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THE ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS AND RECOVERY AFTER ISCHEMIC STROKE

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Abstract: Ischemic stroke is a leading cause of morbidity and long-term disability worldwide. Recent research has revealed that the gut microbiota, the diverse community of microorganisms inhabiting the gastrointestinal tract, plays a critical role in stroke pathophysiology and recovery. The gut-brain axis, a bidirectional communication system connecting the gut and the central nervous system (CNS), regulates immune responses, systemic inflammation, neuronal plasticity, and metabolic homeostasis. Dysbiosis, or an imbalance of gut microbiota, is associated with increased infarct size, exacerbated neuroinflammation, and impaired functional recovery. This review provides a comprehensive overview of current evidence linking gut microbiota to ischemic stroke, detailing mechanisms of action, clinical and experimental studies, and potential microbiota-targeted interventions. Understanding these relationships may inform novel therapeutic strategies to improve recovery outcomes in stroke patients.

Introduction

Stroke remains one of the primary causes of mortality and long-term disability globally, with ischemic stroke accounting for approximately 85% of cases1. Traditional risk factors, including hypertension, diabetes, atrial fibrillation, and atherosclerosis, contribute to stroke susceptibility but do not fully account for variability in outcomes2. In recent years, the role of the gut microbiota—the trillions of bacteria, viruses, fungi, and other microorganisms residing in the gastrointestinal tract—has emerged as a critical factor influencing both the pathogenesis and recovery of ischemic stroke3.

The gut microbiota interacts with the CNS via the gut-brain axis, a complex bidirectional network involving neural, immune, endocrine, and metabolic pathways. Microbial metabolites such as short-chain fatty acids (SCFAs), tryptophan derivatives, and secondary bile acids regulate neuroinflammation, neurogenesis, and blood-brain barrier (BBB) integrity4. Dysbiosis, defined as disruption in microbial diversity and composition, has been implicated in worsening stroke outcomes by promoting systemic inflammation, altering immune cell function, and impairing neuronal repair processes5.

The purpose of this review is to consolidate current knowledge regarding the impact of gut microbiota on ischemic stroke, examine underlying mechanisms, summarize findings from both clinical and preclinical studies, and discuss therapeutic strategies aimed at modulating microbiota to enhance post-stroke recovery.

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Gut-Brain Axis and Mechanisms of Interaction

Neural Pathways

The vagus nerve constitutes the primary neural conduit connecting the gut and the brain. Signals from gut microbes can influence CNS activity, modulate neuroinflammation, and affect neuronal survival6. For instance, certain microbial metabolites stimulate vagal afferents, which in turn modulate microglial activity and systemic immune responses. Stroke-induced damage often disrupts vagal signaling, potentially amplifying neuroinflammatory responses and neurological deficits.

Immune Modulation

Gut microbiota plays a pivotal role in shaping the host immune system. Commensal bacteria influence the differentiation and activation of T helper cells, particularly Th17 and regulatory T cells (Tregs). Dysbiosis can disrupt this balance, promoting pro-inflammatory Th17 responses while reducing Treg-mediated immunosuppression7. This imbalance contributes to increased neuroinflammation, exacerbates neuronal injury, and can increase infarct volume following ischemic stroke.

Microbial metabolites such as SCFAs directly modulate immune cell function. Butyrate, for example, enhances Treg differentiation and suppresses pro-inflammatory cytokine production8. Consequently, reductions in SCFA-producing bacteria can worsen neuroinflammatory outcomes after stroke.

Metabolite Signaling

Gut-derived metabolites affect stroke outcomes through multiple mechanisms:

Short-chain fatty acids (SCFAs): Butyrate, acetate, and propionate promote neurogenesis, modulate microglial homeostasis, and reinforce BBB integrity9.

Tryptophan metabolites: These compounds influence serotonin synthesis and neuroplasticity, impacting post-stroke cognitive and motor recovery10.

Secondary bile acids: Regulate systemic and CNS inflammation, endothelial function, and neuronal survival11.

Deficiency in these metabolites due to dysbiosis correlates with impaired recovery and increased post-stroke complications.

Endocrine and Neurotransmitter Pathways

Gut microbes produce or modulate neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and dopamine, which influence cognition, mood, and neural plasticity12. Disruption of microbial composition can lead to altered neurotransmitter levels, affecting post-stroke behavioral and cognitive outcomes.

Stroke-Induced Gut Dysbiosis

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Clinical and experimental evidence demonstrates that ischemic stroke itself alters gut microbiota composition:

Reduced microbial diversity and richness13

Increased abundance of pro-inflammatory taxa, including Proteobacteria and Enterobacteriaceae14

Depletion of beneficial SCFA-producing bacteria, including Lactobacillus, Bifidobacterium, and Faecalibacterium15

This stroke-induced dysbiosis contributes to systemic inflammation, increases susceptibility to post-stroke infections, and impairs neurological recovery16.

Illustrative Figure: Timeline of gut microbiota alterations post-stroke, highlighting early dysbiosis, immune modulation, and metabolite changes.

Immune System Modulation and Neuroinflammation

Dysbiosis after ischemic stroke drives neuroinflammation through several mechanisms:

1. **Treg/Th17 Imbalance:** Dysbiosis reduces Treg populations while promoting Th17 activation, exacerbating neuroinflammatory responses17.

2. **Pro-inflammatory Cytokine Elevation:** IL-6, TNF-α, and IL-1β levels increase, contributing to neuronal apoptosis and expansion of infarct volume18.

3. **Microglial Activation:** Microbial metabolites influence microglial polarization. Dysbiosis skews microglia toward a pro-inflammatory phenotype, amplifying neuronal injury19.

Experimental studies demonstrate that interventions restoring microbial balance reduce inflammatory cytokines, modulate T cell populations, and limit infarct size20.

Metabolic Interactions and Neuroprotection

SCFAs and other microbial metabolites exert neuroprotective effects:

SCFAs: Promote histone acetylation, enhancing neurogenesis and synaptic plasticity.

Tryptophan catabolites: Regulate serotonin signaling, impacting mood, cognition, and motor recovery.

Secondary bile acids: Support vascular integrity and reduce systemic inflammation.

Animal models show that supplementation with SCFAs improves motor function and cognitive recovery21. These findings highlight the therapeutic potential of targeting microbiota-derived metabolites.

Clinical Evidence and Functional Outcomes

Human studies demonstrate clear correlations between gut microbiota composition and stroke recovery:

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Preserved microbial diversity is associated with better functional outcomes, as measured by the modified Rankin Scale (mRS) and NIH Stroke Scale (NIHSS)22.

Dysbiosis predicts higher risk of post-stroke infections and delayed rehabilitation23.

Certain microbial taxa, such as Faecalibacterium prausnitzii, are predictive of better functional recovery24.

Illustrative Figure: Graph showing SCFA levels and correlation with NIHSS and mRS scores in stroke patients over time.

Therapeutic Implications

Probiotics and Prebiotics

Probiotics restore beneficial microbial populations and increase SCFA production. Prebiotics, such as dietary fibers, promote growth of commensal bacteria and enhance metabolite-mediated neuroprotection25.

Dietary Interventions

High-fiber diets and Mediterranean-style nutrition support microbial diversity, enhance SCFA production, reduce systemic inflammation, and promote neuroplasticity26.

Fecal Microbiota Transplantation (FMT)

FMT has been shown in animal models to normalize gut microbiota, reduce neuroinflammation, and improve neurological outcomes27. Human trials are limited but suggest feasibility and safety28.

Discussion

Current research demonstrates that gut microbiota is a key modulator of ischemic stroke outcomes. Mechanistic studies elucidate immune regulation, metabolite signaling, and neural pathway involvement. However, limitations remain:

Most mechanistic data are derived from animal models, and translation to humans is challenging.

Individual variability in microbiota composition complicates standardization of interventions.

Longitudinal data on microbiota dynamics during acute and chronic post-stroke phases are limited.

Despite these challenges, targeting gut microbiota represents a promising adjunct to conventional stroke therapy, with potential to improve functional recovery and reduce complications.

Future Directions

1. **Longitudinal Human Studies:** To map temporal changes in microbiota post-stroke29.

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2. **Personalized Interventions:** Probiotics, prebiotics, and dietary modifications tailored to individual microbiomes30.

3. **Integration with Neuroimaging:** Linking microbiota changes with infarct size, neuroplasticity, and functional outcomes31.

4. **Multi-omics Approaches:** Combining microbiome, metabolome, and immune profiling to identify biomarkers and therapeutic targets32.

5. **Randomized Controlled Trials:** To validate efficacy of microbiota-targeted interventions33.

Conclusion

Gut microbiota plays a pivotal role in the pathogenesis and recovery of ischemic stroke. Dysbiosis exacerbates neuroinflammation, increases neuronal injury, and impairs functional recovery. Modulation of the gut microbiota through probiotics, prebiotics, dietary interventions, or FMT represents a novel therapeutic avenue. Future research should focus on longitudinal studies, personalized interventions, and integration with neuroimaging and clinical biomarkers to enhance post-stroke recovery.

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