PHARMACOLOGY OF SEROTONIN: WHAT A CLINICIAN SHOULD KNOW

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SUMMARY

The pharmacology of serotonin (5-hydroxytryptamine or 5-HT) in the gut has been the centre of intense interest and research for several decades. Although it is now recognised that 5-HT is contained in intrinsic enteric neurones (where it works as a neurotransmitter), enterochromaffin cells of the mucosa are the main source (more than 90%) of the body's 5-HT. In the gut, 5-HT is an important mucosal signalling molecule targeting enterocytes, smooth muscle cells, and enteric neurones. Application of exogenous 5-HT evokes so many responses that it is difficult to determine which are physiologically relevant. This bewildering range of effects is largely due to the presence of multiple receptor subtypes, which appear to be present on several classes of myenteric neurones, on smooth muscle cells, and on epithelial cells. 5-HT is thought to be involved in the pathophysiology of several clinical entities such as functional gut disorders (namely, irritable bowel syndrome), carcinoid diarrhoea, and chemotherapy induced emesis. In this review, the possible targets for pharmacological intervention are analysed in the light of the most recent advances of our understanding of the role of 5-HT in gut pathophysiology. Indeed, the recent regulatory interventions on cisapride (a $5-HT_4$ receptor partial agonist) and alosetron (a $5-HT_3$ receptor antagonist) have prompted a rethinking of our approaches to the pharmacological modulation of serotonergic pathways. In gut disorders, the most interesting targets for pharmacological intervention are: (1) the 5-HT receptor subtypes known to affect gut function such as those belonging to the $5-HT_1$, $5-HT_3$, $5-HT_4$, and $5-HT_7$ subtypes; and (2) the 5-HT reuptake mechanism which, apart from the central nervous system, is expressed in enteric neurones and enterocytes and is blocked by antidepressants.

INTRODUCTION

The pharmacology of 5-HT in the gastrointestinal tract has been the centre of intense interest and research for several decades since Vialli and Erspamer[1] showed that the gut is an important source of 5-HT. Originally, Erspamer and Asero called this substance enteramine and only in 1952 was enteramine found to be identical to the vasoconstrictor substance known as serotonin.[2]

The gut is by far the main source of 5-HT in the body.[3] Although enterochromaffin cells in the mucosa contain >90% of the body's 5-HT, it is now recognised that 5-HT is also contained in intrinsic neurones of the gastrointestinal tract (box 1).[4] [5]

5-HT is thought to be involved in the pathophysiology of several clinical entities, including functional gut disorders (namely, irritable bowel syndrome (IBS)), carcinoid diarrhoea, and chemotherapy induced emesis. The aim of this review is to analyse the possible targets for pharmacological intervention in the light of the most recent advances of our understanding of the role of 5-HT in gut pathophysiology. Indeed, the recent regulatory interventions on well known drugs such as cisapride (a $5-HT_4$ receptor partial agonist, withdrawn in most countries because of its effects on cardiac repolarisation[6]) and alosetron (a $5-HT_3$ receptor antagonist, withdrawn for the possible occurrence of ischaemic colitis and then reintroduced into the US market in 2002[7]) have prompted a rethinking of our approaches to the pharmacological modulation of serotonergic pathways.

In gut disorders, the most interesting targets for pharmacological intervention are: (1) the 5-HT receptor subtypes known to affect gut function such as those belonging to the $5-HT_1$, $5-HT_3$, $5-HT_4$, and $5-HT_7$ subtypes[8]; and (2) the 5-HT reuptake mechanism which, apart from the central nervous system, is expressed in enteric neurones and enterocytes[9] and is blocked by antidepressants.

5-HT: enteric neurotransmitter and mucosal signalling molecule

Because so many responses are seen when exogenous 5-HT is applied to the gut, it is difficult to determine which of these are physiologically relevant (box 2). 5-HT works both as a neurotransmitter and a mucosal signalling molecule.

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The role of 5-HT as a neurotransmitter started to be appreciated in the mid 1960s.[10–12] In an elegant study, Bülbring and Gershon[13] showed thar desensitisation of 5-HT receptors and depletion of 5-HT interfered with vagal relaxation of the stomach: the vagus nerve was proposed to activate an intrinsic inhibitory neural circuit containing one or more serotonergic neurones connected in series with vagal motor nerve fibres. By the mid 1980s, 5-HT was known to be synthesised and stored in enteric neurones, released in response to depolarasing stimuli, and inactivated by reuptake into 5-HT containing neurones.[5 14] Namely, 5-HT is localised in descending interneurones (fig 1) which project to other myenteric ganglia and/or submucous ganglia.[4] 5-HT is responsible for induction of slow excitatory postsynaptic potentials in enteric neurones[15] and plays a (minor) role as a transmitter for fast excitatory postsynaptic potentials (fEPSPs) in myenteric neurones.[16]

Concerning the role of 5-HT as a mucosal signalling molecule, mucosal enterochromaffin cells appear to act as sensory transducers, responding to mechanical pressure[17] or nutrients,[18–20] to secrete 5-HT into the wall of the bowel and initiate peristaltic[21] and secretory reflexes (fig 1).[22] This role of enterochromaffin cells was first demonstrated by the pioneering studies of Bülbring and colleagues[17 23–25] and was confirmed subsequently.[15]

5-HT released by enterochromaffin cells may affect several subtypes of enteric neurones (intrinsic and extrinsic sensory neurones as well as motor and secretomotor neurones) and final effector cells (smooth muscle cells and enterocytes) (box 3). 5-HT is also a key mediator in signalling to the central nervous system[19] and is viewed as a major cause of nausea associated with ingestion of a number of toxins, including chemotherapeutic agents.[26]
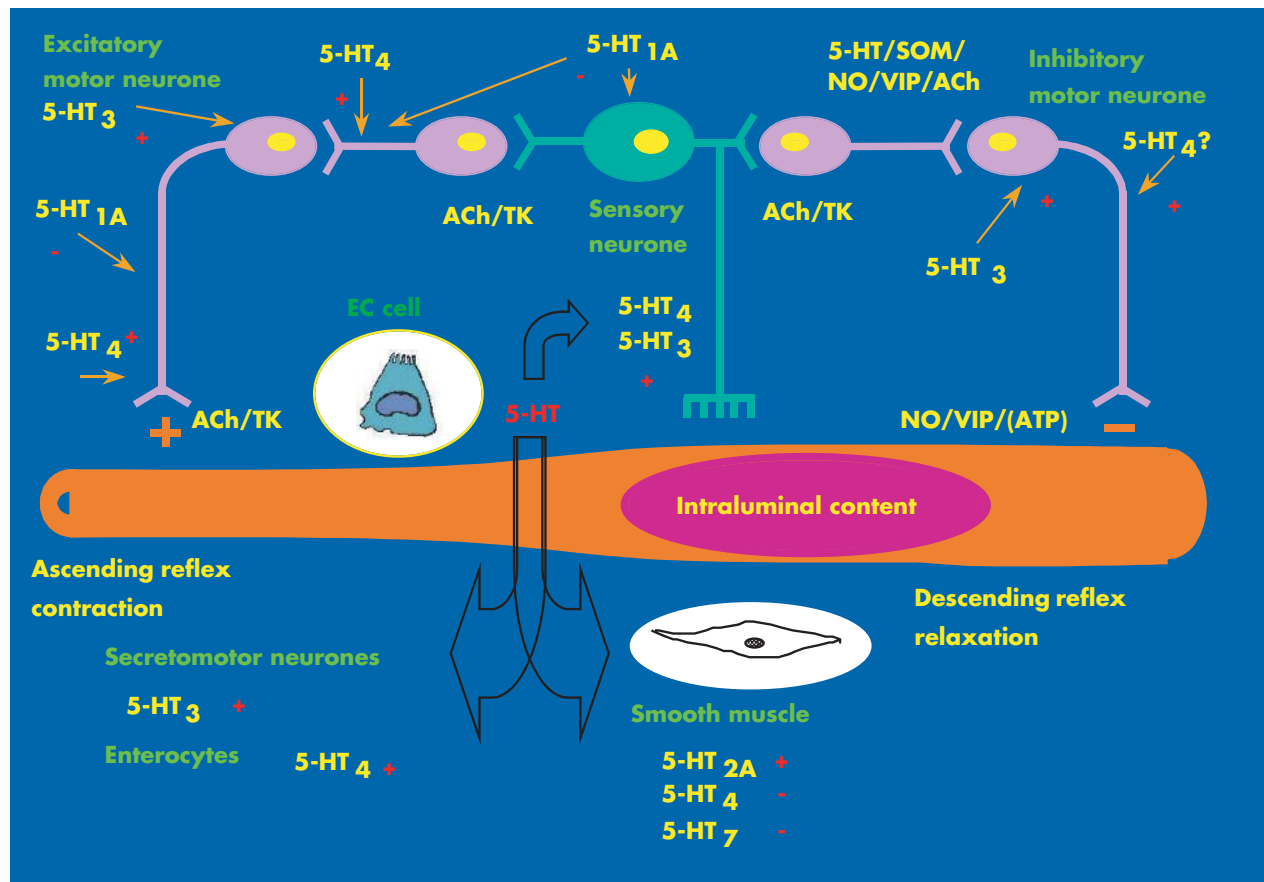

Figure 1 Modulation of intestinal function by serotonin (5-hydroxytryptamine or 5-HT) receptors. Distension by intraluminal contents stimulates sensory neurones (intrinsic primary afferent neurones) which trigger an ascending excitatory reflex (leading to contraction) and a descending inhibitory reflex (leading to relaxation). Transmitters released by interneurones in the ascending reflex include acetylcholine (ACh) and substance P (a tachykinin) whereas descending interneurones belonging to different subpopulations may use 5-HT, somatostatin (SOM), vasoactive intestinal polypeptide (VIP), nitric oxide (NO), ACh, and other mediators as transmitters. Excitatory motor neurones release ACh and tachykinins (TK) at the neuromuscular junction whereas inhibitory motor neurones may release NO, VIP, or ATP depending on the gut level and on the animal species. 5-HT released from enterochromaffin (EC) cells may affect several subtypes of enteric neurones (sensory, motor, and secretomotor neurones) as well as final effector cells (smooth muscle cells and enterocytes). +, stimulation; −, inhibition; ?, circumstantial evidence.

Table 1 Main serotonin (5-hydroxytryptamine or 5-HT) receptor subtypes in the gut

	5-HT$_{1A}$	5-HT$_{1B/D}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_3$	5-HT$_4$	5-HT$_7$	5-HT$_{1P}$*
Agonists	8-OH-DPAT	Sumatriptan	α-Me-5-HT	α-Me-5-HT	2-Me-5-HT	Tegaserod	5-CT 8-OH	Hydroxylated indalpines
	Buspirone	Rizatriptan Naratriptan		BW723C86	CPBG	Prucalopride	DPAT	
Antagonists	WAY100635	GR127935 (5-HT$_{1B/D}$ antagonist)	Ketanserin,	SB200646	Ondansetron	GR113808	Methiotepin	5-HTP-DP
		SB216641 (5-HT$_{1B}$-selective)	MDL100907	SB204741	Alosetron	GR125487	Metergoline	
		BRL15572 (5-HT$_{1D}$ –selective)			Cilansetron	Piboserod	SB258719	
							SB269970 SB656104	
Effectors	G$_{i/o}$	G$_{i/o}$	G$_{q/11}$	G$_{q/11}$	Ligand gated ion channel	G$_s$	G$_s$	G$_o$
Distribution in the gut	Enteric neurones	Enteric neurones (?)	Smooth muscle	Longitudinal smooth muscle	Enteric neurones	Enteric neurones, smooth muscle, enterocytes	Smooth muscle, enteric neurones (?)	Enteric neurones
		Circular smooth muscle (?)						
Functional response on stimulation	↓ Transmitter release	Gastric relaxation	Contraction	Contraction	fEPSP, ↑ transmitter release, ↑ secretion	↑ Transmitter release, relaxation, ↑ secretion	Relaxation	Slow EPSP

8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylaminotetralin); 5-CT, 5-carboxamidotryptamine; CPBG, chlorophenyl-biguanide; 5-HTP-DP, N-acetyl-5-hydroxytryptophyl-5-hydroxytryptophanamide (a dipeptide); fEPSP, fast excitatory postsynaptic potential.
*5-HT$_{1P}$ receptors are not included in the IUPHAR nomenclature of 5-HT receptors and are still considered an ''orphan'' receptor subtype.

5-HT secretion from enterochromaffin cells occurs predominantly at the interstitial side and is finely regulated by a complex pattern of receptor mediated mechanisms. Stimulatory receptors (for example, β-adrenoceptors, muscarinic, nicotinic, and 5-HT$_3$ receptors) and inhibitory receptors (for example, α$_2$-adrenoceptors, histamine H$_3$, GABA$_A$, GABA$_B$, and 5-HT$_4$ receptors) are involved in the control of 5-HT release from enterochromaffin cells.[27]

5-HT RECEPTORS AS TARGETS FOR PHARMACOLOGICAL INTERVENTION

5-HT has a bewildering range of effects in the intestine, largely due to the presence of multiple receptor subtypes which appear to be present on several classes of myenteric neurones, on smooth muscle cells, and on enterocytes (table 1, figs 1 and 2). The issue is further complicated by the recent report that genes for 5-HT receptors display marked population and molecular genetic complexity.[28]

5-HT receptors that are known to affect gut motor function are those belonging to the 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, and 5-HT$_7$ subtypes.[5 29–32] In addition, the presence of 5-HT$_{1P}$ receptors is reported in enteric neurones[33] where they are proposed to mediate slow EPSPs[15]; however, this receptor subtype is not included in the official International Union of Pharmacology (IUPHAR) classification of 5-HT receptors and is considered an ''orphan'' receptor.[34]

Neuronal 5-HT receptors may inhibit or enhance transmitter release and include the 5-HT$_{1A}$ (inhibitory[35]), 5-HT$_3$, and 5-HT$_4$ (both excitatory) subtypes.[5] Smooth muscle 5-HT receptors may contract or relax effector cells and belong to

the 5-HT$_{2A}$ (mediating contraction), 5-HT$_4$, and 5-HT$_7$ subtypes (both mediating relaxation). In the human small bowel, 5-HT$_{2A}$ receptors mediating contraction and 5-HT$_4$ receptors mediating relaxation coexist on smooth muscle cells.[36]

In the past 15 years, the increased availability of selective 5-HT receptor agonists and antagonists prompted a large number of investigations aimed at developing therapeutic agents for functional gut disorders. However, it should be acknowledged that drug selectivity is a relative concept and that the tendency to label a drug as a ''selective'' ligand for a given 5-HT receptor subtype often leads us to ignore that a single molecule, at therapeutic doses, may have several, sometimes disparate, biological targets. For instance, cisapride is a partial 5-HT$_4$ receptor agonist, a 5-HT$_3$ receptor antagonist, and a fairly potent HERG K$^+$ channel blocker.[6 8] This action on K$^+$ channels is responsible for the proarrhythmic effect but, paradoxically, it is also possible that part of the motor effects of cisapride depend on this property because it is now known that HERG K$^+$ channels are expressed in gut smooth muscle and interstitial cells of Cajal.[37 38]

Conversely, although selectivity for a given receptor subtype is desirable to reduce side effects, it is also true that single receptor modulating drugs are less likely to achieve a substantial therapeutic gain because of the multifactorial pathophysiology of functional gut disorders. Indeed, designing clinical trials of new therapeutic agents for functional syndromes presents a considerable challenge.[39 40] Currently available agents for the treatment of functional disorders were developed in the past three decades, focusing mainly on the underlying motor disorder (for example, delayed gastric emptying) which indeed affects a significant proportion of patients. More recently, visceral hypersensitivity (altered peripheral sensation or central processing of peripheral sensory signals) has become a major target for drug development.

Box 3

▶ 5-HT released from EC cells may affect several subtypes of enteric neurones (intrinsic and extrinsic sensory neurones as well as motor and secretomotor neurones) and final effector cells (smooth muscle cells and enterocytes).
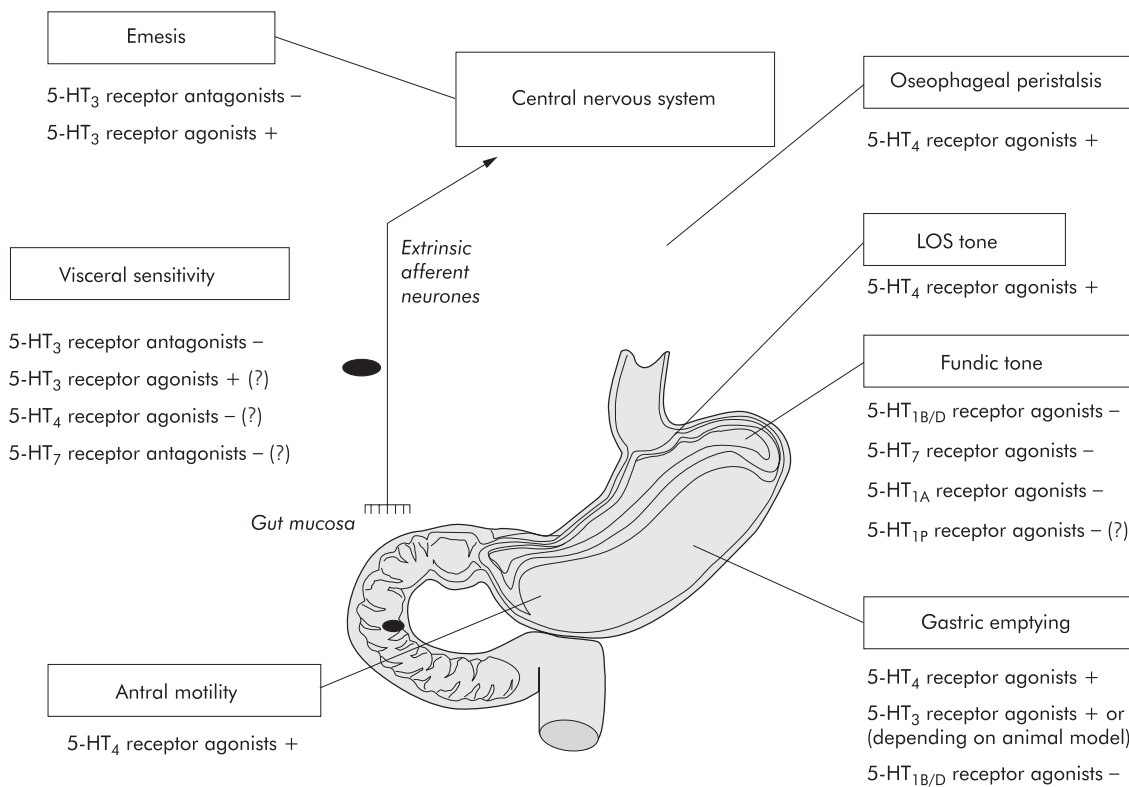
Figure 2 Effects of serotonin (5-hydroxytryptamine or 5-HT) receptor ligands on the upper gut. LOS, lower oesophageal sphincter; +, stimulation; −, inhibition; ?, there is debate in the literature or the effect is not conclusively proved.

The aforementioned difficulties in clearly defining a drug target explain why the exponential growth of compounds of potential interest for the treatment of functional gut disorders[41] has not yet filled the gap between basic and clinical research. Indeed, only a few 5-HT receptor ligands have received marketing authorisation for the treatment of gut disorders and the recent regulatory interventions on cisapride and alosetron have left some uncertainties on whether achieving a significant therapeutic gain with drugs modulating 5-HT receptors is a realistic goal.

In the next sections, the different 5-HT receptor subtypes and relevant agonist or antagonists of therapeutic interest will be dealt with in some detail, outlining the possible difficulties in achieving therapeutically useful agents.

5-HT$_1$ RECEPTORS

5-HT$_1$ receptor agonists

In the past decade, several studies documented the effects of the 5-HT$_{1B/D}$ receptor agonist sumatriptan on gastric motility and sensitivity in the same dose range used in migraine.[42–45] In 1992, Houghton and colleagues[42] showed that intravenous sumatriptan delayed gastric emptying of a nutrient liquid meal in healthy subjects. A few years later, Coulie et al showed that sumatriptan caused a notable delay in gastric emptying of both liquids and solids[44] and that it caused significant relaxation of the gastric fundus, thus enabling accommodation of considerably larger volumes before thresholds for perception or discomfort were reached during isovolumetric distension.[45] The fact that perception thresholds were altered by sumatriptan in response to isovolumetric, not isobaric, distension suggests that the effect of sumatriptan was determined by the change in gastric tone

rather than by an effect on visceral sensitivity. These observations provide a rationale for testing sumatriptan as a means for relieving symptoms in dyspeptic patients with defective postprandial gastric accommodation, although the effect on gastric emptying may theoretically be detrimental in patients with already delayed gastric emptying. Indeed, in dyspeptic patients, injection of subcutaneous sumatriptan was shown to restore gastric accommodation, improving the symptoms of early satiety.[46]

In subsequent studies, however, sumatriptan failed to reduce satiation symptoms after a challenge test in dyspepsia.[47 48] Malatesta and colleagues[47] evaluated the effect of sumatriptan and of the anticholinergic hyoscine on gastric accommodation after liquid ingestion in normal subjects and dyspeptic patients. In this study, in both dyspeptic patients and normal controls, gastric size measured after water distension was modified by sumatriptan, with a reduction in transverse and an increase in longitudinal size. Gastric distension with 500 ml of water evoked nausea, bloating, heartburn and, to lesser extent, epigastric pain, and the symptom score was higher in dyspeptics than controls. Sumatriptan was beneficial only on nausea induced by gastric distension (both in dyspeptics and controls) without affecting the other symptoms.

Because distension of the proximal stomach is a potent stimulus for the occurrence of transient lower oesophageal sphincter relaxations (TLOSRs, a major mechanism of reflux in patients with gastro-oesophageal reflux disease), the effect of sumatriptan was also studied on the frequency of postprandial TLOSRs and gastro-oesophageal reflux in healthy subjects.[49] Oesophageal manometry and pH monitoring were performed in 13 healthy volunteers for 30 minutes
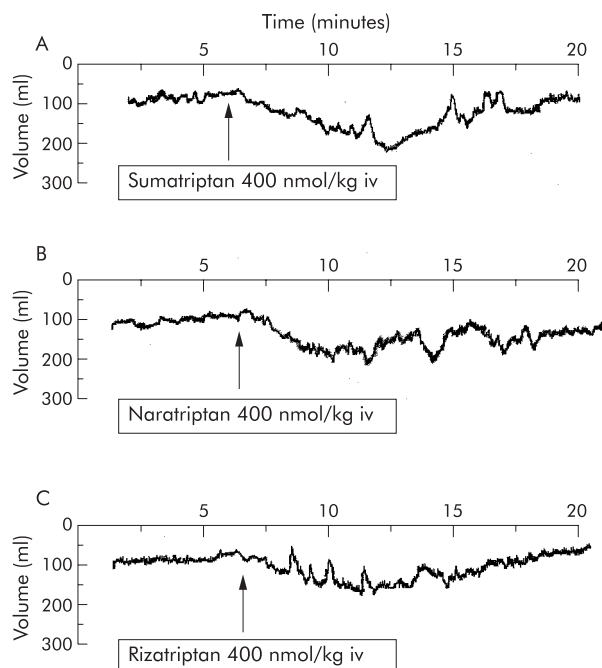
Figure 3 Representative tracings of intragastric volume in the canine proximal stomach, measured by a barostat at a distending pressure of 2 mm Hg, before and after intravenous (iv) administration of sumatriptan (A), naratriptan (B), and rizatriptan (C), all at a dose of 400 nmol/kg. Reproduced, with permission, from Moro and colleagues.[52]

before and 90 minutes after a semi liquid meal. Sumatriptan 6 mg subcutaneously or placebo was administered on separate days 30 minutes after the meal. Sumatriptan significantly increased postprandial lower oesophageal sphincter (LOS) pressure without reducing reflux events. In contrast, reflux and TLOSRs were more frequent after sumatriptan than after placebo. The authors concluded that sumatriptan prevents the natural decay in rate of TLOSRs occurring after a meal and favours gastro-oesophageal reflux in spite of the increase in LOS pressure. The sustained postprandial high rate of transient LOS relaxations after sumatriptan may be a consequence of prolonged fundic relaxation and retention of the meal in the proximal stomach.

Animal models have allowed more insight into the possible mechanism mediating the gastric motor effects of suma-triptan. Coulie and colleagues[43] using an in vivo cat model suggested that sumatriptan induced fundic relaxation occurs through activation of a nitrergic pathway. However, they did not investigate the 5-HT receptor subtype involved in this response. In guinea pigs, it was demonstrated that 5-HT induced gastric relaxations are mediated through activation of a $5-HT_1$-like receptor.[50] Some authors also considered the orphan $5-HT_{1P}$ receptors and suggested that sumatriptan might act via this receptor subtype.[45] However, none of the authors reporting the gastric motor effects of sumatriptan in vivo has ever tested the effect of $5-HT_{1P}$ receptor antagonists because of the lack of selective agents suitable for in vivo use. In a canine model, full antagonism of the effect of sumatriptan by GR127935 (dual $5-HT_{1B/D}$ receptor antago-nist) and SB216641 (selective $5-HT_{1B}$ receptor antagonist) supports the involvement of $5-HT_{1B}$ receptors, at least in this

model.[51][52] Involvement of $5-HT_7$ receptors in the response to sumatriptan is unlikely because the affinity value of sumatriptan for this receptor subtype is low.[52] Interestingly, gastric relaxation and enhanced accommodation to a distending stimulus seem to be a class effect of triptans as they occur not only with sumatriptan but also with second generation triptans (rizatriptan and naratriptan), at least in a canine model (fig 3).[52]

Whether the site of action of sumatriptan is central or peripheral remains to be determined. The fact that the compound penetrates poorly the blood-brain barrier and can relax the guinea pig isolated stomach[53] would argue against a central site of action although direct evidence for the presence of $5-HT_{1B/D}$ receptors in the gut is still lacking.

The possible role of $5-HT_{1A}$ receptors in modulating gastrointestinal motility has been suggested by some animal and human studies but information is still fragmentary. Rouzade *et al*, using flesinoxan (a $5-HT_{1A}$ receptor agonist), suggested that activation of these receptors in the central nervous system can increase gastric tone and, at the same time, decrease gastric sensitivity to distension in rats.[54] However, Xue and colleagues[55] have recently reported a peripheral inhibitory effect exerted by the $5-HT_{1A}$ receptor agonist buspirone on murine fundic tone. Likewise, flesi-noxan induced gastric relaxation in conscious dogs via $5-HT_{1A}$ receptors (as indicated by blockade with the selective $5-HT_{1A}$ receptor antagonist WAY-100635), a response mediated through a non-nitrergic vagal pathway.[56] These data are consistent with a preliminary account of a crossover study of buspirone in patients with functional dyspepsia where a reduction in symptoms and enhanced gastric accommodation to a meal were shown.[57] However, in healthy subjects, buspirone (10 mg twice daily) reduced postprandial aggregate symptom and nausea scores but did not increase the total volume of nutrient drink ingested or the post-prandial change in gastric volume with respect to placebo.[58]

In conclusion, although the results of clinical trials are not univocal, gastric relaxing drugs (such as $5-HT_1$ receptor agonists) could decrease early satiety, a cardinal symptom of dyspepsia, in those dyspeptic patients with impaired fundic relaxation to a meal/altered gastric sensitivity to distension. In these patients, conventional prokinesia (for example, achieved via motilin receptor agonists) would be contra-indicated (because of the possible further impairment of fundic relaxation): this probably explains the disappointing results obtained with conventional prokinetics in subgroups of dyspeptic patients. In contrast, because agonists acting at different $5-HT_1$ receptor subtypes have shown some clinical benefit, long term studies with different classes of orally active fundus relaxing drugs seem warranted to confirm their therapeutic potential.

$5-HT_3$ RECEPTORS

$5-HT_3$ receptors are a key target for therapeutic interventions as they are located at several peripheral and central sites. Apart from their well known effects on emetic pathways, they have the potential to control motility, intestinal secretion, and visceral sensitivity (figs 1 and 2, table 2) (box 4).

In functional experiments carried out in the isolated ileum, $5-HT_3$ receptor antagonists do not affect peristalsis when applied to the serosal side.[5] Conversely, they exert an inhibitory effect when applied intraluminally, suggesting blockade of $5-HT_3$ receptors on intrinsic sensory neurones.[59][60]

Table 2 Potential mechanisms by which 5-HT$_3$ and 5-HT$_4$ receptor ligands may influence gut function

	Examples	Motility	Absorption/secretion	Visceral sensitivity
5-HT$_3$ receptor agonists	MKC-733	↑ Transmitter release from enteric neurones, hence ↑ gut transit (the reported delay in gastric emptying in humans may be a consequence of nausea)	↑ Secretion, hence diarrhoea	Stimulation of vagal afferents with possible occurrence of nausea
5-HT$_3$ receptor antagonists	Alosetron, cilansetron, ondansetron	↓ Transmitter release from excitatory and inhibitory neurones: hence ↓ of peristalsis and ↑ compliance	↑ Absorption and/or ↓ secretion via an action on secretomotor neurones: hence inhibition of diarrhoea	↓ Visceral sensitivity through an action on intrinsic or extrinsic primary afferent neurones; antiemetic effect
5-HT$_4$ receptor agonists	Tegaserod, prucalopride, ML10302	(1) ↑ Transmitter release (acetylcholine, tachykinins, etc) from excitatory, inhibitory, and sensory neurones, hence prokinesia (2) Direct relaxation of smooth muscle cells (↑ compliance with indirect effect on visceral sensitivity)	↑ Secretion, hence loose stools and diarrhoea	↓ Visceral sensitivity through an action on afferent pathways (circumstantial evidence)
5-HT$_4$ receptor antagonists	Piboserod	↓ Transmitter release, hence delay in transit	↓ Secretion	?

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Both neurogenic contraction and relaxation can be induced in vitro by 5-HT$_3$-receptor activation in experimental animals.[61 62]

In vivo, more complex interactions seem to occur because of the multiple peripheral and central sites of action.[5 41] In rodents, the observation that 5-HT and restraint stress induced increase in faecal pellet output were antagonised by 5-HT$_3$ receptor antagonists was suggestive of a role for 5-HT$_3$ receptors in modulating colonic transit.[63 64] Autoradiographic studies indeed detected high densities of [^{125}I](S)-iodozacopride (a 5-HT$_3$ receptor ligand) in the myenteric plexus of the human colon.[65 66]

In humans, ondansetron has no effect on small bowel transit in healthy volunteers[67] or in patients with diarrhoea predominant IBS.[68] However, ondansetron slows colonic transit[69 70] and inhibits the colonic motor response to a meal[71] in healthy subjects. In a double blind placebo controlled study in 50 IBS patients, ondansetron reduced bowel frequency and improved stool consistency in the diarrhoea predominant subgroup (28 patients).[72]

Further evidence in favour of a role for 5-HT$_3$ receptors in humans was provided by Prior and Read[73] who found a dose dependent reduction in postprandial colonic motility with granisetron, and by von der Ohe and colleagues[74] who reported reduction of the postprandial colonic hypertonic response in carcinoid diarrhoea with ondansetron. Constipation induced by alosetron is discussed in the next section.

Concerning the effect on visceral sensitivity, several animal models point to the role of 5-HT$_3$ receptors in modulating visceral sensitivity.[41] Granisetron and tropisetron (but not ondansetron) were found to inhibit the fall in blood pressure and intragastric pressure observed in rats after duodenal distension.[75] Whether the site of 5-HT receptors modulating afferent information is on peripheral afferent nerve fibres or outside the gut, however, is unclear. For instance, alosetron, administered either centrally or peripherally in dogs, seems to modulate the visceral nociceptive effect of rectal distension.[76]

In humans, reduced perception of colonic distension may also depend on increased compliance of the colon to distension.[77] In other studies, granisetron was found to reduce rectal sensitivity in patients with IBS[73] whereas ondansetron had no effect.[78] Interestingly, however, ondansetron reduced nausea and gastric sensitivity to distension during intraduodenal lipid infusion in healthy subjects.[79] In female patients with diarrhoea predominant IBS, alosetron reduced colonic hypersensitivity induced by duodenal lipids.[80]

The hypothesis that 5-HT$_3$ receptors may modulate perception of visceral sensations by acting at the central level has also been explored. Mayer et al carried out a randomised placebo controlled functional brain imaging study[81] to assess the effect of alosetron (1–4 mg twice daily for three weeks) on IBS symptoms, regional brain activation by rectosigmoid distension, and associated perceptual and emotional responses. Fifty two non-constipated patients with IBS (28 females) were enrolled. Thirty seven patients completed both brain scans following randomisation. Rectosigmoid stimulation was performed with a computer controlled barostat. Changes in regional cerebral blood flow were assessed using positron emission tomography. Alosetron, but not placebo, was associated with a decrease in symptom ratings and reductions in emotional stimulus ratings. Compared with baseline, alosetron treatment was associated with reduced regional cerebral blood flow in bilateral frontotemporal and various limbic structures, including the amygdala. Compared with placebo, decreases in activity of the amygdala, ventral striatum, hypothalamus, and infragenual cingulate gyrus were significantly greater after alosetron. Thus alosetron decreased brain activity in response to aversive rectal stimuli in structures of the emotional motor system, and this was associated with a decrease in gastrointestinal symptoms.

In another study,[82] the effect of alosetron on regional cerebral blood flow (rCBF) in the absence and presence of rectal or sigmoid stimulation was assessed to evaluate two hypothesised mechanisms of therapeutic action: peripheral antinociception and inhibition of emotional motor system regions in the brain. Forty nine non-constipated patients with IBS (26 females) received positron emission tomography (PET) brain scans before a randomised, placebo controlled, three week trial with alosetron (1–4 mg twice daily). rCBF during baseline, rectal distension, and anticipation of undelivered rectal distension was assessed. The three

Box 4

▶ 5-HT$_3$ receptors are a key target: they have the potential to control motility, fluid secretion, and visceral sensitivity.

conditions were repeated after a series of noxious sigmoid distensions. Alosetron treatment, as compared with placebo, improved IBS symptoms and reduced rCBF in $5\text{-}HT_3$ receptor containing regions of the emotional motor system but not in areas activated by pain. Reduction of rCBF appeared greatest in the absence of visceral stimulation, and was partially reversed by rectal or sigmoid distension. Symptom improvement across sessions was significantly correlated with rCBF decreases in the $5\text{-}HT_3$ receptor rich amygdala, ventral striatum, and dorsal pons. The authors concluded that reduction in IBS symptoms correlated with a drug induced reduction in the activity of central autonomic networks mediating emotional expression. This was maximal in the absence of nociceptive input.

$5\text{-}HT_3$ receptor antagonists in therapeutics

Apart from their well known antiemetic effect, $5\text{-}HT_3$ receptor antagonists have several potential therapeutic actions (table 2) in functional gut disorders[83–85]: modulation of visceral sensitivity,[86] enhanced compliance (that is, increasing the ability of the gut to adapt to distension),[77] blockade of excitatory $5\text{-}HT_3$ receptors located on sensory, ascending, and descending neuronal pathways involved in peristalsis, and increase in fluid absorption.[83] For all of these reasons, $5\text{-}HT_3$ receptor antagonists may slow transit. A recent study,[87] which paradoxically failed to observe a significant effect of alosetron on transit parameters, discusses important issues to optimise experimental design of trials designed to find mechanistic explanations for drug action in functional gut disorders.

Among $5\text{-}HT_3$ receptor antagonists, alosetron was initially approved by the FDA for the treatment of diarrhoea predominant IBS in women but safety concerns (ischaemic colitis affecting between 1 in 700 and 1 in 1000 patients receiving the drug) led to drug withdrawal only a few months after approval.[88] Recently, alosetron was reintroduced into the US market with restrictions on its use: it has an indication only for women with severe diarrhoea predominant IBS who have failed to respond to conventional therapy (see the FDA dedicated internet address: http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm). The starting dose of alosetron is now 1 mg once daily which, if well tolerated, after four weeks may be increased to 1 mg twice daily (that is, the dose used in controlled trials)[89 90] if control of symptoms is not adequate. The regulatory case of alosetron was highly debated in the literature.[7 91] Other $5\text{-}HT_3$ receptor antagonists are now under development. Cilansetron is currently undergoing phase III trials[92] but only limited information is at present available in the published literature.[93 94]

Concerning trials available on the use of alosetron in IBS, in a double blind, placebo controlled, parallel group study,[95] a 12 week treatment period was carried out on a total of 462 patients with IBS (335 females) with the following doses of alosetron: 0.1 mg twice daily, 0.5 mg twice daily, and 2 mg twice daily. In the total population and in the female subpopulation (but not in males), alosetron 2 mg twice daily significantly increased the proportion of pain free days and decreased the visual analogue scale score for diarrhoea. It also led to significant hardening of stool and a reduction in stool frequency in the total population.

In another study,[96] 623 non-constipated females with IBS were randomised to receive alosetron 1 mg twice daily or mebeverine 135 mg three times daily for 12 weeks. The primary efficacy end point was monthly responders for adequate relief of IBS related abdominal pain and discomfort (defined as patients reporting adequate relief on at least two out of four weeks). There were significantly more responders in the alosetron group compared with mebeverine at months 2 and 3.

Camilleri and colleagues[89] studied 647 female IBS patients with diarrhoea predominant or alternating bowel patterns: 324 patients were assigned 1 mg alosetron and 323 placebo orally twice daily for 12 weeks. Once again, adequate relief of abdominal pain and discomfort was the primary end point. The dropout rate was 24% in the alosetron group and 16% in the placebo group: the difference was mainly due to a greater occurrence of constipation in the alosetron group. Adequate relief for all three months of treatment was reported in a greater proportion of alosetron treated patients (difference 12%). Alosetron also decreased urgency and stool frequency. Constipation occurred in 30% and 3% of patients in the alosetron and placebo groups, respectively.

A recent meta-analysis on the efficacy of alosetron in IBS concluded that the average number need to treat (NNT) is approximately 7 and that one in four patients may develop constipation (box 5).[97]

The pathophysiology of ischaemic colitis associated with the use of alosetron is still unclear: more importantly, it is at present unknown whether this is a class effect of $5\text{-}HT_3$ receptor antagonists when used in patients with IBS (notably, ischaemic colitis is not an issue when $5\text{-}HT_3$ receptor antagonists are used for chemotherapy induced emesis). A preliminary account of a study carried out in rats[98] reports a decrease in mesenteric blood flow and vascular conductance with alosetron and cilansetron (but not with tegaserod). However, the predictivity of this model for ischaemic colitis is unknown, and it is too early to draw conclusions from these findings.

Concerning the possible use of $5\text{-}HT_3$ receptor antagonists in functional dyspepsia, Talley and colleagues[99] performed a pilot, dose ranging, placebo controlled, multicentre, randomised trial with 320 functional dyspepsia patients who received placebo (n = 81) or alosetron 0.5 mg twice daily (n = 77), 1.0 mg twice daily (n = 79), or 2.0 mg twice daily (n = 83) for 12 weeks, followed by one week of follow up. Primary efficacy was the 12 week average rate of adequate relief of upper abdominal pain or discomfort. Twelve week average rates of adequate relief of pain or discomfort were 46%, 55%, 55%, and 47% in the placebo, 0.5 mg, 1.0 mg, and 2.0 mg alosetron groups, respectively. Alosetron 0.5 mg or 1.0 mg showed potential benefit over placebo for early satiety and postprandial fullness. Constipation was the most commonly reported adverse event. Thus the therapeutic gain with alosetron appeared to be relatively modest in this population of dyspeptic patients.

Another trial carried out in 36 healthy volunteers[100] assessed the effects of placebo, 0.5, and 1 mg twice daily alosetron on fasting and postprandial gastric volumes (using

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Box 5

▶ In patients with IBS, according to a meta-analysis to determine the effect of alosetron on adequate relief of pain or global improvement of symptoms, the average number needed to treat is 7; one in four patients may develop constipation.

single photon emission computed tomography) and symptoms based on 100 mm visual analogue scale, 30 minutes after maximum volume ingested. Alosetron significantly reduced postprandial symptoms (1 mg alosetron reduced aggregate score by approximately 40% with respect to placebo) and nausea, and tended to reduce bloating. Effects on pain and fullness were not statistically significant. There was no significant effect of the 5-HT$_3$ antagonist on volume of meal tolerated. As 5-HT$_3$ receptors are unlikely to be involved in the control of gastric tone,[101] these observations are probably to be interpreted as effects on visceral afferents and are not due to increased postprandial gastric volume.

5-HT$_3$ receptor agonists in therapeutics: preliminary evidence

The potential therapeutic role of 5-HT$_3$ receptor agonists is now under scrutiny. Stimulation of 5-HT$_3$ receptors can, on the one hand, exert a prokinetic effect but it can also stimulate nausea and vomiting (table 2). Indeed, the 5-HT$_3$ receptor agonist MKC-733 can accelerate gastric emptying in animal models but it was recently reported to delay gastric emptying in humans[102]: a delay in gastric emptying may be a consequence of nausea. In this recent study,[102] Coleman *et al* determined the effect of oral MKC-733 (0.2, 1, and 4 mg) on upper gastrointestinal motility compared with placebo in three randomised, double blind, crossover protocols in healthy males. Antroduodenal manometry was recorded for eight hours during fasting and three hours postprandially (n = 12). Gastric emptying and small intestinal transit were determined by gamma scintigraphy (n = 16). Gastric emptying, accommodation, and antral motility were determined by echoplanar magnetic resonance imaging (n = 12). MKC-733 (4 mg) increased the number of migrating motor complexes recorded in the antrum and duodenum but had no effect on postprandial motility. MKC-733 delayed scintigraphically assessed liquid gastric emptying and accelerated small intestinal transit. Echoplanar magnetic resonance imaging confirmed delayed gastric emptying and demonstrated a significant increase in cross sectional area of the proximal stomach. Thus MKC-733 delays liquid gastric emptying in association with relaxation of the proximal stomach, stimulates fasting antroduodenal migrating motor complex activity, and accelerates small intestinal transit.

To date, no other studies are available in the literature on the gastrointestinal effects of 5-HT$_3$ receptor agonists in humans.

5-HT$_4$ RECEPTORS

5-HT$_4$ receptors mediate several responses in the gut (figs 1 and 2, table 2) (box 6).[41] Prokinesia may result from increased release of acetylcholine (and tachykinins) from excitatory neurones and may operate in human small bowel and stomach,[103] [104] but early investigations failed to identify this pathway in human colonic circular muscle.[105] An in vivo study in dogs showed that tachykininergic pathways play an important role in mediating the colonic motor response to administration of the 5-HT$_4$ receptor agonist ML10302 whereas they are not involved in ML10302 induced prokinesia in the small bowel.[106] Besides these actions, 5-HT$_4$ receptors also affect secretory processes at the mucosal level.[107]

There are animal[21] and human[108] data suggesting that 5-HT released by mucosal stimulation initiates a peristaltic reflex by activating 5-HT$_4$ receptors on sensory neurones containing

Box 6

▶ 5-HT$_4$ receptors are another key target for pharmacological intervention: their stimulation induces prokinesia and favours fluid secretion.

calcitonin gene related peptide. These effects are mimicked by mucosal application of selective 5-HT$_4$ receptor agonists (prucalopride and tegaserod).[109] In humans, experimental evidence for this mechanism is so far limited to the small bowel.

In the human colon, circular muscle strips are endowed with 5-HT$_4$ receptors located on smooth muscle cells (fig 1) where they mediate relaxation.[65] [110] [111] This is an important difference with one of the most widely used experimental models (the guinea pig colon where neuronal 5-HT$_4$ receptors mediate contractile responses that are mainly cholinergic in nature[112] [113]). However, a recent report[114] suggests the presence of 5-HT$_4$ receptors on cholinergic neurones supplying the longitudinal muscle in the human colon.

With hindsight, the conflicting results (prokinesia versus absence of prokinetic effect in the colon) observed in the early studies with cisapride (reviewed by De Ponti and Malagelada[41]) are not surprising if one considers that the net in vivo response to 5-HT$_4$ receptor stimulation is the result of multiple actions at different levels and that cisapride is a mixed 5-HT$_4$ receptor agonist/5-HT$_3$ receptor antagonist, with the latter property negatively affecting the prokinetic potential of the compound.

From a pharmacological point of view, it is noteworthy that all 5-HT$_4$ receptor agonists so far developed for clinical use are partial agonists (intrinsic activity ranging from 0.2, as in the case of tegaserod,[115] to 0.8, as in the case of prucalopride[116] [117]). One important aspect of partial agonists is that they may surrogate the functions of 5-HT when its release is impaired but may work as antagonists by opposing the effect of endogenous 5-HT (which is a full agonist) in case of 5-HT overload. In addition, partial agonists may help to overcome, at least in part, the problem of 5-HT$_4$ receptor desensitisation.

Whether 5-HT$_4$ receptor agonists can affect visceral sensitivity by activating 5-HT$_4$ receptors is still controversial. In healthy volunteers, cisapride (which is also a 5-HT$_3$ receptor antagonist) significantly lowered thresholds for perception and discomfort during gastric distension but also significantly enhanced the size of meal induced fundus relaxation (that is, improved gastric accommodation).[118] In another study,[119] eight healthy subjects were studied on two different days, each after seven days of treatment with either placebo or cisapride. Intraduodenal infusion of lipids caused relaxation of the gastric fundus and this effect was unchanged by cisapride. Cisapride did not influence gastric sensitivity to distension or gastric compliance.

A study carried out in awake rats suggests an effect of tegaserod on colorectal sensitivity not linked to alterations in compliance at doses of 0.1 and 0.3 mg/kg intraperitoneally: tegaserod was found to increase pain threshold to colorectal but not to gastric distension.[120] Schikowski and colleagues[121] studied the involvement of 5-HT$_4$ receptors in modulation of the extrinsic afferent sensitivity of the intestinal wall. During distension ramps, mechanoreceptive rectal afferents in sacral dorsal roots were examined in decerebrate anaesthesia free cats using tegaserod and the 5-HT$_4$ receptor antagonist SB 203186. The static discharge rate of the afferents evoked by

rectal distension decreased after intravenous tegaserod at intraluminal pressures above 30 mm Hg, with the most effective reduction occurring at 50 mm Hg. The effect was dose dependent and could be partly reversed by intravenous SB 203186 (fig 4). Tegaserod did not alter the pressure-volume relationship (compliance) of the rectum. Notably, however, inhibition of rectal afferents by tegaserod was seen only at high distension levels and there was no significant effect on pressure threshold or spontaneous firing rate.

The potential of a drug to modulate visceral sensitivity is sometimes assessed by studying the RIII reflex, a polysynaptic reflex elicited by electrical stimulation of a cutaneous sensory nerve and recorded from a flexor muscle on the ipsilateral limb. Graded visceral distension inhibits the RIII reflex response.[122] In healthy subjects, tegaserod (6 mg twice daily for seven days) was reported to decrease sensitivity to rectal distension, as assessed by inhibition of the RIII reflex evoked by slow rectal distension up to the pain threshold.[122] The effects of rapid rectal distension or the intensity of subjective pain perception were not altered by tegaserod.

Although all of these data provide circumstantial evidence for an effect of tegaserod on visceral sensitivity, no firm conclusions can be drawn on the role of 5-HT$_4$ receptors on extrinsic afferent fibres. Indeed, 5-HT$_4$ receptors are coupled to G$_s$ (table 1) and their stimulation promotes cyclic AMP formation: thus 5-HT$_4$ receptor agonists would be expected to enhance rather than inhibit afferent firing. On the other hand, the effects observed by Schikowski and colleagues[121] might be ascribed to functional antagonism by the partial agonist tegaserod of the effect of endogenous 5-HT, although this hypothesis does not fit with the observation that the effect of tegaserod was partly reversed by SB 203186 (fig 4). Thus further studies are needed to clarify this issue.

5-HT$_4$ receptor agonists in therapeutics

The most extensively studied 5-HT$_4$ receptor agonists are cisapride, tegaserod, and prucalopride. A large number of studies have been published on cisapride but these will not be discussed here because cisapride is no longer used (except on a limited access basis[123]).

Among second generation 5-HT$_4$ receptor agonists, tegaserod[124][125] and prucalopride[126][127] have already undergone clinical trials which have been targeted mainly to the treatment of lower gut disorders.[8] However, because of
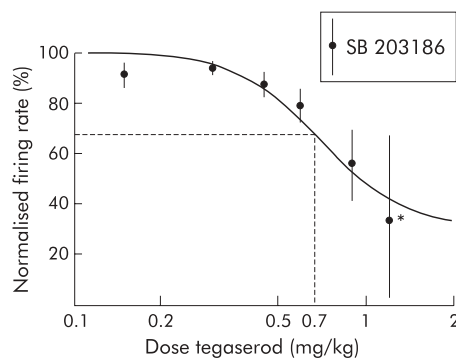

Figure 4 Relationship between dose of tegaserod and firing rate of nine rectal afferents in decerebrate cats. Half maximal reduction was obtained with a dose of 0.7 mg/kg. The 5-HT$_4$ receptor antagonist SB203186 reversed the tegaserod induced reduction in firing rate. *p<0.05. Reproduced, with permission, from Schikowski and colleagues.[121]

carcinogenicity in animals, it is unclear whether prucalopride will reach clinical practice.

Second generation 5-HT$_4$ receptor agonists such as tegaserod and mosapride have no significant HERG K$^+$ channel blocking properties[128–131] and at least some of them (tegaserod,[132] prucalopride[133–135]) may be more active at the colonic level than cisapride. Interestingly, mosapride, whose main metabolite is a 5-HT$_3$ receptor antagonist,[136] displays little or no prokinetic activity in the colon,[137] similar to what is observed with cisapride. Mosapride is marketed in Japan and is targeted for the treatment of upper gut disorders, such as gastro-oesophageal reflux disease.[138] It was found to be similar to placebo in the treatment of functional dyspepsia.[139]

Concerning tegaserod in health, Degen and colleagues[140] have shown that intravenous (0.6 mg) and oral (6 mg) tegaserod accelerate gastric emptying, and small bowel and colonic transit. Tack and colleagues[141] reported that tegaserod 6 mg twice daily enhances fasting gastric compliance and allows for larger intragastric volumes both before and after a meal. The absolute bioavailability of tegaserod is approximately 10% and food reduces the Cmax of tegaserod and area under the plasma concentration curve. The terminal elimination half life is approximately 11 hours.[125]

As regards the use of tegaserod in functional gut disorders, Prather et al studied the effects of tegaserod on gastric, small bowel, and colonic transit in 24 patients with constipation predominant IBS who were randomised to one week of tegaserod (2 mg twice daily) or placebo.[142] Interestingly, tegaserod accelerated orocaecal transit, leaving gastric emptying unaltered and also tended to accelerate colonic transit. No serious adverse events were reported.

Tegaserod results in global relief of IBS symptoms in females with symptoms of constipation predominant IBS.[143–146] Effective doses of tegaserod are 4–12 mg per day in two divided doses (2 mg or 6 mg twice daily). Relief was associated with significant improvement in a number of secondary end points such as pain free days, frequency of bowel movements, and stool consistency. The drug was significantly effective, providing 8–21% advantage over placebo in female patients, and particularly in those with documented constipation during the baseline run-in period. Tegaserod appeared relatively safe with no serious adverse effects reported in the clinical trials programme and in the cohort treated in open evaluation for over six months.[147]

In a recent Cochrane review,[148] the efficacy and tolerability of tegaserod for the treatment of IBS were evaluated. Randomised or quasi randomised controlled trials comparing tegaserod with placebo, no treatment, or any other intervention (pharmacological or non-pharmacological) in subjects aged 12 years and above with a diagnosis of IBS, focusing on clinical end points, were considered for review. Eight short term placebo controlled studies fulfilled the inclusion criteria. These were predominantly conducted in women. Seven studies evaluated the efficacy of tegaserod on global gastrointestinal symptoms in patients with constipation predominant IBS. The relative risk of being a responder in terms of global relief of gastrointestinal symptoms was significantly higher with tegaserod 12 mg and 4 mg compared with placebo, with an NNT of 14 and 20, respectively (box 7). Although the pooled results indicated statistically significant benefit with tegaserod, the a priori minimal clinically important differences set in two of the four pooled studies were not reached. Tegaserod did not significantly

improve individual symptoms of abdominal pain and discomfort although bowel habit showed a statistically significant improvement with tegaserod 4 mg and there was a non-significant trend in favour of tegaserod 12 mg. The proportion of patients experiencing diarrhoea was significantly higher in the tegaserod 12 mg group compared with placebo, with a number needed to harm (NNH) of 20.

In the USA, tegaserod is contraindicated in patients with a history of bowel obstruction, abdominal adhesions, or symptomatic gall bladder disease due to a non-significant difference in abdominal surgery between tegaserod using and placebo using patients in phase III trials. A recent study[149] calculated the incidence of abdominal and pelvic surgery in tegaserod using and placebo using patients in randomised controlled trials and to assess the possible association between medication and surgery, using pre-specified criteria in a blind adjudication procedure. Thirteen randomised controlled trials (n = 9857 patients) met the primary study selection criteria. No significant difference in the incidence of abdominal/pelvic surgery was identified between tegaserod using and placebo using patients: pelvic surgery, 0.16% versus 0.19% (p = 0.80); abdominal surgery (non-cholecystectomy), 0.15% versus 0.19% (p = 0.61); cholecystectomy, 0.13% versus 0.03% (p = 0.17); total abdominal/pelvic surgery, 0.44% versus 0.41% (P = 1.00). Post-adjudication, there was no significant difference in the incidence of abdominal/pelvic surgery between tegaserod using and placebo using patients.

The other 5-HT$_4$ receptor agonist prucalopride[133 150 151] is being investigated for a range of conditions, including constipation predominant IBS and slow transit constipation.[134 135 152] In a double blind crossover study in 24 healthy volunteers,[126] prucalopride 1 and 2 mg for one week significantly increased number of stools and percentage of loose/watery stools compared with placebo. These parameters returned to baseline within one week after stopping prucalopride. Prucalopride also significantly shortened mean colonic transit time and total gut transit time.

Administration of prucalopride 1 and 2 mg for one week in healthy volunteers accelerated orocaecal and whole gut transit while having no effect on gut sensitivity to distension or electrical stimulation.[153]

5-HT$_4$ receptor antagonists in therapeutics

Because of the different locations of 5-HT$_4$ receptors in the gut, it is difficult to predict the net effect of selective antagonists in vivo. 5-HT$_4$ receptor antagonists do not usually affect normal bowel motility in animals[154] or humans[155] although they may antagonise both the ability of 5-HT to sensitise the peristaltic reflex and 5-hydroxytryptophan induced defecation/diarrhoea, at least in animals.[154 156 157] In rats, piboserod was reported to strongly inhibit the migrating motor complex.[158]

Box 7

► In patients with constipation predominant IBS, according to a Cochrane review on the efficacy of tegaserod, the relative risk of being a responder in terms of global relief of gastrointestinal symptoms was significantly higher with tegaserod 12 and 4 mg compared with placebo, with a number need to treat of 14 and 20, respectively.

Only preliminary clinical data on the possible role of selective 5-HT$_4$ receptor antagonists in the treatment of functional gastrointestinal disorders are available. Piboserod (SB207266A) is one of the best characterised 5-HT$_4$ receptor antagonists to date. It displays subnanomolar affinity (pK$_B$ value 9.98) in the human intestine[154] and, at single oral doses of 0.5–5 mg in healthy male volunteers, significantly and dose dependently antagonised the effects of cisapride in a pharmacodynamic model of 5-HT$_4$ receptor activation (increase in plasma aldosterone levels).[159] Dynamic modelling in this study predicted that a dose of ~1 mg piboserod would block 90% of the cisapride induced aldosterone response.

Piboserod prolongs orocaecal transit time in patients with diarrhoea predominant IBS,[160] hence the proposed indication in this subset of patients. The ability of piboserod to affect visceral sensitivity is unclear. At variance with 5-HT$_3$ receptors, only limited data are available to support a role for 5-HT$_4$ receptors in controlling visceral sensitivity.[161] Although oral piboserod (20 mg daily for 10 days) tended to increase the distension volume required to induce the sensation of discomfort in diarrhoea predominant IBS patients, this effect did not reach statistical significance.[160] Interestingly, in a rat model of intestinal hyperalgesia,[162] piboserod per se had no effect but potentiated the effects of submaximal doses of granisetron, suggesting that 5-HT$_4$ receptors may cooperate with 5-HT$_3$ receptors in inhibiting intestinal hyperalgesia. This observation poses a rationale for the development of dual antagonists (5-HT$_3$/5-HT$_4$ receptor antagonists).[64]

Interestingly, because 5-HT$_4$ receptors are present in human atrial cells and when stimulated may cause atrial arrhythmias,[129] piboserod is under investigation in clinical trials for atrial fibrillation.[163] It is unknown at this time whether this indication will have a clinical role, all the more so because the role of 5-HT$_4$ receptors in humans is uncertain (for an overview of extraintestinal locations of 5-HT$_4$ receptor see Tonini and colleagues[129]).

5-HT$_7$ RECEPTORS

The pharmacological profile of the 5-HT$_7$ receptor is similar to that of the 5-HT$_{1A}$ receptor subtype. Indeed, 8-OH-DPAT, a compound previously considered a selective 5-HT$_{1A}$ receptor agonist, is now known to be a partial agonist at the 5-HT$_7$ receptor.[164]

5-HT$_7$ receptors mediate relaxation in human colonic smooth muscle[32] and in the guinea pig ileum.[165] In addition, they may modulate relaxation of the proximal stomach in conscious dogs by a mechanism not involving nitric oxide.[166 167] 5-HT$_7$ receptors may also have a role in inhibition of peristalsis by 5-HT.[168] Theoretically, blockade of 5-HT$_7$ receptors may also increase the threshold pressure to trigger intestinal peristalsis and decrease the compliance of the intestinal wall.[169]

One intriguing finding that may open new perspective for 5-HT$_7$ receptor ligands is that this receptor subtype is expressed by rat primary afferent nociceptors terminating in the superficial layers of the spinal cord dorsal horn and seems to be involved in nociceptor activation by 5-HT.[170]

To the best of my knowledge, no selective 5-HT$_7$ receptor ligands are yet available for clinical use but selective antagonists suitable for in vivo administration are being developed and are awaited soon.

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5-HT REUPTAKE AS A TARGET FOR PHARMACOLOGICAL INTERVENTION

5-HT, because of its acid dissociation constant of 10, is highly charged at physiological pH and does not cross plasma membranes. On the other hand, the fact that catabolism of 5-HT depends entirely on intracellular enzymes (monoamine oxidase and glucuronyl transferase)[9] makes 5-HT transport across plasma membranes a key mechanism for termination of its effects. The high affinity transporter for 5-HT, known as the serotonin transporter (SERT), is widely expressed, apart from central or peripheral serotonergic neurones, by intestinal epithelial cells[171] and platelets.[172] In particular, enterocytes express SERT in mice, rats, guinea pigs, and humans and are thought to play an important role in inactivation of 5-HT in the mucosa where no serotonergic neurones are found. Inhibition of mucosal SERT by fluoxetine leads rapidly to potentiation of mucosally stimulated enteric reflexes and a pronounced increase in the number of intrinsic primary afferent neurones recruited by a given strength of mucosal stimulus.[173] Interestingly, transgenic mice lacking SERT exhibit abnormal gastrointestinal motility and usually display accelerated colorectal motility associated with an increased water content in their stools.[174] Diarrhoea occasionally alternates with constipation, possibly because of plasticity of serotonergic mechanisms.[9]

Wade and colleagues[171] investigated the effect of desensitisation to 5-HT and of 5-HT reuptake blockade with fluoxetine on the peristaltic reflex in the guinea pig large intestine in vitro. This reflex can be evoked in the absence of input from the central nervous system because the responsible neural pathways are intrinsic to the intestine. Desensitisation of 5-HT receptors was demonstrated to inhibit the peristaltic reflex; low concentrations of fluoxetine (1.0 nM) potentiated the reflex whereas higher concentrations blocked it, suggesting that the reflex depends on 5-HT transporter mediated inactivation of 5-HT.

Concerning possible pathophysiological roles of SERT, apart from changes in the expression or pharmacological profile of SERT associated with dysfunctions of central serotonergic transmission (for example, depression and migraine), it is noteworthy that in guinea pigs with experimental colitis, a concomitant increment in 5-HT availability and a decrease in mRNA SERT expression were detected in the inflamed colonic mucosa.[175] Clinical evidence suggests that similar alterations may also occur in patients with either IBS or inflammatory bowel disease.[176] Moreover, SERT polymorphisms may be responsible for pharmacogenetic differences, as suggested by the colonic transit response to alosetron in patients with diarrhoea predominant IBS.[177]

As regards SERT in platelets (a good surrogate to study affinity constants and kinetics of SERT in other tissues), a recent study[172] examined the binding profile of platelet SERT in healthy volunteers and in patients with diarrhoea predominant IBS, both before and after treatment with alosetron (1 mg twice daily for eight weeks). At baseline, maximal binding capacity (B_{max}) and dissociation constant (K_d) values of [^{3}H]-paroxetine binding were respectively lower and higher in diarrhoea predominant IBS patients than in healthy volunteers. Symptom severity score in diarrhoea predominant IBS patients was negatively correlated with B_{max}, but not K_d, values. After treatment with alosetron, symptom severity score decreased significantly whereas B_{max} and K_d values remained unchanged. Thus SERT expressed on platelet membranes of diarrhoea predominant IBS patients is characterised by low density and binding affinity and there is a possible correlation between reduced capacity of 5-HT reuptake and severity of diarrhoea predominant IBS symptoms.

Because of the key role played by SERT in the gut, there is a strong rationale to use antidepressants in functional gut disorders: these agents, by prolonging the availability of physiologically released 5-HT, may modulate gut sensorimotor function. Table 3[178] reports affinity values of some antidepressants (both non-selective and selective 5-HT reuptake inhibitors) for monoamine transporters. It should be kept in mind that antidepressants share a myriad of additional pharmacological actions, some of which may be important to determine desired and undesired effects. Apart from blockade of monoamine uptake, antidepressants display a composite pharmacological action at Na^+, K^+, and Ca^{++} channels.[179] In particular, their effects on Na^+ channels may have a bearing on their effects on visceral sensitivity (Na^+ channel blockers are indeed under investigation for their potential in neuropathic and inflammatory pain[180]) whereas blockade of HERG K^+ channels may result in prolongation of the QT interval and occurrence of arrhythmias.[6]

Adaptation to the acute effect of antidepressants is an important aspect of their pharmacology: it may be hypothesised that the entity and/or type of effect at the gut level eventually depends on adaptive changes both through 5-HT receptor desensitisation[181] secondary to inhibition of SERT and through 5-HT backup transporters (such as the organic cation transporters and the dopamine transporter, with much lower affinity for 5-HT) which, under certain circumstances, may compensate for SERT blockade.[174]

A new dimension to our understanding of the mechanism of action antidepressants could also be provided by the observation that upregulation of BDNF and trkB receptors occurs in the central nervous system after administration of antidepressants, consistent with the time course of the antidepressant action.[182] No data are available on the effects of antidepressants on BDNF/trkB receptor expression in the human enteric nervous system. Interestingly, recombinant BDNF and NT-3 can accelerate intestinal transit in humans.[183]

Antidepressants in therapeutics

Antidepressants (both tricyclic compounds and selective 5-HT reuptake inhibitors) are included in management algorithms for functional gastrointestinal syndromes[184] but their role is still debated because only a limited number of

Table 3 Affinities of serotonin (5-hydroxytryptamine or 5-HT) and some antidepressants for monoamine transporters

Compound	SERT	NET	DAT
Amitriptyline	4.30 (0.12)	35 (2)	3250 (20)
Citalopram	1.16 (0.01)	4070 (80)	28 100 (700)
Desipramine	17.6 (0.7)	0.83 (0.05)	3190 (40)
Fluoxetine	0.81 (0.02)	240 (10)	3600 (100)
Imipramine	1.40 (0.03)	37 (2)	8500 (100)
Paroxetine	0.13 (0.01)	40 (2)	490 (20)
5-HT	2100 (100)	>100 000	>100 000

Values are expressed as K_D values (geometric mean (SEM) in nM) and are taken from Tatsumi and colleagues.[178]
SERT, 5-HT transporter; DAT, dopamine transporter; NET, noradrenaline transporter.

controlled studies are available. Antidepressants are recommended for severe or refractory symptoms of pain and most of the studies on the use of antidepressants in functional syndromes were carried out in patients with IBS. In a meta-analysis of 11 randomised placebo controlled trials of antidepressant treatment of functional gut disorders (nine of the trials included patients with IBS), seven studies were abstracted for the dichotomous outcome of symptom improvement.[185] The odds ratio for overall improvement of gastrointestinal symptoms was 4.2 (2.3–7.9), with one study[186] largely contributing to this result. On average, the NNT was 3.2—that is, on average 3.2 patients needed to be treated to improve symptoms in one patient.[185]

In a recent trial on 431 patients with functional bowel disorders (IBS, functional abdominal pain, painful constipation, and unspecified functional bowel disorder),[187] statistically significant benefit was achieved with desipramine over placebo only in the per protocol analysis (NNT = 5.2), especially if participants with undetectable blood levels were excluded from the analysis (NNT = 4.3). No significant effect was seen with desipramine in the intention to treat analysis. These observations suggest that antidepressants may be effective provided that subjects can tolerate the side effects and detectable blood levels are achieved.

Because of their complex pharmacological properties (both central and peripheral), antidepressants may exert useful actions at more than one site along the brain-gut axis.[188] Two studies showed that imipramine can prolong orocaecal and whole gut transit times in diarrhoea predominant IBS subjects and controls (tricyclic antidepressants, because of their anticholinergic action, tend to induce constipation (box 8)) while paroxetine reduced orocaecal transit times with no effect on whole gut transit times.[189 190] Although, as the authors acknowledge, demonstration of altered transit by antidepressants does not imply therapeutic usefulness, the above studies have shown that antidepressants can alter motor function independently of mood effects as the antidepressants were taken for only 4–5 days. As regards modulation of afferent information from the gut by antidepressants, a report[191] suggests that this is a possible mechanism of action: in healthy volunteers, imipramine can increase pain and perception thresholds to oesophageal balloon distension. Thus antidepressants seem to have analgesic and neuromodulatory properties independent of their psychotropic effects, and these effects may occur sooner and at lower doses than is the case when these drugs are used for the treatment of depression.[192 193] However, it should be noted that amitriptyline (50 mg for 21 days) reduced perception of cutaneous stimulation but failed to alter perception of rectal or oesophageal distension in healthy subjects.[194]

Several authors have investigated the effects of 5-HT reuptake inhibitors, such as paroxetine,[58 195] sertraline,[196] and venlafaxine,[58] on gastric sensorimotor function. In particular, Tack and colleagues[195] reported that pretreatment with oral paroxetine (20 mg daily for seven days) had no influence on fasting gastric tone, fasting gastric compliance, or perception of gastric distensions in healthy volunteers studied with a barostat. The authors suggested an effect of paroxetine on gastric accommodation to a meal because of a significant difference in postprandial fundic relaxation between paroxetine and placebo. However, it should be noted that the difference was small and that, in another study,[58] paroxetine did not have any effect on fasting or postprandial gastric volume, measured using SPECT imaging of the stomach.

Mertz and colleagues[197] tried to determine how amitriptyline affects digestive symptoms and perceptual responses to gastric distension. Patients were randomised to four weeks of amitriptyline 50 mg taken at bedtime versus placebo. Seven of seven patients reported significantly less severe gastrointestinal symptoms after four weeks on amitriptyline compared with placebo. Five of seven patients had evidence for altered perception of gastric balloon distension during placebo. However, the subjective symptom improvement on amitriptyline was not associated with normalisation of the perceptual responses to gastric distension. The authors concluded that the beneficial effect of low dose amitriptyline was not related to changes in perception of gastric distension and that increased tolerance to aversive visceral sensations may play a role in the therapeutic effect, but the results need to be confirmed in sufficiently powered studies.

Although two recent studies on the effects of antidepressants on colonic sensorimotor function only partly match initial expectations for activity on visceral sensitivity,[198 199] it is probably too early to dismiss the hypothesis of a beneficial effect in IBS. More basic work on the plasticity of serotonergic pathways will help to identify possible specific targets for therapeutic intervention.

SUMMARY AND FUTURE PERSPECTIVES

In the gut, 5-HT works as a neurotransmitter and a paracrine signalling molecule. Although it certainly has a prominent role in modulating gut motility, secretion as well as visceral sensitivity, 5-HT should be viewed as an important voice (probably a soprano) in a well orchestrated choir of mediators. Although modulation of serotonergic responses per se does not provide conclusive answers to the therapeutic needs of all patients with functional gut disorders, there is a strong rationale to target therapeutic agents to 5-HT receptors or 5-HT reuptake mechanisms.

$5-HT_1$ receptor agonists, in spite of the interesting profile of sumatriptan on gastric sensorimotor function in dyspeptic patients, do not seem plausible contenders for the everyday management of functional dyspepsia, because of the uncertainties of possible undesired effects: promotion of TLOSRs associated with a delay in gastric emptying, possible enhancement of oesophageal visceral sensitivity (induction of chest pain), and constriction of coronary arteries. More basic work is needed to define the exact mechanism of action of sumatriptan in dyspeptic patients and clarify whether $5-HT_{1B/D}$ receptor agonists deserve further clinical development.

$5-HT_3$ receptor antagonists have a strong rationale for the treatment of female patients with diarrhoea predominant IBS who may also benefit from reduction of visceral sensitivity. However, the safety issues of alosetron (which is not approved in the European Union) limit its use to severe cases of IBS. Ongoing studies will determine whether IBS and other functional gut disorders are responsive to other $5-HT_3$ receptor antagonists and whether ischaemic colitis

Box 8

▶ Tricyclic antidepressants tend to induce constipation because of their anticholinergic properties whereas selective 5-HT reuptake inhibitors tend to induce prokinesia.

occurs with other agents of this class. Because accelerated delivery of colonic contents into the rectum with reduced compliance is not specific for IBS (it may occur in inflammatory conditions or radiation induced colonic damage), 5-HT$_3$ receptor antagonists may turn out to be useful even in some organic conditions with altered bowel habits and lower abdominal pain.

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Selective 5-HT$_4$ receptor agonists and antagonists have the potential to become new classes of drugs with colonic prokinetic or antiprokinetic effect, respectively. However, their role in functional disorders still needs to be fully characterised, especially as regards the control of visceral sensitivity. Among 5-HT$_4$ receptor agonists, tegaserod is already marketed in several parts of the world (not yet in the European Union) for constipation predominant IBS in women.

5-HT$_7$ receptor ligands may offer interesting opportunities for drug development but, at the present state of knowledge, a deeper insight into the function of 5-HT$_7$ receptors along the brain-gut axis is a prerequisite to development of new agents to be exploited clinically.

Finally, concerning the possible therapeutic use of 5-HT reuptake inhibitors, although SERT expressed at central and peripheral sites seems to be identical,[171] the design of drugs targeting specifically the gut transporter may be feasible and would probably represent a step forward with respect to currently available antidepressants, provided that the role of central versus peripheral actions of antidepressants in functional disorders is clarified.

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