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Narrative Review

Post-Stroke Gut Microbiota Dysbiosis: Mechanisms, Clinical Evidence, and Therapeutic Frontiers

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Abstract
Stroke remains a leading cause of death and disability worldwide, yet therapeutic strategies to enhance recovery are limited. Emerging evidence highlights the gut microbiota as a crucial regulator of post-stroke inflammation, neuroplasticity, and systemic health. Post-stroke gut dysbiosis disrupts intestinal barrier integrity, alters microbial metabolite profiles, and drives maladaptive immune responses, negatively influencing neurological recovery. Preclinical studies indicate that probiotics, fecal microbiota transplantation (FMT), and short-chain fatty acid (SCFA) supplementation can reduce neuroinflammation and improve functional outcomes. This narrative review synthesizes mechanistic insights and clinical findings, emphasizing studies by Benakis et al. (2016), Singh et al. (2016), Peh et al. (2022), Zhao et al. (2018), Lee et al. (2020), and Hammond et al. (2022). We also discuss microbiota-targeted therapeutic strategies, current challenges, and future directions for translating these findings into personalized interventions.

Keywords- *Stroke, Gut microbiota, dysbiosis.*

Introduction

Stroke imposes a substantial global health burden, causing long-term complications such as cognitive decline and recurrent vascular events. Beyond the brain, stroke triggers systemic interactions among the immune system, peripheral organs, and the gut microbiota. The gut microbiota regulates metabolism, immunity, and neural signaling. Stroke induces rapid microbial alterations, termed gut dysbiosis, compromising intestinal barrier function, altering metabolite profiles, and promoting systemic inflammation (Benakis et al., 2016; Singh et al., 2016). Clinical studies reveal reduced microbial diversity, depletion of beneficial taxa, and disrupted metabolite production in stroke patients (Peh et al., 2022; Zhao et al., 2018).

Microbiota-targeted therapies—including probiotics, prebiotics, FMT, and dietary interventions—show promise for enhancing recovery. However, clinical translation remains limited due to small cohort sizes, heterogeneous methodologies, and safety concerns. This review integrates mechanistic and clinical evidence, emphasizing key studies to provide a foundation for microbiome-centered post-stroke interventions.

The Healthy Gut–Brain Axis

The gut microbiota, a complex ecosystem of bacteria, viruses, and fungi, co-evolved with the host to support nutrient metabolism, immune regulation, and epithelial integrity.It communicates bidirectionally with the central nervous system (CNS) via neural, endocrine, immune, and metabolic pathways, maintaining homeostasis and neuroprotection.

Microbial Diversity and Metabolite Production

High microbial diversity underpins ecosystem resilience. Commensals produce metabolites, notably SCFAs such as acetate, propionate, and butyrate, which strengthen intestinal barrier function, modulate systemic inflammation, and support neuroplasticity (Benakis et al., 2016; Lee et al., 2020). Gut microbial metabolism of tryptophan generates indoles and kynurenine derivatives, influencing neurotransmission, mood regulation, and neuroinflammation (Peh et al., 2022).

Immune Regulation

Commensals maintain immune tolerance by promoting regulatory T cells (Tregs) and anti-inflammatory cytokines. Dysbiosis skews immune responses toward pro-inflammatory phenotypes, exacerbating post-stroke neuroinflammation (Benakis et al., 2016; Singh et al., 2016).

Neural and Endocrine Pathways

The gut communicates with the brain via vagal nerve signaling and the hypothalamic–pituitary–adrenal (HPA) axis, influencing stress responses and inflammation. Dysbiosis can impair these pathways, intensifying neuroinflammation and delaying recovery (Zhao et al., 2018; Lee et al., 2020).

Homeostasis and Neuroprotection

Under normal conditions, the gut–brain axis maintains intestinal barrier function,
balanced immunity, and neuroprotective metabolite production. Stroke-induced
dysbiosis disrupts this balance, triggering maladaptive systemic and central processes that impair recovery (Hammond et al., 2022).

Stroke-Induced Gut Dysbiosis

Acute cerebral ischemia significantly shifts microbial diversity and composition, with loss of beneficial commensals and expansion of pro-inflammatory taxa (Singh et al., 2016; Peh et al., 2022). Dysbiosis exacerbates systemic inflammation, impairs metabolite signaling, and contributes to post-stroke complications such as infection, cognitive decline, and delayed neurological recovery (Benakis et al., 2016; Zhao et al., 2018).

Preclinical studies demonstrate causality: germ-free mice colonized with post-stroke microbiota exhibit larger infarcts and poorer neurological function (Singh et al., 2016).

Enrichment of SCFA-producing bacteria, including *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, improves outcomes, highlighting therapeutic potential (Lee et al., 2020). Dysbiosis affects recovery through four interconnected mechanisms, with deeper cellular and molecular insights such as:

Barrier Dysfunction:

Stroke-induced dysbiosis disrupts tight junction proteins (occludin, claudin-1) and
mucin layers, increasing intestinal permeability. This facilitates translocation of bacterial lipopolysaccharides (LPS) and other pathogen-associated molecular patterns (PAMPs) into systemic circulation, triggering peripheral and

central inflammatory cascades (Benakis et al., 2016; Delgado Jiménez et al., 2021).

Metabolite Signaling:

Microbial metabolites influence host physiology through receptor-mediated and epigenetic mechanisms. SCFAs (acetate, propionate, butyrate) bind G-protein-coupled receptors (GPR41/43) and inhibit histone deacetylases, modulating Treg differentiation, blood–brain barrier integrity, and neurotrophic factor expression. Tryptophan derivatives activate aryl hydrocarbon receptor (AhR) signaling in astrocytes and microglia,fine-tuning neuroinflammation, while bile acids regulate vascular tone and glial homeostasis (Peh et al., 2022; Zhao et al., 2018).

Immune Trafficking: Dysbiosis alters gut-associated lymphoid tissue (GALT) homeostasis, promoting differentiation of pro-inflammatory Th1/Th17 cells. These gut-derived lymphocytes traffic to the CNS via circulation, where they interact with resident glia and endothelial cells, modulating neuroinflammatory tone according to local cytokine milieus (Singh et al., 2016; Benakis et al., 2016).

Neuroglial Priming: Dysbiotic signals, including microbial metabolites and circulating cytokines, prime microglia and astrocytes toward pro-inflammatory phenotypes. Primed glia exhibit heightened responsiveness to secondary insults, increasing neurotoxicity, synaptic loss, and neuronal apoptosis, which exacerbate infarct size and hinder recovery (Winek et al., 2016).

This integrated framework underscores how gut dysbiosis orchestrates a multi-level influence—from epithelial disruption and metabolic imbalance to immune modulation and glial activation—culminating in impaired neurological recovery.

Clinical Evidence

Observational studies in stroke patients show reduced microbial diversity, depletion of SCFA-producing taxa, and overrepresentation of *Streptococcus* and *Escherichia* (Peh et al., 2022; Zhao et al., 2018). These alterations correlate with infarct severity, functional outcomes, and systemic metabolic disturbances (Hammond et al., 2022). Combined preclinical and clinical evidence underscores the significance of gut dysbiosis in stroke Pathophysiology.

Therapeutic Opportunities

Microbiota-targeted interventions represent a promising avenue for enhancing post-stroke recovery by modulating inflammation, barrier function, and metabolite signaling. Probiotics, including strains such as *Lactobacillus rhamnosus* GG and *Bifidobacterium longum*, have been shown in preclinical models to attenuate neuroinflammation, restore microbial balance, and support functional recovery. These effects are mediated through increased SCFA production, enhanced gut barrier integrity and modulation of systemic immune responses (Lee et al., 2020).Dietary interventions and prebiotics further complement these effects by promoting the growth of beneficial commensals, leading to higher levels of butyrate, acetate, and propionate, which not only support intestinal health but also influence neuroplasticity and neuroprotection. Nutritional strategies rich in fibers and polyphenols can therefore indirectly fine-tune post-stroke immune responses through the microbiota.

Fecal microbiota transplantation (FMT) from healthy donors has demonstrated the ability to restore microbial diversity, correct dysbiosis, and improve neurological outcomes in animal models of stroke (Chidambaram et al., 2022). FMT acts by reintroducing a balanced microbial community, normalizing metabolite profiles, and modulating peripheral and central immune responses. Although promising, clinical application remains limited by donor selection, standardization of procedures, and safety concerns.

Direct supplementation with SCFAs has emerged as another targeted strategy, with butyrate, acetate, and propionate administration enhancing epithelial barrier integrity, reducing systemic and neuroinflammation, and supporting neuronal

survival. These interventions bypass the variability of host-dependent microbial fermentation, providing a more controlled approach to restoring the gut–brain axis.

Despite encouraging preclinical data, translation to human trials faces challenges including heterogeneity in formulations, variable patient microbiomes, and safety considerations. Rigorous clinical studies with standardized protocols are required to evaluate efficacy, optimal dosing, and long-term safety, paving the way for precision microbiota-based therapeutics in post-stroke recovery (Peh et al., 2022).

Challenges and Future Directions

The translation of microbiota-targeted therapies for post-stroke recovery faces several key challenges that must be addressed to optimize efficacy and safety. One major obstacle is inter-individual variability; baseline differences in microbial composition, lifestyle factors, diet, and prior medication exposure profoundly influence therapeutic responses, making standardized interventions difficult (Peh et al., 2022; Singh et al., 2016). Animal models, while invaluable for mechanistic insights, often fail to fully replicate the complexity and dynamics of the human microbiome, limiting the direct extrapolation of preclinical findings (Benakis et al., 2016). Moreover, numerous confounding factors, including comorbidities, age, environmental exposures, and poly-pharmacy, further complicate the interpretation of outcomes and the design of clinical trials (Delgado Jiménez et al., 2021; Zhao et al., 2018).

Significant mechanistic gaps also remain, particularly concerning the roles of microbial metabolites beyond short-chain fatty acids. While SCFAs have been extensively studied, other bioactive compounds such as tryptophan derivatives, secondary bile acids, and microbial peptides may contribute to neuroimmune modulation, barrier function, and neural repair, yet their precise contributions remain underexplored (Peh et al., 2022; Winek et al., 2016). Clinical evidence is still in its infancy; randomized controlled trials are scarce, and concerns around the safety, reproducibility, and regulatory oversight of interventions such as fecal microbiota transplantation persist (Chidambaram et al., 2022; Lee et al., 2020).

Future research should prioritize longitudinal, multi-omics profiling of patients, integrating microbiome sequencing, metabolomics, and immune phenotyping with advanced neuroimaging to track post-stroke recovery trajectories (Singh et al., 2016; Peh et al., 2022). The development of predictive microbial biomarkers could facilitate personalized therapeutic approaches, enabling clinicians to tailor probiotics, prebiotics, SCFA supplementation, or FMT to an individual's unique microbial landscape.

Ultimately, overcoming these challenges will require interdisciplinary collaboration, standardized methodologies, and carefully designed trials to unlock the full potential of microbiota-based interventions for stroke rehabilitation (Benakis et al., 2016; Chidambaram et al., 2022).

Conclusion

Post-stroke gut dysbiosis has emerged as a central driver of neuroinflammation, systemic metabolic disturbances, and impaired neurological recovery. The gut microbiome communicates with the brain through complex mechanisms, including immune modulation, metabolite signaling, and neuroglial priming, creating a bidirectional axis that influences post-stroke outcomes (Benakis et al., 2016; Winek et al., 2016). Preclinical evidence strongly supports the therapeutic potential of microbiota-targeted interventions, such as specific probiotics (e.g., Lactobacillus rhamnosus GG, Bifidobacterium longum), fecal microbiota transplantation, and metabolite supplementation, particularly with short-chain fatty acids, which collectively demonstrate neuroprotective and anti-inflammatory effects (Lee et al., 2020; Chidambaram et al., 2022; Peh et al., 2022).Despite these promising findings, clinical translation

remains constrained by several challenges, including inter-individual variability in microbial composition, heterogeneity in intervention protocols, safety concerns, and the limited scale of human trials (Singh et al., 2016; Delgado Jiménez et al., 2021). Moreover, the functional contributions of less studied microbial metabolites, such as tryptophan derivatives and secondary bile acids are not yet fully understood, leaving gaps in our mechanistic knowledge (Zhao et al., 2018; Peh et al., 2022).

Looking forward, precision microbiome strategies guided by multi-omics profiling—integrating metagenomics, metabolomics, immune phenotyping, and neuroimaging—hold promise for tailoring interventions to an individual's unique microbial and physiological landscape. This approach could shift stroke care from a one-size-fits-all model to personalized, proactive rehabilitation, optimizing recovery trajectories while minimizing adverse effects. Unlocking the full potential of microbiota-based therapies will require rigorous, interdisciplinary research, standardized methodologies, and well-powered clinical trials to ensure safety, efficacy, and reproducibility (Benakis et al., 2016; Chidambaram et al., 2022; Peh et al., 2022).

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