Modulatory Effects of Gut Microbiota on the Central Nervous System: How Gut Could Play a Role in Neuropsychiatric Health and Diseases

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Gut microbiome is an integral part of the Gut-Brain axis. It is becoming increasingly recognized that the presence of a healthy and diverse gut microbiota is important to normal cognitive and emotional processing. It was known that altered emotional state and chronic stress can change the composition of gut microbiome, but it is becoming more evident that interaction between gut microbiome and central nervous system is bidirectional. Alteration in the composition of the gut microbiome can potentially lead to increased intestinal permeability and impair the function of the intestinal barrier. Subsequently, neuro-active compounds and metabolites can gain access to the areas within the central nervous system that regulate cognition and emotional responses. Deregulated inflammatory response, promoted by harmful microbiota, can activate the vagal system and impact neuropsychological functions. Some bacteria can produce peptides or short chain fatty acids that can affect gene expression and inflammation within the central nervous system. In this review, we summarize the evidence supporting the role of gut microbiota in modulating neuropsychological functions of the central nervous system and exploring the potential underlying mechanisms.

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Key Words
Anxiety; Brain-Gut axis; Depression; Gut microbiota; Stress

Introduction

Over the past decade, experimental data has suggested a complex and bidirectional interaction between the gastrointestinal (GI) tract and the central nervous system (CNS), the so-called “Gut-Brain axis.”1 Derangements of this axis (typically in the brain-to-gut direction) have been implicated in the pathogenesis of symptoms of many functional bowel disorders such as the irritable bowel syndrome (IBS).2,3 In recent years, however, emerging knowledge about gut microbiota has compelled us to re-examine the directionality of this process.4-11 The presence of a healthy and diverse gut microbiota appears to be imperative not only for normal gastrointestinal function, but may also influence a variety of systemic and mental processes. Our understanding of the interaction between gut microbiota and the CNS is incomplete and only at its starting point. In
this article, we will review the current evidence in the literature that points towards a role for gut microbiota in various developmental and psychiatric disorders such as anxiety, depression, schizophrenia and autism. We will also review the possible mechanisms through which gut microbiota might be involved in the pathogenesis of these disorders.

The gut microbiota at infancy is usually diverse and highly variable, trending towards its final composition between 6-12 months of age,\(^{12}\) reflecting a combination of genetic factors, maternal health, method of delivery, subsequent nutrition, and maternal and postnatal exposure to antibiotics.\(^ {13-16}\) Germ-free mice show developmental abnormality in the GI tract that can be reversed by reconstructing the gut microbiota, suggesting a role for gut microbiota in postnatal development of the enteric nervous system (ENS).\(^ {17,18}\) This period is also critical for the development of the CNS leading to the suggestion, based on experimental models, that gut microbiota may be an important factor participating in the development of cognitive, emotional, and behavioral processes shortly after birth.\(^ {19,20}\) For example, germ free mice show significant alteration in the concentration of the key neurotransmitters such as serotonin in the hypothalamus.\(^ {21}\) Alterations in serotonin concentration can in turn affect several aspects of the development of central nervous system, including synapse formation and connectivity between various regions in the central nervous system and their plasticity.\(^ {22}\) The picture becomes more complicated because serotonin is also a key factor in the development of the ENS, and alteration of its concentration in the blood may modulate ENS structure and function;\(^ {23}\) in turn this can affect the composition of gut microbiota, thus potentially providing a closed loop system for mutual regulation of the 2 nervous systems.

**Microbiota and Modulation of the Central Nervous System—General Mechanisms**

A central issue in any discussion on this topic relates to the question of how microbes that live in the colon can influence a remote organ such as the brain. We are just beginning to scratch the surface of this problem, but theoretically there are multiple, possible overlapping mechanisms, that amplify each other in short as well as long loops (Figure). With the exception of the microbe-epithelial interface, all these mechanisms imply some degree of access of either the microorganism itself or its products to the deeper layers of the gut, in turn activating a myriad of factors. Thus, as is being increasingly recognized, gut permeability is perhaps the most important factor in initiating microbial interactions with the rest of the body. These factors will now be briefly described.

**Effect of Gut Microbiota on Intestinal Permeability**

The normal intestinal barrier consists of multiple layers that includes gut flora and external mucus layer, epithelial layer, and lamina propria, to name them from outside to inside.\(^ {24}\) Mucus is secreted by goblet cells and acts as a mechanical protective layer that also contains digestive and antibacterial enzymes and antibodies, and will hydrate the epithelial layer and helps it regenerate.\(^ {25}\) The epithelial layer, in addition to playing an important part in absorption of the nutrients, also serves as a physical barrier due to the tight junctions between the epithelial cells. Furthermore, enteroendocrine cells are distributed through the epithelial layer.\(^ {26}\) This layer along with lamina propria is also the host of the largest repository of im-
immune cells in the body which is known as mucosa-associated immune cells. The population of immune cells in the epithelial layer is mostly CD8+ lymphocytes, while the immune cells in the lamina propria are more diverse and consisted of macrophages, plasma cells, antigen presenting cells, and mast cells in addition to lymphocytes.27

Normal gut microbiota is essential in preventing colonization of the harmful bacteria by competing with them for vital resources such as food and growth factors. If the population of normal gut microbiota is reduced, for example due to antibiotic therapy, pathogenic organisms find the opportunity to colonize the gut epithelium. Toxins produced by pathogenic organisms and the focal inflammation created by immune responses to them can increase gut permeability.28 For example, Clostridium difficile that can colonize the gut in the absence of normal gut flora produces an enterotoxin that increase the gut permeability by impairing epithelial tight junctions through damaging aggregation of actin filaments.29 Another way that gut microbiota can enhance the function of the intestinal barrier is through protecting and improving epithelial tight junctions. Most of the evidence that supports this role of microbiota in the normal function of the intestinal barrier comes from studies that have shown that probiotic treatment can reduced gut permeability in models of GI tract disorders. For example, in experimental models of colitis, several species of probiotics including Lactobacillus, Escherichia coli, and Bifidobacterium can reduce gut permeability by upregulating trans-membrane proteins that are important in preserving tight junctions between epithelial cells.30-33 It has also been shown that treatment with these probiotics can enhance mucus production and consequently improve the physical barrier protecting the epithelial layer.34,35 Products of bacterial fermentation can also play an important role in maintaining the intestinal barrier. It has been shown that short-chain fatty acids can act as trophic factors for mucosal and epithelial layers. Also, normal bacteria can produce trophic peptides such as glucagon-like peptide-2 (GLP-2) that can enhance the proliferation of crypt cells and villi.36-37

Impaired intestinal barrier function and consequent increased gut permeability can lead to increased translocation of gut bacteria across the intestinal wall and into the mesenteric lymphoid tissue.34 Increased exposure of the ENS or mucosal immune cells to bacteria can provoke an immune response that can lead to release of inflammatory cytokines and activation of the vagus nerve and spinal afferent neurons. Inflammatory cytokines and the vagal system in turn can modulate the activity of the CNS and ENS.38,39 Furthermore, increased permeability of the gut can also increase the translocation of metabolic products such as lipopolysaccharide (LPS) or neuro-active peptides created by the bacteria that can alter the activity of the ENS and CNS.40 For example, LPS can activate Toll-Like receptors that are present on epithelial cells, enteric neurons, sensory afferent neurons in the spine, and various cells in the brain, modulating their activity and affecting the function of both ENS and CNS.41-44

As mentioned above, the interaction between the gut and brain is bidirectional- the CNS can affect gut permeability and increased gut permeability in turn can alter CNS function. In both animal models of stress and human subjects who were exposed to stress, the intestinal barrier is impaired. It has been shown that both acute and chronic stress can reduce water secretion and increase ion secretion in the intestine, and therefore impair the physical protection of the epithelial layer and lamina propria against adhesion of harmful bacteria and noxious chemicals.45-47 Activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased production of corticotropin-releasing factor (CRF), altered activation of the vagal system, mast cell activation, and release of certain cytokines such as IFN-γ, TNF-α, and IL-4 are suggested culprits in this interaction.48-54 Additionally, stress can change the function of mucosal-associated immune cells and cause increased antigenic and bacterial uptake.55,56 Multiple studies have been published that have shown that the composition of gut microbiota is changed in the face of acute or chronic stress, and this in turn can subsequently change the function of intestinal barrier as explained above.57 There is limited data regarding the changes in intestinal barrier or GI physiology and the underlying mechanisms of it in neuropsychiatric disorders. It has been reported that the frequency of GI symptoms is increased in children with autism but the mechanism is not known.58 In patients with schizophrenia, there are increased intestinal permeability and change in intestinal function.59 Emotional stress and depression have been shown to increase prevalence of disorders of the digestive system.60

Effect of Bacterial Metabolites on the Central Nervous System

Theoretically, bacterial products like other luminal contents, can be absorbed into the blood stream and affect remote sites in the brain. Alternatively, or in addition, bacteria can interact with local elements in the gut such as nerves or endocrine cells that then in turn signal to the brain. Experimental data suggest that a variety of biologically active products derived from gut microbiota can directly or indirectly influence the brain. These include well known, although non-specific, factors such as LPS, which can influence the CNS directly by activating Toll-like receptor 4 on microglial cells
causing release of inflammatory cytokines by them within the CNS, or indirectly by inducing release of inflammatory cytokines from the GI tract. LPS can cause behavioral changes during an acute illness or cause a delayed change in mood after sickness. IgA and IgM against LPS of gut bacteria are found in the blood of patients with depression or chronic fatigue syndrome, suggesting a potential role for LPS in the pathogenesis of these diseases. Other bacterial products reflect the role of colonic microbiota in the fermentation of undigested carbohydrates to short chain fatty acids (SCFA). SCFAs can act as signaling molecules by binding to G protein-coupled receptors, Gpr41, and Gpr43. It has been shown that Gpr41 and Gpr43 receptors are abundantly present on the surface of gut epithelial and immune cells and are activated by SCFAs. This activation can provoke an inflammatory and immune response that can be helpful in the setting of an acute infection, but dysregulation can produce an exaggerated response leading to increased gut permeability and increased absorption of neuro-active metabolites. SCFAs can also directly activate the sympathetic nervous system through Gpr41 receptors that are found on sympathetic ganglionic neurons. Furthermore, it has been shown that SCFAs can pass through the blood-brain barrier and influence behavior, neural signaling, the production of neurotransmitters and, ultimately, behavior.

Change in Central Nervous System Neurotransmitters

Studies have reported on CNS neurotransmitter changes in response to more specific biological factors that may be restricted to certain types of bacteria, thus providing a mechanistic link to changes in microbial metabolism. Germ free mice have elevated levels of dopamine and tryptophan in striatum, but not serotonin or gama-aminobutyric acid (GABA). Another study has reported increased levels of serotonin in the hippocampus of germ free mice. It has been recently shown that indigenous bacteria from gut of mice and humans can induce serotonin production in enterochromaffin cells and increase the level of serotonin in blood. Histaminergic pathways are found in areas of the limbic system and also areas in the brain heavily involved in cognitive functions. Lactobacillus reuteri, a commensal in the human gut, expresses histidine decarboxylase that converts histidine to histamine. Therefore, a change in the population of this gut microbe can potentially modulate the levels of circulating histidine and histamine, which in turn can affect the concentration of CNS histamine.

Gut Microbiota and Specific Neuropsychological Processes and Phenotypes

Vagus Nerve as a Mediator of the Effect of Gut Microbiota on the Central Nervous System

One potential unifying mechanism through which these various processes can influence the activity of CNS is via vagal nerve activity. In animal models, administration of Campylobacter jejuni into the gut can induce anxiety like behavior. These animals show increased fos activity in vagal sensory nucleus and other areas in brain stem related to this nucleus. Furthermore, intraduodenal administration of a non-pathogenic bacterium, Bifidobacterium longum, is anxiolytic but also requires an intact vagus. Another anxiolytic probiotic, Lactobacillus rhamnosus, results in region specific change in the expression of GABA receptor subunits. GABA type B subunit 1 mRNA showed the opposite changes. These effects were abolished by subdiaphragmatic vagotomy. The vagus nerve might also be involved in behavioral effects of microbial LPS. It is known that LPS can induce depressive-like and anxious behavior in animal models. Studies have shown that rat or mice that undergo vagotomy before exposure to LPS, do not show the expected cytokine profile changes in the CNS or the same depressive or anxious behavior. However, the role of the vagus may be restricted to specific models or pathogenic processes. Thus, mice infected with the noninvasive parasite Trichuris muris exhibit anxiety-like behavior, associated with colitis and decreased hippocampal brain derived neurotrophic factor (BDNF) expression, along with increases in circulating TNF-α and IFN-γ, as well as the kynurenine and kynurenine/tryptophan ratio. Although anxiety behavior was normalized by both anti-inflammatory agents and the probiotic B. longum, it persisted in infected animals after a vagotomy.

Stress Response and Anxiety

It has been shown that stress can alter gut permeability as well
as the composition of gut microbiota. In a mice model of stress due to social disruption, Bacteroids are reduced while Clostridia are increased, resulting in a pro-inflammatory change in the profile of cytokines produced by gut microbiota. More recently, the interaction between stress and gut microbiome has been shown to be bidirectional, and that gut microbes can modulate the stress response and the activity of the corticosterone pathway orchestrated by the HPA, a key stress regulatory system in the CNS. Germ-free mice show an exaggerated HPA response to stress and the amount of CRF released in response to stress. Introduction of B. infantis corrects the abnormal response of the HPA to stress in this model, but only if administered within the first 6 weeks of age in this model. This finding is in line with the idea that the effect of microbes on the host is confined to a window of opportunity during neonatal life, and the presence or absence of any specific microbe during that window might have a durable and long-life effect. Germ-free mice also show reduced anxiety in behavioral tasks which can be reversed by re-introduction of gut microbiota. An anxiety prone behavioral phenotype is also seen in germ-free rats, along with elevated CRF expression in the hypothalamus and reduced glucocorticoid receptor (GR) expression in the hippocampus, (GR in this region regulates the CRF response in a negative feedback loop) and along with a lower dopaminergic turnover rate in specific CNS regions.

Exposing rats in the early postnatal period to stress by maternal separation also leads to a change in composition of gut microbiota, which is linked to a long-term increase in anxiety-like behavior. Introducing probiotics containing Lactobacillus in early stages of separation can ameliorate the effects of separation on HPA and reduce the corticosterone release. Other events that lead to a change in the composition of gut microbiota such as infection or use of probiotics can also change the level of anxiety.

Further, it is shown that the behavioral phenotype of anxiety-prone strains of mice is also dependent on their existing microbiota. For example, BALB/c mice exhibit a highly anxious phenotype that does not show much exploratory locomotion in a new environment, while NIH Swiss mice show less anxiety and more exploratory motions in the same environment. Transferring gut microbiota from one of the species to another can change their behavior to the one typical of the donor. In another study, described above, injecting mice with Trichuris led to anxiety related behavior in mice, an effect that was reversed by administration of B. longum but not lactobacillus showing a species specific effect for gut microbiota. The underlying mechanisms, however, remain unclear as this was not vagally mediated. Further, anti-inflammatory agents normalized behavior and reduced cytokine and kynurenine levels without an effect on BDNF expression, whereas B. longum normalized behavior and BDNF mRNA but did not affect cytokine or kynurenine levels.

It has also been suggested that the modulatory effects of gut microbiota on the level of anxiety are exerted through alterations in serotonin signaling. This idea is in part based on the finding that reduced anxiety-like behavior in germ free mice is associated with increased expression of serotonin receptor 1A in the hippocampus. However, experimental data from mice showed that while reintroduction of gut microbiota to germ free mice can normalize the anxious behavior, it fails to reverse the changes in serotonin levels in the hypothalamic-pituitary pathway. Another mechanism that has been described is increased release of the adreno-corticotropin hormone from the HPA axis in response to stress. A link between hypersensitivity of the HPA axis and reduced BDNF expression in the prefrontal cortex and hippocampus, and subsequently reduced N-methyl-d-aspartate receptor expression in germ-free mice is observed and was thought to play a role in regulation of HPA activity. Alteration of BDNF expression in the hippocampus was seen in mice that were treated with non-absorbable antibiotics such as neomycin, but not in mice treated with systemic intraperitoneal injection of antibiotics, suggesting that this effect is a result of elimination of gut microbiota, not the antibiotic treatment itself.

**Gut Microbiota and Depression**

In animal models of depression, it has been reported that the composition of gut microbiota has been changed. These data however, have not been validated in patients with depression. In one study on human subjects with depression, no significant difference in the composition of gut microbiota was found between depressed patients and a control group. However, another recent study examined the composition of fecal microbiota in 46 patients with depression and 30 healthy controls, and reported significant differences with increased population of Bacteroidetes, Proteobacteria, and Actinobacteria, and decreased population of Firmicutes in patients with depression. Other evidence that might suggest a role for gut microbiota in the pathogenesis of depression is from studies that have shown certain probiotics can alleviate depressive symptoms in rodent models. Rats that are exposed to stress in early stages of life show behavior traits that are consistent with mood disorder that persists through their adulthood. Treatment of these rats with probiotics containing B. infantis can reduce the mood disturbance and correct the abnormalities in the concentration of norepinephrine in the brain. L. rhamnosus and L. helveticus strains have also been reported to ameliorate maternal separation-induced depression.
through a corticosterone and GABA mediated mechanism. In a model of depression post myocardial infarction, treatment with probiotics including *L. helveticus* and *B. longum* has been reported to reduce the depression, presumably by reducing the pro-inflammatory cytokines and gut permeability. Some antibiotics such as minocycline have been shown to be effective in treatment of depression. Their mechanism of action is not exactly understood, and a potential role for changes in gut microbiota has been proposed, although not studied in detail.

**Gut Microbiota and Cognition**

In mice, elimination of gut microbiota can alter performance in tasks that require intact spatial memory, hippocampal function or working memory. Similarly, altering the composition of gut microbiota in mice by infection or dietary modifications also can change the performance of the animal in memory tasks. For example, adding lean beef to the mice diet will alter composition of gut microbiota and will improve their performance in cognitive tasks. In this experiment, a temporal relationship with dietary induced changes in gut microbiota and working memory performance was reported. Mice infected with *Citrobacter rodentium* show impairment of cognitive function that can be reversed with probiotics. Diabetic rats are known to have impaired memory and learning due to impaired long-term potentiation and long-term depression in hippocampal synapses. It has been reported that treating the diabetic rats with a mixture of *Lactobacillus acidophilus*, *Bifidobacterium lacti*, and *Lactobacillus fermentum*, can ameliorate this effect of diabetes on memory and behavior, as well as electrophysiological changes. Evidence of similar effects in humans is limited but it has been shown that in normal human subjects, consumption of probiotics can alter the functional activity of the areas in the brain that are involved in cognitive functions.

**Emerging Areas**

Given the explosion of interest in the microbiota and the gut-brain axis, it is not surprising that investigators are moving beyond more traditional phenotypes such as anxiety/depression to other neuropsychological syndromes including schizophrenia and autism. Increased gut permeability and translocation of gut bacteria has been shown in schizophrenic patients. The fundamental cause of this is unknown and could include both the controversial association with gluten sensitivity and celiac disease as well as primary changes in gut microbiota. These theories may not be mutually exclusive as it is possible that certain compositions of gut microbiota can lead to changed metabolism of certain food products such as gluten, and subsequent production of neuroactive peptides, increased absorption of these products due to local inflammation, and alteration of dopaminergic and serotonergic pathways in individuals who are genetically susceptible to schizophrenia. Germ-free mice tend to show a schizoid type behavior, not spending more time in a chamber with another mice in it when put in a 3-chamber sociability test. In a mice model that shows behavioral changes that resemble schizophrenia, treatment with *Bacteroides fragilis* can ameliorate the symptoms. However, a randomized clinical trial of a probiotic regimen containing *Lactobacillus* and *Bifidobacterium* strains failed to show any significant change in the psychiatric outcome measures was observed.

Another area in which information is rapidly evolving is that of autism spectrum disorders (ASD). In a study in rodent model, it was found that the composition of gut microbiota in animals with ASD-like behavior is significantly changed compared with control animals. These changes were similar to those found in human patients with most changes observed in *Clostridia* and *Bacteroidia* species (see below). Treatment of these animals with *B. fragilis* restored the altered composition of gut microbiota and significantly reduced the stereotypical behavior. It has been hypothesized that these effects are mediated by specific chemical metabolites produced by gut microbes. For example, in the same rodent model of autism, elevated circulating levels of 4-ethylphenylsulfate normalized after probiotic treatment. However, systemic administration of this metabolite did not cause autistic behavior and only created anxiety-related behavior. Other mechanisms involve changes in the availability of tryptophan and histidine, and consequent alterations in serotonin and histamine in the CNS. Propionic acid, a SFCA that is produced by gut microbiota can also induce significant changes in social development and behavior and create a similar picture to ASD. Intraventricular administration of propionic acids to rats can cause structural abnormalities similar to those found in patients with ASD.

Some of these findings have parallels in humans. Children with ASD also show altered composition of gut microbiota with a reduced population of *Bacteroides* and increased levels of *Clostridium* species. It has been postulated that altered gut microbiota in children with ASD can lead to potential imbalances in metabolism of carbohydrates and amino acids in the gut, and altered levels of metabolites in the blood and urine. To test this hypothesis, a few studies of metabolic products have been performed in patients with ASD. For example, studies using metabolomics techniques have reported a different urinary amino acid profile in patients with ASD compared to healthy subjects with lower anti-oxidant levels in the...
urine, and abnormal levels of hippurate and N-methyl nicotinic acid in children with ASD.\textsuperscript{137,138} Hippurate is an end-product of the metabolism of dietary proteins and phenolic acids, and is formed by the liver from benzoic acid.\textsuperscript{139} Benzoic acid is a product of protein metabolism by gut microbiota, and altered hippurate level points towards altered metabolism in protein, potentially caused by altered gut microbiota.\textsuperscript{140} Another study has reported significant difference in children with autism and normal children in the fatty acid composition of phospholipids, with autistic children having an increased level of most of the saturated fatty acids, except for propionic acid, and a decreased level of polyunsaturated fatty acids.\textsuperscript{141} This change in composition of fatty acids can lead to abnormalities in oxidative stress, or cause mitochondrial dysfunction that might play a role in pathogenesis of ASD.\textsuperscript{142}

Another bacterial genus that has been linked to autism is \textit{De-sulfovibrio}. This microbe is found with significantly higher prevalence in children with autism compared to developmentally normal children, and has sulfur-reducing properties that can explain the known sulfur deficiency in children with autism.\textsuperscript{143} Sulfate deficiency can potentially lead to inefficient detoxification through sulfation, leading to accumulation of neurotoxins. Increased gut permeability and elevated level of bacterial metabolic products such as LPS leading to increased proinflammatory cytokines such as IL-6 have also been shown in children with ASD.\textsuperscript{144}

A few small clinical trials have shown beneficial effects for gluten free and casein free diets on symptoms of children with ASD\textsuperscript{145,146} that could potentially be attributed to the change in gut microbiota.\textsuperscript{4,8,19,61,128,147} Furthermore, in children with autism, the frequency of GI symptoms is increased\textsuperscript{148,149} and has been attributed to a low-grade chronic inflammation in the GI tract caused by altered gut microbiota. In a clinical study, oral vancomycin was used as a minimally absorbed antibiotic to treat the GI problems, based on this theory. Interestingly, in addition to improvement in GI symptoms, autistic behavior was also improved in these children.\textsuperscript{150}

**Conclusions**

The influence of gut microbiota on several aspects of CNS function is increasingly supported by a growing body of experimental data. The mechanism of this influence is complex and involves multiple direct and indirect pathways. Increased gut permeability appears to be the cornerstone of the microbiome-gut-brain interaction. This provides a pathway for gut bacteria and their metabolic products to access the immune system, ENS, the blood stream, and centripetal neural pathways. Much of this evidence comes from recent studies, and considerable work has to be done to validate these findings in humans before we can understand how best, if at all, to modulate the gut microbiota for clinical benefit.

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