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REVIEW

The emerging roles of neuroactive components produced by gut microbiota

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Abstract

Background As a multifunctional ecosystem, the human digestive system contains a complex network of microorganisms, collectively known as gut microbiota. This consortium composed of more than 10^{13} microorganisms and Firmicutes and Bacteroidetes are the dominant microbes. Gut microbiota is increasingly recognized for its critical role in physiological processes beyond digestion. Gut microbiota participates in a symbiotic relationship with the host and takes advantage of intestinal nutrients and mutually participates in the digestion of complex carbohydrates and maintaining intestinal functions.

Method and Result We reviewed the neuroactive components produced by gut microbiota. Interestingly, microbiota plays a crucial role in regulating the activity of the intestinal lymphatic system, regulation of the intestinal epithelial barrier, and maintaining the tolerance to food immunostimulating molecules. The gut-brain axis is a two-way communication pathway that links the gut microbiota to the central nervous system (CNS) and importantly is involved in neurodevelopment, cognition, emotion and synaptic transmissions. The connections between gut microbiota and CNS are via endocrine system, immune system and vagus nerve.

Conclusion The gut microbiota produces common neurotransmitters and neuromodulators of the nervous system. These compounds play a role in neuronal functions, immune system regulation, gastrointestinal homeostasis, permeability of the blood brain barrier and other physiological processes. This review investigates the essential aspects of the neurotransmitters and neuromodulators produced by gut microbiota and their implications in health and disease.

Keywords Gut-brain axis · Neurotransmitters · Microbiota · GABA · Catecholamines

Introduction

Gut microbiota refers to the collection of microbes that reside in the gastrointestinal tract with bacteria being the main constituent. Despite the physical distance between the gut and the brain, extensive evidence has demonstrated two-way communication between the gut microbiota and the central nervous system (CNS), referred as the microbiota-gut-brain axis [1]. These communication pathways influence the immune system, vagus nerve, enteric nervous system (ENS) and neuroendocrine system through the generation of neuroactive components, metabolites, and hormones [2].

Since our body has slightly more microbial cells than human cells, it is surprisingly said that our body is more microbial than human, hosting trillions of microorganisms that outnumber our own cells [3]. These microorganisms include bacteria, archaea, viruses, fungi and protozoa [3]. Bacteria make up the majority of the intestinal microbiota

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and two main groups are dominant in the gut. Firmicutes, which include species of Lactobacillus, Clostridium, Enterococcus and Faecalibacterium of the microbiota. They usually constitutes 50–60% of the intestinal bacterial population. Bacteroidetes are another phylum that include species of Bacteroides and Prevotella of the microbiota that usually include 20–30% of the microbiota population [3, 4]. Archaea are less than bacteria in the microbiota and mostly include methanogens such as Methanobrevibacter smithii. Their share is usually less than 1% [3, 5]. Fungi such as Candida and Saccharomyces are also present in the gut, but their percentage is much lower than bacteria and usually make up about 0.1 to 0.5% of the total microbiota. In the health situation, enteric tract viruses are mainly bacteriophages that infect bacteria and play an important role in the regulating bacterial populations. Their share is generally small and usually less than 1% [6]. Protozoa such as Entamoeba and Blastocystis are also present in the intestine, but in general, their number is small compared to bacteria and usually their share is less than 1% [5, 7].

Neurotransmitters are the main chemical messengers in the nervous system that play an essential role in regulating the current of ions such as Ca^{2+}, Na^{+}, K^{+}, and Cl^{-} into or out of the neurons and create neuronal excitation and inhibition [8]. Recently, various roles for neurotransmitters beyond the CNS have been discussed. Gut microbiota produces neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, dopamine, norepinephrine, serotonin (5-HT), and histamine [8]. Moreover, some microbial metabolites, including short chain fatty acids (SCFAs), nitric oxide (NO) and tryptophan, also interact with the CNS [9]. These microbial neuroactive components can affect vagus nerve, ENS, intestinal enterochromaffin cells and neuronal activity to regulate various physiological mechanisms, including the mucosal immune responses, gastrointestinal motility, the secretion of proinflammatory cytokines and brain functions [2]. The communication pathways in microbiota-gut-brain axis are critical for maintaining physiological functions. Disruptions in these communications can cause immune system disorders, behavioral and cognitive problems, neuronal dysfunctions and gastrointestinal issues such as diarrhea, ulcerative colitis, Crohn's disease, and irritable bowel diseases (IBS) [8].

Gut microbiota is important in the modulating of immune system functions, which in turn affects neural development and brain function [2]. SCFAs that produced from the fermentation of dietary fibers by gut microbiota have anti-inflammatory effects and protect the intestinal barrier [10]. They also promote the maturation of regulatory T cells (Tregs) and inhibit the generation of inflammatory T helper 17 (Th17) cells, thus influencing overall neuroinflammatory responses [10]. Bacteria can influence immune responses by alteration in the release of cytokines such as interleukin-1β (IL-1β) and IL-6 that can induce the hypothalamic–pituitary–adrenal (HPA) stimulation, leading to neuroendocrine changes [2]. The intestinal microbiota composition can effect on producing of various neuroactive components [2]. For instance, some gut bacteria can increase 5-HT levels by affecting tryptophan metabolism in the enterochromaffin cells [11]. The vagus nerve is affected by the cytokines produced in the intestine as well as the neurotransmitter and neuromodulator compounds of the intestinal environment and the ENS. The vagus nerve transmits the signals to the CNS and influence behaviors and emotional states [12, 13]. Disturbances in this communication network can lead to digestive disorders and neuropsychological disorders [13]. Moreover, gut-brain axis involves systemic signaling processes in which the cytokines and neuroactive components produced by the gut enter the circulation to influence brain function [5]. The gut microbiota influences the secretion of hormones, such as oxytocin and corticotropin-releasing hormone. Changes in these hormones can affect stress responses and social behaviors [14]. Hormones, such as glucagon-like peptide-1, produced by the gut, are associated with neuroendocrine responses and can cross the blood brain barrier (BBB) [15]. The gut microbiota has critical role not only in gastrointestinal functions but also in neurodevelopment and regulating mood and behavior [15]. Ongoing research continues to unravel the complexities of these interactions, particularly in relation to neurodevelopmental, neurodegenerative and psychological disorders.

The gut-brain *axis*

The adult human gastrointestinal tract contains more than 10^{13} microorganisms [5]. Intestinal microbiota symbiotically takes advantage of both intestinal nutrients and is beneficial to the host in the digestion of complex carbohydrates as well as maintaining intestinal function. In addition, microbiota plays a crucial role in regulating of the intestinal lymphatic tissue activity, strengthening the integrity of the intestinal epithelial barrier, and maintaining the tolerance of immune cells and epithelium to food immunostimulating molecules and symbiotic microorganisms [5].

Previously, it was believed that the digestive system is germ free until birth, but new studies have shown that the intestinal environment may contain a specific community of bacteria in the uterus, and after birth, it is gradually influenced by nutrition, genetics and lifestyles [16, 17]. The way an infant is born and fed is effective in expanding the gut microbiome. It has been shown that children born vaginally have high levels of bifidobacteria and lactobacillus, while children born by cesarean section have high levels of Escherichia coli and Clostridium difficile [18]. Additionally, breastfed infants have been reported to have more bifidobacteria than formula-fed infants [18]. Gradually, the

intestinal microbiota composition evolves with the consumption of various nutritional substances. The feeding pattern has a great impact on shaping the gut microbiota. It has been shown that there are more herbal polysaccharides in the diet of African children, and they have a higher abundance of Bacteroides and the most abundant of Prevotella and Xylanibacter bacteria in their intestine [19]. These two microbial species are absent in the gut of European children with a diet rich in sugar, fat and protein. Consistent with these observations, higher levels of SCFAs are found in stool samples from African children. Consequently, diet may play a role in the selection of SCFA-producing bacteria that allow the gut to incorporate natural indigestible fibers such as cellulose into the cycle of metabolism and energy production [19]. Throughout the lifespan, the composition of gut microbiota is affected by dietary impacts, which can affect health and disease outcomes. For example, dietary fiber from fruits, vegetables, legumes, and whole grains acts as a prebiotic and promotes the resistance of beneficial bacteria including bifidobacteria and lactobacillus. Increasing fiber intake promotes microbial diversity and metabolic functions, leading to the production of SCFAs. Fermented foods such as yogurt, kefir, and kimchi that contain live probiotics can directly introduce beneficial bacteria including Bifidobacterium, Lactococcus lactis, Lactobacillus and Leuconostoc into the gut [20]. They help restore microbial balance, improve digestion, and boost immune system function [20]. The high levels of healthy fats in diet (like omega-3 fatty acids) can promote the growth of beneficial bacteria. Conversely, high consumption of saturated fat may lead to an increase in Gram-negative lipopolysaccharide (LPS) producing Proteobacteria, such as Escherichia coli and increase in the Firmicutes/Bacteroidetes ratio both of which induce inflammation [21]. A diet high in animal protein can increase the production of toxic microbial metabolites in the large intestine, including amines, H2S, and ammonia, increase the permeability of these compounds to the circulation and elevate the risk of developing intestinal disorders, type 2 diabetes, obesity, CNS disorders and cardiovascular diseases [22]. Plant proteins like soy proteins, increased the activity of obesity regulating Clostridium and Ruminococcus corresponding to beneficial microbiota profile [23]. Diets high in refined sugars and processed foods can promote the growth of Escherichia coli and Clostridium perfringen and reduce microbial diversity [24, 25]. This imbalance is linked to obesity, diabetes and other metabolic disorders. Fruits, vegetables, tea, coffee, and dark chocolate contain polyphenol compounds that have antioxidant properties and can modulate the intestinal microbiota by promoting beneficial bacteria including lactobacillus and Bifidobacterium [26]. A Mediterranean diet rich in fruits, vegetables, whole grains, healthy fats, and plant proteins increases Clostridium of cluster XIVa and Faecalibacterium Prausnitzii and reduces presence of Fusobacterium nucleatum, often exist in the colon of patients with colorectal cancer [27, 28]. A balanced diet with high levels of fibers, fermented foods, healthy fats and antioxidants promotes a diverse microbiome that contributes to reduced risk of gastrointestinal, CNS and cardiovascular diseases. However, diets rich in sugars and processed foods can lead to micribiota dysbiosis [21].

The gut-brain axis is a two-way communication pathway that links the gut microbiota to the CNS and importantly is involved in neurodevelopment, cognition, emotion and synaptic transmissions. The most important connection between microbiota in gut and brain includes endocrine system, immune system (cytokines) and nervous pathway (vagus and ENS) [5]. Figure 1 shows the important pathways involved in gut-brain axis.

a. Endocrine system and gut-brain axis

The CNS regulates the release of cortisol in stress situations through the HPA axis, and cortisol regulates inflammatory responses and cytokine release in local and systemic communications [29]. Leary et al. reported that chronic stress increased immunomodulatory microbiota, such as Clostridia, in the gut of rats, which is associated with increased anxiety-like symptoms and depression [30]. Along with these changes, the levels of pro-inflammatory cytokines including IL-6 and IL-1β in the hippocampus also increased. Transferring the microbiome of these animals to the normal animals increases anxiety and depression in association with increased pro-inflammatory interleukins in their hippocampus [30]. In addition, cortisol alters the blood intestinal barrier and BBB permeability. It has been reported that elevated level of peripheral cortisol causes increase in the systemic inflammatory factors including IL-6, IL-8 and tumor necrosis factor alpha (TNF-α) as well as decrease in the anti-inflammatory cytokine IL-10. These inflammatory outcomes induce intestinal dysbiosis and decrease GABA absorption from the intestinal blood barrier [31]. The supplementation with GABA-producing probiotics enhanced the abundance of Lactobacillus in the gut and GABA level in the plasma, and reverse cortisol-induced intestinal dysbiosis [32]. Cortisol directly influences on intestinal function through its receptors on various intestinal cells, including epithelial, immune, and endocrine cells. Cortisol can also alter the nutrients available to gut microbes by altering gut motility and permeability, which in turn can alter gut microbiome composition and diversity [33]. In addition, glucocorticoid receptors are presented in various brain areas including the hippocampus, amygdala, and prefrontal cortex, and cortisol can affect brain function through them.

It has also been shown that microbes living in the gut can activate stress circuits in the CNS via the vagus nerve and ENS sensory neurons. Induction of intestinal dysbiosis

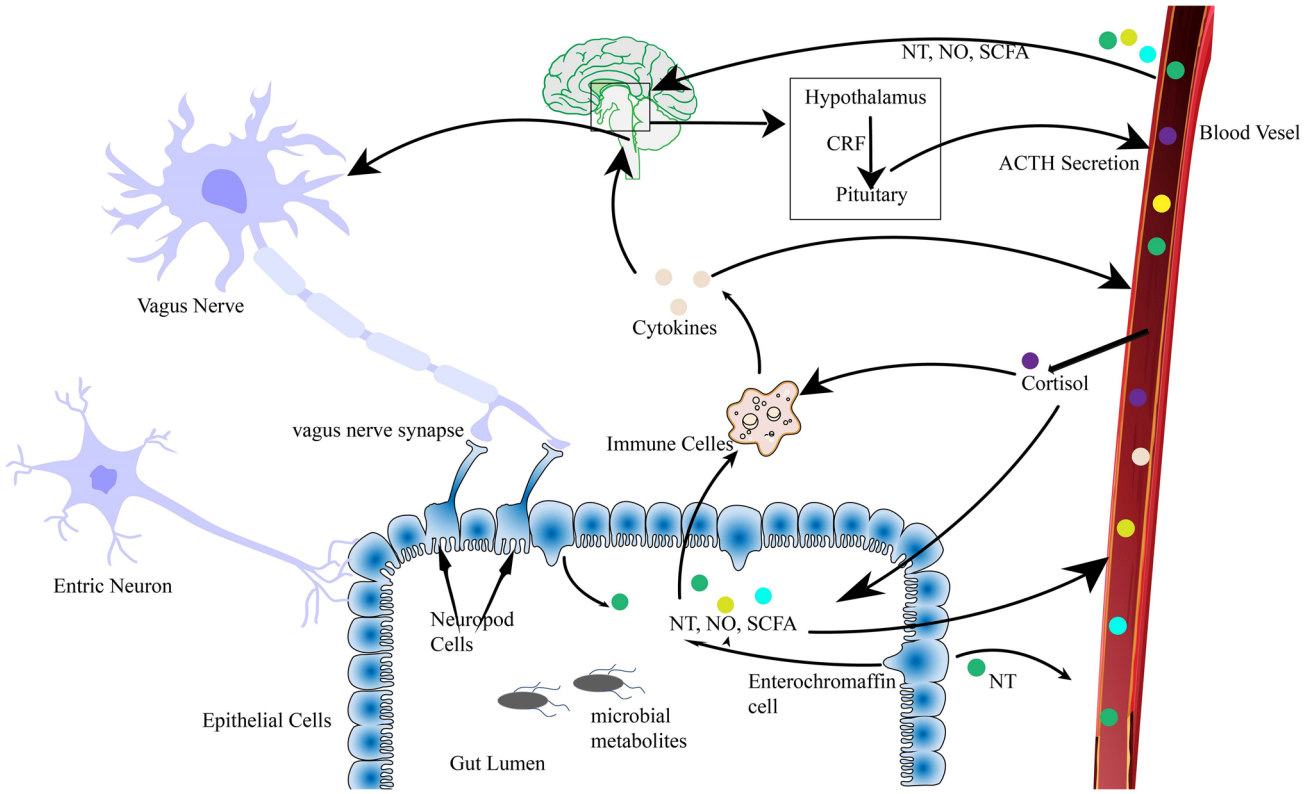

Fig. 1 The mechanism of two-way interactions of the gut-brain axis and the effect of neuroactive compounds produced by microbiota. The hypothalamic–pituitary–adrenal axis is involved in hormonal pathway. Cortisol can enter the intestinal lumen. Cortisol affects the composition of microbes, inflammatory pathways in the gut, and gut motility. Intestinal immune cells are involved in the production of inflammatory cytokines. These cytokines circulate in the body and they can enter the CNS. The vagus nerve and the enteric nervous system are also involved in bowel movements and secretions of enterochromaffin cells. Neurotransmitters, SCFAs and NO are also produced by intestinal microbiota. These molecules can affect enteric and vagus nerves, immune cells, and the CNS

in marmoset monkeys caused changes in intestinal metabolites, including GABA, 5-HT, short and long fatty acids, and bile acids, along with increased stress-related behaviors and increased systemic cortisol [1]. Moreover, in animal and human studies, intestinal dysbiosis is associated with an increase in inflammation in different areas of the brain, including the amygdala and hippocampus [34].

b. Immune system and gut-brain axis

The immune system importantly distinguishes between foreign and endogenous signals and organizes proper reactions, especially in the gastrointestinal tract, where the innate and acquired immune systems permanently interact with different antigens [35]. Although enterocytes have innate immune receptor molecules including Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on their membrane surface and can secrete inflammatory cytokines and chemokines through pathways dependent on these receptors, however, the gut lymphoid cells provide the specific immunity which involved antibodies [2]. Important immune receptor, TLR, recognize microorganism-associated molecular patterns (MAMPs) including LPS and polysaccharide-A in Gram-negative bacteria and peptidoglycan in Gram-positive bacteria, which are recognized by enterocytes. This detection process allows the immune system to recognize and give feedback to microorganisms in the gut tract, detect changes in microbial balance, and preserve gut homeostasis [5]. The TLR4 has been shown to be important in the regulation of the Escherichia coli bacterial population in the gut, as activation of this receptor stimulates Src signaling and subsequently activates the caveolae-mediated endocytosis pathway, leading to bacterial internalization by monocytes [36].

Particularly, stimulation of the immune system enhances the levels of inflammatory intermediaries. Adequate intestinal immune cytokines are necessary for gut homeostasis, and subsequently regulate the number and composition of the intestinal microbiota. Significant amounts of inflammatory cytokines produced by intestinal immune responses enter the systemic circulation. These inflammatory cytokines can cross the BBB and directly alter CNS homeostasis and induce neuroinflammation in the CNS. Disruption of the gut

microbiota balance can damage the intestinal barrier and the BBB, allowing microbes and their products to enter the circulation and CNS to cause neuroinflammation [2].

The immune system of the brain is characterized by resident immune cells such as microglia, which provokes the pro-inflammatory state. Remarkably, chronic intestinal inflammation is associated with learning and memory disorders and anxiety behaviors. It has been reported that IBS is associated with an increase in inflammatory cytokines including IL-6, IL-1β and TNF-α in the intestinal tissue, which causes a decrease in the expression of ZO-1 and ZO-2 proteins in the intestinal epithelial cells [37]. Since these proteins are in the structure of tight junctions of the intestinal barrier, inflammation reduces the integrity of the intestinal barrier and increases pro-inflammatory cytokines systemically [37]. Moreover, systemic inflammation causes a decrease in the expression of ZO-1 and ZO-2 in the cerebral vascular epithelium and an increase in BBB permeability, which induces neuroinflammation, impairs memory, and increases anxiety [38].

Reduction of intestinal microbes by antibiotic administration and germ free condition results in impairments in immune response regulation in gut and CNS immunity [39]. Administration of oral antibiotics in the early life of rat decreased the diversity of the intestinal microbiota and replaced Firmicutes and Actinobacteria with Proteobacteria and Bacteroidetes. Also, the levels of SCFAs decreased in the feces of mice treated with antibiotics. These changes caused a stronger immune response in the lymph nodes and increased inflammation and autoimmune reactions in the CNS [39].

Intestinal probiotics containing Streptococcus salivarius, Bifidobacterium, and Lactobacillus reduce microglial stimulation and cerebral monocyte migration through the regulation of TNF-α. This pathway can reduce neuroinflammation and improve cognitive function by modulating the migration of monocytes from the environment to the CNS [35]. Mice with mutation in recombinant activator gene 1 (Rag1) that lacked lymphocytes showed cognitive and behavioral changes associated with anxiety, underlining the critical function of the immune responses in gut-brain axis. Brain dysfunction in these animals improved by administering the probiotic combination of L. rhamnosus and L. helveticus [40]. Therefore, probiotic therapy proposes promising treatment for reducing acquired immunodeficiency and improve behavior.

c. Vagus nerve and gut-brain axis

The vagus nerve is a major ingredient of the peripheral nervous system, which derives its name from the Latin word means "wanderer." This nerve contains 80% afferent fibers and 20% efferent fibers, which potently transfer important signals from the viscera, including the digestive and cardiorespiratory systems to the brain (bottom-up signal) and backward projections to the visceral organs (signal from top to bottom). Vagal projections have important roles in the management of craving for food, anxiety-related behaviors, inflammatory pathways, and cognitive functions [34].

Vagal afferents give rise to three distinct classes of nerve connections in the ENS: slow intraganglionic terminals and intramuscular axons, both of them terminate in smooth muscles. There are vagal terminals in the mucosal layer, in synaptic communication with a group of enteroendocrine cells called neuropods [5]. Vagal afferents have wide spreading and express the large number of receptors that are able to detect different molecules including bacterial metabolites, inflammatory signals, intestinal hormones and neurotransmitters. Consequently, they respond to a wide range of mechanical, chemical, and hormonal signals [5].

The ENS is important in mediating the gut-brain axis, and the vagus nerve is involved in establishing this connection [14]. Because of the complex network of neurons embedded in the intestinal wall, the ENS is often referred to as the 'second brain'' [41]. It contains approximately 200–300 million neurons organized into two main networks: the myenteric network, which regulates gastrointestinal motility, and submucosal network, which manages secretory processes and blood flow [41, 42]. The ENS can function independently of the CNS to coordinate local reflexes for digestion, including peristalsis and digestive enzyme secretion [43]. This allows for a rapid response to gut stimuli, without requiring direct input from the brain [43]. The ENS produces a wide variety of neurotransmitters and neuropeptides such as 5-HT, acetylcholine, GABA, and NO, that contribute to regulation of intestinal functions [44]. It is noteworthy that approximately 90% of the body 5-HT is found in the gastrointestinal tract, which affects bowel movements and mood regulation [11]. The ENS communicates with the CNS through various pathways, including the vagus nerve, and signals directly to the intestinal immune cells and other local cells [44]. This signal is critical for gut homeostasis, and can influence the perception of pain, stress, and anxiety. Recent studies have suggested that the ENS plays a role in influencing emotional and behavioral responses through interactions with microbiota and the immune response [45]. The integration of ENS signals with signals transmitted via the vagus nerve results in dynamic interactions that are essential for gastrointestinal balance and regulating neuropsychological states [46]. ENS dysfunction can contribute to digestive disorders and is associated with conditions such as mood disorders, cognitive problems, and IBS. While the vagus nerve provides an important communication between the gastrointestinal tract and brain, the ENS serves as a fundamental regulatory network within the gut [43, 47].

Projections of the vagus nerve reach to solitary nucleus (SN) in the medulla oblongata of the brainstem. This signals are then transmitted to structures in the brainstem and forebrain that are involved in the networks of behavioral, emotional and cognitive regulation [5]. SN projections send information to complex neural networks directly or via multi-synaptic pathways and communicate visceral signals to different brain areas. For instance, axons from SN to the insula and amygdala are involved in emotional regulation [48]. Comparably, signals from SN to the hippocampus and basolateral amygdala are also involved in memory formation [5]. Moreover, projections to the lateral hypothalamus enhance appetite; however, the SN also sends some axons to the pituitary, therefore affect the HPA pathway. Some neurons in SN send projection to the arcuate nucleus to joint endocrine and behavior, in the way of adjustment of eating behavior and satiation. The SN also affects neurotransmitter regulation such as norepinephrine and 5-HT [5]. Fundamentally, the SN effectively integrates the gut-brain information pathway via the vagus nerve and is a central node for gut-brain axis coordination.

The vagus nerve is crucially involved in neurogenesis and neural survival in the brain. Impairments in the vagus nerve reduce neurogenic signaling and stimulate microglial inflammatory signals in the hippocampal tissue, which result in increased stress-related behaviors and memory impairments [2, 49]. Meanwhile, vagus nerve stimulation ameliorated hippocampal damages, regulated neurotransmitter release, and improved hippocampal brain-derived neurotrophic factor (BDNF) levels, thereby recovering synaptic plasticity, learning, and memory [49].

Gut microbiota, neurotransmitters and neuromodulators

To investigate how the microbiota interacts with the host physiological systems, the primary scenario is through the production of neuroactive components and their effects on the various biological pathways. The gut microbiota produces many common neurotransmitters and neuromodulators of the nervous system. The essential impacts of microbial neuroactive components including glutamate, GABA, histamine, dopamine, norepinephrine, 5-HT, NO and SCFAs on physiological functions have been considered in Table 1.

Table 1 Neuroactive components produced by gut microbiota and their functions

Neurotransmitter	Microbiota	Function	Reference
GABA	Lactobacillus, Bifidobacterium, Streptococcus Pseudomonas aeruginosa	IL-6, IL-1β, NLRP3, and TNF-α regulation, reducing anxiety, sleep regulation, improving insulin sensitivity	[31, 47, 50]
Glutamate	Lactobacillus rhamnosus, Lactococcus lactis, Lactobacillus paracasei	ENS stimulation, vagus-intestinal communication	[42, 47, 65, 142]
Catecholamines	Bacillus, Enterococcus, Lactobacillus, Klebsiella, Morganella, Escherichia coli	Regulation of learning and memory, emotions, and bowel movements, modulation of inflammatory pathwats	[143, 144, 145]
Serotonin	Candida, Streptococcus, Escherichia, Enterococcus, Pseudomonas	mood regulation, regulation of BBB permeability, immune response modulation	[50, 88, 146, 147]
Histamine	Lactococcus lactis, Enococcus ioni, Pediococcus parulo, Streptococcus thermophilus, morganella morgani, Klebsiella pneumoniae, Enterobacter, Citrobacter freundi and Citrobacter	increasing alertness and motivational behaviors, increasing inflammation, bacterial communications	[111, 114, 148]
Acetylcholine	Lactobacillus plantarum, Bacillus subtilis, Escherichia coli, Staphylococcus aureus	preservation of skeletal muscles, autonomous nervous system regulation, immunomodulation	[149, 150]
Nitric oxide	streptomyces, Rhodococcuses, staphylococcus aureus, lactobacillus, Bifodobacterium, Escherichia coli	increasing cerebral blood flow, inflammatory pathways, regulation of glutamate signaling in the ENS and CNS, regulation of gastrointestinal motility, increasing BBB permeability	[151, 152, 153, 154]
Short Chain Fatty Acids	Bifodobacterium, Lactobacillus, Lachnospirase, Blavatia, Coprococcus, Roseboria, and Faecium	ENS modulation, preservation of gut microbiota composition, epigenetic modulation, regulation of neurotransmitters and neurotrophic factors production	[124, 155, 156]

IL-6, interleukine 6; NLRP3, NLR family pyrin domain containing 3; TNF-α, tumor necrosis factor α, BBB, blood brain barrier; ENS, enteric nervous system

γ-amino butyric acid (GABA)

Many bacteria of the normal intestinal flora, including Lactobacillus spp., Bifidobacterium spp. and Escherichia coli, produce GABA. Moreover, transcriptomic study of human stool revealed that enzymes involved in GABA production are abundantly expressed by Bacteroides, Parabacteroides and Escherichia species [50]. Sequencing of 16S ribosomal RNA in the stool samples of patients with severe depression in correlation with functional magnetic resonance imaging showed that the abundance level of GABA-producing bacteroides in stool samples was negatively correlated with depressive symptoms [50].

GABA is the most important inhibitory neurotransmitter in the CNS and is involved in the regulation of the action potentials as well as reduction of neurotransmitter release [51]. It has been shown that GABA can pass cross the BBB by simple diffusion, solution passage via intracellular pathways, and transporter-mediated mechanism [52]. GABA transporter-2 (GAT2) and beta/GABA transporter-1 (BGT-1) expressed on endothelial cells are involved in GABA transportation across the BBB [53]. Radiolabeling studies of GABA have shown that GABA enters the brain in neonatal and adult rats, and there is a non-specific distribution of BBB-mediated GABA transport [53]. In addition, evidence showed that NO increases the permeability of the BBB, thereby increasing the GABA intake from BBB into the brain tissue [52].

GABA modulates the inhibitory-excitatory neutral balance, decreases NLRP3, IL-1β and TNF-α secretion, and reduces neuropeptide secretion by intrinsic ENS and extrinsic sympathetic and parasympathetic innervation fibers in the intestine [51]. Peripheral GABA administration ameliorated neuroinflammation and reduced adverse T-cell array in multiple sclerosis (MS) in rat model [54]. GABA administration reduced IL-6 release and inflammatory responses in astrocytoma cells [51]. Oral administration of GABA inhibited the stress induced anxiety like behavior and improved the early stage of sleep in human and animal studies [55].

Because GABA in the ENS stimulates both excitatory and inhibitory pathways by targeting excitatory and inhibitory motor neurons, this neurotransmitter can differentially affect smooth muscle behavior and secretion [56]. Experimental study showed the presence of $GABA_A$ and $GABA_B$ receptor on cholinergic excitatory and nonadrenergic, noncholinergic inhibitory neurons of the ENS [57]. Electrophysiological study showed that intestinal GABA mediates the depolarization of myenteric neurons [58]. Chloride-dependent and bicuculline sensitivity properties of these neurons mediated by $GABA_A$ receptor is similar to $GABA_A$ depolarization function on dorsal root ganglion neurons and can be a therapeutic target in regulating bowel movements [59]. Moreover, glial cells in the ENS network express GABA receptors to regulate the immune responses [14]. $GABA_B$ receptor activation in ENS glial cells suppresses intestinal inflammatory pathways by inhibiting pro-inflammatory cytokines, enhancing IgA and IgG levels and inhibiting the Nuclear factor-κB (NF-κB) pathway [60].

$GABA_A$ and $GABA_B$ receptors are widely located in the nucleus ambiguous, dorsal motor nucleus of the vagus, and the peripheral vagal ganglia, and they are crucially involved in modulating the sensory input signals, reducing heart rate, ameliorating gastrointestinal motility and reducing anxiety [13]. A study by Nakamura et al. showed that increased intestinal GABA lead to increased circulating GABA concentrations that suppressed feeding behavior. GABA increased postprandial vagal afferent activity, thereby induced postprandial satiety. Consequently, gastrointestinal GABA promotes vagal afferent signals associated with feeding stimulations and regulates brain networks involved in feeding behavior and eating habits [61]. Moreover, it has been reported that GABA signaling in vagus nerve modulated the cortical excitability of brain regions associated with epileptogenesis through $GABA_A$ receptor plasticity [62].

Manipulation of gut microbiota can affect GABA levels in the blood and CNS [2]. Dietary interventions are adequate strategies to alter the composition and activity of the gut microbiota, and a ketogenic nutritional regime has been reported to enhance GABA levels in the CSF of children with refractory epilepsy, showing promise in improving the symptoms of refractory epilepsy [63]. More definitively, GABA was identified as the most altered metabolite in obese individuals receiving allosteric stool transplants by lean donors, and this was associated with improved insulin sensitivity in obese patients [64]. However, further studies are required to elucidate the exact roles of GABA produced by the gut microbiota.

Glutamate

Glutamate is the major excitatory neurotransmitter in the CNS, and both glia and neurons have molecular machinery for regulation of its biosynthesis, release, and reuptake. Glutamate has crucial role in learning and memory. Glutamate is released from presynaptic terminals and binds to glutamate receptors especially AMPA and NMDA ionotropic receptors located in postsynaptic terminals [49]. These receptors import positive ions, especially Ca^{2+}, enter the cell. This high concentration of calcium provokes the synaptic plasticity pathway and memory formation. The neurotransmission of glutamate is carefully regulated by several mechanisms. Excess glutamate enters glial cells by excitatory amino acid transporter. Then, inside the glial cell, glutamate is converted to glutamine, and returns to the presynaptic neuron and is converted to glutamate with the activity of

glutaminase enzyme. Overstimulation of neurons with glutamate neurotransmission causes neuronal excitotoxicity [49].

Although food is an important source of glutamate in the intestinal tract, but glutamate is also produced by several types of bacteria in the intestine [5]. Several bacteria in the gastrointestinal tract including Corynebacterium glutamycum, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillus lactis, synthesize glutamate [65]. About 15% of Lactobacillus strains in Asian fermented dietary produce glutamate and strain Lactobacillus plantarum was identified as the highest glutamate producer [66]. Low peripheral glutamate level has been reported to be associated with cognitive impairments in Alzheimer's patients [67].

It seems that the microbial glutamate is essential for the ENS stimulation. Electrophysiological properties of primary afferent neurons of the myenteric plexus in germ free animals showed dysregulated function with diminished excitability, which was restored following recolonization with normal intestinal microbiota [68]. Gut microbiome have been reported to affect the excitability of vagal afferents that synapse with intrinsic primary afferent neurons [69]. For example, components of Lactobacillus rhamnosus (JB-1) stimulate the vagal afferent neurons [68]. This stimulatory effect of microbes on the vagus may contribute to the direct transmission of signals to the brain and could explain the beneficial effect of probiotics on the CNS function [2].

The ENS regulates secretion, sensation signals and movement of the gastrointestinal tract. Various ionotropic and metabotropic glutamate receptors are presented in the ENS networks, which innervate the small and large intestine [42]. NMDA receptors are presented abundantly in the intestinal submucosal and myenteric neurons, representing a functional relevance of this receptor pathway in the intestinal ganglia [70, 71]. In the intestinal myenteric network, NMDA receptor is involved in contractile cholinergic pathway through interaction with NO signaling [72]. Moreover, NMDA receptors in ENS, are involved in the transmission of visceral sensitivity from the gastrointestinal tract to the CNS and vagus nerve [73]. In rats, GluN1 subunit was found in the soma of thoracolumbar afferents of dorsal root ganglions and peripheral terminals innervating the colon mucosal layer [74]. Inhibition of NMDA receptor in ENS inactivated hypersensitivity responses to innocuous (light) and noxious (heavy) stimulations in animal model of colorectal distension [75]. AMPA receptor in cholinergic and non-cholinergic interneurons and ENS is involved in spontaneous contractions and electrical stimulation of the intestine [76]. Moreover, glutamate metabotropic receptors are expressed in the myenteric plexus of the intestine and have a facilitating effect on motility. Theses receptors are also involved in motility responses in the pseudomyenteric plexus of intestinal tract [42, 71, 77]. In the colon, metabotropic glutamate receptors control colonic peristalsis and electrolyte transport [78]. Interestingly, these receptors modulated the function of intestinal mucosa through glutamate via acting on intestinal neurons and epithelial cells [78, 79]. Inhibition of mGlu7 receptor in the mucosal and submucosal layer strengthens secretion during stress situations, which represented the involvement of mGlu7 receptors in secretion disorders including diarrhea and constipation caused by stress [78].

Serotonin

Serotonin (5-HT), a monoamine neurotransmitter, has prominent roles in the brain functions including mood regulation, motivation, cognition and important physiological procedures such as vasoconstriction and vomiting [80]. Germ free mice exhibited reduced levels of 5-HT in the circulation and intestine, and enhancement in the rate of 5-HT turnover in the CNS [81]. Reduced 5-HT level in these animals was reversed by bacterial recolonization or administration of spore-forming species [82]. Several classes of microbiota including Candida, Streptococcus, Escherichia, Enterococcus and Pseudomonas in the intestine can biosynthesize and secrete 5-HT [14]. Candida and Escherichia convert dietary tryptophan into 5-HT. Intestinal tryptophan also can be involved in the immunity kynurenine mechanisms and cause 5-HT dysregulation and pathophysiological consequences [2].

5-HT is an important neurotransmitter involved in the regulation of CNS networks and gastrointestinal functions. In the digestive system, 5-HT signaling controls the movements of the digestive system [83]. Central 5-HT is significantly involved in important brain processes including mood, sleep, and food regulation. Because 5-HT is produced simultaneously with peristaltic contractions in the gut, it was once considered a major regulator of peristaltic contractions [83]. D'andrea et al. investigated the levels of 5-HT and 5-hydroxyindoleacetic acid (5HIAA) in plasma and platelets of cluster headache patients in the acute phases of the disease. They reported that cluster headaches are associated with an increase in serotonergic metabolism, which indicates the possible association of the serotonergic neurotransmission with the pathophysiology of cluster headache [84].

In the gastrointestinal tract, 5-HT is especially synthesize in the enterochromaffin cells of the intestinal lining [11]. 5-HT in the gut plays a role in regulating appetite and satiety. 5-HT regulates intestinal movement by affecting the contraction of intestinal muscles and plays a role in maintaining the rhythmic movements necessary for proper digestion and absorption of nutrients. 5-HT receptors in the gut are involved in sensory perception related to the digestive process, such as the satiety and irritation. Moreover, these receptors influence eating habits, and can also help the process of digestion in the gastrointestinal tract

[85]. 5-HT and the molecules involved in its metabolism, especially serotonin reuptake transporter (SERT), are involved in the pathophysiology of functional gastrointestinal disorders including IBS [86]. Through 5-HT receptors in the gastrointestinal tract, 5-HT regulates the processes of vasodilation, visceral pain perception and nausea in the gastrointestinal tract. Through intestinal absorption, tryptophan enters the bloodstream, crosses the BBB and is converted to 5-HT in the brain [87, 88].

There are increasing studies that show that 5-HT plays a significant role in the environment as a hormone capable of modulating metabolic processes in the peripheral organs [89]. 5-HT increases hepatic gluconeogenesis and fat lipolysis [83]. Lowering blood sugar, increased intestinal Tph1 and plasma 5-HT levels leading to increased glucagon [90]. However, obese conditions also lead to higher levels of 5-HT in plasma and gut [91]. Furthermore, peripheral 5-HT reduces glucose-induced insulin secretion, and could increase the risk of hepatic steatosis [83, 92]. Because 5-HT signaling is a critical mediator of many important gastrointestinal activities and CNS functions, it is a promising candidate to modulate the digestive tract diseases.

5-HT biosynthesis by microbiota in gut tract has a major impact on the CNS, as enterocytes are in communication with 5-HT receptor afferent fibers of vagus nerve and dorsal root neurons [93]. Evidence of the effect of gut microbes-vagal nerve axis on emotion and anxiety has been reported [2]. Mice with sub-diaphragmatic vagotomy were impaired in emotion-related behaviors regardless of the enhancement in neurotransmitters produced by intestinal microbiota [94].

Moreover, concentration of 5-HT in the blood affects the permeability of the BBB, which indirectly affects brain function. It has been reported that 5-HT induced a short-term leakage in the BBB, possibly through 5-HT2 receptors [95]. Peripheral 5-HT is a potent modulator of immune responses in autoimmune diseases. For instance, 5-HT decreased MHC class II levels and antigen-presenting capacity in macrophages in the development of rheumatoid arthritis [96]. Moreover, 5-HT reduces proinflammatory cytokines including IL-6 and TNF-α levels in macrophages and lymphocytes [97].

It has been reported that oral administration of Lactococcus lactis spores in mice model of chronic stress increases 5-HT in the intestinal space, which reduces depression and anxiety symptoms [98]. In addition, increasing intestinal 5-HT suppressed oxidative stress, neuroinflammation and autophagy and increased BDNF and 5-HT levels in the hippocampus [99]. It has been observed that the administration of probiotic Lactobacillus rhamnosus reduces weight loss, depressive and anhedonia behaviors in rat model of chronic stress and increases 5-HT in the hippocampus and prefrontal cortex [100].

Oral administration of 5-HT has been shown to induce colonization of Turicibacter sanguinis in the human intestine, a bacterium that expresses a neurotransmitter-sodium symporter protein that is mechanistically resembling the mammalian SERT. Certain neurotransmitters may serve growth substrates for gut microbiota. High levels of 5-HT may decrease intestinal wall permeability, while low levels of 5-HT decrease occludin expression and weaken the intestinal barrier, leading to increased permeability and leaky gut [101]. Additional amount of 5-HT in the circulation is transported into the cells by membrane SERT and is deactivated by MAO [85]. Many of the current antidepressant drugs inhibit the reuptake of biological amines. Conversely, significant portion of individuals affected with major depressive disorder do not respond to antidepressant medicines [49]. This highlights the need for a therapeutic approach to the link between gut microbiota and emotional behaviors.

Catecholamines

Catecholamines, including dopamine and norepinephrine are crucial in the regulation of various central and peripheral neural functions such as learning and memory, emotions, and bowel movements. In the digestive system, the concentration of dopamine and noradrenaline is higher in the colon lumen [29]. The level of catecholamines in germ free mice is lower than control animals. The colonization of Clostridium species or specific pathogen free fecal flora in germ free mice led to a strong increase in catecholamines. The inoculation of Escherichia coli strain to these animals also caused a significant increase in catecholamines in intestinal lumen, but the colonization of the β-glucuronidase mutated strain, which is not able to produce catecholamine, did not have this effect [9]. This indicates that microbiota in the gut tract are importantly involved in the production of catecholamines in the intestinal lumen. However, catecholamines can cross the BBB in the periventricular sites, where the BBB has more permeable. Ethanol facilitates the entrance of catecholamines to the CNS by increasing the permeability of the BBB [102].

Gut microbiota are crucially participate in dopamine bioavailability in the ENS and CNS. The phenylalanine-tyrosine-dopa-dopamine biosynthetic pathway is activated in some gut bacteria to produce dopamine. Therefore, these bacteria contain homologues of mammalian enzymes that are involved in dopamine biosynthesis. Several common gut microbes generate dopamine such as, staphylococcus and Enterococcus [103]. Dopamine regulates immune cell stimulation and cytokine release by activated T cells. In the brain, dopamine modulates the synthesis of NO in microglial cells through D1 dopamine receptor [104]. Moreover, dopamine modulates migration of microglial cells [104]. It is shown that $CD4^+$ $CD25^+$ regulatory T-cells (Treg) are involved in

neurodegenerative pathways following neuroinflammatory processes. Dopamine, through type 1 dopamine receptors in Treg cells decreases the stimulation, adhesion and migration of Treg cells [105]. Elevation of systemic dopamine or its type 1 receptor agonist, inhibited Treg mediated inflammation and significantly enhances protective mechanisms against neuronal loss following mechanical and biochemical CNS injury [105]. Dopamine enhances resting T cells and prevents the activation of stimulated T cells in a receptor dependent pathway [14].

In the brain, dopamine neurotransmitter is synthesized by the neurons in the substantia nigra, ventral tegmental area and hypothalamus and is secreted in the nucleus accumbens and the frontal cortex. Dopamine is known as the reward neurotransmitter, but it is also involved in modulating learning and memory, intentional movement, impulsiveness, inhibition of prolactin release, sleeping, dreaming, anxiety and attention[2, 29]. Dysfunction of the dopaminergic system is associated with Parkinson's disease and schizophrenia. Dopamine dysregulation in the brain can activate NF-κB, leading to the activation of inflammatory pathways including the NLRP3 inflammasomes and the pro-inflammatory cytokines IL-1β and IL-18 [106].

Norepinephrine is important neurotransmitter involved in alertness, arousal and sensory recognition, learning and attention. Disorders in the neurotransmission of norepinephrine in the CNS are associated with the development of mental and neurological diseases including depression, anxiety, attention deficit hyperactivity disorder (ADHD) and epilepsy. Bacteria such as Escherichia coli (K-12), Proteus vulgaris, Serratia marcescens, Bacillus subtilis, and Bacillus mycoides have elevated levels (0.45–2.13 mM) of norepinephrine in their biomass and have been reported as norepinephrine-producing microorganisms [107]. The norepinephrine molecule in bacteria plays a role in the detection of the quorum of the bacterial population. Also, norepinephrine stimulates adrenergic receptors QseC and QseE in the membrane of bacteria, which have histidine kinase properties [108]. Activation of these receptors causes the alteration in bacterial motility and leads to expression of virulence genes in bacteria [109]. Bacterial quorum detecting system also sense the host hormones norepinephrine/epinephrine, and can enable the microbiota to interact with signals reaching the gut [29]. Toral et al. showed that fecal microbiota transplantation from spontaneously hypertensive rats to normotensive Wistar-Kyoto rats elevated the concentration of norepinephrine in the proximal colon and serum and increased the blood pressure in normotensive rats. In addition, the elevation in systemic norepinephrine due to the alteration of gut microbiota increased oxidative stress and the production of pro-inflammatory cytokines IL-1β, IL-6, TNF-α and interferon (IFN)-γ in the paraventricular nucleus area of the brain [110].

Histamine

Histamine is a neurotransmittrer that is involved in physiological processes including wakefulness, feeding behaviors and cognition. In the CNS, histamine regulates the release of other neurotransmitters including dopamine, neurepinephrine and 5-HT [5]. Dysregulation of histamine signaling has been reported in several neurological and neuropsychological disorders such as schizophrenia, depression and Parkinson's disease. Histamine is a biogenic amine with different effects on several cells, through four types of histamine receptors (H1-H4 receptors) [2].

The gut harbors high levels of histamine and the immune cells, specially mast cells and basophils produce and release histamine. Dendritic and T cells, express histidine decarboxylase, an enzyme involved in histamine production following stimulation [49]. In addition, food is a significant source of histamine. Intestinal microbiota are also involved in histamine generation via histidine decarboxylase pathway. Histamine production by microbiota in the gastrointestinal tract increases the immune response. In the gastrointestinal tract, histamine is involved in various gut disorders, such as dietary allergy, histamine intolerance and IBS [29].

Histamine is involved in homeostatic pathways, increases alertness, and induces motivational behaviors [111]. Research shows that histamine neurotransmission enhances learning and retention of tasks in laboratory animals [112]. Histamine also plays a role in reducing appetite [113]. Histamine is an important regulator of the hypothalamus functions especially vasopressin release. Histamine also is involved in the physiological regulation of oxytocin, prolactin, adrenocorticotrophic hormone (ACTH), and beta-endorphin release [2].

Gut bacteria including Lactobacillus, Lactococcus lactis, Enococcus ioni, Pediococcus parulo, Streptococcus thermophilus, Morganella morgani, Klebsiella pneumoniae, Enterobacter, Citrobacter freundi and Citrobacter produce histamine in significant quantities [81]. Histamine released by gastrointestinal microbes activates histamine receptors. Moreover, microbial histamine can be absorbed by epithelial cells and enter the blood circulation [114]. Systemic histamine alters the permeability of the BBB [115]. Study on mice brain showed that histamine increases the intake of IgG in the brain parenchyma via induction of BBB breakdown and stimulates astrocyte activation as shown by high level of glial fibrillary acidic protein (GFAP) and finally induces neural damages [115]. However, Lu et al. showed that histamine H1 receptor expression in endothelial cells reduces BBB permeability which importantly preserved cerebrovascular integrity. In addition, with the transgenic expression of H1 receptor in Hrh1-knok out (H1RKO) mice, they reported that the expression of this receptor in the BBB reduces the risk of autoimmune encephalomyelitis and multiple sclerosis

in mice [116]. De Palma et al. reported that colonization with the fecal microbiota of IBS patients in the germ free mice, increases visceral pain and mast cell activation. Moreover, these fecal bacteria from IBS individuals, synthesized high levels of histamine in cultures. Klebsiella aerogenes, harboring a type of histidine decarboxylase enzyme, was extracted as the main producer of this identified histamine in the feces of IBD patients. The stool microbiota of patients with IBS had increased amount of Klebsiella aerogenes, in compare to healthy individuals [117].

Acetylcholine

Acetylcholine is an important neurotransmitter that acts as a mediator in the central and peripheral nervous system to transmit excitatory signals. Disruption of cholinergic synapses is closely related to cognitive impairments and Alzheimer's disease [2]. Acetylcholine was first identified in the early 1900s in a study of ergot on wheat rye, though future studies discovered that the bacterium Bacillus acetylcholini in ergot produced acetylcholine instead of ergot [49]. After these studies, acetylcholine has been reported to be synthesized by several bacteria, such as Lactobacillus plantarum, Bacillus subtilis, Escherichia coli, and Staphylococcus aureus. Acetylcholine is catalyzed by choline acetyltransferase to choline and acetate. Peripheral choline can reach the CNS through carrier proteins of capillary endothelial cells [49].

The autonomous nervous system, which prepares the body for resting state and excitation, uses cholinergic synapses for ganglion neuron innervations. In the parasympathetic nervous system, outgoing axons from ganglion neurons to target cells also release acetylcholine to acts on muscarinic receptors. In the sympathetic nervous system, efferent projections primarily release noradrenaline, however acetylcholine is released in some synapses, including the projections to sweat glands [118]. Moreover, acetylcholine is an essential neurotransmitter in the neuromuscular junctions [14].

Interestingly, depressive phenotypes have been shown in mice lacking the α-7 subunit of the nicotinic acetylcholine receptor (Chrna7 KO mice). Fecal transplantation from Chrna7 KO mice to normal animals, induced depressive phenotypes, systemic inflammation, and damaged synaptic structures in the cortex neurons [12]. Also, the differences between the compositions of bacteria in the focal samples of depressed Chrna7 KO mice and normal mice were significant. Subdiaphragmatic vagotomy blocked the development of depressive phenotypes in mice treated with fecal transplantation from Chrna7 KO mice. These data show that the cholinergic synapses of vagus nerve in association with the composition of gut microbiota are involved in the development of depressive phenotypes [12].

Nitric oxide (NO)

NO is a small signaling molecule with a short half-life that modifies the function of various proteins directly and indirectly through post-translational modification resulting from their attachment to thiol groups and other amino acid sites. NO acts as a retrograde neurotransmitter in synapses, is important in increasing cerebral blood flow, and also plays a crucial role in intracellular signaling in neurons from regulating neuronal metabolism to dendritic spine growth [29, 49, 119].

Nitric oxide synthase (NOS) enzyme is involved in the production of NO in organisms. Inducible NOS is activated in response to microbial metabolites and pro-inflammatory cytokines released following infections and cellular damages [119]. These enzymes and some bacterial NOS synthesize NO from L-arginine in a process requiring oxygen and NADH, leading to the production of L-citrulline and NO. Bacterial NOS (bNOS) also catalyzes the synthesis of NO from arginine. This enzyme is present in several bacterial species (streptomyces, bacilli, Rhodococcuses, staphylococcus aureus, etc.) that live in the intestines, oral cavity, and vagina [120]. The classical L-arginine-NO pathway is associated with unconventional pathways of NO production. The unconventional pathway is characterized in the gut bacteria that gain nitrate and nitrite from digesting substance in gut and convert it to NO. Together with their own NO synthesis, gut microbiota, including probiotic strains (lactobacilli, bifidobacteria and Escherichia coli), induce NO generation in host epithelial cells [120].

NO is important in the communication between bacteria, in the regulation of biofilm formation and in the expression of bacterial genes involved in iron metabolism. Because NO increases the activity of the bacterial catalase enzyme, it has antioxidant properties [121]. NO increases bacterial resistance to antibiotics through chemical alteration of antibiotics or reduction of antibiotic-induced oxidative stress.

Microbial NO induces various effects on the host organism. For instance in the experimental organism, Caenorhabditis elegans (C. elegance), NO produced by Bacillus subtilis and Escherichia coli alters gene expression profile to increase heat resistance mechanisms and prolong the host's lifespan [121]. NO also is involved in the regulation of ionotropic glutamate receptors (iGluRs) and acid-sensitive ion channels(ASIC) in the CNS and ENS. NO modifies these proteins by S-nitrosylation of cysteine residue or by protein kinase G (PKG)-dependent phosphorylation [122].

Short chain fatty acids and neurotransmission

SCFAs such as butyrate, acetate, lactate, and propionate are produced in the large intestine by Bifodobacterium, Lactobacillus, Lachnospirase, Blavatia, Coprococcus,

Roseboria, and Faecium and are absorbed by epithelial cells [49]. SCFAs are organic acids with less than six carbons in their carbon chains. SCFAs bind to free fatty acid receptors (FFARs) which are G-protein coupled receptors. FFAR2 and FFAR3 are presented on the epithelial cells, ENS neurons, and sensory ganglia cells. FFAR3 in the ENS transmits signals produced by SCFAs directly to the CNS. FFAR3 also are on the adipocytes, interacts with SCFAs to modulate energy metabolism in skeletal muscles and liver [123]. Moreover, SCFAs have antimicrobial properties via the cathelicidin LL-37 mechanism and inhibiting the growth of Shigella in the gut. In fecal samples of IBD patients, low SCFA levels have been reported along with a decrease in Firmicutes and Bacteroidetes [124].

SCFAs can cross epithelial cells by specialized monocarboxylate transporters [125]. In addition, SCFAs can released from the membranes of endothelial cells and enter the circulatory system [124]. Butyrate protects intestinal barrier function by regulating the expression of the tight junction protein, claudin-1. Butyrate also is used as an energy source for colonocytes [126]. Butyrate also induces apoptosis in colon cancer cells and is critical for regulating oxygen metabolism in epithelial cells via increasing the expression of Aryl Hydrocarbon responsive genes including *Cyp1a1/CYP1A1* [123].

SCFAs have epigenetic effects through histone deacetylase (HDAC) inhibition. It has been reported that butyrate suppresses NLRP3 expression via increasing in acetylated histones due to HDAC inhibition [124]. Subsequently butyrate leads to autophagic cell death, activation of extrinsic and intrinsic apoptotic pathways, and decreased expression of pattern recognition receptors, and inflammatory cytokines [124]. Therefore, downregulation of NLRPs inhibits inflammasome formation, reduces NF-κB and mitogen-activated protein kinase (MAPK) signaling and ameliorates autophagy. This cascade of events counteracts autoimmune and inflammatory disorders. Moreover sodium butyrate inhibited colorectal cancer by reducing the gut microbiota dysbiosis and inhibiting colitis via suppression of NLRP3 and IL-1β proteins [124].

SCFAs regulate the concentration of neurotransmitters and neurotrophic factors. Acetate increses glutamate, and GABA levels and stimulates the production of anorexic neuropeptides in the hypothalamus [127]. Acetate increases the secretion of ghrelin and plays a role in reducing appetite [127]. Butyrate also has antidepressant properties and its lower levels in the fecal samples correlate with depressive behaviors [127]. Oral administration of butyrate ameliorates depression and depression-induced memory impairment and increases the levels of neurotrophic factors including BDNF, nerve growth factor (NGF), and glial drived neurotrophic factor (GDNF) in the hippocampus of rats [128]. Wang et al. reported that dysbiosis promoted subordinate state behaviors, while dysbiotic mice gained social dominance after microbiota transplantation via increasing butyric acid levels. Clostridium butyricum colonization was also sufficient to restore dominance. Increased social dominance has been associated with increased HDAC2 activity in neurons in the medial prefrontal cortex [129].

In addition, SCFAs increase the expression of tryptophan 5-hydroxylase 1. This enzyme is responsible for the synthesis of 5-HT, as well as tyrosine hydroxylase, which is involved in the biosynthesis of dopamine, adrenaline and noradrenaline [124]. Reigstad et al. reported that bacterial regulation of SCFAs is involved in Tph1 expression in Enterochromaffin cells and 5-HT production and homeostasis. Moreover, propionic acid increases the expression of CREB transcription. CREB pathway is necessary for the activation of TH I (tyrosine hydroxylase-1) gene transcription by propionic acid. At lower concentrations, propionic acid also causes the accumulation of TH mRNA and protein, which indicates an incensement in the cellular capacity to produce catecholamines [130]. Therefore, SCFAs play an important role in the brain neurochemistry by affecting the production of neurotransmitters. Although their exact functional mechanisms in the CNS is not clear, studies have revealed that SCFAs have a wide-ranging effect on important neurological and behavioral processes and are involved in significant stages of neurodevelopmental and neurodegenerative disorders [2].

A prebiotic, mixed bimono-galacto-oligosaccharide (B-GOS) was administered to rats as pharmacological intervention. It was observed that fermentation of B-GOS in the gut led to acetate production and alterations in HDAC in the CNS which could improve cognitive functions [131]. Moreover, acetate derived from intestinal microbes exhibited protective effects on microglial maturation and metabolic status in the brain [132]. Acetate also had a regulatory effect on gene expression profile of microglial cells. Absence of intestinal microbiota led to disruption of mitochondrial metabolism in CNS, which was improved by acetate supplementation [132, 133]. Propionate produced in the intestine prevented the neural damage caused by Alzheimer's disease and also repaired the tissue damage in the spinal cord injury model by reducing the secretion of pro-inflammatory cytokines [134]. In another study, a rodent model of nitroglycerin-induced migraine, oral administration of sodium propionate decreased hyperalgesia and pain attacks and ameliorated trigeminal nerve degeneration by reducing intestinal dysregulation [135]. SCFAs have anti-inflammatory properties by reducing cytochrome oxidase 2 (COX2) and NOS in the brain tissue, reducing pro-inflammatory cytokines in intestinal tissue, restoring intestinal mucosa alterations, and regulating neurotransmitter release in the ENS[135, 136]. It has been observed that butyrate produced in the gut is effective for modulating the transcription of neuroactivating

and neurotransmitter genes involved in beneficial social behaviors [137]. Butyrate improves behavioral alterations caused by stress-induced neural damage [133]. A promising role for SCFAs in bacterial CNS disorders is also evident. Pneumococcal meningitis is a fatal CNS infection associated with severe pathology. The reduction of neurotrophic factors in the hippocampus is related to infection. Interestingly, mice that received butyrate along with pneumococcal meningitis infection showed increased BDNF and GDNF levels after 10 days of pneumococcal meningitis induction [138]. Butyrate exerted neuroprotective effects in mice fed a high-fat diet by suppressing apoptosis and inflammatory cytokines [139]. Furthermore, butyrate inhibited HDAC and altered cytokines in a rodent model for schizoaffective disorders[120, 128]. Oral butyrate, through HDAC inhibition, significantly reduced epileptogenesis in temporal lobe epilepsy, so butyrate can be proposed as a strong therapeutic candidate to prevent chronic epilepsy. The NRF2 pathway is involved in the antiepileptic effects of butyrate [140, 141].

Conclusion and future perspective

Gut microbiota is importantly involved in the production of neuroactive components including GABA, glutamate, 5-HT, acetylcholine, histamine, NO and SCFAs. Neurotransmitters and neuromodulators produced by gut microbiota have some local effects including regulation of bowel movements and enterochromaffin cell and various systemic effects including modulation of immune responses and regulation of autonomic nervous system [5]. Moreover, these components or their metabolites can affect the activity of neurons and change the neural networks involved in behavior and neurodegenerative diseases. The relationship between gut microbial metabolites and the CNS activity has been highly controversial in the last decade. The microbiota in the gut produces a wide range of neurotransmitters and their precursors, which suggest a potential role in the regulation of neural and immune processes [2].

In this regard, the identification of host-derived neurochemical compounds under the influence of complex biological relationships between the gastrointestinal microbiota and the neural functions can be an important area for research [47]. Moreover, this is challenging to evaluate the direct effect of gut microbial metabolites on the CNS. One of the important aspect of this challenge is insufficient understanding about the rate of microbial metabolite accessibility to the brain as well as the lack of adequate information about the transporters and carriers involved in this pathway [81]. Some microbial neurotransmitters cannot cross the BBB, however their microbial precursors (including tyrosine and tryptophan) circulate in the body and reach the neurons and glial cells [14]. Indeed, it is difficult to distinguish direct effects of bacterial neuroactive components on the CNS from other communication mechanisms (including immunological or neural pathways). Some of these neurochemicals are produced by gut microbiota and interact with the host peripheral and central nervous system and immune system through circulation, some others affect gut microbial metabolism and enteric immune system locally, and some affect ENS neurons and vagus nerve afferent pathways [47].

The increase in the neurodegenerative diseases and the lack of effective drugs for many of these diseases raise the need for newer strategies involving alternative treatment methods. The microbiota gut-brain axis is an important regulator of CNS function, making it a potent target for ameliorating neurological diseases [47]. Understanding the complex relationship between gut microbiota and cognitive and neurological disorders can help to discover new therapeutic targets.

Dysregulation in the gut microbiome negatively affects the brain neurochemistry and dysregulates the intestinal barrier and the BBB. Animal studies and preclinical evidence support the use of microbiota to reduce neuroinflammation, mood disorders and cognitive impairment. However, providing microbiome-based therapies remains challenging and requires continued studies to uncover the complexities of the microbiota gut-brain axis and fully utilize their potentials. By manipulating the gut microbiota, we may have a new way to manage psychiatric disorders such as depression, anxiety and even neurological diseases such as Parkinson's and Alzheimer's [2]. More extensive and in-depth studies are needed to clearly understand the mechanisms of communication between the gastrointestinal tract and the brain, and to clarify the scope and limits of microbiota influence.

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