**Abstract.** – 5-Hydroxytryptamine (5-HT) is a major transmitter molecule within the gastrointestinal tract. It is contained in enterochromaffin (EC) cells, which form part of the epithelial lining of the gut and in enteric neurones in the submucosal and myenteric plexuses. 5-HT is present in murine mucosal mast cells in the lamina propria and some studies have suggested that human mast cells may also contain 5-HT especially in conditions associated with mastocytosis. The strategic positioning of the enteric and extrinsic sensory innervation in close proximity to these sources of 5-HT, in conjunction with their demonstrated sensitivity to this mediator, suggests the involvement of 5-HT in the transduction of visceral stimuli and reflex responses affecting motor and secretory function. Under physiological conditions, the release of 5-HT from these storage sites may result in the orchestration of reflexes responsible for transit of material along the bowel at a rate that is appropriate for digestion and absorption of nutrients. However, in the pathophysiological state, 5-HT acting together with other inflammatory mediators may cause inappropriate intestinal secretomotor activity and/or initiate sensations such as nausea or discomfort/pain. Current evidence suggests that the bioavailability of 5-HT within the gut wall is altered in a number of post-inflammatory models of gut dysfunction with increased numbers of EC cells and mast cells with increased 5-HT content in proximity to sensory nerve endings, and decreased serotonin reuptake mechanisms. Changes may also occur in the sensory innervation or pathways within the central nervous system. These processes may contribute to pain mechanisms in the irritable bowel syndrome, in which visceral hypersensitivity is a predominant feature and may also contribute to motor dysfunction leading to altered bowel habit.

**Key Words:**
5-hydroxytryptamin, Gastrointestinal tract, Vagal afferente, Spinal afferente, Irritable Bowel Syndrome.

**Introduction**

Gastrointestinal (GI) motility and secretion are controlled and coordinated by the autonomic nervous system (ANS) which includes elements that are intrinsic to the bowel wall that make up the enteric nervous system (ENS) and extrinsic elements that connect the gut wall to the central nervous system (CNS). The ENS is considered an independent nervous system comprising ganglionated plexuses that run uninterrupted along the length of the bowel. Sensory neurones, inter-neurones and motor neurones make up the “hard-wired” reflex circuits that are the basis for coordinated peristalsis and secretion essential for digestion. 5-Hydroxytryptamine (5-HT) is an important mediator in these reflex pathways. The ENS also receives input from the sympathetic and parasympathetic division of the ANS and this helps coordinate different regions of the gut in tune with the needs of the individual. The extrinsic nerve bundles also contain sensory fibres that carry information to the CNS and help regulate digestive function, provide inputs to central autonomic circuits that regulate feeding and illness behaviour, and give rise to both painful and non-painful sensations. It is the role of 5-HT in these sensory functions that is the focus of this review.

**Extrinsic Sensory Innervation**

There are two sources of extrinsic afferents innervating the GI tract: vagal and spinal. Vagal afferent fibres arise from cell bodies in the inferior nodose and superior jugular ganglia, located bilaterally, proximal to the carotid bifurcation, and innervate the digestive tract from the pharynx to the proximal colon. Spinal afferent fibres arise from cell bodies located within the dorsal root ganglia (DRG) and project centrally into the spinal cord. Spinal afferents are subdivided into splanchnic and pelvic afferents. These afferent fibres follow the path of sympathetic and
parasympathetic neurones respectively, and have their cell bodies in thoracolumbar and sacral dorsal root ganglia.

**5-HT Receptor Expression and Function**

5-HT can act on a number of G-protein coupled receptors as well as on ligand-gated channels known as 5-HT_3_ receptors\(^2\). Many of these different receptor subtypes are widely distributed within the gut wall. However, in the context of sensory signalling most attention has focused on 5-HT_4_ and 5-HT_3_ receptors. In particular, evidence for the importance of 5-HT_3_ mediated signalling is given by the abundance of mRNA for the 5-HT_3_ receptor in nodose ganglion cell bodies\(^3\). Immunohistochemical evidence suggests that 5-HT_3_ receptors are present on both DRG and nodose ganglion cells that innervate the GI tract\(^4,5\). More recently the relative expression of a variety of ion channels and receptors on nodose and DRG neurones has been examined and one of the most striking differences was in the expression of 5-HT_3_ receptors which was 15 fold greater in nodose neurones innervating the abdominal viscera than DRG neurones\(^6\). In contrast, 5-HT_4_ receptor expression was equally low in both sensory neuronal populations.

Many aspects of ligand-5-HT_3_ receptor interaction were established using isolated nodose neurones\(^7\). 5-HT has been shown to activate an inward current which is mimicked by 2-methyl 5HT, and antagonized by the selective 5-HT_3_ receptor antagonists. Ion substitution experiments show this to be predominantly a Na\(^+\) and K\(^+\) conductance. Taken together these experiments indicate that 5-HT_3_ receptors, located on GI mucosal vagal afferents, may be an important modulator of activity. Similar currents have been described in DRG neurones.

Peripheral actions of 5-HT on sensory signalling have been examined by recording from afferent neurones as they emanate from the bowel wall at different levels of the GI tract. In the small intestine, 5-HT triggers mesenteric afferent firing, which is the result of both a direct action on 5-HT_3_ receptors and an indirect action through an increase in motility\(^8\). The action on motility is likely to arise from the widespread distribution of 5-HT receptors on enteric neuronal and muscle elements leading to contraction, and since many visceral afferents are also mechanosensitive this would lead to an increase in afferent discharge secondary to contraction. In the small intestine the direct effect on afferent firing is via activation of vagal, rather than spinal afferents, and since the latter are considered the major pathway for nociception this would suggest that peripheral 5-HT is not directly involved in visceral pain signalling\(^9\). However, in the colon 5-HT has been shown to activate spinal afferents via both 5-HT_3_ receptor- and non-5-HT_3_ receptor-dependent mechanisms\(^4\). This would be in keeping with a role for 5-HT signalling in the pathogenesis of irritable bowel syndrome (IBS) and altered visceral sensitivity in the context of post-inflammatory states. Interestingly, colonic afferents that respond to 5-HT have receptive fields in the serosa and mesenteric connections, well away from sources of endogenous 5-HT in the mucosa and ENS. However, 5-HT may also be derived from mast cells some of which reside in the peritoneum and which may be recruited under inflammatory conditions to augment afferent sensitivity\(^10\). Furthermore the 5-HT_3_ antagonist, alosetron, inhibits spinal cord c-fos expression in response to noxious colorectal distension\(^11\). This indicates that 5-HT may play a role in signalling noxious information within the spinal cord although these studies did not distinguish between central and peripheral actions of 5-HT_3_. In this respect, 5-HT has been shown to play an important role in descending spinal pathways that modulates synaptic transmission in the dorsal horn\(^12\). 5-HT_3_ receptor knockout mice have not been used to investigate GI sensory signalling but 5-HT_3_ receptors have been shown to contribute to somatic nociceptive signalling\(^13\).

**Enterochromaffin Cells**

Chemosensory mechanisms are highly conserved in evolution. Sensory elements in the gut wall include sensory nerve terminals of extrinsic and enteric origin which respond directly to their chemical milieu and specialized chemosensory cells within the mucosal epithelium that monitor the luminal environment and indirectly activate sensory endings following the release of a variety of chemical mediators, including 5-HT. In this respect, enterochromaffin (EC) cells share a number of morphological features with other secondary sense cells such as taste buds on the tongue, and this similarity has led to the cells in the gut being referred to as intestinal “taste” cells. EC cells have an apical tuft of microvilli exposed to the intestinal lumen which is proposed to monitor luminal contents and, in response to an appropriate stimulus, releases the contents of storage granules across the basolateral membrane to
stimulate afferent terminals in close proximity within the lamina propria. Sensory nerve terminals do not penetrate the epithelium into the hostile environment within the lumen and so these “taste cells” provide an important interface between the gut and the gut contents.

EC cells sense chemical changes in the gut lumen and release 5-HT which then activates the processes of both enteric and extrinsic sensory neurones. In the case of vagal afferents recorded in vivo, it is those endings close to the mucosal epithelium that are particularly sensitive to 5-HT. Sensitivity to 5-HT is lost after topical anaesthesia while the response of muscle mechanoreceptors to distension persists. Responses of myenteric after-hyperpolarization (AH) cells to 5-HT are also mediated by 5-HT3 receptors although 5-HT4 and the orphan 5-HT1P receptors may also play a role in chemical transduction.

EC cells are distributed along the length of the GI tract, although the highest numbers are located in the small intestine and rectum. Release of 5-HT from the EC cells is Ca2+-dependent, and is mediated by luminal (chemical or mechanical) or neuronal stimuli. Stimuli known to release 5-HT from EC cells include mucosal stroking, chemical stimulation with nutrients (e.g., glucose), toxins (e.g., cholera toxin, chemotherapeutics) and endogenous chemical stimuli such as adenosine. Recent evidence has demonstrated that EC cell number and 5-HT bioavailability are also influenced by GI inflammation. EC cell number is increased in clinical and experimental models of inflammatory bowel disease at a time when expression of the serotonin reuptake transporter (SERT) is reduced. Similar changes have been reported in patients with IBS, particularly in post-infectious IBS. These changes may potentially contribute the visceral hypersensitivity, which is one of the hallmarks of IBS since 5-HT can have a profound effect on visceral afferent signalling. A recent study has examined the effect of supernatant from mucosal biopsies taken from IBS patients and control subjects to examine the potential for altered mediator release in the mucosa to modulate afferent sensitivity. Indeed, supernatant from control subjects had no effect on mesenteric afferent firing or calcium signals recorded from isolated DRGs, while that from patients had a marked effect on firing. 5-HT acting via 5-HT3 receptor contributed to this augmented sensory activity since the response was blunted by blocking 5-HT3 receptors. This suggests that altered 5-HT bioavailability may play a role. However, mast cells have also been implicated in the response and a similar study has identified a role of mast cell proteases in altered sensory signalling.

**Pharmacotherapy for IBS**

5-HT3 antagonists such as alosetron have proved effective in the treatment of IBS but subsequently withdrawn because of a small number of cases of ischaemic colitis in patients treated with the drug. This might implicate 5-HT3 receptors in the regulation of mesenteric blood flow and, indeed, 5-HT causes vasodilation of submucosal arterioles in vitro via a neurogenic mechanism involving 5-HT3 receptors. However, a detailed in vivo study found no evidence that blocking 5-HT3 receptors interfered with baseline colonic blood flow or haemodynamic responses to ischaemia and reperfusion.

Another 5-HT ligand, tegaserod, which is a partial agonist at the 5-HT4 receptor has also been found to be effective in patients with constipation predominant IBS but again use has been restricted because of a small number of cardiovascular adverse events. The mechanism of action of 5-HT4 agonists on visceral afferent signalling may be complicated because of prokinetic effects leading to a reduction in constipation. However, direct actions of 5-HT4 receptors on afferent activity have been described some of which are consistent with an anti-nociceptive effect, while others describe an increase in afferent firing via positive coupling of the receptor to adenylate cyclase. There is also striking evidence suggesting that 5-HT4 receptors may have an enteric neuroprotective role which may counter some of the degenerative effects that have been described in the ENS with ageing and which may contribute to the aetiology of constipation.

**5-HT, Vagal Afferents and Emesis**

The emetic response is an adaptive mechanism for the elimination of harmful contents from the GI tract. Detection of toxins by specialized cell types such as EC cells serves to protect the gut and the organism from potentially harmful ingesta. 5-HT has been shown to be a major mediator of emetic and diarrhoeal responses to luminal toxins, and emesis induced clinically, for example as a side effect of chemo- and radiotherapy, appears to be caused through this toxin detection system. In the ferret, for example, intravenous cisplatin (a chemotherapeutic agent used in the treatment of some solid...
tumours) induces prodromal retching and emesis that can be attenuated both by vagotomy and by 5-HT<sub>3</sub> receptor antagonism<sup>33</sup>. Cisplatin also causes a profound increase in mesenteric afferent firing that is reversed by 5-HT<sub>3</sub> receptor blockade<sup>34</sup>. Radiation-induced emesis is also significantly attenuated by 5-HT<sub>3</sub> blockers<sup>35</sup>. These experiments indicate that the major mechanism whereby chemotherapeutic agents like cisplatin and radiation cause emesis is via release of intestinal 5-HT, which then subsequently acts on vagal afferents stimulating the emetic reflex. These experiments are further supported by the clinical experience with 5-HT<sub>3</sub> antagonists which have revolutionized the treatment of vomiting associated with the treatment of malignancy. They also further highlight the role of the EC cell as a luminal sensor, in this case causing a massive release of serotonin in response to a perceived toxin.

**Conclusion**

The GI tract is a major source of the body’s 5-HT which can have profound effects on motility and secretion, blood flow regulation and may also have a neuroprotective role. 5-HT is also a signalling molecule for sensory transmission both in the ENS and via extrinsic afferents to the CNS. A role in vagal afferent signalling is particularly evident with chemosensory mechanisms serving as an emetic trigger, and 5-HT<sub>3</sub> receptor antagonists have had a major impact on the treatment of cancer therapy-induced nausea and vomiting. 5-HT<sub>3</sub> and 5-HT<sub>4</sub> ligands are also effective in treating IBS but treatment has been limited by adverse events in a small number of patients. New drugs aimed at targeting these sensory mechanisms may be able to provide effective symptomatic relief without side effects.

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