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Review article: the many potential roles of intestinal serotonin (5-hydroxytryptamine, 5-HT) signalling in inflammatory bowel disease

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Summary

Background: Serotonin (5-hydroxytryptamine, 5-HT) is an important mediator of every major gut-related function. Recent investigations also suggest that 5-HT can influence the development and severity of inflammation within the gut, particularly in the setting of inflammatory bowel disease (IBD).

Aim: To review the roles that the intestinal serotonin signalling system plays in gut function, with a specific focus on IBD.

Methods: We reviewed manuscripts from 1952 to 2017 that investigated and discussed roles for 5-HT signalling in gastrointestinal function and IBD, as well as the influence of inflammation on 5-HT signalling elements within the gut.

Results: Inflammation appears to affect every major element of intestinal 5-HT signalling, including 5-HT synthesis, release, receptor expression and reuptake capacity. Importantly, many studies (most utilising animal models) also demonstrate that modulation of selective serotonergic receptors (via agonism of 5-HT_4R and antagonism of 5-HT_3R) or 5-HT signal termination (via serotonin reuptake inhibitors) can alter the likelihood and severity of intestinal inflammation and/or its complicating symptoms. However, there are few human studies that have studied these relationships in a targeted manner.

Conclusions: Insights discussed in this review have strong potential to lead to new diagnostic and therapeutic tools to improve the management of IBD and other related disorders. Specifically, strategies that focus on modifying the activity of selective serotonin receptors and reuptake transporters in the gut could be effective for controlling disease activity and/or its associated symptoms. Further studies in humans are required, however, to more completely understand the pathophysiological mechanisms underlying the roles of 5-HT in this setting.

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1 | INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is a signalling molecule that plays critical roles in a large and varied number of human physiological functions, ranging from modifying mood to blood pressure control. Nowhere is the influence of 5-HT more ubiquitous, however, than in the gastrointestinal tract. The gastrointestinal mucosa harbours the largest store of 5-HT in the body.[1] Specifically, 5-HT is stored in granules and released from enterochromaffin (EC) cells residing in the lining of the intestinal crypts. Once released into the underlying lamina propria, 5-HT interacts with serotonergic receptors to affect a variety of functions in the gut before being removed by the serotonin selective reuptake transporter (SERT) (Figure 1). 5-HT influences every major function inherent to the gut, including motility, secretion, blood flow and sensation. Therefore, it is not surprising that when intestinal serotonergic signalling elements are disrupted (through disease processes, medications and/or inherent disorders of intestinal neuroendocrine function), these functions are impacted, resulting in myriad problematic symptoms that include abdominal pain, diarrhoea and/or constipation. It has been demonstrated, in both animal and human studies, that serotonergic signalling elements can have a major impact on inflammation development and severity within the gut, particularly in inflammatory bowel disease (IBD).[2,3] There is strong evidence that modulation of a variety of 5-HT signalling components (including proteins related to 5-HT production and signal termination, as well as 5-HT-responsive receptors) can alter the risk of intestinal inflammation and its complications. In this article, we review the roles of 5-HT in normal intestinal functions, as well as more recent evidence demonstrating the impact that 5-HT signalling elements and inflammation within the gut have on each other. We propose the concepts that (1) the intestinal 5-HT signalling system exerts significant influence on the course of IBD and its symptomatic sequelae and (2) should be studied further as a target for disease modulation.

2 | SEROTONIN SIGNALLING AND FUNCTION WITHIN THE GUT

A common feature of visceral sensory, secretory, vasodilatory and motility pathways is that they can all be initiated by the action of 5-HT. In the gut, 5-HT can be found in specific enteric neurons, primarily descending interneurons in the myenteric plexus, but it is also produced, stored and secreted by EC cells in the mucosa. In fact, the vast majority of the body's 5-HT is located in EC cells.[4] They represent a specialised subset of enteroendocrine cells, that are themselves one of the four main descendants of endodermally derived GI epithelial stem cells.[5] The first described isoform of tryptophan hydroxylase (TPH-1) is the rate-limiting enzyme involved in the majority of 5-HT synthesis within the periphery, including the gastrointestinal tract, where it is responsible for 5-HT synthesis within the EC cells.[6] Once synthesised, 5-HT is stored in granules within the EC cell until released by an appropriate stimulus. The more recently discovered TPH-2 enzyme is responsible for 5-HT synthesis in enteric neurons (and neuronal 5-HT synthesis, in general).

Bulbring and colleagues revealed that intestinal mucosa releases 5-HT when mechanically stimulated and they provided evidence suggesting that EC cells are responsible for this release.[7-9] Subsequent studies demonstrated that a variety of alterations in GI luminal conditions, including acidity, pressure and increased nutrient concentration, induce intestinal mucosa to release 5-HT.[10-13] While other neuroactive compounds, such as cholecystekinin (CCK) and motilin, are released by luminal stimulation,[14,15] it is 5-HT that seems to play a particularly critical role in sensory perception, secretion and peristalsis. The 5-HT released from EC cells is important because it represents the earliest intercellular event in the transduction of mucosal stimuli that initiates the neuronal reactions responsible for visceral sensation and peristalsis.[16] It is worth noting, however, that Spencer et al. have demonstrated that peristalsis can be initiated and carried out in the absence of mucosal 5-HT.[17] Therefore, it seems that 5-HT is not essential for the activation of peristalsis.[18,19]

After release from EC cells into the lamina propria, 5-HT can interact with serotonergic receptors on the projections of neurons intrinsic or extrinsic to the gut, as well as receptors on nearby epithelial and immune cells. These interactions can stimulate secretion of a variety of signalling mediators and can potentiate neurons to make them more likely to respond to another stimulus or directly activate an action potential.[20] The influence that 5-HT has on a particular cell's activity varies depending upon the prevalent receptors. Seven different classes of 5-HT receptor (5-HT_1-5-HT_7) have been identified, using their structural and transductional characteristics, and there are currently at least 13 distinct human subtypes[21] (Table 1). A variety of 5-HT-specific receptors have been identified in tissues of the gut, including on neurons as well as smooth muscle, epithelial and EC cells. For example, immunocytochemical studies have demonstrated that 5-HT_3 receptors are expressed on the subepithelial terminals of extrinsic sensory neurons.[4,22,23] Electrophysiological studies show that when these neurons are exposed to a 5-HT_3-selective antagonist, such as alosetron, the normally robust response they have to 5-HT stimulation is attenuated.[24] In addition, 5-HT_{2A} receptors located on gut smooth muscle cells can stimulate muscle contraction when activated by 5-HT and thereby indirectly activate 5-HT-sensitive mechanosensitive nerve fibres in the gut wall.[25] Intrinsic neurons involved with GI motility utilise a different combination of serotonin receptors. In vitro studies, using isolated guinea pig intestine, have revealed that peristaltic activity is significantly diminished when an antagonist to the 5-HT_7 receptor (such as 5-HTP-DP) is applied alone or when antagonists or an antagonist to the 5-HT_3 and 5-HT_4 receptors together (eg, tropisetron) are applied to the tissue.[4,16,26] As previously indicated, recent studies have also demonstrated that several cell types associated with immunological function, including antigen presenting cells, B cells, T cells, eosinophils, basophils and mast cells, express a variety of serotonergic receptors (such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_4 and

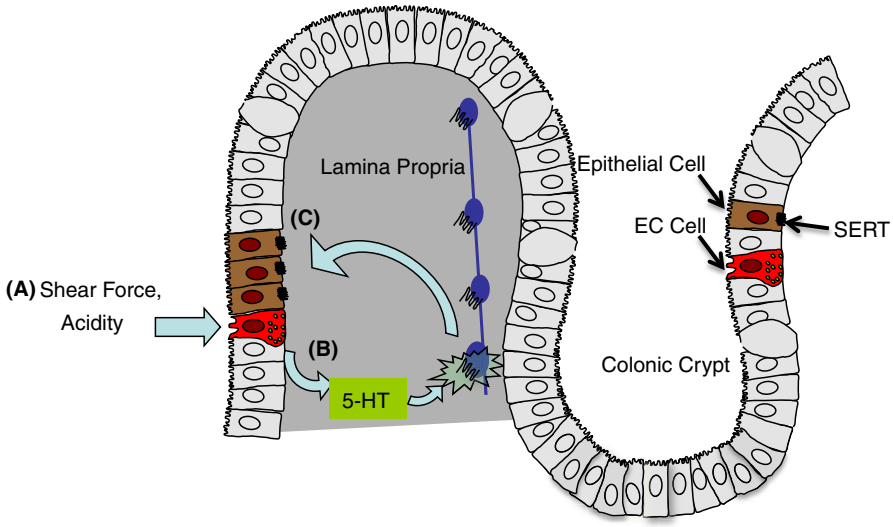

FIGURE 1 Normal Intestinal Serotonin Signaling Cycle. (A) An appropriate stimulus (acidity, shear force) triggers 5-HT release from enterochromaffin (EC) cells into the lamina propria. (B) 5-HT interacts with serotonin-specific receptors on neurites and other mucosal cells expressing serotonergic receptors. This results in activation of sensory, motor and interneurons associated with the gut. (C) 5-HT is taken up by the selective serotonin reuptake transporter (SERT), found throughout the epithelium, thereby terminating its receptor stimulation

TABLE 1 5-HT receptors and their general function

Serotonin receptor type	Location	Function
5-HT_{1A}	CNS GI	Neuronal hyperpolarisation Mast cell degranulation; Mediator release
5-HT_{1B}	CNS	Inhibits neurotransmitter release, CV effects
5-HT_{1D}	CNS	Inhibits neurotransmitter release, CV effects
5-HT_{1E}	CNS	
5-HT_{1F}	CNS	Integrates sensorimotor info with limbic function
5-HT_{2A}	CNS GI	Influences effects of psychostimulants Contracts gut smooth muscle
5-HT_{2B}	GI	Enhances response of colonic smooth muscle
5-HT_{2c}	CNS	Influences emotional state
5-HT_{3}	CNS GI	Modulates release of several neurotransmitters Modulates motility and visceral pain transmission
5-HT_{4}	CNS GI	Impacts memory, cognitive function, affect Contracts gut smooth muscle
5-HT_{5A}	CNS	Regulates affect, learning and memory, perception, neuroendocrine function
5-HT_{5B}	CNS	
5-HT_{6}	CNS	Regulates affect
5-HT_{7}	CNS GI	Regulates affect Relaxes gut smooth muscle

CNS, central nervous system; GI, gastrointestinal; CV, cardiovascular.

5-HT_{7}) and that modulation of these receptors can induce significant changes in immune activity.[27,28]

As with neurochemical transmission, to acheive precise reflex control with a paracrine transmitter, it is necessary to have a highly efficient mechanism to terminate the signal. This is primarily accomplished by the reuptake of 5-HT from the lamina propria by the SERT and its subsequent intracellular degradation by type A monoamine oxidase (MAO-A) or repackaging into vesicles.[29-31] SERT is a transporter protein with 12 transmembrane-spanning domains whose activity is sodium-dependent.[32] It is a highly selective 5-HT transporter that is expressed by serotonergic neurons in the ENS,[4] but also by essentially all intestinal epithelial cells.[24,29,31,33] Transgenic mice lacking SERT frequently exhibit diarrhoea associated with watery stools interspersed with periods of constipation.[30] We also know that SERT is involved in normal gut function in humans because alterations in bowel habits (eg, diarrhoea) are the most common side effect of serotonin selective reuptake inhibitors (SSRIs).[34-36] Importantly, SERT synthesis in the gut involves a transcriptional start site that is downstream of that used by neurons,[37] and so appears to be regulated differently compared to what occurs in neurons. Finally, 5-HT that is not transported into epithelial cells enters the blood stream where it circulates in platelets that also express SERT.

All of the factors described above (5-HT synthesis and storage, release, receptor interaction and reuptake) are critical elements within the intestinal serotonin signalling system. Understanding how each of these factors work independently and in a coordinated fashion within the gut wall is important to properly understand not only intestinal serotonergic function, but also healthy and pathological gut physiology, including what occurs with inflammatory disorders of the gastrointestinal tract.

3 | IBD EPIDEMIOLOGY AND CHALLENGES

Inflammatory bowel disease, including ulcerative colitis (UC) and Crohn's disease (CD), affects an estimated 3 million people 18 years of age or older (1.3% of the adult population) in the USA alone.[38,39] Despite recent advancements in therapy, many patients struggle finding adequate and/or consistent control of their disease and/or symptoms. Forty per cent or more of all IBD patients are eventually found to be refractory or intolerant to even the most efficacious therapies.[40,41] Many find adequate control, but the path to success is frequently arduous and costly and, even when achieved, an

estimated 40% still report problematic symptoms (including abdominal pain and/or bowel habit changes) that significantly impact their quality of life.[42,43] Patients with resistant disease and/or persistent symptoms incur higher healthcare expenditures and are more likely to miss work and report poor quality of life.[44]

The symptoms described above, as well as the inflammatory state associated with IBD, may be affected by a variety of disparate factors, including genetic alterations relating to immune and epithelial barrier function, myriad environmental factors including diet and the gut microbiome and inherent host immune factors. Another underappreciated potential set of factors, however, are alterations in neuroendocrine signalling within the gut. In fact, there are many signalling molecules that can influence either the inflammation or symptoms associated with IBD. However, as indicated above, none has more wide-ranging effects and capability in this regard than 5-HT and perhaps no other neuroendocrine signalling system has demonstrated such profound changes as those seen with intestinal serotonergic signalling in IBD.

4 | RELATIONSHIPS AMONG INTESTINAL SEROTONIN SIGNALLING, INFLAMMATION AND ASSOCIATED SYMPTOMS

Several animal and human studies have demonstrated profound changes in one or more elements of 5-HT signalling in the setting of IBD (Tables 2 and 3), as well as significant effects of intestinal serotonergic signalling on the nature of inflammation in the gut (Tables 4 and 5). There is also evidence that 5-HT may be critical for development of a variety of symptoms in IBD, including abdominal pain and diarrhoea (Table 6). Here, we review the findings of those investigations, based upon the serotonergic signalling component(s) involved, the study models used and the inflammatory and/or functional end points evaluated.

4.1 | 5-HT synthetic capacity, content and EC cell density

4.1.1 | Animal studies

Most studies involving intestinal inflammation in mouse, rat and guinea pig (including those involving use of dextran sodium sulfate [DSS], trinitrobenzene sulfonic acid [TNBS], dinitrobenzene sulfonic acid [DNBS], acetic acid [AA] and *Trichuris suris* [TS] administration into the colon) have demonstrated significant increases in colonic mucosal 5-HT content and EC cell density.[45-51] A separate model using TNBS to stimulate ileitis in guinea pigs also demonstrated EC cell hyperplasia in the small intestine,[52] while a canine enteritis model demonstrated elevated 5-HT content and EC cell density.[53] Two murine studies involving targeted cytokine knockouts (IL-2 and IL-13) did not exhibit these changes.[54,55] Of note, the investigations utilising non-murine models are important in part because mice have mast cells within their intestinal tract that contain 5-HT (while the other models do not) and the relative prevalence of these cells may contribute to changes in mucosal 5-HT levels during states of intestinal inflammation.[56]

What is particularly interesting is the apparent impact that 5-HT has on the inflammatory process and certain symptoms associated with IBD. Two previous studies, using rodent models of colitis, demonstrated that application of the 5-HT precursor 5-hydroxytryptophan (5-HTP) worsened inflammation in each case.[55,57] Concordantly, other studies that limited 5-HT production in murine models of colitis through either "genetic ablation" and/or pharmacological blockade of TPH-1 found that the inflammatory responses were significantly delayed or subdued as a result.[58-60] Interestingly, this effect appeared to be specific to 5-HT localised in mouse intestinal mucosa.[60] Beyond this, another study, using croton oil to induce colitis in mice, found that application of the 5-HT precursor 5-HTP could induce more diarrhoea in these animals.[61]

4.1.2 | Human cell line and tissue studies

As early as the 1960s, physician-investigators started reporting that serotonergic elements are altered in the intestines of individuals with IBD. Verity[62] and Capurso and Friedmann[63] were the first to demonstrate that 5-HT content was diminished in UC. A subsequent study including UC and CD patients also demonstrated a drop in colonic mucosal 5-HT content.[56] However, at least three studies demonstrated a rise in 5-HT content and/or EC cell density compared to healthy controls.[64-66] These differences, however, may be explained by disease severity. For example, investigations that included specific assessment of severe UC demonstrated significant drops in EC cell density and 5-HT content in patients with the worst degree of inflammation.[33,63]

Serotonin modifies gut inflammation in humans as well. In a study utilising three different human intestinal epithelial cell lines (CCD, HT-29 and CaCo-2), 5-HT application was found to significantly increase production of reactive oxygen species and monocyte epithelial adhesion.[57]

Serotonin synthetic capacity and prevalence can also play an important role in symptoms frequently associated with IBD, regardless of disease activity state. Patients with colonic CD who demonstrate persistent irritable bowel syndrome (IBS)-like symptoms exhibit increased levels of TPH-1 RNA in colonic mucosal biopsies.[67] Individuals with an ileal pouch anal anastomosis (IPAA) who report persistent lower abdominal discomfort and alterations in bowel habits without overt inflammatory changes have also been found to have increased EC cell density in pouch biopsies.[68]

4.2 | 5-HT release

4.2.1 | Animal studies

Every animal model of colitis (performed in mice and guinea pigs) evaluating 5-HT release has demonstrated an increase in epithelial 5-HT secretion compared to control conditions.[46,52,69]

TABLE 2 Impact of inflammation on intestinal mucosal serotonin signaling in animal models of IBD

Citation	Study design	5-HT content	EC cell density	5-HT release	5-HT receptor Expression/function	SERT expression/ function
Oshima et al.[45]	Rat DSS colitis	↑	↑			
Qian et al.[54]	Mouse IL-2 knockout		NC			
Linden et al.[46]	Guinea Pig colitis	↑	↑	↑		↓ (mRNA, IR)
O'Hara et al.[52]	Guinea Pig TNBS ileitis		↑	↑		↓ (IR)
Linden et al.[84]	Mouse TNBS colitis					↓ (mRNA, IR, uptake)
Magro et al.[51]	Mouse TNBS colitis	↑				
O'Hara & Sharkey[49]	Guinea Pig TNBS colitis		↑			
Bertrand et al.[69]	Mouse DSS colitis		↑	↑		↓ (mRNA)
Haub et al.[90]	IL-10 knockout		↓			
Matsumoto et al.[72]	Mouse DSS colitis	↑			↑ (5-HT_3R), ↓ (5-HT_4R)	
Shajib et al.[55]	Mouse IL13 Knockout/DSS colitis	↓	↓			
Guseva et al.[82]	Mouse IL10 Knockout/DSS colitis				↑ (5-HT_7R)	
El-Salhy et al.[50]	Rat TNBS colitis		↑			
Tada et al.[85]	Mouse DSS colitis					↓ (mRNA)
Bailey et al.[53]	Dog enteropathy	↑	↑		NC (5-HT_{2B}R)	NC

↑=increased, ↓=decreased, NC=no change, IR=immunoreactivity.

No animal studies have thus far investigated the impact of 5-HT release modulation on risk or severity of inflammation in this setting.

4.2.2 | Human cell line and tissue studies

An isolated EC cell line exposed to the inflammatory mediators IL-1-beta and LPS, exhibited increases in 5-HT release,[70] while the sole investigation looking at human IBD (UC) tissue found that 5-HT release was similar to that seen in tissue from healthy controls.[33] In addition, in a study of 85 patients with IBD who had undergone an IPAA, patients with the most severe endoscopy subscore on the Pouchitis Disease Activity Index demonstrated the highest levels of 5-HT in their blood.[71]

4.3 | 5-HT receptor expression and function

4.3.1 | Animal studies

There is surprisingly little published research that systematically describes 5-HT receptor distribution within the gut wall in the setting of intestinal inflammation. There is one animal study, which utilised a DSS colitis model in mice, that demonstrated an increase in 5-HT_3R and a decrease in 5-HT_4R within the colonic wall.[72]

There is a growing body of literature, however, describing the influence that intestinal serotonergic receptors can exert on inflammation within the gut. Blocking 5-HT_{1A}R activity worsens TNBS-induced colitis in mice while stimulating the 5-HT_{1A}R or inhibiting the 5-HT_{2A}R reduces the severity of inflammation.[73] Conversely, 5-HT_{2A}R agonism created a "super-potent" reduction in pro-inflammatory markers in the small intestine of rats.[74] In the case of 5-HT_3R, two other studies incorporating mouse and rat AA colitis models demonstrated that its antagonism (using granisetron and tropisetron, respectively) reduced inflammatory severity.[75,76] Studies of 5-HT_4R agonism using animal colitis models suggested either no significant impact on inflammation[73,77] or a protective effect of this receptor against inflammation.[78] Of note, Spohn et al. demonstrated that 5-HT_4R stimuation via enema administration had a protective effect against murine intestinal inflammation, but it was not protective when delivered by intraperitoneal injection.[78] In addition, normal animals treated by enema with a 5-HT_4R antagonist (GR113808) developed signs of early inflammation. Increased enteric neuronal proliferation has also been demonstrated in mouse and guinea pig models of DSS-induced colitis through a 5-HT_4R-dependant mechanism.[79,80] Finally, research evaluating intestinal 5-HT_7R function initially suggested that inflammation in DSS and DNBS colitis in mice could be reduced through pharmacological antagonism of this receptor or via genetic knock-out.[81] However, a more recent study (utilising a similar murine colitis model) suggests that 5-HT_7R may play more of a protective role, reducing intestinal inflammatory activity when activated.[82] In summary, it is clear that 5-HT receptors play important, though potentially differing, roles in the modulation of intestinal inflammation. Available data suggest that 5-HT_{1A}R, 5-HT_{2A}R, and 5-HT_4R activation is likely protective against inflammation in the gut while 5-HT_3R is more likely to worsen the inflammatory process. The evidence for the influence of 5-HT_7R is less clear.

5-HT receptor modulation could also have a significant impact on symptoms associated with gut inflammation. In the murine croton oil colitis study described above, it was found that application of a 5-HT_3R antagonist (ondansetron) could resolve the 5-HTP-induced diarrhoea exhibited in these mice.[61] Another study, utilising DSS-induced colitis in mice, found that these animals not only

TABLE 3 Impact of inflammation on intestinal mucosal serotonin signaling in human studies of IBD

Citation	Disease type	5-HT content	EC cell density	5-HT release	5-HT receptor Expression/function	SERT expression/ function
Verity[61]	UC	↓				
Capurso & Friedmann[63]	UC and healthy controls	↓				
El-Salhy et al.[64]	UC and CD	↑	↑			
Stoyanova et al.[65]	UC, surgical specimens		↑			
Magro et al.[56]	UC and CD, surgical specimens	↓				
Coates et al.[33]	UC, mucosal biopsies	↓	↓ (severe)	NC		↓ (mRNA, IR)
Foley et al.[93]	CaCo-2 cells; IFNγ/TNFα Exp					↓ (mRNA, uptake)
Minderhoud et al.[67]	CD, ileal and colonic biopsies	↑ (TpH-1)	NC			
Kidd et al.[70]	EC Cell Isolates; IL-1b, LPS Exp			↑		
Latorre et al.[94]	CaCo-2 Cells	↑				↓ (low IL-10) ↑ (high IL-10)
Wang et al.[71]	IPAA	↑ (severe)				
Guseva et al.[82]	CD				↑ (5-HT_7R)	
Sikander et al.[66]	Microscopic colitis, UC, Control	↑				
Tada et al.[85]	UC					↓
Yu et al.[83]	UC			↑ (Plasma 5-HT and 5-HIAA)	↑ (5-HT_3R, 5-HT_5R)	

↑=increased, ↓=decreased, NC=no change, IR=immunoreactivity, IPAA=ileal pouch anal anastomosis.

demonstrated visceral hypersensitivity, but that use of a 5-HT_3R antagonist (tropisetron) could attenuate this effect.[72] More recently, Spohn et al.[78] demonstrated in a murine DSS colitis model that tegaserod (a 5-HT_4R agonist) improved intestinal motility while use of a 5-HT_4R antagonist (GR113808) in otherwise untreated mice resulted in the development of inflammation, dysmotility and obstruction in non-inflamed animals.

4.3.2 | Human cell line and tissue studies

In a study evaluating UC patients in remission, 5-HT_3R and 5-HT_5R transcript levels were both increased in colonic mucosal biopsies, while 5-HT_7R was unchanged.[83] 5-HT_7R density was also found to be increased in the setting of CD.[82] It should be noted that these changes in receptor expression likely reflect receptors expressed by local cells in the mucosal layer, as opposed to neurons, because neuronal RNA is probably not collected in a routine colonic biopsy, as neuronal cell bodies are found either in deeper layers within the intestinal wall or outside of the gut all together.

4.4 | SERT expression and function

4.4.1 | Animal studies

Linden et al. were the first to demonstrate significant decreases in SERT expression in an animal (guinea pig) model of colitis.[46] Every subsequent study of SERT expression and/or function in animal models of colitis or enteritis has demonstrated this same finding.[48,52,84-86]

Interestingly, use of SSRIs has been shown to be protective against inflammation in several animal models. Administration of fluoxetine in mice with DSS colitis resulted in reduction in inflammatory markers (eg, NFκB) and histological inflammatory scores.[87] Intra-colonic fluvoxamine therapy reduced intestinal inflammatory activity and assessment scores in mice with AA-induced colitis.[88] Fluoxetine treatment of IL-10 deficient mice reduced intestinal inflammatory cell infiltration and reduced colitis scores.[89] However, other studies utilising SERT knockout (KO) mice demonstrated significantly worsened intestinal inflammation in the absence of the transporter.[90,91]

4.4.2 | Human cell line and tissue studies

UC patients display markedly reduced SERT immunoreactivity and mRNA expression[33] and the latter has been observed in another cohort of UC patients with mild inflammation.[85] Similar findings were demonstrated in a cohort of diverticulitis patients.[92] It is likely that interferon-gamma and TNF-alpha contribute to the down-regulation of SERT in colitis because SERT expression and function are decreased in CaCo-2 cells (which natively express SERT) when they are exposed to these pro-inflammatory cytokines.[93] In another study, interleukin-10 demonstrated the ability to up- and down-regulate SERT concentration and activity in CaCo-2 cells depending on the concentration of cytokine applied.[94]

Several studies have also evaluated the impact of antidepressant medications on IBD symptom severity. Most of these investigations have found that the use of these antidepressants is associated with improved IBD symptom severity and/or disease scores.[95,96] Although

TABLE 4 Effects of alterations in intestinal mucosal serotonin signaling on inflammation in animal models of IBD

Citation	Study design	Impact on inflammation
Shajib et al.[55]	Increasing 5-HT Stores (5-HTP) in mouse IL-13 knockout or DSS colitis	↑
Regmi et al.[57]	5-HT applied in rat TNBS colitis	↑
Ghia et al.[58]	TPH-1 knockout or inhibitor (PCPA) in mouse DSS, DNBS colitis Increasing 5-HT stores (with 5-HTP)	↓ ↑
Margolis et al.[60]	Peripheral inhibition of TPH-1 in mouse TNBS colitis	↓
Kim et al.[59]	Peripheral TPH-1 inhibitor (Telotristat) in Mouse DSS or *Trichuris suris* colitis	↓
Rapalli et al.[73]	Selective 5-HT receptor agonism/antagonism in mouse TNBS colitis 5-HT_{1A}R agonist 5-HT_{1A}R antagonist 5-HT_{2A}R agonist 5-HT_{3}R, 5-HT_{4}R agonist, 5-HT_{7}R antagonism	 ↑ ↓ ↓ NC
Nau et al.[74]	5-HT_{2A}R agonist in rat enteritis	↓
Mousavizadeh et al.[76]	5HT_{3}R antagonist (Tropisetron) in Rat AA Colitis	↓
Fakhfouri et al.[75]	5HT_{3}R antagonist (Granisetron) in mouse AA colitis	↓
Spohn et al.[78]	5-HT_{4}R agonist (Tegaserod) in rectal mouse DSS or TNBS colitis 5-HT_{4}R antagonist (GR113808)	↓ ↑
Koh et al.[87]	5-HT_{7}R knockout or inhibitor in mouse DSS colitis	↓
Kim et al.[81]	5-HT_{7}R knockout or antagonist in mouse DSS or DNBS colitis	↓
Guseva et al.[82]	5-HT_{7}R knockout or antagonist in mouse IL-10 knockout or DSS colitis 5-HT_{7}R agonist	↑ ↓
Bischoff et al.[91]	SERT knockout in mouse TNBS colitis	↑
Haub et al.[90]	SERT knockout in mouse IL-10 knockout	↑
Koh et al.[87]	Fluoxetine in mouse DSS colitis	↓
Minaiyan et al.[88]	Fluvoxamine in normal and reserpenised rats acetic acid colitis	↓
Koh et al.[89]	Fluoxetine in mouse IL-10 colitis	↓

↑=increased, ↓=decreased, NC=no change; 5-HTP=5-HT precursor.

TABLE 5 Effects of alterations in intestinal mucosal serotonin signaling on inflammation in human studies of IBD

Citation	Study design	Impact on inflammation
Regmi et al.[57]	Application of 5-HT to three human cell lines; measured ROS and MEA	↑
Fernandez-Banares et al.[98]	Retrospective assessment of risk for microscopic colitis in setting of SSRI use	↑
Bonderup et al.[97]	Case-control study assessing risk for microscopic colitis in setting of SSRI use	↑
Sikander et al.[66]	Presence of 5-HTTLPR s/s in microscopic colitis or UC (vs Control)	↓

↑=increased, ↓=decreased, ROS=reactive oxygen species, MEA=monocyte epithelial adhesion, s/s=homozygous for "short allele".

most of the agents in question could modulate 5-HT activity, none of these studies specifically evaluated selective serotonin reuptake inhibitor use alone in comparison to IBD disease activity. Although some of these assessments utilised questionnaires that targeted somatic symptoms (including abdominal pain and changes in bowel habits), it should be noted that psychiatric symptoms were a component for many of the disease activity indices utilised for these investigations. In addition, no human studies have utilised rigorous measures to objectively assess intestinal inflammatory status and/or other alimentary complications of IBD in relation to use of these agents. Of note, SSRI use has previously been linked to increased incidence of microscopic colitis, though the exact mechanism underlying this relationship is unclear.[97,98]

5 | CONCLUSIONS

The intestinal serotonergic signalling system appears to play a significant and multi-faceted role in IBD. The studies described above demonstrate a profound effect of intestinal inflammation on mucosal serotonergic signalling. A variety of effects have been observed in different elements of intestinal 5-HT signalling in the setting of experimental colitis and IBD in humans, depending on the disease type or model, severity of disease and/or experimental design. Despite these variations, a few consistent themes have emerged from studies conducted to date. First, intestinal and serum 5-HT levels and synthetic capacity are altered in the setting of IBD. Second, mucosal 5-HT release is either unchanged or increased in these

TABLE 6 Impact of alterations in intestinal mucosal serotonin signaling on symptoms in animal and human models of IBD

Citation	Study design	Impact on symptoms
Pascual et al.[61]	5-HTP application mouse croton oil colitis $5HT_3R$ antagonist (Ondansetron)	↑ (diarrhoea) ↓ (diarrhoea)
Matsumoto et al.[72]	$5HT_3R$ antagonist (Tropisetron) in mouse DSS colitis	↓ (visceral hypersensitivity)
Spohn et al.[78]	$5HT_4R$ agonist (Tegaserod) in mouse DSS colitis $5HT_4R$ antagonist (Tegaserod)	↓ (obstruction) ↑ (obstruction)
Minderhoud et al.[67]	Increased TpH-1 levels in colonic biopsies from CD colitis patients	↑ (IBS symptoms)
Shen et al.[68]	Increased EC cells in pouch biopsies from irritable pouch syndrome patients	↑ (IBS symptoms)

↑=increased, ↓=decreased; 5-HTP=5-HT precursor.

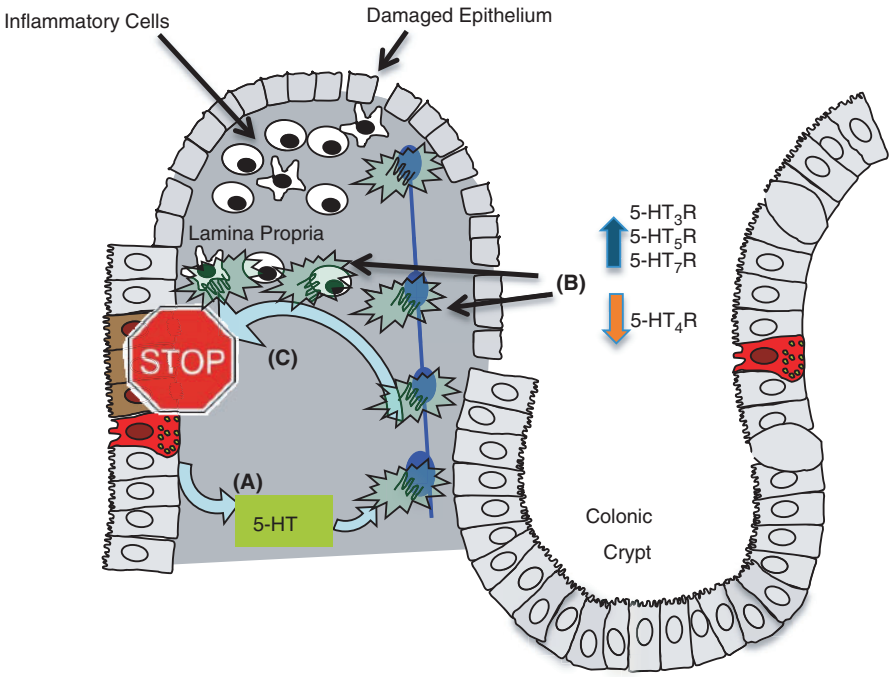

FIGURE 2 IBD impacts the intestinal serotonin signaling cycle. (A) 5-HT release appears to be the same or increased in the setting of inflammation. (B) Inflammation induces changes in serotonin-specific receptors (eg, increased $5\text{-}HT_3R$, $5\text{-}HT_5R$, $5\text{-}HT_7R$ and decreased $5\text{-}HT_4R$) on neurites and other mucosal cells. (C) SERT prevalence is reduced in IBD, leading to reduced uptake (symbolised by the "stop sign"), increased 5-HT availability in the mucosa and variably modified activation of neurons and immune cells expressing serotonergic receptors

disorders. Third, SERT expression (and function based upon a few studies) is consistently and significantly diminished in IBD. Finally, 5-HT receptor expression (for a variety of subtypes) is altered in colitis. These findings suggest that intestinal 5-HT availability is increased overall in the setting of IBD and that many serotonergic signalling capabilities can be affected by inflammation (Figure 2).

Conversely, intestinal 5-HT and its receptors also appear to play a major role in modulating the development and intensity of inflammation. Empiric observations of populations associated with increased exposure to 5-HT and its metabolites (eg, carcinoid syndrome) suggest that there is an increased risk for IBD.[99,100] It has also been demonstrated that several serotonergic components within the gut can enhance or diminish the inflammatory process in IBD and that these elements have the potential to be manipulated to significant effect. Increased 5-HT production and release along with the agonism of certain serotonergic receptors (eg, $5\text{-}HT_3R$) appear to worsen the inflammatory process in IBD, while reduction in 5-HT availability and the activation of different receptors (eg, $5\text{-}HT_{1A}R$, $5\text{-}HT_4R$) appear to reduce or delay the same inflammatory process (Figure 3). There are contradictory findings in animal models of colitis regarding the influence of SERT on disease activity and limited human data. SERT knockout models in rodents with colitis demonstrate worsening of the disease while SSRI administration in non-modified animals appeared to be protective against it. Of note, there is evidence that SSRIs may increase the risk for microscopic colitis and some preliminary data has suggested that SSRIs may actually put IBD patients at greater risk for disease flares[95] but there are no completed studies that have specifically evaluated this latter relationship. As previously stated, there are also no prior studies evaluating any anti-depressant in the setting of IBD that have utilised objective measures of inflammation (eg, endoscopy and/or histology scores).

Manipulations of 5-HT availability (including via use of agents that modulate SERT function) and certain serotonergic receptors (including $5\text{-}HT_3R$, $5\text{-}HT_4R$) also have the potential to impact risk for development of common problematic symptoms in IBD, including visceral hypersensitivity and alterations in bowel habits. Those symptoms directly account for a great deal of the morbidity and reduced quality of life associated with CD and UC, as well as the costs

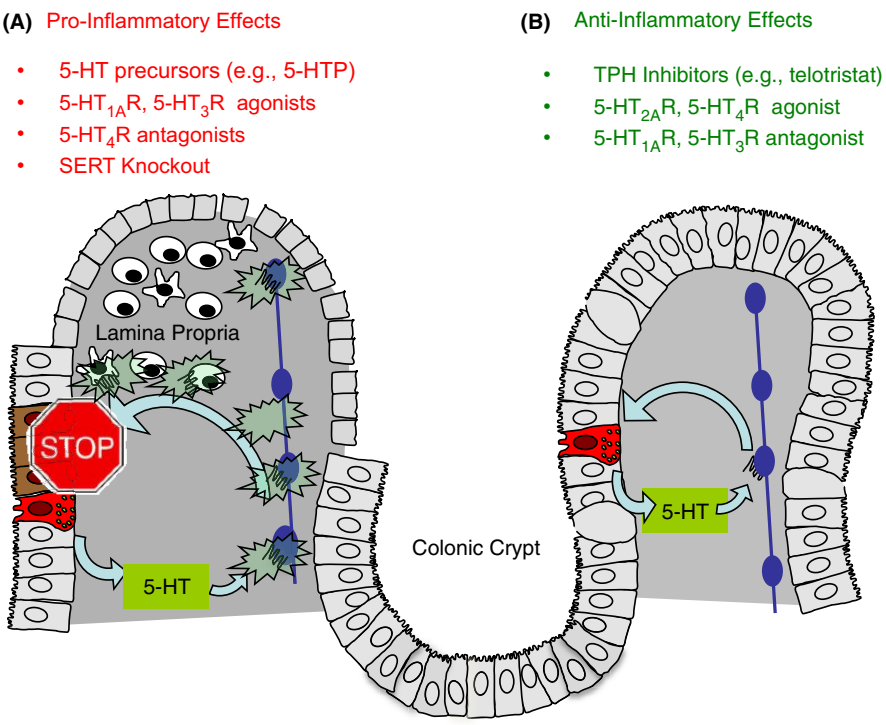

FIGURE 3 Serotonin signaling components impact inflammatory bowel disease activity and symptoms. (A) 5-HT (and its' precursors), 5-HT_3R agonists, 5-HT_4R antagonists and serotonin reuptake inhibitors promote inflammation and problematic symptoms in IBD. (B) Agents that decrease 5-HT production and release, 5-HT_4R agonists, 5-HT_3R antagonists reduce the likelihood of inflammation and symptoms

associated with increased healthcare resource utilisation and lost work hours. These findings closely mirror those found in investigations of IBS, another set of conditions associated with visceral hypersensitivity and altered bowel habits. Studies in both humans and animal models attempting to mimic IBS have demonstrated that increasing 5-HT availability and/or manipulating serotonergic receptor function can either induce or prevent development of visceral hypersensitivity and/or diarrhoea depending on the factors involved.[33,61,101-105] Selective 5-HT receptor manipulation can also have a dramatic effect on visceral sensation and motility in IBS and animal models of IBS, as has been demonstrated with agonists and antagonists of the 5-HT4 receptor.[106,107] Although seemingly quite divergent from many phenotypic perspectives, IBD and IBS share many symptomatic similarities that may well share certain pathophysiological parallels. In fact, this has been hinted at by prior studies looking at 5-HT signalling factors in IBD and IBS populations simultaneously.[33]

There remains a gap in our knowledge regarding the impact of alterations in intestinal serotonergic signalling on symptoms in IBD, particularly in humans (Table 6). There is also a dearth of information regarding the variability in every major element of intestinal 5-HT signalling with regard to intestinal region and disease severity. This is particularly true for CD. In addition, the expression and/or function of most 5-HT receptors have not been systematically evaluated in the context of either UC or CD. More comprehensive, longitudinal investigations utilising tissue samples throughout the intestinal tract during both quiescent and active phases of UC and CD would clarify the role that various serotonergic enzymes, transporters and receptors play in gastrointestinal signalling and in IBD.

In conclusion, the findings outlined in this review demonstrate the powerful influence that the neuroendocrine signalling mediator 5-HT can have on the development and perpetuation of IBD and associated symptoms and suggest new diagnostic and therapeutic opportunities to consider in the management of these disorders. In particular, more selective 5-HT receptor activation (eg, utilising 5-HT_{1A}R or 5-HT_4R agonists) and/or inhibition (eg, with 5-HT_3R anatagonists), using targeted delivery strategies (eg, enemas or other topically applied approaches) to help enhance efficacy and reduce the potential for adverse side effects, may prove very effective as adjunctive therapy in the control of inflammation and symptoms of IBD. In addition, while judiciously selected and monitored serotonergically active antidepressant agents in these patients can help to address the mood disorders frequently associated with IBD and have the potential to mitigate problematic symptoms, these medications need to be evaluated more carefully as there is at least some evidence that they may increase risk for intestinal inflammation. Given the number of patients with IBD who continue to struggle achieving control of their disease and its associated symptoms, and the apparent influence of serotonergic signalling factors in this setting, further studies incorporating objective assessments of intestinal inflammation and 5-HT signalling in these disorders are certainly warranted. In time, it is likely that more serious consideration will need to be made to evaluate and intervene on serotonergic factors within the gut in the setting of IBD.

AUTHORSHIP

Guarantor of the article: Dr. Coates.

Author contributions: Dr Coates developed the idea for this article, performed literature searches, was the primary author and editor. Dr Tekin performed an independent literature review for this article and she helped to write and edit the manuscripts and tables. Dr. Vrana helped to write and edit every component of this submission. Dr. Mawe helped to write and edit each component of this submission. All authors have approved the final version of this submission.

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