Biology

Metabolites from the Gut Microbiota and the Role in the Gut-Brain Axis

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The gut microbiota is highly capable of biotransformation, exposing the host to a wide variety of physiologically active compounds. These metabolites participate in signaling between the gastrointestinal tract and the central nervous system and may regulate physiological and pathological processes in the central nervous system. This bidirectional communication can take place in a variety of ways, including binding to receptors in the host brain, stimulating the vagus nerve in the gut, modifying central neurotransmission, and influencing neuroinflammation. The purpose of this article is to discuss the mechanism of action of microbial metabolites such as short-chain fatty acids, bile acids, and neurotransmitters in the gut-brain axis and to propose new strategies for treating related neurological illnesses from a gut microbiota regulation perspective.

Keywords: Gut Microbiota; Metabolites; Gut-Brain Axis; Central Nervous System; Neuromodulation

THE human gut microbiota contains between 500 and 1000 species of bacteria and around 2 million genes, which is more than 100 times the total number of human genes, many of which encode proteins that conduct metabolic tasks and create microbial-specific compounds (1). This function of the microbiota broadens the breadth of host biotransformation applications and the variety of substances that can be processed. This extensive metabolic capacity enables the microbiota to react with a variety of substrates that enter the gut, creating a huge number of metabolites, many of which are critical molecular precursors for the host. The gut-brain axis (GBA) is a signaling network that runs in both directions between the gastrointestinal tract and the central nervous system (CNS) (2). The autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal axis (HPA axis), and the immune system all contribute to this axis' signaling. Microbe-associated metabolites control CNS function and behavior via these diverse routes. Significant alterations in the structure of the gut microbiota have been documented in a variety of CNS illnesses, including autism spectrum disorder (ASD), anxiety, and depression (3). While the underlying association between microbial changes and neurological disease is not entirely understood, mouse studies have demonstrated that changes in the gut microbiome can affect mental psychology and behavior (4). This review focuses on the functions and mechanisms of bioactive chemicals generated by bacteria, such as short-chain fatty acids (SCFAs), bile acids (BAs), and neurotransmitters, in gut-brain transmission (**Figure 1**).
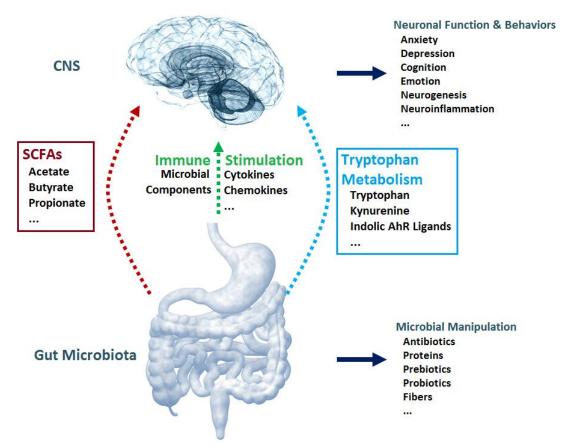
SCFAs

Figure 1. Interaction between Gut Microbiota and Control Nervous System.

SCFAs are small-molecule organic acids created by bacteria in the caecum and colon during anaerobic fermentation of dietary carbohydrates. They have a variety of effects on the central nervous system. The principal SCFAs created were acetic acid, propionic acid, and butyric acid, whereas isobutyric acid, valeric acid, and isovaleric acid were formed in trace levels (5). The feces of people with a high quality of life have a high concentration of *Faecalibacterium* and *Coprococcus*, which are gram-positive anaerobic bacteria capable of fermenting dietary fiber to create SCFAs (6, 7). In comparison to nondepressed controls, patients with major depressive disorder (MDD) had reduced SCFA levels in their stool, urine, and plasma (8, 9). Prebiotic-induced increases in SCFA have been shown to reduce depressive and anxious behaviors in mice and to alleviate cognitive impairment in dementia model mice (10, 11). SCFAs have also been implicated in a number of neurodegenerative and cerebrovascular illnesses, including Huntington's disease, Alzheimer's disease, Parkinson's disease, and stroke (12-15).

SCFAs can interact with GBA by binding to cell-expressed receptors and affecting the expression of host genes (16). SCFAs have the ability to bind to and activate the free fatty acid receptors 2, 3 (GPR43 or FFAR2), 2 (GPR41 or FFAR3), and 2 (GPR109A or HCAR2) (17). These receptors are expressed ubiquitously throughout the human body in a variety of tissues, including enteroendocrine cells, adipocytes, immune cells, and neurons. SCFA and GPR43 have host-dependent effects in the CNS, where microglia are resident macrophages that are dependent on the gut microbiota for maturation and function, and SCFA and GPR43 are essential for microglia homeostasis (18). Additionally, via influencing histone acetylation and methylation, SCFAs can exert epigenetic control on gene expression (19).

Enteroendocrine cells can indirectly modulate GBA by promoting the release of intestinal hormones and peptides by SCFA (20). SCFAs may also influence feeding behavior by increasing the release of anorectic hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and leptin (21-23). Along with acting on brain receptors, these appetite hormones also have an effect on the vagus nerve. The vagus nerve participates in the gut microbiota's control of hunger by showing that SCFA's anorectic impact was dramatically reduced in vagotomized mice (24, 25). SCFAs can also regulate appetite via central processes. Enteric acetate can pass the blood-cerebrospinal fluid barrier and exert a direct effect on appetite regulation in the hypothalamus via neuropeptide expression changes (26).

SCFAs also influence GBA via the maintenance of gut and blood-cerebrospinal fluid barrier function (27). Butyrate has been shown to increase tight junction protein expression and stabilize the intestinal mucosal barrier function, hence limiting the passage of bacteria and other pathogens from the gut to the blood (28). Increased permeability of the intestinal barrier increases host exposure to bacterial lipopolysaccharide (LPS), resulting in chronic inflammatory responses. Chronic inflammation is implicated in a variety of neuropsychiatric illnesses, including depression and anxiety, and pro-inflammatory cytokines have been shown to impact neurotransmission and behavior. Consistent with their role in the gut, SCFAs can help maintain the blood-cerebrospinal fluid barrier's integrity by boosting the expression of tight junctions (29). While SCFAs have been shown to have a number of direct and indirect effects on the CNS, the evidence supporting their ability to alleviate neurological disorders remains inconsistent, and a greater understanding of the underlying mechanisms is required.

BAs

BAs are cholesterol-derived steroids that have direct and indirect effects on the central nervous system. The two primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA), are produced in the liver and subsequently released into bile together with glycine or taurine (30). BA is released into the gut in response to a feeding stimulus, where it is reabsorbed in 95% of cases. A limited amount of BA is carried to the colon, where it is 7-dehydroxylated by the gut flora to form secondary BAs, especially deoxycholic acid (DCA) and ursodeoxycholic acid (UDCA) (31).

As with SCFA, BA can operate as a signaling molecule, activating the farnesoid X receptor (FXR), the G protein-coupled bile acid receptor 5 (TGR5), the pregnane X receptor (PXR), and the vitamin D receptor (VDR) (32, 33). At the same time, BA regulates glucose homeostasis, lipid metabolism, and energy expenditure, among other metabolic processes, with considerable influence on host metabolism (34). Changes in the function of the gut microbiota can modify the makeup of the BA pool and thus its signaling capacity (35). BAs have been discovered in the brains of humans and rodents, and their receptors and transporters are expressed in CNS cells (36, 37). This shows that BAs may function as signaling molecules in the CNS. Although our understanding of this signaling potential is limited at the moment, it has been demonstrated that deletion of FXR disrupts several neurotransmitter systems and alters affective, cognitive, and motor abilities in mice (38).

By breaking tight junctions, BAs can directly modify the permeability of the gut and blood-cerebrospinal fluid barrier, consequently impacting brain function (39). Neither DCA nor CDCA have been shown to increase the permeability of the blood-cerebrospinal fluid barrier, but UDCA has been shown to protect brain endothelial cells by inhibiting apoptosis (40). BA may also have an effect on the immunological response, as UDCA has been shown to diminish neuroinflammation in rats by binding to the TGR5 protein produced by microglia (41). Alternatively, BA can communicate with the CNS via activating FXR in the gut, hence increasing the production of intermediate molecules such as GLP-1 and fibroblast growth factor 19

(FGF19) (42). GLP-1 has the ability to enter the bloodstream, activate brain receptors, and transmit to the central nervous system via vagal afferent fibers (43). Through receptors expressed in the hypothalamic arcuate nucleus (ARC), FGF19 can inhibit agouti gene-related protein (AGRP) and neuropeptide Y (NPY) neurons (44).

Neurotransmitters

Cellular neurotransmitters are also found in the gastrointestinal system and are involved in the regulation of intestinal motility, cell secretion, and cell signaling (45). The gut microbiota is capable of synthesizing a number of neurotransmitters: *Lactobacillus* and *Bifidobacterium* make gamma-aminobutyric acid (GABA) (46, 47), *E. coli* produces serotonin (5-HT) and dopamine (DA) (48), and *Lactobacillus* produces acetylcholine (49). Numerous bacteria generate and release additional neuroactive. The gut microbiota has been shown to influence neurotransmitter levels in mouse models, with microbial depletion dramatically lowering neurotransmitter levels such as DA and GABA (50). It is unknown whether circulating neurotransmitters originate directly from the microbiota or the host, as microbial metabolites (e.g. secondary BA, SCFA) have been shown to activate enterochromaffin cells to create neurotransmitters and enter the blood circulation (51).

Another method in which the gut microbiota influences host neurotransmission is through the regulation of neurotransmitter precursors. Tyrosine is a precursor of levodopamine (L-DOPA), a neurotransmitter that can be decarboxylated to generate dopamine (DA). DA is then converted to other catecholamines, including norepinephrine and epinephrine. Tyrosine can be received by food or phenylalanine, two amino acids that can be broken down into a variety of compounds by gut microorganisms, altering their availability to the host. The gut microbiota also regulates the conversion of L-DOPA to DA, with *Enterococcus* and *Lactobacillus* expressing tyrosine decarboxylase and participating in the decarboxylation of L-DOPA (52). This has significant implications for Parkinson's disease treatment, as inhibiting peripheral L-DOPA metabolism can enhance brain L-DOPA concentrations.

By activating the vagus nerve, gut microbial metabolites can also alter CNS transmission. The vagus nerve is engaged in GABA transmission and *Lactobacillus rhamnosus* can modify the expression of central GABA receptors while alleviating anxiety and depression-like symptoms in vagotomized mice (53). Gut neurotransmitters can potentially influence brain function by influencing the immune system, with 5-HT activating immune cells and GABA reducing intestinal inflammation (54). These findings imply that neurotransmitters produced directly or indirectly by gut bacteria have an effect on host psychology and behavior via their binding to specific receptors in the CNS or on peripheral cells. There may be additional active molecules similar to neurotransmitters that must be discovered and explored further. This neurotransmitter metabolic communication between the gut microbiota and the host is inherently bidirectional: in addition to synthesizing neurotransmitters capable of altering host physiology, the gut microbiota responds to host-produced neurotransmitters, affecting the microbiota's growth and abundance (55).

Additional Metabolites of the Gut Microbiota

Numerous other compounds from the gut microbiome may potentially participate in GBA communication. Choline is an essential nutrient that is derived mostly from lecithin and carnitine in the diet, although it is also generated in the liver in modest amounts in humans (56). Choline plays a role in biofilm formation, epigenetic regulation, and cell signaling. It is a precursor of acetylcholine and the cell membrane components phosphatidylcholine and sphingomyelin. Although choline is not a bacterial product, it can be broken down by the gut microbiota into a variety of metabolites, including betaine and trimethylamine (57, 58). Because the gut microbiota's metabolism of choline depletes the available choline in the host, an excess of bacteria consuming choline results in a choline deficit, which increases the risk of metabolic disorders and cardiovascular illness, as well as affects the host's neuropsychiatric behavior (59). Additionally, choline provides a significant supply of methyl groups, which are necessary for proper DNA methylation regulation. The reduction of choline by bacteria decreased methyl availability and DNA methylation in various organs, including the brain.

Lactic acid is an organic acid produced by human metabolic processes and by *Lactobacillus*, *Bifidobacterium*, and *Proteus* fermentations of dietary fiber (60). Although lactate concentrations in the gut are modest, they can enter the bloodstream and penetrate the blood-cerebrospinal fluid barrier. Lactic acid is well known as a signaling molecule in the brain; it serves as an energy source for neurons, contributes to synaptic plasticity, and is involved in memory formation (61). Astrocytic lactate acts as an energy substrate to fuel learning-induced de novo neuronal translation critical for long-term memory (62). Lactate influences emotional behavior via directly activating G-protein-coupled receptor 81 (GPR81), which is found in the hippocampus, neocortex, and cerebellum (63). Lactate regulates lipid and glucose metabolism, has anti-inflammatory effects via GPR81 activation, and inhibits GABAergic neurotransmission (64, 65). Although microorganisms have been shown to affect central lactate concentrations in germ-free mice, the magnitude of these effects on lactate and mood remains unknown (66).

Vitamins are synthesized in the gut by the gut microbiota, and human vitamin metabolism is highly dependent on the availability of bacteria (67). B vitamins such as riboflavin (B2), folic acid (B9), and cobalamin (B12) are required for central metabolic responses and their shortage can appear as a variety of neurological symptoms such as aberrant motor function, sleep memory abnormalities, and psychological-emotional symptoms (68). The microbiome is estimated to provide 31% of the recommended B12 intake for humans, and B12 deficiency has been linked to a variety of psychiatric and neurological diseases, including mental retardation, memory impairment, attention deficit, and dementia (69, 70).

Conclusions

The bidirectional communication between the gut microbiota and the mammalian host is the result of these two complimentary systems co-evolving, and this information exchange can take place in a variety of ways. Microbial metabolites have the potential to alter the CNS directly or indirectly, thus impacting host behavior and cognitive function. Our understanding of the pathogenic mechanisms behind GBA will continue to grow as we delve more into the multifarious relationships between microbial metabolites and CNS disorders. In the future, microbial metabolites having the potential to play critical roles in CNS illness treatment and prevention may be exploited.■

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