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CLINICAL AND SYSTEMATIC REVIEWS

Serotonin and GI Disorders: An Update on Clinical and Experimental Studies

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The gastrointestinal (GI) tract is the largest producer of serotonin (5-hydroxytryptamine (5-HT)) in the body, and as such it is intimately connected with GI function and physiology. 5-HT produced by enterochromaffin (EC) cells is an important enteric mucosal signaling molecule and has been implicated in a number of GI diseases, including inflammatory bowel disease and functional disorders such as irritable bowel syndrome. This review will focus on what is known of basic 5-HT physiology and also on the emerging evidence for its novel role in activation of immune response and inflammation in the gut. Utilizing pubmed.gov, search terms such as ''5-HT,'' ''EC cell,'' and ''colitis,'' as well as pertinent reviews, were used to develop a brief overview of EC cell biology and the association between 5-HT and various GI disorders. It is the aim of this review to provide the readers with an update on EC cell biology and current understanding on the role of 5-HT in GI disorders specifically in inflammatory conditions.
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INTRODUCTION

The discovery of 5-hydroxytryptamine (5-HT) was accomplished by two independent research endeavors, one searching for vasoconstrictors causing hypertension described a molecule called serotonin, the other characterizing the granules found in intestinal enterochromaffin (EC) cells described a molecule called enteroamine.[1,2] 5-HT is a well-known neurotransmitter of the central nervous system and traditionally it is known to influence a range of behavioral, physiological, and cognitive functions. However, most of the 5-HT in the body is synthesized from EC cells in the gastrointestinal (GI) tract and is an important mediator in normal gut physiology. Abnormal regulation of 5-HT (Table 1) in the human gut has been implicated with a diverse array of GI disorders, such as inflammatory bowel disease (IBD),[3,4] and functional disorders such as irritable bowel syndrome (IBS).[3,5,6] In addition, alteration in 5-HT signaling is shown to be associated with celiac disease,[7] colorectal cancer,[8,9] and diverticular disease.[10] Despite this association with a variety of GI disorders it is not clear how the changes in 5-HT occur, what role 5-HT has in intestinal pathophysiology, and whether by modulating 5-HT production and signaling is it possible to elicit a therapeutic effect.

EC CELLS AND 5-HT

The association between altered EC cells numbers, 5-HT production, and GI diseases highly emphasizes the significance of 5-HT in intestinal pathophysiology. Understanding EC cell biology, mechanisms of 5-HT production, and the precise roles of EC cells/5-HT in intestinal pathology may ultimately lead to improved therapeutic strategies in GI disorders.

Origin and differentiation of EC cells. The GI tract contains the largest endocrine organ in the body; however, in contrast with other endocrine organs the various types of enteroendocrine cells are scattered throughout the intestinal tract. Enteroendocrine cells are responsible for releasing various biologically active compounds such as gastrin, secretin, stomatostatin, cholecystokinin, chromogranins, and 5-HT.[11] The best-characterized subset of enteroendocrine cells are EC cells and are found throughout the gut.[12] EC cells are found at the base of the crypts in the GI tract, where they originate from stem cells also located near the base of the crypt.[13] The turnover of EC cells is considerably slower, EC cells last 15–150 days in comparison with enterocytes, which last 2–4 days in rats.[14]

There are potentially two distinguishable pools of stem cells within the intestinal crypt from which EC cells could originate.[15] The regulators of intestinal cell lineage and maintenance of the intestinal stem cell niche seems to be the Notch, Wnt, and bone morphogenetic protein signaling pathways.[16–18] Lateral inhibition of Notch signaling down regulates cellular expression of Hes-1, the key transcription factor for the enterocyte cell lineage.[19] This allows endocrine cells in particular to begin to express transcription factors such as Math 1 and neurogenin 3, which direct a more secretory cell lineage.[20–23] The necessity of neurogenin 3 in the development of EC cells has been demonstrated in neurogenin $3^{-/-}$ mice, which develop without any endocrine cells.[20]

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Table 1 Studies of EC cell numbers and 5-HT synthesis in IBD and IBS

GI disorders	EC cells	5-HT	TpH mRNA	Reference
CD		Increased	Increased	Kidd *et al.*[77]
CD			Increased	Minderhoud *et al.*[78]
UC		Decreased	Decreased	Coates *et al.*[3]
CD and UC		Decreased		Magro *et al.*[4]
CD and UC	Increased			El-Salhy *et al.*[60]
UC	Decreased			Ahonen *et al.*[62]
IBS	Increased			Ahonen *et al.*[62]
IBS	Unchanged	Decreased		Coates *et al.*[3]
IBS-C		Increased		Miwa *et al.*[5]

Abbreviations: CD, Crohn's disease; EC, enterochromaffin; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; TpH, tryptophan hydroxylase; UC, ulcerative colitis; 5-HT, 5-hydroxytryptamine.

5-HT synthesis and release. Synthesis of 5-HT by intestinal EC cells begins with the conversion of dietary tryptophan to 5-hydroxy-L-tryptophan, which is catalyzed by tryptophan hydroxylase (TpH). Recent studies have identified two isoforms of the TpH enzyme, TpH1, which is present in mainly peripheral organs such as the gut, and TpH2, which is associated with the nervous system and present predominantly in the brain stem.[24,25] The second step catalyzed by L-amino acid decarboxylase, which is also present in EC cells, converts 5-hydroxy-L-tryptophan to 5-HT.[26] The 5-HT is then packaged into granules by vesicular monoamine transporter 1 at both the apical and basal ends of the EC cell, just below the surface of the plasma membrane.[27,28] Degradation of 5-HT is facilitated by monoamine oxidase A that drives the conversion of 5-HT into 5-hydrosyindoleacetic acid (5-HIAA).

The release of 5-HT from EC cells follows intraluminal distension, vagal-nerve stimulation, ingestion of a meal, or the presence of acid, amino acids, or hypo- or hyper-osmotic solutions in the duodenum. Microvilli present on the apical end of the EC cell project into the lumen and function as sensors of luminal content, turning the physiochemical signals of the lumen into biochemical endocrine signals.[28] The released 5-HT from EC cells either enters the lumen or lamina propria where it can act upon enterocytes or cells of the enteric nervous system and initiate secretion and enteric pulsation patterns.[28,29] Cholera toxin has been shown to release 5-HT into the human jejunum[30] this is relevant for both the small and large intestine. Short-chain fatty acids, produced by bacteria in the colon, can also stimulate 5-HT release.[29] The diet may also influence 5-HT release, D-glucose, and D-galactose, but not fructose induced the release of 5-HT from human BON cells.[31] The complex interaction of the microbiota, diet, and the cells of the intestine all have an influence on 5-HT synthesis, release, and degradation, and therefore all may be responsible for the altered 5-HT function seen in many GI diseases.

Turnover of EC cells and the release of 5-HT can be altered by signaling molecules released by surrounding cells. Cells associated with the immune, neural, and vascular system are in close proximity to EC cells.[32,33] Our work using *Trichuris muris* infection in severe combined immunodeficiency mice exemplifies the role of CD4 + T cells in modulating the EC cell number and 5-HT content.[34] Wild-type mice (BLK6/C57) infected with *T. muris* produce a predominantly Th2 immune response, and this same study found the interleukin-13 receptor on murine EC cells, which solidifies the role of Th2 cytokines in EC cell biology.[34] The close proximity of immune cells with EC cells and the ability of 5-HT and cytokines to regulate the function of both the immune and endocrine system are suggestive that this interaction governs many of the pathophysiological aspects associated with GI disease.

Role of 5-HT in immune activation and inflammation. We have previously shown how the immune system can influence 5-HT-expressing EC cell biology, however, in turn 5-HT can also influence the immune system (Figure 1).[34–37] There are many serotonergenic receptors that have been found on various immune cells such as B and T lymphocytes, monocytes, macrophage, and dentritic cells.[38] In addition, mast cells, macrophage, and T cells also have the ability to synthesis 5-HT from tryptophan.[39–41] 5-HT is also a chemotactic molecule for eosinophils, dendritic cells, and mast cells.[42–44] Previous studies have described 5-HT receptors on human monocyte-derived dendritic cells; immature dendritic cells primarily expressed 5-HT_{1B}, 5-HT_{1E}, and 5-HT_{2B} receptors, whereas mature dendritic cells express 5-HT_4 and 5-HT_7 receptors.[45] This shift in the expression of 5-HT receptors may help to explain the differential functions of 5-HT, for instance 5-HT can function as a chemotactic molecule in immature but not lipopolysaccharides-matured dendritic cells.[42] We have found that dendritic cells isolated from mice with decreased ability to synthesize 5-HT ($TPH1^{-/-}$) in the intestine produced less interleukin-12p70 but cytokine production could be restored by adding 5-HT.[46]

In the experimental models of colitis induced by trinitrobenzene sulfonic acid, dinitrobenzenesulfonic acid, and dextran sodium sulfate, an increase in 5-HT content has been observed.[47,48] Studies from our laboratory recently reported reduced severity of colitis in $TPH1^{-/-}$ mice as compared with wild-type mice after dextran sodium sulfate- and dinitrobenzenesulfonic acid-colitis.[35] Restoration of 5-HT in $TPH1^{-/-}$ mice by administration of a 5-HT precursor (5-hydroxy-L-tryptophan) enhanced the severity of colitis. These findings are supported by studies from other groups, which have shown that chemical-induced colitis or spontaneous colitis associated with interleukin-10 deficiency is increased in severity when coupled with the 5-HT-enhancing effects of the knockout of 5-HT reuptake transporter (SERT).[49,50] In clinical studies, in patients with diarrhea-predominant IBS duodenal immune activation is associated with reduced levels of SERT mRNA in platelets.[51] Taken together, these studies suggest an important role of 5-HT in the pathogenesis of GI disease by influencing pro-inflammatory mediator production and immune modulation.

5-HT IN GI DISORDERS

5-HT and pathophysiology of GI diseases. The role of 5-HT in the pathophysiology of GI diseases can vary, among the most important roles of 5-HT is its influence on the motility of the GI tract and its ability to modulate the immune system. Extensive reviews on receptors for 5-HT (Table 2),

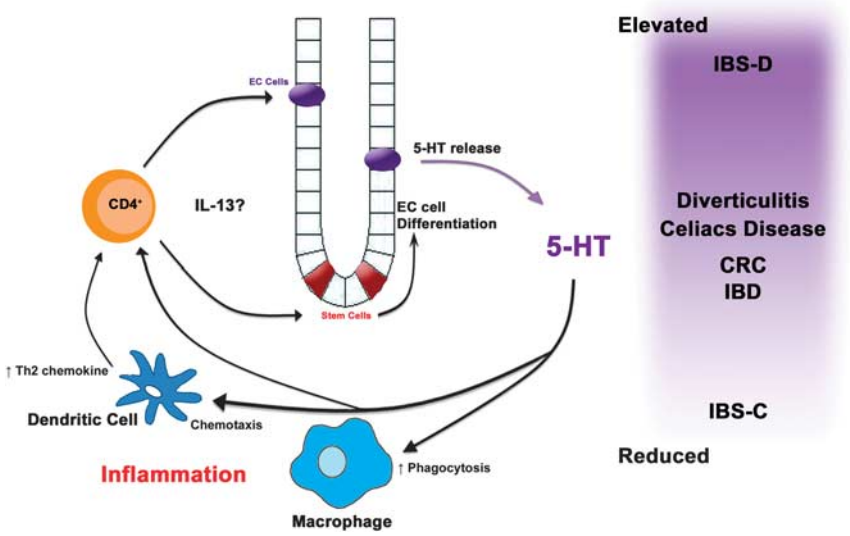

Figure 1 Modulation of EC cell biology by immune cells and modulation of immune cells by 5-HT in GI disease. The role of 5-HT in modulating the innate and adaptive immune system can vary by cell type. 5-HT has been shown to enhance phagocytosis in murine macrophages.[40] In addition, 5-HT can increase chemotaxis of dendritic cells and promote the release of the Th2-attracting chemokine CCL22 while decreasing the Th1 chemokine CXCL10.[42] Finally 5-HT has a proliferative effect on CD4 + T cells, which when coupled with 5-HT effect on dendritic cells create a more permissive environment for a Th2 immune response. CD4 + T cells[50] particularly Th2 cytokines, such as interleukin-13,[49] in turn may influence on EC cell biology, 5-HT synthesis, and 5-HT release.

Table 2 Clinical utility of agonists and antagonists associated with 5-HT metabolism in gastrointestinal disorders

Target	Mechanism	Potential and documented clinical utility
5-HT_1 receptor family	Agonist	FD; IBS-D
	Antagonist	FD; IBS; GERD
5-HT_2 receptor family	Agonist	None
	Antagonist	IBS-D (women only)
5-HT_3 receptor	Agonist	GERD; constipation-predominant IBS
	Antagonist	IBS-D; FD; nocturnal GERD; chemotherapy-induced nausea and vomiting; radiation induced nausea and vomiting; post-operative vomiting
5-HT_4 receptor	Agonist	Chronic constipation; gastroparesis; GERD; IBS-C; IBS-M; FD
	Antagonist	GERD
5-HT_7 receptor	Agonist	No known applications in GI disorders, however, receptor is thought to mediate colonic relaxation, therefore a potential role in functional GI disorders
	Antagonist	

Abbreviations: FD, functional dyspepsia; GI, gastrointestinal; IBS-C, constipation-predominant irritable bowel syndrome; IBS-M, mixed IBS; GERD, gastroesophageal reflux disease; IBS-D, diarrhea-predominant IBS; 5-HT, 5-hydroxytryptamine.
Table adapted from references 58,79–86 as well as company websites and FDA.gov.

such as $5\text{-HT}_{3\ \text{and}\ 4}$, have been developed outlining the pivotal role of 5-HT in both altered motility and sensation of nausea and pain commonly associated with GI disorders.[13,52,53] Alosetron (5-HT_3 receptor antagonist) became the first agent approved by the US Food and Drug Administration for the treatment of diarrhea-predominant IBS. However, the drug unexpectedly was associated with ischemic colitis and, rarely, with severe constipation-induced complications.[54] The case of alosetron prompts a rethinking of our approaches to the pharmacological modulation of serotoninergic pathways and warrants more studies on 5-HT in the context of intestinal pathology and pathophysiology.

The pathophysiology of GI diseases is also associated with aberrant immune responses, such as lymphocyte infiltration and hyperplasia, resulting in inflammation of the enteric mucosa. 5-HT receptors have been found on cells associated with the immune system and has been shown *in vitro* to affect the proliferation of lymphocytes and recruitment of T-cells.[55,56] The influence of 5-HT on immune cell function may have a critical role in the pathogenesis of various GI diseases as a significant reduction of colonic 5-HT was associated with decreased inflammation in two different animal models of colitis.[35] Furthermore, the expression of cytokine receptors on 5-HT-expressing EC cells supports the

existence of an immuno–endocrine axis in the context of various GI disorders.[34]

5-HT in GI disease translational medicine. Understanding 5-HT signaling in GI disorders is very important not only because of the alteration in 5-HT response observed in various GI diseases but also in light of serious and unforeseen complications caused from the use of 5-HT receptor antagonist in clinical practice (Table 2). The location of 5-HT-expressing EC cells within the epithelial mucosa of the GI tract is perfect for the delivery of an oral administered small molecule modulator of 5-HT synthesis. Recent clinical trials using a small molecule inhibitor of TpH1 have shown the ability to alleviate the symptoms associated with IBS, especially diarrhea predominate IBS. Treatment with TpH1 inhibitor decreased blood 5-HT level, relieved pain/discomfort, and increased stool consistency.[57,58] Modulation of tryptophan metabolism, especially 5-HT synthesis may be a novel target for developing therapies for GI disorders.

Modulation of the 5-HT signaling pathway in GI disease has been extensively investigated; however, adverse side effects have restricted the use of many 5-HT receptor targeted drugs.[13,52,53,59] Drugs released specifically at the site of inflammation could decrease collateral damage by requiring a lesser amount of drug. For example, addition of covalently linked hydrophilic carriers would enhance the retention of the pro-drug within the GI tract until it reached a specific site. At this point, specific enzymes from the intestinal cells or microflora could cleave the compound allowing its absorption by the intestine.[60]

5-HT and IBD. IBD includes two chronic GI diseases, ulcerative colitis and Crohn's disease, which are relapsing inflammatory conditions of unknown etiology. Inflammation of the intestinal mucosa has been found to affect 5-HT signaling in both humans and animal models.[4,35,61,62] Changes in EC cell numbers and in 5-HT content have been reported in association with both Crohn's disease and ulcerative colitis.[61,63–65] Approximately 50% of patients with IBD in long-standing remission have IBS-like symptoms, which may be related to these inflammation-induced alterations in EC cells and 5-HT signaling.[66] It is also shown that consumption of selective 5-HT reuptake inhibitors is associated with microscopic colitis.[67] Increases in 5-HT content have also been observed in experimental models of colitis.[47,48] In our opinion, the intersection between 5-HT-expressing EC cells (5-HT itself) and the immune responses that drive IBD are paramount to the pathogenesis of this disease.

5-HT and IBS. IBS is associated with abdominal pain and cramping, as well as changes in the functionality of the bowel. It is a disorder of dichotomous extremes, with many patients experiencing predominantly constipation, diarrhea, or both. Diarrhea-predominant IBS is associated with elevated 5-HT whereas constipation-predominant IBS is associated with decreased levels of 5-HT in the colon mucosa.[13,52] Alterations in gut motility are paramount to this disorder and contribute to prevalence of both diarrhea and constipation. The etiology of IBS is unclear, however, alterations in 5-HT metabolism have been suggested to contribute to the pathophysiology of this disease.[68]

There are several studies both in humans and in experimental models that have reported associations of symptoms of IBS and: the number of EC cells, the presence of 5-HT, mRNA levels of TpH, and the expression of SERT in mucosal biopsies.[3,5,69,70] In addition, a recent study examining the microbiota of patients who self-reported the severity of IBS, it has been found that the severity was associated with the presence of a *Ruminococcus torques*-like (94% similarity in 16S rRNA gene sequence) phylotype.[71] It is reasonable to assume that the microflora can also influence the function of 5-HT, potentially modulating its content, and signaling in the intestinal mucosa resulting in GI disease.

5-HT and celiac disease. Celiac disease is caused by an immune reaction to gliadin, a prolamin (gluten protein) found in wheat, and is associated with chronic diarrhea and fatigue. Small intestine crypt hyperplasia and an increase in the number of 5-HT-expressing EC cells is also associated with Celiac disease.[72,73] With more EC cells there is also increased 5-HT content in the duodenal mucosa of in both adults and children.[74] A recent study by Coleman *et al.*[7] evaluated both fasting and postprandial plasma 5-HT levels in patients after a high-carbohydrate meal. Celiac patients had increased 5-HT-containing EC cell numbers as well as significantly higher peak plasma 5-HT levels.[7] These observations point to altered EC cell biology, increased 5-HT release, and impaired 5-HT uptake resulting in altered 5-HT metabolism. This disease promotes a predominantly Th1 cytokine environment, therefore elevated levels of both tumor necrosis factor-α and interferon-γ can decrease the expression of SERT and reduce 5-HT uptake by cells in the intestine.[75] Further studies are required to understand the precise role of 5-HT in the pathogenesis of celiac disease.

5-HT and diverticulitis. Although diverticulosis is a common affliction in the western society, there is very little known about its pathogenesis. Altered mobility is an important aspect of the disease, which suggests that alter 5-HT signaling and metabolism may be as well. Diverticulitis develops from diverticulosis, which is the formation of pouches (diverticular) on the outside of the inflamed colon. In a recent study, asymptomatic diverticulosis patients as well as patients with a history of acute diverticulitis were compared with healthy controls.[10] The only difference observed in the study was that patients with a history of acute diverticulitis exhibited decreased expression of 5-HT transporter (SERT) expression.[10] The requirement of an inflammatory event seems to be associated with a change in 5-HT signaling further emphasizing the intimate relationship between 5-HT metabolism and inflammation. Further studies such as this would be useful to understand the mechanisms involved in the development and progression of this disease.

CONCLUDING REMARKS

The regulation of 5-HT- and 5-HT-expressing EC cells is intimately associated with the inflammatory processes that

drive many GI disorders. Recent studies on EC cells and 5-HT have generated a number of concepts that provide insight into how the immune and endocrine systems of the gut interface. It is evident from these studies that mediators from immune cells such as cytokines have an important role in EC cell biology and production of 5-HT in the gut. In addition, 5-HT has a key role in the pathogenesis of experimental colitis and in generation of pro-inflammatory mediators from immune cells. If this is not complex enough, this entire relationship is occurring in the presence of varying diets and mediators secreted by the microbiota, which may directly or indirectly influence the EC cell function.

Recently, Margolis *et al.*[75] has shown that inhibition of 5-HT synthesis using a specific inhibitor of the TpH1 enzyme reduces the severity of trinitrobenzene sulfonic acid-induced colitis in mice. This finding furthers supports our observation that 5-HT is a critical molecule in pathogenesis of colitis and suggest that targeted inhibition of 5-HT synthesis may ultimately help in the development of improved therapeutic strategies in GI inflammatory disorders.

5-HT exerts a wide range of effects in the gut, largely due to the presence of multiple receptor subtypes that are present on smooth muscle, enteric neurons, enterocytes, and immune cells. Agonist or antagonist for various 5-HT receptor is used in a variety of GI disorders, which include IBS, functional dyspepsia, and chronic constipation (Table 2). The 5-HT_7 receptor, coupled to Gs proteins and stimulating cAMP production, is the most recently identified member of the family of 5-HT receptors. Our lab has evaluated the 5-HT_7 receptor antagonist (SB-269970) and found that disruption of 5-HT_7 receptor signaling significantly reduces the severity of both dextran sodium sulfate and dinitrobenzenesulfonic acid-induced colitis in mice.[76] Pharmaco-modulation of 5-HT signaling using specific agonists and antagonists represents one of the best strategies for alleviating many of the symptoms associated with GI disease; however, the effect on the immune system should also be considered.

CONFLICT OF INTEREST

Guarantor of the article: Waliul I. Khan, MD, PhD.

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