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Gut Microbiome Brain Axis and its Role in Parkinson's Disease

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder with a rising global burden and limited treatment options. Increasing evidence suggests that Parkinson's disease is not only a central nervous system disorder, but also involves gut-derived signaling through the gut-microbiome-brain axis. Gut dysbiosis in Parkinson's disease may contribute to α -synuclein aggregation through various mechanisms that may promote neuroinflammation and dopaminergic neuronal injury. Bearing this concept in mind, various microbiome-targeted strategies, such as fecal microbiota transplantation, dietary modification, prebiotics, probiotics, and exercise, have shown potential improvements in patients with Parkinson's disease. However, current evidence remains limited by inconsistent microbial signatures, uncertain causality, small clinical trials, and a lack of standardized therapeutic protocols. Further mechanistic and large-scale clinical studies are required before gut microbiome-based therapies can be integrated into routine Parkinson's disease care.

Keywords: Alpha-synuclein, Braak's hypothesis, dietary modification, dysbiosis, enteric nervous system, gut-microbiome-brain axis, microbiota, Parkinson's disease

1. Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders worldwide, profoundly impacting patients' quality of life (QoL) and diminishing functional independence. Over recent decades, its global burden has escalated dramatically, with cases rising from 3.15 million in 1990 to 11.77 million in 2021¹. East Asia has experienced a great surge, reporting 5.21 million cases in 2021, a staggering 675.21% increase since 1990 (Figure 1). China, in particular, has emerged as the nation with the highest age-standardized incidence rate (ASIR) and disability-adjusted life years (DALY)². Despite advances in symptomatic therapies, current treatments for PD only offer partial and often costly relief, benefiting just half of those affected.

The motor degenerative symptoms such as tremors and stiffness appear after 60-80% dopaminergic neurons in the substantia nigra are destroyed. However, gastrointestinal (GI) symptoms such as severe, chronic constipation develop 15-20 years before the motor symptoms. The time in between is referred to as the prodromal period. Consequently, there is a growing focus on therapeutic strategies involving the GI system and its microbiome³. This article explores the emerging role of the gut-microbiome-brain (GMB) axis in the

pathogenesis of PD and evaluates their promise as future therapeutic targets.

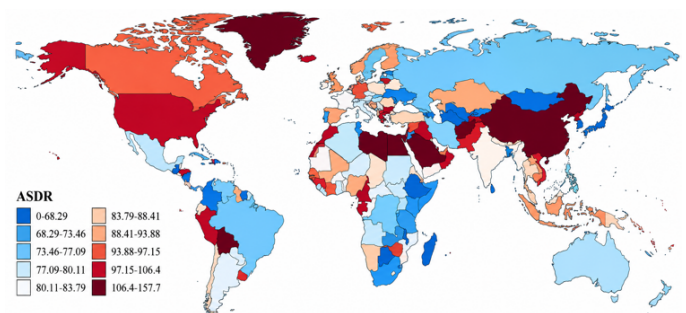


Figure 1: The ASDR/100,000 population of Parkinson's disease at the national level in 2021¹

ASDR: Age standardized disability-adjusted life years rate

2. Overview of Gut-Microbiome-Brain Axis

The GMB axis is centered on the gut microbial community, a complex and dynamic ecosystem comprising approximately 100 trillion microorganisms. These microbes support host health through metabolic functions while also contributing to the communication between the GI

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system and brain.

This axis integrates the enteric nervous system (ENS), central nervous system (CNS), autonomic nervous system (ANS), hypothalamic-pituitary axis (HPA), immune network, and endocrine signaling. Gut bacteria may influence brain activity by producing neurotransmitters, which include dopamine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, and norepinephrine⁴.

3. Core Communication Pathways of Gut-Microbiome-Brain Axis

3.1. Neural

Vagal nerve afferents transmit microbial and gut-derived signals from the intestine to the brain stem and higher brain regions. It involves 80% afferent fibers and 20% efferent fibers, thus creating a bidirectional circuit⁵. The ENS also serves as a mediator⁶.

3.2. Immune

Macrophages, lymphocytes, and dendritic cells can be activated by the gut microbiome via pattern recognition receptors (PRRs). This releases cytokines which affect CNS inflammation. They can also affect neuronal function, synaptic plasticity and glial cell activation⁷.

3.3. Metabolic

Short-chain fatty acids (SCFAs) come from microbial fermentation of dietary fiber in the colon. They can enter circulation through monocarboxylate transporters or diffusion. They regulate brain function by modulating the blood-brain barrier (BBB), G protein-coupled receptor (GPCR) signaling, epigenetic regulation, and gut hormone release. Gut microbiome metabolism of tryptophan also plays a role. It affects serotonin synthesis, produces kynurenine pathway metabolites eventually activating the aryl hydrocarbon receptor (AhR) pathways⁸.

3.4. Endocrine

The microbiome influences the HPA by producing gut peptides and hormones that can help modulate stress and mood changes. Additionally, microbial metabolites such as ammonia and bile acids can influence BBB permeability, thus allowing for further CNS modulation⁹.

4. Factors Causing Gut-Microbiome-Brain Axis Alterations and Microbiome Dysbiosis

Gut microbiota is shaped at birth by the delivery method and it loses diversity with age. Diet remains one of the strongest modulators: high-fiber, plant-based, and Mediterranean dietary patterns support beneficial bacteria and SCFA production, whereas Western diets are associated with reduced diversity. Furthermore, antibiotic exposure, geography, migration, hygiene practices, travel, physical activity, and psychological stress can disturb microbial balance. Additional contributors include genetic background, gastric acid production, refined-sugar or ultra-processed diets, and non-antibiotic medications such as proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), metformin, antipsychotics, and catechol-O-methyltransferase (COMT) inhibitors¹⁰.

5. Mechanisms Involved in Gut-Microbiome-Brain Axis Alterations and Microbiome Dysbiosis

5.1. Braak's hypothesis and gut-to-brain propagation of α -synuclein

Parkinson's disease has been linked to GI pathology as proposed in Braak's hypothesis¹¹. This neuroanatomical staging proposes that the

initiation of sporadic PD is within the gut lumen. An environmental pathogen or a local toxic microbial shift can lead to the misfolding of the α -synuclein protein and accumulation in the ENS. The aggregates mimic prions in their propagation, corrupting normal protein. These pathological protein sheets then ascend via retrograde transport to the dorsal motor nucleus of the vagus nerve in the brainstem. From there, the pathological protein progresses through the well-connected neural networks, subsequently reaching the substantia nigra pars compacta, causing dopaminergic cell death¹².

5.2. Gut microbiome dysbiosis and its role in α -synuclein pathology

Parkinson's disease-associated dysbiosis is marked by reduced SCFA-producing gut bacteria, particularly *Faecalibacterium* and *Roseburia*, along with increased pro-inflammatory bacterial taxa¹³. This may weaken anti-inflammatory and gut-barrier protective effects, while elevated circulating trimethylamine N-oxide and reduced SCFA may contribute to α -synuclein aggregation, neuronal toxicity, systemic inflammation, and possible retrograde α -synuclein transport through the vagus nerve¹⁴.

5.3. SCFA-GPCR signaling, gut barrier dysfunction, and neuroinflammation

The activity of two GPCRs, GPR41 and GPR43 is impacted greatly by the depletion of SCFAs. Physiologically, SCFAs bind to GPR41 and 43 and hence maintain mucosal homeostasis by repressing pro-inflammatory cytokine cascades. In the case of chronic dysbiosis associated with PD, the lack of receptor activation impairs the homeostasis and cytokine balance. This destabilizes the intestinal epithelial barrier by cellular redistribution and reduction of key transmembrane tight junction proteins, such as claudin-1, occludin and zonula occludens-1 (ZO-1), which makes the gut leaky¹⁵. This results in translocation of immunogenic bacterial components, predominantly lipopolysaccharide (LPS), across the lamina propria into the systemic circulation, leading to peripheral immune activation that ultimately triggers the CNS and results in microglial and dopaminergic activation.

5.4. The *Akkermansia muciniphila* paradox and gut-neural dysfunction

Recent taxonomical profiling has revealed a critical discrepancy in the pathophysiology, which has been given the name of *Akkermansia muciniphila* paradox. *A. muciniphila*, a traditionally beneficial symbiont that degrades mucin, is overrepresented in the fecal microbiomes of PD patients. In an environment that already is depleted of dietary fiber and SCFAs, excessive *A. muciniphila* activity leaves the underlying epithelial structures exposed and vulnerable to luminal endotoxins. As a result, mitophagy and mitochondrial function is disrupted, inducing severe oxidative stress. Simultaneously, the reduction in the amount of indole-producing bacteria alters tryptophan metabolism resulting in elevated indoxyl sulfate levels causing further damage and hence activating microglia and astrocytes. This allows for the localized aggregation of α -synuclein within the ENS^{16,17}.

5.5. Body first and brain first pathways and phenotypic heterogeneity

While the classic Braak's hypothesis points at an ascending pathway for the spread of the disease from the ENS via vagal transmission, emerging neuropathological and clinical evidence points towards substantial phenotypic heterogeneity¹⁸. Recent imaging and research have classified patients into two clear subtypes namely the body first and the brain first. Body first refers to the gut being impacted first and brain first refers to the brain being impacted first. In the body first subtype, α -synuclein originates in the gut due to luminal stressors before it ascends to the brainstem. This type produces prodromal autonomic failure and it also causes sleeping disorders¹⁹. In contrast to this, the brain first variant initiates within the CNS before moving to the periphery via efferent vagus nerve fibers²⁰. Hence, primary GI tract origin and consequent

vagal transmission does not account for all the cases of PD. It is in fact an active debate and α -synuclein propagation is contested. Recognition of these dual trajectories explains the clinical heterogeneity seen in patients. The impact of gut dysbiosis is not uniform, but is rather dictated by the specific disease subtype.

The key communication pathways and factors causing GMB axis alterations, as well as the mechanism of action involved are presented in Figure 2.

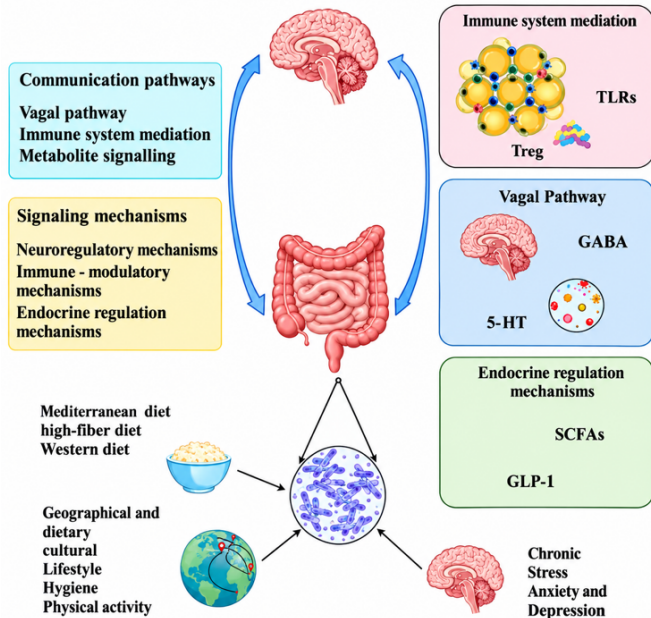


Figure 2: Key signaling pathways and factors causing GMB axis alterations and their mechanism of action⁵

GMB: Gut-microbiome-brain

6. Therapeutic Strategies

Despite encouraging findings reported from early phase clinical trials, microbiome targeted interventions remain preliminary²¹. Small pilot studies have been conducted for the evaluation of fecal microbiota transplantation (FMT), probiotic strains and high fiber diets yielding variable efficacy. Currently no gut linked intervention is clinically approved in standard clinical practice for PD treatment and management²². The various gut microbiota-based therapeutic interventions are discussed below.

6.1. Fecal microbiota transplantation

The gut microbiota is preserved and has been reported to help in neuroinflammation, GI dysfunction, and motor symptoms. Reported studies show improved microbiome diversity, constipation, QoL, and an acceptable safety profile. Donor FMT has also reduced pathogenic bacterial species, while increasing fecal dopamine and E-cadherin, suggesting improved epithelial barrier integrity. Adverse side effects seem to be mild and self limited²³.

6.2. Nutritional and dietary modifications

Dietary patterns can strongly shape gut microbiota composition and gut-brain signaling, thereby affecting the GMB axis. Mediterranean, high-fiber, plant-based, and polyphenol-rich diets may promote beneficial bacteria, enhance microbial fermentation, increase SCFA production, and reduce harmful metabolites. Ketogenic diets may also shift microbial composition, although their long-term impact remains uncertain. In contrast, western diets rich in animal protein and saturated fats are associated with reduced microbial diversity, impaired barrier function, and inflammation^{24,25}.

6.3. Prebiotics and probiotics

Prebiotics such as inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS) may support PD management by selectively promoting beneficial gut microbiota. Their effects include increased SCFA production, reduced intestinal inflammation, improved gut-barrier integrity, and possible reduction of neuroinflammation. Short-term prebiotic fiber intervention in PD was also reported to be safe, well-tolerated, and associated with higher fecal and plasma SCFA levels²⁶.

Probiotics may serve as adjunctive therapy in PD by restoring microbial balance, reducing oxidative stress and inflammation, and improving digestive symptoms. Reported trials showed improved constipation, stool consistency, bloating, and abdominal pain, lower MDS-UPDRS scores and improved inflammatory markers^{27,28}.

6.4. Exercise

Exercise may improve PD through the GMB axis by restoring gut flora diversity, increasing beneficial taxa, raising SCFA production, reducing systemic inflammation, suppressing neuroinflammation, supporting brain-derived neurotrophic factor (BDNF) related signaling, neuronal metabolism, and synaptic plasticity. Moderate resistance exercise appears to be safer, while excessive high endurance exercise may transiently increase gut permeability²⁹.

Some of the interventions for gut microbiota modulation are presented in Figure 3.

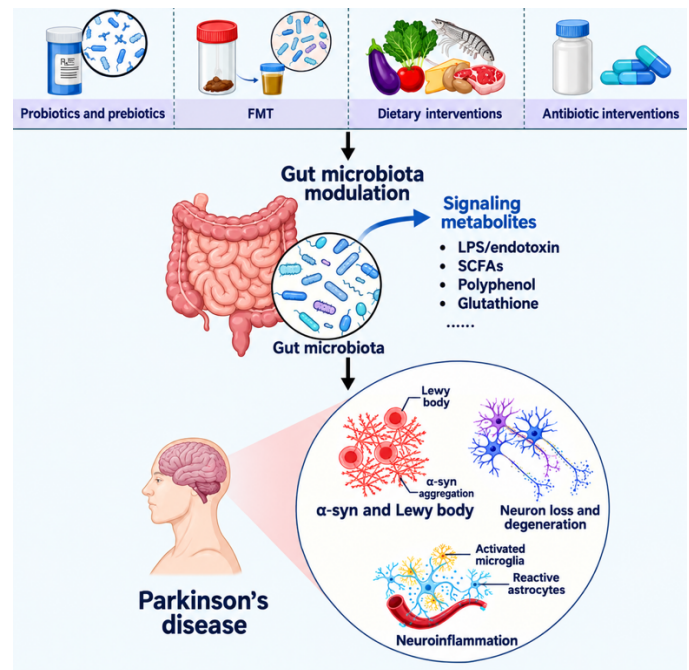


Figure 3: Therapeutic interventions for gut microbiome dysbiosis⁴

7. Gaps and Limitations

Regardless of the compelling nature of the GMB axis framework, several clinical and methodological barriers prevent the amalgamation of these insights into routine care. The one that stands out most is that the majority of the human microbiome profiling datasets are obtained from diagnosed patients who are actively taking therapy to cure this disease. The antiparkinsonian medications, especially COMT inhibitors and L-dopa directly reshape the taxonomic architecture of the microbiome³⁰. This makes it very difficult to determine whether the dysbiosis present is driving the α -synuclein pathology or a consequence of chronic dopaminergic medication use.

Adding on, there is no definitive microbial signature for PD due to high variability in sequencing platforms (shotgun metagenomics vs 16S rRNA gene profiling), dietary patterns, bioinformatic classification pipelines, genetics, and geographical factors³¹. Furthermore, usage of certain

drugs such as L-dopa and certain non-motor features such as constipation also alter the environment. Current literature does not focus on the dynamic metabolic function, which leaves the exact mechanics of α -synuclein transmission unknown. Finally, the utilization of physical exercise as a meaningful method for microbiome modulation remains constrained.

Human microbiome research faces a lot of methodological challenges such as a lack of standardized protocols for stool collection, storage, and DNA extraction. This further constrains the interpretation of current literature³². Moreover, confounding variables such as subclinical systemic inflammation, gastric motility disorders, concurrent pharmacological therapies and recent antibiotic exposure remain inconsistently controlled across cohorts, contributing to decreased cross-sectional study reproducibility.

8. Conclusion

Parkinson's disease should be viewed not only as a disorder of dopaminergic neurodegeneration, but also as a condition influenced by gut-derived immune, metabolic, and neural signals. The GMB axis links intestinal dysbiosis with α -synuclein pathology, neuroinflammation, and systemic dysfunction, making it a meaningful target for future preventive and supportive care strategies.

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Disclosure of AI Use

No generative AI tool was used to write the manuscript, which is the author's original work. However, during the editorial phase, ChatGPT (OpenAI, free version) was used to enhance the quality of the figures.

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