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Review Article

The Gut-Brain Axis in Neurodegeneration: Mechanistic Insights and Emerging Therapeutic Perspectives

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ABSTRACT

The gut-brain axis (GBA) is an intricate, bidirectional communication network connecting the central nervous system (CNS) and gastrointestinal tract (GIT) via neural, immune, endocrine, and metabolic pathways. This dynamic interaction, modulated by the gut microbiota, influences essential physiological and cognitive functions, including mood regulation, stress response, and neuronal signaling. Dysbiosis, an imbalance in gut microbial composition, contributes to neurodegenerative disorders (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) by promoting inflammation and neuroinflammation, oxidative stress, neurotransmitter production and regulation, blood-brain barrier integrity, protein aggregation, and misfolding. Microbial metabolites, such as short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives, play a crucial role in maintaining CNS homeostasis, whereas neurotoxic metabolites, like trimethylamine N-oxide (TMAO), exacerbate neurodegenerative pathology. Therapeutic interventions, including dietary modulation, prebiotics, probiotics, psychobiotics, fecal microbiota transplantation (FMT), vagus nerve stimulation (VNS), and small-molecule modulators, represent promising approaches to restore GBA balance and delay neurodegeneration. However, challenges remain in translating preclinical evidence into human application due to interindividual microbiome variability and limited mechanistic understanding. Emerging methodologies such as organ-on-a-chip models, wearable biosensors, and artificial intelligence-driven microbiome analytics hold potential for personalized, microbiota-based therapies. Standardization of biomarkers and study protocols will be essential to further clarify the GBA's mechanistic involvement and therapeutic potential in neurodegenerative disease management.

Key words: Gut-brain axis, gut microbiota, dysbiosis, neurodegenerative disorders, microbial metabolites

INTRODUCTION

The gut-brain axis (GBA) refers to the complex, bidirectional communication network between the central nervous system (CNS) and the gastrointestinal tract (GIT). It comprises the neural pathways, immune signals, hormonal communication, and metabolic routes that allow the brain and gut to influence each other's functions. The main components are the vagus nerve and the gut microbiota, a diverse microbial community in the GIT that produces neuroactive compounds, including neurotransmitters, immune mediators, and hormonal signals. This axis

plays a crucial role in maintaining homeostasis, regulating mood, cognition, stress responses, and gut motility, while disturbances can contribute to neurodegenerative and psychiatric disorders. [1, 2] Neurodegenerative disorders (NDDs) comprise a group of diseases characterized by progressive neuronal loss leading to cognitive, motor, and behavioral impairments. Common examples of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). These conditions often involve the abnormal accumulation of proteins, neuroinflammation, mitochondrial dysfunction, and oxidative stress, which contribute to neuronal degeneration. [1] The GBA plays a critical role in neurodegenerative diseases, as dysregulation of this bidirectional communication pathway can significantly influence disease onset and progression. Alterations in gut microbiota composition, known as dysbiosis, have been associated with NDDs, which modify systemic and neuroinflammation. Microbial metabolites, including short-chain fatty acids (SCFAs), influence brain function, neural plasticity, and immune responses. Dysbiosis may improve gut permeability, facilitating the entry of neurotoxic substances into circulation and prompting inflammation within the CNS. Understanding this connection permits exploration of therapeutic interventions targeting the gut microbiota, including dietary modifications, probiotics, prebiotics, fecal microbiota transplantation (FMT), and natural bioactive compounds, to potentially modify disease trajectory and improve brain health. [2–4]

COMPONENTS AND COMMUNICATION PATHWAYS OF GBA

It involves multiple components and communication pathways that integrate neural, immune, endocrine, and microbial signals to maintain gut and brain homeostasis. **Figure 1** shows various components and pathways involved in the GBA.

GBA COMPONENTS

Enteric Nervous System (ENS)

Often referred to as the "second brain," the ENS is a vast network of neurons located in the lining of the GIT. It autonomously regulates gut motility, secretion, and blood flow, and communicates with the CNS through autonomic pathways. The ENS interfaces with gut microbiota via enteroendocrine cells, which sense microbial signals and release neuroactive peptides and amines, thereby controlling brain function and behavior. [5, 6] According to research, the ENS contributes to glycemic control by communicating with the hypothalamus about nutritional status, which is especially vital in conditions such as type 2 diabetes. [7]

Vagus Nerve

The vagus nerve is the key parasympathetic conduit between the gut and CNS. It is made up of about 80% afferent (sensory) and 20% efferent (motor) fibers, which carry sensory information from the gut to the brain and motor signals from the brain to the gut. It is involved in myriad functions, such as emotion modulation, food intake, and fat metabolism. It acts as a line between the gut and the brain, contributing to a cholinergic anti-inflammatory pathway that can impact both local gut function and broader immune responses. [8, 9] It plays a crucial role in transmitting serotonin signals, which influence emotional regulation and stress responses. This highlights how gut-derived biochemical signals can affect brain functions and potentially influence neuropsychiatric conditions. [10]

Gut Microbiota

The gut microbiota is composed of trillions of microorganisms that play an essential role in regulating brain function and behavior. The gut microbiota itself is now identified as a vital signaling component of the GBA, impacting neurodevelopment and behavior through the production of neuroactive compounds, and it modulates the immune function and the interaction with neuronal and endocrine pathways. Dysbiosis occurs due to alterations in the gut microbiota composition, which can affect brain function and is associated with neuropsychiatric and neurodevelopmental conditions like autism, anxiety, AD, PD, and epilepsy. [11–13]

Immune System

The gut-associated lymphoid tissue (GALT) and immune cells in the lamina propria are key modulators of the GBA. The role

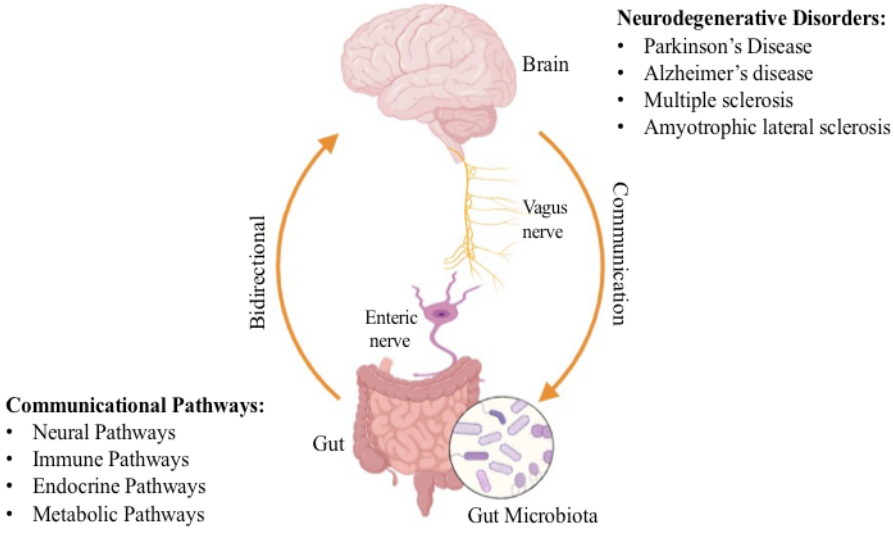

Figure 1: Key components and communication pathways of the gut-brain axis.

of GALT in the GBA is pivotal for developing novel therapies that aim to modify the gut microbiome and treat brain-related disorders by enhancing gut health and preserving microbial balance. [14] Cytokines and immune mediators generated in response to microbial or dietary antigens can affect neuronal activity and brain function, connecting with gut immune status to central neuroinflammatory processes and psychiatric conditions. [6, 15]

Endocrine System

Gut endocrine cells release hormones such as serotonin, peptide YY, and cholecystokinin, which act locally, enter systemic circulation, or affect vagal afferents to influence appetite, mood, and stress responses. This endocrine signaling represents a critical pathway for gut-brain communication, integrating metabolic and emotional states. [5, 6]

COMMUNICATIONAL PATHWAYS

Neural Pathways

Neural pathways, also known as Rapid signaling. Neural pathways play a crucial role in facilitating bidirectional communication between the gut lumen and brain. These include the enteric nervous system, a complex network of neurons located in the gut wall, and extrinsic nerves such as the vagus, spinal, and sympathetic nerves. The vagus nerve serves as a primary afferent sensory route transmitting the signals from the gut to the brain. The intrinsic primary afferent neurons and the enteroendocrine cells play a central role in the gut, detecting luminal signals and releasing peptide messengers that locally affect neural circuits in the brain. [5, 11, 16]

Immune Pathways

The immune pathway is also known as inflammatory signaling. Cytokines, signaling molecules, act as the primary language of the immune pathway. Pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), transmit inflammatory signals to the brain. [17] Research highlights TNF-α as a critical "bridge" that links the gut-derived peripheral inflammation to central neuroinflammatory responses within the brain. [18] Lipopolysaccharides are immunogenic components found in the cell walls of gram-negative bacteria. The healthy blood-brain barrier (BBB) has low permeability to LPS. Gut dysbiosis can lead to a "leaky gut," allowing LPS to enter the systemic circulation and trigger microglial activation in the brain. [19]

Endocrine Pathways

Endocrine pathways, also known as hormonal signaling. In this pathway, the hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that manages stress responses and modulates gut function through hormonal signals. Stress activates the release of both corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), which stimulates cortisol production. These hormones alter both intestinal permeability and local immunity, directly impacting the microbial environment. [20]

Metabolic Pathways

Gut microbes produce a wide array of chemical messengers, like short-chain fatty acids (SCFAs), which are protective and help to maintain the integrity of the BBB. [21] They also produce potentially neurotoxic metabolites, such as trimethylamine N-oxide (TMAO) and bile acids (BAs), as well as precursors of neurotransmitters such as serotonin and GABA. This integrative system maintains physiological homeostasis and has implications in gastrointestinal, neurological, and psychiatric disorders. Understanding the components and pathways of the GBA underpins emerging therapeutic strategies targeting microbiota, neural, immune, or endocrine pathways to treat diseases ranging from irritable bowel syndrome to depression and epilepsy. [6, 13]

MICROBIOME AND ITS ROLE IN THE GBA

Composition of the Gut Microbiome

The gut microbiome comprises a diverse community of microorganisms, including bacteria, viruses, fungi, and archaea, that reside in the GIT. The composition of this microbial community is modulated by genetics, diet, environment, health status, and other factors, with diet playing a pivotal role in shaping the microbiota's composition and functions. [22, 23]

Functions of Gut Microbiota

The functions of the gut microbiota extend beyond digestion and the metabolism of dietary nutrients that humans cannot digest; they also play significant roles in immune modulation and influence distant organs, such as the brain, through the GBA. This axis forms a bidirectional communication system involving neural, hormonal, and immune signaling pathways, including the vagus nerve and neuroendocrine factors. The gut microbiome can influence brain functions through the production and regulation of neurotransmitters, hormones, and diverse metabolites. [24–26]

Microbiome-Derived Metabolites and Their Effects on the Brain

The gut microbiota plays a crucial role in maintaining the integrity of the intestinal barrier. Dysbiosis can increase intestinal permeability, allowing neuroactive compounds to access brain regions that control cognitive and emotional functions. Furthermore, altered microbiota composition can disrupt inflammatory responses, thereby affecting neuropsychological health. This dysregulation may contribute to the pathology of neurodegenerative and neuropsychiatric disorders, including AD, PD, depression, autism spectrum disorder, and traumatic brain injury outcomes. [24, 35, 36] Dietary components, such as polyphenols, are biotransformed by gut bacteria into bioactive metabolites that may cross the BBB to exert neuroprotective, anti-inflammatory, and cognitive-enhancing effects. This reinforces the critical role of diet in maintaining both a healthy microbiome and optimal brain function. [37] Similarly, exercise modulates gut microbiome composition, a mechanism that may partly mediate exercise's beneficial effects on brain health (**Table 1**). [9]

Table 1: Key microbial metabolites and their impact on CNS pathophysiology.

Metabolite class	Source/microbial origin	CNS impact and mechanism	Relevance to NDDs	Reference
1) Short-chain fatty acids E.g., Butyrate, acetate, propionate	Fermentation of dietary fiber by species like *Lactobacillus* and *Eubacterium rectale*	Maintain BBB integrity; anti-inflammatory effects (Treg induction); support neurogenesis	Reduced levels associated with increased neuroinflammation	[27–29]
2) Tryptophan derivatives E.g., Serotonin, Kynurenine	Microbial and host metabolism	Neurotransmitter function: modulates immune activation (Kynurenine pathway)	Altered profiles linked to neuroinflammation and mood disorders	[30–32]
3) Neurotoxic metabolites E.g., TMAO (trimethylamine N-oxide)	Microbial breakdown of dietary choline and carnitine	Promotes A$/beta$ and Tau aggregation via PI3K/AKT/mTOR; activates microglia and astrocytes	Elevated levels associated with accelerated AD progression	[27, 33]
4) Bile acids (BAs) E.g., Secondary Bas (deoxycholic, lithocholic)	Conversion of primary BAs by bacterial enzymes(e.g., Bacteroides)	Modulate nuclear receptors; regulate neuroinflammation and brain amyloid kinetics	Altered BA profiles in AD and PD	[34]

GUT DYSBIOSIS AND ITS CONSEQUENCES

Gut microbiome imbalance known as dysbiosis, and it is characterized by a reduction in microbial richness and abundance, involving the reduction of beneficial bacteria, such as Bacteroides and Firmicutes, and an overgrowth of harmful microbes, like *Prevotellaceae* and Enterobacteriaceae. One critical aspect of gut dysbiosis is its impact on the immune system. An imbalanced gut microbiota can compromise the intestinal barrier and immune function, allowing pathogens to invade and promote inflammatory conditions such as ulcerative colitis and Crohn's disease. This compromised barrier can increase intestinal permeability, commonly known as "leaky gut," thereby permitting harmful bacteria and toxins to enter the bloodstream and cause systemic inflammation. [38, 39] The gut microbiota also plays a pivotal role in chronic diseases, including metabolic disorders such as obesity and diabetes. Dysbiosis is believed to potentially impact metabolic homeostasis via the GBA, a pathway implicated in neurological conditions such as AD. [40, 41] Furthermore, dysbiosis has been associated with bone conditions, including osteoporosis and rheumatoid arthritis. The intricate connection between the gut microbiota and bone health, involving nutrient uptake and the gut-brain-bone axis, reveals that gut disruptions can diminish bone density and health. [41, 42] Alcohol consumption further promotes dysbiosis, compromising the gut, liver, and brain by increasing intestinal permeability, thereby allowing bacterial byproducts to affect other organs and worsen associated diseases. [43]

Potential Biomarkers for Gut Dysbiosis and Its Implications

The detection of urolithin (a class of metabolites derived from colonic microbial degradation of dietary fiber in the human gut) in urine provides a noninvasive method for identifying gut dysbiosis and inflammation in PD. At the same time, reduced levels of *Roseburia* species show promise as a PD marker. [44] Microbial metabolites, such as indoxyl sulphate, could serve as diagnostic biomarkers for dysbiosis and neurological conditions, and an abundance of Enterobacteriaceae may predict poststroke cognitive impairment. [3]

MECHANISMS LINKING GBA TO NEURODEGENERATION

The dysregulation of the GBA contributes significantly to the pathogenesis and progression of NDDs through multiple interconnected mechanisms (**Figure 2**).

Inflammation and Neuroinflammation

The gut microbiota modulates immune responses via the GBA, and dysbiosis can trigger systemic inflammation that promotes neuroinflammation. An altered microbiota produces endotoxins and reduces beneficial metabolites, activating immune cells and disrupting the intestinal and BBB. This disruption facilitates the entry of peripheral proinflammatory cytokines, which stimulate microglia in the brain and exacerbate neurodegenerative processes. Therapeutic interventions targeting microbiota restoration, reduction of inflammation, and neuroimmune modulation are promising strategies. [45, 46]

Oxidative Stress

Reactive oxygen species (ROS) are upregulated in NDDs such as PD and AD, compromising BBB integrity and neural cells. Oxidative stress induces lipid peroxidation, DNA damage, mitochondrial dysfunction, and protein modifications, thereby increasing BBB permeability to neurotoxic agents and aggravating neuroinflammation. Nutritional compounds that activate antioxidant pathways, such as Nrf2, including polyphenols, can suppress ROS overproduction, thereby protecting the BBB and neurons. [47–49]

Neurotransmitter Production and Regulation

The gut microbiota influences the synthesis and regulation of key neurotransmitters, including dopamine and serotonin, modulating neural signaling and brain function. Dysbiosis can impair intestinal and systemic neurotransmitter balance, contributing to neurodegeneration, especially in disorders like PD, where dopaminergic neurons are lost. Restoring gut microbial balance may improve neurotransmitter regulation. [50]

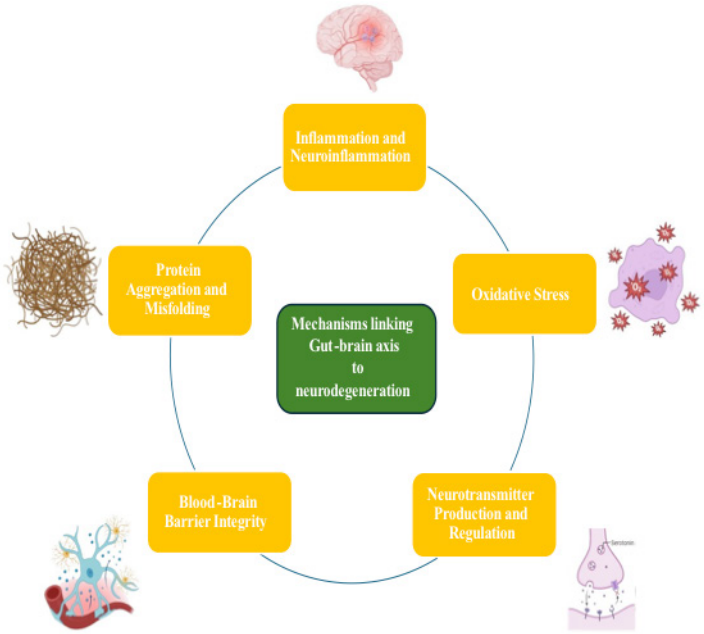

Figure 2: Mechanisms linking gut-brain axis to neurodegeneration.

BBB Integrity

BBB plays a pivotal role in shielding the brain from peripheral insults. Dysregulation of the gut microbiota and peripheral inflammation precipitate BBB disruption, increasing its permeability to cytotoxic substances and inflammatory mediators. This barrier dysfunction amplifies neuroinflammatory cascades and neuronal damage, phenomena exacerbated by oxidative stress. Furthermore, regional heterogeneity in BBB vulnerability influences disease progression. Emerging therapeutic strategies aim to preserve or restore BBB integrity by modulating the gut microbiota and employing targeted anti-inflammatory interventions. [51–53]

Protein Aggregation and Misfolding

Gut microbiota dysbiosis has been implicated in pathological protein misfolding and aggregation, notably α-synuclein in PD and amyloid-β in AD. Microbially mediated chronic inflammation and impaired clearance and mechanisms precipitate protein aggregation within the enteric nervous system, which may subsequently propagate to the CNS via the GBA. Epigenetic modifications driven by the microbiota also contribute to these pathogenic pathways, underscoring the gut microbiome as a viable target for therapeutic strategies to mitigate proteinopathy-related neurodegeneration. [45, 54] Collectively, GBA dysregulation orchestrates a complex interplay of inflammation, oxidative stress, neurotransmission disruption, barrier dysfunction, and proteinopathy that underpins NDDs. Targeting these interconnected mechanisms, particularly by modulating the gut microbiome and its metabolites, holds significant promise for developing preventive and therapeutic strategies for these debilitating diseases.

GBA ALTERATIONS IN SPECIFIC NDDS

Parkinson's Disease (PD)

The GBA plays a pivotal role in the etiology and progression of PD. This axis constitutes a bidirectional communication network between the gut and brain, encompassing neural, endocrine, and immune pathways, with the vagus nerve playing a fundamental role. [55, 56] A pathological hallmark of PD is the accumulation of misfolded α-synuclein proteins in both the brain and the enteric nervous system, implicating a pathogenic link mediated by the GBA. [55, 67] Gastrointestinal dysfunction often precedes the motor symptoms of PD, suggesting that gut health may be integral to the early identification and diagnosis of the disease. Dysbiosis, or imbalances in the gut microbiota, can increase intestinal permeability and inflammation, thereby contributing to the neurodegenerative processes characteristic of PD. [56, 58] Emerging research highlights the gut-brain connection as a crucial role in PD development through mechanisms involving neuroinflammation, mitochondrial dysfunction, and the aggregation of α-synuclein. Modulation of the gut microbiome through dietary interventions or probiotics holds promise for modifying disease progression or symptom severity. [59, 60]

Alzheimer's Disease (AD)

Research on the GBA highlights the profound implications of gut microbiota for the progression and management of AD. Studies suggest that alterations in the gut microbiome contribute to increased intestinal permeability, BBB dysfunction, and neuroinflammation, collectively exacerbating AD pathology. Dysbiosis, characterized by reduced microbial diversity and increased pro-inflammatory bacteria, has been linked to AD pathogenesis and may indicate potential targets for intervention. Therapeutic strategies emphasize modulating the gut microbiota to mitigate or prevent AD. Probiotics, such as Bifidobacterium breve, have been shown to attenuate neuroinflammation and synaptic dysfunction and to alleviate cognitive deficits in AD models by restoring gut microbiota composition and gut-brain communication. [61] Additionally, oral administration of gut metabolites, such as indole-3-acetic acid, has been shown to cross the BBB and reduce AD pathology, further underscoring the therapeutic

potential of targeting the GBA. [62] Physical activity, acting through the muscle-GBA, also beneficially modulates the gut microbiome and may ameliorate AD symptoms, highlighting the critical role of lifestyle factors in AD management. [63] In summary, the GBA presents a promising paradigm for understanding and potentially treating AD. By harnessing the gut microbiome and leveraging its influence on brain health, we may develop novel, effective interventions to delay or modify the trajectory of AD. [64]

Multiple Sclerosis (MS)

MS is a chronic, immune-mediated inflammatory disease of the CNS characterized by demyelination, gliosis, and neuronal loss. Individuals with MS often exhibit an altered gut microbiome, increased intestinal permeability, and changes in bile acid metabolism. [65] Methods for modifying this axis have included administering antibiotics, FMT, and probiotic supplements, with promising results in preventing CNS inflammation. [66] The microbiota's relationships with MS underscore the need to understand the gut microbiota in patient responses to disease-modifying drugs and overall disease activity. [67] SCFAs, metabolites produced by gut bacteria, have anti-inflammatory effects in both the gut and the CNS. They play a crucial role in modulating regulatory T lymphocyte expression and influencing BBB permeability, and they offer potential therapeutic implications for MS. [68]

Amyotrophic Lateral Sclerosis (ALS)

ALS is a devastating neurodegenerative disease that primarily affects the voluntary muscles and often leads to muscle paralysis and respiratory failure. [40] Studies indicate that alterations in the gut microbiota, including dysbiosis characterized by changes in composition and diversity, are associated with ALS. These alterations can lead to neuroinflammation, oxidative stress, and potentially exacerbate the progression of ALS. [69] This dysbiosis is characterized by reduced microbial community diversity and shifts in specific microbial types, including a decline in *Ruminococcus* species and a low Firmicutes/Bacteroidetes ratio, both of which are essential for maintaining gut health. [70] The studies also reveal that these microbiome deviations can lead to increased intestinal inflammation, which may facilitate neurodegenerative processes through the GBA. [71]

THERAPEUTIC IMPLICATIONS AND POTENTIAL INTERVENTIONS

Therapeutic modulation and the Promising interventions include dietary modifications (high-fiber), prebiotics, probiotics, and psychobiotics, fecal microbiota transplantation (FMT), vagus nerve stimulation (VNS), small-molecule modulators of the GBA, as shown in **Figure 3**, which hold significant potential for treating neurological and psychiatric disorders by targeting gut microbiota to reduce neuroinflammation, regulate the HPA axis, and restore intestinal permeability.

Dietary Interventions and Nutritional Approaches

Research in nutritional psychiatry highlights the important role of diet in mental health through its effects on the gut microbiota. For instance, a "healthy" diet characterized by a high intake of fruits, vegetables, legumes, nuts, whole grains, and quality protein sources, such as fish, is associated with a reduced risk of mood disorders. Conversely, a "Western" diet is associated with increased risks. [72] The Mediterranean diet is recognized as a beneficial dietary pattern for promoting gut health and enhancing cognitive and emotional well-being. It is well known for its beneficial effects on mood regulation and mental health. [73, 74] Moreover, this diet, combined with fermented foods and dietary fiber, can significantly influence the gut microbiota, thereby affecting the signaling pathways

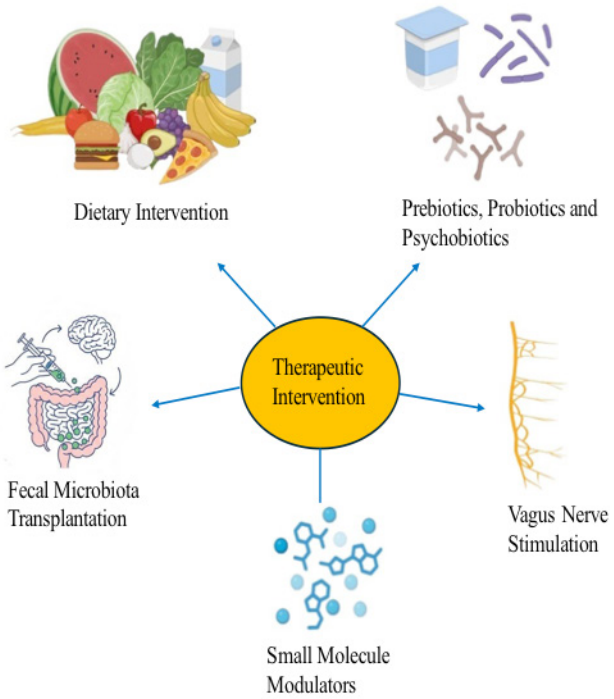

Figure 3: Current and emerging therapeutic perspectives.

of the GBA and promoting cognitive health. [75] Dietary fibers, known for their gastrointestinal health benefits, also contribute to mental health by serving as substrates for beneficial gut bacteria, which produce SCFAs that support neuroprotection. [76] These SCFAs, along with vagus nerve activity and various gut-derived metabolites, facilitate communication between the gut and brain and modulate processes such as inflammation and neurotransmitter production, which are vital for mental health. [74, 77]

Prebiotics, Probiotics, and Psychobiotics

Prebiotics are non-digestible fibers that selectively promote the growth and activity of beneficial microorganisms in the gut. [78] Prebiotics enhance the diversity and metabolic activity of the microbiota, thereby improving intestinal function and regulating immune responses that may, in turn, indirectly influence mental health. Recent studies have highlighted the potential role of prebiotics in modulating AD and other NDDs; however, robust human clinical trials are required to confirm these effects. [79] Probiotic strains such as Bifidobacterium breve A1 have been shown to improve cognitive function in AD models by downregulating immune-response genes and reducing inflammatory markers in the hippocampus. [80] Psychobiotics are a novel class of probiotics and prebiotics that act on CNS functions and behaviors through the immune, humoral, and metabolic pathways of the GBA, showing potential to improve motor function in PD. [81] These strains have been reported to suppress inflammation and reduce cortisol levels, thereby alleviating symptoms associated with anxiety and depression. [82] Moreover, they show therapeutic potential in NDDs like AD and PD, with evidence suggesting enhanced cognitive function in AD and improved motor outcomes in PD patients. [83] Additionally, meta-analyses of PD clinical trials indicate that probiotics and synbiotics effectively mitigate non-motor symptoms, such as chronic constipation. [84]

Fecal Microbiota Transplantation (FMT)

FMT, traditionally used to manage Clostridium difficile infections, is now being explored as a strategy to restore microbial homeostasis and modulate the GBA in NDDs. [85] Studies highlight that FMT can yield non-GI benefits. For example, patients with irritable bowel syndrome indicate that FMT can significantly improve neuropsychiatric symptoms, such as anxiety and depression, independently of changes in GI function. These findings highlight that microbiota restoration can directly influence brain function. [86] Despite these promising observations, the clinical translation of FMT in NDDs remains complex and challenging. A pilot study evaluating the safety and tolerability of FMT in patients with MS was terminated prematurely, resulting in inconclusive findings regarding CNS outcomes, such as magnetic resonance imaging (MRI) parameters and Expanded Disability Status Scale (EDSS) scores. Nevertheless, the study reported alterations in gut microbial composition and improvements in small intestinal permeability. Although FMT shows promise, researchers face significant challenges due to stringent regulations, safety concerns, and interdonor variability. [86] A central observation across microbiota-targeted trials is the substantial gap between observed peripheral GI efficacy and consistent central, that is, cognitive and motor, efficacy in large human cohorts. Although specific microbial strains have been shown to attenuate hippocampal inflammation in preclinical models, convincing clinical evidence demonstrating direct reversal or substantial modification of core NDD symptoms remains limited. This discrepancy suggests that current intervention and delivery strategies may not reliably achieve the therapeutic concentration necessary to elicit the CNS effects. Consequently, future research should prioritize the development of optimized, targeted delivery systems and the incorporation of validated central biomarkers, such as cerebrospinal fluid (CSF) metabolomics, to confirm CNS pathway engagement, rather than relying solely on GI effects. [84, 87, 88]

Vagus Nerve Stimulation (VNS)

VNS is developing as a powerful non-microbial strategy that directly controls the microbiota-GBA. VNS interferes with vagus nerve activity, thereby regulating the cross-system network that connects neuroimmune and neuroendocrine function. Its mechanisms include indirectly regulating gut microbiota composition, inhibiting central and peripheral neuroinflammatory responses, modifying HPA axis function, and enhancing brain plasticity and neurotrophic factor secretion. VNS is particularly relevant in PD, as it directly targets the primary bidirectional neural communication pathway connecting the GBA and may confer therapeutic benefit, particularly in patients with a CNS-first disease subtype in which gut-derived pathology is less prominent. [89]

Small-Molecule Modulators

Small-molecule inhibitors of trimethylamine (TMA) formation, such as 3,3-dimethyl-1-butanol, have successfully reduced trimethylamine N-oxide (TMAO) levels and attenuated A$/beta$ pathology in AD mouse models, resulting in improved cognitive function. This precision metabolic targeting represents a highly promising avenue for developing pharmaceutical interventions that modulate the downstream effects of dysbiosis without wholesale alteration of the gut environment. [33]

CHALLENGES AND FUTURE DIRECTIONS

Current Limitations in Research

Current research on the GBA faces several challenges and limitations. Interindividual variation in gut microbiota composition complicates the ability to draw consistent conclusions, especially in conditions such as obesity and metabolic syndrome. The translational relevance of preclinical findings to human physiology remains uncertain due to these complexities and the multifactorial influences on the microbiome. [90, 91]

Emerging Technologies and Methodologies

Emerging technologies are significantly advancing research into the GBA. Organ-on-a-chip platforms, particularly on gut-brain-on-a-chip models, recreate key structural and cellular features of both gut and brain under controlled in vitro conditions. These techniques enable researchers to study biological and pathophysiological processes in real time without relying on animal models, which often have limitations due to poor reproducibility and interspecies differences. Consequently, organ-on-a-chip technologies offer a more

precise means of studying bidirectional communication between the GBA, with promising applications in drug development and personalized research. In addition, recent advances in wearable and miniaturized sensors enable non-invasive monitoring of biomarkers related to gut and brain health. [92, 93]

Potential for Personalized Medicine Approaches

Advances in Artificial Intelligence (AI) and bioengineering techniques allow for precision therapies personalized to an individual's microbiota profile and genetic makeup. These approaches potentially improve patient stratification, diagnosis, and therapeutic outcomes. Microbiota-based biomimetic innovations, consisting of personalized probiotics and artificial microbiomes, are being developed to optimize microbial ecosystem functions and address health challenges. However, ethical concerns, such as privacy and equitable access, as well as the complexity of reproducing the microbial ecosystem in artificial environments, present ongoing challenges. [94, 95]

Need for Standardized Protocols and Biomarkers

Standardization would enhance the reproducibility and comparability of studies by addressing the variability inherent in microbiome and metabolite analyses. Reliable biomarkers are crucial for evaluating GBA function, diagnosing disorders, and monitoring therapeutic responses. This consists of developing robust methods for tracking microbiome dynamics, metabolomic profiling, and integrative multi-omics analysis. The complexity and inter-individual variability of the GBA necessitate multidisciplinary, longitudinal studies to characterize mechanisms and fully develop targeted interventions. [90, 91]

CONCLUSIONS

The GBA characterizes a crucial integrative system linking gastrointestinal physiology and neural function through a diverse network of biochemical, immunological, and neuroendocrine mechanisms. Evidence progressively supports its significant effect on the onset and progression of NDDs through interactions including inflammation, oxidative stress, neurotransmitter regulation, and barrier integrity. Dysbiosis, driven by disruptions in this network, can initiate or amplify neurodegenerative cascades, highlighting the gut microbiota as both a biomarker and a therapeutic target. Nutritional interventions, probiotic and prebiotic formulations, and advanced strategies, including FMT and VNS, offer encouraging avenues for modulating gut-brain communication. Nonetheless, variability in clinical outcomes underscores the need for more precisely defined mechanistic frameworks, standardized methodologies, and validated biomarkers that accurately reflect GBA function. The future of neurodegenerative disease management lies in personalized, systems-based approaches integrating microbiome profiling, metabolomics, and bioengineering innovations. Through such integrative efforts, targeting the GBA could enable novel, effective interventions to preserve cognitive and neural health across diverse clinical contexts.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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