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5-Hydroxytryptamine (serotonin) in the gastrointestinal tract

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Abstract

Purpose of review—Although the gut contains most of the body's 5-hydroxytryptamine (5-HT), many of its most important functions have recently been discovered. This review summarizes and directs attention to this new burst of knowledge.

Recent findings—Enteroendocrine cells have classically been regarded as pressure sensors, which secrete 5-HT to initiate peristaltic reflexes; nevertheless, recent data obtained from studies of mice that selectively lack 5-HT either in enterochromaffin cells (deletion of tryptophan hydroxylase 1 knockout; TPH1KO) or neurons (TPH2KO) imply that neuronal 5-HT is more important for constitutive gastrointestinal transit than that of enteroendocrine cells. The enteric nervous system of TPH2KO mice, however, also lacks a full complement of neurons; therefore, it is not clear whether slow transit in TPH2KO animals is due to their neuronal deficiency or absence of serotonergic neurotransmission. Neuronal 5-HT promotes the growth/maintenance of the mucosa as well as neurogenesis. Enteroendocrine cell derived 5-HT is an essential component of the gastrointestinal inflammatory response; thus, deletion of the serotonin transporter increases, whereas TPH1KO decreases the severity of intestinal inflammation. Enteroendocrine cell derived 5-HT, moreover, is also a hormone, which inhibits osteoblast proliferation and promotes hepatic regeneration.

Summary—New studies show that enteric 5-HT is a polyfunctional signalling molecule, acting both in developing and mature animals as a neurotransmitter paracrine factor, endocrine hormone and growth factor.

Keywords

enteric nervous system; enteric neurogenesis; gastrointestinal motility; intestinal inflammation; osteoblast proliferation

INTRODUCTION

The mention of the word, serotonin, or its abbreviation, 5-hydroxytryptamine (5-HT), often provokes thoughts about the functions of 5-HT in the central nervous system (CNS). People tend to free associate and thus link 5-HT to depression, sleep, appetite, sex or temperature control. Brain 5-HT gets much more respect, and certainly more press, than the vastly larger store of 5-HT in the gut. This difference may reflect the awe in which the brain is appropriately held, but it does not reflect the history of our knowledge of 5-HT. Although at the time of World War II, 5-HT, the molecule, had not yet been discovered, its presence in

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Conflicts of interest
There are no conflicts of interest.

the bowel had made itself known. Just before the war, Vittorio Erspamer [1], in Italy, had discovered an intriguing substance in gastrointestinal extracts that they showed came from enterochromaffin cells. Because Erspamer identified the substance as an amine, he called it 'enteramine'. Further characterization of 'enteramine' awaited the end of the war and resumed after it [2,3]. By then, however, a long-known serum vasoconstrictor had caught the attention of Irvine Page and his colleague, Maurice Rapport, who thought the identification of the responsible molecule might shed light on the problem of hypertension [4,5]. Work on 'enteramine' and the serum vasoconstrictor had been independent; however, the research on the two substances turned out to be interrelated. Rapport made the breakthrough because he identified the serum vasoconstrictor, called it 'serotonin' and proved its structure by biosynthesis [5]. Erspamer's earlier name, 'enteramine', failed to stick because 'enteramine' turned out to be serotonin, which was already a named molecule when the structure of 'enteramine' was finally determined [3]. Still, we now know that virtually all the 5-HT in blood is carried in platelets, which do not make 5-HT [6] but take it up as they circulate through the gut [7–9]. 'Enteramine' thus becomes 'the serum vasoconstrictor (serotonin)' after it is secreted in the bowel and acquired by platelets. Unfortunately, after 5-HT was discovered to be present and synthesized in the CNS [10], peripheral 5-HT, whether circulating or enteric, became to many–peripheral.

The scientific eclipse of enteric 5-HT was unfortunate. Mundane 'housekeeping' functions of peripheral organs are as important in their own right as mood, learning and thought. Not only is 95% of the body's 5-HT located in the gut, but also enteric 5-HT plays vital roles as a growth factor, a hormone, a paracrine factor and a neurotransmitter [11■■,12■■,13–18]. Perhaps, because so much more attention was focused on the role of brain 5-HT, much of what is known about the function of gastrointestinal 5-HT has only recently been discovered.

THE PERISTALTIC REFLEX AND 5-HYDROXYTRYPTAMINE

The modern era of enteric 5-HT research dates from an elegant series of experiments on the peristaltic reflex carried out in the late 1950s at Oxford in the laboratory of Edith Bülbring [19–23]. The peristaltic reflex is a fundamental manifestation of propulsive motility, consisting of oral contraction and aboral relaxation, which occurs in response to elevations of intraluminal pressure. The peristaltic reflex was first observed *in vivo* in a dog's intestine [24–26] but was later shown to occur also in the guinea pig gut *in vitro* [27]. The manifestation of a neural reflex *in vitro*, in a preparation that contains neither sensory ganglia nor the CNS, established that the reflex is mediated by intrinsic components of the bowel wall. Prior work had established that 5-HT release from the gut increases when motor activity is manifest [28]. Bülbring demonstrated that applications of 5-HT mimic the peristaltic reflex, that pressure causes 5-HT to be secreted from the intestinal mucosa, that whenever the peristaltic reflex is stimulated (*in vitro* and *in vivo*), 5-HT is released from the bowel and that 5-HT synthesized endogenously in the mucosa from 5-hydroxytryptophan stimulates the peristaltic reflex [19–23]. Bülbring suggested that enterochromaffin cells are pressure sensors that secrete 5-HT into the wall of the gut wherein it stimulates the mucosal processes of submucosal primary afferent neurons to evoke peristaltic reflexes [21]. Bülbring stipulated, however, that she could not be certain that enterochromaffin cell 5-HT secretion is essential for peristaltic reflex initiation because she had not succeeded in totally depleting the gut of 5-HT or in totally blocking its action. In fact, a disconcerting follow-up study [29] that showed that peristaltic reflexes persisted in rats fed a tryptophan-deficient diet to deplete 5-HT suggested that 5-HT might not be necessary to evoke peristaltic reflexes, but only to modulate them.

The nuances of the discussion over the role that 5-HT plays in peristaltic reflexes were masked by the general enthusiasm that greeted the observation that drugs that affected 5-HT receptors were useful in treating irritable bowel syndrome (IBS) [30,31]. IBS is a sometimes disabling and inadequately treated, female-predominant condition, which affects up to 20% of the American population [32,33]. Alosetron, a 5-HT_3 antagonist, proved to be effective against IBS with diarrhoea [30], whereas tegaserod, a 5-HT_4 agonist, was effective against IBS with constipation and chronic constipation [31]. The utility of these serotonergic agents in treating a syndrome that was frustratingly resistant to other forms of therapy dovetailed nicely with basic observations on the mechanism of the drugs' effects. 5-HT_3 antagonists block the effects of the 5-HT that enterochromaffin cells release on intrinsic primary afferent neurons of the myenteric plexus [34–36] and 5-HT_4 agonists evoke peristaltic reflexes [37,38■■]. Further evidence implicating 5-HT release from enterochromaffin cells and 5-HT_3 receptors in the activation of sensory nerves provided a reason to believe that interference with the transmission to the CNS of nociceptive information together with a dampening of reflex motor activation in the bowel contribute to the ability of 5-HT_3 receptors to provide simultaneous relief from diarrhoea and discomfort [30,39–42]. Observations that 5-HT_4 receptors are located on nerve terminals [43] and that they enhanced the release of acetylcholine provided additional reasons to believe that 5-HT_4 agonist stimulate a prokinetic counterforce to 5-HT_3 antagonismand can be useful in individuals suffering from constipation [16,38■■,44–46]. Unfortunately, the safety of both alosetron [47] and tegaserod [48,49] came into question for reasons that probably had nothing at all to do with their respective actions on 5-HT_3 and 5-HT_4 receptors. The clinical employment of these compounds has thus been severely curtailed. More recent data, moreover, have caused the original idea of the action of enterochromaffin cell 5-HT to be reconsidered.

SEROTONERGIC NEURONS ARE MORE CRITICAL THAN ENTEROCHROMAFFIN CELLS IN REGULATING CONSTITUTIVE GASTROINTESTINAL MOTILITY

An important type of experiment that reveals the physiological roles that endocrine glands and their hormones play is to determine functions that are lost when the glands are removed. Obviously, sources of 5-HT cannot be surgically removed from the gut, but they can be removed genetically. The molecules responsible for 5-HT biosynthesis differ in different 5-HT depots. The largest store of enteric 5-HT is found in enterochromaffin cells and, in rats and mice, mast cells [50]. Tryptophan hydroxylase 1 (TPH1) is responsible for 5-HT biosynthesis in this depot [51,52]. In contrast, as in the CNS, TPH2 is the rate-limiting enzyme in the biosynthesis of enteric neuronal 5-HT [52]. Surprisingly, as Bülbring cautioned might happen, the deletion of TPH1 (TPH1KO), which eliminates enterochromaffin cell 5-HT, does not interfere with constitutive gastrointestinal motility [11■■,13,53■]. It is not yet clear whether or not the peristaltic reflex can be evoked in TPH1KO mice; nevertheless, a report that the reflex can be evoked, even after removal of the mucosa, suggests that enterochromaffin cells are not essential for reflex initiation [54]. If enterochromaffin cells are not required, it follows that their release of 5-HT is similarly nonessential. The report that the peristaltic reflex can be evoked in preparations that lack a mucosa, however, has been challenged. Contrary evidence, which cannot easily be reconciled, suggest that enterochromaffin cell 5-HT is required, necessary and sufficient to activate peristaltic reflexes [55,56]. Further studies of the reflex with gut from mice in which TPH1 or TPH2 are separately deleted are needed to settle the controversy on the role of mucosal 5-HT. Necessary or not, enterochromaffin cell secretion of 5-HT clearly can evoke peristaltic reflexes and thus would modify intestinal motility under circumstances that cause it to be secreted. Whatever 5-HT does constitutively, therefore, it may, when released under

pathological or stressful circumstances, participate in the pathophysiology of IBS and other disorders of gastrointestinal motility [16,53■,57–59]. Certainly, there is evidence that depletion of the enterochromaffin cell store of 5-HT is beneficial in the treatment of nonconstipating forms of IBS [53■].

In contrast to enterochromaffin cells, serotonergic neurons appear to be essential for normal gastrointestinal motility. The 5-HT content of the enteric nervous system (ENS) is vanishingly small in comparison to that of enterochromaffin cells [16]; however, small does not mean unimportant. Deletion of TPH2, which in the gut is restricted to serotonergic neurons [60,61], slows total gastrointestinal transit time, small intestinal propulsion and colonic motility, while accelerating gastric emptying [11■■]. The effect on gastric emptying appears to reflect a role of 5-HT in vagal relaxation of the stomach [62], a 5-HT_4-mediated component of gastric accommodation [63■]. The deletion of TPH2, moreover, exerts the same effect on gastrointestinal motility as the double deletion of TPH1 and TPH2 [11■■]. This reinforces the idea that neuronal 5-HT is more important for constitutive gastrointestinal motility than is that of enterochromaffin cells.

5-HYDROXYTRYPTAMINE IS AN ENTERIC NERVOUS SYSTEM GROWTH FACTOR

Unfortunately, although 5-HT is an enteric neurotransmitter [16,61], the effects of TPH2 deletion do not unambiguously establish that the associated loss of serotonergic neurotransmission explains the abnormal motility of the TPH2-deficient bowel. That is because neuronal 5-HT is not only a neurotransmitter in the adult ENS but also an essential growth factor for ENS development. During foetal life, enteric neurons are born in a specific phenotype-associated order [64,65]. Serotonergic neurons are among the first to arise and they conclude their birthdays while the precursors of other neurons, such as those that will express calcitonin gene related peptide, gamma amino butyric acid and dopamine, are still dividing. The coexistence of early-born neurons with still-dividing precursors makes it possible for the activity of early-born neurons to influence the fates of the precursors fated to give rise to late-born cells. Indeed, 5-HT was found to promote the development of neurons from isolated neural crest-derived precursors through an action on 5-HT_{2B} receptors [66]. More recently, 5-HT was observed to be able to stimulate stem cells to divide and give rise to new neurons, even in adult animals [14]. This action of 5-HT appears to be essential for the postnatal growth and maintenance of the ENS because the postnatal accretion of neurons that normally persists in postnatal mice through 4 months of age is deficient in animals in which 5-HT_4 receptors are deleted. The idea that neuronal 5-HT is essential for the normal development of the ENS was confirmed when it was found that the total number of enteric neurons in mice that lack TPH2 is significantly lower than that of wild-type littermates [11■■]. Consistent with the hypothesis that serotonergic neurons selectively affect late-born enteric neuronal phenotypes, these neurons are selectively deficient in mice that lack TPH2. Because mice that lack TPH2 are deficient not only in 5-HT but also in neurons, it is unclear whether the motility defect in TPH2KO mice is the result of the loss of serotonergic neurotransmission within the ENS – the neuronal deficit, or both.

The ability of serotonergic neurons to sculpt the ENS potentially enables environmental stimuli that alter the activity of serotonergic neurons to produce long-lasting changes in the structure and function of the ENS. IBS, for example, may begin in childhood [67]; adults with IBS often have a memory of childhood pain, colic or frank IBS [68]. Children with IBS, moreover, have evidence of serotonergic dysfunction in the bowel [57]. In animals, irritating the developing colon [69] or subjecting newborns to psychological stress [70,71] induces, after maturity, changes similar to those seen in IBS. These observations support a hypothesis that epigenetic alterations during enteric neurogenesis, which extend into

postnatal life, cause subtle but lasting changes in the ENS [72]. Psychosocial trauma, stress and inflammation alter serotonergic neuronal activity, and if that activity affects the subsequent generation of neurons, the serotonergic neuronal regulation of neuronal development might provide a common pathway for events that may be psychological or infectious/inflammatory to influence the ultimate nature of the ENS.

SEROTONERGIC PROMOTION OF INTESTINAL MUCOSAL GROWTH

Enteric neuronal 5-HT affects growth/maintenance of the intestinal mucosa as well as the ENS [73■■]. Growth of the mucosa and proliferation of mucosal cells are significantly greater in mice that lack the plasmalemmal 5-HT reuptake transporter (SERT; SERTKO mice), which is responsible for the inactivation of 5-HT, than in wild-type mice. Similar changes are induced in mice, given selective serotonin reuptake inhibitors (SSRIs). Effects of SERTKO are diminished by the deletion of TPH2 but not TPH1. Ketanserin, a 5-HT_{2A} blocker, and the acetylcholine (muscarinic) antagonist, scopolamine, each prevent the ability of SERTKO or SSRIs to increase mucosal growth and proliferation. Neuronal 5-HT, but not that from enterochromaffin cells, thus promotes growth and turnover of the intestinal mucosal epithelium. Serotonergic neurons are myenteric [74,75], but they evidently project to 5-HT_{2A} receptors, which are expressed on submucosal cholinergic neurons [73■■]. These cells provide a muscarinic innervation to epithelial effectors and appear to be the final driving force in promoting the proliferation of transit amplifying or stem cells of the mucosa.

ENTEROCHROMAFFIN CELL DERIVED 5-HYDROXYTRYPTAMINE AND INTESTINAL INFLAMMATION

The first indication that an enteric source of 5-HT plays a role in driving intestinal inflammation was the observation that the deletion of SERT, which prolongs and enhances the action of 5-HT secreted in the mucosa, increases the severity of 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis [15] as well as that associated with the deletion of interleukin (IL)-10 [76]. Because enterocytes normally express SERT [77], it is not surprising that the effects of 5-HT released from enterochromaffin cells are amplified in animals that lack SERT. That enhancing the effects of 5-HT also enhances inflammation suggests unmistakably that 5-HT is proinflammatory. Later experiments not only confirmed the proinflammatory effect of 5-HT but also showed that it is dependent on enterochromaffin cell secreted 5-HT; thus, the deletion of TPH1 protects the gut from inflammation [18]. Studies suggest that this 5-HT stimulates 5-HT_7 receptors on dendritic cells to launch the innate immune mechanisms [78■] that eventually bring adaptive immunity to bear and mediate the full force of inflammation on the bowel. In addition to dendritic cells, many immunoeffectors of the lymphoid system express 5-HT receptors and are 5-HT-responsive [79■]. In contrast to TPH1 deletion, the knockout of TPH2 increases the severity of inflammation (Margolis and Gershon, personal observation), suggesting that neuronal 5-HT opposes enterochromaffin cell 5-HT and is anti-inflammatory. The neuroprotective effect of TPH2-derived 5-HT [14] is likely to protect the ENS from the neurotoxic effects of inflammation [80]. 5-HT can thus act simultaneously as a ‘sword and shield’ of the gut.

ENDOCRINE FUNCTIONS OF THE 5-HYDROXYTRYPTAMINE IN ENTEROCHROMAFFIN CELLS

Enterochromaffin cells are a type of enteroendocrine cell; therefore, the observation that their paracrine secretion of 5-HT is not as critical as once thought for constitutive motility raises a question as to whether the large amount of 5-HT they pour into the bloodstream acts

as an endocrine hormone. Because this circulating 5-HT would seem to be locked within the dense granules of platelets, it is not obvious how 5-HT could be delivered to distant targets in the absence of clot formation and platelet activation. That problem has yet to be solved; nevertheless, albeit controversial, recent evidence implies that 5-HT is indeed a hormone. Evidence favouring such a role for enterochromaffin cell derived 5-HT comes from studies of the mechanism of action of the low-density lipoprotein receptor-related protein 5 (LRP5) on bone formation [81]. LRP5 is expressed in both osteoblasts and enterochromaffin cells and is a Wnt coreceptor. LRP5 inhibits the expression of TPH1 in enterochromaffin cells. This reduces their secretion of 5-HT and thus lowers the level of 5-HT in blood and platelets. Osteoblasts respond directly to the 5-HT that reaches them from the circulation because they express 5-HT_{1B} receptors, which, via cAMP response element-binding protein, inhibit osteoblast proliferation. The net result of diminishing 5-HT biosynthesis in enterochromaffin cells (secondary to LRP5 inhibition of TPH1 expression), therefore, is to enhance osteoblast proliferation and to increase bone mass. If LRP5 is deficient or selectively inactivated in the gut, blood levels of 5-HT are elevated and bone mass is reduced; this effect can be reversed if blood 5-HT levels are normalized. In contrast, osteoblast-selective inactivation of LRP5 or beta-catenin does not affect the bone mass.

The demonstration that enteric inhibition of TPH1 increases bone mass suggests that administration of a peripheral TPH inhibitor that does not cross the blood–brain barrier might be a useful therapeutic tool to use to address conditions, such as osteoporosis, in which increasing bone mass is desirable. In fact, administration of a peripheral TPH inhibitor has been found to enhance bone formation in ovariectomized mice and rats, as well as in LRP5-deficient mice [13]. Peripheral TPH inhibitors can safely be used to affect bone mass because they do not interfere with constitutive gastrointestinal motility [13] or alter the biosynthesis of 5-HT in the brain. Interestingly, brain 5-HT exerts an effect on bone formation that is the opposite of that of peripheral 5-HT [82]. TPH2 deletion leads to an increase in the activity of sympathetic nerves, which inhibit bone mass accrual. The action of CNS 5-HT on bone thus is indirect and related to the ability of central 5-HT to diminish sympathetic outflow.

New discoveries are often challenged. It is not surprising, therefore, that a contrary report has appeared disputing the idea that LRP5 influences bone mass because it inhibits TPH1 expression and thus 5-HT biosynthesis in enterochromaffin cells [83■■]. This report presents results obtained with mice carrying osteocyte-specific inducible mutations in Lrp5, which are associated with high or low bone mass in humans. Bone properties in these mice were reported to be comparable to those of mice with inherited Lrp5 mutations; moreover, restriction of Lrp5 mutations to cells that form the skeleton of the limbs but not that of axial structures was reported to give rise to skeletal abnormalities of the limbs and not the spine. Bone density was reported to be undisturbed in mice with a global knockout of TPH1 despite very low levels of intestinal and blood 5-HT. These data would appear to contradict the earlier observations that the gut-selective knockout of TPH1 increases bone mass because it prevents enterochromaffin cell 5-HT biosynthesis and circulation to bone [81]. The conclusion was thus that LRP5 affects bone formation through a local effect on bone [83■■]. At this time, it is difficult to reconcile conflicting reports that appear to be irreconcilable. It is possible that the gut-selective deletion of 5-HT reveals an effect that is masked when TPH1 is deleted globally or, alternatively, is age related. Those possibilities would require a compensating action of TPH1 in another tissue, such as bone, or age-dependent differences in the effects of TPH1 deletion. An increase in bone mass has been confirmed in mice that lack TPH1 globally, but only until the animals reach 4 months of age; bone mass returns to normal as mice continue to mature [84■■]. Osteoclast precursors, moreover, express TPH1 when they are exposed *in vitro* to receptor activator of nuclear factor kappa-B ligand; moreover, 5-HT promotes osteoclastogenesis, both through 5-HT1B

and 5-HT2A receptors, suggesting that 5-HT is produced in bone and that bone-derived 5-HT is a component of a local paracrine/autocrine network that regulates bone resorption [84■■]. Mice that lack TPH1 globally, therefore, are deficient in osteoclastogenesis. Although the role(s) that 5-HT plays in regulating bone formation and resorption is/are complex and controversial, the observations that 5-HT in both the gut (directly) and the brain (indirectly) affect bone mass have prompted the effects on bone of some of the large number of widely prescribed drugs that alter the actions of 5-HT to be studied. The SSRIs, for example, which would be expected to amplify actions of 5-HT, have recently been shown to increase the risk of osteoporetic fractures [85■■]. Clearly, enteric 5-HT cannot be considered any longer to be a factor that acts only in the gut, nor is the gut the only peripheral site of 5-HT biosynthesis, which can affect the bone. Serotonergic regulation of bone formation and resorption is a subject in need of further research.

ENTEROCHROMAFFIN CELL-DERIVED 5-HYDROXYTRYPTAMINE PROMOTES LIVER REGENERATION

A second distant target, in addition to bone, which has recently been found to be influenced by the TPH1-dependent hormonal action of the 5-HT that EC cells secrete into the circulation is the liver. In this organ, as in the developing ENS, 5-HT acts as a growth factor and fosters regeneration after partial hepatectomy [9]. The regenerative capacity of the liver is directly related to numbers of 5-HT-laden platelets [86]; moreover, 5-HT activates 5-HT2 receptors, which hepatocytes express [87], which promote proliferation and DNA synthesis [88] in hepatocytes. Deficient liver regeneration in mice that lack TPH1 confirms the essential nature of the role that enterochromaffin cell derived 5-HT plays in that process. The relative normality of liver regeneration in mice that lack SERT suggests that the low level of 5-HT in the plasma of these animals might be able to act adequately on regenerating liver when platelet uptake of 5-HT is absent [89].

CONCLUSION

The functions of enteric 5-HT have turned out to be extensive and far more complicated than originally supposed. Understanding of this multifaceted signalling molecule has been revolutionized by the utilization of genetic tools that permit gain or loss-of-function investigations to be carried out. The selective deletion of specific isoforms of TPH has enabled enterochromaffin cell 5-HT to be distinguished from that of neurons. It is now clear that 5-HT may act as a paracrine factor, an endocrine hormone or a growth factor. It is important in gastrointestinal motility, enteric neurogenesis, mucosal growth/maintenance, intestinal inflammation, osteogenesis and hepatic regeneration.

Acknowledgments

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 75).

1. Erspamer V. Experimental research on the biological significance of enterochromaffin cells. Arch Fisiol. 1937; 37:156–169.
2. Erspamer V. Concerning the 5-hydroxytryptamine (enteramine) content of the gastrointestinal tract lining. Naturwissenschaften. 1953; 40:318–319.
3. Erspamer V. Pharmacology of indolealklyamines. Pharmacol Rev. 1954; 6:425–487. [PubMed: 13236482]
4. Page IH. The discovery of serotonin. Perspect Biol Med. 1976; 20:1–8. [PubMed: 794814]
5. Rapport MM, Green AA, Page IH. Serum vasoconstrictor (serotonin). IV. Isolation and characterization. J Biol Chem. 1948; 176:1243–1251. [PubMed: 18100415]
6. Morrissey JJ, Walker MN, Lovenberg W. The absence of tryptophan hydroxylase activity in blood platelets. Proc Soc Exp Biol Med. 1977; 154:496–499. [PubMed: 300878]
7. Humphrey JH, Toh CC. Absorption of serotonin (5-hydroxytryptamine) and histamine by dog platelets. J Physiol. 1954; 124:300–304. [PubMed: 13175132]
8. Hughes FB, Brodie BB. The mechanism of serotonin and catecholamine uptake by platelets. J Pharmacol Exp Ther. 1959; 127:96–102. [PubMed: 14403856]
9. Lesurtel M, Graf R, Aleil B, et al. Platelet-derived serotonin mediates liver regeneration. Science. 2006; 312:104–107. [PubMed: 16601191]
10. Twarog BM, Page IH. Serotonin content of some mammalian tissues and urine and a method for its determination. Am J Physiol. 1953; 175:157–161. [PubMed: 13114371]
11. Li Z, Chalazonitis A, Huang YY, et al. Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. J Neurosci. 2011; 31:8998–9009. [PubMed: 21677183] The study describes the effects of the selective knockouts of TPH1, TPH2 and TPH1 along with TPH2. It demonstrates that constitutive gastrointestinal motility depends far more on the small neuronal pool of 5-HT than on the much larger store of 5-HT in enterochromaffin cells. The study also shows for the first time the dependence of ENS development on neuronal 5-HT and supports the hypothesis that the activity of enteric serotonegic neurons, which are early-born, affects the development of late-born enteric neurons, including the dopaminergic subset.
12. Karsenty G, Gershon MD. The importance of the gastrointestinal tract in the control of bone mass accrual. Gastroenterology. 2011; 141:439–442. [PubMed: 21699800] A concise review of the evidence that enterochromaffin cell derived 5-HT is a hormone that inhbits osteoblast proliferation and is thus involved in the regulation of bone mass.
13. Yadav VK, Balaji S, Suresh PS, et al. Pharmacological inhibition of gut-derived serotonin synthesis is a potential bone anabolic treatment for osteoporosis. Nat Med. 2010; 16:308–312. [PubMed: 20139991]
14. Liu MT, Kuan YH, Wang J, et al. 5-HT4 receptor-mediated neuroprotection and neurogenesis in the enteric nervous system of adult mice. J Neurosci. 2009; 29:9683–9699. [PubMed: 19657021]
15. Bischoff SC, Mailer R, Pabst O, et al. Role of serotonin in intestinal inflammation: knockout of serotonin reuptake transporter exacerbates 2,4,6-trinitrobenzene sulfonic acid colitis in mice. Am J Physiol Gastrointest Liver Physiol. 2009; 296:G685–G695. [PubMed: 19095763]
16. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology. 2007; 132:397–414. [PubMed: 17241888]
17. Gershon MD, Liu M. Serotonin and neuroprotection in functional bowel disorders. Neurogastroenterol Motil. 2007; 19:19–24. [PubMed: 17620084]
18. Ghia JE, Li N, Wang H, et al. Serotonin has a key role in pathogenesis of experimental colitis. Gastroenterology. 2009; 137:1649–1660. [PubMed: 19706294]
19. Bülbring E, Crema A. The action of 5-hydroxytryptamine, 5-hydroxytryptophan and reserpine on intestinal peristalsis in anaesthetized guinea-pigs. J Physiol (Lond). 1959; 146:29–53. [PubMed: 13655214]
20. Bülbring E, Crema A. The release of 5-hydroxytryptamine in relation to pressure exerted on the intestinal mucosa. J Physiol (Lond). 1959; 146:18–28. [PubMed: 13655213]
21. Bülbring E, Lin RCY, Schofield G. An investigation of the peristaltic reflex in relation to anatomical observations. Q J Exp Physiol. 1958; 43:26–37. [PubMed: 13494679]

22. Bülbring E, Lin RCY. The effect of intraluminal application of 5-hydroxytryptamine and 5-hydroxytryptophan on peristalsis, the local production of 5-hydroxytryptamine and its release in relation to intraluminal pressure and propulsive activity. J Physiol (Lond). 1958; 140:381–407. [PubMed: 13514713]
23. Bülbring E, Crema A. Observations concerning the action of 5-hydroxytryptamine on the peristaltic reflex. Br J Pharmacol. 1958; 13:444–457.
24. Bayliss WM, Starling EH. The movements and innervation of the large intestine. J Physiol (Lond). 1900; 26:107–118. 407. [PubMed: 16992563]
25. Bayliss WM, Starling EH. The movements and innervation of the small intestine. J Physiol (Lond). 1900; 26:125–138. [PubMed: 16992571]
26. Bayliss WM, Starling EH. The movements and innervation of the small intestine. J Physiol (Lond). 1899; 24:99–143.
27. Trendelenburg P. Physiology and pharmacology of the peritaltic reflex of the guinea pig. Pathologie Pharmakologie. 1917; 81:55–129.
28. Toh CC. Release of 5-hydroxytryptamine (serotonin) from the dog's gastrointestinal tract. J Physiol (Lond). 1954; 126:248–254. [PubMed: 13222281]
29. Boullin DJ. Observations on the significance of 5-hydroxytryptamine in relation to the peristaltic reflex of the rat. Brit J Pharmacol. 1964; 23:14–33.
30. Mangel AW, Northcutt AR. Review article: the safety and efficacy of alosetron, a 5-HT_3 receptor antagonist, in female irritable bowel syndrome patients. Aliment Pharmacol Ther. 1999; 13(Suppl 2):77–82. [PubMed: 10429745]
31. Prather CM, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates orocecal transit in patients with constipation- predominant irritable bowel syndrome. Gastroenterology. 2000; 118:463–468. [PubMed: 10702196]
32. Dorn SD, Morris CB, Hu Y, et al. Irritable bowel syndrome subtypes defined by Rome II and Rome III criteria are similar. J Clin Gastroenterol. 2009; 43:214–220. [PubMed: 19623100]
33. Minocha A, Johnson WD, Abell TL, Wigington WC. Prevalence, sociodemography, and quality of life of older versus younger patients with irritable bowel syndrome: a population-based study. Dig Dis Sci. 2006; 51:446–453. [PubMed: 16614950]
34. Patel BA, Bian X, Quaiserova-Mocko V, et al. In vitro continuous amperometric monitoring of 5-hydroxytryptamine release from enterochromaffin cells of the guinea pig ileum. Analyst. 2007; 132:41–47. [PubMed: 17180178]
35. Bertrand PP, Bertrand RL. Serotonin release and uptake in the gastrointestinal tract. Auton Neurosci. 2010; 153:47–57. [PubMed: 19729349]
36. Bertrand PP, Kunze WAA, Furness JB, Bornstein JC. The terminals of myenteric intrinsic primary afferent neurons of the guinea pig ileum are excited by 5-HT acting at 5-HT_3 receptors. Neuroscience. 2000; 101:459–469. [PubMed: 11074168]
37. Grider JR, Foxx-Orenstein AE, Ji-Guang J. 5-Hydroxytryptamine$_4$ receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. Gastroenterology. 1998; 115:370–380. [PubMed: 9679042]
38. Hoffman JM, Tyler K, MacEachern SJ, et al. Activation of colonic mucosal 5-HT (4) receptors accelerates propulsive motility and inhibits visceral hypersensitivity. Gastroenterology. 2012; 142:844–854. e844. [PubMed: 22226658] This is an extraordinary work demonstrating that 5-HT_4 receptors can work to activate peritaltic reflexes, even when administered intraluminally. The study presents compelling evidence in favour of mucosal 5-HT4 receptors and shows that their activation not only evokes a prokinetic action but also opposes the perception of visceral pain.
39. Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology. 2007; 132:26–37. [PubMed: 17241857]
40. Grundy D, Schemann M. Enteric nervous system. Curr Opin Gastroenterol. 2006; 22:102–110. [PubMed: 16462164]
41. Chey WD, Cash BD. Cilansetron: a new serotonergic agent for the irritable bowel syndrome with diarrhoea. Expert Opin Investig Drugs. 2005; 14:185–193.

42. Johanson JF. Options for patients with irritable bowel syndrome: contrasting traditional and novel serotonergic therapies. Neurogastroenterol Motil. 2004; 16:701–711. [PubMed: 15601419]
43. Liu MT, Rayport S, Jiang Y, et al. Expression and function of 5-HT3 receptors in the enteric neurons of mice lacking the serotonin transporter. Am J Physiol Gastrointest Liver Physiol. 2002; 283:G1398–G1411. [PubMed: 12388212]
44. Ren J, Zhou X, Galligan JJ. 5-HT4 receptor activation facilitates recovery from synaptic rundown and increases transmitter release from single varicosities of myenteric neurons. Am J Physiol Gastrointest Liver Physiol. 2008; 294:G1376–G1383. [PubMed: 18436623]
45. Pan H, Gershon MD. Activation of intrinsic afferent pathways in submucosal ganglia of the guinea pig small intestine. J Neurosci. 2000; 20:3295–3309. [PubMed: 10777793]
46. Galligan JJ, Parkman H. Recent advances in understanding the role of serotonin in gastrointestinal motility and functional bowel disorders. Neurogastroenter Motil. 2007; 19(Suppl 2):1–4.
47. Gallo-Torres H, Brinker A, Avigan M. Alosetron: ischemic colitis and serious complications of constipation. Am J Gastroenterol. 2006; 101:1080–1083. [PubMed: 16696787]
48. Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. J Cardiovasc Pharmacol Ther. 2010; 15:151–157. [PubMed: 20200325]
49. Brandt LJ. The FDA's decision-making process: isn't it time to temper the principle of protective paternalism? Am J Gastroenterol. 2008; 103:1226–1227. [PubMed: 18477347]
50. Erspamer, V. Occurrence of indolealkylamines in nature. In: Erspamer, V., editor. Handbook of experimental pharmacology: 5-hydroxytryptamine and related indolealkylamines. New York: Springer-Verlag; 1966. p. 132-181.
51. Cote F, Thevenot E, Fligny C, et al. Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function. Proc Natl Acad Sci U S A. 2003; 100:13525–13530. [PubMed: 14597720]
52. Walther DJ, Peter JU, Bashammakh S, et al. Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science. 2003; 299:76. [PubMed: 12511643]
53. Brown PM, Drossman DA, Wood AJ, et al. The tryptophan hydroxylase inhibitor LX1031 is effective for patients with nonconstipating irritable bowel syndrome. Gastroenterology. 2011; 141:507–516. [PubMed: 21684281] This is a promising clinical study that suggests that peripheral inhibition of TPH with compounds that do not cross the blood–brain or myenteric plexus barrier will, if they adequately deplete the enterochromaffin cell derived 5-HT pool, provide relief from the pain and discomfort of nonconsitpating IBS.
54. Keating DJ, Spencer NJ. Release of 5-hydroxytryptamine from the mucosa is not required for the generation or propagation of colonic migrating motor complexes. Gastroenterology. 2010; 138:659–670. [PubMed: 19782081]
55. Smith TK, Dickson EJ, Heredia DJ, et al. Controversies involving the role of 5-hydroxytryptamine in generating colonic migrating motor complexes: what is spontaneous? Gastroenterology. 2010; 138:1213–1214. [PubMed: 20102760]
56. Dickson EJ, Heredia DJ, Smith TK. Critical role of 5-HT1A, 5-HT3, and 5-HT7 receptor subtypes in the initiation, generation, and propagation of the murine colonic migrating motor complex. Am J Physiol Gastrointest Liver Physiol. 2010; 299:G144–G157. [PubMed: 20413719]
57. Faure C, Patey N, Gauthier C, et al. Serotonin signaling is altered in irritable bowel syndrome with diarrhea but not in functional dyspepsia in pediatric age patients. Gastroenterology. 2010; 139:249–258. [PubMed: 20303355]
58. Spiller R, Garsed K. Infection, inflammation, and the irritable bowel syndrome. Dig Liver Dis. 2009; 41:844–849. [PubMed: 19716778]
59. Spiller R. Serotonin and GI clinical disorders. Neuropharmacology. 2008; 55:1072–1080. [PubMed: 18687345]
60. Neal KB, Parry LJ, Bornstein JC. Strain-specific genetics, anatomy and function of enteric neural serotonergic pathways in inbred mice. J Physiol. 2009; 587:567–586. [PubMed: 19064621]
61. Gershon MD. Enteric serotonergic neurones … finally! J Physiol. 2009; 587:507. [PubMed: 19182271]

62. Bülbring, E.; Gershon, MD. Serotonin participation in the vagal inhibitory pathway to the stomach. Advance Pharamcol; Symposium on the biological role of indolealkylamine derivatives; 1967. p. 323-334.

63. Tack J, Janssen P, Bisschops R, et al. Influence of tegaserod on proximal gastric tone and on the perception of gastric distention in functional dyspepsia. Neurogastroenterol Motil. 2011; 23:e32–e39. [PubMed: 20979591] Evidence of the participation of 5-HT (through 5-HT4 receptors) in the vagal reactions of gastric compliance.

64. Pham TD, Gershon MD, Rothman TP. Time of origin of neurons in the murine enteric nervous system. J Comp Neurol. 1991; 314:789–798. [PubMed: 1816276]

65. Chalazonitis A, Pham TD, Li Z, et al. Bone morphogenetic protein regulation of enteric neuronal phenotypic diversity: relationship to timing of cell cycle exit. J Comp Neurol. 2008; 509:474–492. [PubMed: 18537141]

66. Fiorica-Howells E, Maroteaux L, Gershon MD. Serotonin and the 5-HT (2B) receptor in the development of enteric neurons. J Neurosci. 2000; 20:294–305. [PubMed: 10627607]

67. Chitkara DK, van Tilburg MA, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol. 2008; 103:765–774. quiz 775. [PubMed: 18177446]

68. Chitkara DK, Talley NJ, Schleck C, et al. Recollection of childhood abdominal pain in adults with functional gastrointestinal disorders. Scand J Gastroenterol. 2009; 44:301–307. [PubMed: 19016078]

69. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. Gastroenterology. 2000; 119:1276–1285. [PubMed: 11054385]

70. Gareau MG, Jury J, Yang PC, et al. Neonatal maternal separation causes colonic dysfunction in rat pups including impaired host resistance. Pediatr Res. 2006; 59:83–88. [PubMed: 16326990]

71. Gareau MG, Jury J, Perdue MH. Neonatal maternal separation of rat pups results in abnormal cholinergic regulation of epithelial permeability. Am J Physiol Gastrointest Liver Physiol. 2007; 293:G198–G203. [PubMed: 17510196]

72. Dinan TG, Cryan J, Shanahan F, et al. IBS: an epigenetic perspective. Nat Rev Gastroenterol Hepatol. 2010; 7:465–471. [PubMed: 20585338]

73. Gross ER, Gershon MD, Margolis KG, et al. Neuronal serotonin regulates growth of the intestinal mucosa in mice. Gastroenterology. 2012; 143:408–417. e402. [PubMed: 22609381] A strikingly new observation that serotonergic neurons of the myenteric plexus project to submucosal cholinergic secretomotor neurons and drive them, via 5-HT_{2A} receptors. The submucosal neurons that receive this serotonergic input project to the mucosa and regulate division of crypt epithelial cells. In mice that lack SERT, 5-HT effects are potentiated, causing villus height in small intestine and crypt depth in small and large intestine to increase in size. These increases are blocked by deletion of TPH2 (but not TPH1), the 5-HT_{2A} antagonist ketansin, and by the muscarinic agonist scopolamine.

74. Furness JB, Costa M. Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: their projections in the guinea pig small intestine. Neuroscience. 1982; 7:341–350. [PubMed: 7078730]

75. Costa M, Furness JB, Cuello AC, et al. Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: their visualization and reactions to drug treatment. Neuroscience. 1982; 7:351–363. [PubMed: 6210850]

76. Haub S, Ritze Y, Bergheim I, et al. Enhancement of intestinal inflammation in mice lacking interleukin 10 by deletion of the serotonin reuptake transporter. Neurogastroenterol Motil. 2010; 22:826–834. e229. [PubMed: 20219086]

77. Wade PR, Chen J, Jaffe B, et al. Localization and function of a 5-HT transporter in crypt epithelia of the gastrointestinal tract. J Neurosci. 1996; 16:2352–2364. [PubMed: 8601815]

78. Li N, Ghia JE, Wang H, et al. Serotonin activates dendritic cell function in the context of gut inflammation. Am J Pathol. 2011; 178:662–671. [PubMed: 21281798] An important study summarizing the authors' evidence for enterochromaffin cell providing a drive for inflammtion

and a suggestion that the effect of 5-HT is mediated, at least in part, by activation of 5-HT_7 receptors on dendritic cells, allowing 5-HT to activate innate immunity.

79. Ahern GP. 5-HT and the immune system. Curr Opin Pharmacol. 2011; 11:29–33. [PubMed: 21393060] An excellent review of the actions of 5-HT on immunoeffect cells as well as of the distribution of 5-HT receptors in the immune system.
80. Linden DR, Couvrette JM, Ciolino A, et al. Indiscriminate loss of myenteric neurones in the TNBS-inflamed guinea-pig distal colon. Neurogastroenterol Motil. 2005; 17:751–760. [PubMed: 16185315]
81. Yadav VK, Ryu JH, Suda N, et al. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. Cell. 2008; 135:825–837. [PubMed: 19041748]
82. Yadav VK, Oury F, Suda N, et al. A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. Cell. 2009; 138:976–989. [PubMed: 19737523]
83. Cui Y, Niziolek PJ, MacDonald BT, et al. Lrp5 functions in bone to regulate bone mass. Nature medicine. 2011; 17:684–691. A strong study attempting to refute the evidence that 5-HT from enterochromaffin cells regulates bone. This study proposes instead that LRP5 acts locally in bone through the cononical WNT pathway and not by regulating TPH1 expression in mucosa. The ideas are irreconcilable.
84. Chabbi-Achengli Y, Coudert AE, Callebert J, et al. Decreased osteoclastogenesis in serotonin-deficient mice. Proc Natl Acad Sci U S A. 2012; 109:2567–2572. [PubMed: 22308416] This study complicates the serotinergic regulation of bone by extending 5-HT action to the regulation of bone ressorption and proposes a local soruce of TPH1-mediated 5-HT biosynthesis in bone.
85. Rizzoli R, Cooper C, Reginster JY, et al. Antidepressant medications and osteoporosis. Bone. 2012; 51:606–613. [PubMed: 22659406] An examination of the clinical consequences of 5-HT participation in the regulation of the accrual of bone mass. Evidence suggests that SSRIs, which enhance serotonergic effects, increase the chances of fracture in patients with osteoporosis.
86. Murata S, Ohkohchi N, Matsuo R, et al. Platelets promote liver regeneration in early period after hepatectomy in mice. World J Surg. 2007; 31:808–816. [PubMed: 17354025]
87. Papadimas GK, Tzirogiannis KN, Panoutsopoulos GI, et al. Effect of serotonin receptor 2 blockage on liver regeneration after partial hepatectomy in the rat liver. Liver Int. 2006; 26:352–361. [PubMed: 16584399]
88. Balasubramanian S, Paulose CS. Induction of DNA synthesis in primary cultures of rat hepatocytes by serotonin: possible involvement of serotonin S2 receptor. Hepatology. 1998; 27:62–66. [PubMed: 9425918]
89. Matondo RB, Punt C, Homberg J, et al. Deletion of the serotonin transporter in rats disturbs serotonin homeostasis without impairing liver regeneration. American journal of physiology. Am J Physiol Gastrointest Liver Physiol. 2009; 296:G963–G968. [PubMed: 19246633]

KEY POINTS

- 5-HT secretion from gastrointestinal enterochromaffin cells has been thought to initiate peristaltic reflexes; nevertheless, normal gastrointestinal transit in enterochromaffin 5-HT-deficient tryptophan hydroxylase 1 knockout mice (TPH1KO) suggests that enterochromaffin cell 5-HT is unnecessary for constitutive gastrointestinal motility.
- Slow gastrointestinal transit in TPH2KO mice, which lack neuronal 5-HT, suggests that gastrointestinal motility depends on neuronal 5-HT.
- Enterochromaffin cell derived 5-HT contributes to the severity of intestinal inflammation.
- Enterochromaffin cell derived 5-HT is an endocrine hormone, which promotes hepatic regeneration and lower bone mass by inhibiting osteoblast proliferation.
- Enteric 5-HT thus plays multiple roles acting as a paracrine factor, endocrine hormone, neurotransmitter and growth factor.