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Direct and Indirect Mechanisms by which the Gut Microbiota Influence Host Serotonin Systems

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Abstract

Mounting evidence highlights the pivotal role of enteric microbes as a dynamic interface with the host. Indeed, the gut microbiota, located in the lumen of the gastrointestinal (GI) tract, influence many essential physiological processes that are evident in both healthy and pathological states. A key signaling molecule throughout the body is serotonin (5-hydroxytryptamine; 5-HT), which acts in the GI tract to regulate numerous gut functions including intestinal motility and secretion. The gut microbiota can modulate host 5-HT systems both directly and indirectly. Direct actions of gut microbes, evidenced by studies using germ-free animals or antibiotic administration, alter the expression of key 5-HT-related genes to promote 5-HT biosynthesis. Indirectly, the gut microbiota produce numerous microbial metabolites, whose actions can influence host serotonergic systems in a variety of ways. This review summarizes the current knowledge regarding mechanisms by which gut bacteria act to regulate host 5-HT and 5-HT-mediated gut functions, as well as implications for 5-HT in the microbiota-gut-brain axis.

Keywords

tryptophan; gut-brain axis; bacteria; tryptophan synthase; enteric nervous system; microbial metabolites

Despite decades of research, we are only beginning to fully appreciate the immense complexity in which microbes colonize the gut and interact dynamically with the host in healthy and pathological conditions. Located in the lumen of the gastrointestinal (GI) tract on the order of tens of trillions of microorganisms, the gut microbiota demonstrate remarkable capacity to influence nearly every physiological system in the body[1,2].

Research into the ecology of the microbiome demonstrates that bacteria colonization is diverse and varies along the GI tract[3]. Notably, the microbial communities become increasingly heterogeneous progressing from the oral to distal ends of the gut due to

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the diverse microhabitats associated with each region of the GI tract. For example, fewer bacteria are present in the small intestine of the gut where transit time is short and pH is low, in comparison to the colon, which harbors the highest numbers and biodiversity of bacteria and is the primary site for bacterial fermentation.

Pivotal early insights into host-microbiota interactions stem largely from germ-free (GF) and fecal microbiota transplantation (FMT) studies[2]. GF studies exploit the postnatal timing of microbiota colonization of the GI tract, such that rodents born and raised in a sterile environment develop without a microbiome. Studies employing this strategy demonstrate that GF mice exhibit abnormal physiology, such as slowed colonic motility[4] and total intestinal transit time[5]. Notably, colonization with either normal mouse-derived or human-derived microbiota can restore these GF-induced deficits in motility[6].

FMT is the process by which stool harvested from a donor is transplanted into the intestines of a recipient in order to alter the microbiota composition[7]. Preclinical FMT studies demonstrate remarkable transfers of microbiota-driven disease symptomologies in both rodent models and humans, including transfers of slow transit constipation[8], rapid transit diarrhea[9], and intestinal barrier dysfunction[9]. While GF and FMT approaches certainly have clinically translatable limitations, they nevertheless reliably demonstrate that healthy gut function is microbiota-dependent.

Serotonin in the gut

Serotonin (5-hydroxytryptamine; 5-HT) is a prominent signaling molecule throughout the body. The major source of 5-HT is from the enterochromaffin (EC) cells in the epithelium of the GI tract[10]. EC cells are a subset of enteroendocrine cells that synthesize, store, and release 5-HT in a regulated manner[10]. EC cells synthesize 5-HT from tryptophan (Trp) using the rate-limiting enzyme tryptophan hydroxylase 1 (Tph1), and since Tph1 is not saturated under baseline Trp concentrations, it is likely that elevated Trp could increase metabolic 5-HT output[11]. Myenteric neurons also express 5-HT, though at much lower levels than in the mucosa.

Termination of 5-HT signaling involves a serotonin-selective reuptake transporter (SERT) to remove 5-HT from the interstitial space. 5-HT is then degraded intracellularly by monoamine oxidase A (MAO-A) to form 5-hydroxyindoleacetic acid (5-HIAA). SERT is expressed by all mucosal epithelial cells in the intestines and functions as an important regulator of interstitial 5-HT availability[12].

In the gut, 5-HT released from EC cells in response to luminal chemical and mechanical stimuli functions as a critical activator of many GI reflexes by signaling through a variety of receptors located on intrinsic and extrinsic afferent nerve fibers[10]. Mucosal 5-HT can initiate the peristaltic reflex, a component of propulsive motility[10]. In the intestinal epithelium, 5-HT stimulates secretory responses acting primarily on the 5-HT_3 receptor (5-HT_3R) and the 5-HT_4R, with evidence for paracrine-mediated secretion through the 5-HT_2R as well[12]. 5-HT release and activation of 5-HT_3R located on vagal afferent neurons can result in various reflex responses including pancreatic secretion, gallbladder contraction, and inhibition of

gastric emptying when released as part of the normal digestive response, as well as nausea and vomiting when released at higher concentrations in pathological conditions.

Numerous approaches to treat clinical GI disorders target the enteric serotonergic system with the goal of promoting healthy gut function. For example, in patients with irritable bowel syndrome, 5-HT_3R antagonists have been used to treat diarrhea[13], and 5-HT_4R agonists are used to treat constipation[14,15]. Taken together, 5-HT is a critical mediator of many important gut functions and consequently is an important target in the context of GI dysfunction.

Direct Mechanisms

5-HT's prominent role in the regulation of GI function is well documented[15]. However, the contribution of gut microbes in impacting host gut-derived 5-HT signaling is a burgeoning field that may offer key insights into the link between the microbiota and GI function.

Early studies examining the role of the microbiota in gut-derived 5-HT regulation demonstrated that GF mice have significantly lower serum 5-HT levels[16,17], decreased colonic Tph1 mRNA expression[17], and increased colonic SERT mRNA expression[17] as compared to control mice.

More recently, two landmark studies provided further strength toward the notion that the microbiota can regulate gut-derived 5-HT levels[5,18] (FIG. 1A). A study by Kashyap and colleagues examined the impact of the gut microbiota on host colonic 5-HT production[18]. The authors utilized three groups of mice with differing microbiotas: GF mice, GF mice colonized with human gut microbiota (HM), and conventionally raised (CR) mice with normal mouse microbiomes. HM and CR mice exhibit significantly higher colonic Tph1 mRNA and protein levels, as well as higher colonic 5-HT concentrations, compared to GF mice. Notably, there is no difference in EC cell density in the proximal colon between the groups, suggesting a microbiome-induced effect of increased Tph1 transcription.

Along similar lines, Hsiao and colleagues demonstrated that the gut microbiota promotes host 5-HT biosynthesis[5]. Consistent with the findings described above, adult GF mice exhibit decreased colonic 5-HT levels as well as decreased colonic mRNA expression of Tph1, while also exhibiting significantly higher concentrations of Trp in feces. Colonization of GF mice with spore-forming bacteria from healthy mice restores colonic 5-HT levels and elevates colonic Tph1 expression. Notably, the restorative increases in 5-HT are blocked by the administration of the Tph inhibitor para-chlorophenylalanine (PCPA), suggesting that host Tph activity is necessary for promoting 5-HT biosynthesis.

Taken together, it is now generally accepted that the gut microbiota plays a key role in regulating the serotonergic system of the host primarily through altering the expression of 5-HT-related genes. Specifically, intestinal microbiota influence Tph1 transcription, thereby promoting 5-HT biosynthesis. While the microbiota have also been shown to influence SERT expression[5,17], this likely represents an indirect, compensatory effect to deficient 5-HT biosynthesis, rather than a direct effect by the microbiota. Inhibition of Tph via PCPA administration modulates SERT expression[5], suggesting that changes in SERT

expression occur independently of the intestinal microbiota. Furthermore, the strong positive correlations between colonic mRNA expressions of SERT and other key 5-HT-related genes such as 5-HT_4R does not depend on microbiota colonization status[19], providing further support that SERT is not directly mediated by the gut microbiota. Additionally, GF mice do not exhibit differences in mRNA expression of enzymes that release, package, or break down 5-HT[5]. Therefore, it is likely that the microbiota influence enteric 5-HT biosynthesis primarily through the elevation of Tph1 expression.

Gut microbiota may also alter expression levels of a key 5-HT receptor, the 5-HT_3R, known to be involved in intestinal secretion and peristalsis. Indeed, Bhattarai et al. found a microbiota-mediated modulation of host colonic secretion through altered epithelial 5-HT_3R expression[20]. GF mice display elevated 5-HT_3R expression levels compared to HM mice, which correspond with increased colonic secretory responses. Notably, there was no microbiota-mediated effects on 5-HT_4R expression, or on 5-HT_4R-dependent colonic secretory responses.

Further support for the notion that the microbiota influence the enteric serotonergic system comes from antibiotic studies. Administration of broad-spectrum antibiotics can deplete luminal bacteria in an inducible and temporally controlled manner. Unlike GF studies, in which microbiota alterations are persistent throughout development, antibiotics provide an alternative strategy to alter microbiota composition following normal development, and to assess microbiota-dependent physiological processes and behavior.

Perturbation of the gut microbiota using antibiotic administration alters host 5-HT, 5-HT-mediated gut functions, and enteric nervous system (ENS) neuroanatomy. Mice treated with antibiotics exhibit lower levels of colonic 5-HT and decreased Tph1 expression[5,21], which parallel the findings of GF-associated deficits to the gut 5-HT system. Furthermore, these alterations in 5-HT levels result in functional changes to intestinal transit, as antibiotic-treated mice display slower whole gut transit[21–24] and slower colonic motility times[21,24] compared to controls. In addition, these functional deficits are accompanied by loss of enteric neurons[22]. Interestingly, antibiotic-induced changes are reversible. Following reconstitution of the microbiota, mice display restored GI motility and enteric neurogenesis[22].

The evidence for whether specific commensal bacteria found in the human gut synthesize 5-HT *de novo* in physiologically relevant concentrations remains unclear. Indeed, certain bacteria have been shown to synthesize 5-HT *in vitro*[25,26]. However, this 5-HT synthesis may occur through indirect means and independent of Tph[27]. Thus far, no human commensal bacteria that synthesize 5-HT have been identified.

Indirect Mechanisms

Insights into host-microbiota dynamics further demonstrate that gut bacteria actively produce microbial metabolites capable of impacting the host. Emerging evidence suggests that these metabolites are key aspects of communication between the microbiota and the host to regulate physiological function in health and disease states. In the context of the

enteric 5-HT system, microbial metabolites can stimulate 5-HT biosynthesis and release, leading to alterations in gut functions. This section highlights four key categories of microbial metabolites and summarizes the evidence of how they influence gut-derived 5-HT (Fig. 1 B–E).

Short chain fatty acids

A notable group of microbial metabolites known to influence host physiology are short chain fatty acids (SCFAs). SCFAs are the products of bacterial fermentation of dietary fiber in the colon[28]. The most abundant SCFAs are acetate, propionate, and butyrate, which are present in an approximate molar ratio of 60:20:20, respectively. These dietary-derived microbial metabolites play a prominent role in the regulation of a variety of host physiological processes[29].

SCFAs influence the enteric 5-HT system by stimulating the release of 5-HT by intestinal EC cells, which express SCFA receptors[30]. An early study by Fukumoto et al. demonstrated that intraluminal perfusion of SCFAs into the proximal colon of rats induced release of 5-HT, and consequently accelerated colonic transit and motility[31].

SCFAs can also promote 5-HT biosynthesis. Stimulatory actions of acetate and butyrate on EC cells promote colonic Tph1 expression and 5-HT production in an *in vitro* human EC cell model[18]. Furthermore, application of butyrate or propionate on RIN14B chromaffin cell culture leads to an elevation of 5-HT release and increase in Tph1 expression[5]. In addition to regulating Tph1 expression, SCFAs can also impact expression levels of key 5-HT receptors. Indeed, acetate has been shown to decrease 5-HT_3R expression *in vitro* in GF mouse-derived colonoids[20]. Taken together, SCFAs are microbial metabolites that play an important role in the stimulation of enteric 5-HT biosynthesis.

Tryptophan

A critical process that is influenced by gut microbes is Trp metabolism[32]. Trp is an essential amino acid, indicating that it cannot be synthesized *de novo* and therefore must be supplied through dietary intake. The recommended daily allowance of dietary Trp for adults is 4 mg/kg/day, or roughly 250–450 mg/day. Considering that the average intake for most adults is approximately 800–1000 mg/day[33], most individuals achieve this recommended daily intake of dietary Trp readily to meet their protein metabolic demands.

Once ingested, Trp is absorbed nearly completely in the small intestine of the GI tract, specifically within intestinal epithelial cells known as enterocytes[34]. Two transporters facilitate this absorptive process. On the apical membrane of enterocytes, Trp absorption is mediated by the epithelial amino acid transporter B^0AT1 (Slc6a19)[34], along with all other neutral amino acids. On the basal membrane of enterocytes, Trp transport occurs via the basolateral aromatic amino acid transporter TAT1 (Slc16a10)[35]. Internalized Trp is then distributed to tissues through the body via the circulatory system.

Trp functions primarily as a component of protein synthesis. In the GI tract, Trp undergoes three different avenues of metabolism: 5-HT synthesis, kynurenine synthesis, and production of metabolites that act as ligands of the aryl hydrocarbon receptor (AhR). Though it is

estimated that the kynurenine synthesis pathway accounts for over 90% of Trp metabolism, the significance of Trp metabolism in the kynurenine and AhR pathways is outside the scope of this manuscript, but this information can be found in recent reviews of the topic[36,37].

The gut microbiota plays an active role in Trp availability, although the mechanisms and functional implications of this remain to be elucidated. While the majority of Trp is absorbed in the small intestine, it is possible some Trp can also reach the colon where it is subject to catabolism by the gut bacteria. GF mice exhibit 40% greater levels of plasma Trp than their conventional counterparts[38]. These increased Trp levels could result from a variety of factors, such as GF-induced deficits in host Tph1 activity[5,18], lack of tryptophanase activity by enteric bacteria to metabolize dietary Trp[38], or altered metabolism down other pathways. Consistent with GF mice, antibiotic-treated mice also display elevated levels of Trp, in both the colonic mucosa[39] and cecal contents[40].

Microbially-mediated changes in Trp availability may have an impact on gut 5-HT availability and 5-HT-mediated intestinal functions, though more research is needed to characterize these effects. Some bacteria are known to possess the enzymatic capabilities to metabolize Trp directly using key enzymes in its catabolic and anabolic pathways. Specifically, Trp-catabolizing bacteria produce tryptophanase, the enzyme responsible for metabolizing Trp into indole, pyruvate, and ammonia[36]. Conversely, Trp-synthesizing bacteria produce tryptophan synthase, an enzyme that catalyzes the biosynthesis of Trp from the metabolite indole[36]. However, it remains to be determined whether these bacteria are present as human gut commensals.

Tryptamine

Another key metabolite indirectly influenced by gut microbes is tryptamine. Tryptamine is an indoleamine that is formed by the decarboxylation of L-tryptophan. Though it is present at relatively low concentrations in mammalian tissue, it is known to have a physiologically significant role in interacting with the host.

The characterization of tryptamine's potential functions in the ENS was brought about by an early study by Takaki et al. demonstrating that tryptamine stimulates the release of endogenous 5-HT within the GI systems of guinea pigs[41]. More recent work indicates that tryptamine acts as a 5-HT_4R ligand[42]. 5-HT_4Rs are G-protein-coupled receptors that are expressed in the epithelium of the GI tract, with the greatest level of expression in the distal colon[14]. Stimulation of 5-HT_4Rs produces prokinetic effects[15], and 5-HT_4R agonists promote colonic propulsive motility[14,43].

Tryptamine-induced activation of 5-HT_4Rs accelerates gut transit through increased secretion by intestinal epithelial cells[42]. Tryptamine can also, acting as a 5-HT_4R agonist, stimulate mucus release from goblet cells and prevent epithelial barrier disruption[44], which has important implications for gut-derived inflammatory conditions such as irritable bowel syndrome.

The gut microbiota can play a role in tryptamine production. For example, GF mice exhibit significantly lower levels of tryptamine in feces compared to HM mice[45]. Furthermore,

specific microbes present in the human intestinal microbiota possess the enzymatic capacity to decarboxylase Trp to produce tryptamine[27]. It remains an open question whether, and to what degree, microbiota-mediated metabolism of Trp into tryptamine influences host physiology and 5-HT-related gut functions. Nonetheless, bacterially-mediated metabolism of Trp into tryptamine represents an exciting avenue for future investigation in the context of potential therapeutic applications.

Bile acids / secondary bile acids

Bile acids (BAs) are water-soluble, cholesterol-derived surfactants that are critical for digestive and absorptive processes. The effects of BAs in the lumen of the intestine have been shown to be region-specific. Colonic EC cells express the G protein-coupled bile acid receptor 1 (GPBAR1; also known as TGR5), for which BAs are endogenous ligands[46]. Notably, activation of GPBAR1 by intestinal BAs promotes 5-HT release and mediates prokinetic actions[47,48].

The gut bacteria play an active role in biotransforming primary BAs in the colon through deconjugation and dehydroxylation to produce the secondary BAs, deoxycholic acid (DCA) and lithocholic acid (LCA). The regulation of secondary BA metabolism by the gut microbiota is further supported by GF studies in which GF mice exhibit nonexistent levels of secondary BAs in intestinal tissue compared to conventional mice[49,50]. Similarly, antibiotic-treated mice display decreased levels of secondary BAs[21].

Secondary BAs are key microbial metabolites that can impact the enteric serotonergic system. DCA, induced by spore-forming microbes, has been shown to elevate 5-HT levels and increase Tph1 expression, both *in vitro* in RIN14B chromaffin cells and *in vivo* in mice[5]. Furthermore, reductions in relative abundances of bile-metabolizing bacteria is associated with impaired Trp metabolism, leading to reduced 5-HT bioavailability and delayed intestinal motility[51]. Taken together, it is evident that microbially-regulated alterations in secondary BAs can influence 5-HT bioavailability and consequently induce changes in gut function.

Beneficial bacteria applications

A transient approach to manipulate the gut microbiota is through oral administration of isolated bacterial strains such as those included in non-colonizing “probiotic” formulations. Numerous studies report beneficial effects on host physiological processes of orally-delivered bacteria in both animal models and humans. In the context of GI function, for example, administration of certain bacteria can prevent stress-induced intestinal barrier dysfunction[52,53] and colonic dysfunction[54], as well as reduce whole gut transit time[55–57].

Despite evident impacts of bacteria administration on many functions, the underlying mechanisms of action of such bacteria are not well elucidated. Along with the need for more mechanistic-based investigations, it is becoming clear that there is a need for a deeper understanding of bacterial species and strain-specific effects. Certainly these investigations are underway and will yield stimulating findings in the coming years.

A developing avenue of exploration and potential therapeutic exploitation is the use of specific microbial strains that can alter the production and regulation of key bioactive metabolites. Indeed, certain strains have been shown to change the bioavailability of enteric 5-HT. A study by Nzakizwanayo et al. (2015) demonstrated that *Escherichia coli* Nissle 1917, a bacteria found in "probiotics" currently available on the market, enhances 5-HT bioavailability in a dose-dependent manner in an *ex-vivo* model[58]. Furthermore, this strain increases intracellular 5-hydroxytryptophan (5-HTP) levels and decreases 5-HIAA levels, supporting a hypothesis that *Escherichia coli* Nissle 1917 alters 5-HT through synthesis and clearance, respectively.

Spore-forming bacteria can promote 5-HT biosynthesis through the elevation of host colonic Tph1 expression[5]. Furthermore, monoassociation of GF mice with the strain *Clostridium ramosum* increases host 5-HT bioavailability[59]. Expression levels of ileal and colonic Tph1 and MAO-A are significantly greater in *Clostridium ramosum* monocolonized mice compared to GF controls. In addition, *in vitro* stimulation with *Clostridium ramosum* provokes an increased 5-HT release in RIN14B chromaffin cells as well as organoids from murine small intestine and colon.

Commensal lactic acid bacteria represent another class of "beneficial" bacteria known to exert effects on the enteric serotonergic system. For example, studies report that increased intestinal SERT concentrations are associated with *Bifidobacterium (B.) dentium*[60], *B. longum*[61], *Lacticaseibacillus* (formerly classified as *Lactobacillus*) *rhamnosus*[62,63], *Lactobacillus acidophilus*[61], and *Limosilactobacillus* (formerly classified as *Lactobacillus*) *reuteri*[64]. Additionally, monoassociation with the strain *B. dentium* promotes the secretion of microbial metabolites, including the SCFA acetate, that act to modulate the host serotonergic system[60]. Specifically, mice monoassociated with *B. dentium* displayed increased intestinal 5-HT levels and upregulated colonic 5-HT_4R and SERT mRNA expression.

Taken together, mounting evidence suggests that the administration of beneficial isolated bacteria can alter host gut-derived 5-HT and influence 5-HT-mediated gut functions in a transient, inducible, and reversible way. Further resolution of the underlying mechanisms of actions of specific bacteria will move the field forward to encourage investigations into potential therapeutic applications.

Implications for 5-HT in the microbiota-gut-brain axis

Overview of the microbiota-gut-brain axis

The gut-brain axis refers to the bidirectional line of communication between the gut and the brain through neural, immune, and endocrine means. Dating back to the foundational theoretical work of William James and Carl Lange in the 1800s, a wealth of research has since demonstrated top-down contributions of psychological stress and emotions on GI function[1]. Recently, a growing body of research on the microbiome highlights its remarkable capacity for bottom-up modulation, leading many in the field to expand the concept into the "microbiome-gut-brain axis".

The brain communicates with the GI tract in a top-down fashion primarily through parallel efferent pathways originating in the hypothalamus, amygdala, and cortical regions. Such pathways include the sympathetic and parasympathetic components of the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and descending monoaminergic pathways. Sympathetic effects on the gut are inhibitory and act to slow intestinal transit and secretion[1]. Parasympathetic effects, on the other hand, act in an excitatory manner to stimulate motility, secretion, and release of key signaling molecules such as serotonin, gastrin, and somatostatin[1]. The HPA axis coordinates adaptive stress responses and regulates numerous homeostatic systems, including digestion and metabolism[65].

The gut communicates with the brain primarily through neural and endocrine means. The vagus nerve acts as a bidirectional conduit for information passing between the GI tract and the brain[1,66]. Moreover, gut peptides and neuropeptides, released in response to luminal stimuli, can act in a paracrine manner to activate receptors located on adjacent vagal afferents. These peptides can also act in an endocrine manner when released into the circulation to signal to various brain regions, particularly circumventricular organs such as the hypothalamus and area postrema[66].

Serotonin in the brain

In the central nervous system (CNS), the primary sites of 5-HT synthesis and storage are clusters of neurons in midbrain and pontine regions, with the raphe nuclei accounting for the majority of serotonergic cell bodies and projection fibers[67]. The rate limiting enzyme of neuronal 5-HT synthesis is the isoform tryptophan hydroxylase 2 (Tph2)[68]. Notably, gut 5-HT and CNS 5-HT are considered separate pools, since 5-HT does not cross the blood-brain barrier (BBB).

5-HT activates a variety of receptors located pre- and post-synaptically, with the 5-HT_1, 5-HT_2, and 5-HT_4 families being most common in the CNS. The diverse array of receptor subtypes offers an expansive range of 5-HT-mediated actions in the brain[69]. In the CNS, 5-HT availability, in addition to serotonergic neurons expressing SERT, is also controlled by presynaptic autoreceptors that act as negative feedback mechanisms to inhibit further 5-HT release into the synaptic cleft[70]. While 5-HT's functions in the gut are fairly well characterized, its actions in the brain, though extensively studied, remain more elusive. Serotonin has been implicated in a myriad of functions, including but not limited to mood[71], anxiety[72], food consumption[73], reward[74], and sleep[75,76].

Converging lines of evidence indicate that dysfunctions in microbiota-gut-brain communication can have salient pathophysiological consequences, and at least some of these appear to involve 5-HT. Indeed, it is estimated that nearly 60% of individuals diagnosed with anxiety or depression also report symptoms of intestinal dysfunction[77]. Clinically, pharmacological treatments for anxiety and depression target the 5-HT system and act to increase 5-HT levels by a variety of mechanisms, including selectively inhibiting or impairing 5-HT reuptake, inhibiting 5-HT metabolism, or increasing 5-HT release[67]. 5-HT's enigmatic role in mood is of particular relevance to gut-brain communication given the high comorbidities of anxiety and depressive symptoms and GI dysfunction. However, such

treatments pose distinct disadvantages. Notably, the delayed onset of action of selective serotonin reuptake inhibitors (SSRIs) as well as mixed efficacies[67] suggest alternative or adjuvant treatment options are worth pursuing. The microbiome is one such promising target.

Tryptophan as an potential microbiota-gut-brain target

Given that 5-HT does not cross the BBB, changes in circulating 5-HT levels are unlikely to influence 5-HT signaling in the CNS. However, intervention in microbiota-gut-brain 5-HT signaling may be possible through Trp acting as a precursor-mediated signal. Given that Trp metabolism is decisively regulated by the gut microbiota, it is possible that Trp is a critical point of intersection within the microbiota-gut-brain axis. Early studies demonstrate that the relationship between brain Trp concentrations and 5-HT synthesis is directly proportional, such that an injection of Trp produces a rapid elevation of brain Trp concentrations, and consequently a rapid rise in 5-HT synthesis[78,79].

Subsequent work to elucidate this relationship reveals that the ability of Trp to influence brain 5-HT synthesis depends principally on three factors. The first factor is the competitive nature by which Trp crosses the BBB. Upon absorption in the gut, circulating Trp must compete with other large neutral amino acids (LNAAs) to enter the brain through the amino acid transporter. The bioavailability of Trp to cross the BBB therefore depends on the sum of the competing amino acids, often expressed as the “tryptophan ratio”[33,80]. Altering the tryptophan ratio by either raising plasma Trp levels or lowering concentrations of other LNAAs can thus maximize the amount of Trp available for brain 5-HT synthesis.

The competitive transport mechanism for Trp is particularly relevant during food consumption. Studies in rats suggest the composition of a meal can indirectly determine brain Trp uptake and subsequent 5-HT synthesis due to the meal’s effects on the Trp ratio. A protein-rich meal, for instance, raises both plasma Trp and other LNAA levels to a similar degree, thus the net effect on brain Trp and 5-HT is negligible[81]. On the other hand, a carbohydrate-rich meal increases plasma Trp concentrations and decreases concentrations of the other LNAAs through insulin activation, which therefore favors Trp transport into the brain to increase precursor availability and 5-HT synthesis[33,82].

The second main factor depends on the enzyme kinetics of Tph2, which like Tph1, is only partially saturated under normal conditions. Thus, in theory, raising or lowering brain Trp concentrations could respectively increase or decrease the rate of brain 5-HT synthesis[78,83]. Further investigation is warranted to determine the characteristics by which this occurs.

Lastly, in order to influence CNS 5-HT-mediated behaviors, changes in Trp levels must ultimately affect neuronal 5-HT release, following which 5-HT can interact with various receptors to influence behavior. In support of this concept, Sharp et al. used *in vivo* microdialysis in rats to demonstrate that pre-treatment with Trp significantly enhanced 5-HT release upon electrical stimulation of serotonergic dorsal raphe nucleus neurons[84].

Though it is thought that less than 5% of dietary Trp is used for 5-HT synthesis throughout the body, the serotonergic impacts on the CNS are demonstrated in experiments involving

manipulations of dietary Trp availability. Indeed, acute Trp depletion via consumption of a Trp-free diet produces striking reductions in brain Trp and 5-HT levels in both animal models and humans[85–88]. Conversely, Trp loading via ingestion of pure Trp, α-lactalbumin, or carbohydrates induces robust increases in brain 5-HT levels[80,89]. Furthermore, such modulation of 5-HT levels may have impacts at the behavioral level, as several rodent studies report Trp manipulations impact anxiety- and depressive-like behavior[85,90].

Certain gut bacteria may also have the ability to alter Trp levels as well. A novel, microbiome-targeted strategy to manipulate Trp availability and subsequent 5-HT synthesis could exploit certain bacteria's biochemical capacity to manipulate Trp. By possessing key enzymes in Trp catabolism or anabolism, such bacteria may be able to alter availability of the amino acid for absorption. Oral administration of these bacteria may impact microbiota-gut-brain signaling by altering Trp levels, and ultimately modulate 5-HT-mediated physiological and behavioral effects. Further investigation is necessary to better understand how to utilize orally administered bacteria as a potential therapeutic interface between microbiota-gut-brain communication and function.

Conclusion

The dynamic interactions between the host and the gut microbiota underlie many physiological processes. It is evident that a deeper understanding of how gut microbes act to mediate the enteric serotonergic system will drive the field forward towards clinical applications for the targeted use of bacteria to enhance intestinal function and behavior.

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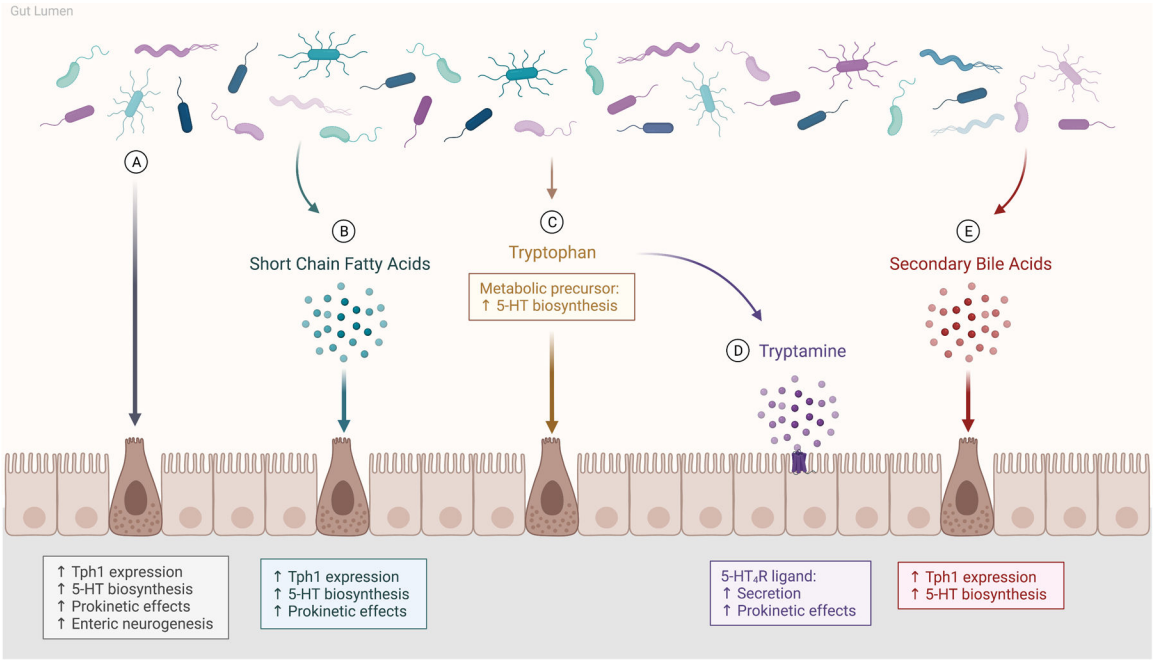

Figure 1.

The gut microbiota mediate host serotonin (5-HT) through direct and indirect means. (A) Gut bacteria act directly on enterochromaffin (EC) cells to increase colonic tryptophan hydroxylase 1 (Tph1) expression and promote 5-HT synthesis. (B-E) Enteric bacteria alter host 5-HT indirectly through microbial metabolites, including short chain fatty acids, tryptophan, tryptamine, and secondary bile acids. (B) Short chain fatty acids are dietary-derived metabolites produced by bacterial fermentation that stimulate 5-HT synthesis and release by EC cells, and induce prokinetic effects on intestinal motility. (C) Tryptophan is an essential amino acid and its metabolism is under control of the gut microbiota. It functions as the metabolic precursor to 5-HT as well as tryptamine. (D) Tryptamine acts as a ligand for the 5-HT_4 receptor ($5\text{-HT}_4\text{R}$) to stimulate secretion by intestinal epithelial cells, thereby inducing prokinetic actions. (E) Secondary bile acids, formed by the gut microbiota from primary bile acids, promote Tph1 expression and stimulate 5-HT synthesis. Created with BioRender.com.