HHS Public Access

Author manuscript

Handb Exp Pharmacol. Author manuscript; available in PMC 2017 July 25.

Published in final edited form as:

Handb Exp Pharmacol. 2017 ; 239: 319–342. doi:10.1007/164_2016_103.

Serotonergic Mechanisms Regulating the GI Tract: Experimental Evidence and Therapeutic Relevance

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Abstract

Serotonin (5-hydroxytryptamine; 5-HT) is best known as a neurotransmitter critical for central nervous system (CNS) development and function. 95% of the body's serotonin, however, is produced in the intestine where it has been increasingly recognized for its hormonal, autocrine, paracrine, and endocrine actions. This chapter provides the most current knowledge of the critical autocrine and paracrine roles of 5-HT in intestinal motility and inflammation as well as its function as a hormone in osteocyte homeostasis. Therapeutic applications in each of these areas are also discussed.

Keywords

Bone; Enteric nervous system; Intestinal inflammation; Intestine; Motility; Serotonin

1 Introduction

Serotonin (5-hydroxytryptamine; 5-HT) is best known as a neurotransmitter critical for central nervous system (CNS) development and function (Kepser and Homberg 2015; Brummelte et al. 2016). 95% of the body's serotonin, however, is produced in the intestine where it has been increasingly recognized for its hormonal, autocrine, paracrine, and endocrine actions (Fig. 1) (Gershon 2013). The critical importance of 5-HT as a modulator of hormonal communication is evidenced by its presence in this role in primitive organisms, without a nervous system (i.e., sponges), that evolved over 500,000 years ago (Mukherjee et al. 2015). Despite this historical presence in animals, 5-HT wasn't identified until the 1940s (Erspamer 1940) and its vast roles in gastrointestinal (GI) function have begun to be elucidated relatively recently. Intestinal 5-HT has been found to modulate enteric nervous system (ENS) development and neurogenesis, motility, secretion, inflammation, sensation, and epithelial development (Gershon 2013; Margolis et al. 2014, 2016; Hoffman et al. 2012; Mawe and Hoffman 2013). Current knowledge of 5-HT in these areas, as well as its

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hormonal role in bone formation, is reviewed. A summary of relevant potential therapeutic applications is also discussed.

2 Background

Serotonin derives its name from its origin, the serum, and its ability to increase tone or vasoconstriction, hence the name “sero-tonin” (Page 1976). Its discovery was first noted by Dr. Vittorio Erspamer who discovered “enteramine” in gastrointestinal extracts from enterochromaffin (EC) cells in a rabbit (Erspamer 1940). Within a decade, the group of Rapport, Green, and Page were studying the serum vasoconstrictor, named “serotonin,” for its potential role in hypertension, ultimately publishing its isolation in 1948 and its structure as 5-HT (Rapport et al. 1947, 1948; Rapport 1949). Drs. Espamer and Rapport’s findings merged in 1952 when Erspamer purified and identified “enteramine” as Rapport’s previously identified 5-HT (Erspamer and Asero 1952). Intestinal 5-HT would likely have garnered more immediate attention had 5-HT in the central nervous system (CNS) not been found so shortly after its discovery in the intestine (Twarog 1954). Given the key functions that CNS-derived 5-HT plays in the modulation of brain development, sleep, mood, appetite, and temperature regulation, it is understood why it has attained so much relative fame (Brummelte et al. 2016). The prestige regarded to these CNS-related functions, however, has decreased the attention paid to intestinal 5-HT, likely leading to its delay in understanding of function.

3 5-Hydroxytryptophan Homeostasis and Signaling

5-HT synthesis begins with its precursor amino acid L-tryptophan that is converted by the rate-limiting enzyme tryptophan hydroxylase (TPH), to 5-hydroxytryptophan (5-HTP). 5-HTP is then converted by aromatic L-amino acid decarboxylase to 5-HT (Gershon 2013; Gershon and Tack 2007) (Fig. 2). There are two different isoforms of TPH that are separate gene products, tryptophan hydroxylase 1 (TPH1) and TPH2. In the intestine, TPH1-dependent 5-HT biosynthesis occurs in the enterochromaffin cells of the mucosal epithelium and in mast cells of mice and rats, and accounts for 90% of intestinal 5-HT production (Gershon and Tack 2007; Walther and Bader 2003). TPH2 is located in the neurons of the enteric nervous system (ENS) and the central nervous system (CNS) and accounts for the remaining 10% of intestinal 5-HT production (Zhang et al. 2004; Walther et al. 2003; Sakowski et al. 2006). Loss of TPH1, as seen in TPH1 global loss-of-function (TPH1 knockout; KO) mice, thus leads to an almost complete loss of intestinal 5-HT production but does not affect the brain in any discernible fashion whereas TPH2 global loss of function (TPH2 knockout; KO) leads to a loss of both brain and enteric neuronal 5-HT biosynthesis (Walther and Bader 2003). The differences of TPH1 and TPH2 in 5-HT production in location and function serve to play major and very different roles in intestinal development and function (Yadav et al. 2008). For example, although the minority of intestinal 5-HT is synthesized by TPH2, its absence has profound effects on ENS development and many of the GI functions discussed below that are distinct from TPH1 (Margolis et al. 2014; Li et al. 2011a; Heredia et al. 2013).

The actions of 5-HT are mediated by 15 different receptors that have been identified in mammals, separated into seven different subclasses. Six of the seven subclasses are G-protein-coupled receptors while the 5-HT_3 receptors are ligandgated ion channels (Hannon and Hoyer 2008). In the intestine, five receptor classes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7) are expressed (Hoyer et al. 2002). The most well-studied intestinal receptors are 5-HT_3 and 5-HT_4. 5-HT_4 receptors are localized to presynaptic enteric neurons while 5-HT_3 receptors are localized to sensory and myenteric neurons (Gershon 2004). Once activated, the receptors serve to affect a variety of intestinal functions (see below for details).

Once 5-HT is synthesized by TPH1 or TPH2, and stimulates one or more of its receptor subtypes, mechanisms must exist for deactivation. If 5-HT is not inactivated in a timely fashion, persistent extracellular 5-HT can have toxic effects and mediate receptor desensitization (Chen et al. 1998; Gershon and Ross 1962; Wade et al. 1994). The enzyme required for 5-HT inactivation, monoamine oxidase (MAO), is intracellular. Further, because 5-HT is a highly charged molecule, an active transporter is thus required for its intracellular transport and subsequent inactivation. The plasma-lemmal serotonin transporter (SERT) is the primary transporter by which 5-HT is transported intracellularly (Wade et al. 1996). Intestinal SERT is expressed in neurons of the ENS and in enterocytes of the intestinal mucosa (Gershon 2013; Gershon and Tack 2007). Selective serotonin receptor inhibitors (SSRIs) reduce the activity of SERT, thus increasing available 5-HT. In animal models, the study of SERT global loss-of-function (SERT KO) mice, which possess increased levels of extracellular 5-HT, and the study of mice possessing a constitutively hyperactive SERT (SERT Ala56), which decreases the extracellular 5-HT pool, have led to valuable insights into neurogenesis and motility as reviewed below (Gershon 2013; Gershon and Tack 2007; Margolis et al. 2016).

Platelets, which continuously circulate throughout the intestine, also express SERT (Beikmann et al. 2013). Platelet uptake of 5-HT thus contributes to the termination of its enteric activity (Lesch et al. 1993; Morrissey et al. 1977; Hughes and Brodie 1959; Matondo et al. 2009). Further, because platelets take up peripheral 5-HT, and the majority of peripheral 5-HT comes from the intestine, platelet-derived 5-HT provides a mechanism for long-range signaling by transporting 5-HT to distant targets, such as liver (Lesurtel et al. 2006) and bone (Kode et al. 2014). Importantly, because platelets take up peripheral 5-HT but do not synthesize it, blood 5-HT levels are an indicator of intestinal 5-HT production (Foley et al. 2011). On the other hand, neuronal SERT is important in regulating serotonergic neurotransmission both in the central and enteric nervous system.

4 5-HT and Neurogenesis

In addition to its function as a neurotransmitter, neuronal 5-HT is also a growth factor for neurons of the ENS, both prenatally and in adult life (Li et al. 2011a; Liu et al. 2009). 5-HT is present in the earliest born enteric neurons where it has been demonstrated to promote neuronal development and is, therefore, in a position to shape the development of the ENS. In vitro, 5-HT has also been shown to promote development of dopaminergic neurons in cultures of isolated enteric neural crest-derived precursor cells (ENCDCs) (Li et al. 2011a). The major source of 5-HT necessary for enteric neuronal development is neuronal. In

TPH1KO mice, which lack the 5-HT produced by enterochromaffin cells, there are no evident abnormalities in neural subpopulations (Li et al. 2011a). In TPH2KO mice, however, the absence of neuronal 5-HT causes gross ENS hypoplasia results with severe deficits of later developing 5-HT-dependent enteric neuronal subsets including those expressing gamma-aminobutyric acid (GABA), nitric oxide (NO), calcitonin gene-related peptide (CGRP), and tyrosine hydroxylase (TH; indicative of dopaminergic neurons) (Li et al. 2011a). ENS hypoplasia is also present in SERT Ala56 mice, a mouse model with an alanine substituted for a glycine on the SERT locus, in which SERT hyperactivity causes enhanced 5-HT clearance and thus reduced serotonin available for signaling (Margolis et al. 2016). Consequently, the enteric neuroanatomy of SERT Ala56 mice is similar to that of TPH2 KO; total enteric neurons, as well as GABA-, CGRP-, and TH-expressing neuronal subsets, are significantly less abundant in SERT Ala56 mice (Margolis et al. 2016). In contrast, ENS hyperplasia results when an overabundance of enteric 5-HT is present during development, as demonstrated in SERT KO mice and mice exposed to the SSRI, fluoxetine, during embryogenesis (Margolis et al. 2016). These models support the idea that neuronal 5-HT activity is necessary for neurogenesis.

5-HT promotes enteric neurogenesis and differentiation during development and postnatally at least partly through its actions on the 5-HT_{2B} and/or 5-HT_4 receptors (Liu et al. 2009; Fiorica-Howells et al. 2000). Stimulation of 5-HT_{2B} receptors enhances the differentiation of enteric neurons from both dissociated cultures of mixed fetal gut cells and in cultures of isolated ENCDCs (Fiorica-Howells et al. 2000). 5-HT_4 agonism is neurogenic and neuroprotective; 5-HT4 agonists increase enteric neurogenesis in vivo and in vitro, and postnatal enteric neurogenesis is deficient in 5-HT4 KO mice (Liu et al. 2009). 5-HT_4 KO and wild-type (WT) mice have the same number of enteric neurons at birth but the neuronal accumulation that occurs during the first 4 months of life in wildtype (WT) mice does not occur in those mice without 5-HT4 receptors (Liu et al. 2009). 5-HT_4 signaling directly impacts postnatal gut-derived enteric neural stem/progenitor cell (ENSCs) proliferation as well. Neuronal proliferation and neuronal differentiation increase significantly in postnatal ENSCs and colon explants cultured with 5-HT_4 receptor agonist (RS67506)-loaded liposomal nanoparticles (Hotta et al. 2016). Results are mimicked in vivo as co-transplantation of ENSCs with 5-HT4 receptor agonist-loaded nanoparticles leads to significantly increased neuronal density and proliferation (Hotta et al. 2016).

5 Therapeutic Implications for Neurogenesis

Enteric neuropathies and degenerative diseases are not often diagnosed until after birth. It is thus exciting that 5-HT_4 agonists may have therapeutic benefits in the postnatal period. Older 5-HT_4 agonists, such as cisapride and tegaserod, have been restricted in use secondary to adverse cardiovascular side effects based on their off-target effects on hERG potassium channels (Tack et al. 2012). Newer, more highly selective 5-HT_4 agonists, however, have not been associated with these side effects (Shin et al. 2014). Prucalopride, a newer, more targeted 5-HT_4 agonist, has been found to increase neurogenesis in vivo though it has not yet been trialed in neuropathic conditions (Margolis et al. 2016; Gershon 2016).

6 Modulation of Intestinal Motility

6.1 The Peristaltic Reflex

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 purpose of the peristaltic reflex is to increase movement of GI contents down the intestinal tract in a sequential manner. The reflex was first described by Bayliss and Starling, at the end of the nineteenth century, when they found in a dog's intestine that elevated intraluminal pressure would evoke a reproducible oral contraction and anal relaxation in vivo (Bayliss and Starling 1899, 1900, 1901). Because this reflex persisted, even when deprived of all of the intestine's extrinsic innervation, they attributed the activity to a local intrinsic intestinal mechanism that they termed the "local nervous mechanism" (Bayliss and Starling 1899, 1900, 1901). Trendelenburg confirmed that the peristaltic reflex was indeed due to a "local nervous mechanism" in 1917, when he demonstrated that the reflex could be elicited in vitro (absent of the brain, spinal cord, and sensory ganglia) (Trendelenburg 2006). He coined this behavior the "peristaltic reflex" and "the local nervous mechanism" that Bayliss and Starling referred to is now called the ENS.

It was the work of Edith Bulbring and colleagues that first highlighted the link between 5-HT, the peristaltic reflex, and the stimulation of intestinal propulsion. Bulbring showed, in isolated preparations of guinea pig ileum, that either applied or endogenously synthesized intestinal 5-HT instigates the peristaltic reflex and, further, that pressure or stimulation of the peristaltic reflex causes 5-HT to be secreted from the intestine (Bulbring and Crema 1958, 1959a, b; Bulbring and Lin 1958; Bulbring et al. 1958). While these data have been relatively conclusive in implicating 5-HT in colonic motility, there is a continuing controversy regarding whether mucosal or neuronal 5-HT is necessary for the initiation or propagation of propulsive contractions. Clinical data supports the idea that it is specifically EC cell derived, and not enteric neuronal, 5-HT that stimulates peristaltic reflexes. Carcinoid tumors, which are derived from EC cells and secrete copious amounts of 5-HT, are associated with severe diarrhea and enhanced peristaltic activity (Ahlman 1985). Moreover, serotonin receptor 3 (5-HT_3) receptor antagonists oppose this carcinoid-associated diarrhea, supporting the idea that mucosal 5-HT secretion promotes motility.

6.2 The Roles of Neuronal and Enteroendocrine Cell-Derived 5-HT in Motility

The relative importance of mucosal versus neuronal 5-HT in motility has been examined more thoroughly in recent years with mice in which mucosal and/or neuronal 5-HT synthesis has been selectively blocked either genetically or pharmacologically (Margolis et al. 2014; Li et al. 2011a). The genetic models studied, TPH1 KO, TPH2 KO, and the double knockout (TPH1/2dKO), have made it easier to investigate whether EC cell-derived, neuronal, or both depots of intestinal 5-HT participate in the modulation of peristalsis and GI motility (Li et al. 2011a). Neuronal 5-HT is critical to GI motility; small intestine, colonic, and total GI transit (GIT) are significantly slower in TPH2 KO and TPH1/2dKO mice compared to their WT littermates (Li et al. 2011a). Whether these abnormalities are due solely to the associated developmental defects in neurogenesis is not yet known. These observations are consistent, however, with prior suggestions that 5-HT mediates propagating contractile

complexes, as well as slow and fast excitatory synaptic transmission (Wade et al. 1994; Erde et al. 1985; Neal et al. 2009; Takaki et al. 1985). A contrasting feature of the TPH2 KO mice, however, is an increase in gastric emptying despite the otherwise diffuse hypomotility. This observation is consistent with prior reports, using pharmacologic blockade, that neuronal 5-HT excites gastric inhibitory neurons, which promote accommodation and delay gastric emptying (Booth et al. 1986; Bulbring and Gershon 1968; Coleman et al. 2003; Mawe et al. 1989; Takahashi and Owyang 1997). Although the quantity of enteric 5-HT neurons is small (2–3%), motility could easily be influenced by the extensive projections that these neurons have with critical effectors of gut motility, including other 5-HT neurons, nitric oxide synthase-containing neurons that are the main inhibitory neurons of the myenteric plexus, and/or the interstitial cells of Cajal (ICC). It thus makes sense that the motility defects in these mice are the consequence of disrupted neurogenesis and an ongoing loss of serotonergic signaling.

Although initial studies did not support evidence of an essential role for enteric mucosal 5-HT in GI motility (Margolis et al. 2014; Bian et al. 2011), more recent data has provided evidence for a subtle, yet distinct, role for mucosal 5-HT in GI peristalsis; contracting migrating motor complexes (CMMCs), the motor complexes that trigger peristaltic waves, that are elicited in isolated TPH1KO colons of male and female mice are poorly disseminated and tend to move in the retrograde direction (Heredia et al. 2013; Smith et al. 2014; Balasuriya et al. 2016).

6.3 The Role of SERT in Motility

The roles that 5-HT play in GI motility have been further elucidated by transgenic mouse models in which SERT activity is altered or absent, and pharmacologic studies involving the selective serotonin reuptake inhibitor (SSRI), fluoxetine. The SERT Ala56 mutation, that causes SERT to become hyperactive, leads to less available 5-HT for neurotransmission (Margolis et al. 2016). The SERT Ala56 mouse exhibits not only a neuronal hypoplasia but a decrease in in vivo and in vitro intestinal motility as well (Margolis et al. 2016). These observations further suggest, as noted in the section above on neurogenesis, that it is the ENS abnormality (in this case hypo-ganglionosis) that impairs the generation and conduction of peristaltic reflexes and also affects in vivo GI motility, as there are similar effects to these parameters in the ENS-hypoplastic TPH2 KO mouse (Li et al. 2011a).

In contrast to the SERT Ala56 mice, genetic ablation of SERT (SERT KO mice) or antagonism to SERT (after developmental fluoxetine exposure) decreases 5-HT inactivation and thus increases its signaling impact. Accordingly, SERT KO and SSRI-exposed mice possess a hyperinnervated ENS; the resulting motility patterns are both abnormal yet more complex (Margolis et al. 2016). Mice exposed to fluoxetine during development demonstrate significantly slower total GI, small intestinal, and colonic motility compared to nonexposed controls (Margolis et al. 2016). Although SERT KO mice also have slower colonic transit, total GI transit is similar to control mice. One critical difference between these models is that, in fluoxetine-treated animals, SERT is not inhibited at the time that motility is tested (6–8 weeks of age) because fluoxetine administration ceases after the mice are weaned from breastfeeding at 3 weeks of age. In contrast, in SERT KO mice, the deletion of SERT is not

time limited, which may lead to desensitization of 5-HT receptors (Margolis et al. 2016). Alternation of diarrhea and constipation in SERTKO mice, for example, has been attributed to bouts of receptor desensitization in these animals and thus may account for the lack of change in average total intestinal transit time (Chen et al. 2001).

The abnormal motility parameters normalized in both SERT KO and fluoxetine-exposed animals after chemical sympathectomy with 6-hydroxydopamine (Margolis et al. 2016). This suggests that sympathetic slowing of GI motility can exert a substantial effect on in vivo measurements of murine GI motility and that both the deletion of SERT and its inhibition during development increase central sympathetic input to the intestine (Adamec et al. 2006).

There are several potential areas of clinical relevance that are related to the SERT-based abnormalities defined in these studies. The SERT Ala56 mutation is the most common SERT-based mutation overexpressed in children with autism spectrum disorders (ASD) (Veenstra-VanderWeele et al. 2012). In addition to ENS hypoplasia and the GI abnormalities described above, SERT Ala56 animals display increased blood 5-HT (hyperserotonemia), increased clearance of 5-HT, supersensitivity at central 5-HT_{1A} and 5-HT_{2A} receptors, as well as communication deficits and repetitive behaviors that are reminiscent of ASD (Sutcliffe et al. 2005; Veenstra-Vanderweele et al. 2009; Veenstra-Vander Weele et al. 2012; Kerr et al. 2013). Other hyperefficient SERT-coding variants have also been found in subjects with ASD (Sutcliffe et al. 2005; Prasad et al. 2005, 2009). Interestingly, GI motility problems, and especially constipation, are over fourfold more common in children with ASD, implying that the findings in the SERT Ala56 mouse may implicate developmental perturbations of 5-HT signaling to both the behavioral and medical features of ASD (McElhanon et al. 2014). Further, hyperserotonemia, secondary to high-platelet 5-HT, is present in about 30% of individuals with ASD (Mulder et al. 2004; Cook et al. 1993; Geller et al. 1988; Ritvo et al. 1970), and is also consistent with a GI abnormality.

Another clinical parallel has been demonstrated in humans exposed to SSRIs in utero; a retrospective clinical study showed that children exposed to tricyclic antidepressants and SSRIs in utero were tenfold more likely to require laxatives for constipation (Nijenhuis et al. 2012a, b). As demonstrated in the preclinical studies, it is likely that antenatal exposure to these medications causes defects in ENS development (i.e., hyperplasia) that lead to long-lasting changes in GI motility.

6.4 The Roles of 5-HT Receptors in Motility

Once 5-HT is released, it then binds to specific receptors to initiate gut motility; the 5-HT_3 and 5-HT_4 receptors have been the most widely studied in regard to gut motility (Mawe and Hoffman 2013). 5-HT_3 antagonists and 5-HT_4 agonists both evoke peristaltic reflexes (Hoffman et al. 2012; Bertrand et al. 2000; Galligan et al. 2000; Grider et al. 1998). Both are present on neurons within the myenteric and submucosal plexuses of the ENS, intrinsic and extrinsic sensory neurons, and EC cells. The stimulation of 5-HT_3 receptors results in the activation of intrinsic and extrinsic afferent nerves and also the stimulation of a small number of excitatory postsynaptic potentials (EPSPs) (Paintal 1973; Hillsley and Grundy 1998; Hillsley et al. 1998; Ireland and Tyers 1987). 5-HT_4 receptor agonists augment the

peristaltic reflex pathways by acting presynaptically on nerve terminals to enhance the release of acetylcholine (Tonini et al. 1989; Galligan et al. 2003; Pan and Galligan 1994; Liu et al. 2005; Fang et al. 2008). By acting in this manner, 5-HT_4 receptor agonists are thought to enhance naturally occurring reflex activity rather than to generate neurotransmission (Hoffman et al. 2011). Further, colonic epithelial cells also express the 5-HT4 receptor where they have been demonstrated to activate 5-HT release, mucus discharge from goblet cells, and chloride secretion by enterocytes (Hoffman et al. 2012). These actions, as a whole, can alleviate constipation and visceral pain, a component of irritable bowel syndrome (IBS). Intraperitoneal or intraluminally administered tegaserod, which stimulates 5-HT4, attenuated nociceptive responses in a rat visceral hypersensitivity model, though the mechanism by which this occurs has not been fully elucidated (Hoffman et al. 2012; Greenwood-Van Meerveld et al. 2006).

Less is known about 5-HT_{2B} receptor modulation of motility. The 5-HT_{2B} receptor is also expressed by interstitial cells of Cajal (ICC), and is important for the integrity of the ICC network. 5-HT promotes the survival of ICC in culture via actions on 5-HT_{2B} receptors, and the density of ICC is decreased in 5-HT_{2B}-receptor-deficient mice (Tharayil et al. 2010). Because ICCs serve as a GI “pacemaker” that leads to contraction of the smooth muscle, alterations of the ICC network might impair slow-wave propagation and, as a consequence, slow intestinal motility (Du et al. 2010).

7 Therapeutic Implications of 5-HT Modulation for Intestinal Motility

Drugs targeting the 5-HT3 and 5-HT4 receptors have been demonstrated to be effective in the treatment of functional diarrhea, functional constipation, or irritable bowel syndrome (IBS). IBS is a disorder in which diarrhea (IBS-D), constipation (IBS-C), or alternating types of both (IBS-M) are accompanied by abdominal discomfort or pain. 5-HT3 receptor antagonists have been shown to be effective in treating both the diarrhea and abdominal discomfort symptoms of IBS-D (Andresen et al. 2008; Rahimi et al. 2008). One such example is alosetron, which has been used to treat diarrhea, presumably by blocking 5-HT3 receptors on intrinsic neurons that stimulate motility. Although the precise pain-relieving mechanisms of 5-HT3 antagonists have not been determined, it is possible that they inhibit pain by blocking the effects of 5-HT on extrinsic sensory neurons that signal pain and discomfort (Barbara et al. 2007; Mangel and Northcutt 1999; Johanson 2004). Efforts have focused on partial agonists because stimulation of 5-HT_3 receptors on vagal and spinal afferent fibers can lead to nausea and abdominal discomfort, respectively. On the other hand, since stimulation of extrinsic sensory neurons can exacerbate nausea and emesis, specific 5-HT_3 receptor antagonists are being used to inhibit chemotherapy- and radiation-induced nausea and emesis, in part due to their activation of the vagal afferents, in addition to the area postrema in the CNS (Bertrand et al. 2000; Tyers and Freeman 1992; Evans et al. 2007; McCallum et al. 1988). One partial 5-HT_3 antagonist, pumosetrag, has also been shown to reduce reflux events in individuals with gastroesophageal reflux disease (GERD) (Evangelista 2007; Choung et al. 2008; Costall et al. 1986).

5-HT_4 receptor agonists alleviate constipation and abdominal pain that are associated with IBS-C and also accelerate the rate of gastric emptying (Evans et al. 2007; McCallum et al.

1988). In humans, oral administration of the 5-HT4 receptor agonist tegaserod reduces rectal sensitivity to distension in individuals with IBS (Sabate et al. 2008). While the older generation of 5-HT4 agonists, including tegaserod, were effective against chronic constipation and constipation-predominant IBS, they were removed from the consumer market because of their adverse effects. These side effects were thought to result from nonspecific actions on other targets, including the cardiac hERG potassium channels, dopamine receptors, and 5-HT1 and 5-HT_2 receptors (Tack et al. 2012; De Maeyer et al. 2008). More specific 5-HT_4 antagonists, such as prucalopride, naronapride (ATI-7505), mosapride, and velusetrag (TD-5108), have been developed to fill this need and some have been demonstrated, in clinical studies, to effectively treat constipation without associated adverse cardiac events (Tack et al. 2012; Manabe et al. 2010). Prucalopride is currently available for therapeutic use in Europe and Canada (Gershon 2016).

Since 5-HT signaling can be disrupted in the CNS and ENS, therapeutic agents with either functional specificity to the intestine or regional specificity (i.e., do not cross the blood-brain barrier) are necessary for the treatment of 5-HT-driven gastrointestinal disorders.(Margolis et al. 2014; Crane et al. 2015) Results of a doubleblind, placebo-controlled study of one of these compounds, LX-1031, indicate that this approach shows promise for treating the symptoms of non-constipating IBS (Brown et al. 2011).

8 5-HT and Inflammation

As a critical entrance to the body from the external world, the intestine is a “bodyguard” for the mammalian immune system. It must contend with the continuous assault of a vast number of potentially pathogenic organisms while simultaneously maintaining balance of a commensal microbiome (Kedees et al. 2013)(Goyal et al. 2015;Sanchez de Medina et al. 2014). Immune defenses against microbial invasion are thus well developed and neuroimmune interactions, between enteric neurons and immune cells, are important in regulating and integrating these defenses (Margolis and Gershon 2009). When this process goes awry, intestinal inflammatory disease can develop. The neuroimmune interactions that underlie intestinal inflammation involve the action of neuromodulators and cytokines that carry signals, often bidirectionally, between enteric neurons and immune cells (Buhner and Schemann 2012; Verheijden et al. 2015). One of the most fundamental paracrine/neurocrine messengers that participate in this cross talk is 5-HT. 5-HT modulates immune cell trafficking, chemotaxis, activation, and proliferation (Arreola et al. 2015; Baganz and Blakely 2013; Askenase et al. 1980, 1991; Gershon et al. 1975). 5-HT influences these actions of immune cells, in part, by stimulation of the 5-HT receptor subtypes they express, including $5\text{-HT}_{2A, 2B, 2C}$, 5-HT_3, 5-HT_4, and 5-HT_7 (Shajib and Khan 2015). Macrophages and T cells also produce 5-HT themselves (Baganz and Blakely 2013)while rat and mousemast cells synthesize, store, secrete, and take up 5-HT (Manning et al. 2015). The vast interactions that take place between the immune system and 5-HT are highlighted in greater detail outside of this chapter (Baganz and Blakely 2013; Worthington 2015). This evidence, however, has led to a research focus of 5-HT in intestinal inflammatory diseases. 5-HT has been implicated in the modulation of several intestinal inflammatory diseases, including Crohn’s disease, ulcerative colitis, diverticulitis, and celiac disease (Foley et al. 2011; Coleman et al. 2006; Costedio et al. 2008; Magro et al. 2002; El-Salhy et al. 1997).

Data from both humans and animal models support a proinflammatory role for mucosal 5-HT in intestinal inflammatory disease. EC cells, the major producers of enteric 5-HT, are increased in intestinal biopsy specimens taken from individuals with Crohn's disease and ulcerative colitis (El-Salhy et al. 1997; Belai et al. 1997; Coates et al. 2004a). Further, the EC cells isolated from individuals with Crohn's disease secrete significantly more of the proinflammatory cytokine interleukin (IL)-1p and also exhibit more lipopolysaccharide-induced 5-HT secretion, relative to individuals without Crohn's disease (Kidd et al. 2009). The effects of adenosine receptors that drive 5-HT secretion from EC cells are amplified in IBD, providing a mechanism for its continuous increased release (Chin et al. 2012). Enteric 5-HT levels and duodenal EC cells are also increased in patients with celiac disease, and a significant correlation is observed between peak postprandial 5-HT levels and postprandial dyspepsia scores, suggesting a role for 5-HT in promoting associated pain-related symptoms (Coleman et al. 2006). Postinfectious irritable bowel syndrome (PI-IBS), which has been suggested to represent a low-grade inflammatory state, has also been associated with an increase in the peak of postprandial 5-HT release and EC cell hyperplasia (Spiller 2007; Gershon 2005). All of the conditions described above, as well as diverticulitis, are also associated with decreased epithelial SERT expression levels (Coates et al. 2004b). A decrease in SERT, the major transporter responsible for the inactivation of 5-HT, would further increase enteric 5-HT availability. Taken together, this evidence suggests that increased levels of available 5-HT contribute to the pathogenesis of intestinal inflammation and/or to the severity of GI symptoms.

Animal models of intestinal inflammation have both confirmed the data from human studies and expanded our knowledge of the potential mechanisms underlying the role of mucosal 5-HT in enteric inflammation and/or infection. The inflammatory bowel disease models studied have included two forms of chemical colitis: trinitrobenzene sulfonic acid (TNBS)-induced colitis, that shares pathologic features of Crohn's disease, and dextran sodium sulfate (DSS)-induced colitis, a colonic inflammation that more closely resembles ulcerative colitis. Infections that have been studied include *Citrobacter rodentium, Trichinella spiralis*, and enteropathogenic *E. coli* (Buhner and Schemann 2012; O'Hara et al. 2006, 2007; Wheatcroft et al. 2005; Bertrand et al. 2010). The common feature underlying these disease models is that all result increased EC cell numbers and decreased levels of epithelial SERT. Not surprisingly, where measured, 5-HT levels are also increased.

The role of increased mucosal 5-HT thus appears to be proinflammatory in its contribution to the pathogenesis of intestinal inflammation. It thus makes sense that inflammation is ameliorated when mucosal 5-HT production is eliminated. When mucosal 5-HT is selectively depleted, in TPH1 KO mice and in animals that receive a nonabsorbable TPH antagonist (LP-920540), the effects are anti-inflammatory; the severity of dinitrobenzene sulfonic acid- (DNBS; similar to TNBS) or DSS-induced colitis is significantly diminished (Shajib and Khan 2015; Ghia et al. 2009) (Margolis et al. 2014). Downregulation of SERT, however, may be both a consequence and cause of inflammation. SERT expression and function are downregulated in an inflammatory microenvironment; SERT is decreased in the Caco-2 human epithelial cells exposed to the proinflammatory cytokines interferon gamma (IFN-γ) and tumor necrosis factor (TNF), or by conditioned medium from activated lymphocytes (Bayliss and Starling 1900). Importantly though, studies evaluating mice that

lack SERT (SERTKO) support the idea that decreased levels of SERT, with a consequent increase in levels of 5-HT, are the cause of intestinal inflammation rather than its consequence; these mice develop an increased severity of TNBS-induced or IL-10 KO-associated colitis (Bischoff et al. 2009). While the precise mechanisms underlying the proinflammatory effects of mucosal 5-HT have yet to be fully elucidated, it is evident that after inflammation has been initiated, the participation of 5-HT gathers force in a positive feedback loop. Inflammation leads to the downregulation of SERT and an increase in EC cell quantity, which presumably further increases the amount of 5-HT available for signaling (Linden et al. 2003, 2005; Spiller et al. 2000; O'Hara et al. 2004).

5-HT may modulate inflammatory signaling via the 5-HT_4 receptor in both pro- and anti-inflammatory ways. In animal models of colitis, 5-HT4 receptor activation on the colonic epithelium reduces the development of, and accelerates recovery from, colitis (Spohn et al. 2010). Beyond the epithelial layer, colitis promotes enteric neurogenesis in the adult colon through a serotonin-dependent activation of 5-HT_4 that drives glial cells to transdifferentiate into neurons (Belkind-Gerson et al. 2015). Though the effect of this 5-HT_4-induced neurogenesis is not yet known, ENS hyperplasia is repeatedly found in inflamed segments of bowel in patients with Crohn's disease and has been shown in animal models to increase predisposition to both TNBS- and DSS-induced colitis (Margolis et al. 2011). The neurogenic actions of 5-HT_4 may actually be protective; 5-HT_4 receptors promote neuroprotection specifically against the oxidative stress that is released during inflammation (Liu et al. 2009; Belkind-Gerson et al. 2015; Goto et al. 2016). Other 5-HT receptors may be involved in the inflammatory cascade, such as dendritic cell 5-HT_7 receptors (Shajib and Khan 2015; Li et al. 2011b; Kim et al. 2013). Unfortunately, the studies evaluating the effects of 5-HT on dendritic cells are conflicting; one group has demonstrated proinflammatory effects of 5-HT_7 receptor activation while the other group showed anti-inflammatory effects (Idzko et al. 2004).

9 Therapeutic Implications for 5-HT Signaling in Inflammatory Bowel Disease

Small-molecule drugs that modulate 5-HT signaling pathways have been developed for the treatment of IBS, but despite their potential, the utility of related neuroprotective agents in intestinal inflammatory diseases has not yet been trialed (Brown et al. 2011; Hornby 2015).

10 Serotonin and Bone Mass Accrual

The association between 5-HT and osteoporosis was made over a decade ago in patients on SSRIs for depression and continues to be extensively studied with a variety of clinical studies trying to reduce confounding variables (Bruyere and Reginster 2015; Diem et al. 2007; Haney et al. 2007). Recent meta-analyses continue to support the association of patients on SSRIs having decreased bone mineral density and increased fracture risk. Even in a pediatric population, treatment with SSRIs is linked to low bone mass (Eom et al. 2012; Feuer et al. 2015; Rabenda et al. 2013).

The effect of SSRIs on blocking bone mineral accrual has been recapitulated in mice treated with SSRIs (Warden et al. 2005). Similar to SSRI treatment, deletion of the 5-HT transporter, SERT, also leads to reduced bone mass, indicating that it is SERT inefficacy, rather than off-target drug effects of SSRIs, that accounts for this decrease in bone density (Warden et al. 2005). The mechanism of serotonin's effect on bone has been actively studied, with effects from brain and gut 5-HT. Interestingly, brain 5-HT is downstream of leptin that is secreted from adipocytes. Receptors in the brain stem respond to leptin to produce 5-HT which in turn decreases sympathetic tone via 5-HT2c (Ducy 2011). In the Tph2 KO mice, depletion of central 5-HT and increased sympathetic tone leads to decreased bone formation and increased bone resorption (Yadav et al. 2009). The SSRI-mediated increase of central 5-HT should thus improve bone mass instead of precipitating osteoporosis, suggesting a role for peripheral 5-HT.

The role of intestinal serotonin as a hormone affecting bone homeostasis has been suggested by studies of the LDL receptor-related protein 5, LRP5, that works with its co-receptors, members of the frizzled family, to activate the Wnt-β-catenin signaling pathway, which is crucial for bone formation (Baron and Rawadi 2007). Loss-of-function mutations in LRP5 are implicated in osteoporosis pseudoglioma (OPPG), an autosomal recessive disorder of blindness, and low bone mass while high-bone-mass syndrome is related to gain-of-function mutations in LRP5 (Boyden et al. 2002; Gong et al. 2011). A mouse model of global LRP5 loss recapitulates the eye and bone findings of OPPG, and links the bone phenotype to decreased osteoblast proliferation and function (Kato et al. 2002). Whether or not the effect of LRP5 is cell or non-cell autonomous is still controversial. One group has reported no change in bone mass in intestinal specific Lrp5 knockouts with a decrease in bone mass with an osteocyte-specific Lrp5 knockout (Cui et al. 2011). Conversely, separate studies with a conditional Lrp5 knockout have demonstrated low bone mass in the intestinal specific Lrp5 knockout (Yadav et al. 2008).

In order to more directly test the role of intestinal 5-HT in bone growth, both groups tested bone mass in TPH1 KO mice and again received similar conflicting results. Three 5-HT receptors are expressed in bone with 5-HT_{1b} the most prevalent (Yadav et al. 2008; Westbroek et al. 2001). In one study, osteoblast-specific HT_{1b} mutant mice, in combination with TPH1 intestinal mutants and Lrp5 mutants, among others, support a model in which LRP5 expression in the intestinal 5-HT-expressing EC cells inhibits TPH1 (Yadav et al. 2008). This decreased serotonin production causes a decreased activation of 5-HT_{1b} in the bone to inhibit osteoblast proliferation (Yadav et al. 2008). A second study, however, did not detect significant changes in 5-HT content or bone mass after *Lrp5* deletion or when a high bone mass-causing allele was expressed in intestinal epithelial stem cells using a villin promoter to drive Cre expression (Cui et al. 2011). Different outcomes of the two studies have been hypothesized to be due to the use of different mouse models, the structure of transgenes, and other differing experimental conditions (Bonewald 2011).

11 Therapeutic Modalities for Osteoporosis

Therapeutics that modulate 5-HT may hold promise in the treatment of osteoporosis. Nonselective 5-HT_{1b} modulators have potential off-target effects (Ducy 2011). The

nonabsorbable TPH inhibitor, LP533401, however, was found to reduce serum and intestinal 5-HT levels and have a rescuing bone effect in ovariectomized mice with osteoporosis (Yadav et al. 2008, 2010; Shi et al. 2008). No clinical trials with either therapeutic option have been trialed yet.

12 Conclusions

The expansive roles that 5-HT play in ENS neurogenesis and GI function have been increasingly recognized. The recognition of 5-HT as being more than just a modulator of motility and secretion is likely to provide critical insights into many disorders whose etiologies are not fully elucidated, including those involving abnormal ENS development and intestinal inflammatory diseases. A major obstacle to understanding the physiologic roles of enteric 5-HT includes the multiplicity of responses to applied 5-HT. Because of the widespread actions of 5-HT, drugs that target specific functions must be focused to specific receptors. Even receptor targets are complex, however, because of the large number of enteric 5-HT receptors that can serve different, and even contrasting, roles. Another important goal is to understand more precisely the distributions of 5-HT receptors and to determine which receptors in specific locations are physiologically relevant. Many of these receptors are located in the CNS as well as the gut. Study of these receptors may lead to an increased understanding of brain-gut interactions and treatments for brain-gut axis disorders such as IBS. Further, specific targeting of serotonin signaling exclusively in the gut, as was accomplished with the development of a nonabsorbable tryptophan hydroxylase inhibitor, may help us to target disease more effectively while limiting off-target drug effects. Areas of importance that could not be covered in the space limitations of this chapter, but are ongoing areas of investigation, include the role of 5-HT signaling in enteric epithelial homeostasis, microbiota composition, immunity, and liver regeneration.

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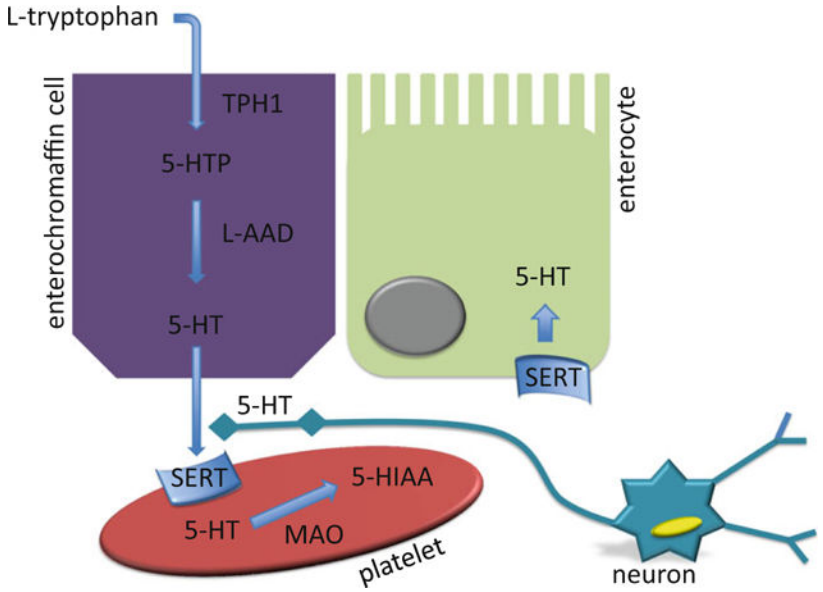

Fig. 1.

5-HT biosynthesis. L-tryptophan is taken up by enterochromaffin (EC) cells (purple) where it is converted by tryptophan hydroxylase 1 (TPH1) to 5-hydroxytryptophan (5-HTP). The enzyme L-amino acid decarboxylase (L-AAD) then produces 5-hydroxytryptophan (5-HT) which is released into the extracellular space and can either act locally in the intestine, via its receptors in the intestinal mucosa or intercalated dendrites of the submucosal and myenteric plexuses, or be taken up by platelets (*red*) via the serotonin transporter (SERT). Locally acting 5-HT will be taken up by the enterocytes, via SERT, where it is broken down by monoamine oxidase (MAO) and metabolized to 5-hydroxyindoleacetic acid (5-HIAA). The 5-HT taken up by platelets is either released at a distal site, where it can execute hormonal actions, or metabolized, as in the enterocytes, by MAO within the platelet, and later excreted by the kidneys

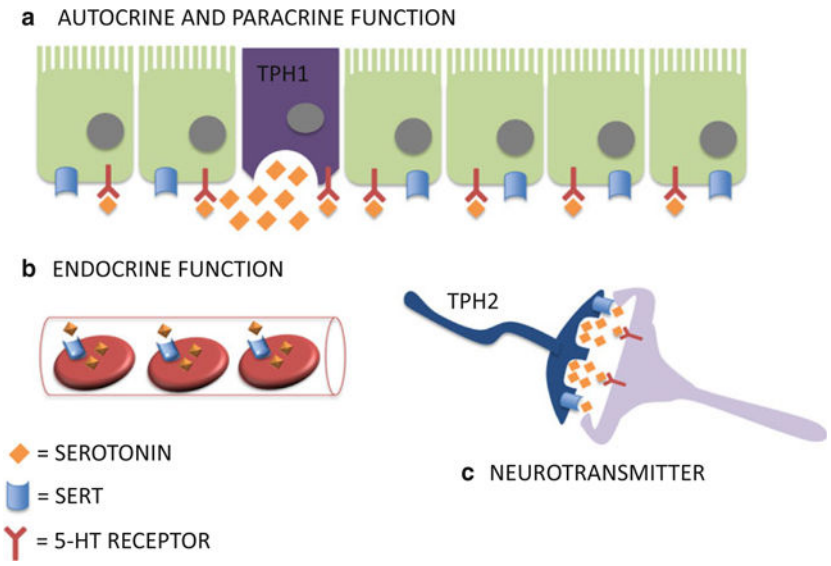

Fig. 2.

5-HT signals in an autocrine, paracrine, and endocrine fashion. (**a**) In the intestinal epithelium, mucosal 5-HT (*orange diamonds*) is produced by TPH1 in the enterochromaffin cells (*dark purple*) where, once secreted, it will signal in an autocrine or paracrine fashion, to itself or to neighboring enterocytes (*green*), respectively, via 5-HT receptors (pictured in red). Once 5-HT has perpetrated its actions it needs to be inactivated or receptor desensitization can occur. In order to undergo inactivation, mucosal 5-HT must be taken up by the serotonin reuptake transporter (SERT; *blue spheres*), located on intestinal epithelial cells, where, once intracellular, it can be broken down by monoamine oxidase. (**b**) 5-HT secreted into the intestine can also be taken up via SERT (*blue sphere*) in platelets to be transported in the bloodstream to distal sites for endocrine function. (**c**) In the enteric nervous system, 5-HT is produced by TPH2 in 2–3% of enteric neurons. 5-HT is released into the synapse and activates postsynaptic 5-HT receptors. It is then taken up by SERT in the presynaptic neuron for deactivation