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THE ROLE OF THE GUT-BRAIN AXIS IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE: A CURRENT LITERATURE REVIEW

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ABSTRACT

Parkinson's Disease (PD) is a chronic neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. Recent scientific paradigms have shifted focus from the central nervous system to the bidirectional communication between the gastrointestinal tract and the brain, known as the gut-brain axis. This literature review aims to explore the mechanisms by which intestinal microbiota imbalance (dysbiosis) and gut inflammation contribute to PD pathogenesis through the spread of misfolded alpha-synuclein protein. Key factors such as immune responses, intestinal permeability, and microbial metabolites are identified as crucial elements in disease progression. A deeper understanding of this axis highlights the potential for novel microbiota-based therapeutic interventions to improve patient prognosis and mitigate the global burden of Parkinson's Disease.

Keywords: Parkinson's Disease (Pd), Gut-Brain Axis, Gut Microbiota, Alpha-Synuclein, Neuroinflammation.

1 INTRODUCTION

Parkinson's Disease (PD) stands as the second most common neurodegenerative disorder worldwide, following Alzheimer's disease. Globally, the prevalence of PD has more than doubled in the last two decades, and current projections suggest a "Parkinson's pandemic" where the number of afflicted individuals is expected to double again to approximately 12.9 million by 2040 [1]. Clinically, PD is defined by motor symptoms including tremors, rigidity, and bradykinesia. However, non-motor symptoms, particularly gastrointestinal dysfunction, frequently manifest years before the onset of formal clinical diagnosis. Epidemiological data indicates that chronic constipation affects approximately 70-80% of PD patients and can precede motor symptoms by 10 to 20 years, serving as a significant prodromal marker [2, 3].

Over the past decade, the understanding of PD pathophysiology has expanded beyond the brain.

Emerging evidence, spearheaded by the Braak Hypothesis, suggests that the pathological process may originate in the enteric nervous system (ENS) due to exposure to environmental pathogens or triggers. This disturbance leads to the aggregation of misfolded alpha-synuclein proteins, which subsequently migrate to the brain via the vagus nerve. The

interaction between the gut and brain involves complex neural, endocrine, and immunological pathways, making it a critical focus for early detection and therapeutic intervention.

2 MECHANISMS OF THE GUT-BRAIN AXIS

2.1 The Prion-like Spread of Alpha-Synuclein

The central mechanism linking the gut and the brain in PD is the aggregation and spread of misfolded alpha-synuclein (α-syn) protein. Based on the Braak Hypothesis, this pathology often begins in the enteric nervous system. These α-syn proteins exhibit "prion-like" properties, inducing normal proteins to misfold and form toxic aggregates known as Lewy bodies. A landmark study by Kim et al. (2019) demonstrated that injecting α-syn pre-formed fibrils (PFFs) into the gastrointestinal muscles of mice led to the spread of these proteins to the brainstem within 1 month and to the substantia nigra within 7 months, resulting in significant dopaminergic neuron loss [4, 5].

2.2 The Vagus Nerve Pathway

The primary anatomical route for this transmission is the vagus nerve. Experimental evidence shows that α-syn aggregates travel retrogradely from gut nerve terminals to the dorsal motor nucleus of the vagus nerve in the brainstem. Clinical observations reinforce this, as individuals who have undergone a full truncal vagotomy exhibit a significantly lower risk of developing PD compared to the general population, suggesting that the vagus nerve acts as a crucial "highway" for the progression of pathology from the gut to the brain [6, 7].

3 THE ROLE OF MICROBIOTA AND DYSBIOSIS

3.1 Microbial Signatures and Intestinal Permeability

Dysbiosis, or the imbalance of gut microbiota, is a consistent feature in PD. Research by Scheperjans et al. revealed that the abundance of the Prevotellaceae family is reduced by approximately 77% in PD patients compared to healthy controls. This reduction is critical as Prevotellaceae are involved in producing essential short-chain fatty acids (SCFAs) and maintaining the intestinal mucus barrier. Conversely, there is often an increase in pro-inflammatory bacteria like Enterobacteriaceae and Akkermansia muciniphila, the latter of which can excessively degrade the protective mucus layer if imbalanced [8, 9].

3.2 "Leaky Gut" and Systemic Inflammation

Increased intestinal permeability, or "leaky gut," allows bacterial products such as lipopolysaccharides (LPS) to translocate into the systemic circulation. This activates Toll-like receptor 4 (TLR4) on peripheral immune cells, triggering a massive release of pro-inflammatory cytokines (e.g., TNF-α, IL-6). These inflammatory mediators can weaken the blood-brain barrier (BBB), facilitating neuroinflammation and accelerating the degeneration of dopaminergic neurons in the substantia nigra [10, 11].

4 HOST GENETIC FACTORS IN THE GUT-BRAIN AXIS

4.1 The LRRK2 Gene and Intestinal Inflammation

Mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene are the most common genetic cause of both familial and sporadic PD. Interestingly, LRRK2 is also highly expressed in the immune cells of the gut and is a known risk factor for Crohn’s disease. Studies indicate that LRRK2 mutations promote excessive inflammatory responses in the gut, which may accelerate the aggregation of alpha-synuclein in the ENS [12].

4.2 The GBA Gene and Lysosomal Dysfunction

Mutations in the GBA gene, encoding the enzyme glucocerebrosidase, represent a major risk factor for PD. Reduced GBA activity leads to lysosomal dysfunction, impairing the clearance of misfolded alpha-synuclein. In the context of the gut-brain axis, GBA deficiency may increase the susceptibility of enteric neurons to environmental triggers, facilitating the initial misfolding of proteins in the gut lumen [13].

5 IMMUNE RESPONSE AND NEUROINFLAMMATION

5.1 Microglial Activation and Gut-Derived Signals

Microglia, the resident immune cells of the brain, play a pivotal role in PD neurodegeneration. Signals originating from the gut, including pro-inflammatory cytokines and microbial metabolites, reach the brain and shift microglia from a resting state to a chronically activated pro-inflammatory state. This persistent activation leads to the sustained release of neurotoxic factors, further damaging the dopaminergic system [14, 15].

5.2 The Protective Role of SCFAs

SCFAs like butyrate are vital for maintaining BBB integrity and suppressing microglial overactivation. In PD, the reduction of SCFA-producing bacteria deprives the brain of these neuroprotective metabolites. Studies have shown that SCFA supplementation can mitigate motor deficits and neuroinflammation in animal models of PD, highlighting their potential as a therapeutic target [16, 17].

6 CONCLUSION

The gut-brain axis represents a fundamental shift in understanding Parkinson's Disease pathophysiology. Evidence strongly suggests that PD may originate in the gut through alpha-synuclein aggregation, driven by microbiota dysbiosis and chronic intestinal inflammation. Communication via the vagus nerve and systemic immune pathways leads to microglial activation and subsequent loss of dopaminergic neurons. This paradigm shift offers new avenues for early diagnosis through gastrointestinal markers and novel therapeutic strategies, such as probiotics, prebiotics, and fecal microbiota transplantation, aimed at restoring gut-brain homeostasis and slowing disease progression.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

REFERENCES

[1] Dorsey ER, Bloem BR. The Parkinson pandemic—a call to action. JAMA Neurol. 2018;75(1):9-10. doi:10.1001/jamaneurol.2017.3299.

[2] Abbott RD, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology. 2001;57(3):456-462. doi:10.1212/WNL.57.3.456.

[3] Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord. 2012;27(5):617-626. doi:10.1002/mds.24996.

[4] Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197-211. doi:10.1016/S0197-4580(02)00065-9.

[5] Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. Neuron. 2019;103(4):627-641.e7. doi:10.1016/j.neuron.2019.05.035.

[6] Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78(4):522-529. doi:10.1002/ana.24448.

[7] Yang R, Gao G, Yang H. The pathological mechanism between the intestine and brain in the early stage of Parkinson's disease. Front Aging Neurosci. 2022;14:861035. doi:10.3389/fnagi.2022.861035.

[8] Scheperjans F, Aho V, Pereira PAB, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord. 2015;30(3):350-358. doi:10.1002/mds.26069.

[9] Chi F, Chen K, Yin Y, Hakovirta JR, Saris PEJ. From dysbiosis to dysfunction: specific gut microbes and metabolites in the pathogenesis of Parkinson's disease. Sustain Microbiol. 2026;3(1):qvag002. doi:10.1093/sumbio/qvag002.

[10] Gorecki AM, Dunlop SA, Rodger J, Anderton RS. The gut-brain axis and gut inflammation in Parkinson's disease: stopping neurodegeneration at the toll gate. Expert Opin Ther Targets. 2020;24(7):601-604. doi:10.1080/14728222.2020.1763956.

[11] Kearns R. Gut-brain axis and neuroinflammation: the role of gut permeability and the kynurenine pathway in neurological disorders. Cell Mol Neurobiol. 2024;44(1):64. doi:10.1007/s10571-024-01496-z.

[12] Wallings RL, Tansey MG. LRRK2 regulation of immune-pathways and inflammatory disease. Biochem Soc Trans. 2019;47(6):1581-1595. doi:10.1042/BST20180463.

[13] Schapira AHV. Glucocerebrosidase and Parkinson disease: recent advances. Mol Cell Neurosci. 2015;66(Pt A):37-42. doi:10.1016/j.mcn.2015.03.013.

[14] Stefanova N. Microglia in Parkinson's disease. J Parkinsons Dis. 2022;12(Suppl 1):S105-S112. doi:10.3233/JPD-223237.

[15] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016;167(6):1469-1480.e12. doi:10.1016/j.cell.2016.11.018.

[16] Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Bürmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord. 2016;32:66-72. doi:10.1016/j.parkreldis.2016.08.019.

[17] Sommer A, Marxreiter F, Krach F, Fadler T, Grosch J, Maroni M, et al. Th17 lymphocytes induce neuronal cell death in a human iPSC-based model of Parkinson's disease. Cell Stem Cell. 2018;23(1):123-131.e6. doi:10.1016/j.stem.2018.06.015.