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REVIEW

Role of serotonin in the pathophysiology of the irritable bowel syndrome

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The irritable bowel syndrome (IBS) is a complex disorder that is associated with altered gastrointestinal motility, secretion, and sensation. Serotonin (5-HT) is an important neurotransmitter and paracrine signalling molecule in the gastrointestinal tract. 5-HT release from enterochromaffin (EC) cells initiates peristaltic, secretory, vasodilatory, vagal and nociceptive reflexes. The enteric nervous system (ENS) comprises a semiautonomous effector system that is connected to the central autonomic network. Parasympathetic and sympathetic nerves modulate the ENS *via* afferent and efferent communications. Ongoing, bidirectional brain–gut interactions involving 5-HT pathways occur that significantly influence the effector systems. Altered 5-HT signalling may lead to both intestinal and extraintestinal symptoms in IBS. 5-HT directly and indirectly affects intestinal motor and secretory function and abnormalities may lead to either constipation or diarrhea. 5-HT modulates sensation and perception of visceral stimulation at peripheral and central sites. Therapeutic agents targeting altered 5-HT signalling may provide new, effective treatments for patients with IBS.
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Abbreviations: ACh, acetylcholine; ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; C-IBS, constipation-predominant IBS; D-IBS, diarrhea-predominant; EC, enterochromaffin; ENS, enteric nervous system; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NO, nitric oxide; 5-HT, serotonin; SERT|5-HTT, serotonin transporter; SSRIs, selective serotonin reuptake inhibitors; VIP, vasoactive intestinal peptide

Irritable bowel syndrome (IBS)

Chronic or recurrent abdominal pain or discomfort along with altered bowel function characterizes the IBS. Symptom severity can range from mild to severe. The Rome criteria (Thompson *et al*., 1999) for IBS requires the presence of continuous or recurrent abdominal pain or discomfort that is relieved with defecation, or associated with a change in frequency or consistency of stool for at least 3 months in the last year. Although not specifically addressed by the Rome criteria, subgroups of IBS exist and demonstrate varying responses to therapeutic intervention.

The most common subdivision of IBS is based on alterations in bowel habit. IBS is most often classified as constipation-predominant (C-IBS), diarrhea-predominant (D-IBS) and alternating forms. Approximately one-third of patients fit the D-IBS subtype and one-third C-IBS; the remainder tends to report normal or alternating stools without significant urgency, and a primary complaint of abdominal pain or discomfort (Ragnarsson & Bodemar, 1999). Altered bowel function in these subgroups appears to be related to stool consistency, with similar stool frequencies most often being reported. Physiologically, colonic transit and the resulting absorption of water from the colon determine stool consistency. The frequency of defecation, on the other hand, is dependent on a complex of codependent factors that includes rectal filling, rectal sensation, socialization and motivational behaviors (Azpiroz *et al*., 2002). Overall, symptoms appear to be related to alterations in GI motility and/or enhanced visceral sensitivity (Camilleri & Prather, 1992). Symptoms are often associated with exaggerated GI responses to food ingestion and may suggest an excess release of neuroendocrine transmitters peripherally or centrally (Ragnarsson & Bodemar, 1998). Additionally, comorbid psychosocial factors, including depression and anxiety, may also contribute to overall expression of symptoms in these patients.

Although physiological differences between patients with C-IBS and D-IBS have been demonstrated (Prior *et al*., 1990), the pathophysiology remains unclear. Recent studies have implicated alterations in serotonin (5-HT) signalling in gastrointestinal disorders of function, such as the IBS, chronic constipation, diarrhea, and functional dyspepsia. Alterations in enteroendocrine cells have been reported in 'post dysenteric' IBS with recurrent abdominal pain and diarrhea (Spiller *et al*., 2000). Preliminary findings have also been reported in IBS patients with diarrhea not directly related to a previously diagnosed gastroenteritis (Bose *et al*., 2000). These findings suggest that altered enterochromaffin (EC) cells might be one pathophysiologic mechanism contributing to symptoms in D-IBS.

EC cells were reported to be reduced in patients with functional constipation (El-Salhy *et al*., 1999). However, other studies have shown similar EC and 5-HT cell alterations in patients with constipation and diarrhea (Zhao *et al*., 2000;

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Baig *et al*., 2002). Recently, MIWA *et al*. (2001) evaluated colonic mucosal specimens from endoscopic biopsies in healthy volunteers and in IBS patients with constipation and IBS patients with diarrhea as their primary bowel complaint. IBS patients with constipation compared with normal controls and IBS patients with diarrhea were found to have significantly higher mucosal 5-HT concentrations. The observation of elevated vesicular 5-HT concentrations in patients with C-IBS may suggest normal synthesis, but alterations in exocytosis of 5-HT into the submucosal space following a variety of stimuli. Altered EC cells and/or 5-HT signalling can result in gastrointestinal dysmotility, visceral hypersensitivity, and secretomotor abnormalities. Evidence is beginning to link disturbed 5-HT signalling with the pathophysiology of diarrhea and constipation in IBS and with slow-transit constipation, but the exact alterations remain to be elucidated.

Currently, few therapeutic agents are available that effectively treat all symptoms associated with the IBS. Treatment, therefore, is most often based on individual symptom patterns (i.e., constipation or diarrhea) and associated biopsychosocial factors (Drossman & Thompson, 1992). Therapeutic recommendations have included the use of supplemental dietary fiber for constipation; opioids for diarrhea; and, in patients with sustained pain or bloating, low doses of antidepressants such as tricyclic agents and selective serotonin reuptake inhibitors (SSRIs) (Drossman, 1999). Limited efficacy and prominent side effects have restricted these therapeutic approaches for many patients with IBS. Newer agents that modulate 5-HT receptors may provide more specific targeting of altered communications between the central nervous system and the enteric nervous system and reduced side effects associated with previous interventions.

5-HT and brain–gut communication

5-HT is an important neurotransmitter and paracrine signalling molecule in the gut (Gershon, 1999a). Comorbidities involving gastrointestinal and nonintestinal symptoms are commonly present in IBS patients and suggest alterations in gut–brain–gut communications. Bidirectional communication alters visceral perception and motor function through the influences of the sympathetic, parasympathetic, and enteric nervous systems (ENSs). 5-HT signalling plays a major role in the modulation of brain–gut communication and functional gastrointestinal disorders.

5-HT is a major signalling molecule in the central nervous system and has been implicated in a number of diverse physiologic functions, including mood, appetite, sleep, memory and learning, homeostasis, and sexual behaviors. Altered levels of 5-HT are thought to play a role in many CNS disorders including anxiety, depression, obsessive compulsive disorder, phobias, and even severe psychiatric disorders such as schizophrenia. 5-HT modulators, such as SSRIs and more specific 5-HT receptor agonists and antagonists have been successfully used to treat many of these disorders including migraine, nausea, obesity, chronic pain, hypertension, vascular disorders, and sexual dysfunction.

Many intestinal and extraintestinal disorders associated with abnormal 5-HT signalling are also commonly reported as comorbid conditions in patients with functional gastrointestinal disorders, such as the irritable bowel syndrome. Altered autonomic regulation and extraintestinal symptoms suggest a more generalized brain–gut dysfunction. Altered sleep patterns, particularly REM sleep, provides further evidence for CNS dysfunction that may be related to 5-HT (Orr *et al*., 1997). Therapies aimed at CNS symptoms that affect the serotonergic systems, such as antidepressants and anxiolytics, have shown promise in treating the symptoms associated with IBS (Whitehead *et al*., 2002).

Although there are many important neurotransmitters in the CNS and the gut, 5-HT clearly plays a significant role. 5-HT exerts its wide range of effects through actions on numerous receptor subtypes. Investigators have identified and classified seven families of 5-HT receptors (5-HT_1–5-HT_7) that have yielded 15 subtypes of or recognition sites. In the gastrointestinal tract, 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 subtypes have been most studied. Additionally, accumulating evidence suggests a potential role for the 5-HT_7 receptor subtype in gastrointestinal motor function (Prins *et al*., 1999; Tuladhar *et al*., 2003).

Pharmacology mechanism of action and rationale for 5-HT agents

Gastrointestinal motor and sensory functions have been shown to be regulated by neurotransmitters that include substance P, calcitonin gene-related peptide (CGRP), and 5-HT (Kirchgessner *et al*., 1990). The majority of 5-HT is synthesized and stored in EC cells and functional 5-HT receptors are located throughout the human gastrointestinal tract (Gershon, 1999a). These observations suggest that 5-HT plays an important role in regulation of physiological functions within the gastrointestinal tract. Recent investigations have provided strong support that 5-HT and associated receptors are involved in the modulation of gut motility, intestinal secretion, and visceral sensitivity (Hansen, 2003a, b).

Alterations in 5-HT biosynthesis, content, release, or reuptake may contribute to gastrointestinal dysfunction and hypersensitivity found in IBS patients (Hansen, 2003a, b). 5-HT, secreted by EC cells, initiates peristaltic and secretory reflexes by acting on receptors located on the processes of intrinsic and extrinsic primary afferent neurons that project to the lamina propria. Enterocytes, all of which express the serotonin transporter (SERT; 5-HTT), are largely responsible for the termination of the actions of 5-HT by removing it from the interstitial space (Wade *et al*., 1996; Chen *et al*., 1998; Chen *et al*., 2001).

5-HT activates the enteric neural circuitry to initiate peristalsis, and 5-HT is removed from the interstitial space by the highly selective 5-HT transporter, SERT. Altered 5-HT signalling may influence GI function in IBS *via* alteration in SERT. Inflammatory bowel disease (IBD) and disorders of gastrointestinal function, including the IBS, are typically associated with changes in propulsive motility of the colon. We, therefore, tested the hypothesis that 5-HT signalling is altered in IBD and IBS (Moses *et al*., 2002). Human rectal biopsies were evaluated from normal controls, ulcerative colitis, IBS patients with diarrhea, and IBS patients with constipation. Consistent with this hypothesis, SERT-immunoreactivity was significantly less intense in biopsies from the ulcerative colitis and C-IBS specimens compared with normal tissues or D-IBS biopsies. (Camilleri *et al*., 2002) Camilleri and co-workers have also shown that alterations in SERT may

influence symptom presentation and the response to treatment in patients with IBS and diarrhea. They suggested that genetic polymorphisms at the SERT promoter region influenced response to a 5-HT_3 antagonist in D-IBS. These findings may have a significant impact on the evaluation of risk–benefit ratios with newer 5-HT compounds. The specific roles played by altered 5-HT signalling in the pathophysiology of IBS remains to be determined (Gershon, 1999a). However, recent work has demonstrated distinct changes in EC cell numbers, 5-HT content, 5-HT release, and 5-HT uptake in animal and human models of intestinal inflammation that appear to have relevance to the pathophysiology of IBS (Linden *et al*., 2002; 2003; Moses *et al*., 2002). Furthermore, studies of the numbers of EC cells and the mucosal content of 5-HT suggest that 5-HT availability may be altered in IBS.

5-HT and gastrointestinal motility and transit

The ENS controls the neuromuscular function of the gastrointestinal tract. Even though the ENS operates in a semi-autonomous manner, both the parasympathetic and sympathetic nervous systems modulate it. The ENS contains most of the neurotransmitters and recognition sites found in the central nervous system, including 5-HT and its associated receptors. 5-HT receptors are involved in the mediation of reflexes controlling gastrointestinal motility and secretion, and appear to play a role in the perception of GI sensation. 5-HT is secreted from EC cells located in the mucosa of the gut. When secreted, 5-HT can excite afferent nerves with submucosal terminals, thus initiating the peristaltic reflex and modulating intestinal secretion (Gershon, 1999b; Cooke, 2000). In the gastrointestinal tract, 5-HT appears to play an important role in modulating motility and transit (Talley, 1992).

Local mucosal stimulation induces the release of 5-HT from EC cells within mucosal crypts and initiates the peristaltic reflex. 5-HT stimulates the intrinsic, primary, afferent neurons (IPANs) that synapse in the myenteric plexus with ascending and descending interneurons, thus inducing excitation and inhibition locally (Pan & Gershon, 2000). Ascending interneurons activate excitatory motor neurons by releasing substance P and acetylcholine (ACh) onto myocytes resulting in circular muscle contraction. Descending cholinergic neurons stimulate inhibitory motor neurons releasing nitric oxide (NO), vasoactive intestinal peptide (VIP), and adenosine triphosphate (ATP) leading to circular muscle relaxation. The resulting peristaltic reflex is largely responsible for bolus movement from proximal to distal sites within the GI tract (Goyal & Hirano, 1996). Grider *et al*. (1998) evaluated the role of 5-HT receptors in the peristaltic reflex and demonstrated the intricate involvement of CGRP. These investigators proposed that the primary intrinsic afferent involved in this reflex is a CGRP neuron activated by 5-HT acting on 5-HT_4 receptors. In human jejunum, rat colon, and guinea-pig colon, the 5-HT_4 agonist tegaserod stimulated ascending contraction and descending relaxation *in vitro*. The resulting peristaltic reflex was blocked by the CGRP antagonist hCGRP8-37. They concluded that 5-HT was involved in the peristaltic reflex pathway acting at 5-HT_4 receptors.

Coordinated neuromuscular activity associated with the peristaltic reflex facilitates the oro-aboral transit of materials through the GI tract. Coordinated intestinal contractions and transit appear to be modulated by 5-HT acting on specific receptor subtypes. Activation of $5HT_3$ or $5HT_4$ receptors enhances gastrointestinal transit. Additionally, intrinsic afferents, utilizing 5-HT_3 receptors, may be involved in a reflex circuit within the gut that increases motility and intestinal secretions (Bardhan *et al*., 2000; Houghton *et al*., 2000). Antagonism of the $5HT_3$ receptors with ondansetron or alosetron delays colonic transit in healthy controls (Gore *et al*., 1990) and in patients with D-IBS. The predominant transit effect of blocking the 5-HT_3 receptor appears to be on the left colon (Talley *et al*., 1990). The $5HT_3$ receptor antagonist, ondansetron, has been shown to increase stool consistency in both healthy volunteers and IBS patients (Goldberg *et al*., 1996) and to delay colonic transit in patients with D-IBS (Steadman *et al*., 1992). Alosetron, a more potent and specific 5-HT_3 antagonist, has also been shown to delay colonic transit in both healthy volunteers and IBS patients with diarrhea (Houghton *et al*., 2000; Viramontes *et al*., 2000).

Cilansetron is the newest 5-HT_3 receptor antagonist to be studied in randomized, double-blind, placebo-controlled studies. Preliminary data suggest that cilansetron may be efficacious for the treatment of IBS symptoms in nonconstipated men and women (Stacher, 2001). However, empirical data in the published literature are currently lacking. In clinical trials, the most frequently reported side effect with cilansetron has been constipation.

Preclinical studies suggest that $5HT_4$ receptor antagonists should also induce significant slowing of intestinal transit and provide potential therapeutic benefits to D-IBS patients (Bharucha *et al.,* 2000). However, piboserod (SB-207266A), a $5HT_4$ receptor antagonist previously under evaluation for the treatment of diarrhea-predominant IBS failed to demonstrate significant effects in clinical trials (De Ponti & Tonini, 2001). $5HT_4$ receptor agonists, such as tegaserod and prucalopride, accelerate gastrointestinal transit. Prucalopride appears to have little effect on gastric or small bowel transit (Bouras *et al*., 1999; Poen *et al*., 1999). However, tegaserod has been shown to accelerate both gastric emptying and small bowel transit (Degen *et al*., 2001). These data suggest that antagonizing the $5HT_3$ receptor slows intestinal transit and that agonizing the $5HT_4$ receptor accelerates gastrointestinal transit. These observations have led to increased efforts to develop and evaluate the clinical utility of these agents for inhibiting or enhancing gastrointestinal transit and motility.

5-HT agents with promotility effects

Enhancement of contractile force, coordination of intestinal contractions, and augmentation of intestinal secretions can facilitate the movement of bowel contents through the gastrointestinal tract (Wolfe, 1993; Stoner *et al*., 1999). Although their performance in clinical trials have been inconsistent, drugs with prokinetic activity in the GI tract may help to normalize gut neuromuscular function and play an important role in the treatment of functional bowel disorders, such as the IBS (Milo, 1980; Fielding, 1982; Cann *et al*., 1983; Van Outryve *et al*., 1991; Schutze *et al*., 1997; Farup *et al*., 1998). Several 5-HT receptor ligands have either been approved or are in clinical development for the treatment of IBS (Table 1, Spiller, 2002). Some compounds have demonstrated increased specificity for individual 5-HT recep-

Table 1 Drugs acting *via* serotonergic mechanisms: sites of action and potential therapeutic areas (adapted from Spiller (2002))

Class	*Site of action*	*Action*	*Potential therapeutic use*
$5HT_3$ antagonists	Vagal afferents	↓Nausea	5-HT related nausea
Ondansetron	Enteric interneurons	↓Motility	Diarrhea
Granisetron	Secretomotor neurons	↓Sensitivity	Visceral sensitivity
Alosetron	Mesenteric afferents	↑Compliance	Dyspepsia
Cilansetron			
$5HT_4$ agonists	ENS	↑Peristalsis	Constipation
Tegaserod	IPANs	↑Transit	C-IBS
Prucalopride	Enterocytes	↑Secretion	Dyspepsia/gastroparesis
	Mesenteric afferents?	↓Sensitivity	Intestinal dysmotility
Combined $5HT_4$	ENS	↑Peristalsis	Dyspepsia/gastroparesis
Agonist and $5HT_3$	Enterocytes	↑Transit	Intestinal dysmotility
Antagonist	Mesenteric afferents	↑Secretion	C-IBS/constipation?
Cisapride			
Mosapride			
Renzapride			

tors over others. The most studied agents in this group include cisapride, renzapride (BRL 24924), prucalopride (R093877) and tegaserod (HTF-919) (Bouras *et al*., 2001; Camilleri, 2001).

Cisapride

Cisapride is a benzamide derivative that has mixed pharmacologic actions on 5-HT receptors. It both antagonizes the 5-HT_3 receptor and agonizes the 5-HT_4 receptor. Cisapride's prokinetic mechanism of action is thought to result from facilitation of ACh release at the myenteric plexus (Taniyama *et al*., 1991). Cisapride was shown to accelerate gastric emptying and intestinal transit, but to have limited effects on altering bowel function (Edwards *et al*., 1987). Some studies demonstrated efficacy for cisapride in the treatment of chronic constipation (Krevsky *et al*., 1987; Muller-Lissner, 1987). However, the data regarding the clinical efficacy of cisapride in C-IBS patients has been inconsistent (Van Outryye *et al*., 1991; Schutze *et al*., 1997; Farup *et al*., 1998). The availability of cisapride is currently limited commercially due to its association with cardiac dysrhythmias and patient deaths (FDA, 2003).

Renzapride

A new substituted benzamide compound, renzapride, with similarities to cisapride is currently in clinical development. Renzapride also demonstrates both 5-HT_3 and 5-HT_4 receptor activity and has been reported to possess prokinetic activities (Bermudez *et al*., 1990; Gullikson *et al*., 1991; Gullikson *et al*., 1993). Renzapride's promotility actions are thought to be due to its stimulating actions *via* the 5-HT_4 receptor agonist activity and subsequent facilitation of cholinergic neuronal function (Craig & Clark, 1990; Meulemans & Schuurkes, 1992; Ford & Clarke, 1993). The pharmacologic properties of this compound may prove beneficial for the treatment of IBS; however, published clinical data are not available to support this assertion. In an early controlled trial in patients with IBS and constipation, the drug demonstrated acceptable global improvements over placebo for both men and women. In contrast to cisapride, renzapride has not been reported to be associated with cardiac side effects.

Prucalopride

Prucalopride represents a new chemical class of benzofurans. It is a selective agonist at 5-HT_4 receptors and has been shown to enhance colonic motility (Emmanuel *et al*., 1998; Bouras *et al*., 1999). Studies have demonstrated a lack of measurable affinity for muscarinic type 3 (M_3) receptors, 5-HT_{2A} and 5-HT_3 receptors, and cholinesterases. The relatively long half-life, rapid C_{max}, and rapid plasma uptake provides an excellent pharmacokinetic profile (Bouras *et al*., 2001). Prucalopride has been shown to enhance GI transit in patients with functional constipation compared to placebo (Coremans *et al*., 2003). No published data are available regarding the efficacy of prucalopride in patients with IBS, but IBS patients have been included in clinical studies. The current state of development of this compound is unclear following early concerns over carcinogenicity in animal studies, and possible cardiac effects (Kamm, 2002).

Tegaserod

Tegaserod, an aminoguanidine indole, represents another new class of compounds with demonstrated prokinetic effects in the GI tract. It is a 5-HT_4 receptor partial agonist, which may convey certain benefits over full agonism of these receptors. Preclinical data suggest that in addition to its promotility properties, it may also augment intestinal secretion and effect neuronal pathways carrying sensory signals from the gut (Appel *et al*., 1997; Fioramonti *et al*., 2000; Huge *et al*., 2000; Prather *et al*., 2000; Schikowski *et al*., 2002). The clinical efficacy of tegaserod has been demonstrated in randomized clinical trials (Muller-Lissner *et al*., 2001). Replicated trials have demonstrated acceptable clinical efficacy for tegaserod in treating women with irritable bowel syndrome with predominant constipation.

Four controlled clinical trials have evaluated the efficacy of tegaserod in IBS patients with constipation. A therapeutic gain over placebo ranging between 5 and 19% was demonstrated for the primary efficacy variable, the Subject's Global Assessment of relief (Chey, 2003). The latest published clinical trial evaluated 881 patients with IBS using twice daily dosing of 2 or 6 mg compared to placebo. Both the 2 and 6 mg b.i.d. doses were statistically better than placebo in improving the patient's reports of overall symptom relief. Patients receiving

tegaserod also reported increased bowel frequency and improved consistency (Muller-Lissner *et al*., 2001; Muller-Lissner *et al*., 2003). Tegaserod is the only 5-HT_4 receptor agonist that is currently approved for the treatment of female IBS patients with constipation in the U.S.

5-HT in gastrointestinal sensation

A subset of patients with IBS have heightened visceral sensitivity or enhanced perception of gut distention (Ritchie, 1973). Whitehead *et al*. (1980) demonstrated that IBS patients had significantly lower pain thresholds than controls using rectosigmoid balloon distention. However, few empirical studies have compared colonic and rectal sensory thresholds between IBS patients with primary bowel complaints of constipation to those with primary complaints of diarrhea. Hypersensitivity to colorectal distention has generally been reported in IBS-D compared to healthy controls (Prior *et al*., 1990; Bradette *et al*., 1994; Simrén *et al*., 2001), but conflicting data have been reported for IBS-C patients (Slater *et al*., 1997; Harraf *et al*., 1998). A recent study by Steens *et al*. (2002) compared sensory thresholds in subgroups of IBS patients and found that IBS-D patients had a lower sensory threshold for rectal urgency. However, even though both IBS groups demonstrated hypersensitivity compared to controls, no significant difference was noted in pain threshold between IBS-D and IBS-C patients.

Cook *et al*. (1987) evaluated somatic pain thresholds in IBS patients and controls using electrical stimulation. These investigators found that IBS patients were less sensitive to low-intensity nonpainful stimuli and had higher thresholds for painful somatic stimuli than controls. These findings suggest that IBS patients experience visceral-specific hypersensitivity with essentially normal or increased tolerance thresholds to acute somatic pain.

Intraluminal distention or irritation releases 5-HT from EC cells within the mucosal crypts. 5-HT stimulates 5-HT_3 and 5-HT_4 receptors located on primary afferent neurons of both splanchnic and vagal fibers, thereby modulating both sensory and motor responses. Nociceptive signals are transmitted from the viscera to specific laminae of the dorsal horn. Synaptic input activates specific subsets of second-order projection neurons leading to activation of specific brain stem and thalamic regions, the sensation and perception of pain, and subsequently evaluative and discriminative processes in higher brain centers. Bulbospinal pathways activated by nociception send descending projections from the periaquaductal gray and raphe nuclei to neurons in the dorsal horn, resulting in inhibition or facilitation of nociceptive inputs. The descending bulbospinal fibers utilize serotonergic, noradrenergic, and opiate transmitters (Crowell, 2001).

The immediate early gene *c-fos* is expressed in discrete areas within dorsal horn neurons following visceral stimulation and has been used to index neuronal activation secondary to visceral nociception. Several studies have shown that 5-HT_3 receptor antagonists modify visceral sensation in animal and human models. However, the specific mechanisms involved in these responses have remained unclear. Kozlowski *et al*. (2000) demonstrated that the 5-HT_3 receptor antagonist, alosetron, inhibits the depressor response and Fos-like immunoreactivity in the spinal cord following noxious colorectal distention.

5-HT_4 receptors may modulate pain from the viscera at the level of transmission, transduction within the spinal neurons or possibly through activation of inhibitory bulbospinal descending pathways acting on presynaptic dorsal horn neurons. Recent work by Schikowski *et al*. (2002) suggested that the 5-HT_4 receptor partial agonist, tegaserod, directly inhibited mechanosensitive afferents in response to rectal balloon distention in an animal model. The mechanism by which 5-HT_4 receptors, or 5-HT_4 receptor agonists specifically, might modulate pain transmission is not currently known. 5-HT_4 receptors are G protein-coupled receptors that are positively coupled to Gs and promote cyclic AMP formation in nerves and muscle. Thus, activation of 5-HT4 receptors by pharmacological agonists would be expected to augment afferent excitability rather than inhibit it (Grundy, 2002). It has been proposed that tegaserod might reduce afferent transmission from the periphery by competitively antagonizing endogenous 5-HT at peripheral 5-HT_4 receptors. Mucosal stimulation from balloon distention could stimulate the release of 5-HT from EC cells and activate afferent pathways. Tegaserod, a highly selective partial agonist, might be expected to compete with endogenous 5-HT to functionally antagonize these 5-HT4 receptors, thus reducing afferent transmission (Grundy, 2002). Clearly, additional work is needed to clarify the role of 5-HT_4 receptors in the modulation of pain pathways.

5-HT signalling and antinociception

5-HT_3 receptor antagonists

5-HT_3 receptors are located on postsynaptic neurons of afferent pathways of the parasympathetic nervous system (Gershon, 1999a). 5-HT_3 receptors are unique within the 5-HT receptor family in that it is not a G-protein receptor. Activation of the 5-HT_3 receptor leads to the opening of a nonspecific cation channel, which allows an influx of Na^+ and Ca^{2+} and an efflux of K^+ ions (Hargreaves *et al*., 1994). These ligand-gated cation channels result in depolarization of the postsynaptic neuron and propagation of signals proximally. Antagonists at the 5-HT_3 receptor block the transmission of the afferent signal. Granisetron, one of the earlier 5HT_3 antagonists, has been shown to reduce rectal sensitivity and postprandial motility in IBS patients (Prior & Read, 1993). Alosetron also increased the threshold for discomfort during balloon distension, but was also associated with an increase in compliance, an effect which may well contribute to a reduction in abdominal pain (Delvaux *et al*., 1998).

Odansetron and Granisetron, both 5-HT_3 antagonists, are indicated for use in patients with chemotherapy-induced nausea and vomiting. Both agents block the binding of 5-HT at the 5-HT_3 receptors, located on the vagal sensory nerve terminals, thus blocking 5-HT signalling at the level of the gut. The resulting reduction in afferent signalling is responsible for the clinical effects on nausea and vomiting in these patients (Hargreaves *et al*., 1994). These observations led to the hypothesis that antagonism of the 5-HT_3 receptor might reduce visceral hypersensitivity and exaggerated postprandial motility in IBS patients (Moss and Sanger, 1990; Prior and Read, 1993; Goldberg *et al*., 1996).

Alosetron is the only 5-HT_3 antagonist that has been approved for the treatment of irritable bowel syndrome in women, whose predominant bowel symptom was diarrhea. Alosetron in addition to its blockade of afferent neuronal

signals slows small bowel and colonic transit (Viramontes *et al*., 2001). Efficacy and tolerability of alosetron has been addressed in multiple trials to date (Camilleri *et al*., 2001; Lembo *et al*., 2001). Constipation, sometimes severe, has been the most common side effect reported in these studies. Severe constipation and several reports of ischemic colitis led to the withdrawal of alosetron from the U.S. market in 2000. However, alosetron was reintroduced to the market in 2002 under a restricted-use program. Cilansetron, a new 5-HT_3 antagonist, has demonstrated clinical efficacy with a more favorable side effect profile in IBS patients with diarrhea and is currently under review in clinical development.

5-HT_4 receptor agonists

Schikowski *et al*. (2002) have recently shown that tegaserod (a 5-HT_4 receptor partial agonist) induced a dose-dependent reduction in the firing rate of mechanosensitive spinal neurons during noxious colorectal distention in the cat. This observation suggested that tegaserod might decrease visceral pain in IBS patients. However, supporting data in humans are currently limited. To date, only one human study on the effects of tegaserod on visceral pain thresholds has been published. Coffin *et al*. (2003) evaluated the effect of tegaserod on rectal sensitivity by evaluating the RIII nociceptive reflex, an electrophysiological index of pain. Normally, the RIII reflex is inhibited by painful stimuli. A total of 20 healthy women were studied at baseline and following 7 days treatment with tegaserod 6 mg b.i.d or placebo. Slow ramp distensions up to the pain threshold reportedly induced inhibition of the RIII reflex that was subsequently reduced by tegaserod, but not placebo. Phasic distensions were not significantly modified by tegaserod or placebo and no significant effect was noted on subject's pain report. The authors concluded that tegaserod reduces sensitivity to rectal distension. However, several weaknesses limit the interpretability of these findings, including the use of healthy volunteers, effect on pain threshold to slow ramp distention, and no effect on pain reports. Tegaserod only influenced responses during slow ramp distention, whereas most published reports have shown hypersensitivity in IBS patients to phasic distention, but no differences between controls and IBS patients during slow ramp distention (Rey *et al*., 2002). Further studies will be required to confirm a role of 5-HT_4 receptor agonists on visceral pain.

5-HT in gastrointestinal secretion and absorption

Gastrointestinal secretions can be modulated both directly *via* $5HT_4$ receptors on enterocytes and indirectly *via* $5HT_3$ receptors on secretory mucosal nerves and vagal afferents (Cooke, 2000). Locally released substances found in nervous and specialized intestinal EC cells are responsible, in part, for reflex secretion of fluid into the lumen. Vagal afferent impulses mediated by 5-HT, vasoactive intestinal peptide (VIP), and substance *P* appear to be the major agents involved in secretory stimulation (Wapnir & Teichberg, 2002). This reflex response can be blocked by sectioning the vagal afferents or by antagonizing $5HT_3$ receptors. In addition to their involvement in secretory reflexes, the $5HT_3$ receptors also appear to enhance basal absorption. $5HT_3$ receptors acting on mucosal secretory nerves have been suggested to play an important role in the tonic stimulation of intestinal secretion by 5HT (Budhoo *et al*., 1996; Bearcroft *et al*., 1997). The role of $5HT_4$ receptors in secretion is less well described, but both stimulatory and inhibitory actions have been reported (Borman & Burleigh, 1993).

Spiller (2001) suggested that cholera toxin may provide a model for the actions evaluation of 5HT on submucosal and myenteric plexus neurons to stimulate secretion and the role of 5-HT in secretory disorders. Cholera toxin induces secretion by direct effects on the enterocyte and indirectly by releasing 5HT from the enteroendocrine cell (Turvill *et al*., 2000). Secretion mediated by 5-HT involves both stimulation of release of secretagogues such as VIP (Cooke *et al*., 1997; Mourad & Nassar, 2000), NO (Stoner *et al*., 2000) and prostaglandin release from macrophages. $5HT_3$ antagonists such as ondansetron and granisetron (Turvill *et al*., 2000) as well as prostaglandin antagonists and $5HT_2$ antagonists inhibit cholera toxin-induced secretion (Beubler *et al*., 1989).

Summary and conclusions

In summary, the intrinsic neural plexuses of the gut comprise a semiautonomous neural network known as the ENS. The ENS is connected to the central autonomic neural network in the brain by parasympathetic and sympathetic nerves that modulate the ENS *via* afferent and efferent activity. Ongoing, bidirectional brain–gut interactions involving 5-HT pathways occur that significantly influence the effector systems. Altered 5-HT signalling may lead to both intestinal and extraintestinal symptoms in IBS. 5-HT directly and indirectly affects intestinal motor and secretory function and abnormalities may lead to either constipation or diarrhea. Furthermore, 5-HT modulates sensation and perception of visceral stimulation at peripheral and central sites. Therapeutic agents targeting altered 5-HT signalling may provide new, effective treatments for patients with the IBS.

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