Naunyn-Schmiedeberg's Arch Pharmacol (2008) 377:181–203
DOI 10.1007/s00210-008-0276-9

REVIEW

Serotonin pharmacology in the gastrointestinal tract: a review

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Received: 8 October 2007 / Accepted: 15 February 2008 / Published online: 9 April 2008

Abstract Serotonin (5-hydroxytryptamine or 5-HT) plays a critical physiological role in the regulation of gastrointestinal (GI) function. 5-HT dysfunction may also be involved in the pathophysiology of a number of functional GI disorders, such as chronic constipation, irritable bowel syndrome and functional dyspepsia. This article describes the role of 5-HT in the enteric nervous system (ENS) of the mammalian GI tract and the receptors with which it interacts. Existing serotonergic therapies that have proven effective in the treatment of GI functional disorders and the potential of drugs currently in development are also highlighted. Advances in our understanding of the physiological and pathophysiological roles of 5-HT in the ENS and the identification of selective receptor ligands bodes well for the future development of more efficacious therapies for patients with functional GI disorders.

Keywords 5-HT · Gastrointestinal · Enteric nervous system

Introduction

The gastrointestinal (GI) tract is unique among organ systems in that, although under the influence of the central nervous system (CNS), it can function in isolation. A complex and highly organized enteric nervous system (ENS) regulates and coordinates GI absorption, secretion, motility, and sensation (Gershon and Tack 2007). The ENS consists of submucosal and myenteric ganglia and an intricate network of intrinsic and extrinsic afferent neurons, interneurons, and motor neurons, which interact with longitudinal and circular smooth muscle and mucosal endocrine cells. Submucosal intrinsic primary afferent neurons (IPANs), which innervate the secretory epithelium, are critical in the initiation of both secretory and peristaltic reflexes, while myenteric IPANs may participate in the regulation of peristalsis through the initiation of giant migrating contractions. Myenteric motor neurons innervate smooth muscle via the interstitial cells of Cajal and regulate mechanical activity (Gershon 2004; Gershon and Tack 2007). Ascending and descending interneurons play an important role in the activation of excitatory and inhibitory motor neurons, respectively. Considering the complexity inherent in regulating GI function and its physiological importance, it is not surprising that malfunctions occur and that when they do, the quality of life of affected individuals is impacted significantly. It is estimated that digestive diseases, as a whole, affect 60–70 million people in the USA with direct and indirect costs totaling approximately $107 billion (Gershon and Tack 2007). In many cases, no organic etiology can be identified to explain the clinical problem, and a functional disorder is diagnosed. A diverse assortment of functional GI disorders, defined most recently by the Rome III committee, has been identified (Drossman 2006). Of those disorders in which serotonergic dysfunction and/or therapy is indicated, albeit with different levels of validation, the most common are chronic constipation, irritable bowel syndrome (IBS), gastroparesis, functional dyspepsia, and functional heartburn.

In the USA, 10–20% of adults have symptoms consistent with IBS, and the disorder accounts for 2.5–3.5 million physician visits per year and 20–40% of all visits to the gastroenterologist. The burden of IBS in the USA was estimated to be approximately $20 billion in direct and

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indirect costs in 2000 (American Gastroenterological Association 2002). IBS is defined as a "functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, with features of disordered defecation" (Longstreth et al. 2006). It is generally acknowledged that three categories of IBS exist: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or IBS with a mixed stool pattern (IBS-M). Chronic constipation, which affects up to 27% of the population, depending on demographics and definition, presents as persistently difficult, infrequent, or seemingly incomplete defecation, which does not meet the IBS criteria (Longstreth et al. 2006). Gastroparesis is a chronic disorder characterized by delayed gastric emptying, which results in early satiety, nausea and vomiting, bloating, and upper abdominal discomfort (Parkman et al. 2004). Functional dyspepsia, consisting of chronic or recurrent epigastric pain or burning with postprandial fullness and early satiation, is extremely common, affecting 20–30% of the general population each year (Tack et al. 2006c). In contrast to IBS, the pain or discomfort of functional dyspepsia is not relieved by defecation, nor is it associated with a change in defecation frequency or stool consistency (Saad and Chey 2006). Functional heartburn consists of retrosternal burning in the absence of gastroesophageal reflux disease (GERD; Galmiche et al. 2006).

Of all the endogenous factors influencing GI function, both physiologically and pathophysiologically, serotonin (5-hydroxytryptamine or 5-HT) is particularly important. This article discusses the role of 5-HT in the mammalian GI tract and the receptors with which it interacts. In addition, existing and potential future serotonergic therapies for the treatment of GI functional disorders are highlighted. Emphasis is placed on human pharmacological data, where available, and some of the many preclinical animal studies that have been performed. While it is evident that 5-HT activity within the CNS can influence GI function (e.g., gastric tone, intestinal motility, and visceral sensitivity) via an interaction with multiple receptor subtypes (Croci et al. 1995; Sivarao et al. 2004), the focus of this review is serotonin receptor pharmacology within the GI tract.

The physiological and pathophysiological roles of 5-HT in the GI tract

The coordinated movement of food along the GI tract is dependent on 5-HT-mediated regulation of smooth muscle tone, peristalsis, mucosal secretion, and visceral perception (Baker 2005; Hansen and Skadhauge 1997; Jin et al. 1999) via an interaction with intrinsic enteric and extrinsic afferent neurons, the interstitial cells of Cajal, smooth muscle cells, and enterocytes (Gershon and Tack 2007; Read and Gwee 1994; Wouters et al. 2007a,b). Enterochromaffin cells, located primarily at the base of the epithelial crypts in the GI tract, contain more than 90% of the total 5-HT within the human body and contain the enzymes required for its synthesis, including the rate-limiting enzyme, tryptophan hydroxylase 1 (TPH1), which catalyzes the conversion of dietary tryptophan to 5-hydroxytryptophan. In response to mechanical stimulation, as provided, for example by a bolus of food, 5-HT is released from the enterochromaffin cells into the lamina propria (Gershon 2004). The released 5-HT stimulates IPANs containing calcitonin gene-related peptide (CGRP) in the mucosa, which synapse with ascending and descending interneurons and, in turn, with motor neurons (Gershon and Tack 2007; Pan and Gershon 2000). Ascending interneurons activate excitatory motor neurons, which release acetylcholine, substance P, and neurokinin A causing contraction of circular smooth muscle, while descending interneurons stimulate inhibitory motor neurons, which release nitric oxide (NO), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide (PACAP), producing circular smooth muscle relaxation. Longitudinal smooth muscle contracts and relaxes in reverse fashion to circular muscle, under regulation by excitatory neurotransmitters such as VIP, PACAP, and NO (Grider 2003a). This coordinated neuromuscular activity or peristaltic reflex promotes the oral–aboral transit of food along the GI tract (Grider 2003b; Grider and Makhlouf 1990; Pan and Gershon 2000). It is now appreciated that the interstitial cells of Cajal, which regulate smooth muscle rhythmic electrical activity and participate in neuromuscular transmission, are influenced by 5-HT (Wouters et al. 2007a,b). Activation of submucosal IPANs initiates mucosal secretion and peristalsis, while those in the myenteric plexus are thought to be responsible for giant migrating complexes. Extrinsic afferent neurons, which are activated directly by 5-HT following its release from enterochromaffin cells and indirectly via the IPANs, transmit sensation from the GI tract to the CNS. Enteric serotonergic neurons represent only a small proportion of the total number of neurons in the ENS. For example, in the myenteric plexus, 5-HT-containing neurons constitute only 1% of neurons (Costa et al. 1996). 5-HT is, however, an important enteric neurotransmitter in the GI tract. Neuronally released 5-HT mediates fast synaptic transmission in some IPANs (Galligan et al. 2000). 5-HT contained in interneurons and motor neurons participates in a variety of reflex pathways, such as the descending pathways in the myenteric plexus (Galligan 2002; Young and Furness 1995).

Data from many studies indicate that 5-HT is likely to play an important role in the pathophysiology of functional disorders and their symptomatology. Thus, in carcinoid syndrome, a disease resulting from tumors of the enterochromaffin cells, there is excessive release of 5-HT, which

contributes to the severe diarrhea and abdominal discomfort associated with the disease (Carling et al. 2002; Von Der Ohe et al. 1993). Furthermore, elevations in either fasting or postprandial plasma 5-HT concentrations have been noted in patients with IBS-D and in functional dyspepsia (Atkinson et al. 2006; Houghton et al. 2003; Lea et al. 2002). In IBS-C patients, there are reductions in the plasma concentrations of 5-HT and 5-hydroxyindole acetic acid (5-HIAA), its primary metabolite (Atkinson et al. 2006; Dunlop et al. 2005). Moreover, mucosal 5-HT and TPH1 messenger ribonucleic acid (mRNA) or immunoreactivity is reduced in rectal biopsy samples from patients with IBS-C and IBS-D compared to healthy subjects (Coates et al. 2004). In contrast, an increase in 5-HT-containing enterochromaffin cells has been observed in patients with post-infectious IBS (Dunlop et al. 2005). Caution is, however, warranted as some studies have failed to demonstrate significant differences in 5-HT levels between healthy subjects and IBS patients (Mawe et al. 2006). The impact of acute depletion of tryptophan, the dietary source of 5-HT, on GI function of IBS patients and healthy subjects is unclear. In one study, tryptophan depletion was associated with fewer GI symptoms in IBS patients compared to acute tryptophan increase, while in control subjects neither manipulation had any effect (Shufflebotham et al. 2006). However, in another study, visceral perception was increased by tryptophan depletion in patients with IBS-D and healthy control subjects alike (Kilkens et al. 2004). Overall, these data support the hypothesis that 5-HT dysfunction may be involved in the pathophysiology of functional GI disorders, such as IBS. The contributions made by 5-HT receptors and by the serotonin transporter (SERT), in the physiological and pathophysiological actions of 5-HT, will now be addressed.

5-HT and its receptors

5-HT was discovered in the 1930s and named "enteramine" as it was first extracted from the intestine (Erspamer and Vialli 1937). Since its discovery, it has become clear that 5-HT serves many diverse physiological functions, such as the regulation of sleep, appetite, mood, neuroendocrine secretion, sexual behavior, cognition, and GI function via an interaction with multiple 5-HT receptors (Barnes and Sharp 1999; Hoyer et al. 2002). To date, 14 5-HT receptors, belonging to seven families (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7), have been identified (Hoyer et al. 1994; 2002; Table 1). With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel, each of the 5-HT receptors identified is a seven-transmembrane domain, G-protein-coupled receptor (Hoyer et al. 1994; Hartig et al. 1996). The 5-HT_1 and 5-HT_5 receptor families are negatively and the 5-HT_4, 5-HT_6, and 5-HT_7 receptors are positively coupled to adenylyl cyclase. Binding of 5-HT to the Gq-coupled 5-HT_2 receptor activates phospholipase C resulting in the release of inositol triphosphate and an elevation of cytosolic calcium. Selective agonists and antagonists for the majority of the receptor families and their subtypes are now available as pharmacological tools. The use of these ligands and data generated by molecular biology studies have provided a clearer understanding of the roles of each 5-HT receptor in GI function (Table 1). As a result of its diverse physiological and pathophysiological functions and the multiplicity of its receptor subtypes, the serotonergic system has served the pharmaceutical industry well in the search for novel therapies for a variety of human disorders (Jones and Blackburn 2002). Thus, 5-HT_1 receptor agonists, 5-HT_3 receptor antagonists, and selective serotonin reuptake inhibitors (SSRIs) are effective therapies for migraine, cancer chemotherapy-induced emesis, and major depressive disorder, respectively. With regard to GI disorders, various 5-HT receptor ligands have been evaluated clinically to treat conditions such as IBS-D, IBS-C, chronic constipation, functional dyspepsia, and gastroparesis (Table 2). In the USA, however, there are currently only four serotonergic agents approved for the treatment of functional GI disorders (i.e., the 5-HT_3 receptor antagonist, alosetron [Lotronex®], the 5-HT_4 receptor agonist, tegaserod [Zelnorm®], and the dual 5-HT_4 receptor agonist and 5-HT_3 receptor antagonists, metoclopramide [Reglan®] and cisapride [Propulsid®]). Each has significant safety concerns that limit their general utility (see below).

5-HT receptors in the GI tract

5-HT_1 receptor family

The 5-HT_1 receptor family consists of the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} subtypes (Hoyer et al. 2002). Data from receptor distribution studies and preclinical or clinical pharmacodynamic investigations with 5-HT_1 receptor-selective ligands such as sumatriptan, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH DPAT), buspirone, and flesinoxan suggest that several of the 5-HT_1 receptor subtypes have physiological and pathophysiological roles in the GI tract. Radioligand binding and mRNA expression studies in the rat have provided evidence that 5-HT_{1A} receptors are expressed on submucosal and myenteric neurons throughout the GI tract, with a particularly high density in the stomach (Kirchgessner et al. 1993). Submucosal 5-HT_{1A}-immunoreactive cells are principally interneurons within the submucosal plexus while myenteric 5-HT_{1A}-immunoreactive neurons project to submucosal ganglia (Kirchgessner et al. 1996). A subset of 5-HT-

Table 1 Summary of 5-HT receptor characteristics in the GI tract

Receptor type	Receptor subtype	Signal transduction mechanism(s)	Primary localization	Functional role	Subtype selective ligands[a]
5-HT_1	5-HT_{1A}	Gi/o	Intrinsic sensory neurons, interneurons, excitatory motor neurons, enterocytes	Relaxation, modulation of visceral sensitivity	Agonists: 8-OH DPAT, BP554 Antagonists: (S)WAY100135, NAN-190
	5-HT_{1B}	Gi/o	Intrinsic and extrinsic sensory neurons, smooth muscle cells	Contraction/relaxation	Agonists: L694247, CP94253 Antagonists: SB236057, SB224289
	5-HT_{1D}	Gi/o	Intrinsic and extrinsic sensory neurons, smooth muscle cells	Contraction/relaxation	Agonists:PNU10929, L694247 Antagonists: BRL15572
	5-HT_{1E}	Gi/o	Not present	Not applicable	Agonists: none Antagonists: none
	5-HT_{1F}	Gi/o	Cellular localization not described	Relaxation	Agonists: LY334370, LY334864 Antagonists: none
5-HT_2	5-HT_{2A}	Gq/11	Enteric neurons, enterocytes, smooth muscle cells	Contraction/relaxation	Agonists: TCB-2 Antagonists: R-96544, MDL100907
	5-HT_{2B}	Gq/11	Enteric neurons, smooth muscle cells	Contraction	Agonists: BW723C86 Antagonists: RS127445
	5-HT_{2C}	Gq/11	Not present	Not applicable	Agonists: Ro600175, WAY629 Antagonists: SB242084, RS102221
5-HT_3	$5\text{-HT}_{3A/B}$	Cation channel (Na^+, Ca^{2+}, K^+)	Intrinsic and extrinsic sensory neurons, interstitial cells of Cajal, secretomotor neurons, enterocytes	Modulation of visceral sensitivity and motility, secretion	Agonists: SR57227 Antagonists: ondansetron, granisteron, alosetron
5-HT_4	Ten 5-HT_4 splice variants	Gs; increase $[Ca^{2+}]i$ ($5\text{-HT}_{4(a)}$); Gi/o ($5\text{-HT}_{4(b)}$)	Intrinsic sensory neurons, interneurons, interstitial cells of Cajal, excitatory and inhibitory motor neurons, smooth muscle cells, enterocytes	Contraction/relaxation, stimulation of motility, secretion	Agonists: ML10302, TD-5108 Antagonists: GR113808, piboserod
5-HT5	5-HT_{5A}	Gi/o	Not present	Not applicable	Agonists: none Antagonists: none
	5-HT_{5B}	None identified	Not present	Not applicable	Agonists: none Antagonists: none
5-HT_6		Gs	Limited expression mRNA in stomach, cellular localization not described	No definitive role	Agonists: EMD386088 Antagonists: SB271046, SB357134
5-HT_7		Gs	Intrinsic sensory neurons, inhibitory motor neurons, smooth muscle cells	Relaxation, modulation of visceral sensitivity	Agonists: LP44, AS19 Antagonists: SB656104, SB269970

[a] From Alexander et al. 2004, Tocris Bioscience catalog, or this review

Table 2 Selected serotonergic agents in development for the treatment of GI disorders (source: Thompson Pharma, company websites and FDA.gov)

Drug name	Company	Target mechanism(s)	Status[a]	Indication
R-137696	Johnson & Johnson	5-HT_{1A} agonist	Phase 1	Dyspepsia
TZB-30878	Aska-Pharma	5-HT_{1A} agonist, 5-HT_3 antagonist	Preclinical	IBS-D
M0007	Movetis	5-HT_{1A} antagonist	Preclinical	GERD, dyspepsia
Espindolol	AGI Therapeutics	5-$HT_{1A/B}$ antagonist, β-antagonist	Phase 2	Functional dyspepsia, IBS
R-1 (IBS)	Asterand	5-HT_{2B} antagonist	Preclinical	IBS
M0005, M0006	Movetis	5-HT_3 agonist	Preclinical	GERD, dyspepsia
Pumosetrag (DDP-733)	Dynogen Pharm.	5-HT_3 partial agonist	Phase 2 (Canada)	IBS-C, nocturnal GERD
Alosetron (Lotronex®)	GSK	5-HT_3 antagonist	Launched	IBS-D
Ramosetron	Astellas	5-HT_3 antagonist	Pre-registration (Japan)	IBS
Cilansetron	Solvay	5-HT_3 antagonist	Pre-registration (Europe)	IBS-D
DDP-225	Dynogen Pharm.	5-HT_3 antagonist; NET inhibitor	Phase 2	IBS-D
Prucalopride	Movetis	5-HT_4 agonist	Phase 3 (Europe)	Chronic constipation
TD-5108	Theravance	5-HT_4 agonist	Phase 2	Chronic constipation
ATI-7505	Procter & Gamble	5-HT_4 agonist	Phase 2	Gastroparesis, GERD
M0003, M0004	Movetis	5-HT_4 agonist	Phase 1 (preclinical)	Gastroparesis, gastric regurgitation
Mosapride (Gasmotin®)	Takeda Pharm.	5-HT_4 partial agonist	Launched (Japan)	Chronic gastritis GI symptoms
Tegaserod (Zelnorm®)	Novartis	5-HT_4 partial agonist	Restricted use	IBS-C, chronic constipation
Cisapride (Propulsid®)	Johnson & Johnson	5-HT_4 agonist, 5-HT_3 antagonist	Restricted use	Nocturnal GERD
Renzapride	Alizyme	5-HT_4 agonist, 5-HT_3 antagonist	Phase 3	IBS-C, IBS-M
Metoclopramide (Reglan®)	Schwarz Pharma	5-HT_4 agonist, 5-HT_3 and D_2 antagonist	Launched	Diabetic gastroparesis, GERD
M0008	Movetis	5-HT_4 antagonist	Preclinical	GERD, dyspepsia
Venlafaxine (Effexor®)	Wyeth	Dual SERT, NET inhibitor	Phase 4	Functional dyspepsia
Duloxetine (Cymbalta®)	Lilly	Dual SERT, NET inhibitor	Phase 4	IBS
LX-1031	Lexicon Pharm.	5-HT release inhibitor (TPH1 inhibitor)	Phase 1	IBS
Tianeptine	Pharmos	5-HT uptake stimulator, opioid agonist	Preclinical	Dyspepsia, IBS

[a] Most advanced phase in the USA, unless otherwise indicated

containing enterochromaffin cells also express 5-HT_{1A} immunoreactivity (Kirchgessner et al. 1996). 5-HT_{1A} receptor activation produces presynaptic inhibition of fast and slow excitatory neurotransmission in the ENS and hyperpolarization of myenteric IPANs resulting in a reduction in the amplitude of excitatory postsynaptic potentials (Galligan 1996; Pan and Galligan 1994). Many preclinical studies using isolated GI smooth muscle preparations have demonstrated 5-HT_{1A} receptor-mediated activity. Thus, 5-HT_{1A} receptor activation is associated with inhibition of electrically evoked contractions of guinea pig ileum and stomach circular smooth muscle (Buchheit and Buhl 1994; Mir et al. 1988), and relaxation of the dog proximal stomach and mouse fundus (Janssen et al. 2003; Xue et al. 2006). The 5-HT_{1A} receptor may also have a role in visceral sensitivity; in rats, buspirone attenuates colorectal distension-mediated abdominal withdrawal and changes in blood pressure, although its site of action is unclear (Sivarao et al. 2004). Data on the pharmacological effects of 5-HT_{1A} receptor activation in humans are rather limited. Relaxation of the human gastric fundus has been observed following application of R137696, a selective 5-HT_{1A} receptor agonist (Boeckxstaens et al. 2006). In addition, modest antiemetic activity of buspirone has been reported clinically in cancer patients (Alfieri and Cubeddu 1995), although it remains unclear whether a CNS or peripheral site of action is involved. In healthy human subjects, buspirone fails to affect sensorimotor functions, nor does it influence gastric emptying, colonic compliance, or tone, although it reduces postprandial aggregate symptom and nausea scores (Chial et al. 2003a,b). Clinical utility of 5-HT_{1A} receptor agonists in patients with functional dyspepsia remains a possibility, although this requires further investigation (Talley 2003a). The selective 5-HT_{1A} receptor agonist, R137696, developed by Janssen, had no significant efficacy in patients with functional dyspepsia (Tack et al. 2004). It has been speculated that this was a consequence of receptor desensitization, and other companies continue to pursue the development of 5-HT_{1A} receptor agonists or partial agonists for indications such as functional dyspepsia and GERD. TZB-30878 (Aska Pharmaceutical) possesses 5-HT_{1A} receptor agonist activity and 5-HT_3 receptor antagonist activity and, on the basis of preclinical rodent data, may have potential in the treatment of IBS-D, at least in part via an action within the CNS (Tamaoki et al. 2007).

Although the human 5-HT_{1B} and 5-HT_{1D} receptors were cloned and characterized in the early 1990s (Hamblin et al. 1992; Jin et al. 1992; Weinshank et al. 1992), a detailed

analysis of their expression in the GI tract is lacking. Expression of 5-HT_{1B} and to a lesser extent 5-HT_{1D} mRNA has been described in the bovine ileum and colon (Engel et al. 2006). mRNA for both receptor subtypes is present in human and rat sensory neurons consistent with an involvement in sensory neurotransmission generally (Pierce et al. 1996; 1997). Definition of the GI pharmacology of 5-HT_{1B} and 5-HT_{1D} receptor ligands is based almost exclusively on data generated with sumatriptan, an agent marketed for the acute treatment of migraine headache. Although sumatriptan has significant affinity, for and agonist activity at, the 5-HT_{1F}, in addition to 5-HT_{1B} and 5-HT_{1D} receptors, there is only limited evidence for involvement of the former receptor subtype in regulating GI function (see below). Sumatriptan produces relaxation of the gastric fundus and inhibition of antral contractility in a number of species including humans, actions attributed to activation of the 5-HT_{1B} or 5-HT_{1D} receptor (Coulie et al. 1997, 1999; Tack et al. 2000). In the dog, gastric accommodation has also been described (De Ponti et al. 2003). There is a corresponding delay in the gastric emptying of solids and liquids following sumatriptan administration to healthy human subjects (Coulie et al. 1997). Sumatriptan increases the periodicity of the migrating motor complex and reduces the occurrence of postprandial coordinated motor activity involving the gastric antrum, pylorus, and duodenum (Calvert et al. 2004). It is interesting to note that in healthy human subjects, sumatriptan increases postprandial lower esophageal sphincter pressure but, seemingly paradoxically, increases the frequency of reflux, actions that may stem from prolonged fundic relaxation and retention of proximal stomach contents (Sifrim et al. 1999). 5-HT_{1D} receptor activation may be responsible for the 5-HT-mediated contraction of the circular and longitudinal muscles of the human ileum (Borman and Burleigh 1997a). On the basis of cost alone, sumatriptan is unlikely to be utilized by gastroenterologists in chronic functional GI disorders, and it remains to be determined whether the available data are sufficiently promising to stimulate the development of other 5-HT_{1B} or 5-HT_{1D} receptor agonists in this therapeutic area.

The 5-HT_{1E} receptor (McAllister et al. 1992) appears to be localized entirely within the CNS (Bai et al. 2004; Barnes and Sharp 1999). The lack of selective ligands for the 5-HT_{1E} receptor precludes a definition of its GI pharmacology, although a functional role in the ENS seems unlikely based on the absence of 5-HT_{1E} receptor mRNA in guinea pig intestine and rat sensory nerves, at least at the level of the dorsal root ganglion (Bai et al. 2004; Chen et al. 1998; Nicholson et al. 2003). The 5-HT_{1F} receptor is closely related to the 5-HT_{1E} subtype, possessing greater than 70% sequence homology across the seven transmembrane domains and like the latter appears to be largely restricted to the CNS, although limited expression in peripheral tissues has been described (Adham et al. 1993; Barnes and Sharp 1999; Hoyer et al. 2002). Data indicative of a role for the 5-HT_{1F} receptor in the GI tract are sparse. In the cat stomach, LY-344864 and BRL-54443, selective 5-HT_{1F} receptor agonists, produce relaxation (Janssen et al. 2004), and it is therefore possible that some of the gastric effects of sumatriptan, described above, are 5-HT_{1F} receptor mediated, although this requires further investigation.

A number of studies have indicated an important physiological role in GI function for a peripheral 5-HT receptor characterized by high affinity for [^{3}H]5-HT, and termed the 5-HT_{1P} subtype (Mawe et al. 1986). The 5-HT_{1P} receptor has not been cloned, and its molecular identity therefore remains elusive. 6-Hydroxyindalpine and *N*-acetyl-5-hydroxytryptophyl-5-hydroxytryptophan amide have agonist and antagonist activities, respectively, at the 5-HT_{1P} receptor, with some selectivity. Interaction of sumatriptan with the 5-HT_{1P} receptor on myenteric neurons of the guinea pig gastric antrum has also been proposed (Tack et al. 2007). It has been suggested that the 5-HT_{1P} receptor is either the 5-HT_7 receptor (see below) or a heterodimer of the dopamine D_2 receptor with either the 5-HT_{1B} or 5-HT_{1D} receptor (Liu and Gershon 2005b; Monro et al. 2005; Tonini 2005). 5-HT_{1P} receptors are localized on IPANs in the submucosal and myenteric plexuses and in the intestinal mucosa (Branchek et al. 1988; Kirchgessner et al. 1993), and data from a number of studies suggest that the 5-HT_{1P} receptor has a functional role in the ENS of a variety of species (e.g., rat, guinea pig, and human; Cooke et al. 1997; Foxx-Orenstein et al. 1996; Tack et al. 1992). 5-HT, released from enterochromaffin cells, following mucosal stimulation, initiates reflexes via activation of 5-HT_{1P} receptors on the submucosal IPAN terminals (Pan and Gershon 2000). 5-HT_{1P} receptor activation and subsequent stimulation of submucosal VIP- and CGRP-containing afferent neurons are considered to have a critical role in initiation and maintenance of the peristaltic reflex. To date, no drugs specifically targeting the 5-HT_{1P} receptor have been developed for GI disorders. It has been postulated that while a 5-HT_{1P} receptor agonist should increase and an antagonist decrease GI transit, intractable diarrhea and paralytic ileus, respectively, may be unavoidable (Gershon 2004).

5-HT_2 receptor family

The 5-HT_2 receptor class comprises the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes, which possess 46–50% sequence identity. The 5-HT_{2A} and 5-HT_{2B} receptor subtypes are present in the CNS and periphery, while 5-HT_{2C} receptors appear to be restricted to the CNS (Hoyer et al. 2002; Leysen 2004). 5-HT_{2C} receptors are considered to lack a role in GI physiology and pathophysiology, in contrast to the 5-HT_{2A} and 5-HT_{2B} receptor subtypes.

Following its cloning from a variety of species, including humans (Saltzman et al. 1991), 5-HT_{2A} receptor mRNA and immunoreactivity have been localized to myenteric and submucosal neurons, enterocytes, and longitudinal and circular muscle cells of the GI tract (Bonaventure et al. 2005; Fiorica-Howells et al. 2002; Leysen 2004). 5-HT_{2A} receptor activation mediates secretory responses in human and rat isolated colonic mucosa (Borman and Burleigh 1996; Hansen and Skadhauge 1997; Imada-Shirakata et al. 1997). In the rat and guinea pig stomach antrum or corpus, 5-HT_{2A} receptor activation results in contraction (Komada and Yano 2007; Tamura et al. 1996), while in the rat fundus, a relaxation is observed (Komada and Yano 2007). Activation of 5-HT_{2A} receptors in canine and guinea pig isolated colonic longitudinal muscle results in contraction (Briejer et al. 1995a; Prins et al. 1997), and in vivo, motility is stimulated in the middle and distal colon (Nagakura et al. 1996a). 5-HT_{2A} receptor activation also produces contraction of human isolated jejunal smooth muscle cells (Kuemmerle et al. 1995). It is interesting to note that in mice, ENS morphology and resting GI transit or colorectal motility are unaffected by "knocking out" the 5-HT_{2A} receptor despite the fact that 5-HT-evoked contraction of the isolated colon of these animals is absent (Fiorica-Howells et al. 2002). This observation may indicate that 5-HT_{2A} receptors are not important physiologically or pathophysiologically in the GI tract. 5-HT_{2A} receptor agonist activity should increase transit in humans with disorders of reduced GI transit (e.g., IBS-C or chronic constipation), although the anticipated generalized vasoconstriction associated with this approach is likely to preclude any therapeutic opportunity.

The 5-HT_{2B} receptor was originally cloned from the rat stomach fundus (Foguet et al. 1992) with the human receptor cloned in 1994 (Kursar et al. 1994). mRNA for the 5-HT_{2B} receptor is widely expressed in the human and rodent GI tracts (Fiorica-Howells et al. 2000; Borman et al. 2002). In human colon, 5-HT_{2B} receptor mRNA and protein are present in the longitudinal and, to a lesser extent, circular muscle layers and in myenteric neurons (Borman et al. 2002). The 5-HT_{2B} receptor is also expressed on interstitial cells of Cajal in the human and mouse intestine and is postulated to have a proliferative role (Wouters et al. 2007a,b). Rodent studies implicate activation of 5-HT_{2B} receptors in the development of the ENS (Fiorica-Howells et al. 2000). Indeed, it has been suggested that the primary role of the 5-HT_{2B} receptor in the human GI tract may be in the developmental regulation of the ENS (Gershon 2000). However, the 5-HT_{2B} receptor may serve other functions too. It has long been recognized that 5-HT contracts the rat stomach fundus (Vane 1957), an effect attributed to 5-HT_{2B} receptor activation (Komada and Yano 2007). 5-HT also produces a 5-HT_{2B} receptor-mediated contraction of the longitudinal smooth muscle of the human ileum (Borman and Burleigh 1995) and augmentation of neuronally mediated contraction of human colonic longitudinal smooth muscle (Borman and Burleigh 1997a; Borman et al. 2002). It is conceivable, based on preclinical data (Beattie et al. 2004; Borman and Burleigh 1997a; Borman et al. 2002), that 5-HT_{2B} receptor agonism and antagonism will, respectively, increase and decrease GI motility in humans, although this remains to be substantiated. The potential clinical utility of a 5-HT_{2B} receptor agonist in chronic constipation or IBS-C is unlikely on the basis of anticipated cardiac valvular toxicity (Hofmann et al. 2002; Horowski et al. 2004). However, the use of a 5-HT_{2B} receptor antagonist for diarrhea and IBS-D may present a feasible yet, at this stage, still speculative therapeutic opportunity. It has been postulated that 5-HT_{2B} receptor antagonism may inhibit visceral hypersensitivity (Borman et al. 2002), although rodent data are inconsistent with this proposal (Greenwood-Van Meerveld et al. 2006a).

5-HT_3 receptor

Molecular biology and receptor localization

In common with the nicotinic acetylcholine, γ-amino butyric $acid_A$ ($GABA_A$), and glutamatergic *N*-methyl-D-aspartate receptors, the 5-HT_3 receptor is a ligand-gated ion channel (Maricq et al. 1991). Several subunits of the 5-HT_3 receptor have been identified (5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E}; Sanger and Andrews 2006). Native 5-HT_3 receptors are pentamers, which are homo-oligomeric assemblies of 5-HT_{3A} or hetero-oligomeric assemblies of 5-HT_{3A} and 5-HT_{3B} subunits. The 5-HT_{3B} subunit imparts distinct biophysical properties upon the hetero-oligomeric assembly relative to the homo-oligomer but has negligible influence on the apparent affinity of agonists or antagonists (Davies et al. 1999). Variants of the human 5-HT_{3B} subunit that differ in the extracellular N-terminal domain have been postulated to be present in the GI tract as a result of polymorphisms in the 5-HT_{3B} gene promoter (Tzvetkov et al. 2007). The role of the other subunits in the heteromeric complexes is unknown at present. Expression analysis of the different 5-HT_3 receptor subunit genes has indicated that each is present in the human intestine and that the 5-HT_{3E} is expressed specifically at this location (Niesler et al. 2003). In the ENS, 5-HT_3 receptor immunoreactivity is expressed on neurons of the myenteric and submucosal plexuses, interstitial cells of Cajal and fibers in the circular and longitudinal muscle layers, submucosa, and mucosa (Glatzle et al. 2002). In addition, 5-HT_3 receptor-immunopositive mucosal terminals of vagal and spinal afferent neurons are also evident (Glatzle et al. 2002; Raybould et al. 2003).

5-HT_3 receptor-mediated activity in the gastrointestinal tract

Data from numerous preclinical studies have demonstrated 5-HT_3 receptor-mediated activity in the GI tract. Thus, 5-HT_3 receptor activation is associated with increased electrically evoked contractions of guinea pig and mouse stomach corpus or fundus circular smooth muscle (Buchheit and Buhl 1994; Xue et al. 2006). In the guinea pig isolated antrum, 5-HT_3 receptor activation produces a contraction (Tamura et al. 1996). Data from electrophysiology studies using the guinea pig ileum indicate that the mucosal processes of myenteric IPANs are excited via 5-HT_3 receptor activation and play a role in initiation or enhancement of myenteric reflexes (Bertrand et al. 2000). The majority of myenteric and submucosal neurons maintained in primary culture respond to 5-HT with a fast inward current that is inhibited by 5-HT_3 receptor antagonists (Galligan et al. 2000). While the role of the 5-HT_3 receptor on the interstitial cells of Cajal is unclear, it is postulated that it participates in the regulation of pacemaker activity (Wouters et al. 2007a). Preclinical studies have demonstrated that the 5-HT_3 receptor antagonists, ondansetron, granisetron, tropisetron, ramosetron, and alosetron, increase whole gut, small intestinal, or colonic transit time in mice, rats, and guinea pigs, presumably by attenuating endogenous, 5-HT_3 receptor-mediated prokinetic activity (Brown et al. 1993; Clayton et al. 1999; Nagakura et al. 1996b; Sanger and Wardle 1994). Similarly, azasetron inhibits 5-HT, corticotrophin-releasing factor, and stress-induced increases in colonic transit in rats (Haga et al. 1995). Preclinical data also support a role for the 5-HT_3 receptor in visceral nociception. Thus, ondansetron, alosetron, and cilansetron attenuate visceromotor and nociceptive responses to mechanical rectal distension or chemical stimulation in rats (Mori et al. 2004; Morteau et al. 1994). It is interesting to note however, that, the efficacy of 5-HT_3 receptor antagonists in colorectal distension studies in rats pretreated with 5-hydroxytryptophan to sensitize the colon and rectum is inconsistent. Granisetron, zatosetron, and bemesetron increase the threshold for the distension-induced visceromotor reflex, while tropisetron and ondansetron have little or no effect (Banner and Sanger 1995). The 5-HT_3 receptor may also have a particularly important role in regulating GI mucosal secretion. Activation of 5-HT_3 receptors results in intestinal chloride secretion (Hansen and Skadhauge 1997) and 5-HT release from enterochromaffin cells (Schworer and Ramadori 1998). Furthermore, ondansetron inhibits 5-HT-induced secretion in the rat distal colon (Budhoo et al. 1996) and 5-hydroxytryptophan-induced diarrhea in mice (Pascual et al. 2002). Cholera toxin and *Salmonella typhimurium*-induced secretion in the porcine jejunum is attributed to the activation of 5-HT_3 receptors (Jensen et al. 1997).

Clinical activity in gastrointestinal disorders

Of the many 5-HT_3 receptor-selective antagonists identified (e.g., ondansetron, granisetron, alosetron, cilansetron, ramosetron, azasetron, tropisetron, dolasetron, and palonosetron), several have proved of considerable value, not only as pharmacological tools but also as clinically efficacious therapies for nausea and vomiting and IBS-D (Aapro 2005; Camilleri et al. 2000; Haga et al. 1995; Humphrey et al. 1999; Nagakura et al. 1996a, b; Sanger and Andrews 2006). 5-HT_3 receptor antagonists have proven particularly useful in reducing the incidence and severity of acute emetic episodes during cancer chemotherapy, providing, upon combination with dexamethasone, complete protection from vomiting in up to 90% of patients (Roila and Fatigoni 2006). The degree of protection is, however, dependent on the chemotherapeutic agent used and its dosing regimen. 5-HT_3 receptor antagonists are less effective in controlling delayed emesis that occurs, for example, more than 24 h after cisplatin administration (Roila and Fatigoni 2006). In general, clinical trial data suggest that the marketed 5-HT_3 receptor antagonists have similar therapeutic profiles with respect to efficacy and safety (McNulty 2007). One possible exception is palonosetron (Aloxi®), which was launched in 2003 for the prevention of chemotherapy-induced nausea and vomiting and is currently in phase 2 trials for the prevention of postoperative nausea and vomiting. Differentiating features of palonosetron from other marketed 5-HT_3 receptor antagonists are its markedly higher 5-HT_3 receptor-binding affinity and antagonist potency and its extended plasma half-life (approximately 40 h in healthy subjects; Navari 2006; Rubenstein 2004). Superiority of palonosetron over ondansetron and dolasetron in the prevention of both acute and delayed chemotherapy-induced nausea and vomiting has been observed in phase 3 clinical trials (Rubenstein 2004), although additional studies are warranted.

The mode of action of 5-HT_3 receptor antagonists in preventing emesis is well understood. Cancer chemotherapeutic drugs release 5-HT from enterochromaffin cells in the GI tract, resulting in activation of 5-HT_3 receptors on vagal sensory afferent neurons. The vagal afferent neurons project to the emetic center in the brainstem via the area postrema, located at the floor of the fourth ventricle (Hesketh 2004; Tyers and Freeman 2002). In ferrets, vagotomy abolishes cisplatin-mediated emesis indicating the importance of the vagus nerve in the emetic reflex (Hawthorn et al. 1988). In patients receiving cisplatin chemotherapy, a rise in urinary 5-HIAA levels has been demonstrated, which correlates with the onset and development of emesis (Cubeddu et al. 1990). The inability of ondansetron to affect the increased 5-HIAA urinary levels is consistent with an action on vagal afferent neurons rather than on the release of 5-HT (Cubeddu et al. 1990).

With respect to human GI motility effects, 5-HT_3 receptor antagonists such as alosetron, ondansetron, and cilansetron are associated with reductions in colonic and whole-gut transit or motility, increased fluid absorption, and stool consistency or attenuation of postprandial dyspepsia-like symptoms (Clemens et al. 2002; Gore et al. 1990; Houghton et al. 2000; Kuo et al. 2002; Stacher et al. 2000). The clinical efficacy of alosetron in IBS-D patients is generally attributed to its ability to prolong intestinal transit and reduce secretions; although some evidence exists for a direct inhibitory effect on visceral sensitivity in humans, this remains uncertain (Baker 2005; Gershon and Tack 2007; Mayer and Bradesi 2003). Data from rodent studies indicate that a direct, peripheral action on visceral nociceptive transmission may be important (Jiang et al. 2000; Kozlowski et al. 2000). Human positron emission tomography (PET) imaging studies have provided evidence that alosetron acts principally within discrete areas of the brain, particularly those associated with emotion, to reduce visceral sensitivity (Berman et al. 2002; Mayer et al. 2002). A central site of action for alosetron is also implicated in rodent studies of stress-induced sensitization of visceral nociception (Bradesi et al. 2007). An analysis of clinical data indicates that to achieve demonstrable efficacy in IBS, the calculated "number needed to treat" (NNT) with alosetron is seven (Cremonini et al. 2003).

While constipation, sometimes severe in nature, is an important adverse effect associated with alosetron, a more serious issue has been its association with a low (0.15% vs. 0% for placebo; Chang et al. 2006) but significant incidence of ischemic colitis, which, in some cases, has led to hospitalization, surgical intervention, and even death (Chang et al. 2006; Gallo-Torres et al. 2006). IBS patients have significantly higher rates of colonic ischemia compared to healthy subjects (Chang et al. 2006; Cole et al. 2004), and it is possible that ischemic colitis constitutes a distinct part of the natural progression of IBS in some patients or is a manifestation of another bowel pathology. However, it is evident that, although rare, there is indeed an association of alosetron with ischemic colitis. The majority of the reports of ischemic colitis occur in the first month of alosetron treatment, although specific risk factors remain to be identified (Chang et al. 2006). Following its withdrawal from the market by Glaxo SmithKline in 2000, the Food and Drug Association (FDA) announced, in June 2002, the approval of a supplemental new drug application that allows restricted marketing of alosetron, with a risk management plan and a revised indication for women with severe IBS-D who have chronic symptoms (generally lasting 6 months or longer), no discernable anatomic or biochemical abnormalities of the GI tract, and a failure to respond to conventional therapy. Development of another 5-HT_3 receptor antagonist, cilansetron, was suspended in the USA despite clinical efficacy in IBS-D patients, as a result of an increased incidence of ischemic colitis (Chey and Cash 2005). The question remains as to whether ischemic colitis is limited to alosetron and cilansetron or whether it is inextricably linked to 5-HT_3 receptor antagonism. Ondansetron and granisteron do not appear to be associated with ischemic colitis when used as antiemetic therapies. However, as these agents are not approved for IBS therapy, it is unclear whether ischemic colitis would occur upon their use in this apparently more susceptible patient population. Therefore, although the efficacy of 5-HT_3 receptor antagonists in IBS-D is established, it remains to be determined whether or not this class of agent will play a significant role in the future given the perceived safety risks. DDP-225 is a 5-HT_3 receptor antagonist, under development by Dynogen, which also exhibits affinity for the norepinephrine transporter (NET). This dual mechanism of action is proposed to offer complementary efficacy in IBS-D with respect to symptoms of visceral hypersensitivity and accelerated motility, although this remains to be seen. It is also unclear at present whether DDP-225 will be associated with a reduced incidence of ischemic colitis relative to 5-HT_3 receptor-selective antagonists.

As 5-HT_3 receptor antagonists reduce GI transit, it is reasonable to assume that a 5-HT_3 receptor agonist would be prokinetic. This appears to be the case as a clinical study in healthy men has shown that pumosetrag (MKC-733), a selective 5-HT_3 receptor partial agonist, stimulates antroduodenal-migrating motor complex activity and accelerates small intestinal transit (Coleman et al. 2003). In the same study, pumosetrag delayed liquid gastric emptying in association with relaxation of the proximal stomach. In constipated women, pumosetrag increases stool frequency suggesting that it may have clinical potential in chronic constipation and IBS-C patients (Fujita et al. 2005). The apparent absence of adverse effects such as nausea and vomiting may be consistent with little or no systemic exposure of pumosetrag (Evangelista 2007) or reflect its partial agonist activity. It has been proposed that a 5-HT_3 receptor partial agonist is more likely to have clinical utility compared to a receptor agonist with high intrinsic activity as the former may be less susceptible to desensitization (Costedio et al. 2007).

5-HT_4 receptor

Molecular biology and receptor localization

The 5-HT_4 receptor was first cloned in 1995 (Gerald et al. 1995), and in recent years, many splice variants of the receptor, which differ only in the sequence of their intracellular COOH-terminal domain, have been identified (i.e.,

5-$HT_{4(a)}$, 5-$HT_{4(b)}$, 5-$HT_{4(c)}$, 5-$HT_{4(d)}$, 5-$HT_{4(e)}$, 5-$HT_{4(f)}$, 5-$HT_{4(g)}$, 5-$HT_{4(i)}$, and 5-$HT_{4(n)}$; Hoyer et al. 2002; Kaumann and Levy 2006; Liu et al. 2005a; Bender et al. 2000). A splice variant with a 14-amino acid insert in the second extracellular domain also has been described and designated 5-$HT4_{(hb)}$ since it was found only in combination with the 5-$HT_{4(b)}$ C terminal tail (Bender et al. 2000). In the mouse, mRNA for the 5-$HT_{4(a)}$, 5-$HT_{4(b)}$, 5-$HT_{4(e)}$, and 5-$HT_{4(f)}$ splice variants is expressed, albeit to different extents, in the submucosal plexus (Liu et al. 2005a). The 5-$HT_{4(a)}$ and 5-$HT_{4(b)}$ but not 5-$HT_{4(e)}$ and 5-$HT_{4(f)}$ isoforms are also expressed in the myenteric plexus of the small and large intestine (Liu et al. 2005a). Nerve fibers in the intestinal circular muscle (but not mucosa) and the neuropil of the submucosal and myenteric plexuses are 5-HT_4-immunoreactive (Liu et al. 2005a). In the human small intestine, 5-$HT_{4(b)}$ receptor splice variant mRNA is expressed at the highest level, followed by 5-$HT_{4(c)}$, 5-$HT_{4(a)}$, 5-$HT_{4(g)}$, and 5-$HT_{4(d)}$ (Medhurst et al. 2001). In the human stomach, expression of these splice variants is generally low, as is the case for 5-$HT_{4(a)}$, 5-$HT_{4(b)}$, 5-$HT_{4(c)}$, and 5-$HT_{4(n)}$ mRNA in the esophagus (Medhurst et al. 2001; Vilaro et al. 2002). In the human colon, 5-$HT_{4(a)}$, 5-$HT_{4(b)}$, and 5-$HT_{4(i)}$ but not 5-$HT_{4(g)}$ mRNA are expressed (Brattelid et al. 2004). It should be noted that, to date, mRNA encoding human 5-$HT_{4(e)}$ and 5-$HT_{4(f)}$ splice variants has not been demonstrated (Kaumann and Levy 2006). While the 5-HT_4 splice variants may have different tissue distributions, the functional significance of these isoforms is unclear. Some subtle differences in agonist potency, efficacy, constitutive receptor activity, desensitization, and signal transduction have been reported (e.g., Claeysen et al. 1999; Bender et al. 2000; Pindon et al. 2002; Mialet et al. 2003; Castro et al. 2005; Ponimaskin et al. 2002). It is interesting to note that 5-HT_4 receptor-mediated responses in human colonic smooth muscle can be demonstrated despite low or even undetectable levels of 5-HT_4 receptor mRNA (Irving et al. 2007). 5-HT_4 receptor immunoreactivity has been identified in IPANs and in the interstitial cells of Cajal in several species (Poole et al. 2006).

5-HT_4 receptor-mediated activity in the gastrointestinal tract

The 5-HT_4 receptor is considered to have a particularly important role, both physiologically and pathophysiologically in the regulation of GI function (Baker 2005; Kim and Camilleri 2000). Activation of neuronal 5-HT_4 receptors, which are located exclusively presynaptically on the terminals of IPANs, at synapses within the myenteric plexus and at the neuromuscular junction, results in prokinetic activity throughout the GI tract (Gershon 2005). The secretion of acetylcholine and CGRP from stimulated submucosal IPANs is enhanced by 5-HT_4 receptor activation (Gershon 2005; Gershon and Tack 2007; Grider 2003b) resulting in a potentiation of excitatory neurotransmission. Augmentation of acetylcholine release also occurs at nerve–nerve synapses in the myenteric plexus and at motor neuron–smooth muscle synapses (Galligan et al. 2003; Grider 2003b; Pan and Galligan 1994; Pan and Gershon 2000). 5-HT_4 receptor-mediated enhancement of neurotransmitter release from myenteric neurons occurs via cyclic adenosine monophosphate- and protein kinase A-dependent facilitation of fast excitatory postsynaptic potentials in the guinea pig ileum/myenteric plexus (Galligan et al. 2003; Pan and Galligan 1994). Data from studies in which mechanical activity is measured using isolated tissues demonstrates the prejunctional role of the 5-HT_4 receptor in the GI tract. Thus, activation of 5-HT_4 receptors on enteric motor neurons produces an acetylcholine-mediated contraction of ileal and colonic longitudinal smooth muscle (Taniyama et al. 2000; Wardle and Sanger 1993). Furthermore, 5-HT_4 receptor activation is associated with augmentation of electrically evoked contractions of guinea pig stomach circular smooth muscle (Buchheit and Buhl 1994). While 5-HT_4 receptor stimulation most frequently results in neurogenically mediated inhibition of electrically evoked contractions of human isolated colonic circular smooth muscle, the release of both inhibitory and excitatory neurotransmitters (i.e., NO and acetylcholine, respectively), together with inhibition and augmentation of neurogenic responses, has been demonstrated (Cellek et al. 2006; Leclere et al. 2005). Activation of 5-HT4 receptors expressed on smooth muscle cells results in relaxation of the rat esophagus and stomach (Komada and Yano 2007; Reeves et al. 1991), canine rectum (Prins et al. 1999b), and human colon (Tam et al. 1994).

The 5-HT_4 receptor has a prosecretory role in the GI tract (Hansen and Skadhauge 1997). Activation of 5-HT_4 receptors on submucosal enteric neurons or enterocytes promotes chloride and bicarbonate secretion from duodenal, colonic, or jejunal epithelial cells (Budhoo et al. 1996; Kellum et al. 1994; Ning et al. 2004; Säfsten et al. 2006). In human ileum and ascending colon, 5-HT produces mucosal chloride secretion via activation of 5-HT_4 receptors (Borman and Burleigh 1996, 1997b). Similarly, in the rat distal colon, antagonism of 5-HT-mediated chloride secretion by SC 53606, a selective 5-HT_4 receptor antagonist, and the agonist rank order of potency are consistent with a prosecretory role for the 5-HT_4 receptor (Budhoo et al. 1996). In mice, 5-hydroxytryptophan-induced diarrhea is inhibited by the selective 5-HT_4 receptor antagonists, RS 39604, GR 113808, and SB 204070, an action attributed to attenuation of 5-HT_4 receptor-mediated secretion (Hegde et al. 1994; Pascual et al. 2002).

Rodent data suggest that 5-HT_4 receptor activation may reduce visceral hyperalgesia. Thus, the 5-HT_4 receptor agonist, tegaserod, attenuates the visceromotor response

evoked by colorectal distension in control animals and in those in which the colon has been rendered hypersensitive with intracolonic infusion of acetic acid or trinitrobenzenesulfonic acid (Greenwood-Van Meerveld et al. 2006b). This activity is attributed to 5-HT_4 receptor agonist activity of tegaserod as 5-HT_4 receptor-selective antagonists reverse, albeit incompletely, its actions (Greenwood-Van Meerveld et al. 2006a, b). Another study demonstrated that intragastric dosing of tegaserod to rats reduces the number of Fos-labeled neurons and substance P immunoreactivity in the dorsal horn of the lumbarsacral spinal cord following intracolonic instillation of trinitrobenzenesulfonic acid (Sun and Luo 2004). In contrast, 5-HT_4 receptor agonists have been shown to lack a direct antinociceptive effect on visceral afferents (Hicks et al. 2001). In healthy human subjects, tegaserod attenuated inhibition of the RIII nociception reflex caused by rectal distension, although its effect on corresponding symptom ratings was not significantly different from placebo (Coffin et al. 2003). In comparison, another 5-HT_4 receptor agonist, prucalopride, appears to lack an effect on rectal sensitivity (Emmanuel et al. 1998; Poen et al. 1999). The precise role of the 5-HT_4 receptor in visceral sensitivity remains unclear.

Appreciation of the role played by the 5-HT_4 receptor in the GI tract has advanced considerably due to the availability of 5-HT_4 receptor ligands. Several 5-HT_4 receptor-selective agonists (e.g., prucalopride, TS-951, and TD-5108) and antagonists (e.g., piboserod and GR 113808) have been described (Beattie et al. 2007; Briejer et al. 2001b; Gale et al. 1994; Kajita et al. 2001; Smith et al. 2007; Wardle et al. 1996). Tegaserod, cisapride, mosapride, BIMU-1, and renzapride have also been used clinically or as pharmacological tools to probe the function of the 5-HT_4 receptor, although each lacks selectivity for the 5-HT_4 receptor. Thus, tegaserod has significant binding affinity at the 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_7 receptors and potent 5-HT_{2B} receptor antagonist activity, while cisapride, mosapride, BIMU-1, and renzapride have varying levels of affinity for the 5-HT_3 receptor (Beattie et al. 2004; Freeman et al. 1992; Rizzi et al. 1994; Taniyama et al. 1991; Theravance, unpublished observations). Tegaserod also has some affinity for SERT (K_i of approximately 3 μM; Ismair et al. 2007). Cisapride has significant affinity at dopamine D_2, α_1 adrenergic, and 5-HT_{2B} receptors (pK_i values of 7.7, 8.1, and 8.4, respectively; Theravance, unpublished observations).

Clinical activity in gastrointestinal disorders

Based on the robust prokinetic activity of 5-HT_4 receptor agonists in the upper or lower GI tract of healthy human subjects (Bouras et al. 1999; Coffin et al. 2003; Degen et al. 2001; Emmanuel et al. 1998; Goldberg et al. 2007a, b; Poen et al. 1999), the utility of this class of agents for the treatment of patients with disorders of reduced GI motility has been investigated.

Clinical efficacy of cisapride, prucalopride, renzapride, mosapride, tegaserod, and TD-5108, among others, has been reported in patients with IBS-C, chronic constipation, functional dyspepsia, or gastroparesis (Abell et al. 1991; Camilleri 2001; Camilleri et al. 2004; Deruyttere et al. 1987; Emmanuel et al. 2002; Johanson 2004; Muller-Lissner 1987). A meta-analysis of clinical trials performed with cisapride in functional dyspepsia concluded that there was significant benefit in favor of cisapride with respect to global assessment of efficacy by investigators and patients alike, in addition to improvement in individual measures of epigastric pain and discomfort, early satiation, abdominal distension, and nausea (Veldhuyzen van Zanten et al. 2001). As cisapride lacks 5-HT_4 receptor selectivity, the extent of the involvement of this receptor in its clinical efficacy is unclear. With respect to tegaserod, some data suggest that it provides modest benefit in improving functional dyspepsia symptoms (Tack et al. 2001). A more robust effect of tegaserod has been demonstrated in many placebo-controlled studies in healthy subjects and IBS-C patients; a reduction in oral–cecal transit time accompanied by an increased frequency of spontaneous bowel movements and softness of stools results (Degen et al. 2005; Muller-Lissner et al. 2001; Prather et al. 2000). Tegaserod also alleviates abdominal discomfort and pain in IBS-C patients (Camilleri 2001; Muller-Lissner et al. 2001). Reductions in visceral sensitivity, when reported, may reflect normalization of bowel function rather than a direct effect on sensory neurons. However, analysis of data from all randomized, placebo-controlled trials performed prior to 2003 indicates that although tegaserod offers significant benefit in the treatment of IBS-C, the NNT ranges from 14 to 20 patients depending on the dose evaluated (Evans et al. 2004). The limited effectiveness of tegaserod may reflect its mixed pharmacology, discussed above. It has been postulated that antagonism of 5-HT_{2A} and 5-HT_{2B} receptors may reduce GI motility (Briejer et al. 1995b; Beattie et al. 2004) and thus interfere with 5-HT_4 receptor-mediated prokinetic activity. Tegaserod and other more selective 5-HT_4 receptor agonists (e.g., prucalopride and TD-5108) have also proven effective in patients with chronic constipation (Emmanuel et al. 2002; Sloots et al. 2002; Goldberg et al. 2007b).

Some limited clinical data suggest that tegaserod and therefore potentially other 5-HT_4 receptor agonists may have a beneficial role in the treatment of functional heartburn, GERD, and gastroparesis. Tegaserod improves the esophageal pain threshold to mechanical distension and upper GI symptoms in patients with functional heartburn (Rodriguez-Stanley et al. 2006). Case reports suggest that tegaserod may also be useful in the treatment of gastroparesis (Banh et al. 2005; Friedenberg and Parkman 2006;

Zuberi et al. 2005). Additionally, tegaserod is associated with a significant reduction in postprandial esophageal acid exposure in GERD patients, possibly as a result of improved esophageal acid clearance, enhanced gastric emptying, or reduced transient lower esophageal sphincter relaxations (Kahrilas et al. 2000). The use of scintigraphy in healthy human subjects has demonstrated that tegaserod can indeed accelerate gastric emptying (Degen et al. 2005). Similarly, the 5-HT_4 receptor-selective agonist, ATI-7505, showed a trend toward increased gastric emptying in healthy volunteers (Camilleri et al. 2006). In a small clinical study, the 5-HT_3 receptor antagonist/5-HT_4 receptor agonist, renzapride, increased liquid gastric emptying in patients with diabetic gastroparesis but not in healthy control subjects (Mackie et al. 1991). Future large-scale clinical studies with more selective 5-HT_4 receptor agonists should establish the clinical activity, if any, attributable to this mechanism in upper GI disorders. The unique dual pharmacological profile of renzapride, which differentiates it from other drugs currently in development for the treatment of IBS, may also help clarify the relative roles of the 5-HT_3 and 5-HT_4 receptors in this disorder. Renzapride produces increases in colonic transit, improvement in stool form, and ease of passage and also reduces abdominal pain in patients with IBS-C (Camilleri et al. 2004; Tack et al. 2006b). Renzapride is currently in phase 3 clinical trials for IBS-C.

The clinical use of cisapride and tegaserod is now restricted on the basis of cardiovascular safety concerns (Barbey et al. 2002; Pasricha 2007). Restrictions on the use of cisapride stem from reports of serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. The occurrence of these adverse effects is further compounded by metabolism of cisapride by the cytochrome P450 3A4 isoenzyme leading to drug–drug interactions with coadministered substrates (Zhou et al. 2005). Cisapride is now restricted to the treatment of severe nighttime heartburn in patients with GERD who do not adequately respond to other therapies and in consequence has limited use. In March 2007, the marketing of tegaserod was suspended in the USA due to concerns with respect to an increased risk of serious ischemic cardiovascular events. An analysis of pooled clinical data from 29 studies involving 11,614 patients on tegaserod and 7,031 on placebo revealed that 13 patients treated with tegaserod (or 0.1%) had serious and life-threatening cardiovascular insults; four had a myocardial infarction (one death), six had unstable angina, and three had a stroke. In the placebo-treated patients, only one (or 0.01%) had a stroke. All of the affected patients had preexisting cardiovascular disease (e.g., prior coronary artery disease) and/or risk factors, namely advancing age, tobacco use, hypertension, or hyperlipidemia (Gerson 2007). While the cardiovascular adverse effects of cisapride are attributed to QT prolongation of the electrocardiogram (ECG) signal, as a result of cardiac human ether-a-go-go related gene (hERG) potassium channel blockade, this is unlikely to be true for tegaserod as it is devoid of such activity (Drici et al. 1999). Furthermore, its adverse effects are ischemic in nature rather than arrhythmogenic. ECG analysis indicates that there is a higher frequency of ST-segment depression in high-risk patients on tegaserod compared to placebo (3.7% vs. 1.3%), although postmarketing cardiac adverse events are claimed to occur at a level similar to that of background (Pasricha 2007).

Assuming that the perceived cardiovascular risk associated with tegaserod is genuine, what is the potential mechanism responsible, and what are the implications for other 5-HT_4 receptor agonists? In cardiac muscle, 5-HT_4 receptor activation may be associated with tachycardia and potentially arrythmias in a pathophysiological setting (Kaumann and Levy 2006). With the exception of renzapride (Meyers and Hickling 2007), tachycardia is not evident in the clinical literature with a 5-HT_4 receptor agonist devoid of significant hERG activity. Several 5-HT receptor types exist in the heart, at the level of the myocardium and its neuronal innervation, but their roles are unclear (Doggrell 2003; Jordan 2005; Kaumann and Levy 2006). With respect to the vasculature, 5-HT_4 receptors are present in some blood vessels and, for example, have been shown to mediate dilation of pulmonary veins (Cocks and Arnold 1992). Non-5-HT_4 receptors are expressed in the vasculature; 5-HT_{1B} and 5-HT_{2A} receptor activation results in vasoconstriction (Nilsson et al. 1999), while 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2B}, and 5-HT_7 receptor activation in either the endothelium or vascular smooth muscle is associated with vasodilation (Centurion et al. 2000; Ellis et al. 1995; Schoeffter and Hoyer 1990; Ishida et al. 1998). 5-HT_{1B} or 5-HT_{2B} receptor activation on vascular endothelium may, under pathophysiological conditions, provide protective vasodilator and platelet antiaggregatory effects via release of NO (Ishida et al. 1998). Furthermore, there is evidence indicating that the 5-HT_{2B} receptor has an important trophic role in cardiac development and that 5-HT_{2B} receptors on cardiac fibroblasts may be involved in tissue regenerative processes and therefore be of potential importance in some pathological scenarios (Jaffré et al. 2004; Nebigil et al. 2000; Nebigil and Maroteaux 2003). As stated above, tegaserod has significant 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_7 receptor affinity and/or antagonist potency. An interaction of tegaserod with one or more of these receptors in the heart or vasculature may be relevant to its perceived cardiovascular risk, although this requires further investigation. It also remains to be established whether other 5-HT_4 receptor agonists currently in development, particularly those with a higher degree of 5-HT_4

receptor selectivity, will prove to be more efficacious and/or better tolerated than tegaserod. TD-5108, under development by Theravance, is a 5-HT_4 receptor agonist with a high degree of selectivity over other 5-HT receptors (Goldberg et al. 2007a, b; Smith et al. 2007). TD-5108 was recently found to be highly effective and well tolerated in a 4-week phase 2a trial in patients with chronic constipation (Goldberg et al. 2007b). Prucalopride, a 5-HT_4 receptor-selective agonist (Briejer et al. 2001a), has GI prokinetic activity in healthy human subjects and patients with chronic constipation (Coremans et al. 2003; Emmanuel et al. 2002; Poen et al. 1999). Following completion of multiple phase 3 trials in chronic constipation, development of prucalopride was halted by Janssen for several years, allegedly on the basis of carcinogenicity concerns (Cash and Chey 2005; Kamm 2002). Recently, the compound was licensed to Movetis whose objective is to gain registration in Europe. Thus, the efficacy of several 5-HT_4 receptor agonists in treating patients with IBS-C or chronic constipation is established. While it remains to be determined whether the modest clinical efficacy of tegaserod outweighs its small, possible risk of cardiovascular adverse effects, the development of more selective 5-HT_4 receptor agonists such as TD-5108 and prucalopride may provide much needed benefit to patients requiring GI prokinetic therapy.

On the basis of the perceived excitatory influence of 5-HT_4 receptor agonists on GI motility, it has been postulated that 5-HT_4 receptor antagonism could confer benefit in patients with IBS-D. In healthy human subjects, piboserod, a selective 5-HT_4 receptor antagonist, inhibits cisapride-mediated increases in oral–cecal transit and tends to delay colonic transit in its own right without affecting gastric emptying, small intestinal transit, colonic motor activity, or colonic perception to balloon distension (Bharucha et al. 2000). These findings suggest that 5-HT_4 receptors may have only a modest tonic role in GI function under resting physiological conditions. This conclusion is supported by animal data from studies indicating that piboserod and SDZ 205-557 have no effect on stool production in mice or on dog colonic contractile activity per se but can inhibit 5-hydroxytryptophan or 5-HT_4 receptor agonist-induced responses (Nagakura et al. 1996a; Sanger et al. 1998). However, in 5-HT_4 "knockout" mice, gastric emptying, small and large intestinal transit, and the number of myenteric neurons in the colon are all reduced compared to wild-type littermates (Cuenca et al. 2006). Furthermore, in a small clinical study with IBS-D patients, piboserod significantly increased oral–cecal transit time and tended to reduce rectal sensitivity, with the majority of patients reporting symptomatic improvement (Houghton et al. 1999). It remains to be determined whether 5-HT_4 receptor antagonists will be efficacious in disorders such as carcinoid syndrome where a profound overstimulation of the 5-HT_4 receptor may be anticipated (Bharucha et al. 2000; De Ponti and Tonini 2001). With respect to a potential clinical utility in upper GI disorders, the selective 5-HT_4 receptor antagonist, R216073, was found to have no significant effect on fundic relaxation, drinking capacity, and upper abdominal symptoms in patients with functional dyspepsia (Van Lelyveld et al. 2006).

Metoclopramide is approved for the treatment of GERD and diabetic gastroparesis. In addition to its established, potent dopamine D_2 receptor antagonist activity, 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist activities may contribute to its clinical efficacy (Tonini et al. 1999). However, metoclopramide-mediated extrapyramidal symptoms and tardive dyskinesias, resulting from dopamine D_2 receptor antagonism in the CNS, limit its utility in the treatment of functional GI disorders. The clinical utility of a 5-HT_4 receptor-selective agonist for the treatment of upper GI disorders has yet to be established. Proctor & Gamble and Movetis have such agents in early clinical development for the treatment of GERD and gastroparesis (Table 2). Furthermore, the Movetis company website indicates that they are pursuing the development of 5-HT_4 receptor agonists that are specific for 5-HT_4 receptors in the upper GI tract. The pharmacological basis for this upper GI selectivity is unclear, although the 5-HT_4 receptor splice variants have region-specific expression in the GI tract (see above) and so perhaps differential activation is achievable. Alternatively, differences in 5-HT_4 receptor reserve may confer regional selectivity on the activity of 5-HT_4 receptor partial agonists.

5-HT_5 and 5-HT_6 receptor families

The 5-HT_5 receptor family consists of two members, designated 5-HT_{5A} and 5-HT_{5B}; only the former member is expressed in the human as the coding sequence of the 5-HT_{5B} receptor is interrupted by stop codons (Nelson 2004). Both receptor subtypes are essentially limited in distribution to the CNS, although the 5-HT_{5A} receptor has also been found in the carotid body. There are no data suggesting a role for the 5-HT_5 receptor in GI function. The 5-HT_6 receptor has been cloned from several species including humans (Kohen et al. 1996; Ruat et al. 1993). Within the CNS, there is considerable interest in the role played by the 5-HT_6 receptor in the regulation of feeding, cognition, affective states, and seizures (Woolley et al. 2004), although there appears to be extremely limited 5-HT_6 receptor expression in the periphery. Despite the interaction of the 5-HT_6 receptor with many neurotransmitter systems known to influence GI function (e.g., cholinergic, dopaminergic, and GABAergic; Mitchell and Neumaier

2005) and detection of weak receptor expression in the rat stomach (Ruat et al. 1993), there are no definitive data demonstrating a functional role for the 5-HT_6 receptor in the GI tract.

5-HT_7 receptors

The 5-HT_7 receptor has been cloned from a number of species (e.g., rat, guinea pig, and human; Bard et al. 1993; Shen et al. 1993; Tsou et al. 1994), and three human splice variants, with similar pharmacology, have been identified. The 5-HT_7 receptor has been detected in the CNS and periphery (Vanhoenacker et al. 2000), although the majority of physiological effects attributed to 5-HT_7 receptor activation occur in the CNS (e.g., increased excitability of hippocampal neurons, regulation of prefrontal cortex development, and thermoregulation; Bacon and Beck 2000; Beique et al. 2004; Hedlund et al. 2003). However, the 5-HT_7 receptor is present in the ENS and is postulated to play a role in GI physiology. Each of the 5-HT_7 receptor splice variants is present in the human stomach, small intestine, and colon (Irving et al. 2007; Jasper et al. 1997; Krobert et al. 2001), while 5-HT_7 receptor immunoreactivity is present in myenteric and submucosal IPANs, NO synthase- and VIP-immunoreactive descending neurons, and in smooth muscle cells of the ileum (Tonini et al. 2005). Activation of 5-HT_7 receptors on IPANs results in a slow excitatory postsynaptic potential, while stimulation of 5-HT_7 receptors in the smooth muscle of the ileum and colon produces relaxation (Carter et al. 1995; Prins et al. 1999a). The ability of SB-269970, a selective 5-HT_7 receptor antagonist, to inhibit 5-HT-induced slow depolarization and excitatory postsynaptic potentials of myenteric IPANs and to reduce accommodation of the circular muscle of the guinea pig ileum during the preparatory phase of peristalsis, is consistent with a physiological role for the 5-HT_7 receptor (Monro et al. 2005; Tonini et al. 2005). With respect to a pathophysiological role for 5-HT_7 receptor activation, it has been postulated that overstimulation of this receptor may lead to exaggerated accommodation of colonic circular muscle and abdominal bloating, a common symptom in many functional bowel disorders (Tonini et al. 2005), although this will remain speculative until supporting clinical data are available.

Serotonin transporter

The paracrine and neurotransmitter actions of 5-HT are terminated rapidly and efficiently by SERT (Ramamoorthy et al. 1993). SERT plays a critical role in ensuring that 5-HT-mediated toxicity and receptor desensitization, likely consequences of maintained agonist exposure, are avoided. Rat, guinea pig, and human mucosal epithelial cells, in common with serotonergic neurons, express mRNA encoding SERT, display SERT immunoreactivity, and transport 5-HT with high specificity (Camilleri et al. 2007; Chen et al. 1998; Coates et al. 2004; Takayanagi et al. 1995; Wade et al. 1996). SERT is expressed at both the apical and basolateral sides of the mucosal cell membrane in the human and rodent GI tract (Van Lelyveld et al. 2007; Martel et al. 2003; Martel 2006). Variation in the density of SERT expression is apparent in human mucosal biopsy samples; levels in the duodenum are markedly higher than those in the stomach fundus and antrum (Van Lelyveld et al. 2007). Any 5-HT that is not "captured" by the mucosa either overflows into the lumen of the GI tract or enters the bloodstream and is rapidly transported into platelets, which also express SERT (Chen et al. 2001; Grønstad et al. 1985; Gershon and Tack 2007). Considering the importance of SERT in removing 5-HT from the vicinity of its many receptors in the GI tract, interference with its function has a major impact on GI physiology. Analysis of rectal biopsies from patients with IBS has demonstrated reductions in SERT mRNA and immunoreactivity in patients with IBS-C and IBS-D (Coates et al. 2004). Furthermore, significant association is observed between an insertion/deletion polymorphism of the promoter region of the human SERT gene and IBS-D suggesting that this and/or other polymorphisms may contribute to GI functional disorders such as IBS-D at least in some individuals (Yeo et al. 2004). Polymorphisms at the SERT promoter also appear to influence colonic responsiveness to the 5-HT_3 receptor antagonist, alosetron, in IBS-D patients (Camilleri et al. 2002).

It is noteworthy that the SSRIs, paroxetine, sertraline, citalopram, and fluoxetine, which are used widely in the treatment of depression, panic disorder, and obsessive–compulsive disorder, are associated with a relatively high incidence of nausea and diarrhea (approximately 20%; Spigset 1999). These adverse effects would be consistent with increased 5-HT-mediated activation of 5-HT_3 and 5-HT_4 receptors in the ENS, respectively. The impact of SERT inhibition on GI function will presumably be dictated by the relative contributions and interplay of each 5-HT receptor at distinct locations in the digestive system, together with the degree and rapidity of any mucosal or neuronal 5-HT receptor desensitization, among other factors. Thus, fluoxetine-induced contraction of the mouse isolated stomach fundus is mediated via 5-HT_{1B} or 5-HT_{1D} receptor activation on the basis of the inhibitory effect of the selective antagonist, GR 127935 (Xue et al. 2006), while in guinea pig isolated antrum and fundus, 5-HT_4 receptors are implicated (James et al. 2005). The 5-HT_4 receptor agonist, tegaserod, was shown recently to inhibit SERT with micromolar potency (Ismair et al. 2007). It has been suggested that inhibition of SERT by high local

concentrations of tegaserod in the GI tract may synergize with 5-HT_4 receptor agonist-induced prokinetic activity (Ismair et al. 2007).

The data from several human studies have demonstrated SSRI-mediated alterations in GI function, presumably as a consequence of an enhancement of 5-HT exposure in close proximity to its receptors. Paroxetine stimulates motor activity in the human small intestine, increasing oral–cecal motility and transit, but appears to have no significant effect on gastric emptying or colonic transit in healthy human subjects (Chial et al. 2003a,b; Gorard et al. 1994). Similarly, sertraline has no effect on gastric compliance or sensitivity in healthy subjects (Ladabaum and Glidden 2002). However, citalopram is associated with increased colonic compliance and phasic activity and increased colonic tone in response to a meal (Tack et al. 2000). In the esophagus, citalopram reduces chemical (acid perfusion) and mechanical (balloon distension) sensitivity without altering motility in healthy humans possessing established esophageal hypersensitivity (Broekaert et al. 2006). In addition to human data, preclinical observations indicate that SSRIs influence GI physiology. Chronic administration of paroxetine to mice reduces upper GI transit, defecation, and colonic sensitivity in response to balloon distension (Coates et al. 2006), while stool water content and colonic motility are increased in the majority of mice with a targeted deletion of SERT. In SERT knockout mice, a subset of animals is constipated, and analysis of GI function in the longer term indicates an alternating pattern of diarrhea and constipation, a phenomenon reminiscent of that in a subset of patients with IBS (Chen et al. 2001). Although SERT is absent in these mice, other mechanisms (e.g., the dopamine transporter) appear to compensate for the deletion, albeit with lower 5-HT-binding affinity compared to SERT.

Clinical data indicate beneficial effects of tricyclic antidepressants in IBS and to a lesser extent, functional dyspepsia (Mertz et al. 1998; Talley 2003b). The clinical efficacy of amitryptiline in functional dyspepsia appears unrelated to any changes in perception of gastric distension, and increased tolerance to aversive visceral sensations may be responsible (Mertz et al. 1998). While tricyclic antidepressants inhibit SERT, they also inhibit NET and interact with a variety of non-5-HT receptors. In consequence, it is difficult to attribute any clinical efficacy definitively to inhibition of SERT. There are, however, some limited clinical data with the SSRIs suggesting that SERT inhibition can confer a therapeutic benefit in patients with functional GI disorders (Creed et al. 2003; Tack et al. 2006a; Talley 2004). As many patients with functional GI disorders have coexisting psychiatric conditions (e.g., depression and anxiety), there has been some discussion related to the precise mechanism of any GI clinical efficacy where it has been noted (Talley et al. 2004). While SERT inhibition in both the CNS and periphery may provide benefits, it remains unclear whether antidepressant or anxiolytic activity contributes to a successful outcome in patients with functional GI disorders. Thus, in one study, citalopram improved abdominal pain, bloating, and quality-of-life measures in nondepressed IBS patients with no correlation in efficacy to changes in depression or anxiety scores (Tack et al. 2006a), but in another, fluoxetine had no effect on rectal sensitivity or global symptom relief in nondepressed IBS patients (Kuiken et al. 2003). There are limited clinical data regarding the efficacy of the new generation of dual 5-HT and norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine. Two novel development compounds of interest are LX-1031 (Lexicon Pharmaceuticals), a selective inhibitor of TPH1, which is responsible for 5-HT synthesis in the GI tract, and tianeptine (Pharmos), which is reported to stimulate 5-HT uptake.

Concluding remarks

In recent years, our understanding of the physiological and pathophysiological roles of the serotonergic system in the GI tract has increased significantly and continues to do so. A number of 5-HT receptor agonists and antagonists have demonstrable clinical efficacy in a variety of functional GI disorders, and preclinical and clinical data suggest that additional opportunities in the future can be anticipated as a result of manipulation of the serotonergic system (Table 2). As with all drug development, clinical failure in terms of inadequate efficacy or unacceptable tolerability has been and will continue to be a challenge. However, advances in our appreciation of the complexity of the ENS and the identification of more selective receptor ligands with suitable properties for therapeutic development bodes well for the future in addressing the clear unmet medical need that remains in the treatment of functional GI disorders.

Acknowledgments The authors are grateful to Dr. Patrick Humphrey and Dr. Sharath Hegde for their comments on the manuscript during its preparation.

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