

Histamine-Producing Bacteria: The Missing Link in Irritable Bowel Syndrome?

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excess weight loss (EWL). Adult patients aged 21-65 years with a body mass index (BMI) of 30-40 kg/m² and who failed nonsurgical weight loss methods were randomized to receive ESG plus moderate-intensity lifestyle modifications or moderate-intensity lifestyle modifications alone. A total of 187 patients were followed for 52 weeks, after which those in the ESG group were offered retightening of the ESG, and those in the control group could crossover into the ESG group and be followed for another 52 weeks.

Patients in the ESG group had a mean percentage EWL of 49.2% and mean percentage total body weight loss (TBWL) of 13.6%, compared with 3.2% and 0.8%, respectively, in the control group ($P = 0.0001$). After adjusting for confounders, patients in the ESG group had a mean difference of 44.7% (95% CI 37.5%-51.9%) EWL and 12.6% (10.7%-14.5%) TBWL. In the ESG patients with extended follow-up at 104 weeks, 83% of the reached EWL was maintained (41.0% EWL and 11.4% TBWL). A total of 14 patients required suture reinforcement for either failure to meet the primary end point ($n = 9$) or investigator discretion ($n = 5$). In ESG patients with baseline comorbidities, significant improvements were noted in HbA_{1c} levels, blood pressure, and metabolic syndrome. Likewise, ESG patients saw significant improvements in liver transaminases, hepatic steatosis index, aspartate transaminase-to-platelets ratio index, and C-reactive protein. Levels of high-density lipoprotein and triglycerides and waist-to-hip ratio also improved. Adverse events were reported in 92% of patients who underwent ESG, most of which (66%) were accommodative and expected in the post-procedure period, including pain, nausea, and vomiting. Most adverse events resolved within 1 week, and only 6 patients required admission for medical management. Three adverse events required re-intervention, including an abdominal abscess, gastrointestinal bleeding, and a case of severe malnutrition.

Overall, these data add further evidence for the role of endoscopic therapy in the treatment of obesity. Limitations of the study include the absence of a sham intervention group, as well as the absence of a control group during extended follow-up to 104 weeks. It is also noted that this trial occurred during the COVID-19 pandemic, which disrupted in-person follow-up and monitoring. ESG is also not covered by most health payers. Nevertheless, ESG appears to be an effective endoscopic option for weight loss.

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De Palma G, Shimbori C, Reed DE, et al. Histamine production by the gut microbiota induces visceral hyperalgesia through histamine 4 receptor signaling in mice. *Sci Transl Med* 2022;14(655):eabj1895.

The interaction between diet, intestinal microbiota, and host plays a role in the pathophysiology of irritable bowel syndrome (IBS). A key mediator in the development of visceral hypersensitivity in IBS is histamine, with its release acting on nociceptive afferents and generating pain signals.

Although it is generally thought that histamine is derived from mucosal mast cells in IBS patients, De Palma et al provide evidence for a different source of histamine in the gut: bacteria. In an elegant series of mechanistic experiments, performed using germ-free mice colonized with fecal microbiota from patients with IBS, *Klebsiella aerogenes* was identified as a major producer of histamine by the activity of a histidine decarboxylase gene specific to these species. *K aerogenes* was abundant in the fecal microbiota of patients with IBS, particularly in those with high and not low urinary histamine concentrations.

In addition, *Klebsiella*-derived histamine led to visceral hypersensitivity in mice colonized with microbiota from IBS patients with high urinary histamine. These effects were mediated by H₄-receptor-dependent signaling; an H₄-antagonist reduced visceromotor responses to colonic distension in mice. Furthermore, an increase in mast cells was also seen in these animals, similarly to mice mono-colonized with a single bacterial strain of *K aerogenes*, capable of producing high amounts of histamine.

Notably, *K aerogenes* derives its name from its ability to produce gas, in particular hydrogen, and can metabolize different sugars, including lactose and fructose. This could also explain why its abundance decreased when patients with high urinary histamine ate a low-fermentable carbohydrate diet, as observed by reanalyzing fecal samples from a previous study (*Gut* 2017;66:1241-1251). Could urinary histamine profile be used to select IBS patients harboring the histamine-producing *K aerogenes* to increase efficacy of therapies such as the low-FODMAP diet?

What remains unclear is how bacterial histamine from the lumen can reach high concentrations in urine without any concurrent increase in intestinal permeability or any other mechanism at operation allowing transepithelial passage of large amounts of histamine. Alternatively, high urinary histamine could be the result of endogenous rather than bacterial histamine production due to the increased influx of mucosal mast cells, which can be induced by the chemo-attractive effects of *K aerogenes*.

Although the novel disease mechanism presented here is particularly intriguing, the fecal microbiota used for the mechanistic studies was derived from just 2 patients with IBS (one with high and the other with low urinary histamine, with different IBS subtypes and different sexes) and a healthy control subject. Whether such a mechanism is operating in a broader group of patients warrants further investigation, and if confirmed, it could represent a true breakthrough in mechanism-driven treatment in IBS.

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Conflicts of interest

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How the Gut Feeds the Brain: A Newly Uncovered Gut-Brain Circuit for Appetite Suppression



Zhang T, Perkins MH, Chang H, Han W, de Araujo IE. An inter-organ neural circuit for appetite suppression. *Cell* 2022;185:2478-2494.

Gastric motility disorders, and the bloating and anorexia that accompany them, are increasingly common yet remain challenging to treat owing to a paucity of understanding regarding their underlying pathophysiology. Glucagon-like peptide 1 (GLP-1), released from intestinal enteroendocrine L cells, exerts appetite-suppressing effects and delays gastric emptying by inducing gastric fundus relaxation. However, the vast majority of GLP-1 is inactivated before exiting the gut, implying that endogenous GLP-1 acts locally to initiate these distal effects on the stomach and brain. Through a comprehensive set of anatomical, chemogenetic, and ablation approaches in mice, Zhang et al identified a novel GLP-1 signaling pathway that ultimately links gastric distention to appetite suppression.

Through L cell-specific opto- and chemogenetic activation or GLP-1 receptor (GLP-1R) antagonism, the investigators demonstrated that L cell-secreted GLP-1 is required for gastric enlargement and appetite suppression. GLP-1R activation also resulted in Fos activation in neurons of the abdominal sympathetic ganglia, thus defining the key subset of neurons responsible for ileal GLP-1 neurotransmission as intestinofugal neurons. Ablation of intestinofugal neurons eradicated the effects induced by ileal GLP infusion, although activation mimicked its effects. Using similar

cell-specific anatomic, chemogenetic, and ablation approaches, the investigators established the neural pathways involved. Surprisingly, they found that spinal and not vagal sensory innervation was instrumental in conveying GLP-1-induced signaling to the brain.

Some limitations of the study are secondary to the constraints inherent in currently available technologies. Although the intravital microscopy technique allowed for imaging of enteric neurons in live mice, animal anesthesia was required to allow for visualization. Therefore, it remains unknown precisely how enteric neuronal and brain-gut circuit activity ensue in awake animals, when feeding is actively taking place. Similarly, a greater understanding of how L-cell activity and ileal GLP-1 secretion in real time affect feeding behavior would also be of significance.

Despite these limitations, Zhang et al delineated a novel gut-brain sensorimotor circuit that forms an inter-organ neural network connecting the intestine, via the stomach, to the medullary reticular formation and hypothalamus and finally to the craniofacial muscles to instigate both gastric fundal enlargement and appetite suppression. This highly novel finding, that enteric gastric neurons may be critical modulators of gastric relaxation and appetite, are likely to lead to further investigation of these neural circuits as therapeutic targets for the symptoms of bloating and anorexia that accompany gastric motility disorders, such as gastroparesis, or those that accompany some disorders of gut-brain interaction.

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