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TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

New Pathways, New Targets: Visceral Hypersensitivity Pathogenesis in Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is the most common gastroenterological syndrome diagnosed by physicians in the United States. Despite its prevalence, however, the pathogenesis of IBS is poorly understood, with multiple pathophysiological processes, including disordered GI motility, psychosocial distress, and visceral hypersensitivity all likely having a role. Yet many of the newest therapeutic options use a monolithic approach to treatment, focusing almost exclusively on motility. Visceral hypersensitivity—enhanced intestinal perception converting otherwise physiologic stimuli into discomfort—no doubt has a dominant role in the abdominal pain that drives the morbidity associated with IBS. There have recently been a number of remarkable advances increasing our understanding of the hypersensitivity in IBS at the basic and translational levels, decoding the complex milieu of bioactive factors that influence enteric nerve function in patients with IBS. Recent research has identified common pathways upon which these factors may converge: a subfamily of capsaicin receptors known collectively as transient receptor potential cation channels (TRPV) involved in the development of visceral hypersensitivity in patients with IBS.

Although a relative increase of nerve fibers expressing TRPV has been previously described in multiple gastrointestinal disorders, including Crohn's disease and idiopathic rectal hypersensitivity, researchers did not find a correlation with abdominal pain in patients with IBS until 2008.¹ TRPV is expressed by sensory neurons in the myenteric ganglia throughout the gut and produces pain when activated by capsaicin, heat, acid, and inflammatory mediators. Three recent studies have since significantly increased our understanding of this complex pathway.

In April 2015, Cenac *et al.*² elaborated on TRPV activation and the resulting sensitization of intestinal mucosa in patients with diarrhea-predominant IBS (IBS-D). Analyzing colonic biopsies of IBS-D patients through use of tandem mass spectrometry and liquid chromatography, the study observed an increase in the concentration of metabolites that activate TRPV-4 (a receptor of the TRPV subfamily) in IBS-D patients with visceral hypersensitivity when compared with healthy controls. In addition, these increases in TRPV-4 metabolites were independently correlated with abdominal pain and bloating severity scores. The researchers then extracted these metabolites from the biopsies and added the extract to mouse sensory neurons *in vitro*, generating visceral hypersensitivity via activation of TRPV-4. Although prior work had shown that transferring the mucosal extracts of IBS patients to naive intestinal tissue increases neuron excitability in the submucosa, this study was the first to implicate TRPV receptors and offer a mechanism for the visceral sensitivity seen in IBS.³

A month later, Dothel *et al.*⁴ published their work on the TRPV pathway in IBS hypersensitivity, developing the concept even further. Analyzing colonic biopsies from over a hundred IBS patients, this work demonstrated that the gut mucosa of patients with IBS had significantly more nervous tissue and the associated mediators of nerve growth when compared with healthy controls. This was the first study to show evidence of specific mediators, regardless of IBS subtype, inducing long-lasting neuroplastic change in the gastrointestinal tract. Through use of immunohistochemistry and enzyme-linked immunosorbent assays, researchers observed an increased concentration of key mediators of nerve sprouting in these samples: growth-associated protein 43 (a plasticity protein expressed during neuronal development), nerve growth factor and its preferential receptor for nerve sprouting (NGF and NTRK1, respectively), and TRPV-1. Although previous studies^{2,5} had demonstrated potential mediators of this neuronal excitability in the tissue of IBS-D patients (but not IBS-C), this work showed a significant increase in multiple mediators of nerve growth for all IBS patients regardless of subtype. In addition to establishing clear evidence of structural changes in the enteric nervous system of patients with IBS, this study also identifies future therapeutic targets among the many potential mediators that contribute to the pathophysiology of intestinal dysfunction and pain transmission in IBS.

This future may not be as distant as it seems. In a promising study accepted for publication in *Gastroenterology* in January, Wouters *et al.*⁶ elegantly translate their TRPV-1 basic science work to the bedside. Although prior studies showed increased pain response to TRPV-1 activation in IBS patients, there was no upregulation of the receptor when agonized, suggesting instead that increased sensitization was at play in visceral hypersensitivity.⁷ With two recent clinical trials failing to demonstrate improvement of IBS symptoms with the anti-inflammatory agent mesalazine,^{8,9} Wouters *et al.*⁶ argue against inflammation as a potential mechanism for TRPV-1 sensitization. Instead, they hypothesized that mast cell products such as histamine and serotonin, which

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have been linked to visceral hypersensitivity,¹⁰ may serve as alternative mediators of TRPV-1 sensitization. Using live calcium imaging to examine submucosal neuron excitability in rectal biopsies, neurons from patients with IBS had increased capsaicin (a TRPV-1 agonist) excitability compared with those of healthy volunteers, suggesting TRPV-1 sensitization in IBS. Incubating samples of healthy patients with histamine increased TRPV-1 sensitization, and antagonizing the histamine receptor H1 (HRH1) blocked this effect; thus, the researchers identified the role of histamine in mediating the sensitization of TRPV-1 via the HRH1 receptor.

In a proof of principle clinical trial of this purported mechanism, the group conducted a placebo-controlled, double-blinded clinical trial of the HRH1 antagonist ebastine, in which IBS patients were given ebastine (20 mg/day; $n = 28$) or placebo ($n = 27$) for 12 weeks. Ebastine resulted in an increased proportion of patients with at least considerable relief at week 12 and an increased percentage of responders compared with placebo, though the absolute benefit should be interpreted cautiously as the study was not powered for clinical end points. Nevertheless, this work represents an exciting breakthrough in the search for therapeutic targets in IBS, a clearly heterogeneous disease that is sorely lacking targeted treatments for patients with visceral hypersensitivity and abdominal pain. The current era represents an exciting time for bench-to-bedside research in IBS. As we begin to unlock the mysteries of visceral hypersensitivity in IBS, the potential for true translational medicine is seemingly robust.

CONFLICT OF INTEREST

Guarantor of the article: Kyle Staller, MD, MPH.

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