ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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The Role of 5-HT Dysregulation in Inflammatory Bowel Disease

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G&H What is the role of 5-hydroxytryptamine in gut function?

WK The gut is the largest producer of serotonin—that is, 5-hydroxytryptamine (5-HT)—in the body. About 95% of the body's 5-HT is located in the gut, and enterochromaffin (EC) cells are its main source. 5-HT is an important enteric signaling molecule that influences gut physiology. 5-HT plays a vital role in intestinal secretion, sensation, and peristalsis. Recent research suggests that 5-HT can act as a proinflammatory molecule and can modulate immune cell function in the gut.

G&H What factors in the gut influence EC function and 5-HT expression?

WK EC cells, as well as the 3 other principal cells of the intestinal epithelium (enterocytes, goblet cells, and paneth cells), arise from a multipotent stem cell located near the base of the crypts of Lieberkühn. In mammals, cells in the epithelial layer continue to proliferate actively throughout life. It is thought that progenitor cells, located in the proliferative compartment, derive from these stem cells and, while leaving the crypts, differentiate further into each of the intestinal cell lineages. One of the most important pathways in control of stem cell function is the Wnt/β-catenin signaling pathway. In addition to the Wnt/β-catenin signaling pathway, there is now evidence that Hedgehog signaling plays a role in the differentiation of stem cells. EC cell development in the intestine is also regulated by members of the basic helix-loop-helix (bHLH) family. It has been shown that bHLH transcription factor neurogenin-3 is required for enteric endocrine cell fate specification in multipotent intestinal progenitor cells. EC cells express mechano- and chemosensitive ion channels, a variety of ligand-gated ion channels, and G-protein–coupled receptors, and EC cells release 5-HT in a regulated and calcium-dependent manner in response to various mechanical and chemical stimuli, including bacterial toxins.

Turnover of EC cells and the release of 5-HT can be enhanced or attenuated by the action of signaling molecules released from surrounding cells. Cells associated with the immune, neural, and vascular systems are in close proximity to EC cells. Recent studies have revealed an important role of the immune system in the regulation of EC cell biology, in which secretory products from $CD4^+$ T cells interact with EC cells or their precursors to enhance 5-HT production in the gut via T helper (Th) 2–based mechanisms. In addition, it has also been observed that EC cells and 5-HT responses that are induced by the same enteric infectious agent are influenced by Th1 or Th2 cytokine predominance, suggesting the importance of the immunologic profile of the inflammatory response in the regulation of EC cell biology. The presence of immunologic control of EC cell biology and 5-HT production has been further supported by the demonstration of the interleukin (IL)-13 receptor on EC cells and by the upregulation of 5-HT production by EC cells in response to exogenous IL-13. These observations suggest that cytokines from immune cells play an important role in regulation of EC cell biology by acting on turnover of EC cells from stem cells and by upregulating synthesis of 5-HT.

G&H What problems arise with 5-HT regulation in the gastrointestinal tract?

WK Dysregulation of 5-HT is associated with diarrhea or constipation. In addition, according to recent research, increased availability of gut 5-HT can contribute to the severity of intestinal inflammation. A study by Minderhoud and colleagues, published in *Clinical Gastroenterology and Hepatology* in 2007, showed an upregulation of the colonic tryptophan hydroxylase (TPH) mRNA of patients with Crohn's disease who were in remission and experiencing irritable bowel syndrome (IBS)-like symptoms. Gut serotonin has also been shown to be important in the regulation of blood glucose concentration, hepatic cell regeneration, and bone metabolism.

G&H What is the putative mechanism of action of 5-HT dysregulation?

WK Considering the strategic location of EC cells in the mucosal layer, it is very likely that both immune cells and gut flora in the lumen contribute to 5-HT dysregulation in the gut. As I mentioned earlier, there is already evidence in favor of a role for immune mediators generated in intestinal inflammation in the dysregulation of 5-HT signaling. It will be important to investigate the role of gut flora in the dysregulation of 5-HT. EC cells express Toll-like receptors (TLRs), and the gut microbial population acting through these TLRs can activate inflammatory gene expression in innate immune cells. In 2009, a report by Kidd and colleagues in *Neurogastroenterology and Motility* demonstrated an increase in 5-HT from EC cells via TLR activation by IL-1β and bacterial products (*Escherichia coli* lipopolysaccharide) in Crohn's disease.

G&H Is a genetic component involved in 5-HT dysregulation?

WK Serotonin-related genes are the most extensively studied genes in IBS research. Released 5-HT can be transported back into epithelial cells and neurons by the specific transporter system known as the serotonin reuptake transporter. The 5-HT transporter–linked polymorphic region comprises a repetitive sequence with an insertion/deletion variation. The *l* allele produces more serotonin transporter and reuptakes more serotonin than the *s* allele.

G&H How does the use of 5-HT reuptake inhibitors for management of other health issues impact existing inflammatory bowel disease?

WK A potential negative impact of selective serotonin reuptake inhibitors (SSRIs) on inflammatory bowel disease (IBD) has been reported in a systematic review by Mikocka-Walus and colleagues in *Clinical Practice and Epidemiology in Mental Health* in 2006. Following treatment with an SSRI for depression, 3 patients were reported to have received a diagnosis of chronic diarrhea and, subsequently, received a diagnosis of IBD (Crohn's disease in 2 patients and nonspecified IBD in another). Fernández-Bañares and colleagues, in a study published in the *American Journal of Gastroenterology* in 2007, showed that the use of an SSRI is associated with development of microscopic colitis, both collagenous and lymphocytic. SSRIs increase the availability of 5-HT in the gut, which may be involved in the pathogenesis of microscopic colitis. Recently, a case of lymphocytic colitis was reported to have developed after initiation of treatment with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine, and the colitis remitted after discontinuation of the drug. More clinical studies are needed to understand the impact of SSRIs and SNRIs on IBD and its treatment.

G&H How is IBD then best managed in patients receiving SSRIs or SNRIs?

WK The findings from the systematic review by Mikocka-Walus and colleagues suggest a minimal benefit of antidepressant medication when compared with placebo in patients with mild or moderate IBD. However, all of the publications included in the review referred to nonrandomized studies. The efficacy of antidepressants for the treatment of IBD should be further studied in properly designed randomized controlled trials. In addition, studies have suggested that treatment with SSRIs may increase the bleeding risk in patients with IBD. Until precise information is available on the effect of SSRIs and SNRIs on gut inflammation, I think physicians should be alerted to use caution when prescribing these agents in patients with IBD. As an alternative to SSRIs and SNRIs, norepinephrine-dopamine reuptake inhibitors could be considered.

G&H What looks most promising in terms of 5-HT–focused therapy for treatment of IBD?

WK In recent years, significant progress has been made in understanding the pathogenesis of IBD, leading to improved strategies to control inflammation with the use of immunosuppressive drugs and the antibody targeting tumor necrosis factor alpha. However, these drugs are not universally effective and can cause adverse effects. There is a need to develop better therapeutic strategies and new therapeutic targets in IBD.

A study by Ghia and colleagues that was published in 2009 in *Gastroenterology* showed that blocking 5-HT synthesis in the gut by disruption of TPH-1 significantly reduced the severity of colitis in experimental models

while replenishing the amount of gut 5-HT in gut-upregulated colitis. 5-HT also can activate immune cells to produce proinflammatory cytokines. Ghia and colleagues' findings identified 5-HT as a key molecule in the pathogenesis of colitis and suggested target inhibition of peripheral 5-HT signaling as a potential treatment strategy.

Recent data from our laboratory revealed a critical role of the 5-HT_7 receptor, which is present on dendritic cells, in immune activation and intestinal inflammation in experimental models of IBD. In addition to using a 5-HT_7 receptor antagonist, 5-HT production can be modulated in the gut by targeting the TPH-1 enzyme.

G&H In your view, what would be the properties or action of the ideal therapeutic agent?

WK I think an ideal therapeutic agent in IBD should be able to effectively induce and maintain remission, promote mucosal healing, improve quality of life, and reduce surgeries and hospitalizations in all IBD phenotypes with minimal toxicity.

Suggested Reading

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