VISCERAL PERCEPTION

Serotonergic modulation of visceral sensation: lower gut

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The role of 5-HT agents in the modulation of lower gastrointestinal function is discussed. Selective serotonin reuptake inhibitors are of potential benefit in functional gastrointestinal diseases although formal evidence is lacking. Novel pharmacological approaches include 5-HT_3 antagonists and 5-HT_4 agonists. These pharmacological classes have shown beneficial effects on a global efficacy end point, and ameliorated more than one symptom of lower gut function in clinical trials. They offer promise for the development of novel therapies for the treatment and control of irritable bowel syndrome.

SUMMARY

Serotonin (5-HT) is a biogenic amine that functions as a neurotransmitter of sensorimotor functions in the digestive tract. This paper addresses the role of 5-HT agents in the modulation of lower gastrointestinal function. Selective serotonin reuptake inhibitors (SSRIs) are of potential benefit in functional gastrointestinal diseases although formal evidence is lacking. Apart from central effects, they may have peripheral actions, as has been shown with paroxetine in the small bowel and citalopram in the colon. Novel pharmacological approaches include 5-HT_3 antagonists such as alosetron and cilansetron, and 5-HT_4 agonists such as tegaserod and prucalopride. These pharmacological classes have had beneficial effects on a global efficacy end point, and ameliorated more than one symptom of lower gut function in clinical trials. They offer promise for the treatment of female patients with symptoms of diarrhoea or constipation predominant irritable bowel syndrome (IBS), respectively.

INTRODUCTION

This paper addresses the role of 5-HT and serotonergic agents in the modulation of small bowel and colon functions. The first section deals with antidepressants, including the evidence for the effect of SSRIs. The second section deals with the evidence for the various novel serotonergic approaches based on modulation of 5-HT_3 and 5-HT_4 receptors. Projected use of novel therapies is also discussed.

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5-HT: A NEUROTRANSMITTER IN SENSORIMOTOR FUNCTIONS OF THE DIGESTIVE TRACT

5-HT is a biogenic amine that functions as a neurotransmitter of sensorimotor functions in the digestive tract. Its actions have been reviewed elsewhere.[1] There are seven main classes of 5-HT receptors with several subclasses that can be differentiated on the basis of structure, molecular mechanisms, and functions. Importantly, 5-HT reuptake is a mechanism that is relevant in the digestive tract as well as in the central nervous system (CNS). Thus the actions of intrinsic primary afferent neurones activated by mucosal stroking are enhanced by SSRIs.

Figure 1 shows a submucosal neurone activated by mucosal stroking, as shown by fluorescence of the neurone. This activation was enhanced in the presence of the SSRI fluoxetine, suggesting that SSRIs may influence digestive function.[2]

PSYCHOTROPHIC AGENTS INCLUDING SSRIs

To date, psychotrophic agents have probably been best reserved for those patients with symptoms of diarrhoea and pain associated with IBS.[3] However, there is increasing interest in the potential application of SSRIs, which are the most widely used antidepressants, and tend not to cause constipation or induce diarrhoea in all patients. One uncontrolled study supports the efficacy of SSRIs in treating patients with IBS.[4] SSRIs, which sometimes cause diarrhoea,[5] are currently being assessed in prospective studies. There is an initial understanding of the effects on gastrointestinal functions of individual agents in this class, specifically buspirone, paroxetine, and citalopram.

Pharmacology and pharmacodynamic effects of SSRIs and novel psychotropics on gastrointestinal function in health

Buspirone is a non-benzodiazepine anxiolytic drug with demonstrated efficacy in the treatment of generalised anxiety disorder. Preliminary studies have suggested that buspirone may be useful in the treatment of a variety of other psychiatric conditions.[6] Although the exact mechanism of action is not known, buspirone has a high affinity for 5-HT_{1A} receptors. The active metabolite of buspirone, 1-pyrimidinylpiperazine, functions as an alpha$_2$ adrenoceptor antagonist.[7] In animal models, buspirone has been shown to suppress stress induced caecal motor responses through 5-HT_{1A} receptors.[8] There is no further understanding of the effects of buspirone on the lower bowel of humans.

Paroxetine is a potent SSRI used in the treatment of a variety of psychiatric

Abbreviations: CNS, central nervous system; IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor; 5-HT, serotonin.

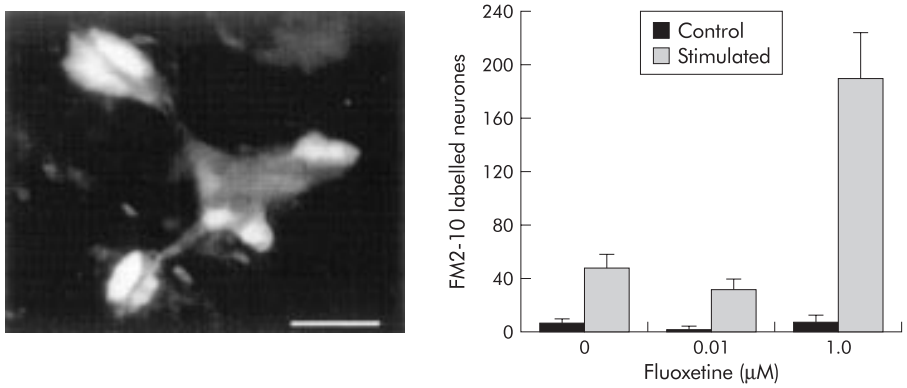

Figure 1 Evidence of stimulation of 5-HT containing submucosal neurones by stroking the small bowel mucosa. Uptake of FM2-10 was quantified on control and mucosally stimulated sides of preparations in the absence or presence of two concentrations of fluoxetine. Reproduced with permission from Chen and colleagues.[2]

conditions.[9 10] Published studies of the effect of paroxetine on the gastrointestinal tract have demonstrated stimulation of the small intestine. One study of paroxetine showed decreased migrating motor complex periodicity and increased propagation velocity of phase III contractions within the small intestine.[11] A decrease in orocaecal transit time following administration of paroxetine has also been demonstrated,[12] suggesting prokinetic activity, but the method used in this initial study does not allow differentiation of the effects on gastric versus small bowel transit. Results of these studies suggest that paroxetine may be useful in the treatment of dyspepsia with delayed upper gastrointestinal transit or in symptoms of constipation IBS, but more formal evaluation of the effects in the colon are required.

Tricyclic agents have varying magnitudes of effects on 5-HT mechanisms and are discussed briefly. This class of agents (for example, amitriptyline, imipramine, and doxepin) are now frequently used to treat patients with IBS, particularly those with more severe or refractory symptoms, impaired daily function, and associated somatisation, depression, or panic attacks. Initially their use was based on the fact that a high proportion of patients with IBS reported significant depression.[4 13–15] Antidepressants have neuromodulatory and analgesic properties which may benefit patients independently of the psychotrophic effects of the medications.[13] It appears that the clinical effects of agents such as amitriptyline result from their central actions. Thus amitriptyline had no significant effects on oesophageal and rectal sensory thresholds or compliance in healthy subjects.[16] Similarly, in upper functional gastrointestinal disorders, clinical benefit was associated with better sleep rather than changes in gastric sensitivity.[17]

Neuromodulatory effects may occur sooner and with lower dosages of tricyclic agents in IBS patients than the dosages used in the treatment of depression (for example, 10–25 mg amitriptyline or 50 mg desipramine). Because antidepressants must be used on a continual rather than on an as needed basis, they are generally reserved for patients with frequently recurrent or continual symptoms. A 2–3 month trial is usually needed before abandoning this therapeutic approach.[4]

Clinical effects of psychotropic agents in the treatment of IBS

Placebo controlled trials of antidepressants in IBS have been summarised elsewhere.[1] Trimipramine has been shown to decrease abdominal pain, nausea, and depression but does not alter stool frequency.[18 19] The beneficial effect seems to be greater in those with abdominal pain and diarrhoea. For example, desipramine improved abdominal pain and diarrhoea[20] but in an earlier study that combined patients with either diarrhoea or constipation there was no significant benefit for desipramine over placebo.[21] In other studies nortriptyline, in combination with fluphenazine, has been shown to reduce abdominal pain and diarrhoea.[15 22]

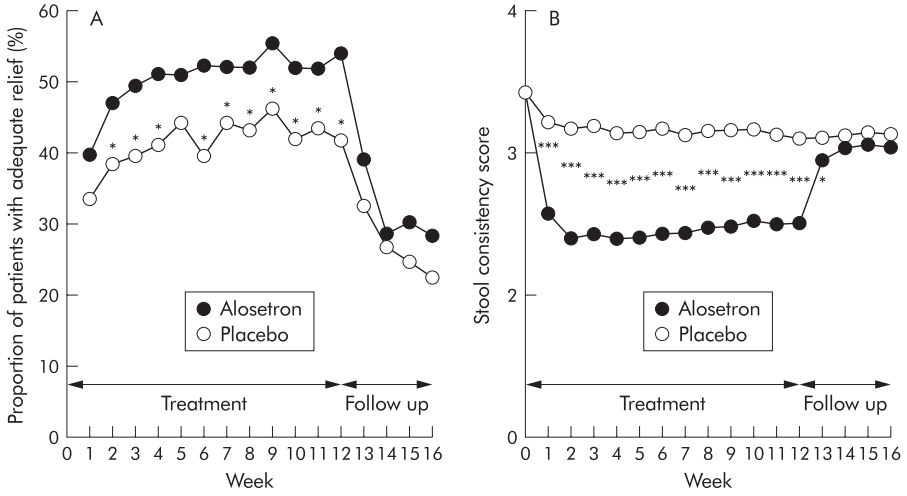

Figure 2 Effect of alosetron 1 mg twice daily and placebo on adequate relief of pain (A) and stool consistency (B) in female patients with symptoms of diarrhoea. Note the improvement in symptoms and the abrupt change in symptoms with cessation of therapy after 12 weeks. *p<0.05; ***p<0.001. Reproduced with permission from Camilleri and colleagues.[35]

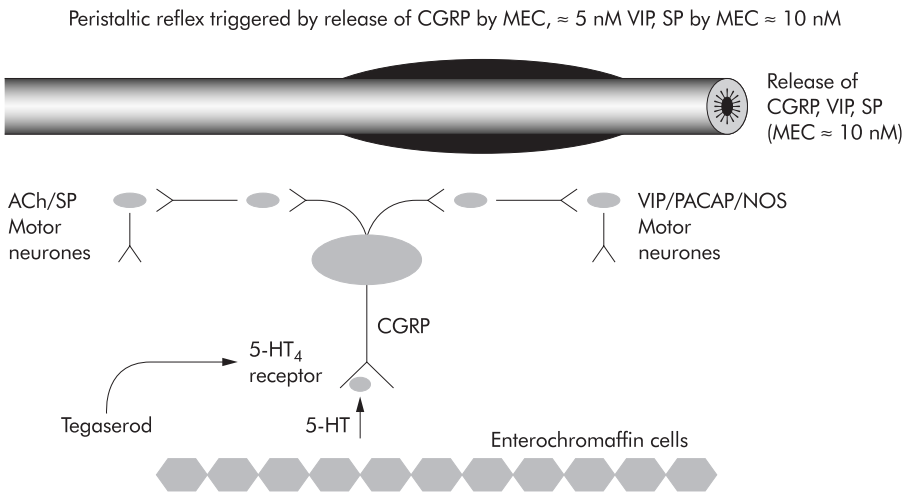

Figure 3 Model of the effect of 5-HT released from enterochromaffin cells or absorbed tegaserod, a partial 5-HT_4 agonist, on activation of intrinsic primary afferent neurones (for example, calcitonin gene related peptide (CGRP)), which in turn stimulate the "peristaltic reflex". This involves orad contraction, mediated through excitatory transmitters such as acetylcholine (ACh) or substance P (SP), and a caudad relaxation, mediated through inhibitory neurotransmitters such as vasoactive intestinal peptide (VIP), pituitary adenylate cyclase associated peptide (PACAP), or nitric oxide synthetase (NOS). MEC, median effective concentration. Adapted from Grider and colleagues.[38]

NOVEL 5-HT MEDICATIONS IN IBS

Novel serotonergic agents may have a significant impact on symptoms in IBS through their visceral analgesic properties and diverse effects on motor functions in the lower gastrointestinal tract. The availability of these agents and their evaluation in mechanistic studies in IBS may provide further insights into mechanisms that are deranged in IBS, and the role of 5-HT.

5-HT_3 receptors: actions and effects of antagonists

5-HT_3 receptors are ligand gated ion channels that elicit the depolarising actions of 5-HT, which facilitate neurotransmitter release. In the CNS, 5-HT_3 receptors are located mostly in limbic and cortical regions and in the vomiting centres. Thus antagonists acting either on vagal afferents or on central receptors in the chemoreceptor trigger zone and vomiting centre in the base of the fourth ventricle result in a marked diminution in emesis following chemotherapy and radiotherapy.[23]

In the gastrointestinal tract, 5-HT_3 receptors are located on postsynaptic enteric neurones (for example, cholinergic) and on afferent sensory fibres.[24 25] 5-HT_3 receptors are also found in dorsal root ganglion neurones[26] conveying sensory information from the distal gastrointestinal tract to the spinal cord. Antagonism of these receptors reduces visceral pain, retards colonic transit, and enhances small intestinal absorption. Inhibition of 5-HT_3 receptors in the motor apparatus results in inhibition of contraction, and inhibition of receptors in the sensory apparatus reduces visceral sensation. When 5-HT_3 antagonists are given intravenously there is no significant relaxation of fasting colonic tone in health or in disease,[27 28] suggesting that changes in sensation during gastrointestinal tract stimulation result from either inhibition of sensory pathways or the motor responses resulting following sensory stimulation.

Hyperactivity of the motor response to meal ingestion or hypersensitivity to luminal distension in IBS, results in symptoms which originate in the small bowel and colon. Antagonism of 5-HT_3 receptors has the potential to restore normal sensory and motor functions in IBS. Alosetron and cilansetron are prototypes of this class of compounds. Clinical pharmacology studies have shown that 5-HT_3 antagonists slow whole gut transit time in health,[29] enhance colonic compliance and reduce perception of volume based distensions in patients with IBS,[30] and retard transit through the colon in patients with symptoms of diarrhoea.[29 31] In a single study using a triple lumen perfusion technique with standard radioactive markers as well as proximal and distal occluding balloons,[32] alosetron was shown to significantly enhance basal absorption of sodium and fluid relative to placebo.

Clinical effects of a 5-HT_3 antagonist, alosetron

Alosetron is a selective 5-HT_3 antagonist and is effective in relieving pain, normalising bowel frequency, and reducing urgency in symptoms of diarrhoea in female IBS patients.[33] In large placebo controlled trials, alosetron was more effective than placebo in inducing adequate relief of pain and discomfort, and improvement in bowel frequency (fig 2), consistency, and urgency[34–37] in women with symptoms of diarrhoea. Another study compared alosetron (1 mg twice daily) to mebeverine, an antispasmodic approved in Europe for the treatment of IBS, and showed similar results over the active comparator.[37]

The beneficial response for pain and bowel dysfunction was observed within 1–4 weeks of beginning therapy, and was sustained throughout the duration of the trial. Within one week after discontinuing the drug, symptoms were comparable with those in women receiving placebo. The benefit appeared to be confined to patients with symptoms of diarrhoea.

The most common adverse event with alosetron treatment was constipation which was significantly more common than among women receiving placebo.[34–36] In the majority of

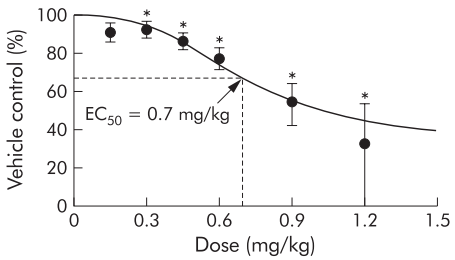

Figure 4 Effect of tegaserod on the firing rate of the pelvic afferent fibres stimulated by 50 mm Hg distension of the rectum in cats (mean (SD), n=9); note the dose related reduction in the firing rate, suggesting an effect of tegaserod on visceral afferent function. *p<0.05. Reproduced with permission from Schikowski and colleagues.[41]

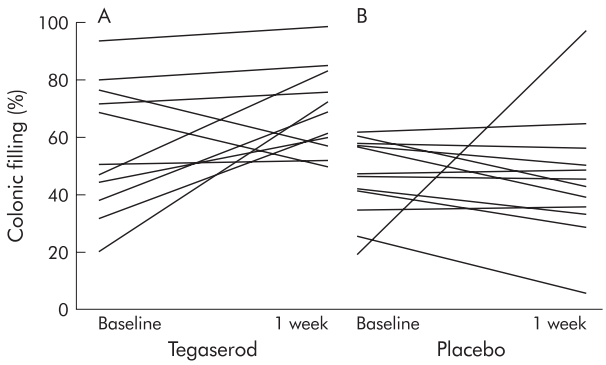

Figure 5 Effect of tegaserod (A) and placebo (B) on orocaecal transit measured as colonic filling at six hours in patients with symptoms of constipation predominant irritable bowel syndrome. Reproduced with permission from Prather and colleagues.[43]

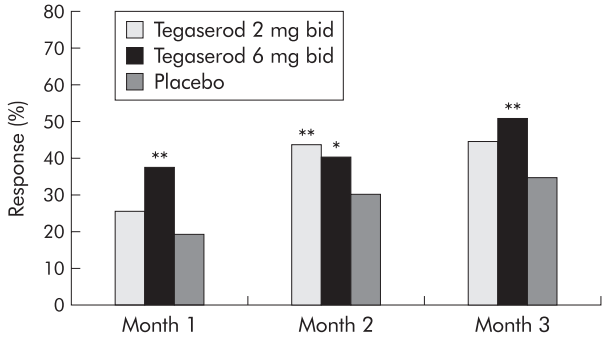

Figure 6 Effect of tegaserod on monthly assessment of the subjects' global assessment of relief; note the significant increase in the proportion of patients achieving the global relief end point with 2 mg and 6 mg twice daily (bid) tegaserod. *p<0.05; **p<0.01. Reproduced with permission from Mueller-Lissner and colleagues.[45]

patients, constipation was mild to moderate in severity. Acute ischaemic colitis however was a significant adverse event with an unclear relationship to alosetron. After initial approval, alosetron has been withdrawn from the USA market following reports of constipation and sequelae that led to colonic surgery. Nevertheless, this class of agents appears to have significant therapeutic potential, and the risk/benefit ratio for each prescribed medication will need to be carefully weighed in each patient.

5-HT$_4$ receptor agonists

5-HT$_4$ receptors belong to the family of seven transmembrane domain receptors coupled to G protein translation. They are responsible for eliciting the depolarising action of 5-HT which results in release of neurotransmitters, such as acetylcholine, from enteric neurones. 5-HT$_4$ receptors are located in the CNS where they modulate dopamine release and have a direct role in cognition and memory. In the heart, these receptors are located in the atria, not the ventricles, and have a chronotropic effect. In the adrenal cortex, activation of 5-HT$_4$ receptors transiently stimulates aldosterone secretion; in the urinary bladder, activation of the receptors increases detrusor tone.

In vitro studies on intestinal tissues, and in vivo animal and human studies of motor and sensory function (discussed below) provide the scientific rationale to suggest that medications acting on 5-HT$_4$ receptors should provide relief of pain, discomfort, and constipation in IBS. Partial or full 5-HT$_4$ agonists appear promising in the treatment of functional constipation or symptoms of constipation.

The partial 5-HT$_4$ agonist, tegaserod

Tegaserod has been shown to enhance peristalsis in an in vitro model, at least in part by stimulating the intrinsic primary afferent neurone (fig 3), activating excitatory and inhibitory intrinsic neurones that result in ascending contraction and descending relaxation, respectively.[38] Tegaserod may also stimulate motility via a systemic action as it increases small bowel and colonic contractions after intravenous administration in dogs.[39] It reduces visceral afferent firing during rectal distension, and reduces abdominal contractions in response to noxious rectal distension, a pseudoaffective model of visceral pain.[40] Tegaserod also reduces visceral afferent firing during noxious rectal distension (fig 4).[41]

These effects of tegaserod in vivo suggest that the drug may activate gastrointestinal motility by a mechanism other than luminal activation of the peristaltic reflex. This alternative activation mechanism is likely to involve 5-HT$_4$ receptors on enteric cholinergic neurones. The effects of tegaserod were inhibited by a selective 5-HT$_4$ antagonist SB203186, consistent with the interpretation that the effects of tegaserod on sensation are mediated through 5-HT$_4$ receptors.

In health, Degen and colleagues[42] have demonstrated that intravenous (0.6 mg) and oral (6 mg) tegaserod accelerate gastric emptying, and small bowel and colonic transit. Prather and colleagues[43] evaluated the effect of tegaserod 2 mg twice daily for one week on whole gut transit using a scintigraphic method; colonic filling, a surrogate of orocaecal transit time, was significantly accelerated by tegaserod relative to placebo (fig 5). Colonic transit time was also accelerated in the tegaserod group

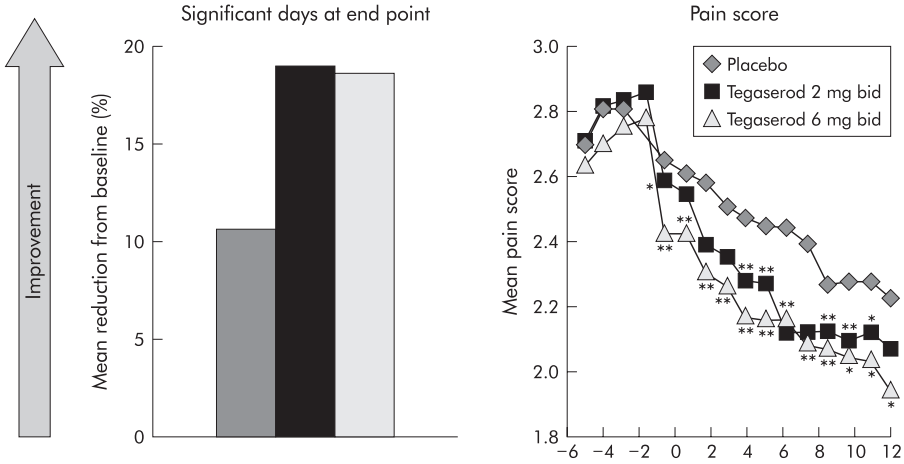

Figure 7 Effect of tegaserod (2 and 6 mg twice daily (bid)) on weekly assessment of pain. *p<0.05; **p<0.01 versus placebo. Significant=at least mild; ≥2 on a six point scale. Reproduced with permission from Mueller-Lissner and colleagues.[44]

relative to pretreatment values although this effect did not reach statistical significance relative to placebo treatment.

Clinical effects of a partial 5-HT$_4$ agonist, tegaserod

Tegaserod results in global relief of IBS symptoms in females with symptoms of constipation IBS.[44] The effective doses of tegaserod are 4–12 mg per day in two divided doses (2 mg or 6 mg twice daily). Tegaserod resulted in significant relief of the subjects' global assessment of relief at study end point, which was preset at the last four weeks of a 12 week trial. Monthly responses from one trial are shown in fig 6. This efficacy is also evident from the beginning of the weekly comparison with placebo for pain and bowel function. Relief was associated with significant improvement in a number of secondary end points such as pain free days (fig 7), frequency of bowel movements, and stool consistency.[45] The drug was significantly effective, providing 8–12% advantage over placebo in female patients, and particularly in those with documented constipation during the baseline run-in period.[46]

Tegaserod appears to be 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.

The 5-HT$_4$ agonist, prucalopride

In the dog in vivo, the full 5-HT$_4$ agonist prucalopride induces strong contractions in the proximal colon.[47] It also accelerates colonic transit in healthy participants[48 49] and in patients with functional constipation.[50] Prucalopride was effective in inducing a significant increase in the number of spontaneous and complete bowel movements in phase II trials of patients with functional constipation.[51 52] While this group is theoretically different from IBS with symptoms of constipation, the differences in these two subgroups of patients are small and, in clinical practice, patients often receive both diagnoses at different times. The effects of prucalopride on abdominal pain have not been thoroughly assessed and hence further studies are needed. These studies are currently on hold however while a more thorough assessment of intestinal carcinogenicity in experimental animals is evaluated.

OTHER RESEARCH APPROACHES INVOLVING 5-HT AGENTS

Citalopram reduces colonic sensation to volume distension in health.[53] The activity of citalopram has to be evaluated further to determine whether inhibition of the colonic motor response to feeding noted with this drug results from the effects on 5-HT reuptake as an SSRI or from other actions.

CONCLUSION

With further understanding of the brain-gut axis, the role of 5-HT in modulation of sensorimotor functions in the lower gut is being clarified and novel therapies are being developed that enhance control of IBS.

ACKNOWLEDGEMENTS

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