Serotonergic modulating drugs for functional gastrointestinal diseases

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After many years of basic research we have now begun to learn how to manipulate the serotonergic mechanisms within the gut. This has led to a number of significant advances including 5HT₃ antagonists for the treatment of functional diarrhoea, 5HT₄ agonists for the treatment of constipation and 5HT₁ agonists for the treatment of impaired fundal relaxation. Initial enthusiasm has been somewhat dented by the withdrawal of alosetron because of ischaemic colitis, but it remains to be seen whether this adverse event will be seen with other 5HT₃ antagonists. Finally it should be recognized that, in a substantial proportion of patients attending clinics complaining of functional symptoms, anxiety is a major component. The drugs so far described are by and large devoid of CNS effects. It remains possible therefore that a drug which combines both peripheral and central effects would likely to be beneficial.

Keywords: drugs, functional gastrointestinal disease, serotonin

It has been known for more than 25 years that there is a substantial amount of serotonin (5-hydroxytryptamine or 5HT) in the gut, distributed mainly in the enteroendocrine cells with a small amount in the enteric nervous system. Bulbring was the first to propose that 5HT played a key role in peristalsis [1] but it has taken over 40 years to clearly demonstrate the relevant pathways involved (see below). Initial difficulties in understanding its role was inevitable, given that it is now recognized that there are over 21 different receptor subtypes. As more specific agonists and antagonists have become available more discriminating studies have become possible to define these many separate and sometimes conflicting responses. However we are now entering an exciting era, as many new 5HT modulating drugs are becoming available for treating functional gastrointestinal (GI) disease. It is now becoming relevant therefore for clinicians to understand the role of serotonin in the normal gut function.

Serotonin and GI physiology

Distribution

Approximately 80% of total body serotonin is found in the GI tract, the remainder being divided between the

platelets, which avidly take up free serotonin, and the central nervous system. Ninety five percent of GI 5HT is found within the granules of the enteroendocrine cells (ECs). These cells, which number about 1 per 100 epithelial cells, lie mainly at the base of the crypts. They have apical microvilli to detect luminal events, while the base of the cell rests on the basement membrane (Figure 1). Secretory granules are pleomorphic, with diameters ranging from 400 to 200 nm, contain 5HT and other peptides including CCK, neurotensin, GLP-1 and PYY [2]. ECs are found throughout the GI tract with greater density in the proximal duodenum and rectum. Throughout the gut, ECs containing 5HT granules are the most numerous subtype, followed by those containing CCK in the upper GI tract and PYY in the lower GI tract [3].

Factors modulating 5HT release from enteroendocrine cells

As shown in Figure 2 there are many factors which stimulates secretion from the granules by exocytosis. These include mechanical stimuli such as luminal pressure or mucosal stroking and bacterial toxins such as cholera toxin and cytotoxic drugs which nonspecifically damage the cells, such as cisplatin [4].

There is also classical receptor mediated stimulation via β -adrenergic, purinergic A_{2A/B} and muscarinic receptors, together with inhibitory α_2 -adrenergic, histamine type 3 receptors and purinergic A₁ receptors. These probably act through modulating intracellular Ca⁺⁺, a surge in which

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Figure 1 Enteroendocrine cell from the rectal mucosa showing numerous secretory granules situated at the base adjacent to the basement membrane.

Figure 2 Cartoon illustrating the many stimuli and receptors which influence enteroendocrine cell granule exocytosis. Increase in intracellular Ca^{++} concentration appears to be the key final step. The precise pathways are not clearly defined in EC but depolarization by high K^{+} does lead to an increase intracellular calcium by opening L-type voltage-dependent calcium channels [89].

is associated with 5HT release. Most of these mechanisms have been described in experimental animal models but there have been a number of studies of 5HT release in humans. Large mixed meals produce a rise in whole blood 5HT from around 220 to a peak of 300 ng ml⁻¹ [5] though the precise mechanism is unclear and could include distension, luminal nutrients and neural reflexes.

Main receptors mediating GI effects of 5HT

5HT has many actions as illustrated in Figure 3. The numerous 5HT-receptor subtypes (21 at present and

Figure 3 Schematic illustration of multiple actions of 5HT-receptor modulating drugs. 5HT₃ agonists inhibit gastric secretions, stimulate MMCs [15] and enhance intestinal secretions thereby accelerating small bowel transit [16]. They also stimulate antral contractions and vagal afferents inducing nausea [15]. 5HT₃ antagonists are excellent antiemetics, counteracting the nauseating effects of opiates and 5HT released by chemo- and radiotherapy. 5HT₄ agonists stimulate oesophageal peristalsis, gastric emptying and small bowel transit. Abbreviations: LOS=lower oesophageal sphincter, MMC=migrating motor complex.

rising) allow for site-specific actions of the same molecule. The main effects relevant to gastrointestinal physiology are mediated via 5HT_{1a}, 1p, 3, 4 receptors.

5HT₁ receptors are G-protein linked. There are however, many subtypes and they appear to be linked to different second messengers in different cells, some showing increase in adenyl cyclase and some showing the reverse with some acting independently of adenyl cyclase. In the gut 5HT_{1p} agonists stimulate release of NO from inhibitory nerves supplying the gastric fundus and thus relax the fundus. 5HT₂ receptors also exist in several forms (A, B and C), all G-protein linked to activation of phosphoinositide metabolism and hence elevation of intracellular calcium [6]. Most induce vascular smooth muscle contraction but in the rat they also mediate gastric fundal contraction. The 5HT₃ receptor is quite different being a ligand-gated cation channel. 5HT binding opens the channels allowing entry of K^{+} and Ca^{++} leading to depolarization with an action potential similar to many neurotransmitters. It shows rapid desensitization and is suitable for transmitting rapidly changing information. By contrast the 5HT₄ receptor is another G-protein linked receptor, ligand binding activating an increase in cAMP via adenyl cyclase. This increase activates a protein kinase, which inhibits K^{+} channels, preventing hyperpolarization, thereby enhancing excitability of the cell. Such an action is longer lasting than the 5HT₃ effect and is well suited to a neuro-modulatory role. Both 5HT₃ and 5HT₄ agonists stimulate propulsion and secretion and excite afferent neurones.

Figure 4 Schematic illustration of selected neuronal and cellular sites where 5HT receptor modulators can act as discussed in the text. 5HT acting via 5HT_{1p} receptors on the gastric inhibitory neurone causes the release of NO which relaxes the gastric fundus. 5HT₃ antagonists inhibit splanchnic afferent nerve response to painful distension and inhibit vagal responses to chemotherapy induced 5HT release. They also inhibit discharge of secreto-motor nerves, which act via VIP, and NO. 5HT₄ agonists induce peristaltic contractions by stimulating IPAN. These activate ascending excitatory pathways, mediated via acetylcholine and substance P, together with descending inhibitory pathways, mediated via NO and VIP release. Abbreviations: IPAN = intrinsic primary afferent neurone, VIP = Vasoactive intestinal peptide, SP = substance P, NO = nitric oxide.

5HT and sensation

As shown in Figure 4, 5HT₃ receptors are found on vagal and mesenteric afferents. Recording from vagal afferents shows that 5HT increases the discharge acting via these receptors [7, 8]. One of the most striking effects of 5HT in the stomach is the induction of nausea and vomiting associated with chemotherapy. The more strongly emetogenic regimes which include cisplatin, produce a marked increase in the plasma level and urine excretion of the metabolite 5-HIAA [9]. Agents with the strongest emetic effect are alkylating agents, which kill cells at all stages of the cell cycle. It is likely therefore that the 5HT release is nonspecific, related to the damage to entero-endocrine cells, along with damage to the rest of the mucosa. Since vagotomy inhibits cisplatin-induced vomiting [8] it is believed that most of the 5HT effect occurs locally on vagal afferents, though of course there are 5HT₃ receptors in the chemoreceptor trigger zone in the nucleus tractus solitarius and the area postrema.

When activation of enteric neurones has been studied histologically using the appearance of the early activation protein, c-fos, it has been shown that activation of sub-mucosal neurones can be blocked by 5HT_{1p} antagonists [10]. However the sensory limb of the peristaltic reflex

appears to require activation of 5HT₄ receptors, at least in man (see below).

Effect on GI motility (Figure 3)

During fasting a regular progression of quiescence (phase I) followed by increasing activity (phase II), culminating in intense regular phasic activity (phase III) migrates through the gut, the so-called 'interdigestive housekeeper'. Intravenous 5HT increases the frequency of such migrating motor complexes (MMC) [11] as do 5HT reuptake inhibitors [12] which increase the effects of endogenously released 5HT. Serotonergic nerves appear to be critical in the MMC since their destruction in the rat disrupts the MMC [13] while ondansetron increases the migrating motor complex interval in man [14]. 5HT₃ agonists stimulate human MMCs [15], antral contractions and excite vagal afferents, inducing nausea [16]. 5HT₃ antagonists block gastric phase III motor activity (vital for emptying the fasting secretions and particulate debris from the stomach) [17]. In man, but not in dogs [18], this is also associated with an inhibition of the fluctuations in plasma motilin which normally precede a gastric MMC in man, raising the possibility that 5HT₃ receptors may be involved in motilin secretion.

The role of 5HT in oesophageal function is less clear but cisapride, with 5HT₄ agonist effects, stimulates oesophageal peristalsis, increasing the amplitude of contractions and increasing lower oesophageal sphincter pressure.

5HT may also be important in controlling gastric tone, inducing a relaxation of the guinea pig's stomach, acting via 5HT₁ receptors, which stimulate nitrergic nerves to release NO [19]. This NO-mediated relaxation is important in the normal receptive relaxation associated with food ingestion [20]. Sumatriptan, a 5HT_{1p} receptor agonist, induces gastric fundal relaxation in man and increases the volumes required to induce a sensation of discomfort [21]. Finally 5HT inhibits gastric secretion [22] probably acting through 5HT₃ [23] and 5HT₁ receptors [22].

Importance of 5HT in peristalsis

The peristaltic reflex depends on the stimulation of primary sensory neurones by contact with a food bolus. This elicits, amongst other effects, an ascending stimulation of circular muscle contraction with a descending relaxation resulting in caudal propulsion. 5HT released from enteroendocrine cells by luminal pressure plays a key role in transducing the pressure stimulus into a nervous stimulus, the peristaltic reflex being abolished by either depleting mucosal 5HT stores or blocking both 5HT₃ and 5HT₄ receptors.

Mucosal stimulation by brushing produces a release of 5HT [24] which acts on 5HT₄ receptors to

stimulate the intrinsic primary afferent neurone (IPAN), one of whose neurotransmitter's is calcitonin gene-related peptide (CGRP). CGRP release is blocked by selective 5HT₄ antagonists in the human jejunum [25] and rat colon [26] and by both selective 5HT₄ and 5HT₃ antagonists in the guinea pig colon.

Using a three-compartment model, in which the medium bathing stripped mucosa is separated into three compartments by glass slides, it is possible to locate where various mediators are released. Stroking produces a local release of CGRP, proximally substance P is released and circular muscle contraction occurs, while in the distal compartment VIP is released and circular muscle relaxation occurs [25]. The effect of this response can be assessed by placing an artificial pellet in the isolated gut, which results in it being propelled distally. This peristaltic movement in the guinea pig colon is the result of at least two redundant pathways, which are separately inhibited, either by 5HT₃ or 5HT₄ antagonists, which must both be used together to block peristalsis [27]. Both these pathways also involve cholinergic neurones and can be blocked by atropine. In addition to the contractile response associated with peristalsis there is also a secretory response.

5HT and intestinal secretion

Serotonin influences gastrointestinal secretions both directly via 5HT₄ receptors on enterocytes and indirectly via 5HT₃ receptors on secretory mucosal nerves and vagal afferents. The best studied example of 5HT-induced secretion is that induced by cholera toxin which induces secretion both by direct effects on the enterocyte and also indirectly by releasing 5HT from the enteroendocrine cell [28]. This 5HT-mediated secretion involves both stimulation of release of secretagogues such as VIP [29, 30] and NO [31] from secretory nerves as well as prostaglandin from macrophages acting via 5HT₂ receptors. 5HT₃ antagonists such as ondansetron and granisetron [28] as well as prostaglandin antagonists and 5HT₂ and 5HT₃ antagonists inhibit cholera toxin-induced secretion without affecting the release of 5HT₃ [32]. These data suggest a model whereby cholera toxin stimulates the release of 5HT from ECs, which then acts on submucosal and myenteric plexus neurones to stimulate secretion and on macrophages and fibroblasts, releasing prostaglandins, which in turn stimulate enterocyte secretion.

During normal digestion locally released 5HT stimulates vagal afferents. This is important in the pancreatic response to intraduodenal chow, maltose and hypertonic sodium chloride. Secretion induced by these stimuli is blocked by vagal afferent section and also by 5HT₃ antagonists. In addition to inhibiting cholera toxin-induced secretion, the 5HT₃ antagonist alosetron also

enhances basal absorption. This implies that there is a basal tonic stimulation of intestinal secretion by 5HT [33], probably via 5HT₃ receptors on mucosal secretory nerves as has been demonstrated in the rat colon [34]. In the human small intestine there are also 5HT₄ receptors on the enterocytes, stimulation of which cause tetrodotoxin-resistant secretion [35].

Colonic response to feeding

Eating is one of the strongest stimuli to colonic motor activity, increasing both phasic contractions and tone, both of which can be blocked by 5HT₃ antagonists. One of the early studies using granisetron (a 5HT₃ antagonist) showed that 40 and 160 mg kg⁻¹ intravenously reduced the increase in postprandial motility noted after a meal [36]. More recently in an important experimental study in healthy volunteers Bjornsson and colleagues [37] showed that granisetron 10 mg kg⁻¹ i.v. blocked the colonic response to both balloon distension of the antrum as well as intraduodenal lipid perfusion. Granisetron did not however, alter the local colonic response to balloon distension within the colon. It seems likely that under these circumstances Granisetron is blocking 5HT₃ receptors on the vagus thereby interrupting the afferent arm of the gastro-colonic reflex.

Intestinal transit

Ondansetron, one of the earlier 5HT receptor antagonists, delays colonic transit in normal volunteers [38], the main impact being on the left colon [39]. Ondansetron also inhibits the postprandial increase in tone in both healthy volunteers and patients with carcinoid diarrhoea [40, 41].

In addition to changes in GI transit, 5HT₃ receptor antagonists also reduce visceral sensation in response to balloon distension [36], mainly by reducing colonic tone rather than any change in neural sensitivity [42].

Now that specific 5HT₄ agonists have been developed for use in man it is possible to test the significance of the mechanisms demonstrated in experimental animals. Two 5HT₄ agonists, tegaserod and prucalopride have both been shown to accelerate colonic transit. Prucalopride is significantly more selective for 5HT₄ receptor and has no effect on gastric or small bowel transit [43, 44]. Tegaserod does accelerate both gastric emptying and small bowel transit [45] and may prove beneficial in upper GI dysmotility.

The sum of these effects implies that 5HT₃ antagonists will slow intestinal transit, decrease intestinal secretions, decrease the water content of stool and diminish colonic pain. By contrast 5HT₄ antagonists would be predicted to accelerate gastric emptying, small and large bowel transit and increase stool water content.

Clinical applications (Table 1)

Gastro-oesophageal reflux

One of the earliest serotonergic-modulating drugs introduced into widespread clinical practice was cisapride, a drug that acts presynaptically via 5HT₄ receptors [46], enhancing acetylcholine release in response to nerve stimulation [47]. Cisapride is a 5HT₄ agonist with partial 5HT₃ antagonist effects. It increases the amplitude of oesophageal contractions and lowers oesophageal sphincter pressure and accelerates gastric emptying and oro-caecal transit. The recent availability of 5HT₄ antagonists suitable for use in man has made it possible to demonstrate that cisapride's acceleration of oro-caecal transit is mediated via 5HT₄ receptors [48]. While relatively ineffective compared with proton pump inhibitors in severe erosive oesophagitis, cisapride is effective in less severe cases. However it has recently been withdrawn owing to the rare occurrence of cardiac arrhythmias, thought to be related to its effect of prolonging the QT interval acting via cardiac 5HT₄ receptors.

Functional dyspepsia

This is a common condition in which patients suffer symptoms of upper gastric discomfort or pain in spite of normal endoscopy, ultrasound and other assessments. About one third of patients demonstrate delayed gastric emptying [49], another third demonstrate impaired gastric relaxation and about the same number demonstrate hypersensitivity to gastric distension [50, 51]. In general symptoms relate rather poorly to the abnormalities demonstrated, though Stanghellini *et al.* [49] found that severe vomiting and postprandial fullness together with female sex were predictive of delayed gastric emptying.

The demonstration of these abnormalities has encouraged the use of drugs to reverse them. In particular, initial interest focused on the role of cisapride, which had been shown to accelerate gastric emptying [52]. Cisapride also enhances postprandial gastric relaxation [53], whilst during fasting it increases fundal tone and perception of distension. These multiple actions may explain the somewhat confusing results in functional dyspepsia

Table 1 Drugs acting via serotonergic mechanisms: sites of action and potential therapeutic areas.

<i>Class and examples</i>	<i>Site</i>	<i>Action</i>	<i>Potential therapeutic areas</i>
5HT _{1p} agonists Buspiron Sumatriptam	Inhibitory gastric motor neurones	Fundal relaxation	Functional dyspepsia
5HT ₃ antagonists Ondansetron Granisetron	Vagal afferents Enteric interneurons & secreto-motor neurones	Inhibit nausea due to 5HT release Inhibit opiate induced nausea	Chemotherapy induced nausea Post operative nausea
Alosetron Cilansetron	Mesenteric afferents	Inhibit sprial evoked responses to intestinal distension	Visceral hypersensitivity in IBS
5HT ₄ agonists Prucalopride	Cholinergic colonic motor nerves (enhances acetylcholine release)	Stimulates peristalsis Accelerates colonic transit	Constipation
5HT ₄ partial agonist Tegaserod	Primary afferent enteric neurones Enterocytes Extrinsic mesenteric afferents	Stimulates peristalsis Stimulates chloride secretion Inhibits afferent firing in response to distension	Constipated IBS
Combined 5HT ₄ agonist and 5HT ₃ antagonist Cisapride	Motor neurones	Stimulates increased amplitude of oesophageal peristalsis contractions and lower oesophageal sphineter pressure Accelerating gastric emptying and small bowel transit	Impaired oesophageal peristalsis Gastroparesis Chronic intestinal pseudo-obstruction

Note that this list of known sites of action is selective and certainly incomplete since the drugs have been studied in different models and in differing detail.

with some negative studies [54, 55], while others have shown significant benefit [56]. Meta-analysis suggests a modest overall positive treatment effect [57].

A common feature of functional dyspepsia is an abnormal distribution of test meals within the stomach immediately after ingestion, with an increased proportion in the antrum. This may relate both to impaired antral motility or impaired fundal relaxation. Cisapride does reduce the postprandial antral area [56] and enhance postprandial fundal relaxation, which may be helpful, however, its enhancement of visceral perception may aggravate symptoms. Interestingly, levosulpiride, a drug with both 5HT₄ agonist effects as well as central D₂ dopamine receptor antagonism, has been shown to be significantly better than cisapride at relieving symptoms in functional dyspepsia. The gastrodukinetic effects of levosulpiride are similar [58], implying that drugs with combined peripheral and central effects may be more effective in this condition, in keeping with the fact that functional dyspeptic patients often show increased anxiety and depression.

Since impaired accommodation is found in 40% of patients with nonulcer dyspepsia [50] it would be logical to try a fundus-relaxing agent in functional dyspepsia. Sumatriptan, a 5HT_{1p} agonist relaxes the gastric fundus [21] as does Buspirone, also a 5HT_{1p} agonist, which showed some benefit in clinical trials [59].

Prevention of chemotherapy-induced nausea

The first successful clinical application for 5HT₃ receptor antagonists was the use of ondansetron to prevent 5HT-induced nausea secondary to cancer chemotherapy. This class of drugs has also been shown to be efficacious in radiation-induced nausea, postoperative nausea, anorexia nervosa, nausea and vomiting in AIDS [60], and nausea due to acute viral gastro-enteritis [61].

Irritable bowel syndrome

IBS is a common chronic disorder affecting between 9 and 12% of the adult population, accounting for a substantial proportion of gastrointestinal outpatients. The symptoms of IBS are characterized by recurring abdominal pain or discomfort associated with disordered defaecation. This can take the form of either loose stools passed with urgency or hard stools associated with straining and a sense of incomplete evacuation. Cluster analysis indicates that about one third of patients fit the diarrhoea predominant IBS (D-IBS) category, one third constipation predominant (C-IBS) and a further third pass for the most part normal stools without urgency, their main complaint being abdominal pain [62]. It should be noted that these subgroups tend to have rather similar

bowel frequencies and the main difference relates to stool consistency. Stool consistency is related to colonic transit and the time for water absorption, whereas defaecation frequency depends on many factors including rectal sensation, social circumstances and habit.

Delaying colonic transit and increasing water absorption would be predicted to help D-IBS. Furthermore IBS patients often experience worsening of pain after eating [63] and many studies have suggested an exaggerated colonic response to feeding so inhibiting this should be helpful. One other characteristic feature of patients with IBS is a reduced threshold for pain during gut distension, leading to much interest in drugs that alter visceral sensitivity.

5HT₃ antagonists and IBS

Mechanistic studies

One of the earliest 5HT₃ antagonists, granisetron, has been shown to reduce rectal sensitivity and postprandial motility in IBS [36]. The related 5HT₃ antagonist, ondansetron has also been shown to increase stool consistency in both normals and IBS [64]. When used to specifically target D-IBS, ondansetron improves stool consistency and tends to delay colonic transit [65]. The more selective and potent 5HT₃ antagonist, alosetron has also been shown to delay in colonic transit in both healthy volunteers [66] and patients with D-IBS [67]. Alosetron also increased the threshold for discomfort on balloon distension due to an increase in compliance, an effect which may well contribute to some of reduction in abdominal pain [42].

Clinical trials

Clinical trials with alosetron showed hardening of stool and a reduction of stool frequency in IBS patients [68, 69]. Sub-group analysis indicated that it was females who benefited most. A subsequent study [70] of females with D-IBS or alternating IBS reported that the proportion experiencing 'adequate relief of pain and discomfort' for all 3 months of treatment was significantly greater for the alosetron-treated patients at 41% *vs* 29% for placebo. Analysing by IBS subtypes shows that this significant difference was due to the effect on the D-IBS patients, the alternating IBS patients receiving no benefit compared with placebo. As expected from the pharmacology, alosetron significantly decreased stool frequency and improved stool consistency compared with placebo, effects that were seen within the first week of commencing treatment. Likewise the number of days with urgency again fell significantly. Thirty-three out of 342 patients treated with alosetron withdrew because of constipation compared with just one out 323 receiving placebo. On stopping the drug diarrhoeal symptoms returned within a

week, supporting the idea that the improvement was pharmacologically specific.

Although there are 5HT₃ receptors in the brain and 5HT antagonists have been shown to have anxiolytic properties in animal models, in IBS patients alosetron, at the dose effective clinically, did not produce any significant change in anxiety or depression [71]. When compared with mebeverine, the commonest drug prescribed for IBS in the UK alosetron was shown to be significantly more effective [72].

Adverse events

Regrettably alosetron has been withdrawn from the market after 446 000 prescription following reports of 49 cases of ischaemic colitis, a pharmacologically unexpected effect. The mechanism is obscure since alosetron does not alter intestinal blood flow in experimental animals. Whether this rare event is unique to alosetron is uncertain, but newer 5HT₃ antagonists are also in development, so clinical studies are awaited with interest, since this class of drug is undoubtedly clinically effective. It does however, illustrate the fact that safety is all-important in a nonfatal disease such as IBS. The other expected adverse event experienced with alosetron was constipation, reported in 29% *vs* 5% placebo in the controlled trials. In most cases this was not sufficient to stop taking the drug but in 21 cases out of 435 000 out of trial prescriptions it was severe enough to require hospitalization. Ten of these went on to laparotomy, which in four cases demonstrated a perforated diverticulum. There were three deaths. It should be noted that the age of these cases ranged from 65 to 82 years suggesting that these were not in fact being given to patients with IBS but rather that their symptoms were due to diverticulitis.

5HT₄ agonists and IBS

Cisapride

Cisapride's prokinetic effects probably depend on its 5HT₄ agonist properties [73]. It accelerates gastric emptying, and mouth to caecum transit without altering stool weight or frequency [74]. Cisapride has been shown to be effective in chronic constipation [75]. However in IBS there are conflicting results with cisapride, some trials showing benefit, particularly in pain and distension [76] and ease of defecation [77], while others have shown no benefit [78]. The lack of effectiveness of cisapride may relate to the combination of a laxative effect from the 5HT₄ agonist effects, counteracted by the constipated effect of the 5HT₃ antagonist effects. With this in mind a selective 5HT₄ agonist, tegaserod, has been developed.

Tegaserod

This drug stimulates motility in both the upper and lower GI tract in dog [79] and in the colon of rats [80]. It also accelerates colonic transit in man [81]. Physiological studies in IBS are as yet few in number. 2 mg twice daily of tegaserod accelerated oro-caecal transit and proximal colonic emptying, though overall colonic transit was not altered [82]. The dose here may have been insufficient, since in subsequent clinical trials using 6 mg twice daily it was shown to significantly decrease the number of hard stools and increase the number of bowel movements per 28 days from 22 to 35 [83]. The same study of 799 patients with constipated IBS showed a significant improvement in bloating [84], something which previous therapies have failed to do, in spite of its undoubted importance to patients. More recently, a study of 881 patients with C-IBS, receiving either 2 or 6 mg twice daily was reported with a significant improvement in 'responder' (defined as marked or moderate improvement for at least 2 out of 4 weeks, or somewhat improved for all 4 weeks) rates for females against placebo. This demonstrated an increment over the placebo response (27.5%) of 10 and 11% for the two doses, respectively [85]. This gain over placebo is small, giving a number needed to treat of eight to get one extra responder compared with placebo. However in a difficult condition like IBS, where there are few effective treatments, even this small effect is likely to be a welcomed addition to the therapeutic armamentarium.

Functional constipation

The enhancement of cholinergic neurotransmission in the colon suggested the use of cisapride in severe constipation [75, 86] and constipation associated with paraplegia [87], and in both conditions it has been shown to be beneficial. Prucalopride is another new 5HT₄ agonists which is highly selective and probably a more potent laxative than tegaserod, though its very efficacy may cause abdominal cramps which may be undesirable in IBS. Several studies have demonstrated efficacy in severe constipation and constipated IBS [82, 88]. Prucalopride has been shown to be of benefit in patients with resistant constipation referred to a tertiary referral centre. 4 mg once daily increased stool frequency from a mean of 1.9 per week to 4.2. Fifteen out of 27 patients required a dose reduction mainly because of nausea and vomiting. Total gut transit decreased and stool consistency normalized. The commonest side-effects were headaches, nausea and abdominal cramps and four patients developed diarrhoea, in keeping with its secretory and prokinetic effect.

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