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THE GUT-BRAIN AXIS: MICROBIOTA DYSBIOSIS AND ITS ROLE IN NEURODEGENERATIVE DISEASES

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Abstract

The gut microbiota is increasingly recognized as a modulator of central nervous system function through bidirectional signaling along the gut-brain axis. Dysbiosis, characterized by altered microbial diversity and composition, has been implicated in the pathogenesis of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Proposed mechanisms include disruption of intestinal and blood-brain barrier integrity, chronic systemic and neuroinflammation, aberrant production of microbial metabolites, and pathological protein misfolding originating in the enteric nervous system. This review summarizes current evidence on microbiota-driven mechanisms of neurodegeneration and emerging microbiota-targeted therapeutic strategies.

Keywords: Gut microbiota, Gut-brain axis, Dysbiosis, Neuroinflammation, Alzheimer's disease, Parkinson's disease, Short-chain fatty acids.

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Introduction

1. Introduction: The Gut Microbiota as a Regulator of Central Nervous System Homeostasis

The human gastrointestinal tract harbors a dense and metabolically active microbial community comprising trillions of organisms that collectively encode a genetic repertoire far exceeding that of the human genome (Cryan et al., 2019). Communication between this microbial ecosystem and the central nervous system occurs through the gut-brain axis, a bidirectional network integrating neural, endocrine, immune, and metabolic signaling pathways (Cryan & Dinan, 2012). The vagus nerve provides a direct afferent route by which luminal signals, including microbial metabolites and enteroendocrine peptides, influence brainstem and higher-order neural circuits (Bonaz et al., 2018). In parallel, the microbiota shapes host immunity by regulating intestinal barrier integrity, mucosal immune cell differentiation, and systemic cytokine tone, all of which have downstream consequences for neuroinflammatory susceptibility (Sampson & Mazmanian, 2015). Because the developing and aging nervous system appears particularly sensitive to fluctuations in microbial composition, sustained dysbiosis has emerged as a candidate contributor to chronic neurodegenerative processes (Fang et al., 2020).

2. Pathophysiological Axis of Microbiota Dysbiosis

Dysbiosis in neurodegenerative disease is characterized by a consistent pattern of reduced microbial diversity, depletion of short-chain fatty acid (SCFA)-producing commensals such as Faecalibacterium and Roseburia, and relative expansion of pro-inflammatory taxa (Sun & Shen, 2018). Loss of SCFA-producing bacteria diminishes butyrate availability, compromising the integrity of tight junction proteins (occludin, claudin-5, ZO-1) in both the intestinal epithelium and the blood-brain barrier, thereby promoting translocation of bacterial components such as lipopolysaccharide (LPS) into systemic circulation (Sun & Shen, 2018). Circulating LPS activates Toll-like receptor 4 (TLR4) signaling on microglia and peripheral monocytes, driving nuclear factor-kappa B (NF-κB)-dependent release of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1beta (IL-1β) (Fang et al., 2020). This peripheral inflammatory state is transmitted centrally, sustaining chronic microglial activation and astrocytic reactivity within the brain parenchyma (Sampson & Mazmanian, 2015). Additionally, dysbiotic microbial communities alter tryptophan metabolism, shifting flux away from serotonin synthesis toward the kynurenine pathway and generating neurotoxic metabolites such as quinolinic acid (Cryan et al., 2019).

3. Role in Neurodegenerative Diseases: Disease-Specific Vulnerabilities

While gut dysbiosis contributes broadly to neuroinflammatory tone, disease-specific mechanisms link the microbiota to distinct neurodegenerative pathologies. In Parkinson's disease, alpha-synuclein aggregates have been detected within enteric neurons years before the onset of motor symptoms, supporting the hypothesis that misfolded protein may propagate from the gut to the brain via the vagus nerve (Braak et al., 2003; Sampson et al., 2016). Patients with Parkinson's disease exhibit reduced abundance of Prevotellaceae and increased Enterobacteriaceae, correlating with disease severity and constipation, a common prodromal symptom (Sampson et al., 2016). In Alzheimer's disease, dysbiosis has been associated with elevated peripheral amyloidogenic protein exposure and increased

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blood-brain barrier permeability, facilitating amyloid-beta and Tau pathology (Fang et al., 2020). Germ-free and antibiotic-treated transgenic mouse models show reduced amyloid plaque burden compared with conventionally colonized controls, implicating the microbiota directly in amyloidogenesis (Harach et al., 2017). In amyotrophic lateral sclerosis, altered microbial metabolite profiles, including reduced butyrate and nicotinamide availability, have been linked to motor neuron vulnerability and accelerated disease progression in animal models (Blacher et al., 2019). In Huntington's disease, microbiota composition changes correlate with intestinal barrier dysfunction and systemic inflammation, which may exacerbate mutant huntingtin-driven neurotoxicity (Kong et al., 2020).

4. Molecular Mechanisms of Neuronal Injury Mediated by Gut Dysbiosis

Dysbiosis-driven neuronal injury converges on several interconnected molecular cascades. Chronic LPS-TLR4 signaling sustains microglial priming, rendering neurons more vulnerable to secondary inflammatory or oxidative insults and lowering the threshold for neurodegenerative cascades (Fang et al., 2020). Loss of SCFA-mediated regulatory T-cell induction reduces immune tolerance, permitting infiltration of pro-inflammatory T-helper 17 (Th17) lymphocytes into the central nervous system, where they amplify neuroinflammation (Sampson & Mazmanian, 2015). Aberrant enteric alpha-synuclein misfolding can propagate in a prion-like manner along vagal afferents, seeding aggregation in the dorsal motor nucleus and subsequently ascending brainstem structures (Braak et al., 2003). Kynurenine pathway metabolites generated under dysbiotic conditions, particularly quinolinic acid, act as N-methyl-D-aspartate (NMDA) receptor agonists, promoting excitotoxic calcium influx and neuronal death (Cryan et al., 2019). Collectively, impaired intestinal barrier function, sustained peripheral and central inflammation, and microbiota-derived neurotoxic metabolites establish a self-reinforcing cycle that accelerates synaptic dysfunction and progressive neuronal loss (Blacher et al., 2019).

5. Therapeutic Perspectives and Conclusion

Modulating the gut microbiota represents a promising adjunctive strategy for neurodegenerative disease management. Probiotic and prebiotic interventions aimed at restoring SCFA-producing taxa have shown potential to reduce peripheral inflammation and improve barrier integrity in preclinical models (Sun & Shen, 2018). Fecal microbiota transplantation has demonstrated preliminary efficacy in reducing motor and non-motor symptom severity in small clinical studies of Parkinson's disease (Sampson et al., 2016). Dietary approaches enriched in fermentable fiber and polyphenols may favorably reshape microbial community structure and downstream metabolite production (Fang et al., 2020). However, substantial challenges remain, including inter-individual variability in microbiome composition, the need for standardized intervention protocols, and uncertainty regarding causality versus correlation in human observational studies. Longitudinal, mechanistic, and interventional research is required before microbiota-targeted therapies can be integrated into standard neurodegenerative disease care.

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