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Review Article

Emerging Insights into Gut-Brain Axis Dysregulation in Neurodegenerative Disorders

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ABSTRACT

This review explores the emerging insights into the gut-brain axis (GBA) and its dysregulation in neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's. The GBA represents a complex communication network linking the intestinal microbiome with the central nervous system (CNS), facilitated by neuro-immuno-endocrine mediators. Such interactions profoundly influence brain health, cognitive functions, and various systemic diseases. Dysbiosis of gut microbiota may be implicated in the pathogenesis of neurodegenerative conditions through mechanisms involving inflammation, metabolic regulation, and neurotransmitter activity. Additionally, dietary habits, lifestyle choices, and environmental factors significantly affect individual gut microbiota profiles, further shaping neurological health. The review highlights the potential of microbiome-based therapies as innovative intervention strategies, emphasizing the metabolic contribution of gut bacteria, such as short-chain fatty acids (SCFAs), to brain function and mood regulation. Understanding these intricate relationships paves the way for novel therapeutic targets to ameliorate neurodegenerative symptoms and enhance overall brain health.

KEYWORDS: Gut-Brain Axis, Alzheimer's, Huntington's, Parkinson's

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1. Introduction

The gut-brain axis is defined as the two-way communication network that connects the intestinal microbiome with the central nervous system (CNS) [1,2]. The two-way communication system, the gut-brain axis, is mediated by the enteric nervous system, microbial metabolites, and gut microbiota. It includes neurological, hormonal, and immunological pathways. The gastrointestinal tract and the central nervous system communicate in both directions through immunological, endocrine, humoral, and neurological connections [3]. The mechanisms underlying GBA communications involve neuro-immuno-endocrine mediators. The gut-brain axis is recognized as one of the major pathways by which properties and health status of the microbiome can influence not just brain health but also various types of diseases across all other systems in the body [4,5]. Alzheimer's, Parkinson's, and Huntington's diseases are some examples of neurodegenerative disorders that are characterized by progressive neuronal loss and dysfunction over time, leading to decreased cognition and motor functions [6,7]. Gut microbiomes play key roles in neurological disorders, mainly through regulating inflammation, communication, and metabolism with the CNS. There is potential for customized microbiome-based therapies due to the complicated interactions between nutrition, microbiota makeup, and neuro-health (Fig. 1) [2,4,8,9]. Complex carbs and fibers are metabolized by intestinal microbiota. This procedure indirectly suggests involvement from a metabolic route because it directly affects the host's energy balance and metabolic health. The gut flora also influences the immune system's maturation and development. It is a crucial defense mechanism against external microorganisms because it increases infection resistance and affects systemic immunity. Additionally, the production of conjugate bile acids and vital vitamins by the gut microorganisms aids in the breakdown of fat. The fermentation of food fibers into short-chain fatty acids (SCFAs), a form of host signaling chemical and energy source, is an example of the gut microbiome's metabolic function [10]. The expression of the individual's gut microbiota can be easily reflected by geographical and cultural differences in lifestyle choices, environmental exposures, and dietary habits (Fig. 2) [11]. Various factors, including drug use, stress levels, sleep patterns, and physical exercise, may impact the gut flora. According to [12], These factors modify the microbial population, which impacts its makeup and capabilities. Hormonal signaling, a crucial pathway in gut-brain communication, is how the gut bacteria work. For instance, changes in tryptophan metabolism linked to the gut microbiota impair serotonin activity in the brain and are a contributing factor to mood disorders that are accompanied by gastrointestinal dysfunction [1]. This modulation can also improve a person's ability to process emotions and thoughts. The brain-gut link depends on SCFAs and other signaling chemicals [5]. The artificial synthesis of these molecules could be a novel therapeutic target for neurodegenerative diseases. Hormonal signaling, a crucial pathway in gut-brain communication, is how gut bacteria work. For instance, changes in tryptophan metabolism linked to the gut microbiota impair serotonin activity in the brain and are a contributing factor to mood disorders that are accompanied by gastrointestinal dysfunction [1]. Progressive loss of neurons or other neurological cells inside the central nervous system is the primary cause of neurodegenerative disorders. These neurodegenerative illnesses can have a wide range of pathologies and symptoms, and the majority of them have different causes and processes. Because of these cell losses, neurons are particularly vulnerable to harm [6]. According to current theories, extracellular amyloid plaques and intraneuronal neurofibrillary tangles composed of tau proteins and amyloid-β peptides are the main components of Alzheimer's disease pathogenesis. In addition to interfering with synaptic processes essential for memory and cognition, these toxic deposits cause synapse loss by impairing axon and dendritic maintenance or neuron death. The development of neurodegenerative illnesses may be impacted by increased gut and blood-brain barrier leakiness, brain amyloid and lipopolysaccharide release, and inflammatory reactions by the gut microbiota [8,13]. According to a study, the gut microbiota and its metabolites, glutamine and serotonin, respectively, raised the risk of Parkinson's and Alzheimer's illnesses. These findings provide insight into the underlying mechanisms of neurodegenerative disorders and demonstrate the potential of gut bacteria and its metabolites as therapeutic targets [14].

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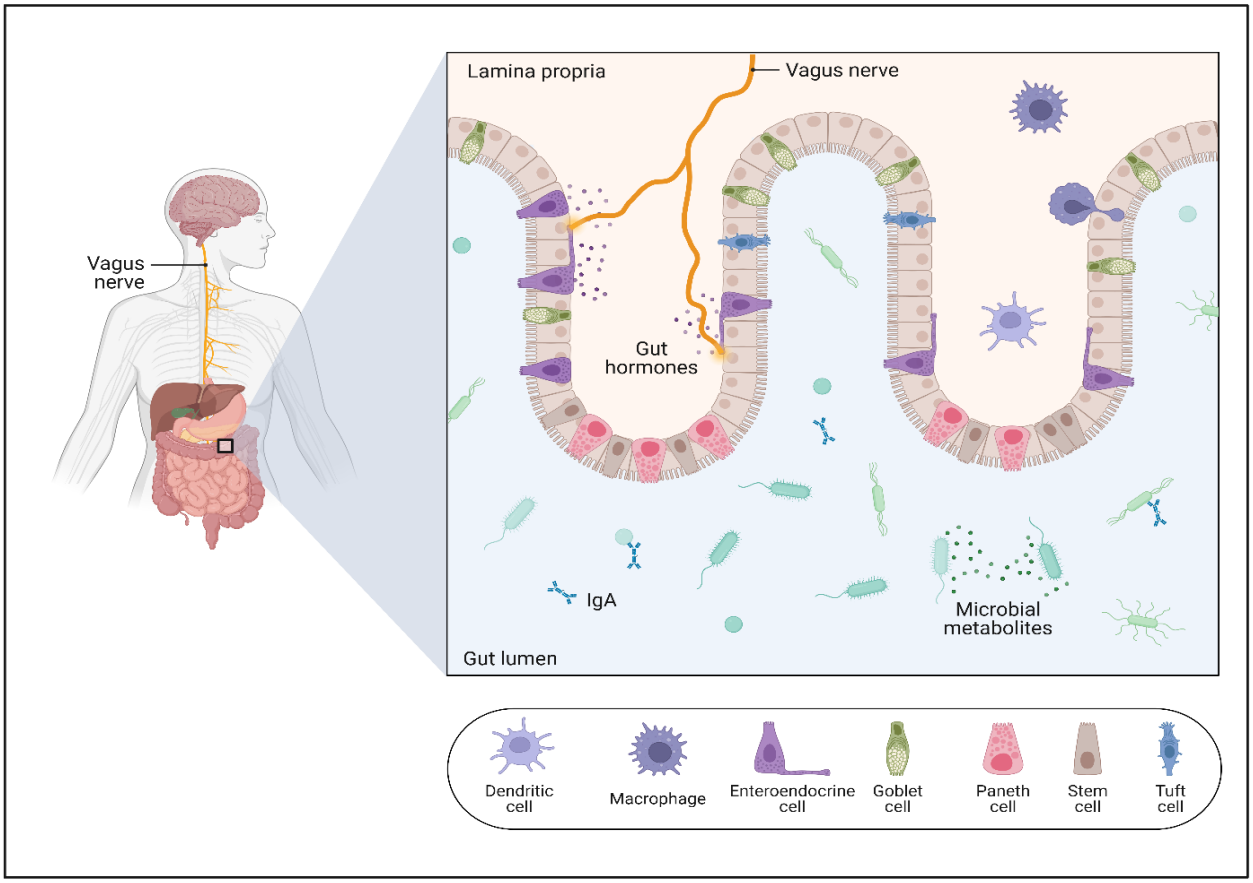

Figure 1. This diagram emphasizes the anatomical and functional link between the gut and brain, mediated by the vagus nerve. It showcases gut hormones, microbial metabolites, and immune cell interactions within the gut epithelium, represented by various cell types, including enteroendocrine cells, goblet cells, and macrophages. The vagus nerve transmits chemical signals from the gut lumen to the brain, influenced by bacterial activity and metabolites. Key immune responses, such as IgA secretion, further underline the complexity of gut-brain interactions.

Another study investigated how certain dietary and lifestyle choices affect how the gut microbiota regulates neurodegenerative diseases and how non-pharmacological therapies targeting gut microbiota, food, and lifestyle can enhance brain resilience or alterations [15]. Dietary behaviors have an indirect impact on adult neurogenesis and gut microbiota composition, as well as a direct impact on neuronal function and brain health [15]. Fatty acids with short-chain SCFAs from the gut microbiota improve the elimination of cellular waste and reduce histone acetylation. It affects neurodegeneration and is an example of the intricate relationships between gut flora and brain function [16]. In addition to influencing neurogenesis and brain aging concerning neurodevelopmental age-related and neurodegenerative illnesses, the gut microbiota also controls the activity of neural stem cells in these brain regions where new neurons are produced [17]. Dysbiosis, an imbalance in the gut microbiota that disrupts the gut microbial ecology, causes neurodegenerative disorders of varying stages and severity [18]. Recently, it has been discovered that some types of gut microbiome dysbiosis are caused by dementia and correlate with autoimmune dysregulation, chronic inflammation, and protein misfolding [18]. For instance, intestinal inflammation and gastrointestinal symptoms have been linked to changes in gut microbiomes in Parkinson's disease.

2. Gut-Derived Metabolites

According to [19], microbial products are crucial for immune system performance, cognitive health, and nutritional absorption. Gut-derived tryptophan metabolites highlight the connection between brain health and microbiota and are linked to neurological diseases [20]. High trimethylamine -N-oxide and indoxyl

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sulfate reflect the intricate relationship between the brain and gut [21]. New therapy options that emphasize the significance of preserving gut and brain health are provided by microbial metabolites in the gut-brain axis that disclose the causes of neurodegenerative illnesses (Fig. 3) [9]. The gut microbiota produces SCFAs from dietary fibers, crucial for brain function and digestive health. Butyrate is the SCFA that has been shown to have the biggest impact on neurodegenerative illnesses. According to one study, butyrate may lessen neuroinflammation in models of Alzheimer's disease [22]. These acids participate in processes that impact the metabolism of fats and cholesterol [19]. Because they alter the blood-brain barrier, lower neuroinflammation, and promote neurogenesis, SCFAs have a major effect on brain health. However, butyrate Histone deacetylase inhibitors provide neuroprotection by controlling gene expression. For instance, a preclinical investigation showed that butyrate can reduce Alzheimer's disease-related amyloid β. Excessive SCFAs can disrupt microglia activity and cause α-synuclein misfolding, linked to Parkinson's disease [23]. However, because it alters the phenotype of microglia, it may cause amyloid β to develop in Alzheimer's disease [24]. It is known that some SCFAs alter microglial activation in Parkinson's disease, suggesting a potential strategy to slow the disease's progression [25]. Through various methods, these metabolites generated by the gut microbiota regulate the brain's inflammatory processes. They penetrate the blood-brain barrier and alter the activity of brain immune cells called microglial cells, which control inflammatory reactions in the central nervous system [25]. SCFAs play a dual role in neurodegenerative diseases, demonstrating the complex interplay between gut microbiota and brain function.

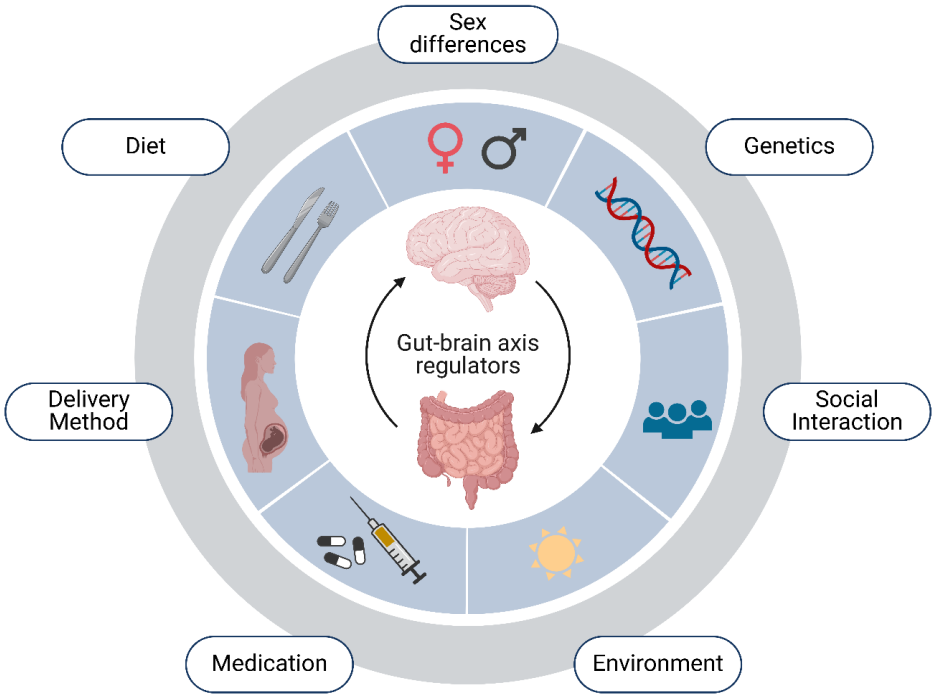

Figure 2. Factors that contribute to the regulation of the gut-brain axis.

According to [26], tryptophan was mostly broken down by the kynurenine pathway, which produced active substances that impacted the brain. Among the chemicals formed are quinolinic acid, kynurenine, and kynurenic acid [27]. By preventing the stimulation of neurotransmitters at NMDA receptors, kynurenic acid protects the brain. Because it activates NMDA receptors, quinolinic acid is neurotoxic and can lead to inflammation and cell death in Parkinson's and Alzheimer's illnesses [28]. Other microbial metabolites also influence CNS's function [29]. One of tryptophan's primary metabolites, kynurenine, is further broken

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down to produce neurotoxic or neuroprotective compounds. Similarly, gut microbiota-derived bile acids and lipopolysaccharides (LPS) influence neuroimmune responses and can accelerate neurodegenerative processes [30]. The gut bacteria's ability to metabolize bile acid appears compromised in Alzheimer's disease, suggesting that it plays a particular function in gut-to-brain communication. In the context of neurodegenerative disorders, lipopolysaccharides and other microbial metabolites may have the capacity to cause neuroinflammation. It has been suggested that quinovic acid glycosides, produced by the gut microbiota, activate neuroinflammatory pathways, including those connected to Parkinson's disease [31-33]. Because LPS-induced neuroinflammation decreases hippocampal progenitor cell proliferation, survival, and differentiation, it is more intimately associated with neurodegenerative processes [34]. Neurological illnesses are further caused by the coexistence of neuroinflammation and chronic systemic inflammation, as well as by BBB destruction during LPS induction and chronic systemic inflammation [35]. In this reciprocal exchange, neurotransmitters are also essential. By altering neurotransmitters, including catecholamines (epinephrine, norepinephrine, and dopamine), serotonin, glutamine, and γ-Aminobutyric acid (GABA), the gut microbiota can have an impact on brain function [36]. These neurotransmitters can be produced by the gut microbiota alone or affect how they are synthesized and metabolized. Neurotransmitters synthesized in the stomach have little chance of getting to the brain since the BBB shields the brain from all undesirable infections and metabolites. GABA, the primary inhibitory neurotransmitter of the host nervous system, is the sole exception [9]. While the neurotransmitters generated in the gut act on the ENS and have a covert effect on the brain, some transporters transfer GABA over the blood-brain barrier [37,38].

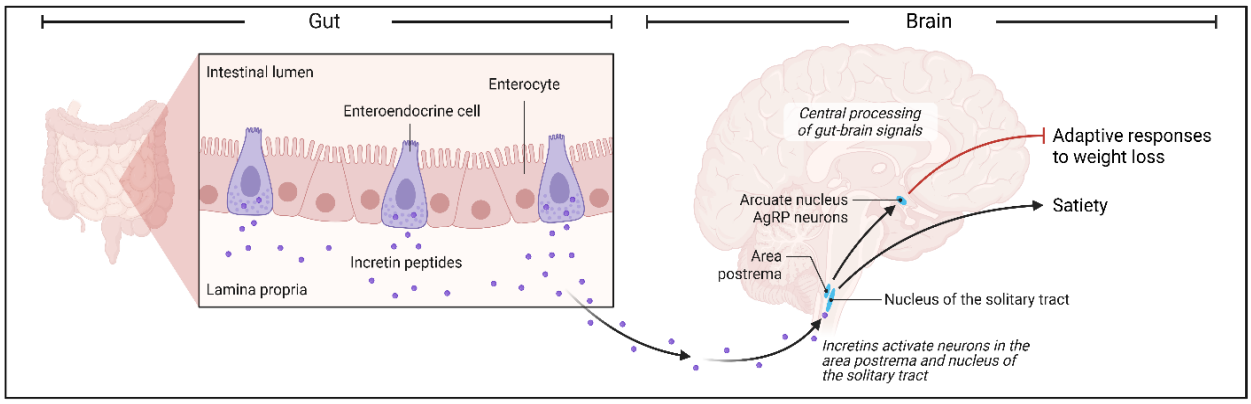

Figure 3. Gut-Brain Axis and Incretin Peptides in Weight Regulation and Satiety. This figure illustrates the interaction between the gut and brain via incretin peptides released by enteroendocrine cells in the intestinal lining. These hormones travel through the bloodstream and stimulate the nucleus of the solitary tract and the area postrema in the brainstem. This signaling pathway influences satiety and adaptive responses to weight loss by modulating the activity of neurons in the arcuate nucleus, including AgRP neurons. Integrating gut-brain signals occurs centrally to regulate energy balance and weight homeostasis.

One of the main causes of neurodegenerative illnesses is oxidative stress, which can result from an imbalance between the body's oxidants and antioxidants. Trillions of helpful bacteria make up the gut microbiota, crucial for preserving redox equilibrium. Dysregulation of the gut microbiota has been closely linked to the emergence of neurodegenerative disorders caused by oxidative stress [39]. According to recent research, the intestinal epithelium cells generate physiological amounts of oxidative stress when the microbiota is present, which alters the gut microbiota's composition and function. By directly altering intestinal permeability, these changes in gut microbiota enhance the changes of biomacromolecules that enter the systemic circulation and central nervous system [40]. By controlling mitochondrial activity [41,42], gut microbiota can change the state of oxidative stress in cells. It is now widely acknowledged that NO is neuroprotective at nanomolar concentrations but that oxidative stress, intimately linked to axonal degeneration, neuroinflammation, and NDs, can occur at greater NO concentrations [43].

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3. How Gut Microbiota Communicate with Brain

Immune signaling, endocrine mediators, and neural communication are direct ways the gut microbiota affects the brain [44]. Various avenues exist for the gut microbiota to communicate with the brain [45,46]. The enteric nervous system, sometimes called a "second brain," is essential for sending signals from the gut to the brain; the vagus nerve transmissions are particularly significant [47-49]. One of the main channels for this communication is the vagus nerve, which transmits sensory data from the gut to the brain. According to research, numerous gastrointestinal parameters, such as food content and signals produced from the gut microbiota, can be detected by sensory neurons of the vagus nerve [50,51]. Because of this two-way contact, the gut can affect brain health and illness states, in addition to the brain influencing gut function (Fig. 4).

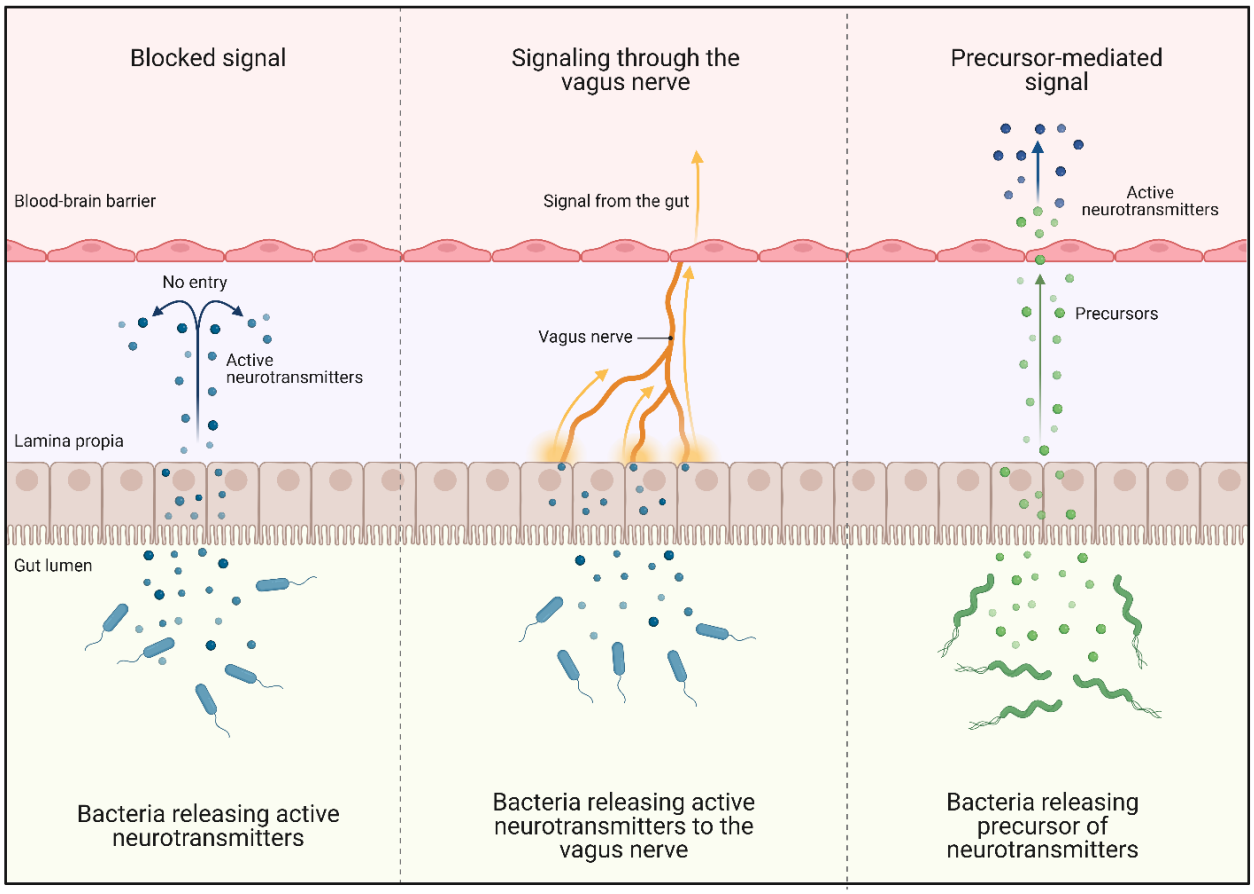

Figure 4. Three pathways through which gut bacteria influence brain function. (1) Blocked Signal: Active neurotransmitters released by gut microbes fail to cross the blood-brain barrier. (2) Vagus Nerve Signaling: Microbial neurotransmitters stimulate the vagus nerve, transmitting signals directly to the brain. (3) Precursor-Mediated Signal: Bacteria produce precursors, such as amino acids, which cross the barrier and are converted into neurotransmitters within the brain. Each mechanism demonstrates the role of the gut microbiota in modulating neural communication and behavior.

By activating vagal neurons and changing neurotransmitters like oxytocin and γ-aminobutyric acid (GABA) in the brain, the gut microbiota affects host behaviors, including anxiety, eating, and depression, according to recent studies [52-54]. A little VN activation causes excessive neurotransmitter activation and increases, hindering digestion and affecting stomach motility [55,56]. Additionally, VN has been shown to have immune-regulating effects on intestinal permeability and local immunity. Electrical vagal stimulation has been shown to reduce the activation of M1 macrophages and elevated levels of proinflammatory cytokines brought on by abdominal surgery. This may reduce inflammatory reactions following surgery and enhance postoperative recovery [57]. Additionally, electroacupuncture's activation of VN encourages the development and appropriate location of tight junction proteins, which reduces intestinal permeability

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and protects the intestinal epithelial barrier [47,58]. For the transmission of physiological signals from the gut to the brain, microbes depend on several kinds of cells found in the epithelium [59]. Less than 1% of epithelial cells are enteroendocrine cells (EECs), which release various substances involved in the metabolic digestion of dietary nutrients [60]. Because of their anatomical location and function, EECs interact with the gut microbiota to transmit hormone-based output signals to afferent neurons [61]. Furthermore, a study discovered that a particular subset of EECs can complete signal transduction from the gut through direct contact with vagal afferent fibers [62,63]. Serotonin, which is mainly produced by gut enterochromaffin cells and regulates several physiological functions, is another pathway that directly or indirectly influences brain activity. Remarkably, probiotic Bifidobacterium treatment reduced depression in a rat model of depression by increasing serotonin and serotonin precursors [64]. The gut barrier is one crucial barrier that supports and preserves health in gastrointestinal and systemic settings. Acting as a selective barrier allows the body to receive nutrients while keeping harmful substances and infectious organisms out of the general circulation [65]. The gut microbiota, which helps control immunological responses, has been directly linked to the operation of the gut barrier [66]. Increased gut permeability, or "leaky gut," results from disruptions in the gut microbiota and has been connected to several illnesses [67]. The BBB is a protective and selective barrier that keeps the brain safe from infections and blood from circulating away. The breakdown of the BBB has been linked to diseases of the gut flora. Accordingly, maintaining a healthy gut microbiota is essential for protecting the BBB [68]. The host's entire immune response is significantly influenced by the makeup and activity of the gut microbiota itself (Fig. 3) [69-71]. Given all of this knowledge, dysbiosis may result in immune-mediated inflammation on a local and systemic level and neuroinflammatory inflammation, which has been shown to contribute to neurodegeneration [72,73]. This dysbiosis of the gut microbiota may also be the source of chronic inflammation, which triggers systemic chronic inflammation by releasing pro-inflammatory cytokines and components of the bacterial cell wall. This increases the neurodegenerative effects of inflammatory mediators and neurotoxic chemicals by facilitating their entrance into the brain [74-76].

4. Gut Microbiota and Neurodegeneration

4.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative condition that gradually deteriorates the central nervous system (CNS) and causes cognitive loss. Amyloid-beta (Aβ) deposition in the extracellular space as neurotic plaques and intracellular buildup of hyperphosphorylated tau as neurofibrillary tangles (NFTs) remain the predominant neuropathological markers for diagnosing AD. Alzheimer's disease patients have severe behavioral, cognitive, and memory problems that significantly impact their day-to-day activities. Deposition of amyloid-β (Aβ) surrounding neurons, progressive synaptic failure, neuronal death, and hyperphosphorylated tau protein (also known as τ protein) aggregation in neuronal dendrites and axons are the hallmarks of this neurodegenerative disease [77]. The primary constituent of the plaques observed in AD patients is Aβ peptide [78]. These plaques are created when many pathogenic bacteria invade the brain, including HSV-1, CMV, Borrelia burgdorferi, Porphyromonas gingivalis, and others. The function of microbial metabolites in AD is also unusual, in addition to the alteration in gut diversity. There are two ways that the metabolites of the gut microbiota affect AD: either they are absorbed from the gut and travel through the systemic circulation to the brain, where they impact brain function, or they act on the local neuronal cells in the gut and surrounding tissues to send signals to the brain. According to [79-82], these metabolites include GABA, monoamines, SCFAs, BDNF, beta-methylamino-L-alanine, dopamine, and serotonin. The scientific community has begun investigating methods to modify the microbiome to alleviate AD pathogenesis. Although the gut microbiota can be altered in several ways, such as probiotics, prebiotics, antibiotics, symbiotics, and dietary changes, diet is still the predominant factor influencing the gut microbiota [83]. Similarly, new research has linked gut microbiota to the genesis of AD. The identification of a metabolic metabolite from the microbiota in the cerebral fluid of AD patients, related to

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biomarkers of the disease (phosphorylated tau and phosphorylated tau/Aβ42), suggests that the gut microbiota plays a role in the pathophysiology of AD [84]. Compared to APP animals under control, APP-mutant germ-free mice exhibit less cerebral Aβ amyloid pathology in an Aβ precursor protein (APP) transgenic mouse model. Rebuilding these germ-free APP animals with standard mouse microbiota could impede anti-Aβ effects [85]. Additionally, long-term broad-spectrum antibiotic therapy improves the neuropathological phenotype of AD animals and decreases Aβ accumulation [86]. When comparing the fecal microbiomes and fecal SCFAs of AD-stricken mice and WT mice at various ages, it is found that the former have significantly lower levels of Ruminococcus and Butyricicoccus and dramatically higher levels of Verrucomicrobia and Proteobacteria. This suggests that the microbiota's composition and diversity have changed, while the decreased level of SCFAs further suggests changes in numerous metabolic pathways [87]. Furthermore, prior research has demonstrated that activated microglia increase Aβ accumulation and limit Aβ clearance, contributing to AD pathogenesis [88]. Increased Aβ deposition causes microglia to generate a variety of proinflammatory mediators, such as iNOS, ROS, COX2, and NF-κB, leading to neuroinflammation in AD pathophysiology [88].

4.2. Parkinson's disease

Tremor, muscular rigidity, slowness of movement, and irregular gait are some of the multiple motor symptoms of Parkinson's disease (PD), a common neurological illness [89]. The primary pathology of PD is the death of dopaminergic neurons in the substantia nigra, which is followed by α-synuclein buildup and Lewy body deposition in the remaining neurons [90]. According to new research, α-synucleinopathy, linked to particular digestive symptoms, is first detected in the enteric nervous system before progressing to the central nervous system in the early stages of the illness [91]. Constipation and decreased colonic motor function have been observed in mice transfected with human wild-type α-synuclein. Notably, PD patients have increased exposure to gut bacteria because of their compromised intestinal function. Regular interaction between toll-like receptors (TLRs) and microbial metabolism results in increased local inflammation and impaired α-synuclein deposition clearance, both of which work together to cause Parkinson's disease neurodegeneration. Also, when PD patients' feces were used to colonize germ-free mice, the result was higher physical impairments than when healthy controls' feces were used [92]. Metagenomic studies of PD patients and healthy age-matched individuals have produced several lines of evidence that, while still debatable, indicate dysbiosis in the gut microbiome of PD patients may alter risk and gradually worsen disease status [92-94]. The microbial profiles of people with PD differ significantly from those of healthy controls [94]. While the genera Akkermansia, Lactobacillus, and Bifidobacterium rise in PD patients, dominant taxa (such as Lachnospiraceae, Ruminococcaceae, Faecalibacterium, Roseburia, and Butyriciccocaceae) that are a part of the core microbial community specializing in carbohydrate and energy metabolism and involved in the production of butyrate and other SCFAs decline [95,96]. Fiber deprivation promotes the growth of specific microbial communities that break down the colonic mucus layer and allow for increased colonization and infiltration of opportunistic pathogens since dietary fiber is essential for preserving the colonic mucus barrier [97].

5. Conclusion

In conclusion, the complex relationship between gut microbiota and brain function underscores the significant role that our gut health plays in neurological well-being. The pathways through which gut bacteria influence brain function, including neurotransmitter modulation, vagus nerve signaling, and the production of neuroactive precursors, highlight the complex mechanisms involved in this interaction. The evidence presented indicates that dysbiosis not only disrupts gut barrier integrity but also correlates with neuroinflammatory processes that can lead to neurodegenerative diseases such as Alzheimer's. As our understanding of the gut-brain axis expands, it becomes increasingly clear that maintaining a balanced gut microbiota is crucial for protecting both gut and brain health. Future research may further explore therapeutic interventions aimed at restoring gut microbiota composition, potentially offering new

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strategies for preventing or mitigating the effects of neurodegenerative disorders and enhancing overall cognitive function.

Author Contributions

Al-Hassan Soliman Wadan: Conceptualization, editing, writing original draft and reviewing. **Dana Saeed El- Gemaie:** writing original draft and reviewing. **Mohamed Abdelsattar Ahmed:** writing original draft.

Conflict of interest

The authors declare no conflict of interest.

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