Modulation of Serotoninergic Pathways for Treatment of Irritable Bowel Syndrome

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SUMMARY

The gut constitutes the main reservoir of the body's serotonin. The latter has effects not only on colonic motility via activation of cholinergic or nitric oxide-dependent neurons but also on the modulation of sensation by excitation of intrinsic sensory neurons. The abundance of serotonin receptors within the enteric nervous system constituted a challenge, as the pharmacological intervention on these receptors could be the etiological treatment of Irritable Bowel Syndrome (IBS). 5-HT_3 and 5-HT_4 are the main subtypes of serotonin receptors in the gut. Therapeutic blockade of 5-HT_3 by alosetron in women with diarrhea- predominant IBS brought a revolution in the treatment of IBS. This drug acts both on colonic motility and the secretory function of the bowel but, despite the spectacular results, it had to be withdrawn due to 49 cases of ischemic colitis. 5-HT_4 agonists have been used for the treatment of patients with constipation-prone IBS. In large comparative trials tegaserod was more effective than placebo although the therapeutic gain over placebo was small. Prucalopride is a potent 5-HT_4 agonist but much concern has been raised by the report of carcinogenicity in animals. Other serotonergic modulators include piboserod (SB207266) and MKC 733 but no clinical trials in humans are available. Sumatriptan, a 5-$HT_{1B/D}$ agonist developed for the treatment of migraine, causes relaxation of the gastric fundus in man, but its intranasal administration limits its use. As abdominal pain constitutes the main complaint of IBS patients, future efforts must concentrate on medications acting on visceral hypersensivity.

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Serotonin has been recognized as a main neurotransmitter in the central and peripheral nervous systems and medications have recently been developed that act on different receptor subtypes or pharmacological targets for treating various disorders, including depression. In the area of digestive diseases, serotonin has been shown to play a significant role in the control of the sensorimotor function of the gut and thereby serotoninergic pathways have become a target for the development of new treatments of various functional digestive disorders.

Functional digestive disorders are a complex set of syndromes defined by the association of clinical symptoms and classified in the Rome II criteria as specific entities.[1] The therapeutic options have so far been very disappointing and were based upon the combination of antispasmodics or low dose anxiolytics with a good patient-physician relationship or psychotherapy.[2] However, antispasmodics have been regarded as poorly effective in most clinical trials.[3] More recently, the understanding of the pathophysiology of functional bowel disorders has been significantly improved with the concept of the "brain-gut" axis that includes the nerve pathways, both afferent and efferent, linking the central nervous system and the gut.[4] A large percentage of the neurones in the brain-gut axis are afferent ones, and relay the information from the gut to the brain. The afferent pathways have received considerable interest over recent decades, as they are thought to be involved in the visceral hypersensitivity that characterises patients with functional digestive disorders.[5] Hence, a wide variety of neurotransmitters have been identified as playing a role in the functioning of these visceral afferent pathways,[6] serotonin being one of the most important.

The purpose of this review is to describe the role of serotoninergic pathways in the control of sensori-motor functions of the gut and the new treatments that act on these pathways and are currently being developed for functional digestive disorders.

1. ROLE OF SEROTONIN IN THE BRAIN-GUT AXIS

Serotonin (5-hydroxytryptamine, 5-HT) is present in both the afferent and efferent neurones of the myenteric plexus and constitutes one of its main neurotansmitters. Almost 95% of serotonin is located in the gut, mainly in enterochromaffin cells (about 90% of the total gut content) and in the enteric neurones (10%).[7,8] The action of serotonin produces complex effects including smooth muscle contraction (via cholinergic pathways activation) or relaxation (via inhibitory nitric oxide-dependent neurones).[9] Modulation of sensations by serotonin appears also to be complex, involving a response of intrinsic sensory neurones that trigger secretory responses and the peristaltic reflex, excitation of extrinsic afferent pathways and vagal efferents.[7]

Peripheral involvement of serotoninergic pathways in functional abnormalities related to irritable bowel syndrome (IBS) has only been indirectly suggested. In patients with diarrhoea-predominant IBS, post-prandial serum levels of serotonin are higher than in controls but adequate control groups were not included in the study.[10] On the other hand, metabolism of 5-HT seems to be different in females and males, females being more sensitive to tryptophane depletion.[11] IBS predominantly affects women and this preponderance could, in part, be linked to a disorder of serotoninergic pathways that has so far not been understood. Serotonin has also been shown to play a role in the control of post-prandial the enhancement of colonic motility, known as the colonic response to eating.[12] In patients with carcinoid diarrhoea, this colonic response to eating appears to be excessive but can be reduced by 5-HT_3 antagonists.[13]

Serotonin may also play a role at the central level where it regulates appetite, sexual function and mood.[7,9] In IBS, a dysfunction of the descending pain-modulating pathways has been assumed to be one of the possible causes of symptoms. Serotonin is present in high concentrations in the endorphin-mediated analgesic system which could modulate the processing of sensations at the level of the spinal cord.[9] Thus, one may assume that these descending pathways could interact with afferent pathways in an up-and-down process to modulate the influx of visceral sensations into the central nervous system and thereby contribute to the fluctuation of IBS-related symptoms.

2. 5-HT RECEPTORS CLASSIFICATION AND DISTRIBUTION

5-HT receptors have been divided into 7 groups and into 21 or more further subtypes, characterised by their respective affinity for agonists and antagonists[14,15] (see Table 1). Some of these receptor subtypes have only been characterised by molecular biology studies. In the gut, two types of receptors predominate: 5-HT_3 and 5-HT_4. 5-HT_3 receptors are located on neurons, smooth muscle and enterochromaffin cells[9,16,17] (Figure 1). Most subtypes of 5-HT receptors are coupled with G proteins but the 5-HT_3 is a transmitter-gated cation channel that exists as pentamer of 4TM units. 5-HT_4 receptors are located on neurones of the myenteric plexus, but some evidence has also been obtained that they are present on intestinal muscle cells and enterochromaffin cells.

3. PHARMACOLOGICAL TREATMENTS OF IBS ACTING ON SEROTONINERGIC PATHWAYS

3.1. 5-HT_3 antagonists

5-HT_3 receptor excitation results in rapid depolarisation of myenteric neurones and release of acetylcholine. However, the effects are complex, its activation releasing both excitatory and inhibitory neurotransmitters in the myenteric, plexus of various experimental models and resulting in either contraction or relaxation of intestinal muscle.[7,9] 5-HT_3 antagonist exert an inhibitory effect on intestinal motility and the hypersensitivity described in IBS patients. Ondansetron delays intestinal[18] and colonic[19] transit in healthy volunteers. Similarly, alosetron inhibits colonic transit in IBS patients, without modifying gastric emptying and intestinal transit.[20] 5-HT_3 antagonists also alter the perception of intraluminal distension at the rectal and colonic levels. Prior and Read have shown that granisetron increases the sensory thresholds of rectal distension in patients with diarrhoea-predominant IBS.[21] In this study, however, sensory thresholds were scaled with the distending volume. When evaluating rectal sensitivity to distension, Hammer et al did not find any effect of ondansetron on sensory thresholds and compliance that characterises the elastic properties of the rectal wall in both healthy volunteers and diarrhoea-predominant IBS.[22] At the colonic level, in a study performed with an electronic barostat and using pressure-scaled dis-

Table 1. 5-hydroxytryptamine (5-HT) receptor subtypes and pharmacological agents acting on them.

Receptor type	Specific Agonists	Specific Antagonists	Location	Type
5-HT 1				
5-HT 1A	8-OH-DPAT Buspirone	WAY 100635	CNS	G_i/G_o
5-HT 1B	Sumatriptan L 694247	Ketanserin Ritanserin GR 55562 SB 224289	CNS Enteric neurones	G_i/G_o
5-HT 1D	Sumatriptan Enteric neurones	BRL 15572	CNS	G_i/G_o
5-HT 1E	-	-	CNS	G_i/G_o
5-HT 1F	LY 334370	-	CNS	G_i/G_o
5-HT 2				
5-HT 2A	DOI	Ketanserin MDL 100907	CNS	$G_{q/11}$
5-HT 2B	BW 723C86	SB 200646 SB 204741	CNS Enteric neurones Intestinal muscle	$G_{q/11}$
5-HT 2C	Ro 600175	Mesulergine SB 242084	CNS	$G_{q/11}$
5-HT 3	SR 7227 m-chlorophenyl-biguanide	Granisetron Ondansetron Tropisetron Alosetron Cilansetron	Enteric neurones CNS Intestinal muscle	Ion channel
5-HT 4	BIMU 8 Zacopride Tegaserod Prucalopride Cisapride	Piboserod Sulamserod GR 113808	Enteric neurones CNS	G_8
5-HT 5				
5-HT 5A	-	-	CNS	G_i/G_o
5-HT 5B	-	-	CNS	None identified
5-HT 6	-	Ro 630563 SB 271046 SB 357134	CNS	G_8
5-HT 7	-	mesulergine SB 258719 SB 269970	CNS Intestinal muscle	G_8

tensions, we did not observe any change in perception and pain thresholds, but a significant increase in volume of the barostat bag, indicating an increase in compliance of the colonic wall.[23] In a recent study including only non-constipated IBS patients, alosetron, however, did not alter perception of rectal distension but had a mild effect on rectal compliance, which was increased as compared to placebo.[24] Differences in methodology and dis-

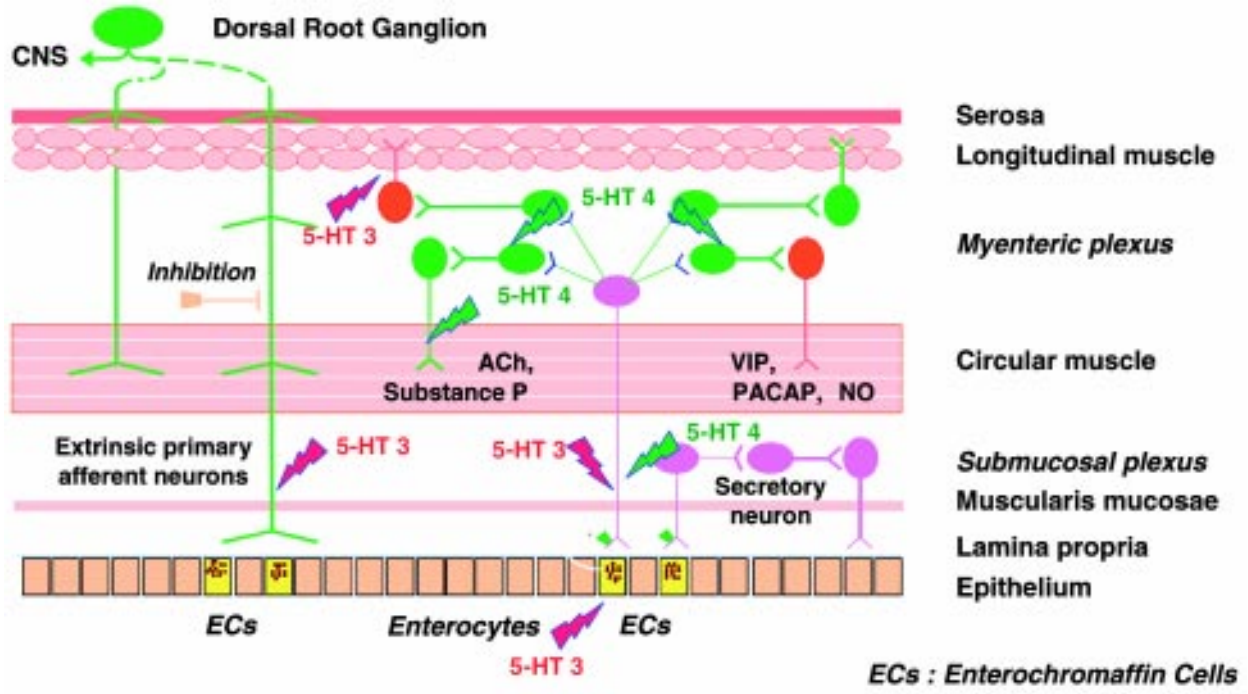

Figure 1.

tension protocols between these studies may explain results the contradictory.

One study showed that alosetron increases the absorption of water at the jejunal level.[25] No data is available on the secretory actions of alosetron or other 5-HT_3 antagonists at the colonic level and a link between the secretory changes and rectal sensitivity has so far not been established.

Several clinical studies have demonstrated the efficacy of alosetron in the treatment of IBS patients with diarrhoea, but this efficacy was found only in female patients. In a first trial including males and females with diarrhoea-predominant IBS, alosetron at daily doses of 1 and 4 mg, decreased stool frequency and increased stool consistency.[26] By contrast, only the 4 mg dose (2 mg bid) significantly improved abdominal pain. In this study, no significant effect was observed in male patients. The difference between male and female responses to alosetron treatment is not fully understood. In previous studies, differences have been demonstrated between men and women in the metabolism of serotonin, women producing higher levels of serotonin.[27] Further clinical studies have thus included only women with diarrhoea-predominant IBS and showed significantly more responders (defined by a global improvement of all IBS-related symptoms) to alosetron than to mebeverine[28] or placebo.[29] In these studies, patients were treated for 12 weeks and followed up for 2 weeks after treatment withdrawal. Clinical improvement was significantly higher for alosetron during the whole treatment but the symptoms quickly returned to baseline after completion of the trial. The therapeutic gain of alosetron was about 25% over placebo and was maintained during the whole treatment period. On the basis of these clinical trials, alosetron was licensed in the United States in April 2000 and prescribed to a range of 350,000 patients until its withdrawal in November 2000, because of the occurrence of 49 cases of ischemic colitis, some requiring blood transfusions or surgical treatment and about 70 cases of severe constipation, some cases needing surgical treatment. Some of the patients died from these adverse events.[30-32] Other 5-HT_3 antagonists are currently under development (cilansetron). The effects of cilansetron on colonic motility seem to be less important than those of alosetron.[33] A few studies have shown a moderate clinical effect of cilansetron in both male and female IBS patients without constipation.[34]

3.2. 5-HT_4 agonists

5-HT_4 receptors mediate the localised release of excitatory neurotransmitters, including acetylcholine, substance P and calcitonin gene-related peptide. Their activation stimulates the peristaltic reflex.[35] However their

effect seems to be more complex since, in vitro, activation of 5-HT_4 receptors results in either contraction or relaxation of smooth muscle. 5-HT4 receptors also stimulate intestinal and colonic fluid secretion.[36,37]

Tegaserod (HTF 919) is a partial 5-HT_4 agonist with a stimulating effect on colonic motility in both animal models and humans. In patients with constipation-prone IBS, tegaserod accelerates intestinal transit significantly and also tends to accelerate colonic transit.[38] However, its effect on visceral sensitivity has so far not been fully documented in humans, although it has been suggested in the animals. In rat, tegaserod has shown a moderate effect on perception of painful rectal distension, with a dose-effect relationship, but this effect was limited to stimuli in the medium range.[39] In humans, tegaserod has a mild effect, detected only with a reflexometric method, but the sensory thresholds defined by the distending pressure are not modified.[40] Clinical studies have demonstrated the efficacy of tegaserod in treating IBS patients with constipation. In a randomized titration study, tegaserod was more effective than placebo after 16 weeks of treatment improving the global impression of the patients, abdominal pain and transit.[41] Four phase III studies have shown a clinical benefit of tegaserod over placebo.[42] In large comparative trials including about 800 patients each, tegaserod improved abdominal pain and transit and was significantly more effective than placebo in patients with IBS and constipation.[43,44] However, the therapeutic gain was modest, only 8 to 15% more responders over placebo, for a 12 week treatment. A secondary analysis of the results has suggested that only female patients responded to the drug, but a firm conclusion may not be drawn from these results. During clinical trials with tegaserod, no cardiac adverse event was noticed.[45]

Prucalopride is a potent full agonist of 5-HT_4 receptors that has been developed for the treatment of idiopathic chronic constipation. Prucalopride induces high amplitude propagating contractions in animals and accelerates colonic transit in healthy volunteers[46,47] and in constipated patients.[48] Clinically, prucalopride significantly increased the number of patients reporting 3 or more spontaneous bowel movements per week in a large phase III trial.[49] However, the clinical future of prucalopride has been seriously jeopardised by the report of cases of intestinal carcinogenicity in animals.

3.3. Other agents modulating serotoninergic pathways

5-HT_4 antagonists have been developed and tested in humans (sulamserod and piboserod). In healthy volunteers, the 5-HT_4 antagonist piboserod (SB207266) antagonised the effects of the 5-HT_4 agonist cisapride but had only a weak delaying effect on colonic transit and did not alter either intestinal transit or gastric emptying. Piboserod also had no effect on colonic sensation.[50]

5-HT_3 agonists would be expected to accelerate transit and inhibit motility, their effect being of possible interest in the treatment of constipation-prone IBS. The MKC 733 compound accelerates small bowel transit in healthy volunteers.[51] However, no clinical study has been published to date.

5-HT_{2B} antagonists which may relax longitudinal smooth muscle in the small bowel have been developed.[52] No result is currently available from in vivo human or clinical studies.

Sumatriptan, a 5-$HT_{1B/D}$ agonist, has been developed for the treatment of migraine. At the gut level, activation of 5-$HT_{1B/D}$-like receptors causes a relaxation of the gastric fundus through activation of intrinsic inhibitory neurones. Administration of sumatriptan induces a relaxation of the gastric fundus in man, allowing larger intragastric volumes before thresholds for perception or discomfort are reached. The effects of sumatriptan on the gastric fundus could thus have therapeutic potential in the treatment of patients with functional dyspepsia.[53] However, this action was not reproduced with intranasal administration of sumatriptan, considerably limiting the therapeutic potential of this approach.[54]

CONCLUSION

The large amount of serotonin present in the gut wall indicates its importance in the control of gut functions. Its multiple actions at the level of the myenteric plexus turn into alterations and control of gut motility and sensory function. These two aspects may be of importance for the treatment of patients with functional bowel disorders and in particular irritable bowel syndrome. However, control of abdominal pain remains the primary challenge as transit disturbances may be easier to control with laxatives and antidiarrheal agents. Medication acting on visceral hypersensitivity should thus be the most promising. However, currently no therapeutic class has been shown to provide a significant improvement in pain over placebo and most serotoninergic agents have limited use because of their parallel effects on transit in subgroups of patients. On the other hand, their action seems to be limited to female patients, a fact that is not fully understood.

A number of questions need further investigation:

adequate definition of responders in clinical trials to increase their statistical weight; definition of biological markers allowing a more precise classification of patients in homogenous subgroups; development of clinical tools allowing the physician a better classification of his patients into these subgroups; evaluation of new administration regimens that would take into account the variability of symptoms over time.

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