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REVIEW

Serotonin receptors and their role in the pathophysiology and therapy of irritable bowel syndrome

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Abstract
Background Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract characterized by abdominal discomfort, pain and changes in bowel habits, often associated with psychological/psychiatric disorders. It has been suggested that the development of IBS may be related to the body's response to stress, which is one of the main factors that can modulate motility and visceral perception through the interaction between brain and gut (brain–gut axis). The present review will examine and discuss the role of serotonin (5-hydroxytryptamine, 5-HT) receptor subtypes in the pathophysiology and therapy of IBS.
Methods Search of the literature published in English using the PubMed database.
Results Several lines of evidence indicate that 5-HT and its receptor subtypes are likely to have a central role in the pathophysiology of IBS. 5-HT released from enterochromaffin cells regulates sensory, motor and secretory functions of the digestive system through the interaction with different receptor subtypes. It has been suggested that pain signals originate in intrinsic primary afferent neurons and are transmitted by extrinsic primary afferent neurons. Moreover, IBS is associated with abnormal activation of central stress circuits, which results in altered perception during visceral stimulation.
Conclusions Altered 5-HT signaling in the central nervous system and in the gut contributes to hypersensitivity in IBS. The therapeutic effects of 5-HT agonists/antagonists in IBS are likely to be due also to the ability to modulate visceral nociception in the central stress circuits. Further studies are needed in order to develop an optimal treatment.

Keywords Irritable bowel syndrome · Serotonin · Serotonin receptors · Brain–gut axis

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Introduction

Irritable bowel syndrome (IBS) is a multifactorial disorder, in which psychological abnormalities are significant factors contributing to both pathogenesis and clinical course. Serotonin (5-hydroxytryptamine, 5-HT) is likely to have a predominant role in the pathophysiology of IBS, through a variety of actions exerted in the central nervous system (CNS) and the enteric nervous system (ENS) [1, 2]. Dysfunctions of the central or peripheral serotonergic system can be involved in the pathophysiology of IBS, as suggested also by the therapeutic effects of both tricyclic

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antidepressants and selective serotonin reuptake inhibitors [3].

Elevated plasma levels of 5-HT have been described in patients with diarrhea-predominant IBS (D-IBS), as compared with control subjects [4, 5]. Spiller et al. [6] reported an increased density of enterochromaffin cells (ECs) in rectal biopsies obtained from patients with D-IBS. In contrast, relatively low post-prandial plasma 5-HT levels have been detected in patients with constipation-predominant IBS (C-IBS) [7].

5-HT, released in the gut from ECs, regulates sensory, motor and secretory functions of the digestive system [8] through interactions with intrinsic and extrinsic nervous pathways. Intrinsic innervation to the gut is supplied by neurons of the ENS, including the myenteric and submucosal plexus. Extrinsic innervation is provided by the autonomic nervous system (both sympathetic and parasympathetic), and it is arranged to work in a bi-directional way: the brain can affect the ENS functions through the branches of the autonomous nervous system and, conversely, the gut can signal to the brain via extrinsic primary afferent neurons (EPANs), whose cell bodies are located in the ganglia of cranial nerves (e.g., ganglion nodosum and petrosum) or dorsal roots. Nociceptive signals are transmitted from abdominal viscera to specific laminae of the dorsal horns. Then, synaptic inputs activate specific second-order spinal neurons, leading to activation of specific brain areas. In parallel, ascending visceral nociceptive transmission is modulated by supraspinal structures (e.g., periaqueductal gray, raphe nucleus, locus coeruleus, thalamic regions), which either inhibit or facilitate nociceptive signaling through descending pathways.

Serotonergic, noradrenergic and dopaminergic fibers are the major components of these efferent descending projections. In this context, it has been suggested that visceral hypersensitivity in patients with IBS could be related to an abnormal signaling in the descending facilitatory pathway [9]. 5-HT has been found to exert opposite actions on intestinal motor activity and peristaltic reflex. On one hand, it can stimulate contractions through the release of acetylcholine from cholinergic neurons. On the other hand, it can facilitate enteric smooth muscle relaxation both by release of nitric oxide from nitrergic neurons and via a direct relaxation of smooth muscles [8].

The different gut effects of 5-HT are mediated by different serotonergic receptor subtypes located in the CNS [10], enteric neurons [11], gastrointestinal (GI) smooth muscle [12, 13] and secreting epithelial cells [14].

The present review article examines and discusses the role of 5-HT receptor subtypes in the pathophysiology and therapy of IBS.

5-HT receptors in the CNS and GI tract

5-HT exerts its biological activity through interaction with different receptors, currently classified into 7 groups on the basis of their structure, transduction mechanism and pharmacological profile [10, 14–16]: 5-$HT_{1–7}$ (Table 1). Most of these receptors are expressed in the GI tract, and their stimulation plays different roles (either inhibitory or excitatory) in the control of intestinal motility and secretion. The 5-HT_3 receptor is coupled to an ion channel, whereas $HT_{1,2,4,5,6,7}$ receptors are coupled to G proteins.

The class of 5-HT_1 receptors [17] is heterogeneous and includes several subtypes, such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1E}, 5-HT_{1F} and 5-HT_1-like. All 5-HT_1 receptor subtypes consist of a single peptide of variable length (from 374 to 421 amino acids), and they share at least 60 % homology in their transmembrane domains. 5-HT_{1A} receptors have a wide distribution in several brain regions involved in the modulation of emotions, such as the hippocampus, septum, dorsal raphe nuclei and amygdala [17], where they act mainly as inhibitory somatodendritic autoreceptors. However, at limbic level, particularly in the hippocampus, 5-HT_{1A} receptors are located post-synaptically, and here, their activation results in hyperpolarization of somatodendritic neuronal membrane [18]. These receptors have been found also in the neocortex and the gelatinous substance of the spinal cord, which are involved in the regulation of proprioceptive and integrative functions [17]. In the GI tract, 5-HT_{1A} receptors are expressed in the ENS, particularly in the submucosal and myenteric plexuses [11], where they mediate degranulation of enteric mast cells and release of mediators, including histamine [19].

5-HT_{1B} receptors are predominantly distributed in the striatum of basal ganglia and the prefrontal cortex, where they act as autoreceptors [18]. The 5-HT_{1C} subtype is similar in structure and transduction mechanism to receptors of the 5-HT_2 family, and for this reason, it has been renamed 5-HT_{2C} [20].

5-HT_{1D} receptors display a high degree of homology with 5-HT_{1B} receptors, but they are expressed with lower density. They inhibit neurotransmitter release [21] and mediate contraction of vascular smooth muscle cells [22]. The highest 5-HT_{1D} receptor densities are found in the raphe nuclei. 5-HT_{1D} receptors are expressed as α and β isoforms, endowed with similar pharmacological profiles [23–25]. The highest densities of 5-HT_{1E} receptor sites have been found in the caudate and putamen [26]. Their specific functional role is still not clear [27]. 5-HT_{1F} receptors have been identified in the CNS, particularly in the neocortex, where they might contribute to the integration of information associated with limbic functions [28]. 5-$HT_{1\text{-like}}$ receptors are located in the CNS and intracranial

Table 1 Receptor subtypes in the brain and in the GI tract

Receptor subtypes	Location	Main functional role
5-HT_{1A}	CNS	Neuronal hyperpolarization [18]
	GI tract	Degranulation of enteric mast cells; release of mediators [19]
5-HT_{1B}	CNS	Autoreceptor; inhibition of neurotransmitter release [18]
5-HT_{1D}	CNS	Inhibition of neurotransmitter release [21]
	Intracranial vessels	Contraction of vascular smooth muscle [22]
5-HT_{1E}	CNS	Unknown [27]
5-HT_{1F}	CNS	Integration of sensorimotor or afferent information associated with limbic functions [28]
5-$HT_{1\text{-like}}$	CNS	Inhibition of noradrenaline release [29]
	Intracranial vessels	Smooth muscle contraction [30]
5-HT_{1P}	GI tract	Excitatory action on vagal afferent fibers [31]
5-HT_{2A}	CNS	Involvement into the neurochemical and behavioral effects of psychostimulants [33]
	GI tract	Contraction of gut smooth muscle [12]
5-HT_{2B}	GI tract	Increased response of the colonic longitudinal smooth muscle [38]
5-HT_{2C}	CNS	Production of regulation of emotional states [39]
	Choroid plexus	Cerebrospinal fluid [39]
5-HT_3	CNS	Modulation of the release of other neurotransmitters such as dopamine, GABA, substance P and acetylcholine [42]
	GI tract	Motility [46] and pain transmission [8, 38]
5-HT_4	CNS	Memory [47], cognitive function [48], affective symptoms [50]
	GI tract	Contraction of smooth colonic muscle
		Prokinetic effect
		Neurotransmitter release [31]
5-HT_{5A}	CNS	Regulation of affective states, learning, sensory perception, neuroendocrine functions and memory [54, 55]
5-HT_6	CNS	Regulation of affective states [58]
5-HT_7	CNS	Regulation of affective states
	GI tract	Muscle relaxant action of GI tract [59]

GI tract gastrointestinal tract, *5-HT* 5-hydroxytryptamine, *CNS* central nervous system, *GABA* gamma-aminobutyric acid

vessels. They inhibit noradrenaline release from sympathetic nerves [29] and vascular smooth muscle cell contraction [30]. 5-HT_{1P} receptors are expressed in the GI tract, where they mediate excitatory actions on vagal afferent fibers [31].

The 5-HT_2 receptor family includes three subtypes, named 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. They are expressed predominantly in peripheral tissues, such as stomach, intestine, heart and kidney [32], while in the CNS they are found in the cerebellum, lateral septum, hypothalamus and middle part of the amygdala. 5-HT_{2A} and 5-HT_{2C} receptors are known to mediate the neurochemical and behavioral effects of psychostimulants [33]. In the GI tract, they promote contractions of smooth muscle cells [12].

The 5-HT_{2B} receptor was first identified in the fundus of rat stomach [32]. Originally classified as 5-$HT_{1\text{-like}}$ receptor [34], it has been recently assigned to the 5-HT_2 receptor family with the name of 5-HT_{2B} [20, 35, 36]. In the rat, 5-HT_{2B} receptor stimulation mediates hyperphagia and reduces "grooming" behavior [37]. Peripherally, 5-HT_{2B} receptors are located in myenteric nerves and colonic smooth muscle cells, where they mediate contractile responses of the longitudinal muscle layer to electrical stimulation [38]. 5-HT_{2C} receptors are predominantly expressed in epithelial cells of the choroid plexus, cerebral cortex, hippocampus, amygdala, some components of basal ganglia, substantia nigra, substantia innominata and ventromedial hypothalamus [39].

5-HT_3 receptors belong to the ion-channel-linked receptor super-family, which includes nicotinic, cholinergic and gamma-aminobutyric acid (GABA) A receptors [40]. They are located in the hippocampus, dorsal motor nucleus of the solitary tract and area postrema [41]. At the CNS level, they are involved in the regulation of emetic responses to various stimuli, including anticancer chemotherapy. The activation of 5-HT_3 receptors elicits central effects comparable to those observed after administration of antipsychotic and anxiolytic drugs, due to their ability to modulate the release of other

neurotransmitters such as dopamine, GABA, substance P and acetylcholine [42]. In the GI tract, 5-HT_3 receptors are expressed in enteric neurons, smooth muscle cells, vagal and spinal primary afferent neurons, and in the spinal cord [43, 44]. 5-HT_3 receptors activate extrinsic sensory neurons which mediate pain [8, 38]. They also regulate the pacemaker activity of the interstitial cells of Cajal [45, 46].

5-HT_4 receptors are localized in the CNS, where it has been suggested they play a role in enhancing memory [47]. Several studies indicate that 5-HT_4 receptors are involved in cognitive functions [48], affective symptoms and the development of Alzheimer's disease [49, 50]. A study of Madsen et al. [51] showed that healthy women had a lower 5-HT_4 receptor binding in the limbic system. In the GI tract, 5-HT_4 receptors are expressed in enteric neurons and smooth muscle cells. After 5-HT_4 receptor activation, acetylcholine is released from enteric interneurons and motor neurons, thus promoting and maintaining propulsive motility [52]. In the heart, 5-HT_4 agonists elicit positive chronotropic and inotropic effects in the isolated human atrium [53].

5-HT_{5A} receptors are distributed predominantly in the cortex, hippocampus, hypothalamus, amygdala and cerebellum. Depending on their localization, 5-HT_{5A} receptors are involved in the regulation of several functions, such as the control of affective states, sensory perception and neuroendocrine functions [54]. The limbic distribution of these receptors suggests a role in learning, memory and emotional state [55, 56]. 5-HT_{5B} receptors are expressed in mice but not in humans [57].

5-HT_6 receptors are located in the striatum, amygdala, nucleus accumbens, olfactory tubercle and cortex. As demonstrated by several pharmacological studies, many antipsychotic drugs (clozapine, olanzapine and quetiapine) and antidepressants (clomipramine, amitriptyline and nortriptyline) act as high affinity antagonists of 5-HT_6 receptors [58].

5-HT_7 receptors are distributed in the limbic system and thalamocortical regions, where they are involved in the modulation of affective states. They are also expressed in smooth muscle cells of peripheral vessels and intestine, where they mediate muscle relaxation [59]. In this respect, Tonini et al. [60] found that 5-HT_7 receptors mediate intestinal smooth muscle relaxation and accommodation in the guinea pig ileum. The authors suggested that an abnormal stimulation of 5-HT_7 receptors may contribute to clinical syndromes, like IBS, and that they could be a possible candidate for therapeutic interventions.

Serotonergic transmission in gut–brain axis

5-Hydroxytryptamine is a very active mediator in both the ENS and the CNS. In the periphery, about 90 % of 5-HT is synthesized in the gut by the ECs. Physiological intraluminal distension of the intestine and its propulsive activity promotes the release of 5-HT from ECs of the enteric mucosa [61]. Once released, 5-HT stimulates 5-HT_3 and 5-HT_4 receptors, located on intrinsic primary afferent neurons (IPANS) of the ENS, which mediate both secretory and motor responses. In the GI tract, both the secretory and peristaltic reflexes are regulated by 5-HT release from ECs and depend on the stimulation of 5-$HT_{1B/1P}$ and 5-HT_4 receptors located on submucosal IPANs [8, 62]. Post-synaptic 5-HT_3 receptors are present in both enteric plexuses, particularly in the motor neurons that innervate smooth muscle [38].

Danzenbrink and Gebhart [63] demonstrated that 5-HT_1, 5-HT_2 and 5-HT_3 receptors mediate noxious visceral stimulus. A main function of 5-HT_3 receptors is the activation of EPANs, which mediate the pain and swelling of bowel wall associated with IBS [8, 38].

It has been suggested that pain signals originate in IPANs and are transmitted by EPANs [64]. The connections to the brain occur through vagal and spinal afferent nerves. Vagal afferent neurons have their cell bodies located in the nodose ganglia and project to the nucleus of the solitary tract, which in turn projects to the thalamus and transmits signals to the limbic system and to the frontal cortex for polymodal association and perception of pain.

First-order spinal afferent nerves synapse in the dorsal horn-lamina II and IV. Second-order neurones project to the brain through the spinothalamic and spinoreticular tract [65]. The second-order neurons synapse with third-order neurons in the thalamus and reticular nuclei. Spinal afferents transmit pain signals to the somatosensory cortex to discriminate and process pain information (Fig. 1).

Serotonergic fibers, descending from brain to the dorsal horn neurons, are responsible for visceral sensitivity, thus modulating perception during gut stimulation [66, 67].

Recently, Keszthelyi et al. [68] showed significantly lower mucosal and higher systemic concentrations of both 5-HT and kynurenic acid, a main kynurenine metabolite, in IBS patients as compared to healthy controls. Also, significant correlation between mucosal but not plasma concentrations of kynurenic acid and 5-HT and psychological state in IBS was observed [67]. Moreover, Stasi et al. [69], in diarrhea-predominant IBS (D-IBS), have shown a correlation between plasma cortisol and 5-HT, which could be explained by the concomitant activation of the hypothalamic-pituitary-adrenal (HPA) axis to limit local inflammatory processes in response to both exteroceptive and interoceptive stress (with the consequent activation of ECs, production of 5-HT, activation of mast cells and secretion of cytokines). These data suggest that an alteration of 5-HT production and consequently neurotransmission could be involved in psychological state and IBS symptoms.

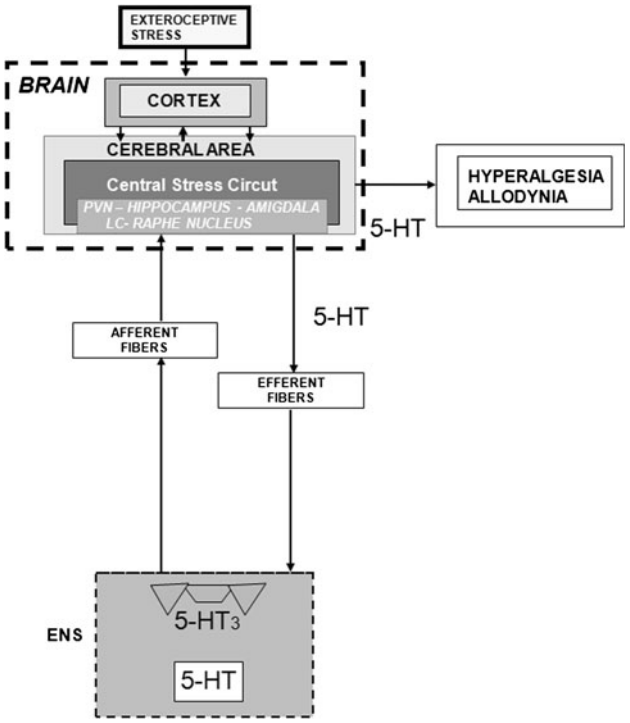

Fig. 1 (Modified from Stasi et al. [2]). Schematic model of serotonin-mediated brain–gut connection. In the ENS, 5-HT binds to 5-HT_3 receptors and via afferent fibers connects the gut to the central stress circuit (PVN, hippocampus, amygdala, LC, raphe nucleus and HPA axis). These cerebral areas are altered in IBS patients, because of exteroceptive chronic stress, leading to a local release of 5-HT. This may result in hyperalgesia and allodynia typical of this condition. The descending pathways may either inhibit or facilitate nociceptive signalling. *5-HT* serotonin, *ENS* enteric nervous system, *PVN* paraventricular nucleus, *LC* locus coeruleus, *HPA* hypothalamic-pituitary-adrenal, *IBS* irritable bowel syndrome

IBS has a strong predominance in women. Reported prevalence rates of IBS range from 8 to 20 % in the general US population, with a 2:1 female-to-male ratio [70]. Nakai et al. [71] showed that 5-HT synthesis in the right medial temporal gyrus (multimodal sensory association cortex) was higher in female IBS patients than in female controls. This suggests a relationship with the pathological visceral pain processing of IBS female patients. It has been demonstrated that the number of 5-HT_4 receptors in the female brain is lower than in the male brain, suggesting that this might be the basis for the sex-specific difference in emotional control and the higher prevalence of affective diseases and visceral hypersensitivity in women [51].

Several factors, such as the high prevalence of anxiety and psychological disorders, have been shown to increase intestinal response to psychological stress [2]. Clinical response to serotonin drugs acting at the central level [72, 73] suggests an involvement of the limbic system in the pathophysiology of IBS. In recent years, the importance of the body's response to stress has repeatedly been underlined and represents one of the main factors that can modulate motility and visceral perception through brain–gut interaction (brain–gut axis) [2, 9].

Irritable bowel syndrome is associated with visceral hypersensitivity, which can be related to deranged processing, representation and modulation of gut signals in the brain [74, 75]. Whitehead et al. [76] showed that patients with IBS have a significantly lower pain threshold than controls. Increased sensitivity to distention of the colon and rectum was observed in patients with D-IBS as compared with healthy subjects [77, 78], while studies in patients with C-IBS have yielded conflicting results [79, 80]. However, no significant differences in pain threshold have been shown in patients with D-IBS when compared with patients with C-IBS [81]. These data suggest that the alterations of 5-HT transmission in the CNS are similar in D- and C-IBS. Drossman et al. [82], using functional magnetic resonance imaging of the brain in a IBS patient, found a correlation between the severity of clinical symptoms and psychosocial state, with activation of the cingulate cortex, the critical center for pain control. Other studies have shown deactivation of the insula, the amygdala and the striatum of patients with IBS compared to controls [83, 84]. These brain areas are part of the central stress circuit, that is, under feedback control through the projections from the brainstem nuclei, in particular from serotonergic nuclei such as the raphe nucleus [2]. 5-HT receptors are expressed in cortical and limbic areas of the brain involved in emotional conditions and perception of visceral pain. Activation of 5-HT_3 receptors on the central terminals of spinal afferents increases the spinal transmission in the entire dorsal horn, which results in increased pain and reflex responses [85].

Moreover, stress may increase the permeability of the blood–brain barrier and enhance the action of some drugs on central targets when they are orally administered [86]. In animal models, transient blockade of the 5-HT_3 receptor by intrathecal injections of the antagonist ondansetron reduces mechanical allodynia after spinal cord injury [87]. Tegaserod antagonizes 5-HT_{2B} receptors at concentrations similar to those that activate 5-HT_4 receptors and has significant binding affinity for human recombinant 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors [88, 89]. The ability of tegaserod to alleviate abdominal pain and discomfort in patients with IBS is likely due not to its effects on peripheral 5-HT_4 receptors, but probably to its actions on 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors located in CNS.

Therapeutic approach to irritable bowel syndrome

Several studies have investigated alterations of serotonergic signaling in IBS; consequently, treatment strategies for

IBS involving 5-HT receptors are currently directed at managing the predominant symptoms. Initial pharmacological attempts have been primarily directed towards those receptors known to regulate intestinal function, such as 5-HT_1, 5-HT_3, 5-HT_4 and 5-HT_7 subtypes.

Ondansetron and alosetron are antagonists of 5-HT_3 receptors. They delay transit throughout the colon both in D-IBS and controls [90]. Moreover, ondansetron increases the consistency of feces both in healthy volunteers and IBS patients [91, 92].

Likewise, alosetron, another 5-HT_3 antagonist, was shown to be able to delay colonic transit in both healthy volunteers and D-IBS patients [5, 93].

Some studies suggest that antagonists of 5-HT_4 receptors may induce a significant slowing of intestinal transit, thus allowing a potential therapeutic benefit in patients with D-IBS [94]. Piboserod, an antagonist of 5-HT_4 receptors, showed no significant effects in the treatment of D-IBS [95]. In contrast, 5-HT_4 receptor agonists, such as tegaserod and prucalopride, accelerate GI transit in humans [96, 97].

In summary, these studies suggest that the antagonists of 5-HT_3 receptors can delay intestinal transit, while the agonists of 5-HT_4 receptors can lead to a transit acceleration.

Some patients with IBS display increased visceral sensitivity and/or an increased perception of intestinal distension. It has been observed that antagonists acting on 5-HT_3 receptors, expressed on post-synaptic neurons of the peripheral nervous system, can modify the visceral sensation [98], thus improving abdominal pain and discomfort.

Consistently with these findings, a recent multicenter, randomized study [99] has shown that ramosetron (5-HT_3 antagonist) can alleviate abdominal pain/discomfort and abnormal bowel habits in male patients with D-IBS. Previous experimental evidence showed that tegaserod (a partial 5-HT_4 receptor agonist) can induce a dose-dependent reduction in the discharge rate from mechanosensory neurons in the spinal cord of the cat [100]. A systematic review by Evans et al. [101] showed that in patients with C-IBS, tegaserod counteracted symptoms when compared with placebo, while it did not increase bowel movements. Since tegaserod was withdrawn from the market owing to cardiovascular adverse events, pharmacological research has been focused on the development of high-selective 5-HT_4 receptor agonists in an attempt to circumvent aspecific adverse effects.

Naronapride (ATI-7505) is a novel selective 5-HT_4 receptor agonist. In a clinical trial, the effects of this drug were evaluated after 9 days of treatment in healthy volunteers, and the assessment of GI and colonic transit by scintigraphy showed accelerated colonic transit and ascending colonic emptying [102].

Prucalopride (a dihydrobenzofuran-carboxamide derivative) is a selective and specific 5-HT_4 receptor agonist endowed with enterokinetic properties, recently approved by the European Medicines Agency (EMA) for treatment of idiopathic chronic constipation. Over a 12-week treatment period, 2 and 4 mg of prucalopride once daily significantly improved bowel habits in three large, randomized, double-blind, multicenter trials in patients with severe chronic constipation. Prucalopride was well tolerated: the incidence of QT interval prolongation was low and similar to that induced by placebo [97]. Prucalopride is able to penetrate the blood–brain barrier, and it binds to 5-HT_4 receptors in the rat brain [103].

Manini et al. [104] reported that the 5-HT_4 agonist velusetrag significantly accelerated intestinal and colonic transit (ascending colon emptying) after a single dose and accelerated gastric emptying after multiple dosing. Hoffman et al. [105] demonstrated that, similar to other 5-HT_4 receptor, velusetrag promotes propulsive motility and attenuates visceral hypersensitivity, but the precise mechanisms remain unclear.

Conclusions

In the CNS and in the gut, altered 5-HT signaling contributes to hypersensitivity and abnormal gut function in IBS, suggesting that this neurotransmitter with endocrine and paracrine functions may play a role in the development of IBS symptoms. The therapeutic effects of 5-HT_3 antagonists and 5-HT_4 agonists in IBS treatment are likely to be due also to the ability to modulate visceral nociception in the central stress circuit. It would be important to continue to investigate other receptor subtypes in the brain, particularly those regulating the affective states and the response to stress, in order to clarify their role in visceral perception. Further studies along these lines are needed in order to develop an optimal treatment for IBS.

Conflict of interest None.

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