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BRAIN GUT MICROBIOTA AXIS IN PARKINSON'S DISEASE: GUT MICROBIOTA DRIVEN ALPHA SYNUCLEIN AGGREGATION AND IT'S ROLE IN PARKINSON NEURODEGENERATION

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Parkinson's disease (PD) is a progressive neurodegenerative disorder traditionally defined by dopaminergic neuronal loss in the substantia nigra and intracellular aggregation of misfolded α-synuclein. However, converging evidence now supports a theory in which pathological processes originate outside of the central nervous system, majorly within the gastrointestinal tract. The brain–gut–microbiota axis has appeared as a critical pathway linking intestinal homeostasis to neurodegeneration, suggesting that gut microbiota–driven mechanisms may play a foundational role in PD pathogenesis.

Several experimental studies have shown that patients with PD have alterations in the composition of the microbiota in the gastrointestinal tract, specially in the form of reduced beneficial anti-inflammatory bacteria and increased pro-inflammatory bacteria. This leads to a reduction in production of short-chain fatty acids that increases the intestinal inflammation. As a result of increased intestinal permeability toxins and inflammatory substances produced in the gastrointestinal tract enter the systemic circulation and increase systemic immune activation.

The major consequence of this procedure is the promotion of α-synuclein overexpression, misfolding, and aggregation within the enteric nervous system. Oxidative stress and cytokine signaling favor changes in α-synuclein, facilitating its assembly into toxic fibrillar aggregates that resemble Lewy pathology observed in the brain. Importantly, enteric α-synuclein abnormalities and gastrointestinal dysfunction particularly constipation often lead to motor manifestations by years or decades, supporting the concept of early peripheral disease initiation.

Recent studies also point to gut mucosal enteroendocrine cells as a potential interface between luminal microbes and neuronal tissues. These enteroendocrine cells contain α-synuclein and establish direct synaptic-like connections with enteric neurons, which would allow the transmission of pathological proteins from the mucosa to neural pathways. The misfolded form of α-synuclein is suggested to be transmitted in a prion-like manner through retrograde axonal transmission along the vagus nerve to the brainstem and then to the other interconnected neural networks to reach the substantia nigra.

In the central nervous system, the aggregation of α-synuclein protein also associated with the activation of microglia, leads to the progression of neuroinflammatory responses through the release of cytokines and oxidative stress. This condition promote the aggregation of protein, which leads to the degeneration of the dopaminergic neurons. This creates a feedback loop where peripheral inflammation leads to central neurodegeneration.

Overall evidence supports a cascade in which gut microbiota imbalance initiates intestinal inflammation, barrier destruction and peripheral α-synuclein aggregation which is followed by its vagal propagation to the brain and then neuroinflammatory neurodegeneration. This gut origin hypothesis reframes Parkinson as a disorder of the brain-gut microbiota axis.