric emptying in a pediatric population

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Background: Childhood constipation is a common problem with frequently underestimated consequences. Failure to recognize and treat constipation appropriately can lead to secondary issues such as feeding intolerance, abdominal pain, and incontinence. Delayed gastric emptying has been associated with fecal impaction in adults, but there is limited data demonstrating this effect in pediatrics. Identifying constipation as a known trigger of delayed gastric emptying may lead to more effective management, and have a significant impact on a large pediatric population.

Methods: We performed a retrospective review of patients treated at Children’s Hospital Los Angeles between January 2012 and January 2015. Eligible sub- jects included patients greater than 1-year-old who had a gastric emptying study and abdominal radiograph within a 30 day period. Delayed gastric emptying was defined as emptying less than 40% of a mixed meal and less than 60% of a liquid meal at 90 min. Radiographs were evaluated independently by both a pediatric gastroen- terologist and radiologist to identify presence or absence of left sided and rectal fecal burden. Clinical diagnosis of constipation was identified using ICD-9 codes. Statistical analysis was performed with Fisher’s P test and kappa analysis of agreement.

Results: Of patients with delayed gastric emptying, 37.6% had a known causative factor and 35% were identified by a radiologist, compared to 19.7% of patients without delay (p = 0.016). There was a trend toward significance with constipation as defined by either reader (p = 0.079). Agreement between readers on radiographic presence of constipation was good with kappa 0.70 (95% CI: 0.59- 0.82). There was no statistically significant association between clinical diagnosis of constipation and delayed gastric emptying.

Conclusions: Our study supports conflicting results on the association between constipation and delayed gastric emptying in pediatric patients. While there was a significant association using radiologist determination of left sided stool burden, this was not consistent using our other definitions of constipation. Future studies should be considered using more stringent criteria such as fecal impaction documented on physical examination.

305 The Groningen defecation and fecal continence questionnaire: a comprehensive measure of anorectal functioning

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Background & aims: Various questionnaires and scoring systems have been developed to aid the diagnosis of constipation or fecal incontinence. These questionnaires are often brief and fail to include questions associated with possible causative factors for defecation disorders. Moreover, only one scoring system combines constipation and fecal incontinence, while these two disorders are known to co-exist. Keeping these points in mind we developed the Groningen Defecation Fecal Continence (DeFeC) questionnaire, a comprehensive questionnaire on anorectal functioning, defecation disorders and their causative factors. The aim of this paper is to introduce our new questionnaire and to explain its clinical and scientific value.

Methods: We incorporated various Rome III criteria and scoring systems for constipation and fecal incontinence in the DeFeC questionnaire. To test its reproducibility, we conducted a test-retest validation study by asking one hundred participants to complete the Groningen DeFeC questionnaire twice. Subsequently, we calculated the weighted Cohen’s kappa (k) coefficient of all
main items. The Groningen DeFeC questionnaire was translated from Dutch into English and back into Dutch to ascertain that the contents of the questionnaire had not changed during translation.

Results: A total of 88 questions covering various aspects of anorectal functioning, associated disorders, and their causative factors were included in the questionnaire. The average weighted $k$ coefficient of the main questions was 0.6, indicating a substantial agreement for the entire questionnaire.

Conclusions: The Groningen DeFeC questionnaire is a reliable pre-diagnostic tool with a substantial degree of reproducibility that allows us to diagnose a certain defecation disorder and to determine its causative factors.

306 On the prevalence of constipation and fecal incontinence, and their co-occurrence, in the Netherlands

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Background & Aims: Numerous studies have investigated the prevalence of constipation and fecal incontinence (FI) in the general population and, even though these disorders are known to co-occur, they were studied independently of each other. Our aim was to investigate the prevalence of constipation and FI, and their co-occurrence, in the general population in the Netherlands.

Methods: We studied a cross-section of the Dutch population ($N = 1259$). All respondents completed the Groningen Defecation & Fecal Continence questionnaire. We defined constipation and FI in accordance with the Rome III criteria.

Results: We found that 24.5% [95% CI, 22.1–26.8] suffered from constipation, 7.9% [95% CI, 6.4–9.4] suffered from FI, and 8.5% [95% CI, 7.5–9.5] suffered from both disorders. Constipated respondents were 2.7 times more likely to suffer from FI than non-constipated respondents (95% CI, 1.8–4.0). Moreover, 48.7% of the respondents with constipation, 35.0% with FI, and 38.6% in whom the disorders co-occurred qualified their bowel habits as either ‘good’ or ‘very good’. We found that 49.4% of the respondents with constipation and 48.0% with FI had not discussed their complaints with anyone.

Conclusions: Constipation and FI, isolated or co-occurring, are common disorders in the general population, even in young and healthy respondents. Since constipation and FI are not always identified appropriately by patients, therefore physicians should take the initiative to diagnose and treat these disorders.

307 Role of excitatory and inhibitory motor neural pathways in generation of post-stimulation response for colonic migrating motor complex in human colon

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Background/Aims: The main contractile wave of colonic migrating motor complex (CMMC) is not initiated upon the onset of stimulation, propagating contractions are initiated when the stimulus ceases. This pattern of activation is suggestive of what is known about post-stimulation response (PSR) in isolated muscle strips. This study aimed to characterize the role of excitatory and inhibitory neural pathways in generation of PSR to understand the more definite mechanism of CMMC.

Methods: Colonic circular muscle strips were obtained from 19 colon cancer subjects who underwent colectomy at Samsung Medical Center. Shortly after colectomy, circular and longitudinal muscle strips were taken from areas free of macroscopic evidence of cancer infiltration in the ascending ($n = 9$) and sigmoid colon ($n = 10$) colon. Isometric force measurements were performed in response to electrical field stimulation (EFS). Peak and area under the curve (AUC) were measured during post-EFS periods in control state and after sequential addition of atropine, N-nitro-L-arginine (L-NNA), and HuC/D inhibitor, and MRS2500 (purinergic receptor Y1 antagonist) to the organ bath.

Results: In the control state, post-EFS contraction response (PSR) was noticed in the circular and longitudinal muscle layers of ascending and sigmoid colon except for the longitudinal muscle layer of ascending colon. In the presence of atropine, PSR however was noticed in both circular and longitudinal muscle layers of ascending and sigmoid colon. Addition of L-NNA in the presence of atropine significantly suppressed PSR in the circular muscle layer of ascending colon, while MRS2500 did in the circular muscle layer of sigmoid colon. In addition, PSR in the longitudinal muscle layer of ascending and sigmoid colon was suppressed by addition of L-NNA.

Conclusions: Nitricergic neural pathway is responsible for generating PSR in the circular muscle layer of the proximal colon while purinergic neural pathway is in the distal colon. Nitricergic inhibition is responsible for PSR occurred in the longitudinal muscle layer along the whole colon.

308 Neuroplastic changes induce functional repercussions in the remaining ‘healthy’ bowel in Hirschsprung disease

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Introduction: Irritable bowel syndrome (IBS) is associated with an increased postprandial symptom response to a combined nutrient and lactulose challenge test compared to healthy controls. Co-morbid Functional Dyspepsia (FD) and psychological comorbidity are highly prevalent in IBS, but are not regularly taken into account. Our aim was to investigate the association between co-morbid FD status and severity of co-morbid psychological symptoms on the one hand and the symptom response to the combined nutrient and lactulose challenge test in IBS and healthy controls on the other hand.

Methods: 205 IBS patients (Rome III, 94 (46%) of whom had co-morbid FD (IBS-FD), Rome III, and 83 healthy volunteers (HV) consumed a 400 mL liquid breakfast [Nutridrink®] combined with 25 g of lactulose after an overnight fast. They completed graded rating scales (0–
20 assessing severity of gastrointestinal (GI) symptoms (abdominal pain, bloating, nausea, gas, urgency) and overall ‘digestive comfort’ before breakfast and every 15 min up to 240 min, postprandially. The relationship between subject health status (HV, IBS, IBS-FD) and the course of GI symptom scores over time were analyzed using linear mixed models with level of anxiety (HADS), depressive (HADS), and somatization (PHQ-12) symptomatology as covariates.

Results: A significant main effect of group, i.e. difference between the three groups in the average symptom level over time, was found for all symptoms (all \( p < 0.001 \)). Post-hoc tests showed that both IBS groups differed significantly from HV for all symptoms, whereas IBS-FD had higher levels of bloating \( (p_{\text{IBS-FD}} < 0.001 \) and abdominal pain \( p_{\text{IBS-FD}} < 0.005 \)), and lower levels of digestive comfort \( p_{\text{IBS-FD}} < 0.01 \) compared to IBS. A significant group-by-time interaction effect was found for bloating \( p = 0.009 \), abdominal pain \( p = 0.006 \), urgency \( p = 0.049 \) and digestive comfort \( p = 0.002 \). A significant difference in symptom increase from baseline between IBS-FD and IBS was found for bloating and abdominal pain \( p_{\text{IBS-FD}} = 0.013 \). In addition, over all groups, anxiety levels were positively associated with symptom levels for all symptoms \( p < 0.05 \) except abdominal pain, levels of which were associated with somatization severity \( p = 0.001 \). Breath test results \( \left( H_2 \right. \) and \( \left. CH_4 \right) \) were not different between groups, yet anxiety levels were positively associated with hydrogen levels \( p = 0.0042 \).

Conclusion: In IBS, co-morbid FD is associated with increased GI symptom reporting, both preprandially and after a combined nutrient and lactulose challenge test, particularly for abdominal pain, and is associated with decreased overall digestive comfort reporting. Anxiety and somatization have independent additional effects. These results indicate that the presence of co-morbid FD and levels of psychological distress are relevant for (nutrient-induced) symptom reporting in IBS.

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Mechanisms of intestinal dysmotility in undernutrition

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Background: Protein-energy undernutrition (PEU) contributes to half of global child deaths and produces comorbidities that impair weight gain. A poorly understood effect of PEU is delayed GI transit, which leads to bacterial overgrowth, abdominal distention, and suboptimal nutrient absorption. We established two mouse models of early-life PEU to identify novel nutrition-sensitive mechanisms of dysmotility.

Methods: Newborn C57BL/6 mice were made PEU by timed separation from the dam. Some were fed rat chow; controls with isocaloric standard chow were unexposed. In the fed state, we assessed progression of nonabsorbable dye 15 min after gavage, measured metabolites known to regulate GI motility by mass spectrometry (MS), and quantified RNA expression in five segments from stomach to colon with PCR. Fold-changes (FC) were reported as PEU/controls.

Results: At 14 days of age, both PEU models were 30% underweight, 15% stunted, had decreased mean progression of dye (128.5 cm vs 176.0 cm in controls), and 2.0-fold increased quantity of fecal pellets retained in the colon. MS revealed no changes in GABA, but PEU decreased plasma serotonin (FC 0.75) and fecal bile acids \( \left( \text{e.g., deoxycholate, FC0.001} \right) \). PCR revealed induction of serotonin transporter \( \text{SerT} \) (FC 2.0), which depletes extracellular serotonin. There was no transcriptional change in tryptophan hydroxylase \( \text{Tph1} \), the rate-limiting step in serotonin synthesis, but PEU mice had less \( \text{Tph2} \) substrate, tryptophan \( \text{FC 0.65} \), by MS. PCR revealed loss of nuclear far upstream X receptor \( \text{FXR} \) signaling with repression of FXR targets organic solvent transporter \( \text{Ostx1} \) and \( \text{Ostj1} \) (FC 0.50 each), which recycle bile acids to liver.

Conclusions: Despite distinct means of inducing early-life PEU, all moderately underweight and stunted mice exhibited delayed small bowel transit and colonic fecal retention. PEU decreased concentrations of two motility-inducing metabolites. Decreased serotonin may be due to enhanced reuptake and tryptophan deficiency. Decreased bile acids are linked to FXR signal loss with repressed transcription of transporters that recirculate bile acids. These data lead us to hypothesize that tryptophan deficiency promotes the downregulation of \( \text{Ostx1} \) and \( \text{Ostj1} \), and FXR-mediated loss of bile acids contributes to dysmotility in PEU. This effect may be amenable to therapeutic amino acid supplementation, serotonin reuptake inhibition, or nuclear receptor targeting.

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Paramagnetic labeled neural crest derived stem cells (NCSCs) can be tracked in the gastrointestinal tract after being transplanted


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The fate of transplanted stem cells can be tracked by magnetic-resonance-imaging (MRI), when the cells have been labeled with magnetic nanoparticles prior to transplantation. So far, in vivo trackings of transplanted neural crest derived stem cells for the treatment of Hirschsprung’s disease have not been performed. We propose a new method to transplant these cells using the mesenteric arteries and follow their integration by MRI. NCSCs have been isolated from the postnatal gut and enteric neurospheres were generated. The neurospheres were labeled with fluorescence-labeling-paramagnetic iron oxide nanoparticles and cultured in three-dimensional extracellular matrix gels to simulate their migration behavior in vivo. MRI pictures from the cultures were taken each day for a period of 4 days. In the following experiments, the NCSCs were transplanted either as neurospheres or cell suspensions in ex-vivo small intestines of the newborn mice. To do so, the mesenteric arterial branch of the individual arcade was identified and freed from connective tissue. A 60-80 \( \mu \text{m} \) wide glass pipette was inserted in the artery and fixed with a suture, so that the cells could be distributed all over the gut segment while perfusing it. The vascular system is visible in MRI-scans through the contrast agent Vasovist, which is bound to albumin contained in blood plasma. Vasovist causes a positive contrast in the MRI-scans whereas the nanoparticles cause a negative contrast. The labeled cells could be tracked both in the gels and after transplantation. In the segments, the nanoparticles could be visualized in T2-weighted MRI-sequences and the contrast agent in T1-weighted scans. After the transplantation that was performed under MRI control the muscle layer with the transplanted cells was dissected and kept in vitro over a period of 4 days. The neurospheres could be seen both during and immediately after transplantation within the gut wall, as well as in the tissues that have been cultivated for 4 days. So we could clearly demonstrate that the transplantation and colonization of the gut by the transplanted cells can be followed by MRI. Additional experiments in the living animal have to be performed to evaluate this method for in vivo transplanta- tion approaches.

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Enteric neurospheres can be cryopreserved

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The gastrointestinal tract is innervated by a largely autonomous nervous system, the enteric nervous system (ENS). This coordinates and controls essential functions such as motility, secretion and absorption. During embryonal development neural progenitor cells overcame from the neural crest into the gastrointestinal tract and differentiate into neuronal- and glial cells of the ENS. If a fault is a migration of progenitor cells, this leads to a partial or complete absence of the ENS with considerable loss of function of the gastrointestinal tract, such as Hirschsprung’s disease. Surgical removal of the non-inervated sections does not completely improve the situation for the patients. They often still suffer from severe complications, so both alternative therapeutic concepts are discussed. One of these is the autologous transplantation of neural stem cells. These cells might be harvested in several steps, so that cells have to be collected until sufficient cells are available to colonize the whole aganglionic area. This means that storage conditions have to be performed. Cryoconservation is usually an optimal way to store cells for longer time periods, unfortunately with some side effects like reduced survival. We therefore investigated several freezing and thawing protocols that have been used for other cells for the cryopreservation of enteric neurons (EnNSs). Neural crest derived stem cells were isolated from newborn rats and cultured to generate EnNSs within 5 days. The EnNSs were frozen in four different media with and without DMSO and kept for 2 weeks at –80 °C. Then the cells were thawed and plated on coverslips to be differentiated. Life-death assay were performed, and the amount and quality of neuronal subgroups were investigated by immunohistochemistry and RT PCR. Initial results show that the cells survive freezing, but not without a significant number of dead cells. The quality of the freezing procedure, respectively the amount of surviving cells depends on the protocols used. In principle the cryconservation of rodent EnNSs is possible without loss of proliferation and differentiation ability, but with decreased viability. This opens up ways to use storing protocols prior to transplantation.
Constipation and fecal incontinence in children do not dissolve but exacerbate after transition to adulthood. M. E. W. TIMMERMAN, M. TRZPIS and P. M. A. BROENS
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Background: Currently, it is not known how symptoms and other factors associated with constipation and fecal incontinence (FI) change during the transition from childhood to adulthood. Therefore, we aimed to study this possible change in constipation and FI by comparing prevalence rates, help seeking behavior and symptoms between children and young adults.

Methods: A cross-sectional study was performed in the Dutch population. 240 children (8–17 years old) filled out the Groningen Pediatric Defecation and Fecal Continence Questionnaire and 189 young adults (18–29 years old) filled out the Groningen Defecation and Fecal Continence Questionnaire.

Results: The prevalence of constipation [child: 18% vs young adult: 26%; p = 0.058] and FI (9% vs 11%, p = 0.42) increased but not significantly in young adults compared to children. In case of constipation, 23% of children and 51% of young adults did not seek help (p = 0.005). In case of FI, 48% of the children and 43% of the young adults did not seek help (p = 0.99). Furthermore, the feeling of incomplete defecations and having to defecate again within 1 h after defeation both had a significant increase in frequency when comparing constipated children to young adults (36% vs 69%, p = 0.017 and 9% vs 26%, p = 0.016, respectively). In case of FI, the frequency of the following complaints significantly increased in young adults compared to children: loss of large amounts of solid stool without feeling urge (19% vs 67%, p = 0.001), strong urge combined with inability of reaching toilet on time (19% vs 71%, p = 0.012), occurrence of accidentally passage of stool shortly after emptying bowels (10% vs 57%, p = 0.003), and having to change underpants and/or trousers due to accidentally passed stool [19% vs 52%, p = 0.019].

Conclusions: Although the prevalence of neither constipation nor FI significantly increased after transition from child to young adult, the complaints associated with these defecation disorders did significantly exacerbate. Thus, since these complaints do not disappear during the transition period, it is important to diagnose and treat constipation and FI as soon as possible, preferably during childhood. Furthermore, the taboo of defecation disorders should be abolished, since most people do not seek help for their defeation complaints.

Constipation and fecal incontinence in children is underestimated and easily unrecognized. M. E. W. TIMMERMAN, M. TRZPIS and P. M. A. BROENS
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Background: Constipation and fecal incontinence (FI) are common in children, but the prevalence rates of these disorders vary widely in different populations. Furthermore, their diagnosis is still challenging due to the variety of symptoms and co-existence with other disorders. Therefore, we aimed to study constipation and fecal incontinence, in terms of prevalence, recognition of these problems by patients, help seeking behavior, and associated symptoms.

Methods: A cross sectional study was performed in the Dutch population. The questionnaire between 8 and 18 years old were approached to fill out the Groningen Pediatric Defecation and Fecal Continence Questionnaire. Children without a history of bowel surgery or comorbidities were classified as the ‘healthy’ population [n = 222]. Results: In the total population, 18% of the children experienced constipation and 9% had FI (8% retentive constipation and 6% non-retentive). Interestingly, also 18% of the ‘healthy’ population experienced constipation, while the prevalence of FI was 3% for retentive FI and 5% for non-retentive FI. Of the children who experienced constipation or FI in the total population, 52% rated the quality of their bowel habits as good or very good. Moreover, 23% of the total children with constipation and 48% of the total children with FI did not talk to anyone about their complaints. Interestingly, 77% of the children with constipation had ‘normal’ stool frequencies, namely once every 2 days or once/twice a day, while 75% had ‘normal’ stool consistencies (defined as Bristol stool chart 3 or 4: sausage with cracks or smooth sausage).

Conclusions: The prevalence of defecation disorders, such as constipation and FI, is relatively high in the Netherlands. A large part of children with a defecation disorder does not recognize it as a problem and does not seek help, which can lead to an underestimation of the prevalence of these problems. Finally, most children with constipation have a normal defecation pattern, which probably contributes to problems with the recognition.

Abnormal autonomic function testing suggests chronic globus sensation is a functional disorder in teenage females. T. CECEIREGA* and N. A. TIPNIS*
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Background: Globus sensation is a condition described a feeling of a foreign body stuck in the throat. It is a troublesome symptom for many, and a specific cause for the symptom can be difficult to elucidate.

Aim: We describe a series of consecutive patients referred for the evaluation of globus sensation to a tertiary care, academic medical center.

Methods: The Investigation Review Board at the University of Mississippi Medical Center approved the case series. From September 2013-February 2016, consecutive cases of globus sensation were reviewed and demographic, clinical, radiographic, endoscopic, manometric and autonomic testing data extracted.

Results: 15 children with a diagnosis of globus sensation were identified. 3 children (2M, ages 9, 10, 13 y) had globus sensation associated with an acute choking episode. All 3 had resolution of symptoms after a normal modified barium swallow and received no additional evaluation. Of the remaining 12, all were female, median age 14.6 y (IQR 13.9-15.2 y), and median symptom duration of 1 year (IQR 0.8-1.4 years). Associated symptoms included fatigue/malaise [11/12], pre-syncpe [12/12], syncope [4/12], headaches [10/12], esophageal dysphagia [8/12], chest pain [12/12], palpitations [9/12], nausea [12/12], abdominal pain [10/12], urinary symptoms [4/12] and joint pains [5/12]. Esophagram was normal in 9/10 (esophagitis 1). Endoscopy was normal in 9/10 (esophagitis 1). Esophageal manometry was normal in 9/10 (weil-cornell). P. M. A.
tachycardia and small fiber neuropathy in all. These findings suggest that chronic glabrous sensation in teen-
age females is a functional disorder. Therefore, treat-
ment should focus on functional disease once
inflammatory conditions are excluded.

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Fecal incontinence is not influenced by age and gender in the ‘healthy’ Dutch population
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Background: Despite fecal incontinence (FI) being a common, devastating disease, studies about the preva-
ience and symptoms in the general Dutch population are lacking.

Aim: We aimed to investigate if different demographic factors influence the prevalence of FI and to evaluate the pattern of symptoms associated with FI in the Dutch population.

Methods: This cross-sectional study was performed in the general Dutch population (N = 1259). All respon-
dents completed the Groningen Defecation & Fecal Continnence questionnaire. We excluded 237 respon-
dents whom suffered from chronic diseases or under-
went surgery that are known to influence fecal continence, after which 1022 ‘healthy’ respondents
remained for analyses. We defined FI as recurrent uncontrolled loss of liquid or solid stool at least once a month during the past 6 months.

Results: Overall, 55 (5.4%) of the ‘healthy’ respondents suffered from different forms of FI, including soiling, urge, and complete, i.e. passive, FI. Single logistic regression analyses showed that the likelihood of FI was not significantly influenced by age, gender, BMI, or educational level. Furthermore, compared to respondents without FI, respondents with FI had to rush to the toilet more often to prevent accidental loss of stools (54.5% vs 7.3%, p < 0.001) and suffered more often from abdominal pain (47.3% vs 18.9%, p < 0.001). Additionally, respondents with FI were more often not able to control their bowel for more than 5 min after feeling urge sensation (24.7% vs 61.8%, p < 0.001) and to differen-
tiate between flatulence, diarrhoea, and solid stool when feeling urge sensation (61.8% vs 17.4%, p < 0.001). Of the 55 respondents with FI, 14 (25%) made adjustments in their daily life at least once a month because of FI.

Conclusions: FI is a relative common disease in the ‘healthy’ Dutch population with a prevalence of 5.4%. FI is not influenced by age, gender, BMI, or educational level. Respondents with FI more often have to rush to the toilet because they are less able to control their bowel, which could possibly result from damage of the pelvic floor muscles or their innervating motor nerves. Furthermore, respondents with FI find it more difficult to differentiate between different types of stool, which indicates that they might suffer from sensory nerve damage.

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Associations between hydrogen breath test and symptom responses during a combined nutrient and
lactulose challenge in IBS patients and healthy controls
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Introduction: Irritable Bowel Syndrome (IBS) is associ-
ated with increased symptom levels after a lactulose
challenge test, compared to healthy controls (Le Nevé et al., AJG 2013), with psychological distress and co-
morbid functional dyspepsia (FD) also being associated with symptom levels (Pohl & Van Oudenhove et al., UEGW 2015). However, it is not known if hydrogen breath test responses and symptom responses to this test are associated.

Methods: 196 IBS patients (Rome III, 81) of which had co-morbid FD (43.6%), and 81 healthy volunteers (HV) consumed a 400-mL liquid breakfast (Nutrinourish®) combined with 25 g of lactulose after an overnight fast. They completed graded rating scales [0–20] assessing severity of gastrointestinal (GI) symptoms (abdominal pain, bloating, nausea, gas, urgency) and digestive comfort before breakfast and every 15 min up to 240 min post-lactulose ingestion, and hourly for 240 more minutes after intake of a standardized lunch. Breath samples were collected and analysed at the same time points up to 240 min post-lactulose ingestion for hydrogen level measurement using a gas chromato-
graph. The relationship between peak hydrogen level [increase from baseline] and GI symptom levels over time was analyzed using linear mixed models, controlling for gender and anxiety (HADS), depression (HADS), or somatization (PHQ-12).

Results: No significant main or interaction effects of delta peak hydrogen were found for bloating and urgency. For nausea, a significant main effect of delta peak hydrogen was found (p = 0.028), driven by a positive association between hydrogen response and symptom level over the entire period of measurement. For gas, a significant delta peak hydrogen-by-time interaction effect was found (p = 0.013), driven by a positive association between hydrogen response and symptom level from 195 min post-lactulose ingestion on. For abdominal pain and digestive comfort, a group-
by-time-by-delta peak hydrogen three-way interaction effect was found (p = 0.003 and p = 0.059, respectively), driven by a lack of association between hydrogen response and symptom levels in healthy controls, a main effect of delta peak hydrogen in IBS patients without FD, and a time-by-delta peak hydrogen interaction effect in IBS patients with FD (with the strongest relationship in the beginning of the mea-
surement and after lunch). The effect of the psychoso-
cial variables was significant for all symptoms, confirming earlier findings.

Conclusions: Increased hydrogen production during a combined nutrient and lactulose challenge is associated with higher levels of nausea, gas, and abdominal pain, and lower levels of digestive comfort.
groups (RE: 1.75 s [1.32–2.17] and 2.50 cm [2.40–3.20],
NERD: 1.60 s [1.10–2.20] and 2.20 cm [2.10–2.65],
Hypersensitive oesophagus: 1.60 s [1.30–1.80] and
2.70 cm [2.30–3.00], Functional heartburn: 1.55 s [1.20–
2.17] and 3.10 cm [2.25–5.00]. Healthy volunteers: 1.50 s
[1.20–1.90] and 2.50 cm [2.10–3.00]. However,

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Fecal transplantation showing the relevance of fungi in post stress visceral hypersensitivity of maternal separated rats
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Background: Despite the vast attention for a possible role of the gut microbiota, fungi are largely excluded from investigations regarding the pathophysiology of irritable bowel syndrome (IBS). In our rat maternal separation model for post-stress visceral hypersensitivity we target increased sensitivity to colonic distension that is also observed in part of the IBS patients. We assessed the visceromotor response (VMR) to colonic distension as an indirect measure for visceral sensitivity to evaluate the role of the gut mycobiome by fungal depeletion and repopulation experiments.

Methods: Three groups of Long Evans rat pups (p = 8/group) were maternally separated (MS) for 3 h daily from postnatal day 2-14. At adult age, all groups were subjected to 1 h water avoidance (WA)-stress. Just before and 24 h after WA, the VMR to colonic distension (1, 1.5 and 2 mL) was assessed, followed by 3 weeks of fungi-cide (fluconazole/nystatin)-treatment. After 7 days wash out rats were gavaged with pooled caecum content of n = 4 donor rats with gavaged with pooled caecum content of n = 4 donor rats with known sensitivity status. Group 1 received content of fungi-cide-treated (normosensitive) MS donor rats, group 2 non-fungi-cide treated (hypersensitive) MS donor rats, group 3 non-fungi-cide treated non-handled (normosensitive) rats. After 7 days of re-colonization, all 3 groups were again subjected to WA and VMR to distension was assessed (expressed as area under the curve, AUC, volume vs response, Wilcoxon signed ranks significant when p < 0.05).

Results: WA significantly increased the VMR in all recipient groups and this response was reversed by subsequent fungi-cide treatment. Donor caecum content did not restore hypersensitivity in group 1 and 3 recipients, but led to significantly enhanced VMR to distension in group 2. Pre-WA vs post-WA vs post-fungi-cide vs post-repopulation AUC in group 1, 76 ± 3, 74 ± 7, 74 ± 4, 79 ± 4, in group 2, 79 ± 6, 105 ± 13°, 74 ± 4°, 91 ± 7°, and in group 3, 83 ± 8, 104 ± 13°, 78 ± 11°, 80 ± 13°.

Conclusion: Gut fungi are involved in post stress visceral hypersensitivity in MS rats and repopulation experiments suggest that this response requires an MS specific microenvironment. Therefore, we suggest that the gut mycobiome should be subject of future investigations in IBS.

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Structural and functional alterations in the colonic microbiome in a chronic stress rat model of irritable bowel syndrome
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Irritable bowel syndrome (IBS) is linked to stress and alterations in colonic microbial ecology. Stress is known to perturb the microbiome. Stress is implicated in the pathogenesis of IBS and exacerbates IBS associated symptoms such as dysmotility, visceral hypersensitivity and colonic permeability. Characterizing structural i.e. microbial composition) and functional (i.e. microbiome metabolic profile) changes in the microbiome is necessary to understand how alterations affect the biologic environment and host biology. We investigated the effects of chronic stress, which causes persistent IBS-like symptoms in the rat, on the structure and function of the colonic microbiome. Sequencing of the V4 hypervariable domain of the 16S ribosomal RNA gene was used to determine the bacterial diversity and abundance of the colonic mucosa-adherent microbiome of control animals (C, n = 13) and animals repeatedly exposed to a water avoidance stressor (WA, n = 13), which induced visceral hypersensitivity, increased colonic permeability, and increased fecal pellet output. In silico analysis of the functional domains of microbial communities was done by inferring metagenomic profiles from 16S data. The colonic microbiome of WA animals exhibited higher alpha-diversity and moderate divergence in community structure (beta-diversity) compared to control animals. Several microbial clades were consistently modified in the WA animals (LEfSe analysis). WA colonic microbial communities were enriched in Proteobacteria, Actinobacteria, Flavobacteria, Sphingobacteria, and depleted in Verrucomicrobia, Porphyromonadaceae and Rikenellaceae compared to control animals. A decreased capacity in fatty acid and sulfur metabolism was inferred for the microbiome of WA animals. Our research provides novel insight into structural changes and functional shifts in the microbiome concomitant with stress induced IBS-like symptoms in the rat. Observed ecological and functional dependencies suggest bacterial phylotypes and functional domains which underlined the microbiome of WA animals. We conclude for the microbiome of WA animals. Our research provides novel insight into structural changes and functional shifts in the microbiome concomitant with stress induced IBS-like symptoms in the rat. Observed ecological and functional dependencies suggest bacterial phylotypes and functional domains which underlined the microbiome of WA animals.
prebiotics may be a useful dietary adjunct for co-morbid gastrointestinal symptoms in obesity.

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Relationships of microbiome markers with gastrointestinal symptoms in irritable bowel syndrome M. HEITKEMPER,1 K. CAIN,2 R. BURR,2 R. SHULMAN,1 Y. ZIA1, C. HAN1 and M. JARRETT*1
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Background/Aims: Irritable bowel syndrome (IBS) is a poorly understood gastrointestinal (GI) disorder. The gut microbiome may play an important role in the diagnosis of IBS and understanding the pathophysiology of symptoms in IBS. To date, the links between gut microbiome markers and daily symptoms in IBS still remain under-explored. Our aim was to investigate the association between specific gut microbiome markers and daily GI symptoms in women with IBS.

Methods: Fecal samples were obtained at baseline in a randomized clinical trial of behavioral therapy that included baseline measures of daily mean severity of GI symptoms. All women (n = 82) kept a 28-day symptom diary. Symptoms were assessed each day on a 5-point scale from 1 (not present) to 5 (very severe), and summarized as percent of days with moderate to very severe symptoms (ratings 4 and 5). Stool consistency was measured using a 5-point Likert scale (1 = hardest, 5 = loosest) in the daily diary. Fecal samples were measured by 16S ribonucleic acid (rRNA) gene sequencing. Gut microbiome summary measures were analyzed: Shannon and Simpson microbiota diversities, Firmicutes: Bacteroidetes ratio and Clostridia: Firmicutes ratio. Spearman’s rank order correlation analyses were performed.

Results: Looser stools were associated with lower microbiota diversity, lower Clostridia: Firmicutes ratio and higher Firmicutes: Bacteroidetes ratio (p = 0.01). In addition, more severe ratings of daily constipation were associated with higher microbiota diversity, less severe ratings of daily constipation and bloating were associated with higher Firmicutes: Bacteroidetes ratio. Lower ratings of daily diarrhea, urgency, and nausea were associated with higher Clostridia: Firmicutes ratio (p < 0.05).

Conclusions: The associations of stool consistency with microbiota diversity and Firmicutes: Bacteroidetes ratio in women with IBS are consistent with findings of a previous study in healthy participants. The associations of gut microbiota diversity with daily GI symptoms extend those findings and may help us understand the genesis of IBS symptoms as well as provide guidance toward targeted, tailored management approaches for subgroups of IBS patients.

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Mutual Interaction between the enteric nervous system and different bacterial strains L. MARK*, A. BRAUN*, I. THEISINGER*, D. GRUNDMANN*, A. SCHWIERTZ, K. ZIMMERMANN* and K. H. SCHÄFER*
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The enteric nervous system (ENS) is the largest part of the autonomic nervous system. Due to its permanent exposure to changing luminal conditions, it must dispose a significant plasticity. A basic requirement for this adaptive capacity throughout its lifespan is both an intact stem cell niche and the differentiation in specific cell types within the gastrointestinal tract. An inflammatory induced maintenance of the proliferating capacity of neural stem cells has already been shown in studies with bacterial lipopolysaccharides (LPS). In this study, we assessed the effects of intact microbiota on the ENS. Primary cultures of the myenteric plexus were grown for 8 days under influence of media conditioned by the bacterial strains Escherichia coli and Enterococcus faecalis to assess their impact on neural stem cells and differentiation. In the stem cell cultures the size and the number of newly formed neurospheres are determined. Additionally, luminal perfusion experiments of the murine small intestine with the intact bacteria were performed. It could be shown that both bacterial strains could increase gut motility, although the effect induced by E. faecalis was not as pronounced as the one seen with E. coli. The most effective stimulus was achieved when both bacterial strains were simultaneously perfused. The effect of bacterial metabolites upon the neural stem cells was determined by varying numbers and adhesion properties of the enteric neurospheres. While the supernatant of E. coli showed an increased number of neurospheres, cultures treated with E. faecalis conditioned media tended to adhere and differentiate. In the context of an additional differentiation study performed for E. coli, a reduced density of neuronal and glial networks could be detected when the postnatal (P1 and P7) myenteric plexus cultures where cultivated under the influence of E. coli conditioned media. In general, we can conclude, that individual bacterial strains do influence both gut and ENS differentially.

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Safety and efficacy of fecal microbiota transplantation on functional bowel disorders - a pilot study T. MASAOKA, T. YAMANE, S. MIYAZO, R. MORI, K. HIRATA, M. MATSUMIYUKA, R. MIYANAGA, M. NAKASHIMA, R. MATSUOKA, M. NAGANUMA and T. KANAI Keio University School of Medicine, Tokyo, Japan

Background: Functional gastrointestinal disorders (FGID) are characterized by the presence of symptoms with the absence of organic, structural or metabolic abnormalities that readily explain symptoms. Functional bowel disorders (FBD), such as irritable bowel syndrome (IBS), functional constipation, functional diarrhea are FGID with symptoms thought to originate from the middle or lower gastrointestinal tract. Because its diagnosis is based on only symptoms, etiology and pathogenesis are multifactorial and heterogeneous. Therefore, despite its high prevalence, established therapeutic option is still lacking. Recently, alterations of gut microbiota, namely dysbiosis have been implicated in a number of pathogenesis of gastrointestinal disease (Gastroenterology 149:223-37, 2015). Its typical example is Clostridium difficile infection (CDI). Fecal microbiota transplantation (FMT) has shown efficacy in the treatment of patients with recurrent CDI. Hope for FMT as treatment option for other gastrointestinal disease, such as Inflammatory bowel disease, FBO is emerging. Aim of this pilot study is to evaluate safety and efficacy of FMT on FBD.

Methods: Refractory FBO patients who did not respond to ordinary medical therapy for longer than 1 year were enrolled. Based on Rome III criteria, FBO were diagnosed. The primary end point was the changes of stool form evaluated by Bristol stool scale (BSS; Scand J Gastroenterol 32:920-4, 1997). When Constipation (IBS Type 1 or Type2) or Diarrhea (IBS Type 6 or Type7) changed to normal type (IBS Type 5-7), the FMT procedure was considered as effective. After screening of infectious agents, donors were selected from spouse, 1st or 2nd degree relatives. After dissolution of feces from the donor by normal saline, FMT was performed via colonooscopy. This study was approved by the research ethical committee of the Keio University School of Medicine (No.201310488) and registered with the UMIN Clinical Trials Registry (UMIN000001617).

Results: 18 refractory FBO patients (9 patients with IBS, 5 patients with functional constipation, 4 patients with functional diarrhea) were enrolled. Because of results from screening of infectious agents, 3 patients with functional constipation could not find donors. Finally, FMT were performed for 15 FBO patients (Mean age of 41.2 years, 7 females). Among 15 patients, FMT procedures were effective on 10 patients (5 patients with IBS, 1 patient with functional constipation, 4 patients with functional diarrhea). No severe adverse effect was observed.

Conclusion: Despite small enrolled numbers, safety and efficacy of FMT on FBD were suggested.

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No clear evidence for benefit of VSL#3 in patients with irritable bowel syndrome: a combined analysis of three prospective trials A. SHIN and T. JAMES-STEVENSON Indiana University, Indianapolis, IN, USA

Background: The use of probiotics in irritable bowel syndrome (IBS) has been extensively studied. A prior systematic review and meta-analysis demonstrated probiotics to have a beneficial effect, however, uncertainty exists due to variations in methodological standards of prior investigations as well as the plethora of available strains for use. VSL#3 is a patented probiotic preparation consisting of eight different strains of bacteria (Biﬁdobacterium longum, B. infantis, B. breve, Lactobacillus acidophilus, L. casei, L delbrueckii ssp.paracasei, L. plantarum and Streptococcus salivarius ssp. thermophilus) for which several clinical trials have suggested efficacy with regards to motor function, bloating and abdominal symptoms in patients with IBS.

Aims: To investigate effects of VSL#3 on patient-reported outcomes of global efficacy and abdominal pain in IBS.
Aim: MMC.

Introduction: and that Mrgs undergo changes in their expression during intestinal inflammation. Our research group has shown involved in functional gastrointestinal disorders and function in mucosal mast cells (MMC), which are regulating pain sensation, although the full spectrum of a specific subset of sensory neurons, suggests a role in pertensive therapies. The expression of Mrg receptors in regulating cytokine release and will employ knockout models to elucidating the response of BMMC to NPAF in terms of modulator of MMC activity in neuro-immune community. Our findings suggest that NPAF is a novel cytokine release and will employ knockout models to elucidating the response of BMMC to NPAF in terms of modulator of MMC activity in neuro-immune community. Our findings suggest that NPAF is a novel

Methods: This was a combined analysis of three randomized placebo-controlled trials comparing 8 weeks of treatment with VSL#3 to placebo among patients with IBS. Global efficacy was defined by the proportion of responders reporting satisfactory relief in bloating or symptoms for at least 4 of 8 treatment weeks. Abdominal pain was measured as mean improvement from baseline. Data were pooled using random-effects model and reported as relative risk (RR) or standardized mean difference (SMD) with 95% confidence intervals (CI).

Results: A total of 97 patients [16 constipation-predominant IBS, 69 diarrhea-predominant IBS, and 12 alternators] were enrolled in prospective studies investigating VSL#3 vs placebo for treatment of IBS. Global efficacy data were available for a total of 73 patients. Data for mean improvement in abdominal pain were available in 49 patients. Relative to placebo, treatment with VSL#3 was associated with increased global efficacy with satisfactory relief in at least 4 of 8 weeks for IBS symptoms or bloating; however this was not statistically significant (RR = 1.19, 95% CI: 0.66, 2.15). A higher mean improvement in abdominal pain was observed with VSL#3 when compared to placebo, but this was not statistically significant (SMD = 0.48, 95% CI: –0.10, 1.06). No adverse events were reported.

Conclusions: Treatment with VSL#3 does not confer a clear benefit in patient-reported outcomes of global satisfaction or abdominal pain. However, studies are limited and follow-up limited. Additional investigation with longer follow-up and inclusion of rigorous clinical efficacy endpoints are needed.

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Protective effects of milk fat globule membrane and L. fermentum CECT 5716 on gut functions and on T cells response in a newborn rat model

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*Inserm U993, IMAD, Nantes University and Lactalis Research and Development, Retiers

Background: Impaired intestinal functions together with an abnormal immune response are incriminated in the pathophysiology of gut disorders affecting infants and children. Recent studies highlighted the crucial role of intestinal microflora, probiotics and MFGM lipids in promoting postnatal maturation and strengthening the intestinal epithelial barrier [JEB]. We characterized, in a rat pup model, the impact of oral administration of Lactobacillus fermentum CECT 5716 (LF) and Milk Fat Globule Membrane (MFGM) on gut functions and on spleen T cells cytokine production.

Methods: Newborn rats received by gavage, from postnatal day (PND) 7 to 24, a mixture of LF+MFGM (10⁶ CFU and 150 mg/100 g body weight/day, resp.), an isocaloric lipid solution or water (controls). Gut morphometric, histological and immunohistological analyses were performed in isolated preadipocytes and human colonic epithelial cells. LF+MFGM shifted Th1/Th2 balance towards a Th1 response in isolated splenocytes. The use of these dietary compounds might therefore provide a new approach in the prevention and/or treatment of functional intestinal abnormalities and food allergies.

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The mas-related gene receptor agonist npal enhances mesocolonic mast cell activity

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Introduction: G-protein coupled mas-related gene receptors (Mrg) have emerged as appealing pharmacological targets for analgesic, antipruritic, and antihypertensive therapies. The expression of Mrg receptors in a specific subset of sensory neurons, suggests a role in regulating pain sensation, although the full spectrum of biological roles of Mrgs is still ill-defined. Evidence points to a function of Mrgs in connective tissue mast cell degranulation, but nothing is known on their function in mesocolonic mast cells [MCC], which are involved in functional gastrointestinal disorders and intestinal inflammation. Our research group has shown that Mrgs undergo changes in their expression during intestinal inflammation, both in enteric neurons and MMC.

Aim: We investigated the expression of Mrg in bone marrow-derived mesocolonic mast cells and the response of these cells to the MrgA4 ligand npal. Furthermore, we explored the potential sources of the NPAF precursor proNPAF.

Methods: Using PCR and immunocytochemistry we studied the expression of Mrgs in bone marrow-derived mesocolonic mast cell (BMMC). We next analyzed the response of BMMC to NPAF with live cell Ca2+ imaging. Degranulation in response to NPAF was evaluated with a beta-hexosaminidase assay and electron microscopy. The potential sources of NPAF were identified using RT-PCR.

Results: BMMC expressed MrgA4, but not MrgD or MrgJ1. BMMC responded to NPAF with an increase in Ca2+ oscillations but this did not result in massive degranulation when compared to stimulation with C48/80, indicating a piecemeal degranulation. This was confirmed by the beta-hexosaminidase assay and electron microscopy. NPAF precursor proteins are expressed in dorsal root ganglia neurons and BMMC, indicating these cells as potential sources of NPAF.

Conclusion: Our findings suggest that NPAF is a novel modulator of MCC activity in neuro-immune communication. Future work will be oriented towards further elucidating the response of BMMC to NPAF in terms of cytokine release and will employ knockout models to pinpoint the observed functional effects to MrgA4. The research was supported by grant G091314N of the Research Foundation Flanders (FWO) to JPT and RB by the Egyptian Ministry of Education under a joint doctoral supervision program to NA.

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Human mesenteric adipose tissue from Cronh’s disease patients induce anti-inflammatory responses in collagen epithelial cells and promote healing during colitis

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Background: Mesenteric adipose tissue hyperplasia is a hallmark of Crohn’s Disease (CD). Recently, we showed that conditioned media from adipocytes isolated from CD, Ulcerative Colitis (UC) and control patients alter expression of inflammatory mediators in collagen epithelial cells in a disease-dependent manner. The goal of this study was to examine the mRNA expression profiles of human mesenteric adipocytes and assess the effects of adipocyte-derived mediators on intestinal epithelial cell signaling in vitro and experimental colitis in vivo.

Methods: Adipocytes were isolated from the mesenteric fat of control and CD patients and conditioned media and total RNA collected from cultured cells. Microarray profiling of mRNA transcripts was performed in isolated adipocytes and human colonic
epithelial NMC460 cells treated with conditioned media. Network analysis was performed using Ingenuity Pathway Analysis (IPA). NMC460 proliferation was assessed using the CellTiter Glo system. Experimental colitis was induced in C57BL/6 mice by administering dextran sodium sulfate (DSS) in their drinking water (3.5% w/v) for 5 days. Mice received daily intracolonic injections of vehicle or conditioned media from control or CD preadipocytes. Separate groups were switched to water and received injections on days 6-15. RNA was extracted from the distal colon for qPCR.

Results: CD preadipocytes had differential mRNA expression compared to controls, and network analysis predicted activation of pathways promoting phagocytosis of bacteria, as well as cell growth and proliferation. A central regulator in the highest predicted network was caspase 8. CD patient media increased cell proliferation and SERPINE-1 mRNA in NMC460 cells compared to control patient media, and network analysis predicted alterations in injury and inflammation pathways. DSS-treated mice injected with CD media had decreased severity of colitis as indicated by histological scores and decreased CXCL1 mRNA compared to controls during acute colitis, while injections of CD media decreased CCL2 mRNA compared to control media during recovery from colitis.

Conclusion: Preadipocytes isolated from control and CD patients show disease-dependent inflammatory responses and alter colonic epithelial cell signaling in vitro and proinflammatory cytokine expression in DSS-treated mice in vivo. We suggest that mesenteric adipose tissue-derived mediators may participate in the pathophysiology of CD by promoting colonic epithocyte proliferation and the resolution of inflammation.

336 Targeting the glucocorticoid and mineralocorticoid receptors in the central amygdala for the treatment of stress-induced pain; implications for irritable bowel syndrome

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Background: We have shown previously that chronic stress-induced visceral hypersensitivity, was concomitant with reduced glucocorticoid receptor (GR) expression in the central amygdala (CeA), an important brain nucleus involved in the autonomic and neuroendocrine response to stress. However, a key unanswered question from our previous studies was whether down-regulation of the GR or mineralocorticoid receptor (MR) within the CeA would be sufficient to unravel a selective role for either GR or MR in the regulation of nociceptive behaviors.

Aim: Here we test the hypothesis that knockdown of GR or MR in the CeA in the absence of a stressor would recapitulate the nociceptive behaviors produced by chronic stress.

Methods: Bilateral cannulation of the CeA was performed for the delivery of oligodeoxynucleotides (ODN) of antisense (ASO) or random sequences (RSO) targeting GR or MR. Water avoidance stress (WAS) or Sham WAS was performed for 1-hr daily for 7-days. Visceral sensivity in response to colorectal distension (CRD) was quantified as the number of abdominal contractions, which yielded the visceral motor response (VMR). qRT-PCR was performed to assess changes in GR/MR gene expression, within the CeA.

Results: Following chronic WAS, we confirmed that GR expression was significantly reduced in the CeA (p < 0.05). Furthermore, in the current study we show that MR expression was reduced in rats exposed to chronic WAS (p < 0.05). In a separate group of rats that did not undergo WAS, we found that GR knockdown significantly reduced GR expression in the CeA (p < 0.05) concomitant with visceral hypersensitivity (p < 0.05). Similarly, in non-stressed rats, MR knockdown significantly reduced MR expression in the CeA (p < 0.05). Future studies will address the impact of reduced MR expression in the CeA on visceral nociception.

Conclusion: These studies highlight pivotal roles of GR and MR within the CeA as novel mediators in the facilitation of visceral hypersensitivity. GR and MR communication appears critical to the development of visceral pain, which has significant implications for irritable bowel syndrome patients where stress is a key factor in the complex etiology and pathophysiology.
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Neurodegeneration of the ENS might be prevented by treatment with nanomodified antioxidants
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With increasing life expectancy the number of neurodegenerative disorders such as Parkinson’s and Alzheimer’s disease rose. While the loss of neurons, mainly derived from oxidative stress, in clinically apparent diseases is irreversible, preventive measures are needed. Based on the theory that the pathology in neurodegenerative disorders might start in the enteric nervous system (ENS) before it spreads to the brain, the gastrointestinal tract might be used for either staging and treatment of the diseases. During the onset of the disease oral applications of herbal nutritional supplements with high antioxidant capacity have a promising neuroprotective potential. However, these natural compounds have low solubility in water and consequently poor gastrointestinal absorption. To improve solubility, we applied specific top-down technologies to characterize by light and electron microscopy. We measured cumulative over 0–2 and 8–24 h by HPLC-MS. 10 bioavailability were biopsied and assessed using duodenal and sigmoid colon. Mucosal transcellular resistance (TER), FITC dextran (4 kDa) and 12C mannitol BioParticle flux were measured in Ussing chambers. Endothelial activity (blood) was measured towards gram-negative bacterial lipopolysaccharide. Unpaired two-sided t-tests were used for comparisons.

Results: Mean age was 65.8 year for IBS-C vs 44.6 year for healthy. The duodenal and colonic TER and flux were not different (Table). TER and FITC dextran flux measured cumulatively over 0–2 and 8–24 h by HPLC-MS. 10 bioavailability were biopsied and assessed using duodenal and sigmoid colon. Mucosal transcellular resistance (TER), FITC dextran (4 kDa) and 12C mannitol BioParticle flux were measured in Ussing chambers. Endothelial activity (blood) was measured towards gram-negative bacterial lipopolysaccharide. Unpaired two-sided t-tests were used for comparisons.

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Table: In vivo permeability, mucusal TER, FITC dextran, and K12 BioParticle flux

<table>
<thead>
<tr>
<th>BioParticle flux</th>
<th>IBS-C</th>
<th>Healthy</th>
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<tbody>
<tr>
<td>Duodenum-second part, mean (SEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12C mannitol (mg) [IBS-C = 16, HV=11]</td>
<td>13.04 (1.27)</td>
<td>14.86 (1.19)</td>
</tr>
<tr>
<td>lactulose (mg) [IBS-C = 16, HV=11]</td>
<td>1.12 (0.19)</td>
<td>0.99 (0.12)</td>
</tr>
<tr>
<td>TER (Ω/cm²) [IBS-C = 15, HV=13]</td>
<td>26.90 (1.95)</td>
<td>27.79 (2.05)</td>
</tr>
<tr>
<td>FITC-dextran (mg/mL) [IBS-C = 15, HV=13]</td>
<td>169.3 (37.06)</td>
<td>181.6 (49.35)</td>
</tr>
<tr>
<td>h. coli K12 (CFU/mL) [IBS-C = 12, HV=9]</td>
<td>18 284 (6089)</td>
<td>16 752 (3939)</td>
</tr>
<tr>
<td>Sigmoid colon, mean (SEM)</td>
<td></td>
<td></td>
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<tr>
<td>12C mannitol (mg) [IBS-C = 16, HV=11]</td>
<td>6.04 (1.58)</td>
<td>4.82 (0.74)</td>
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<tr>
<td>lactulose (mg) [IBS-C = 16, HV=11]</td>
<td>1.06 (0.55)</td>
<td>0.72 (0.41)</td>
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<tr>
<td>TER (Ω/cm²) [IBS-C = 16, HV=13]</td>
<td>18.84 (1.25)</td>
<td>15.99 (1.35)</td>
</tr>
<tr>
<td>FITC-dextran (mg/mL) [IBS-C = 12, HV=12]</td>
<td>150.9 (33.79)</td>
<td>321.7 (153.9)</td>
</tr>
<tr>
<td>h. coli K12 (CFU/mL) [IBS-C = 15, HV=9]</td>
<td>22 773 (5601)</td>
<td>10 872 (2245)</td>
</tr>
</tbody>
</table>

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Effects of DA-9701 on the proximal and distal colonic motor function of rat in vitro
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Background/Aims: DA-9701, a new prokinetic agent, enhances gastric emptying and gastrointestinal transit via dopamine D₂ antagonism and 5-HT₄ agonism. Contraction effect of DA-9701 on stomach can be explained by serotonergic receptor’s distribution within the gastric muscle wall. In vitro, pharmacological characterization of the contractile response to DA-9701 in the proximal colon and distal colon of rat still remains unclear. The aim of this study was to evaluate contractile responses of DA-9701 and function of 5-HT₄ receptor in the proximal colon and distal colon of rat in vitro.

Methods: Measurements of contractile force in an organ bath were performed on the isolated proximal and distal colonic muscle strips of male Sprague-Dawley rats (250–300 g). We performed a series of isometric tension experiments in which muscle strips were oriented in the direction of either circular or longitudinal muscle fibers and evaluated the spontaneous contractions and contractile responses to drugs.

Results: DA-9701 induced giant contractions of circular muscle and longitudinal muscle strips of proximal and distal colon in a dose-dependent fashion. Mosapride also induced the giant contractions in these muscle strips. DA-9701 induced contractions of distal colon were significantly inhibited by GR125487, a selective 5-HT₄ receptor antagonist, but not in proximal colon.
Conclusions: These data suggest that differential contractile responses to DA-9701 in the proximal and distal colon. Contraction effect of DA-9701 on the distal colon can be mediated by 5-HT₄ receptors. However, the mechanism of DA-9701 effects on the proximal colon were remained unclear.

341 Investigation of small intestinal luminal pH and intestinal transit in constipated patients with or without clinical response to linacotide
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Introduction: Linacotide is a minimally absorbed, guanylate cyclase C (GCC) agonist approved for the treatment of chronic idiopathic constipation and IBS-C. However, some patients fail to respond to linacotide is unclear. The effects of some GCC agonists may be influenced by the intraluminal pH. We tested the hypothesis that intrinsic changes in small bowel pH may contribute to the efficacy of linacotide.

Aim: To examine and compare 1) small intestinal pH profiles in patients who either responded or failed to respond (Non-responder) to 6 weeks of treatment with linacotide, 2) gastric emptying time (GET), small bowel transit time (SBTT) and colonic transit time (CCT) and population characteristics between the two groups.

Methods: Over a 2-year period, patients with constipation or IBS-C who underwent a wireless motility capsule test (SmartPill)® and who also received linacotide, and followed up in GI clinic were assessed. Patients were defined as Non-responders (NR) if they had received linacotide at a dose of 145 mcg for chronic constipation or 290 mcg for IBS-C for at least 6 weeks and reported no changes in stool frequency or consistency or needed rescue laxatives. Responders (R) were defined as patients who received similar doses of linacotide, and at follow up reported improved stool frequency and consistency.

Results: We evaluated 25 patients [20 F], mean age = 50.6 years. There were no differences in age, gender, constipation type [Slow transit constipation (STC) 54%, Normal transit constipation (NTC) 30%, Rapid transit constipation (RTC) 16%], and luminal perfused (SBTT) cocktail. Therefore, intestinal segments were prepared and luminal perfused (SBTT) in order to evaluate the anti-inflammatory effect of STW5 in these intestinal segments, the cytokines in the gut wall homogenates were analyzed by Multiplex-ELISA. In addition, isolated myenteric plexus was cultured and also stimulated with the cytokine cocktail (SBTT). The supernatants of the myenteric plexus cultures were collected after 24 h and also analyzed by Multiplex-ELISA. A spasmolytic effect of STW5 on the motility of neostigmine stimulated intestinal segments was observed. Interestingly, a reduced motility of intestinal segments could be shown during local inflammation. This inhibitory effect caused by inflammation was abolished by simultaneously luminal instillation of STW5. An increase of the pro-inflammatory cytokines G-CSF, GM-CSF, IL-6 and LIF during local inflammation. This inhibitory effect caused by inflammation was abolished by simultaneously luminal instillation of STW5. An increase of the pro-inflammatory cytokines G-CSF, GM-CSF, IL-6 and LIF under inflammatory conditions was found in both gut wall homogenates and myenteric plexus cultures. The treatment with STW5 leads to decreased cytokine concentrations in both gut wall homogenates and myenteric plexus culture supernatants indicating an anti-inflammatory effect of STW5. In conclusion, as reported the multi-herbal compound STW5 has a spasmylic effect, but otherwise it recovers also inflammatory changes in the evenness of the microbiota were observed within or between groups in the DB phase. The richness of the microbiota in patients treated with DB PBO remained unchanged, whereas richness decreased at Week 2 in patients treated with RFX compared with DB baseline (p = 0.03) and compared with PBO (p = 0.02), this change associated with RFX treatment appeared to be short-lived, as it was not detected in the follow-up period.

Conclusions: Overall, no sustained disturbance of the stool microbiota was observed in patients during repeat treatment with rifaximin in patients taking a single course of OL RFX followed by DB PBO.

344 A randomized clinical trial comparing the efficacy of ramosetron-trimebutine dual therapy versus trimebutine monotherapy in male patients with irritable bowel syndrome with diarrhea (IBS-D)
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Background: The ramosetron, a 5-HT₃ receptor antagonist, is known to be effective for the treatment of diarrhea-predominant irritable bowel syndrome (IBS). But, until now, trimebutine has been prescribed more frequently than in male patients with IBS with diarrhea (IBS-D). The aim of this study was to compare the efficacy of ramosetron-trimebutine dual therapy with trimebutine monotherapy in male patients with IBS-D.

Methods: We performed a randomized, open-label study of 20 male outpatients with IBS-D (according to the

Background: Rifaximin (RFX) is indicated for IBS-D, although the precise mechanism of action is unclear. This analysis assessed the effect of repeated RFX treatments on stool microbiota.

Methods: Adults with IBS-D entered into an open-label (OL) phase and were treated with RFX 550 mg TID for 2 weeks, followed by a 4-week follow-up period. Responders based on a composite endpoint of abdominal pain and stool consistency improvements during ≥2 of 4 weeks were followed until relapse (up to 18 additional weeks), at which time they were randomized to receive 2 double-blind (DB) repeat treatments (RFX 550 mg TID or placebo [PBO] for 2 weeks) separated by 10 weeks. All patients provided stool samples at the beginning and end of OL treatment, beginning and end of the first repeat treatment, and end of study. Patients were randomly selected for the stool microbiota sequencing sub-study in a manner that incorporated responders and nonresponders. Genomic characterization of microbiota was achieved using 16S rRNA bacterial deep gene sequencing. Metrics included the diversity index, composed of measures of richness, evenness (as calculated by Shannon equitability, with values ranging from 0 to 1, and 1 being complete evenness), and Shannon diversity.

Results: 103 patients (mean age, 47.9 years, 74% female) were randomly selected for inclusion in the stool microbiota sub-study, of which 73 (37 in RFX group and 36 in PBO group, evenly matched according to demographic) participated in the DB phase. At baseline of the DB phase, Shannon diversity was 1.786 and 1.733 in the RFX and PBO groups, respectively, after the 2-week treatment period, Shannon diversity was 1.698 and 1.743 (p = 0.4), respectively, and remained essentially unchanged in the follow-up period. No significant changes in the evenness of the microbiota were observed within or between groups in the DB phase. The richness of the microbiota in patients treated with DB PBO remained unchanged, whereas richness decreased at Week 2 in patients treated with RFX compared with DB baseline (p = 0.03) and compared with PBO (p = 0.02), this change associated with RFX treatment appeared to be short-lived, as it was not detected in the follow-up period.

Conclusions: Overall, no sustained disturbance of the stool microbiota was observed in patients during repeat treatment with rifaximin in patients taking a single course of OL RFX followed by DB PBO.
Conclusions: Both groups.

Results: A statistically significantly global improve-
ment was observed in all patients given ramosetron
with trimebutine (9/10, 90%, p < 0.002) than patients
given only trimebutine (2/10, 20%). And patients receiv-
ing ramo-
setron group reported improvement of stool con-
sistency than trimebutine monotherapy.

E. SHAH
H. KIM
Z. Z. R. M. WEERTS
E. JONKERS
†
‡

Table 1 Summary of results [all data expressed as OR with 95% CI, *p < 0.05]

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease</th>
<th>Dosage</th>
<th>Study withdrawal due to diarrhea</th>
<th>Diarrhea as AE</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linaclootide</td>
<td>IBS</td>
<td>290 or 300 mg/day</td>
<td>15.4 (4.2, 56.7)*</td>
<td>8.1 (5.2, 11.4)*</td>
<td>2.4 (1.5, 4.0)*</td>
</tr>
<tr>
<td>Plecanatide</td>
<td>IBS</td>
<td>3 mg/day</td>
<td>11.7 [0.6, 214.5]</td>
<td>18.7 (1.1, 329.9)*</td>
<td>2.2 (1.1, 4.2)*</td>
</tr>
<tr>
<td>Linaclootide</td>
<td>CIC</td>
<td>145 or 150 mg/day</td>
<td>6.4 [2.0, 20.5]*</td>
<td>3.6 (2.5, 5.7)*</td>
<td>3.4 (1.7, 6.8)*</td>
</tr>
<tr>
<td>Plecanatide</td>
<td>CIC</td>
<td>3 mg/day</td>
<td>3.8 [1.5, 9.7]*</td>
<td>3.9 (1.8, 8.1)*</td>
<td>2.0 (1.6, 2.5)*</td>
</tr>
<tr>
<td>Plecanatide</td>
<td>CIC</td>
<td>6 mg/day</td>
<td>3.9 [1.3, 12.0]*</td>
<td>3.83 [2.0, 7.3]*</td>
<td>1.9 (1.5, 2.5)*</td>
</tr>
</tbody>
</table>

Abstract 345

Efficacy and tolerability of linaclootide and plecanatide in treating Irritable Bowel Syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC): A meta-analysis

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†Cedars-Sinai Medical Center, Los Angeles, CA, USA

Background: In this study, we contrast the rates of diarrhea adverse events (AE) and efficacy of the guany-
late cyclic-G agonist linaclootide and plecanatide in treating IBS-C and CIC.

Methods: Literature search: PubMed and Cochrane databases, abstracts from UEGW, DDW, and ACG since 2005, and SEC filings. Study selection: double-blind, placebo-controlled RCTs of IBS-C or CIC patients treated for at least 14 days using dosages that are FDA-approved [linaclootide] or evaluated in Phase III RCTs [plecanatide]. Study endpoints: (a) study withdrawal due to diarrhea, (b) incidence of diarrhea, and, (c) FDA-responder endpoint. Data Analysis: Eligible trials and data were reviewed independently by ES and PS. Data were extracted on an ITT basis. A random effects model of meta-analysis was performed to pool trial results. Results were expressed as an odds ratio (OR) with 95% CI.

Results: Six linaclootide trials (4 CIC, 2 IBS-C) and four plecanatide (3 CIC, 1 IBS-C) met study criteria. Diarrhea incidence was higher with linaclootide than plecanatide, although diarrhea was numerically higher on placebo in the linaclootide trials. This resulted in similar OR of diarrhea and study discontinuation due to diarrhea in IBS-C and CIC for both therapies. Outcomes for FDA-responder endpoints was also similar.

Conclusions: Linaclootide and plecanatide have similar efficacy, and there is no significant difference in odds of diarrhea adverse events in IBS-C or CIC patients.

A randomized, phase 1, double-blind, crossover study on pharmacokinetics of peppermint oil capsules in healthy volunteers: enteric-coating versus colon-targeted-delivery


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Peppermint oil (PO) has been shown to reduce abdominal pain in patients with Irritable Bowel Syndrome (IBS). Menthol, the main constituent of PO, induces intestinal smooth muscle relaxation and desensitizes nociceptive nerve afferents. Enteric-coated (EC) PO capsules, that release PO mainly in the small intestine in peak concentrations and elimination half-lives. No significant differences were found in peak concentrations and elimination half-lives. No differences in vital signs or side effects were observed between both regimens. Remarkably, subjects noticed alterations in fecal odor after CTD PO but not after EC PO, again pointing to more distal delivery with CTD PO. In conclusion, the CTD PO has a significantly delayed peak menthol-glucuronide concentration in plasma. Eight healthy volunteers (50% female), aged between 20 and 65 years (median 22.2, IQR 20–28.8) were included. The Tmax of CTD PO was significantly longer (in all volunteers) compared to EC PO with a median (IQR) of 360 (360–405) vs 180 (120–180) min, respectively, p < 0.05. The Area Under the menthol-glucuronide plasma concentration time Curves were smaller with a median (IQR) of 2331 [g*µg/h] (2006–2510) for CTD compared to 2623 [g*µg/h] (2471–2920) for EC capsules, p < 0.05. No significant differences were found in peak concentrations and elimination half-lives. No differences in vital signs or side effects were observed between both regimens. Remarkably, subjects noticed alterations in fecal odor after CTD PO but not after EC PO, again pointing to more distal delivery with CTD PO. In conclusion, the CTD PO has a significantly delayed peak menthol-glucuronide concentration, and is thereby assumed to release peppermint oil in the more distal part of the intestine. This may enhance the therapeutic efficacy of PO as the application of the CTD results in increased exposure to the colonic mucosal afferents. These results encourage our randomized controlled trial with CTD PO in IBS patients. This research was funded in part by WillPharma.
Linaclotide, a guanylate cyclase-C (GC-C) agonist, reduces abdominal pain and improves constipation in patients with Irritable Bowel Syndrome with Constipation (IBS-C), but not other types of IBS patients. Furthermore, we have shown distinct alterations in key components of the GC-C/cGMP signalling pathway across different subtypes of IBS patients from the Australian population. However, it remains to be determined if these changes extend to other components of this pathway.

The increase in chronic constipation among the elderly may be due in part to a decline in colonic neuromuscular functions. We previously demonstrated a changed balance of cholinergic to nitrergic neuromuscular function in ascending colon, favouring a greater influence of nitrergic inhibition. Macroporous and normal human colon was obtained at surgery for cancer. Macroporous-free biopsies of muscularis propria were homogenized in ice-cold phosphate buffer, supernatants were collected for ChAT analysis. ChAT function was assessed over 1 h using an indirect assay measuring choline utilisation, and using choline oxidase activity to reveal enzymatic function as described previously. ChAT expression was assessed by sandwich ELISA (Aboca, UK) using recombinant human ChAT to determine protein concentration. Samples were measured in triplicate. Statistical analysis was performed using GraphPad Prism 5. Mann-Whitney U-tests between regionally-matched groups were used to test for significance. Muscle samples from each colon region were prepared for functional analysis [1.5-3.5 µg/well] alongside denatured samples. There were no differences in the activity of ChAT within the samples in ascending colon (ascending ≤ 0.18). Here we have demonstrated an increase in acholinergic to nitrergic neuromuscular function in ascending colon, favouring a greater influence of nitrergic inhibition.

The increase in chronic constipation among the elderly may be due in part to a decline in colonic neuromuscular functions. We previously demonstrated a changed balance of cholinergic to nitrergic neuromuscular function in ascending colon, favouring a greater influence of nitrergic inhibition. Macroporous and normal human colon was obtained at surgery for cancer. Macroporous-free biopsies of muscularis propria were homogenized in ice-cold phosphate buffer, supernatants were collected for ChAT analysis. ChAT function was assessed over 1 h using an indirect assay measuring choline utilisation, and using choline oxidase activity to reveal enzymatic function as described previously. ChAT expression was assessed by sandwich ELISA (Aboca, UK) using recombinant human ChAT to determine protein concentration. Samples were measured in triplicate. Statistical analysis was performed using GraphPad Prism 5. Mann-Whitney U-tests between regionally-matched groups were used to test for significance. Muscle samples from each colon region were prepared for functional analysis [1.5-3.5 µg/well] alongside denatured samples. There were no differences in the activity of ChAT within the samples in ascending colon (ascending ≤ 0.18). Here we have demonstrated an increase in acholinergic to nitrergic neuromuscular function in ascending colon, favouring a greater influence of nitrergic inhibition.
presence of PDGFRα+ cells, SK3 channels and P2Y1 receptors in both muscles. Our data are compatible with the hypothesis that purinergic NMT is absent in the IAS because of a lack of coupling between P2Y1 receptors and activation of SK3. Since the excitatory motor innervation of the IAS is sympathetic, the absence of inhibitory purinergic NMT may avoid the potential conflict arising from parasympathetic activation when parasympathetic and sympathetic innervation of the IAS is present. Further experiments are needed to test this hypothesis.

350 Modulation of colonic sensory signaling by novel α-conotoxin Vc1.1 analogues in mice

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Background: We recently demonstrated that the linear α-conotoxin Vc1.1, a small peptide sourced from the venom of marine cone snails, reduces visceral pain via GABARα receptor-mediated inhibition of high voltage-activated calcium channels on colonic afferent nerve endings. As enzymatic degradation is a major obstacle in the use of bioactive peptides as drugs, it is possible to cyclicize, or join the N- and C-termini of the peptide without affecting the three-dimensional structure or biological activity. Here we compared linear Vc1.1 vs two cyclized versions of Vc1.1, which have improved bioactivity, for their anti-nociceptive potential in treating chronic visceral pain.

Methods: Using in vitro electrophysiological recordings we determined the anti-nociceptive actions of linear Vc1.1, the orally active cyclized Vc1.1 (cVc1.1) and a we determined the anti-nociceptive actions of linear Vc1.1, the orally active cyclized Vc1.1 (cVc1.1) and a

Results: In fixed human DRG, PAR1, PAR2, and PAR4 were expressed in 20, 40 and 40% of human sensory neurons respectively. PAR expression was not modified by pre-incubation with PAR2-AP, but not with PAR1-AP or any of the irrelevant peptides (PAR-IP, 100 μM) or proteases trypsin (1 and 10 U) and thrombin (1 and 10 U) were studied in cultured human DRG neurons, which were fixed thereafter, to study PAR expression.

Conclusion: Our study demonstrates that PAR1, PAR2, and PAR4 are expressed in human sensory neurons. In contrast to PAR1 and PAR2, PAR4 activation induced calcium increase in human sensory neurons. PAR2 activation reduced PAR1 induced calcium mobilization. Thus, in Human PAR, and PAR4 seem to play an important role in neuronal activation and may be relevant in IBS research.

351 Protease-activated receptors are expressed and can be activated in human sensory neurons

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Background: IBs is a functional bowel disorder characterized by abdominal pain, associated with constipation and/or diarrhea. Among the mediators studied in IBs, increased colonic proteolytic activity appears as a common feature in all IBs sub-groups. Through Protease-Activated Receptors (PARs) activation, proteases can activate primary afferents and act on visceral pain pathways in rodents, but the relevance of PAR activation in human sensory neurons still has to be determined. Thus, the objective of our study was to decipher the PAR pharmacology in human sensory neurons.

Methods: Cryo-protected or fresh human thoracic dorsal root ganglia (DRG) were obtained from the national disease research collection, and expression of PAR1, PAR2, and PAR4 was studied on slices of DRG (T12, n = 3) by co-staining immunocytochemistry with a pan-neuronal marker (pomp 5) and PAR antibodies. Calcium signaling responses to PAR agonist peptide (PAR-AP): PAR1-AP (TFFLR, 1, 10 and 100 μM); PAR2-AP (SLIGRL, 100 μM) and PAR4-AP (AFamideCR, 100 μM) were studied in their irrelevant peptides (PAR-IP, 100 μM) or proteases trypsin (1 and 10 U) and thrombin (1 and 10 U) were studied in cultured human DRG neurons, which were fixed thereafter, to study PAR expression.

Conclusion: Our study demonstrates that PAR1, PAR2, and PAR4 are expressed in human sensory neurons. In contrast to PAR1 and PAR2, PAR4 activation induced calcium increase in human sensory neurons. PAR2 activation reduced PAR1 induced calcium mobilization. Thus, in Human PAR, and PAR4 seem to play an important role in neuronal activation and may be relevant in IBs research.

352 Evidence for mu and delta opioid receptor coexpression in myenteric neurons of the mouse colon

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*Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Vic, Australia and †Institut des Neurosciences Cellulaires et Intégratives INCI, Strasbourg, France

Background & Aims: Opiate analgesics mediate their actions through activation of the mu opioid receptor (MOR). Opiates are effective drugs, but their use can be severely limited by on-target side-effects, including intractable constipation. The delta opioid receptor

[353] Chromofungin & pancreastatin co-regulate migration and functional plasticity of murine peritoneal macrophages

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Background: Chromogranin A (CgA) and CgA-derived peptides are secreted by neurons, endocrine and immune cells and are elevated in inflammatory bowel diseases (IBD) patients. Chromogranin (CgA) and pancreastatin (PST, CgA273–301) are implicated in innate immunity and somatovisceral pain. During the chronic inflammatory process, macrophages play a major role through an inappropriate response to anti- gens, migration, and through an impaired transition from a pro-inflammatory (classical activated macrophages (CAMs)) to an anti-inflammatory (alternative activated macrophages (AAMs)) phenotype. The aim of the present study is to determine the role of CHR and/or PST on the in vitro migration and functional plasticity of murine macrophages.

Methods: Naïve peritoneal macrophages were isolated from C57Bl/6 mice. 1) They were treated by CHR, PST & CHR+PST (200 ng/ml, 2 h) then exposed to LPS (100 ng/ml, 6 h) to promote CAMs, or to IL-4/IL-13 (20 ng/ml, 6 h) to promote AAMs. CAMs markers (IL-6, IL-1β, TNF-α, MCP-1, MIP-1α, MIP-β) and AAMs

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marks (ARG-1, C-MYC, FIZZ-1) were quantified by ELISA and/or RT-qPCR. ii) In vitro chemotaxis activity of CHR, Pts & CHR+Pts (200 ng/mL) on naïve macrophages were assessed by transwell migration assay using MCP-1 (30 ng/mL) Results CHR-conditioned CAMs expressed significantly less IL-6, IL-1β, TNF-α, MIP-1α, MIP-6, but more ARG-1, C-MYC and FIZZ-1 when compared to LPS control condition. Conversely, no change in IL-6, IL-1β, TNF-α, MIP-1α, MIP-6, ARG-1, C-MYC, FIZZ-1 and FIZZ-1 expression were detected in Pts-conditioned CAMs. However, Pts co-treatment abolished the beneficial effect of CHR pre-treatment on IL-6, IL-1β, TNF-α, ARG-1, C-MYC and FIZZ-1 expression. Moreover, CHR or Pts-conditioned AAMs expressed significantly more and less ARG-1, respectively when compared to IL-4/IL13 control condition respectively, however, Pts abolished the CHR effect.

In undifferentiated macrophages, CHR decreased significantly macrophages migration while Pts increased it, however, co-incubation of Pts with CHR abrogated the decreased migratory properties induced by CHR.

Conclusions: CHR seems to be critical in the reversal of inflammation through the modulation of the macrophages migration and plasticity in favor of a down regulation of CAM, associated to a switch toward AAMs phenotype, but both regulation and switch can be achieved by Pts. Targeting CHR or Pts may lead to novel therapeutic strategies in IBD.

354 Anti-diarrheal effect of FFA3 activation via cholinergic neural pathway in rat proximal colon

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Background & Aim: Short-chain fatty acids (SCFA) are microbial fermentation products that are absorbed from the colon. Although luminal SCFA stimulate colonic secretion and contraction, we have recently reported that activation of an SCFA receptor FFA3, expressed in cholinergic nerves, suppresses nicotine-ACh receptor-mediated transethapheal anion secretion. We further investigated how activation of neurally-expressed FFA3 affects colonic motor function.

Methods: The selective FFA3 agonist MÖC and AR420626 were used. Short-circuit current (Isc) was measured in Ussing chamber. Circular muscle contractions were measured with isolated muscle strips without mucosa and submucosa. The effect of FFA3 agonists on defecation in vivo was investigated with an exogeneous 5-HT4 receptor-deficient model.

Results: In Ussing chambered mucosa-submucosa preparations, contractions were suppressed by MÖC or AR420626 suppressed the Isc increases induced by carbachol (CCh) or nicotine by 65%, but did not affect the response to bethanochol or forskolin. The inhibitory effect of FFA3 activation was reversed by pretreatment with the Gi/o inhibitor pertussis toxin, but not by NPY/PYY receptor antagonist. Circular muscle strips exhibited periodic spontaneous contractions, which frequency was enhanced by the NO synthase inhibitor L-NAME, indomethacin, or AR420626, but not by MÖC. The addition of nicotine (10 µM) transiently relaxed the muscle, inhibited by TTX or L-NAME, while high concentration of nicotine (100 µM) induced large-amplitude contractions that were not altered by TTX, L-NAME, or indomethacin. Pretreatment with FFA3 agonists inhibited the nicotine-induced relaxation and contraction, but had no effect on bethanochol-induced contractions. Nicotine-evoked contractions were abolished by AR420626 and reversed by pretreatment with pertussis toxin, suggesting that FFA3 activation suppresses nicotinic neural activity in the myenteric neurons, consistent with an FFA3-mediated anti-secretory effect. In conscious rats, serotonin (10 mg/kg, i.p) treatment significantly increased the volume of fecal output, compared with the non-treated group. Pretreatment with AR420626 significantly suppressed the serotonin-induced fecal output.

Conclusion: FFA3 agonists may be useful therapeutic agents on diarrheal disorders via anti-cholinergic pathway.

355 TRPA1 channel activation regulates motility in the mouse colon

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Introduction: Transient receptor potential receptor (TRP) channels play an important role in shaping our neuronal response to the environment. In the gastrointestinal tract there is a growing awareness of the role of TRP channels in regulating sensory and motor functions. In this study we used an in-vitro murine model of colonic peristaltic-like complexes (CPMCs) to evaluate the role of TRPA1 signalling processes in regulating colonic motility.

Methods: Experiments were performed on male C57 mice (approxi 3m age). In vitro recordings of intraluminal pressure were used to monitor the presence of CPMC colonic segments using a Trendelenburg-type preparation. Compounds were tested for their effect on CPMC activity using cumulative dosing strategies as previously described (Keating et al, 2010). Statistical analysis was by repeat measures one-way ANOVA or Student's t-test, as appropriate, on n ≥ 4 experiments. p < 0.05 was taken as significant.

Results: At rest, CPMC activity comprised of regular contractile waves which propagated in an aboral direction along the length of the colon. Bath application of the TRPA1 agonists cinnaamaldehyde (CMA, 10–100 µM) or allyl isothiocyanate (AITC, 10–100 µM) caused a dose dependent decrease in CPMC frequency and amplitude. CMA had a greater inhibitory effect upon CPMC activity than AITC. L-NAME (100 µM) attenuated the inhibitory effects of CMA on CPMC frequency and amplitude. Bath application of the TRPA1 antagonist HC 030031 (n = 4; 1–10 µM) had no effect upon basal CPMC activity, but 10 µM HC 030031 significantly attenuated the CMA-induced inhibition of CPMC frequency and amplitude. However HC 030031 only attenuated the AITC-induced change in CPMC amplitude, whilst having no effect upon CPMC frequency. Bath application of 4-hydroxynonenal [4-HNE, 300 nM–30 µM] also caused a dose dependent decrease in CPMC activity, affecting both the CPMC frequency and amplitude.

Conclusion: CMA inhibits colonic motility through activation of TRPA1 channels, and this effect is mediated through nitric oxide signalling pathways. Both the frequency and amplitude of murine CPMCs are attenuated by CMA, whereas AITC-induced changes in CPMC frequency appear to involve non TRPA1 mediated processes. Basal CPMC activity appeared resistant to TRPA1 receptor blockade which suggested that it is unlikely that TRPA1 is acting as a mechanosensory channel in this model of peristaltic activity.

356 Increased serotonin availability contributes to decreased bone formation in colitis

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Increased circulating serotonin has been linked to decreased bone density via preosteoblast 5-HT1B receptor activation. Increased GI serotonin availability has been demonstrated in inflammatory bowel disease (IBD) and in animal models of colitis due to a decrease in expression of the serotonin-selective reuptake transporter (SERT)1 by epithelial cells. Decreased bone density is a feature of IBD and in colitis in animal models. Therefore, we tested the hypothesis that gut-derived 5-HT acting on 5-HT1B receptors is a contributing factor in colitis-related bone formation deficits. Chronic colitis was induced by adding dextran sodium sulphate (DSS) to the drinking water of mice for 21 days (5% for 5 days, followed by 1%). At day 21, the serum of DSS mice had higher levels of 5-HT compared to control mice (p = 0.03). Femurs were scanned and analyzed by micro-computed tomography. A marked decrease in bone formation was observed in DSS-treated mice, including decreased bone volume fraction, trabecular number, and bone surface, and increased trabecular spacing. Interestingly changes in bone formation in control SERT-KO mice and DSS treated SERT-KO mice were similar and both showed more extensive bone loss than wild type inflamed mice. Daily injection of the 5-HT synthesis inhibitor, p-chloro-DL-phenylalanine (pCPA, 300 mg/kg/day IP, begun 5 days prior to DSS treatment) decreased serotonin content in the colon by over 30%. Bone measurements in pCPA-injected mice were not different than saline-injected mice that were not treated with DSS. However, in DSS-treated animals, pCPA suppressed nicotine-induced ACH releases, suggesting a significant protective effect on bone formation. Femurs of mice with DSS-colitis mice that were treated with the 5-HT1B antagonist (GR55662, 1 mg/kg/day SC) exhibited significant improved bone formation as compared to DSS-colitis mice that were treated with saline. Dynamic measurement of bone formation was evaluated by measuring the distance between calcium deposits along the periosteal and endosteal surfaces of the cortical bone following dual injections of the dye 4 days apart prior to euthanasia. Spacing of fluorescent bands was found to be significantly reduced in DSS mice, but comparable to control values in DSS mice treated with the 5-HT1B antagonist. In conclusion, these findings support the novel concept that 5-HT entering the blood stream from the inflamed colon can be a contributing factor in colitis-induced bone deficits. Supported by DK62267 and R37DE012528.

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Stress induces rapid CREB activation and changes glial morphology in the enteric nervous system.

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Background: Stress activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to modulate physiological functions of peripheral organs in order to adapt to the stressful condition. However, chronic exposure to stress can lead to abnormal organ function. Both acute and chronic stress has been associated with gut dysfunction and intestinal diseases including irritable bowel syndrome and inflammatory bowel disease. However, there is a lack of knowledge on how stress alters gut function to cause these intestinal disorders. In this study, we used mouse stress models to investigate the effects of stress on the enteric nervous system (ENS) in the colon.

Methods: Mice were subjected to acute predator odor stress (15 min), chronic forced-swim stress (15 min/day for 5 days), or chronic forced-swim stress followed by a novel predator odor stress (for 15 min) and the changes in the myenteric plexus were studied by immunohistochemistry.

Results: We found that acute stress rapidly induced CREB phosphorylation in most myenteric neurons (95.1 ± 3.2%) within 10 min and this response was inhibited when the mice were pretreated with propranolol (20 mg/kg, i.p) prior to the stress. By contrast, CREB activation was significantly lower in mice exposed to chronic stress (41.2 ± 17.2%). We addressed the mechanism of blunted CREB response to chronic stress by evaluating whether chronic glucocorticoid administration affects the stress response. CREB activation was significantly reduced in mice provided with corticosterone (100 μg/mL) in the drinking water for 7 days prior to acute stress (48.5% ± 18.8%) compared to the vehicle control (98.5 ± 5.2%), suggesting that elevated glucocorticoids, during a chronic stress, can alter the stress response of enteric neurons. We also evaluated the effects of stress on enteric glia. We found that acute stress increased the number of activated enteric glia, which showed increased GEAP immunoreactivity along with thickened processes. Interestingly, glial activation was more pronounced in mice exposed to novel stress, whereas it was suppressed in the mice with chronic stress. Propranolol pretreatment inhibited glial activation in response to novel stress, suggesting that the early stress response is also dependent on beta-adrenergic signaling.

Conclusion: Our study demonstrates that there is a dynamic stress response in the myenteric plexus mediated by beta adrenergic receptor and glucocorticoid signaling. The cellular responses we observed in the ENS may underlie the functional alterations that occur during chronic stress. Propranolol provides clues to how stress may cause gut dysfunction.

Changes in 5-hydroxytryptamine levels in gut epithelium during infectious gastritis

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5-Hydroxytryptamine (5-HT, serotonin) in the gut plays a pro-inflammatory role in rodent models of colitis, but has not been investigated in gastric inflammation. Gastritis is commonly caused by Helicobacter pylori (H. pylori) infection. Approximately half of the global population is estimated to carry H. pylori, but only about 10% of these will develop gastritis symptoms, and approx. 1% of these are predicted to develop gastric cancer. The present study aims to determine if 5-HT plays a pro-inflammatory role during infectious gastritis and if this role changes following vaccination against H. pylori.

Female C57BL/6 mice were split into 5 groups of 4–12 mice: N (no vaccine, no challenge), A (vaccine, no challenge), B (vaccine, challenge), C (Sham vaccine, challenge). Vaccine comprised a single oral dose of live attenuated Salmonella typhimurium (SL3261ypep79) expressing H. pylori UreA&N, sham vaccine did not express this. Challenge was a single oral dose of 10^5 H. pylori SS1 strain, administered 4 weeks after vaccination. Mice were sacrificed 3 weeks after challenge and stomachs collected, half for electrochemical 5-HT detection using carbon fiber amperometry, and half for inflammation and bacterial load analysis. For electrochemistry, stomachs were divided into 3 regions, fundus (gastric, antrum (main site of H. pylori colonization), and corpus (body of the glandular zone). 5-HT was virtually undetectable in fundus in all conditions (<1 μM). Group N had no bacterial load and no inflammation, 5-HT levels were 9.1 ± 1.9 μM in antrum and 6.6 ± 1.0 μM in corpus. Group A had no bacterial load, visible inflammation, and no increase in 5-HT in either antrum (8.5 ± 2.7 μM) or corpus (13.9 ± 4.8 μM). Group B had a high bacterial load (7.9 ± 0.2 logCFU) and inflammation score of 0.2 ± 0.1, but no change in 5-HT levels (antrum: 13.6 ± 3.6 μM, corpus: 6.6 ± 1.1 μM). Groups A and C both had significant (p < 0.05) increases in 5-HT levels compared to group N (A, antrum: 22.3 ± 4.2 μM, corpus 19.7 ± 2.9 μM, load: 6.4 ± 0.2 logCFU, inflammation score: 1.6 ± 0.1, C, antrum: 39.1 ± 8.9 μM, corpus: 21.5 ± 6.2 μM, load: 8.4 ± 0.1 logCFU, inflammation score: 1.9 ± 0.1). These data suggest that the severity of infection, and not the challenge, is a better predictor of 5-HT levels than is bacterial load. In addition, a previous exposure to Salmo nella enhances the inflammatory reaction to H. pylori infection and is associated with greatly increased levels of 5-HT in the glandular zone of stomach.
Summary: We have identified novel non-neuronal sites of TRPV4 expression in the colon, including cells recently identified to regulate motility and inflammation. Furthermore, we provide evidence for indirect TRPV4-dependent activation of FLC, which are involved in neuronal neurotransmission. We predict that TRPV4 activation, through mechanisms including mechanical stimulation and proinflammatory mediators, will have effects on colonic motor activity through actions at non-neuronal cell types.

Mouse colon enterochromaffin (EC) cells express the Scnα3-encoded voltage-gated sodium channel Na+1.3 P. R. STREGE, K. R. KNUTSON*, S. J. EGGERS*, F. WANG†, H. JOYCE‡, A. R. LEITER*, G. FARRUGIA* and A. BEYDER†
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Background: The Gi epithelial enterochromaffin (EC) cell uses the enzyme tryptophan hydroxylase-1 (TPH-1) to produce serotonin (5-hydroxytryptamine, 5-HT). In response to chemical and mechanical stimuli the EC cell secretes 5-HT, which regulates gastrointestinal (GI) motility. Other neurotransmitter and enteroneuroendocrine cell types express voltage-gated sodium channels, which render them electrically excitable. Recent sequencing data suggest that the Scnα3-encoded voltage-gated sodium channel Na+1.3 may be expressed in EC cells. However, voltage-gated sodium (Na+) currents have not been recorded from mouse EC cells.

Aims: To determine whether mouse EC cells express functional Na+1.3 channels.

Methods: Immunohistochemistry in TPH1-CFP mouse was used to identify Na+1.3 in colon and jejunum EC cells. Cultured primary murine colon and jejunum EC cells were examined by single cell RT-qPCR and whole cell voltage-clamp.

Results: Single cell RT-qPCR in both colon and jejunum showed Scnα3 mRNA in CFP (EC) cells but not CFP cells or buffer (n = 8). Immunohistochemistry revealed that Na+1.3 co-localized with TPH1 in 71% of colon and 90% of jejunum EC primary cells. EC primary cells had voltage-dependent sodium currents (elimated by NMDG) in 65% of colon EC cells (n = 15/23) with an average current density of −66 ± 12 pA/pF (n = 15), and in 67% of jejunum EC cells (n = 20/23) with an average current density −81 ± 15 pA/pF (n = 20). EC cell sodium currents rapidly activated (time to peak 0.92 ± 0.08 ms in colon and 1.14 ± 0.18 ms in jejunum) and inactivated (VTAYST 0.64 ± 0.04 ms in colon and 0.84 ± 0.06 ms in jejunum) with a voltage-dependence of activation half-point (V1/2a) of −26.5 ± 2.4 mV and a slope of −6.5 ± 0.4 mV for colon and V1/2a of −25.5 ± 1.8 mV and a slope of −6.5 ± 0.2 mV for jejunum. The voltage-dependence of inactivation half-point (V1/2d) was −52.8 mV with a slope of −12.4 mV for colon, and V1/2d was −49.9 ± 2.5 mV with a slope of −7.0 ± 0.3 mV for jejunum.

Conclusions: Primary mouse colon and jejunum enterochromaffin (EC) cells express functional the Scnα3-encoded voltage-gated sodium channel Na+1.3. Future studies will determine how Na+1.3 contributes to EC cell electrical excitability and 5-HT release.

Grant support: AGA RSA, NIH DK052766 and DK106456.

Smooth Muscle and Interstitial Cells of Cajal in Health and Disease

Comparing phosphodiesterase-dependent cardiovascular and gastrointestinal smooth muscle relaxation
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Cyclic guanosine monophosphate (cGMP) is an important endogenous mediator for vascular relaxation and gastrointestinal motility. The balance between production and degradation is highly important for function of these systems. Degradation of cGMP is mediated by phosphodiesterases (PDEs). One of the main PDEs for cGMP degradation in smooth muscle cells (SMC) is PDE5. Blockade of PDE5 with specific inhibitors is a conceivable aspect for the therapy of several different diseases like heart failure, aortic stenosis, cardiac vasconstriction and diseases like heart failure, aortic stenosis, cardiac vasconstriction and diseases like heart failure, aortic stenosis, cardiac vasconstriction.

363 TRP53 mediates WNT-induced senescence of interstitial cell of Cajal cells
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Background & Aims: Interstitial cells of Cajal (ICC) profoundly decline with age in both humans and mice. We have also demonstrated loss of ICC stem cells (ICC-SC) in the stomach of progeric klotho mice. The molecular mechanisms of ICC-SC/ICC aging remain unclear. The wingless (Wnt) pathway regulates normal stem cell self-renewal but overactive Wnt signaling can lead to cancer or induce senescence. Here, we investigated whether increased canonical Wnt signaling could mediate ICC-SC senescence by upregulating the cellular stress-induced protein Trp53.

Methods: Old (aged 18–24 months) and young (aged 4–8 weeks) C57BL6 mice, as well as progeric klotho mice and age-matched wild-type controls were used. Gastric ICC and ICC-SC were enumerated by flow cytometry. Wnt pathway activation was studied by measuring nuclear β-catenin levels and phosphorylation by Western blotting (WB). Kir, Trp53, Mdm2 (a negative regulator of Trp53 signaling) and the senescence-associated proteins HP1α and γH2AX were analyzed by WB. Wnt signaling was activated by overexpressing constitutively active β-catenin in SCC-SC in the ICC-SC line 2XScsF10. Trp53 was induced with the Mdm2 antagonist Nutlin 3a (10–30 μM). Cell viability was assessed by MTS assay.

Results: Similar to klotho mice and aging humans, ICC and Kit cell protein expression were profoundly reduced in old C57BL6 mice. Both klotho and old mice also had reduced ICC-SC and displayed activated Wnt signaling evidenced by increased nuclear β-catenin and reduced phosphorylated β-catenin. Trp53 was increased and Mdm2 was reduced indicating that both Wnt and Trp53 pathways were activated with age. Overexpression of β-catenin was increased in 2XScS2F10 cells upregulated Trp53, downregulated Mdm2 and reduced cell viability. Trp53 induction with Nutlin 3a caused senescence of 2XScS2F10 cells evidenced by increased HP1α and γH2AX levels. In contrast, Nutlin3a did not increase β-catenin expression, indicating that Trp53 signaling is downstream of Wnt signaling.

Conclusions: Increased canonical Wnt signaling causes ICC-SC senescence and ICC loss by upregulating Trp53. These mechanisms occur in both klotho and naturally aged mice.

Grant support: NIH R01 DK058184 and P01 DK08055.

Patchy loss of Ano1 in interstitial cells of Cajal of the small intestine leads to diverse deficits in Ca2+ transient synchronization and electrical slow wave activity
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Objectives: Myenteric plexus interstitial cells of Cajal (ICC-MY) are Kit+ pacemaker cells in the small intestine and express the Ano1/TMEM16A Ca2+-activated Cl− channel whose functions remain incompletely understood. We established an inducible Cre-LoxP-based conditional knockout (iKO) mouse model to determine how the loss of Ano1 expression affects ICC-MY and musculature.

Methods: Adult Kit+CreERT2, Ano1+FLP mice were treated (i.p.) for 5–7 days with tamoxifen or vehicle. Small intestines (jejunum), mucosa-free, were examined by qRT-PCR, immunohistochemistry (IHC), Ca2+ fluorescence imaging, and microelectrode electrophysiology.

Results: qRT-PCR and IHC confirmed loss of Ano1. Levels of Ano1 mRNA in jejunum of Ano1 KO mice (n = 6
mice) were reduced by ~50% compared to vehicle-treated controls. Ano1 immunoreactivity was detected in a mosaic/patchy pattern in ICC-MY network (n = 14, C6/C0) and CAGCreERT2/+;Sdhcf1/−/C6/C0 ems (n = 7 mice) uniformly co-expressed Kit and Ano1. Ca2+ imaging experiments showed variable patterns of Ca2+ transients in ICC-MY network of knockouts [70 field-of-views (FOV), 14 mice] including synchronized (61%), partially-synchronized (19%) and de-synchronized (20%). Ca2+ transient synchronization ranged with level of Ano1 protein in ICC-MY. However, synchronized Ca2+ transients were observed in FOVs showing partial loss of Ano1 in ICC-MY network. Electrical activity in mucosal of Ano1 C6/C0 (75 cells, 7 mice) was variable. In comparison to controls (77 cells, 9 mice), slow waves in C6/C0 (57 cells, 6 mice) displayed reduced duration and increased inter-slow wave interval, and occurred in both regular (52%) and irregular-amplitude oscillating (23%) patterns. Lack of slow waves and depolarization were also seen (25%).

Conclusions: In adults, Ano1 channel regulates gastrointestinal function by determining Ca2+ transient synchronization, which is similar to previously described findings in neonates (Singh et al., 2014, J. Physiol.). Loss of Ano1 protein in C6/C0 leads to diverse functional profiles of Ca2+ transients in ICC-MY network and smooth muscle electrical activity in the small intestine. Supported by NIH grant DK57091.


Background & Aims: ICC depletion is the most common cellular change in diabetic gastroparesis. Mechanisms of ICC loss include reduced Kit receptor tyrosine kinase expression. In various cancers including rare forms of gastrointestinal stromal tumors [GIST], a sarcoma arising from the ICC lineage, loss of subunit A, B, C or D of the mitochondrial succinate dehydrogenase (SDH) complex leads to succinate-mediated inhibition of Junmön C and TET-family dioxygenases, which remove methyl marks from histones and DNA. Succinate is also elevated in diabetes mellitus. Therefore, we hypothesized that SDH inhibition epigenetically regulates Kit transcription in ICC.

Methods: ICC were studied in CAGCreERT2/+;Sdc6−/− mice by flow cytometry. SDHB protein was reduced by small interfering RNA-mediated knockdown of SDHB (siSDHB) in Kit+ GIST-T1 cells used as an ICC model. Expression of Kit and En1, a key ICC transcription factor, was studied by Western blotting (WB). The repressive histone marks (H3K9me2/3, H3K27me3) and the activating mark H3K4me3 were analyzed by WB in acutely isolated ICC cultures and by chromatin immunoprecipitation-seq (ChIP-seq). The DNA methylation patterns were determined by bisulfite sequencing. NO release regulates tone in the circular smooth muscle cells of the jejunum. The mean amplitude of contractions was 11.66±3.36 mN (C6/C0) and 31.8±29% (p = 0.029 for both). Relative to scrambled sequences, ssSDHB in GIST-T1 cells reduced Kit and ETV1 protein and upregulated H3K27me3 and H3K9me3/2 by WB and 5mC/5hmC ratios by dot blotting. By ChIP-seq we detected increased H3K27me3 occupancy of the Kit transcription start site, and by [h]MeDIP we observed a 7.3-fold increase in the SmC3 Shm ratio in a super-enhancer ~120 kb upstream of Kit.

Conclusions: SDH inhibition leads to repression of Kit and loss of ICC due to epigenetic dysregulation. This mechanism may contribute to ICC depletion in diabetic gastroparesis. Grant support: NIH R01 DK058185, R01 CA166025S and the Paralyzed Foundation.

366 Effects of retigabine on the smooth muscle activity of rat jejunum D. CAO, Y. D. LUI, N. ZHANG, Q. SHEN, Y. R. WANG and L. SHA School of Neuroendocrine Pharmacology, School of Pharmacy, China Medical University, Shenyang, Liaoning, China

Background: Retigabine is an antiepileptic drug which reduces neuronal excitability by enhancing the activity of KCNQ (Kv7.2-7.5) potassium channels. In clinical investigations, patients taking retigabine frequently have side effects such as urinary retention, QT prolongation, constipation and dyspepsia suggesting the presence of Kv7.2-7.5 channels in these systems. It has been reported that Kv7 channel subtypes are present throughout the gastrointestinal tract with Kv7.4 and Kv7.5 found in smooth muscle. However, it is not known how retigabine affects the smooth muscle activity of jejunal ICC. The aim of the present study was to investigate the effects of retigabine on the smooth muscle activity of rat jejunal ICC.

Methods: Adult Sprague Dawley rats were used. Segments of jejunum were dissected and then connected to isometric transducers for contraction recording in a chamber superfused with normal Krebs solution (NKS). For intracellular recordings, a sheet of jejunum muscle wall was pinned serosal side down in a recording chamber after mucosa was removed.

Results: Retigabine inhibited spontaneous phasic contraction of the jejunum. The mean amplitude of contraction was 11.66±6.27 mN in NKS and 6.17±2.25 mN with 20 μM retigabine. The difference is significant (p < 0.05, n = 6 rats). Retigabine also significantly reduced the muscle tone from 4.41±3.14 mN to 2.16±2.06 mN (p = 0.05). Surprisingly, retigabine reduced the frequency of phasic contraction from 35±5 to 32±5 cycles per minute (p = 0.05). The amplitude, tone and frequency of phasic contraction were restored after washing out retigabine. We further investigated the effect of retigabine on resting membrane potential and slow wave of rat jejunum circular smooth muscle cells. Retigabine at 20 μM hyperpolarized the resting membrane potential from ~62 ± 0.8 mV to ~66 ± 0.8 mV (p = 0.3). Retigabine reduced the amplitude of slow wave from 21.96 ± 3.35 to 17.45 ± 3.36 and reduced the frequency of slow wave from 32.4 ± 5 to 26.7 ± 7 cycles per minute. Our results showed that retigabine not only inhibited smooth muscle activity but also inhibited slow waves in rat small intestine. The frequency of phasic contraction and slow wave was reduced with retigabine suggesting that KCNQ (Kv7.2-7.5) potassium channels are present in intestinal cells of Cajal and play a role in controlling the slow wave frequency in rat jejunum.

367 Exploring the diverse effects of nitrergic signaling on smooth muscle activity of murine ileum R. VOUSSEN-LÜDERS, K. RECK, N. MAURO, J. KEPPLER, D. GRÖNBERG AND A. FRIEBE University of Wuerzburg, Institute of Physiology, Wuerzburg, Germany

Gastrointestinal [GI] motility and peristalsis originate from coordinated movements of circular and longitudinal smooth muscle layers. GI diseases affecting motility are often associated with impaired nitrergic signaling. In the enteric nervous systems, NO is released from nitrergic neurons as a major inhibitory neurotransmitter. The specific role of nitrergic inhibitory signaling on the circular and longitudinal muscle layers in the small intestine has not been clearly determined yet. Therefore, in the present study, we investigated the NO-mediated influence on these two muscle layers in murine ileum. As NO-sensitive guanylyl cyclase (NO-GC) is the main receptor for NO in the GI tract, we first looked for NO-GC expression in murine ileum via immunohistochemistry. For functional analyses, we measured spontaneous contractions in ileal tissue from mice lacking NO-GC globally and specifically in smooth muscle cells (SMC). In contrast to findings from other parts of the GI tract, the immunohistochemical stainings showed NO-GC expression in platelet-derived growth factor receptor β (PDGFRβ)-positive cells but not in interstitial cells of Cajal (ICC). Organ bath experiments revealed NO-GC in SMC to be involved in the maintenance of tone of circular smooth muscle: Addition of an NO-GC inhibitor led to an increase and addition of an NO donor to a decrease in tissue tone. In contrast, NO-GC activity in the longitudinal smooth muscle did not affect tone. When activated by NO, NO-GC led to suppression of spontaneous contractions. In conclusion, basal enteric NO release regulates tone in the circular smooth muscle layer via NO-GC in SMC. In contrast, in the longitudinal smooth muscle layer NO, mainly mediates suppression of spontaneous contractions in the murine ileum.

368 Emergent properties of the intestinal pacemaker network: mathematical modeling to understand effects of frequency noise, coupling strength and loss of pacemaker cells R. WEE, S. P. PARSONS*, J. H. CHEN* and I. D. HUIZINGA* *William Beaumont College, Hamilton, ON, Canada and McMaster University, Hamilton, ON, Canada

Background: The ICC-MP associated with the myenteric plexus determine strong propulsive activity in the intestine. Although we know now many properties of intestinal cells of Cajal (ICC), the actual pacemaking comes from ICC as a network. Hence network properties are needed to be understood to elucidate fully the role of ICC in motor pattern development. Our objectives were to study consequences for motor pattern development of 1. Changes in network properties, and 2. Loss of ICC as happens in chronic constipation and diabetes.
Method: A Kuramoto model of coupled oscillators was developed as a two dimensional array of $6 \times 100$ oscillators, each only connected to its immediate neighbors and compared with spatiotemporal mapping of motor patterns of the whole intestine of the mouse. In both actual experimentation in the mouse intestine by inhibiting gap junction conductance and inhibiting the coupling strength in the model, the pacemaker and motor patterns changed dramatically by the appearance of dislocations and ultimately loss of synchronization which meant loss of effective propagation of pacemaker activity and contractions. At certain levels of uncoupling the motor pattern changed from propulsion to segmentation, that is erratic back and forth propagation.

Changes in the intrinsic frequency introduced multiple ectopic pacemakers and reversal of the direction of propagation. Loss of ICC or loss of ICC coupling disrupted slow wave activity, but the consequences for propulsion may be limited. When a complete ring around the intestine lost ICC, the network distal to the ICC continued to fully show propagating activity albeit at a lower frequency and transit might not be interrupted. When a large circumferential section was affected but 10% of the cells were still intact and connecting the proximal and distal parts, then the basic propagation from proximal to distal was not interrupted and the consequences for transit of content might be limited dependent on how large the affected section is. If ICC were randomly lost, it was shown that loss of 10–20% of ICC has little effect on the overall propagating nature of the network, it took 40–50% loss to disrupt significantly the capacity to deliver transit.

Conclusion: The Kuramoto model shows network properties that are mimicked precisely by spatiotemporal mapping of intestinal motility of the mouse. Changes in network characteristics alone can markedly affect pacemaker patterns and hence the propulsive and segmental motor patterns of the intestine. Consequences of loss of ICC or loss of ICC coupling are mitigated by the network configuration of ICC, but random loss of >40% of ICC prevents regular propagating activity.
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Friday Poster Session • Pacific Concourse

Set Up: Thursday, August 25 • 4:00 pm – 6:00 pm
All posters must be up by 10:00 am Friday.

Take Down: Friday, August 26 • Immediately after session
All posters must be taken down by 3:00 pm Friday.

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Note: Presenters should be at their posters from 12:30–2:30 pm

Saturday Poster Session • Pacific Concourse

Set Up: Friday, August 26 • 4:00 pm – 6:00 pm
All posters must be up by 10:00 am Saturday.

Take Down: Saturday, August 27 • Immediately after session
All posters must be taken down by 3:00 pm Saturday.

Viewing: Saturday, August 27 • 12:00 pm – 2:30 pm

Note: Presenters should be at their posters from 12:30–2:30 pm