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Interaction Between Intestinal Serotonin and The Gut Microbiome

Review Article

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Abstract

Greater than 90% of serotonin (5-HT) in the human body is derived from Enterochromaffin (EC) Cells located within the most distal portion of the gastrointestinal tract. Inside of the large intestine can be found a population of trillions of symbiotic microbes. Current evidence shows that these microbes influence host physiology through communication with the nervous system via metabolic byproducts. In the colonic environment, 5-HT is an important signaling molecule for peristalsis, enteric motor and secretory reflexes, and immune responses. 5-HT synthesis within the colon is regulated by host microbiota through stimulation of EC from their short chain fatty acid by products. EC have been shown to release 5-HT into the colonic lumen after stimulation from various non-microbially produced products such as bile acids, allyl isothiocyanate, catecholamines, and tryptamine. Irregular 5-HT signaling has been shown to influence microbial colonization of the colon. Further exploration is necessary to understand the complete mechanism of microbial signaling and colonic 5-HT production.

Keywords: Serotonin; Gut Microbiome; Enterochromaffin Cell.

Introduction

The human gut microbiome consists of a collection of microorganisms, mainly bacteria, present in the gastrointestinal (GI) tract. Found with in the human gut microbiome are 10^{14} resident microorganisms, of which includes bacteria, viruses, fungi and protozoa [1]. The distal most portion of the gastrointestinal tract harbors majority of microorganisms, here their biomass exceeds 10^{11} cells per gram content [2]. Around 1,000 different bacterial species are found in the human gut, their relative distribution is dependent on host age, genetic background, environment, and lifestyle. More than 70% of these bacterial species come from the phyla of Firmicutes and Bacteroides [3, 4].

Numerous factors over the course of one's life contribute to the development of the gut microbiomes ecosystem. One's method of delivery at birth, either vaginally or cesarean, alters the microbial environment. Vaginal birth has been shown to promote the proper development of the gut microbiome, due to the child's exposure to the mother's vaginal flora while passing through the birth canal [5]. Other factors such as infant consumption of breast milk or formula, social and outdoor exposure, diet and lifestyle, as well as antibiotic use, can alter the microbial ecosystem [3, 4]. For example, a short-term change to either a strict animal or plant-based diet alters the gut microbial content within 24 hours and can be reversed in 48 hours after cessation of the strict diet [6].

The gut is known to interact with the brain via the enteric nervous system, the hypothalamus-pituitary-adrenal-gland (HPA) axis, and the central nervous system. The gut microbiome has the ability to alter brain development, functionality, and behavior by modifying immune, endocrine, metabolic, and neural signaling [7]. In general, through the bidirectional communication network between the gut and the brain via multiple systems such as the spinal cord, the peripheral nervous system, and the endocrine system, the gut microbiome regulates many physiological and psychiatric process-

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es in the body [3, 4, 8, 9]. For example, more than half of all the patients with irritable bowel syndrome exhibit mood disorders, modifications of the gut microbiome can cause depressive behaviors, and antibiotic exposure is known to have psychiatric side-effects such as anxiety, panic, and major depressive disorder [9].

Serotonin, or 5-HT, is produced in both the brain and the gastrointestinal tract, with greater than 90% being produced via EC in the distal gut lumen. 5-HT modulates numerous physiological processes from mood disorders to gastrointestinal motility [10]. The two main rate-limiting enzymes for 5-HT synthesis are tryptophan hydroxylase 1 (Tph1), found in EC, and tryptophan hydroxylase 2 (Tph2) in various neurons of the brain [10]. The gut microbiome has been shown to upregulate Tph1 synthesis, and thus 5-HT production from their SCFA metabolites [11]. Butyric acid, a common microbial waste product of fermentation, specifically has been found to offer a significant role in 5-HT production, as an inducer for the Tph1 transcription factor ZBP-89 [11]. Numerous other stimulatory factors such as bile acids (Deoxycholic acid and lithocholic acid), allyl isothiocyanate, and catecholamines have been found to contribute to the release of 5-HT from EC [12, 13].

It is known that serotonin is produced via enterochromaffin cells within the gut mucosal layer and that this gut-derived serotonin has numerous physiological roles. In this review, we summarize the literature regarding the relationship between the gut microbiome and serotonin. Our goal is to present the current understanding of how the gut microbiome contributes to the synthesis of serotonin and the effects serotonin has on the peripheral systems.

Serotonin

Serotonin, 5-hydroxytryptamine or 5-HT, is a neurotransmitter derived from the essential amino acid tryptophan with diverse physiological functions. In the brain, it is involved in the modulation of many behavioral processes such as mood and reward. In the central nervous system (CNS) 5-HT is predominantly produced by neurons. However, most serotonin in the body is outside the CNS, to interact with a variety of seven families of serotonin receptors [14]. The blood-brain barrier separates serotonin in the CNS from that in the peripheral systems. More than 90% of 5-HT in the body is produced in the peripheral systems via the enterochromaffin cells (EC), which are specialized endocrine cells in the intestinal epithelia [15, 16].

The rate-limiting enzyme of the 5-HT synthesis in the EC is Tph1, converting L-tryptophan to L-5-hydroxytryptophan, which is further converted by L-amino acid decarboxylase (AAAD) into 5-HT [17-19]. In neurons, a different hydroxylase, Tph2, is used [16, 20]. The amino acid L-tryptophan is one of the nine essential amino acids that the human body cannot produce and therefore must be acquired from diet.

5-HT signaling in the gastrointestinal tract and the central nervous systems occurs through the activation of seven families of serotonergic receptors: 5-HT1 through 5-HT7. In the gastrointestinal tract 5-HT3 and 5-HT4 are the most prominent. However, they operate differently; the 5-HT3 receptor is a ligand-gated Na+ and K+ cation channel, while the 5-HT4 receptor is a metabotropic G protein-coupled receptor (GPCR) [21]. 5-HT3 is highly expressed in afferent vagal neurons, which are known to innervate the intestinal mucosa and upon activation can directly communicate with the CNS [22]. 5-HT3 receptors are also known to regulate colonic motility and peristalsis [23]. While the GPCR 5-HT4 regulates gastrointestinal motility, visceral pain, immune regulation, and epithelial secretions [24].

Thus, 5-HT is multi-functional as a growth factor, paracrine factor, and a neurotransmitter, with a vast majority of 5-HT being derived from EC in the gut. A host of physiological processes are regulated by 5-HT including depression, sleep patterns, food appetite, libido, and temperature homeostasis [14, 25-27]. 5-HT has been shown to modulate gastrointestinal motility, platelet function, enteric motor and secretory reflexes, immune responses, bone development, and cardiac functionality. It has also been shown that the microbiota can impact hippocampal 5-HT levels showing a connection between the gut and brain serotonergic system [28]. Different concentrations of 5-HT can alter the microbial composition of the colonic environment. Increased levels of gut 5-HT secretion produce a microbial environment that has a higher probability of leading to severe colitis, showing a connection between the serotonin-microbiota axis and gut inflammation [29]. Irregular 5-HT signaling has been observed in gastrointestinal disorders such as inflammatory bowel disease (IBD) and colorectal cancer [29]. It is evident that regulated 5-HT production is essential to numerous physiological processes, and that a combination of host genetics, physiology, and the gut microbiota play a significant role in regulating 5-HT production.

Microbiome Acting On Serotonin

EC act as pressure sensors for the lumen of the colon, where an increase in pressure can increase luminal 5-HT concentrations [30]. EC also act as polymodal chemosensors activated by multiple substances. One study identified three categories of stimulating substances that promote EC to release 5-HT, including allyl isothiocyanate (AITC) - a chemical irritant from dietary wasabi and mustard, fatty acid prokaryotic fermentation products (butyrate, isobutyrate, and isovalerate), and host-derived catecholamines (dopamine, epinephrine, and norepinephrine) [12]. Bile acids are also thought to have a stimulatory effect on EC to release 5-HT. Two bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) activate a cell-surfaced G-protein coupled receptor, TGR5, to release the peristaltic transmitter 5-HT in to the lumen [31]. In addition, endospore-forming microbes, such as Clostridium sporogenes, produce the microbial metabolites cholate, deoxycholate, p-aminobenzoate (PABA), α-tocopherol, and tyramine, which have been shown to promote 5-HT synthesis from cultured rat colonic EC [9].

The effect of microbial stimulation of 5-HT release may or may not depend on EC. Some microbes may directly participate in the chemical synthesis of 5-HT. Multiple bacterial strains are able to produce 5-HT in vitro using tryptophan as the substrate [32]. Tryptophan decarboxylases are also present in the intestinal microbiota. For example, two bacterial species, Clostridium sporogenes and Ruminococcus gnavus express enzymes capable of decarboxylating tryptophan to tryptamine [33]. One model suggests that dietary, non-assimilated tryptophan in the colonic lumen is converted by secreted prokaryotic decarboxylases in to tryptamine, which induces serotonin release from guinea pig EC

[33, 34]. The level of tryptamine in feces was significantly elevated in mice with normal, non-pathogen microbiota, compared to germ-free mice [35]. The increased presence of tryptamine in conventional mice, indicates that the gut microbiome plays a role in the production of the EC stimulator, tryptamine. Interestingly it was demonstrated that tryptamine activates the 5-HT4 receptor and increases anion-dependent fluid secretions in the colon, which is key for regulating gut motility mechanisms like peristalsis [24, 36].

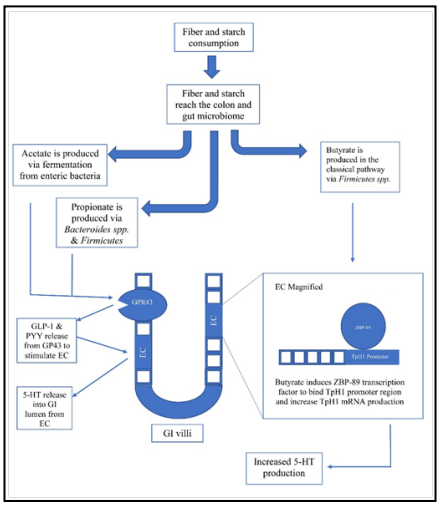
Additionally, the gut microbiota stimulates 5-HT production in EC through its prokaryotic metabolites, mainly short-chain fatty acids (SCFAs) (Figure 1). SCFAs are produced by the gut microbiota through the process of fermentation utilizing incomplete carbohydrates such as starch and fiber. The majority of SCFAs found in the intestinal lumen are acetate, propionate, and butyrate, none of which can be produced by human cells [37, 38]. These three SCFAs are produced in various bacterial species through different metabolic pathways. Acetate is produced mostly by enteric bacteria such as Akkermansia muciniphila, Bacteroides spp., Bifidobacterium spp., Prevotella spp., Ruminococcus spp. [39]. Propionate is produced in two different pathways; the succinate pathway by Bacteroidetes spp. and the lactate pathway by Firmicutes spp. Butyrate is produced through the classical pathway, which involves the condensation of conventional acetyl-CoA by various Firmicutes spp [31]. Butyrate has been identified as the preferred energy source for host colonocytes [39]. The general ratio of acetate, propionate, and butyrate is approximately 3:1:1, a ratio heavily influenced by host diet and intestinal microbial species composition [33, 39], as different phyla in the gut microbiome are enriched with different cocktails of prokaryotic glycosidases, lipases, and peptidases [6]. Before propionate and butyrate are further metabolized by the liver (propionate) and the colon (butyrate), these SCFA molecules directly activate G-protein coupled receptors and affect host physiology [39], including promoting 5-HT synthesis in EC [10]. SCFAs have been shown to upregulate Tph1 levels in EC, and as Tph1 is the rate-limiting enzyme in the synthesis of serotonin, SCFAs thus likely drive 5-HT production by EC [29]. In vitro, human EC treated with sodium acetate and sodium butyrate results in increased Tph1 expression [10]. Butyrate appears to play a direct role in the production of Tph1 mRNA. Butyrate is known as a histone deacetylase (HDAC) inhibitor; this allows butyrate to prevent the removal of acetyl groups from DNA histone proteins [40]. This action allows DNA to remain accessible to larger transcription factors. ZBP-89 is one such transcription factor found in colonic EC that is a butyrate-induced zinc finger which binds to GC-rich DNA elements [40]. In one mouse study [40], it was shown that ZBP-89 directly binds a mouse Tph1 DNA promoter region, thus elevating transcription of Tph1 mRNA (Figure 1) [11, 39, 40]. When the Tph1 gene is knocked out (KO) in a mouse model, mice lack >90% of intestinal and serum 5-HT levels, further emphasizing the importance of Tph1 in 5-HT synthesis [41]. Acetate and propionate in the large intestine lumen drive GPR43+ host colonocytes to secrete Glucagon-like-peptide-1 (GLP-1) and Peptide YY (PYY) [22, 39]. EC express the GLP-1and PYY Y1 receptors [42], and upon appropriate ligand binding EC cells release 5-HT into the colonic lumen [22] (Figure 1). Butyrate functions in a direct manner by upregulating Tph1 mRNA, while acetate and propionate stimulate release of GLP-1 and PYY, which then signal EC to release 5-HT. Thus, for EC cells, butyrate likely drives 5-HT production while acetate and propionate regulate 5-HT release.

In germ-free mice, serum concentrations of 5-HT tend to be lower than colonized mice. Mice raised with a human gut microbiome exhibited more than twice the Tph1 transcription and a 20% increasein Tph1 compared to germ-free mice [11]. When the microbiome was introduced to germ-free mice, they exhibited elevated Tph1 expression and restoration of serum 5-HT concentration [10, 43]. These observations show that the gut microbiome does influence Tph1 expression and in turn, 5-HT production.

Serotonin Acting On The Microbiome

The influence that the gut microbiome has on host physiology through its metabolic byproducts, neural influence, and immune modulation is becoming more apparent in the scientific community. However, less is known about the change in the ecosystem of the gut microbiome in response to host physiological irregularities. Many patients with gastrointestinal disorders such as inflammatory bowel disease (IBD) tend to exhibit dysbiosis of the gut microbiome and have irregular 5-HT signaling [29]. It is unclear as to whether irregular 5-HT signaling leads to microbial dysbiosis or vice versa. However, one study showed [29] that varied 5-HT

Figure 1. The release of 5-HT and upregulation of TpH1 mRNA via short chain fatty acid signaling from the gut microbiome.



signaling regulated gut bacteria growth in a species-specific manner that created an environment more susceptible to colitis. When 5-HT was introduced to the gut lumen at increasing concentrations, bacterial growth was inhibited, and obligate anaerobes were the most affected. The researchers in one study [29] compared the gut microbial composition of Tph1 knockout (KO) mice to conventional wild-type (WT) mice. The Tph1 KO mice showed a significant difference in the composition of their microbial ecosystem compared to the WT mice, further emphasizing that host genetic background strongly determines a host's unique microbiota signature. Further, in Tph1 KO mice, fecal sample analysis revealed significantly decreased levels of the SCFAs acetate, butyrate, and propionate [29]. In contrast, the number of endospore-forming bacteria in the gut is increased as levels of luminal 5-HT are increased. It is known that about 50% of 5-HT produced in the gut is the product of endospore-forming bacteria from families such as Clostridiaceae and Turicibacteraceae [44]. These results suggest that not only does the gut microbiome affect 5-HT synthesis, but also that 5-HT has the ability to alter the microbial composition. 5-HT signaling, and endospore-forming bacteria colonization may form a positive feedback mechanism, that interfaces with host status of genetics, diet, and environmental influence on development of gut bacterial species.

Conclusion

Approximately 10-100 trillion communalistic microbial organisms colonize the human body in various sites including the oral cavity, skin, female vagina, and most prominently the distal portion of the gastrointestinal tract [45]. The bacterial organisms found in the colon play a pivotal role in human health, and specifically 5-HT production. One of the main ways in which the gut bacteria can influence 5-HT production is through the synthesis of SCFA metabolites from fiber and starch fermentation. Butyrate specifically has been identified as one SCFA that promotes the upregulation of the 5-HT rate-limiting enzyme, Tph1. Interestingly it was also identified that increased 5-HT concentrations in the gut lumen promote the growth of spore-forming bacteria, and these same spore-forming bacteria produce metabolites that promote further synthesis of 5-HT. Some gut bacterial organisms exhibit symbiotic relationships with their human hosts. One example is the production of SCFA's, bacterial organisms can produce SCFA's as byproducts of fermentation. However, humans alone are not capable of producing SCFA's. Bacterial organisms use the gastric environment to grow and ferment the dietary starch and fiber to produce energy. While humans use the SCFA's for various purposes from energy sources to signal transduction. The relationship between human host and bacterial organism may have once been viewed as adversarial, but very may well be one of companionship.

Thus, the field of the microbiota-gut-brain (MGB) axis is supported by numerous studies that identify the importance of the gut microbiome and its metabolites in the production of 5-HT, specifically its EC upregulation of the rate-limiting enzyme Tph1. We also presented the research on the influence that 5-HT can have on the composition of the gut microbial environment. Further investigation is necessary to understand the overarching impact the gut microbiome plays on human health, as well as how lifestyle, diet, genetics, and host physiology may impact the composition of the human gut microbiome. Further investigation in to the gut microbiome and its symbiotic relationship with human health is necessary for the advancement of our scientific community and various healthcare sectors. Questions include how can an individual's gut microbiota change with age, diet, exercise, and or injury. Do some microbial signatures make us more or less prone to mental disorders or physical disease?

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