Understanding Microbial Mediation of the Brain-Gut Axis

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KEYWORDS

• Brain-gut-microbiome system • Gut microbiome • Dysbiosis

KEY POINTS

- Communications between the brain, the gut, and its microbiome can best be conceptualized as a complex system with bidirectional interactions and multiple positive and negative feedback loops.
- Communication from the gut to the brain occurs via 3 communication channels, including neural, endocrine, and immune mediators, which are regulated by several barriers.
- Preclinical mechanistic evidence and correlational human evidence supports an important role of the gut microbiome in several brain and gut disorders.
- The gut microbiome provides new potential targets for the treatment of several of these disorders.

INTRODUCTION

The gut microbiome, consisting of trillions of microorganisms, including bacteria, fungi, viruses, and archaea,[1–3] has emerged as a key player in regulating health and disease.[3–6] Based largely on preclinical data, it has become clear that interactions between the gut, its microbes, and the brain are critical for maintaining homeostasis and adapting rapidly to external and internal stimuli, including diet and psychosocial stress.[7–11] In addition, converging data suggest that these bidirectional pathways are crucial in regulating gastrointestinal (GI) and central nervous system (CNS)

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Gastroenterol Clin N Am 54 (2025) 367–381

https://doi.org/10.1016/j.gtc.2024.12.004 **gastro.theclinics.com**

Abbreviations	
BBB	blood-brain barrier
BCSFB	blood-cerebrospinal fluid barrier
CNS	central nervous system
CSF	cerebrospinal fluid
ECCs	enteroendocrine and enterochromaffin cells
FMT	fecal microbiota transplantation
GBM	gut-brain-microbiome
GI	gastrointestinal
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IDO1	indoleamine-2, 3-dioxygenase1
LPS	lipopolysaccharides
MAMPs	microbe-associated molecular patterns
MV	membrane vesicles
SCFAs	short-chain fatty acids

functions,[7,8,12,13] with the gut microbiome playing an influential role. The concept of a gut-brain-microbiome (GBM)system, in which the gut microbiota and their metabolites influence the gut, the brain, and the communication channels between them, has revolutionized our understanding of various GI and brain disorders, even though the clinical implications are largely based on results from correlational studies and remain incompletely understood.

This review focuses on the role of the gut microbiome in gut-brain interactions, particularly in the context of GI and brain disorders. It discusses the mechanisms that drive these interactions and explores how microbial imbalances contribute to the pathogenesis and symptoms of gut disorders like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and of brain disorders such as depression, Parkinson's, Alzheimer's disease, and autism spectrum disorders. The review also highlights current and future therapeutic approaches aimed at modulating the gut microbiome to restore healthy gut-brain communication.

THE GUT-BRAIN-MICROBIOME SYSTEM

The gut-brain microbiome system consists of several bidirectional communication channels that involve neural, blood borne (hormonal), and immune signals between the gut and the CNS. Interactions between the different nodes of the system are dynamic and nonlinear, and involve positive and negative feedback loops, and multiple regulated barriers. The inclusion of the gut microbiome in the known interactions between the gut and the brain introduces a dynamic, rapidly adapting, metabolically active ecosystem that responds to external factors entering through the digestive tract such as food, chemicals, medications, and external microorganisms, and that can modulate gut and brain functions on different time scales, often through the production of microbial metabolites, immune modulation, and neuroactive signaling pathways. This system allows communication between hundreds of thousands of signaling molecules generated by gut-based endocrine, immune, and neuronal systems and the gut microbiome, with the mucosal immune system, and with the brain.

MECHANISMS OF GUT-BRAIN-MICROBIOME INTERACTIONS

The brain influences the composition and function of the gut microbes through the branches of the autonomic nervous system, modulating the microbiota in response

to psychosocial stress and emotional states.[7,8,10,13] The sympathetic nervous system can influence gut microbial composition directly via release of norepinephrine into the gut lumen, interacting with adrenergic-like receptors that are present on many microbes (quorum sensing), and which have shown to induce the expression of virulence genes.[14] Indirect modulation of the gut microbiome via both branches of the autonomic nervous system occurs through changes in the microbial environment by modulation of regional GI transit, gut motility, fluid secretion, Paneth cells, secretion of antimicrobial peptides, and the release of neuroactive molecules, like serotonin into the gut lumen. The gut microbiome communicates with the brain through a complex system composed of multiple communication channels which are regulated by several barriers (**Fig. 1**).[15]

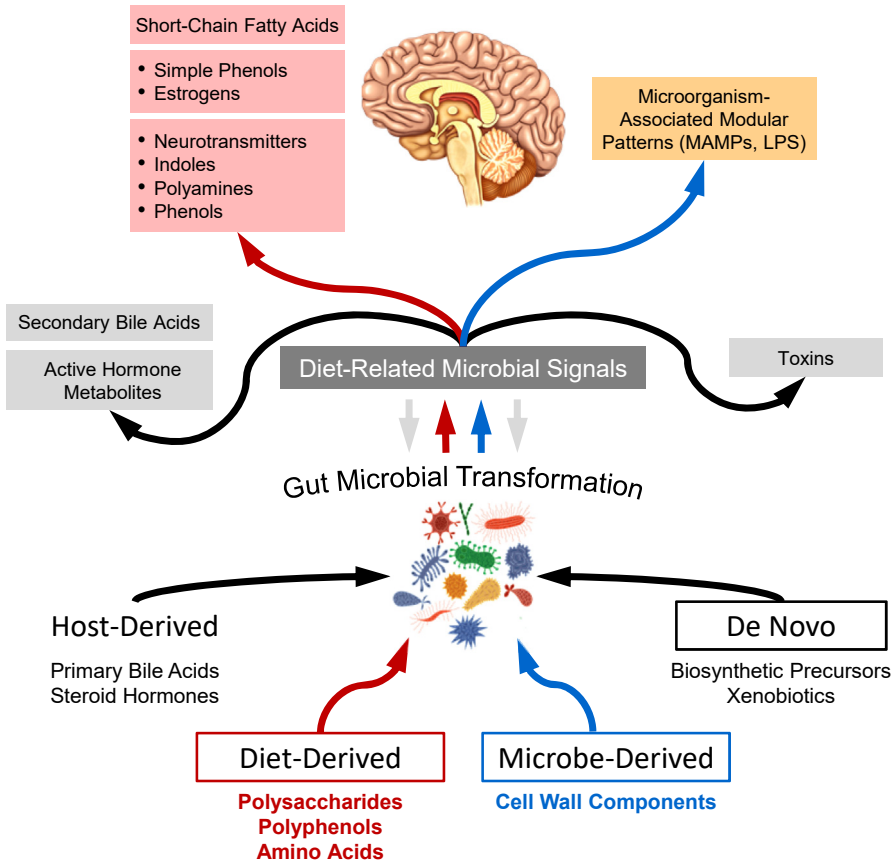

Fig. 1. The microbiome generates host signaling molecules from diet-derived, microbe-derived, host-derived, and from de novo sources. These neuroactive, inflammatory, and anti-inflammatory molecules interact on brain targets to modify brain networks. Diet influences the composition and function of the gut microbes, and microbes metabolize large diet-derived molecules (polysaccharides and polyphenols) and amino acids into neuroactive substances. LPS, lipopolysaccharide; MAMP, microbe-associated molecular pattern. (Modified with permission from Ross FC, Mayer DE, Gupta A, et al. Existing and Future Strategies to Manipulate the Gut Microbiota With Diet as a Potential Adjuvant Treatment for Psychiatric Disorders. Biol Psychiatry 2024;95(4):348-360. https://doi.org/10.1016/j.biopsych.2023.10.018.)

Neural Pathways

The enteric nervous system, often referred to as the "second brain," contains millions of neurons that not only regulate gut function independently of the CNS but also communicate with the brain through the vagus nerve and spinal cord pathways. Distinct, chemically coded subtypes of vagal afferent nerves are a key conduit for microbial signals to the brain, with studies showing that gut microbiota can modulate brain function by influencing vagal tone.[16] For instance, certain probiotic strains, such as *Lactobacillus rhamnosus*, have been shown to modulate gamma-aminobutyric acid receptor expression in the brain via vagal pathways.[17–19]

Neuroendocrine Communication Channel

Intestinal microbes produce metabolites from dietary components (complex carbohydrates, amino acids), bodily secretions (bile acids, estrogens), or chemical substances, so called xenobiotics (including pesticides, microplastics, and some medications). Several of these microbiome-derived metabolites (short-chain fatty acids [SCFAs] such as butyrate, propionate, and acetate[20]; secondary bile acids [2BAs] such as deoxycholic acid and lithocholic acid[21]; and tryptophan-derived metabolites such as kynurenine[22]) have been shown to influence brain structure and function in preclinical studies.[23,24] Intestinal microbes communicate with a variety of cells of the gut-based endocrine system.[25] The gut epithelium contains enteroendocrine cells which release important signaling molecules, including key orexigenic (ghrelin) and anorexigenic (neuropeptide Y [NPY], peptide YY [PYY], glucagon like peptide 1 [GLP-1]) hormones. These signaling molecules can act locally on the vagus nerve as neurotransmitters or reach the CNS via the systemic circulation in an endocrine fashion.[7,8,26] The interaction of such hormones in the peripheral nervous system and in the hypothalamus of the central nervous system plays a key role in the regulation of appetite and satiety,[27,28] and a dysregulation of these signaling systems has been implicated in obesity and food addiction.[29] Neuropods are cell extensions which are formed between enteroendocrine and enterochromaffin cells (ECCs) as close synaptic connections with certain vagal afferent fibers.[30,31] While these gut-based hormones are also released into the systemic circulation and reach the brain directly, these synaptic connections function in the rapid relay of a nutrient and other signals from the gut to the brain.

Tryptophan (Trp) is an essential amino acid that acts as a precursor to serotonin, as well as to other important metabolites in neuroendocrine signaling. The modulation of Trp into various metabolites which include but are not limited to kynurenine, indoles, and tryptamine is facilitated by specific gut microbiota.[28,32,33] Neuroendocrine and neuroimmune mechanisms are regulated by microbiome-derived Trp metabolites which can act on the CNS either through the bloodstream or via vagal afferent signaling.[7] Importantly, the great majority of the body's serotonin is produced and stored in ECCs. This gut-based serotonin plays an important role in modulating the activity of the enteric nervous system and in signaling to the brain via different subtypes of vagal afferents which form synaptic contacts with ECCs.[34] Specifically, SCFAs and 2BAs among other microbial metabolites have been shown to stimulate the production and release of serotonin by ECCs into the lumen and onto vagal afferents.[32] The serotonin synthesized in and released from ECC in the gut plays an important role in GI motility and secretion.[26] Different from serotonin- releasing cells in the gut, serotonergic neurons located in the brainstem show widespread projections to other brain regions and play an important role in modulating vital functions such as sleep, food intake, mood regulation, and pain. In animal studies, germ-free mice have been shown to have half the amount of plasma serotonin when compared to

mice with a normal gut microbiome.[33] Another Trp metabolite worth discussing in this context is kynurenine, the synthesis of which is modulated by *Lactobacillus* taxa.[35] *Lactobacilli* bacteria produce hydrogen peroxide, a reactive oxygen species which normally suppress host kynurenine metabolism by inhibiting the expression of the enzyme indoleamine-2, 3-dioxygenase (IDO1). IDO1 is crucial in the synthesis of kynurenine from Trp in the GI tract.[36] In a rodent model of chronic variable stress, the stress-induced reduction of *Lactobacillus* decreased inhibition of IDO1 by hydrogen peroxide, resulting in an increased synthesis of kynurenine from Trp.[37] In these studies, higher kynurenine concentrations in the brain were correlated with increased depression-like behaviors, which were reversed by administration of *Lactobacillus*.

Gut Brain Signaling by Microbial Membrane Vesicles

Microbial membrane vesicles (MVs) are small, lipid-bound particles released by gut bacteria that play a significant role in the communication between the gut and the brain.[38] These vesicles range from 20 to 300 nm in size and serve as carriers for a variety of bioactive molecules, including proteins, lipids, metabolites, and genetic material (DNA and RNA). MVs can cross biological barriers such as the intestinal epithelium and the blood-brain barrier (BBB), allowing them to transport their cargo from the gut to distant sites, including the brain. Once in the bloodstream, these vesicles can interact with immune cells, influence inflammation, and modulate neurochemical pathways. Through these mechanisms, microbial MVs can affect neural signaling, alter neurotransmitter production, and potentially influence brain function and behavior.

Microbial MV-mediated signaling is thought to play a crucial role in the regulation of neurodevelopment, cognition, mood, and even susceptibility to neurologic disorders.[39] For instance, microbial-derived metabolites and proteins carried by MVs have been linked to the modulation of brain activities associated with conditions like anxiety, depression, and neurodegenerative diseases.[40,41]

The Immune Communication Channel

The cell wall of gram-negative bacteria contains lipopolysaccharides (LPS) and microbe-associated molecular patterns (MAMPs) which can interact locally with receptors on enteric neurons or vagal afferents (toll-like receptors or) and on cells from the gut-based immune system. LPS and MAMPs can also exert their effects distally throughout the body, including the brain. A great body of research has been dedicated to investigating the complex interactions between the gut microbiota and immune activation in the brain. Central immune activation can be mediated by cytokines released from the gut-associated immune system, or by fragments of gut microbes, such as LPS or MAMPs that have leaked into the systemic circulation through a compromised intestinal barrier and passed the BBB. Such inflammatory signals as well as antiinflammatory SCFAs can act on glial cells and different types of neurons in the CNS.[42] The involvement of neuroinflammatory and neurodegenerative mechanisms related to the brain gut microbiome (BGM) system may play a role in various brain disorders, a topic which has recently been reviewed.[43]

BARRIERS TO GUT-BRAIN COMMUNICATION

The gut-brain axis is a complex and dynamic bidirectional communication system between the GI tract and the CNS. This communication is mediated by neural, hormonal, and immunologic signals, and the gut microbiota plays a key role in these processes. To maintain homeostasis and facilitate this communication, several barriers exist

along the gut-brain axis, which ensure that microorganisms and their metabolites interact with the host in a controlled manner. This topic has recently been reviewed in an excellent article by Aburto and colleagues.[44]

Mucus Layer

The mucus layer in the gut is the first line of defense that regulates the interaction between the gut microbiota and the host.[45] It is composed of mucins, which are secreted by goblet cells in the gut lining. This layer serves multiple functions: It provides a barrier to limit the exposure of gut epithelial cells to potentially harmful microorganisms, both commensal and pathogenic. The thickness of the mucus layer increases along the length of the gut, correlating with the density of microorganisms present. This protective layer helps prevent direct contact between gut cells, including the luminal extensions of dendritic cells and microbial communities, reducing the likelihood of engagement of the gut-based immune system.[46] In addition to its barrier function, the mucus layer serves as a nutrient source for certain microbes, such as *Akkermansia mucinophilia*, especially in conditions where dietary fiber is lacking, or during fasting.[47] Thus, the mucus layer plays a dual role by both protecting the host and supporting healthy gut microbiota.[45] Disruptions in the mucus layer, even in the presence of an intact epithelial barrier, can lead to the activation of dendritic cells and immune cell networks in the gut, potentially triggering chronic inflammatory disorders like Crohn's disease and ulcerative colitis. Such disruptions when induced by dietary factors can also contribute to metabolic endotoxemia.[44,48]

Gut Epithelial Barrier

Beneath the mucus layer lies the gut epithelial barrier, which provides a selective, semipermeable boundary between the gut microbiota and the host. This barrier consists of several types of cells, including absorptive enterocytes, goblet cells, Paneth cells, enteroendocrine cells, and immune cells, which collectively form a protective boundary.[49,50] Enterocytes are connected by tight junctions and adherens junctions that regulate paracellular transport and intestinal permeability.[44,51] These junctions prevent the unregulated passage of harmful substances, while allowing selective absorption of nutrients. Substances can cross the gut epithelial barrier through transcellular and paracellular pathways. The transcellular pathway involves passive diffusion, receptor-mediated transport, and endocytosis, while the paracellular pathway relies on the tight junctions between cells.[52,53] Any disruption of this finely tuned balance can lead to increased gut permeability, often referred to as "leaky gut" in the lay press, which has been associated with a variety of health conditions, including IBDs and metabolic syndrome.[50,54]

Gut Vascular Barrier

The gut vascular barrier serves as the final checkpoint before substances from the gut can enter systemic circulation. This barrier regulates the passage of microorganisms and microbial products, including cell wall components from the gut (LPS, MAMPs) into the bloodstream, acting as a crucial defense mechanism.[44,55] The gut vascular barrier is composed of endothelial cells that form tight junctions, preventing the paracellular transport of microorganisms and large molecules. This barrier is selectively permeable, allowing only small molecules up to 4 kDa in mass to pass through. Inflammatory insults can disrupt the gut vascular barrier, potentially allowing microorganisms or membrane fragments to enter the bloodstream. Importantly, gut inflammation has been linked to alterations in the brain, as it can also affect the function of the BBB and the blood-cerebrospinal fluid barrier (BCSFB), indicating a direct connection

between the gut and brain barrier functions.[56,57] The BBB is a highly selective boundary that separates the circulating blood from the brain's extracellular fluid in the CNS. Its main function is to protect the brain from harmful substances while allowing the transport of essential nutrients. The BBB is composed of endothelial cells connected by tight junctions, supported by astrocytes and pericytes, which regulate the passage of molecules. The barrier prevents the entry of pathogens, toxins, and immune cells, maintaining the brain's homeostasis.[44,58] Similar to the other barriers within BGM communication, the BBB is not a static structure but dynamically adjusts its permeability in response to environmental factors, ensuring the brain receives necessary inputs without exposure to harmful substances. For example, in certain regions of the brain, such as the circumventricular organs, the capillaries lack typical barrier functions, allowing them to detect signals from the bloodstream, including hormones and microbial metabolites.[59]

The BCSFB is located at the choroid plexus in the brain ventricles and plays a critical role in maintaining the composition of cerebrospinal fluid (CSF) and protecting the brain. It prevents the unregulated passage of substances from the blood into the CSF and brain parenchyma. Like the BBB, the BCSFB is formed by tight junctions between epithelial cells. The BCSFB can respond to inflammatory insults by modulating its permeability. For example, systemic or gut inflammation can cause the BCSFB to tighten, reducing the risk of harmful substances entering the brain. This indicates a functional connection between the barriers of the gut and the brain, further emphasizing the integrated nature of gut-brain communication.[60–62]

MICROBIAL MODULATION OF BARRIERS

Emerging research suggests that gut microorganisms can influence the function of the brain's barriers, particularly the BBB and BCSFB. Microbial metabolites, such as SCFAs and other bioactive compounds, have been shown to improve barrier integrity.[62,63] The ability of gut microbes to affect brain function via barrier modulation highlights the potential for novel therapeutic interventions targeting the microbiota to treat neurologic conditions.[44]

These barriers along the gut-brain axis are critical for maintaining homeostasis and facilitating adaptive communication between the gut microbiota and the host. Disruptions in these barriers can lead to a variety of disorders, ranging from IBDs to neurologic conditions.[44,58,62] Understanding the mechanisms behind these barriers, as well as how they are modulated by the gut microbiota and other factors such as inflammation or chronic stress, opens new avenues for therapeutic strategies aimed at improving gut-brain communication and overall health.

THE PUTATIVE ROLE OF A BRAIN MICROBIOME

The concept of a brain microbiome is a topic of ongoing research and debate. Traditionally, the brain was thought to be a sterile environment, protected by the BBB from microbial invasion. However, recent studies have suggested that there might be a presence of microorganisms within the brain, though this idea remains controversial. Some research has identified traces of bacterial DNA and other microbial components in the brains of both healthy individuals and those with neurodegenerative conditions like Alzheimer's disease, [64,65] but the mechanisms by which these microbial components gain entry into the brain remain unknown. These findings have led to the provocative hypothesis that the brain may host a unique viable microbial community, which could play roles in brain function, immune responses, and the development of neurologic disorders. However, these results must be interpreted with significant caution, as

contamination during sample collection and analysis, or transport of microbial fragments through the systemic circulation or via MV could also explain the presence of microbial signatures. Moreover, the multiple barriers that control gut to brain communication, and the immune surveillance mechanisms of the brain, such as the activity of microglial cells, make it very unlikely for live microbes to survive and colonize this environment in a way that resembles the gut microbiome. More research is needed to confirm the existence of these microorganisms, understand their origins, and determine their potential roles in brain health and disease.

GUT-BRAIN-MICROBIOME INTERACTIONS IN GASTROINTESTINAL DISORDERS

Irritable Bowel Syndrome

IBS is a common disorder of gut-brain interactions, characterized by recurrent abdominal pain and alterations in bowel habits (diarrhea, constipation, or a mix of both). Patients with IBS often exhibit dysbiosis, or an imbalance in gut microbial composition, which has been implicated in alterations in gut motility, visceral hypersensitivity, and immune activation.[66,67] A hallmark of IBS is visceral hypersensitivity, a condition where the gut becomes overly sensitive to stimuli. Gut microbiota have been suggested to influence this process by producing metabolites (SCFAs, 2BAs, Trp-derived metabolites) that affect enteric nervous system (ENS) neurons, alter serotonin production, and modulate vagal and spinal afferent pathways. Alterations in the gut microbiota in IBS patients have been associated with increased production of gas and osmotic agents, leading to symptoms like bloating and pain.[66] Despite several cross-sectional, correlational clinical studies, causality between alterations in microbial composition and function, and IBS symptoms has not been established. However, mounting evidence suggests that dysbiosis of the gut microbiome in subsets of IBS patients may contribute to GI symptoms, stress responsiveness, and visceral hypersensitivity, characteristic of the disorder.[68] Recent evidence suggests a role of stress responsiveness in the modulation of gut microbial composition and function.[69] However, the specific microbial signatures associated with IBS and their role in disease pathogenesis, particularly in the context of sex-based differences, remain to be elucidated.

Current gut-directed therapeutic approaches for IBS include dietary modifications, such as the low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet, which reduce the intake of fermentable carbohydrates and has been shown to improve IBS symptoms by altering microbial fermentation in the gut as long as the diet is maintained. However, long-term persistent benefit once the diet has been discontinued has not been demonstrated.[70–72] Additionally, antibiotics (like rifaximin) have been used to modulate the gut microbiome, with varying degrees of success, and in our view should not be encouraged. Probiotics and synbiotics can be beneficial in some patients, but well controlled randomized controlled studies are lacking. Brain-targeted therapies, like gut-directed cognitive behavioral therapy,[73–75] hypnosis, and mindfulness-based stress reduction, have been shown to alter the gut microbiome and were associated with clinical improvement.

Inflammatory Bowel Diseases

IBDs are chronic inflammatory condition of the GI tract characterized by dysregulated immune responses. Dysbiosis is a key feature of IBD, with studies showing reduced microbial diversity and an overgrowth of pathogenic bacteria and fungi.[76] These changes in the gut microbiota can lead to compromised intestinal permeability resulting in an overactive immune response, chronic inflammation, and damage to the intestinal lining. In IBD, the GBM axis plays a crucial role in modulating both gut inflammation

and CNS symptoms, such as fatigue and depression. The chronic inflammation in IBD patients can lead to increased intestinal permeability, allowing microbial antigens and toxins to enter the bloodstream and activate gut-based immune cells, which produce proinflammatory cytokines. These cytokines can cross the BBB and affect brain function, leading to neuroinflammation, altered mood states, and ultimately compromised cognitive function.[77–79] Converging evidence also supports an important role of brain-gut communication in IBD.[80–83] In 2 recent studies, the authors have shown that ulcerative colitis (UC) patients with increased stress responsiveness and associated gut microbiome alterations showed a greater frequency of clinical flares.[84,85]

In addition to the use of biologics, emerging therapeutic strategies for IBD focus on restoring microbial balance through probiotics, prebiotics, and fecal microbiota transplantation (FMT). FMT has shown promise in reintroducing beneficial microbial species, leading to remission in some IBD patients, even though results have been inconsistent.[86,87] Moreover, therapies with encapsulated microbial metabolites such as the antiinflammatory SCFA butyrate have been explored in clinical trials to reduce gut inflammation and improve gut-brain communication.[88–90]

GUT-BRAIN-MICROBIOME AXIS IN BRAIN DISEASES

Psychiatric Disorders

Psychiatric disorders such as depression and anxiety have also been linked to changes in the gut microbiome. As explained earlier, the gut microbiota influences the production of neuroactive molecules (eg, serotonin) that can affect brain function. Some studies suggest that individuals with depression exhibit distinct microbial profiles, with reduced microbial diversity and alterations in the levels of SCFAs and other key metabolites.[91] Inflammatory cytokines originating in the gut-associated immune system in response to gut microbial signals, such as LPS or MAMPs, can affect CNS function, contributing to the pathophysiology of mood disorders. The concept of "psychobiotics—probiotics that modulate the microbiome to improve mental health—has emerged as a promising area of research[92,93]; however, clinical meaningful results from such interventions based on high-quality clinical trials are currently not available.

Neurodegenerative Diseases

Neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease are increasingly being viewed as brain-gut microbiome disorders. Changes in gut microbiota composition (dysbiosis) have been observed in patients with these conditions, and gut-derived signals are thought to influence the progression of neurodegeneration through immune modulation and altered neurotransmitter production.[94,95] For instance, gut microbiota can produce amyloid-like proteins that may contribute to the accumulation of amyloid plaques in the brain, a hallmark of Alzheimer's disease. In Parkinson's disease, changes in gut motility and microbiota composition may precede the onset of motor symptoms by more than a decade, highlighting the potential role of altered gut-brain signaling in early disease development.[96] Even though substantial evidence from preclinical models supports a role of altered gut microbiome to brain signaling as one pathophysiological factor in these disorders, human data are largely correlational and do not demonstrate a causative role of the gut microbiome.

THERAPEUTIC IMPLICATIONS

The growing recognition of the gut microbiome's role in brain-gut interactions in GI and liver diseases has spurred the development of microbiome-targeted therapies. These

include dietary modifications, probiotics, prebiotics and synbiotics, bioengineered microbes, antibiotics, fecal microbial transplants, defined live biotherapeutic consortia, and brain-targeted therapies like cognitive behavioral therapies and hypnosis. Overall, despite impressive results in animal models, these therapeutic strategies have shown inconsistent clinical benefits to date and cannot be recommended as first-line therapies. Despite the dramatic increase in our knowledge of the gut microbiome and its communications with the brain, novel therapies have yet to demonstrate an advantage over lifestyle modifications with an emphasis on diet. Diets rich in plant-based foods providing a substrate for the production antiinflammatory metabolites, and various naturally fermented foods have been shown to promote increased diversity and richness of the gut microbiota, reduce markers of inflammation, and create health-promoting signals within gut-brain interactions.[97]

SUMMARY

The gut microbiome, a complex ecosystem of trillions of microorganisms, plays a pivotal role in regulating both GI and CNS functions, influencing health and disease through intricate gut-brain interactions. This review elucidates some of the mechanisms underlying these interactions both under normal conditions and in the context of various disorders such as functional and inflammatory bowel disorders, and neuropsychiatric disorders like depression, cognitive decline, and Parkinson's disease. It highlights the bidirectional communication pathways involving neural, hormonal, and immune signals, emphasizing the dynamic nature of the GBMsystem. Dysbiosis, or microbial imbalance, contributes to the multifactorial pathophysiology of these disorders, with specific microbial metabolites being involved in the regulation of gut and brain functions. The review briefly discusses emerging therapeutic strategies aimed at restoring gut microbiome balance through dietary interventions, probiotics, and fecal microbiota transplantation, while showing that current clinical outcomes remain inconsistent. Overall, the findings underscore the importance of the gut microbiome in maintaining homeostasis and its potential as a therapeutic target for improving gut-brain communication and treating the many related disorders.

CLINICS CARE POINTS

- Despite considerable mechanistic evidence from preclinical studies, causal relationships between altered gut microbial composition or function in human disorders have not been established.
- Translation of preclinical findings into human diseases has been difficult with the exception of a small number of microbiome targeted therapies.
- Dietary and lifestyle modifications remain the most effective interventions to normalize an altered gut microbiome until new generation of probiotics can be evaluated.

FUNDING

Crohn's and Colitis Foundation grant 546296 Brain-gut-microbiome signatures of stress-related IBD symptom flares. NIH U54 DK064539SCORE Center for Neurovisceral Sciences & Women's Health NIH/NIA U19 Alzheimer Gut Microbiome Project.

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