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Review article

Gut-Brain Axis Role of the Microbiome in Regulating Normal Physiological Functions

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Abstract

The Gut-Brain Axis (GBA) represents a complex, bidirectional communication network between the gastrointestinal tract and the central nervous system. Accumulating evidence highlights the critical role of gut microbiota in modulating neural, endocrine, and immune signaling pathways that influence both normal physiological functions and behavior. Microbial metabolites such as Short-Chain Fatty Acids (SCFAs), neurotransmitter precursors, and immune-modulating molecules play integral roles in neurodevelopment, stress response, and cognition. This review explores current insights into the mechanisms underlying the gut-brain axis, emphasizing the regulatory function of the microbiome in maintaining homeostasis and its potential therapeutic implications for neuropsychiatric and neurodevelopmental disorders.

Keywords: Gut-brain axis, Microbiota, SCFA, Neuroimmune interaction, Homeostasis, Cognition

Introduction

The human Gastro Intestinal (GI) tract is colonized by a vast and dynamic community of microorganisms—bacteria, viruses, fungi, and archaea—collectively known as the gut microbiota. This microbial ecosystem, comprising an estimated 100 trillion cells, exceeds the number of human cells in the body and encodes a genomic repertoire (microbiome) vastly larger than the human genome itself. While historically regarded primarily for their roles in digestion and metabolism, gut microbes are now recognized as essential contributors to host development, immunity, and neurological function [1].

A particularly transformative area of research in physiology is the characterization of the Gut-Brain Axis (GBA)—a complex, bidirectional communication system that integrates signals between the gut microbiota and the Central Nervous System (CNS). This axis involves multiple physiological pathways, including neural (e.g., vagus nerve, enteric nervous system), endocrine (e.g., Hypothalamic-Pituitary-Adrenal [HPA] axis), immune, and metabolic routes, forming a multidimensional regulatory network that maintains systemic homeostasis [2].

The gut microbiota exerts profound effects on brain function by producing and modulating a wide array of bioactive molecules, such as Short-Chain Fatty Acids (SCFAs), neurotransmitters (e.g., serotonin, GABA, dopamine), and cytokines. These molecules influence blood-brain barrier integrity, neuroinflammation, synaptic plasticity, and behavior. Conversely, the brain can regulate gut microbial composition and function via stress-mediated pathways, particularly through the HPA axis [3]. Emerging evidence indicates that the microbiome influences fundamental processes of neurodevelopment, emotional regulation, and cognition. Germ-free animal models, which lack any microbial colonization, exhibit marked al-

terations in behavior, stress responsiveness, myelination, and neuronal signaling. Moreover, dysbiosis—an imbalance or disruption in gut microbiota—has been implicated in a wide range of neurodevelopmental, neurodegenerative, and neuropsychiatric disorders, including Autism Spectrum Disorder (ASD), depression, anxiety, Alzheimer's disease, and Parkinson's disease [4,5].

The developmental trajectory of the gut-brain axis begins early in life and is shaped by factors such as mode of birth, infant feeding practices, antibiotic exposure, maternal stress, and environmental stimuli. Thus, understanding the gut-brain-microbiota triad not only offers novel insight into normal physiological regulation, but also presents new diagnostic and therapeutic avenues for disease prevention and intervention. This review aims to elucidate the mechanisms by which the gut microbiome regulates normal physiological functions through the gut-brain axis. We will examine the neural, endocrine, and immune pathways involved in microbiota-brain signaling, and explore how these interactions contribute to homeostasis, behavior, and cognition. In doing so, we underscore the significance of microbiota as an integral component of the body's physiological systems and its potential as a target for precision medicine.

Microbial Modulation of the Nervous System

The gut microbiota has emerged as a crucial modulator of Central Nervous System (CNS) function, influencing neural development, neurotransmission, and behavioral regulation. This communication occurs via microbial production of neuroactive compounds and through neural pathways that relay signals between the gut and the brain. One of the most important mechanisms by which the microbiota exerts its influence is the synthesis of molecules structurally similar to host neurotransmitters.

Among these, serotonin stands out as a key example. Though serotonin is commonly associated with the brain, approximately 90–95% of the body's total serotonin is synthesized in the gastrointestinal tract. This process is highly dependent on microbial stimulation of enterochromaffin cells. For instance, Streptococcus and Escherichia coli strains can enhance serotonin biosynthesis by influencing tryptophan metabolism and activating tryptophan hydroxylase, the rate-limiting enzyme in serotonin production [6].

Gamma-Aminobutyric Acid (GABA), the principal inhibitory neurotransmitter in the brain, is also produced by several species of commensal bacteria, particularly Lactobacillus and Bifidobacterium. Notably, Lactobacillus rhamnosus has been shown to alter GABA receptor expression in regions such as the amygdala and hippocampus, thereby modulating emotional behaviors. These effects are abolished when the vagus nerve is surgically severed, underscoring its role as a key neural conduit in microbiota–brain signaling [7].

Furthermore, some gut microbes such as Bacillus spp. and E.coli can synthesize dopamine and norepinephrine. Although these catecholamines may not directly cross the blood-brain barrier, they can modulate gut motility, influence the enteric nervous system, and indirectly affect CNS activity through systemic pathways [8]. Another group of key bioactive molecules are Short-Chain Fatty Acids (SCFAs), including acetate, propionate, and butyrate, produced via fermentation of dietary fibers. SCFAs not only serve as energy sources for colonocytes but also influence neurophysiological processes by regulating gene expression through histone deacetylase inhibition, modulating inflammation, and maintaining Blood-Brain Barrier (BBB) integrity. Butyrate, for example, has been associated with enhanced expression of Brain-Derived Neurotrophic Factor (BDNF), a critical regulator of neurogenesis and synaptic plasticity [9].

In addition to biochemical messengers, neural pathways such as the vagus nerve play a central role in transmitting microbial signals to the brain. The vagus nerve consists primarily of afferent fibers that carry sensory information from the gut to the CNS. Microbial metabolites, including SCFAs and neurotransmitter-like molecules, can activate vagal afferents and initiate neural cascades that impact emotion, stress response, and cognition [7]. Simultaneously, the Enteric Nervous System (ENS), often referred to as the "second brain," comprises an extensive network of neurons embedded within the gastrointestinal wall. This system operates independently of the CNS but maintains dynamic bidirectional communication with it. The ENS governs gastrointestinal motility, secretion, and mucosal immunity, and it is strongly influenced by microbial presence. Germ-free animals exhibit reduced enteric neuronal density and altered gut motility, which can be reversed following microbial colonization [10].

Moreover, the microbiota influences the maturation and function of enteric glial cells and modulates neurotransmitter release within the ENS. These local changes affect gastrointestinal function directly, but they also contribute to afferent signaling that ultimately shapes brain function. The interface between the microbiota and the ENS plays a critical role in maintaining gut homeostasis and systemic physiological balance, including aspects of cognition and mood regulation. Collectively, these findings support the concept that the gut microbiota regulates the nervous system through a finely tuned interplay of chemical messengers and neural circuits. Through the production of neurotransmitters, modulation of synaptic signaling, and engagement of the vagus nerve and ENS, the gut microbiota has a direct and measurable impact on brain physiology and behavior. Understanding these mechanisms offers novel opportunities for therapeutic modulation of mental health and cognitive function via the gut-brain axis.

Endocrine And Immune Pathways in the Gut-Brain Axis

In addition to neural and metabolic signaling, the gut-brain axis is critically regulated by the endocrine and immune systems, both of which are intimately shaped by the gut microbiota. These systems serve as crucial mediators through which the microbiome can influence neurodevelopment, mood, stress responsiveness, and systemic homeostasis. Disruptions in these pathways have been

increasingly implicated in various psychiatric and neurological disorders.

One of the primary endocrine mechanisms involved in the microbiota–brain interaction is the Hypothalamic-Pituitary-Adrenal (HPA) axis, the body's central stress response system. Under physiological stress, the hypothalamus secretes Corticotropin-Releasing Hormone (CRH), which stimulates the anterior pituitary to release Adreno Cortico Tropic Hormone (ACTH), leading to the production of glucocorticoids (e.g., cortisol in humans, corticosterone in rodents) by the adrenal cortex. These hormones prepare the body for a "fight-or-flight" response but also feedback to suppress further activation of the axis.

Evidence from Germ-Free (GF) animal models has shown that the absence of microbiota results in a hyperreactive HPA axis, characterized by exaggerated corticosterone responses to stress stimuli. Remarkably, colonization of these animals with specific commensal bacteria—particularly Bifidobacterium infantis—can normalize the stress hormone levels, suggesting a causal role for microbial signaling in HPA regulation [11]. The mechanisms underlying this regulation include microbial modulation of neurotransmitter levels (e.g., serotonin, GABA), vagal tone, and immune activity, all of which intersect with endocrine stress circuits.

The immune system is a vital intermediary in gut-brain communication. The intestinal mucosa harbors more than 70% of the body's immune cells, forming the largest and most dynamic immune organ. Gut microbes shape immune development from early life and continue to regulate immune tone and inflammation throughout adulthood. One of the key microbial products involved in immune signaling is lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls. When LPS translocates into systemic circulation due to impaired gut barrier function, it triggers the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), all of which can cross the blood-brain barrier or signal through afferent nerves to influence brain function [12].

Chronic low-grade systemic inflammation—often resulting from dysbiosis or increased intestinal permeability—has been linked to behavioral and cognitive alterations, including anxiety, depression, fatigue, and impaired memory [13]. Elevated levels of peripheral cytokines can activate microglia in the brain, leading to neuroinflammation, synaptic dysfunction, and altered neurogenesis. Furthermore, inflammatory mediators can influence the metabolism of tryptophan, shunting it away from serotonin synthesis toward the production of neurotoxic metabolites such as quinolinic acid, which can exacerbate depressive symptoms.

Recent studies suggest that certain microbial taxa may exert anti-inflammatory effects, promoting the expansion of regulatory T cells (Tregs), production of anti-inflammatory cytokines like IL-10, and suppression of excessive immune activation. SCFAs such as butyrate contribute to this immune balance by reinforcing gut barrier integrity, promoting mucin production, and modulating dendritic cell function. Thus, the gut microbiota plays a dual role: it can promote neuroinflammation under conditions of dysbiosis or sustain immune homeostasis under eubiotic conditions. Collectively, these findings demonstrate that the gut microbiota exerts profound control over neuroendocrine and neuroimmune circuits. By modulating HPA axis activity and shaping systemic and central immune responses, commensal microbes influence emotional regulation, cognition, and stress physiology. Unraveling the complexities of these endocrine and immune pathways provides critical insights into the physiological role of the microbiome in brain health and disease vulnerability.

Microbiota and Brain Development

The gut microbiota plays a pivotal role in shaping the developing brain, particularly during critical early-life windows. From birth onward, microbial colonization contributes to the maturation of neural circuits, regulation of synaptic plasticity, and establishment of cognitive and behavioral patterns. The dynamic crosstalk between gut microbes and the central nervous system during infancy and childhood appears essential for optimal neurodevelopment.

Microbial colonization begins at birth, and the mode of delivery profoundly impacts the initial microbial profile. Infants born via vaginal delivery are exposed to maternal vaginal and fecal microbiota, while those delivered by cesarean section often acquire skin- and environment-associated microbes. This difference is linked to changes in immune programming and neurodevelopmental trajectories [14]. Similarly, early-life antibiotic exposure can disturb microbial diversity and delay the establishment of a healthy microbial ecosystem. Studies in murine models have shown such disruptions impair hippocampal neurogenesis, increase anxiety-like behavior, and alter social interaction [15].

Maternal diet during pregnancy and lactation shapes the initial microbial landscape of the neonate, influencing availability of microbial metabolites crucial for brain development. Maternal high-fat diets associate with reduced beneficial microbial taxa and subsequent behavioral abnormalities in offspring, including impaired memory and social behavior [16]. Experiments transplanting microbiota from children with Autism Spectrum Disorder (ASD) into germ-free mice demonstrated the causal role of microbial communities in neurobehavioral outcomes. Mice receiving microbiota from ASD donors showed repetitive behaviors, altered sociability, and changes in synaptic protein expression, reinforcing early-life dysbiosis's contribution to neurodevelopmental disorders [17].

Gut microbes affect brain development by regulating synaptic plasticity—the brain's ability to reorganize neural connections. SCFAs, especially butyrate, produced by fiber-fermenting bacteria, influence gene expression by modulating histone acetylation. Butyrate acts as a histone deacetylase inhibitor, enhancing transcription of genes involved in neuroplasticity, learning, and memory [18]. Butyrate administration enhances Long-Term Potentiation (LTP) in the hippocampus, a physiological substrate for memory formation. SCFA-mediated regulation of neurotrophic factors such as BDNF contributes to neuronal differentiation and synaptic maturation.

Altered SCFA production links to cognitive impairments and mood dysregulation.

Clinical studies show therapeutic potential of probiotics in cognitive and emotional improvement. Supplementation with specific Lactobacillus and Bifidobacterium strains reduced psychological distress, improved working memory, and enhanced attention in healthy and mildly cognitively impaired individuals [19]. These findings underscore the integral role of gut microbiota in neurodevelopment, particularly through early-life programming and synaptic modulation. Maintaining microbial homeostasis during infancy may determine lifelong brain health.

Therapeutic Implications

Understanding the bidirectional gut microbiota-brain relationship paves the way for novel therapies aimed at maintaining homeostasis and treating neuropsychiatric and gastrointestinal disorders. Probiotics, prebiotics, dietary interventions, and Fecal Microbiota Transplantation (FMT) have shown promising results in modulating the GBA. Probiotics—live microorganisms conferring health benefits—are among the most studied tools. Specific strains of Lactobacillus and Bifidobacterium exhibit anxiolytic, antidepressant, and cognition-enhancing effects. For example, Bifidobacterium longum 1714 reduced stress and improved memory in healthy adults, likely by modulating the HPA axis and cortisol levels [19]. Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 reduced anxiety and depressive symptoms in clinical and preclinical studies [20].

Prebiotics—non-digestible fibers selectively stimulating beneficial bacteria—such as Galacto-Oli Gosaccharides (GOS) and Fructo-Oligosaccharides (FOS) increase Bifidobacterium levels and improve emotional processing [21]. These compounds enhance SCFA production, supporting neuroprotection, anti-inflammatory signaling, and BBB maintenance. Dietary interventions rich in fermentable fibers, polyphenols, and omega-3 fatty acids associate with improved cognition and reduced depression risk. The Mediterranean diet shows neuroprotective effects, likely through microbiota modulation [22]. In contrast, Western diets high in saturated fats and sugars reduce microbial diversity and promote systemic inflammation, harming brain health.

FMT—the transfer of gut microbes from healthy donors to patients—has gained attention for disorders involving dysbiosis. Small clinical trials report improved gastrointestinal and behavioral symptoms in Irritable Bowel Syndrome (IBS) and ASD patients [23]. A landmark study found sustained improvements in ASD children receiving FMT over two years [24]. Altered gut microbiota in Parkinson's Disease (PD) involves reduced SCFA-producing bacteria and increased intestinal permeability. Microbial-targeted therapies may alleviate symptoms, though more large-scale trials are needed [25]. Despite progress, long-term safety, dosing, strain specificity, and individual response variability require further study. Most current evidence comes from animal models or small human cohorts, limiting broad clinical application. Robust controlled trials are essential to develop evidence-based microbiota therapies.

Conclusion

The gut-brain axis is a vital physiological interface highlighting the microbiome's integrative role in brain regulation. Via neurochemical, endocrine, and immunological pathways, gut microbes maintain systemic and cognitive homeostasis. Deeper understanding of this axis offers promising avenues for preventive and therapeutic strategies in neurology and behavioral medicine.

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Conflict of Interest

None.

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