Effects of a high FODMAPS diet on visceral sensitivity: Involvement of advanced glycation end products and colonic mast cells

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Intestinal dysfunctions induced by intrauterine growth retardation are associated with altered autophagy in the enteric nervous system

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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 (P35). 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 nitrergic 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 nitrergic, 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 glial 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 dysfunctions might involve impaired autophagic pathways.
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Diagnostic yield of 24 h esophageal manometry for non-cardiac chest pain

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Background and aim: Non-cardiac chest pain (NCCP) can be caused by reflux or esophageal motor disorders. With the diagnostic improvements brought by pH-impedance monitoring and high-resolution manometry (HRM), the contribution of ambulatory 24 h manometry in the setting of NCCP is uncertain. Our aim was to assess the diagnostic yield of ambulatory 24 h manometry in this patient population.
Methods: Twenty-four-hour ambulatory pressure-pH-impedance monitoring off proton pump inhibitors was used to study all patients who were referred to our tertiary hospital for NCCP between 2011 and 2015. Patients had a preliminary work-up including cardiologic assessment, upper gastro-intestinal endoscopy and esophageal HRM. Diagnostic measurements were independently analyzed by two physicians, and in ambiguous cases a consensus had to be reached. Symptom association probability (SAP) was calculated for both reflux and esophageal spasm using a 2-min time window.
Results: Of the 334 patients selected, 59 (24 males) met the inclusion criteria. Retrosternal pain was present in all patients. However, heartburn, regurgitation, dysphagia, nausea or vomiting, belching and weight loss were also reported, by 9 (15.3%), 15 (25.4%), 14 (23.7%), 2 (3.4%), 4 (6.8%) and 9 (15.3%) patients, respectively. Nine (15.2%) patients had signs of gastroesophageal reflux on upper gastrointestinal endoscopy. Twenty-nine (49.1%) patients had a final diagnosis of functional chest pain, 22 (37%) of gastroesophageal reflux disease, 4 (6.8%) of esophageal spasm, and 4 (6.8%) had other diagnoses. Esophageal spasm was diagnosed in all patients using ambulatory manometry. HRM, using the Chicago Classification v3.0 criteria alone, did not identify any of these patients. However, taking into account suggestive abnormalities on HRM, such as rapid or repetitive contractions, HRM had a sensitivity of 75% and a specificity of 94.5% for the diagnosis of distal esophageal spasms. Eighteen (30.5%) patients did not experience chest pain during the 24 h recording.
Conclusion: Ambulatory 24 h manometry has a low diagnostic yield for esophageal hypertensive peristaltic disorders in non-cardiac chest pain patients. However, it remains the best currently available diagnostic modality. This is particularly relevant if a definitive diagnosis is needed before invasive treatment.

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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 complaints outside the gastrointestinal tract, suggesting abnormal Diffuse Noxious Inhibitory 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 up 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=?]. 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 3.1 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 ($r = 036$; $p = 0.42$).
Conclusions: DNIC is preserved in youth with FGID. Baseline norepinephrine correlated with DNIC activation, suggesting that norepinephrine levels directly regulate pain modulation.
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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 XF96 Extracellular Flux Analyzer (North Billerica, MA), in unbuffered/serum free RPMI assay media supplemented with 1 mM pyruvate. Peripheral Blood Mononuclear Cells (PMBCs) were seeded in a PS V7 cell culture plate at a density of 3.25 × 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 tree tested predictors (among age, gender, basal, ECAR and SRC) of functional outcome (Functional Disability Inventory, FDI) optimized by least absolute deviation and 10% leave out samples for cross validation.
Results: 45 subjects (36 female) with a median (range) age of 16 years (10, 20), did not differ by age or gender between 15 FD and 30 HC FD subjects. FD subjects demonstrated lower resting mitochondrial function (basal respiration BR: FD 33.7 [13.3, 96.8] pmol/min units for all values, HC 56.0 [27.1, 171.1] $p = 0.002$), and lower reserve energy (spare respiratory capacity – SRC: FD 68.4 [5.2, 264.7]; HC 118.0 [32.6, 377.3] $p = 0.016$). BR correlated with SRC ($p < 0.0001$). Interestingly, of all