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Original Article

Unveiling the hidden culprit: How the brain-gut axis fuels neuroinflammation in ischemic stroke

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ABSTRACT

Background: The brain-gut axis represents a bidirectional communication network between the gut microbiome and the central nervous system that plays an important role in homeostasis. Compelling evidence now confirms that ischemic stroke disrupts this delicate balance by inducing gut dysbiosis.

Methods: A comprehensive literature search was performed in PubMed, Web of Science, and Google Scholar for articles published between January 2000 and January 2023 using relevant keywords. Studies were limited to English and included original studies, literature, and systematic reviewers from peer-reviewed journals which discussed gut microbiota composition in models/subjects with ischemic stroke or assessed stroke impact on gut microbiota. Comments, meeting abstracts, and case reports were excluded. From the 80 relevant articles, we summarized key findings related to gut microbiota changes after stroke and their association with stroke outcomes.

Results: Emerging preclinical evidence underscores the pivotal role of the gut microbiome in glial cell development and function. Germ-free models exhibit compromised microglial activation and impaired cellular debris clearance, exacerbating tissue damage following ischemic stroke. Targeted interventions, including prebiotics, probiotics, and fecal microbiota transplantation, have demonstrated efficacy in rescuing glial phenotypes in preclinical stroke models. Beyond its local effects, the gut microbiome significantly influences systemic immunity. Ischemic stroke polarizes pro-inflammatory phenotypes of neutrophils and T cells, amplifying neurovascular inflammation. Microbiota manipulation modulates leukocyte trafficking and metabolic signaling, offering potential avenues to mitigate infarct pathology.

Conclusion: Our review demonstrates that in preclinical stroke models, modulating the lipopolysaccharide, short-chain fatty acid, and trimethylamine N-oxide pathways through the gut-brain axis reduces infarct sizes and edema and improves functional recovery after ischemic stroke. Further exploration of this important axis may unveil additional adjunctive stroke therapies by elucidating the complex interplay between the microbiome and the brain. Rigorously controlled clinical studies are now warranted to translate these promising preclinical findings and investigate whether manipulating the microbiome-brain relationship can help improve outcomes for stroke patients. Overall, continued research on the gut-brain axis holds exciting possibilities for developing novel treatment strategies that may enhance recovery after stroke.

Keywords: Brain-gut axis, Ischemic stroke, Neuroinflammation, Neurovascular inflammation

INTRODUCTION

Ischemic strokes secondary to cerebral blood vessel occlusions deprive brain tissue of oxygen, potentially leading to a secondary injury cascade.[8,37] This disease entity is a leading cause of

morbidity and mortality worldwide, with an estimated incidence of 95/100,000 population and a prevalence of 998/1,000,000 individuals/year.[24,60] Approximately 85% of all strokes are ischemic, with major risk factors including diabetes, heart disease, and hypertension.[33,38,72] Despite advances in the elucidation of stroke pathophysiology, the development of novel therapeutics remains a challenge.

Recently, increasing research has highlighted the potential role of the brain-gut axis, a bidirectional communication network linking the central nervous system (CNS) and gastrointestinal tract, in stroke pathophysiology.[7,54,62,68] It comprises a complex interplay between many signaling pathways, including the enteric nervous system (ENS), autonomic nervous system (ANS), immune system, bacterial metabolites, and its products.[58,62]

The gut microbiota is an essential component of the brain-gut axis involving trillions of microorganisms, including bacteria, viruses, fungi, and protozoa. The predominant population includes three main bacterial phyla, namely *Firmicutes*, *Actinobacteria*, and *Bacteroidetes*, accounting for over 90% of the total gut flora.[37] These phyla interact with the host by helping to maintain a range of homeostatic functions, such as regulating the mucosal immune and inflammatory responses and producing key metabolic components. Their composition is highly dynamic, and in chronic diseases, it is common to see disruption from normal microbiota composition, a process known as dysbiosis.[69]

In the symbiotic relationship with the host, the gut microbiota produces neuroactive metabolites, including neurotransmitters or their precursors and different microbial metabolites, which directly influence the brain-gut axis.[14,15,26] These neurotransmitters cannot cross the blood–brain barrier (BBB), including gamma-aminobutyric acid (GABA), glutamate, acetylcholine, and dopamine.[14,15,26] These molecules can influence different aspects of cognitive function, such as mood, learning, and anxiety.[54,55] Short-chain fatty acids (SCFAs), another key molecule produced by gut microbiota, are composed of three metabolites: acetate, propionate, and butyrate. These metabolites are produced from bacterial fermentation from complex resistant carbohydrates (sugar alcohols and fructose-oligosaccharides) or dietary fibers, which the small intestine cannot digest. Once produced, they can either act directly on the enterocytes to maintain the integrity of the mucosal barrier or indirectly to affect lipid and glucose homeostasis and energy utility regulation.[47]

Gut microbiota is closely associated with the regulation of various neural pathways. For instance, the ENS's maturation, which controls gut processes such as mucosal immunity, peristalsis, and motility, is closely linked to microbiota.[1,37] This occurs when a newborn is exposed to gut microbiota during breastfeeding, enabling certain genera of bacteria (*Staphylococcus*, *Streptococcus*, etc.) to be transferred to the newborn.[45,78] In turn, the proximity of these microbes to the ENS, a network of neurons and glial cells embedded in the wall of the gastrointestinal tract, implies that microbe-derived metabolites and neurochemicals may be able to modify the permeability of the intestinal epithelial barrier and, ultimately the ENS's homeostatic function.[26] Hence, it is reasonable to consider the ENS as the linkage between gut microbiota and the CNS.

Another crucial pathway is the ANS. In the context of the brain-gut axis, the vagus nerve has been studied for its interoceptive awareness.[50] It can detect signals from the microbiota, transmit information from the gut to the CNS for processing, and produce a suitable or inappropriate response. This response may affect the peripheral nervous system by altering gut motility and peristalsis, secretions, and systemic circulation.[9,69] Stimulation of the vagus nerve has also been shown to lead to neuroprotective effects poststroke, potentially improving stroke recovery.[40] Hence, the vagal nerve is a therapeutic target to improve stroke outcomes.

The role of the gut-brain axis has been under investigation in other diseases, including depression, dementia, and Parkinson's disease.[67] Evidence of its role in stroke pathophysiology is multifaceted and complex, particularly its role as an immune system modulator. There is also a lack of translational data connecting mechanistic investigations with therapeutic trials in stroke. This review, thus, aims to summarize the role of the gut-brain axis during stroke pathophysiology, focusing on its potential immune interactions with gut microbiota. Potential future therapeutic options may take advantage of this gut-brain axis to attempt to improve poststroke clinical outcomes.

MATERIALS AND METHODS

A comprehensive literature search was performed in PubMed, Web of Science and Google Scholar for articles published between January 2000 to January 2023 using relevant keywords. Studies were limited to English and included original studies, literature and systematic reviewers from peer-reviewed journals which discussed gut microbiota composition in models/subjects with ischemic stroke or assessed stroke impact on gut microbiota. Comments, meeting abstracts and case reports were excluded. From the 80 relevant articles, we summarized key findings related to gut microbiota changes after stroke and their association with stroke outcomes.

RESULTS

Emerging preclinical evidence underscores the pivotal role of the gut microbiome in glial cell development and function. Germ-free models exhibit compromised microglial activation

and impaired cellular debris clearance, exacerbating tissue damage following ischemic stroke. Targeted interventions, including prebiotics, probiotics, and fecal microbiota transplantation have demonstrated efficacy in rescuing glial phenotypes in preclinical stroke models. Beyond its local effects, the gut microbiome significantly influences systemic immunity. Ischemic stroke polarizes pro-inflammatory phenotypes of neutrophils and T cells, amplifying neurovascular inflammation. Microbiota manipulation modulates leukocyte trafficking and metabolic signaling, offering potential avenues to mitigate infarct pathology.

DISCUSSION

Effect of the Brain-Gut Axis During Physiological Conditions

Under normal physiological conditions, the primary function of the gut-brain axis is to regulate and maintain the homeostasis of the digestive system and its associated organs. It also has secondary modulatory functions affecting the immune system, metabolism, and mood. Several key pathways involving molecules synthesized by gut microbiota are outlined below.

Lipopolysaccharide, simplified as LPS, is an endotoxin derived from the outer membranes of Gram-negative bacteria. Gut flora is the principal source of LPS in healthy people.[12,47] Low quantities of LPS escape from the gut lumen into the bloodstream under normal circumstances, a process known as "leaky gut." LPS serves as a brain signaling molecule, activating appropriate immune cells. It is recognized by toll-like receptor 4 (TLR4), which is found in macrophages and microglia in the brain, as well as intestinal epithelial cells and gut macrophages. To maintain homeostasis, these immune cells secrete cytokines.[19,31,42,67] Interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNFα) stimulates corticotropin hormone-releasing neurons in the hypothalamus. As a result, adrenocorticotropic hormones and cortisol are produced, which maintain homeostatic activities in the body, such as lipid, carbohydrate, and protein metabolism, as well as the stress response.[19,22] Moreover, LPS also acts directly on the vagus nerve, a key component of the parasympathetic nervous system, through TLR4 receptors on the afferent fibers of the vagal nerve. Stimulation leads to the activation of noradrenergic pathways within the brainstem, which project to limbic and cortical areas involved in suitable behavioral responses.[9,69]

Another key metabolite produced by the gut microbiota important in the gut-brain axis is SCFAs. SCFAs are bacterial fermentation byproducts of dietary fibers, particularly from *Prevotella* and *Ruminococcus* gut microbiota species. Acetate is the most abundant SCFA produced by the colon, making up 60–70% of the total SCFA population, while propionate comprises around 20–25%, and butyrate is the least at 15%.[13] While they share some common functions, they also have distinct roles affecting the CNS. For instance, while all 3 SCFAs work by activating G protein-coupled receptors, GPR41 and GPR43, or inhibiting histone deacetylase (HDAC) receptors, they exhibit differing effects. While these receptors are present in multiple tissues in the body, including the brain, heart, liver, and immune cells, GPR41 and GPR43 are present abundantly in the colon.[56] Propionate binding stimulates the production of neurotransmitters, including dopamine, GABA, and others. Butyrate may stimulate the expression of brain-derived neurotrophic factors, with cognitive effects including long-term memory storage. This, in turn, affects cognitive functions such as long-term memory storage. Alternatively, a good proportion of SCFAs pass through the BBB, acting directly on the BBB to improve its integrity or increase neurogenesis, inducing the maturation of microglia and reducing astrocytic inflammation.[60] One major pathway involved in the SCFA metabolism is the aryl hydrocarbon receptor (AhR) signaling pathway. It is a ligand-activated transcription factor found in intestinal epithelial cells, enteric neurons, astrocytes, and microglia. Activation of AhR by agonists such as food indoles and bacterial tryptophan metabolites from the *Lactobacillus reuteri* stimulates other neuroinflammatory pathways downstream. This includes modulating the production of cytokines and chemokines such as IL-6, IL-1B, TNF-α, and CCL2 involved in recruiting immune cells to the appropriate site during an inflammatory response, particularly relevant during ischemic injury.[4,33]

Finally, trimethylamine (TMA) is also important in the gut-brain axis. This metabolite is a product of digestion from dietary choline and L-carnitine by intestinal microbiota, mainly found in red meat and seafood. TMA is transported to the liver through the portal vein and is oxidized to trimethylamine-N-oxide (TMAO) by liver flavin monooxygenase 3.[75] Elevated TMAO can affect processes such as cholesterol regulation, foam cell formation, and platelet formation in the body. Upon crossing the BBB, TMAO can further promote inflammatory processes or induce protein aggregation.[70,71] While the exact molecular mechanisms are not known, elevated TMAO levels may alter homeostatic states with a negative impact on clinical outcomes in stroke, Parkinson's, and Alzheimer's diseases.

GUT-brain axis in stroke pathophysiology

Research has shed light on the significance of gut microbiota on the modulation of neuroimmunological functions modulated by metabolites such as LPS and SCFA. This immunomodulatory role of gut microbiota becomes particularly crucial during stroke, where the immune system can either exacerbate or ameliorate stroke outcomes. Recent studies have shown that respiratory or urinary tract

infections increase the risk of ischemic stroke by 3.19 and 2.72, respectively.[63] This was associated with disruptions of the gut epithelial barrier poststroke.[65] Activation of immunomodulatory cells as a result of these infections triggers the release of proinflammatory and procoagulant mediators such as IL-1β, IL-6, and TNF-α.[65] The upcoming sections will describe the mechanism and ability of the gut microbiota to modulate central and peripheral immune system cells in relation to the outcomes of ischemic stroke.

Central immune system

Stroke pathology in the hyperacute stage involves the extensive release of damage-associated molecular patterns (DAMPs) into systemic blood circulation, such as adenosine triphosphate, high mobility group box 1, nucleic acids, and peroxiredoxin family proteins.[42,43] These DAMPs activate the immune system by binding to pattern recognition receptors (PRRs), such as TLRs and receptors for advanced glycation end products [Figure 1].[29,63]

Microglia

Under normal physiological conditions, diverse gut microbiota regulate microglial maturation and function at the mucosal surface. Under these circumstances, microglia play an important role in the hyperacute phase of stroke by removing cellular debris from infarcted tissues.[20] They limit secondary neuronal damage by engulfing stressed neurons and infiltrating neutrophils.[20] Germ-free (GF) mice models, which lack gut microbiota, show a widespread downregulation of key microglial activation gene pathways, such as mitogen-activated protein kinase (MAPK) 8, Fcgr2β, IL-1α, Ly86, Cd86, and Hif1α.[23,56] This downregulation reduced downstream expression of genes regulating immune receptors, such as Jak3, Stat1, and MHC class I-related β2 microglobulin.[56] Consequently, these GF mice have impaired responses to immunostimulants, with microglia being unable to activate and function properly. For example, after LPS injection, microglia in GF mice do not exhibit normal morphological changes or pro-inflammatory mediator release associated with activation.[23,56] In animal stroke models, GF mice have lower levels of microglial activation and expression of innate immune response markers. Therefore, they have a diminished microglia response and suffer from larger infarct sizes and worse cognitive outcomes.[61,62]

SCFAs likely mediate the effects of gut microbiota on microglial maturation. Studies on GF mice have shown that administering SCFAs in drinking water for 4 weeks can normalize microglial density and morphology, induce a resting phenotype in microglia, and improve stroke prognosis.[23,56] Furthermore, mice lacking the SCFA receptor Ffar2 exhibit severely malformed microglia, dendrite length, and segment numbers, leading to worse stroke outcomes, larger infarct size, and greater cognitive decline.[23,56] Interestingly, while Ffar2 was not expressed on any microglial parenchyma, immunofluorescence revealed its presence on splenic myeloid cells in the red pulp, indicating a neuroimmune interaction mediating the effect of gut microbiota on microglial activation.[23,56] In addition, studies using an antibiotic cocktail (cefoxitin, metronidazole, gentamicin, and vancomycin) on non-GF mouse models have shown reduced microglial activation.[23,56] However, there is controversy and conflicting evidence on whether gut microbiota depletion is neuroprotective or neuro-damaging.

Astrocyte

Astrocytes are another important cell type involved in the neuroinflammatory cascade postacute ischemic stroke, interacting with microglia in a tightly regulated fashion.[59] They are activated by IL-1 and TNF-α release from microglia and peripheral cytokines that further worsen the neuroinflammatory cascade. This results in the astrocyte's cytoskeletal destabilization and astrogliosis induction.[59] The subsequent glial scar formation mediates further neuroinflammatory events, including infarct area expansion and axonal growth inhibition.[59] In addition, astrocytes secrete IL-6 and matrix-metalloproteinase 9, which increase BBB instability and cause direct neurotoxicity to the remaining neurons.[3] These neuro-toxic events are collectively mediated by astrocytes, leading to the blossoming of lesion size and necrosis surrounding the infarct area.[3]

Gut microbiota can modulate astrocyte function through TLR and LPS signaling pathways.[72] The binding of LPS to TLR activates adaptor proteins, such as myeloid differentiation primary response gene 88 (MyD88) or TIR domain-containing adaptor-inducing interferon-β (TRIF). These regulate downstream pathways, such as MAPK and interferon regulatory factor signaling pathways.[72] An additional modulation pathway is through the G protein-coupled receptors on unmyelinated vagal afferents that respond to metabolites, lipids, and inflammatory factors released in the gastrointestinal system.[22]

Histological studies conducted on GF mice and specific pathogen-free (SPF) mice showed a lower proportion of astrocytes in GF mice compared to SPF mice.[32] Moreover, the microbiota metabolite of dietary tryptophan, an AhR agonist, modulated astrocytic activity in mouse models of autoimmune encephalomyelitis. The binding of AhR agonist to its receptors induces the release of vascular endothelial growth factor B and tumor growth factor (TGF)-α from microglia, driving astrocytes toward a neuroprotective phenotype.[57] The current literature lacks investigation into the effects of gut microbiota dysbiosis on the astrocytic population in stroke models. Exploring this relationship could

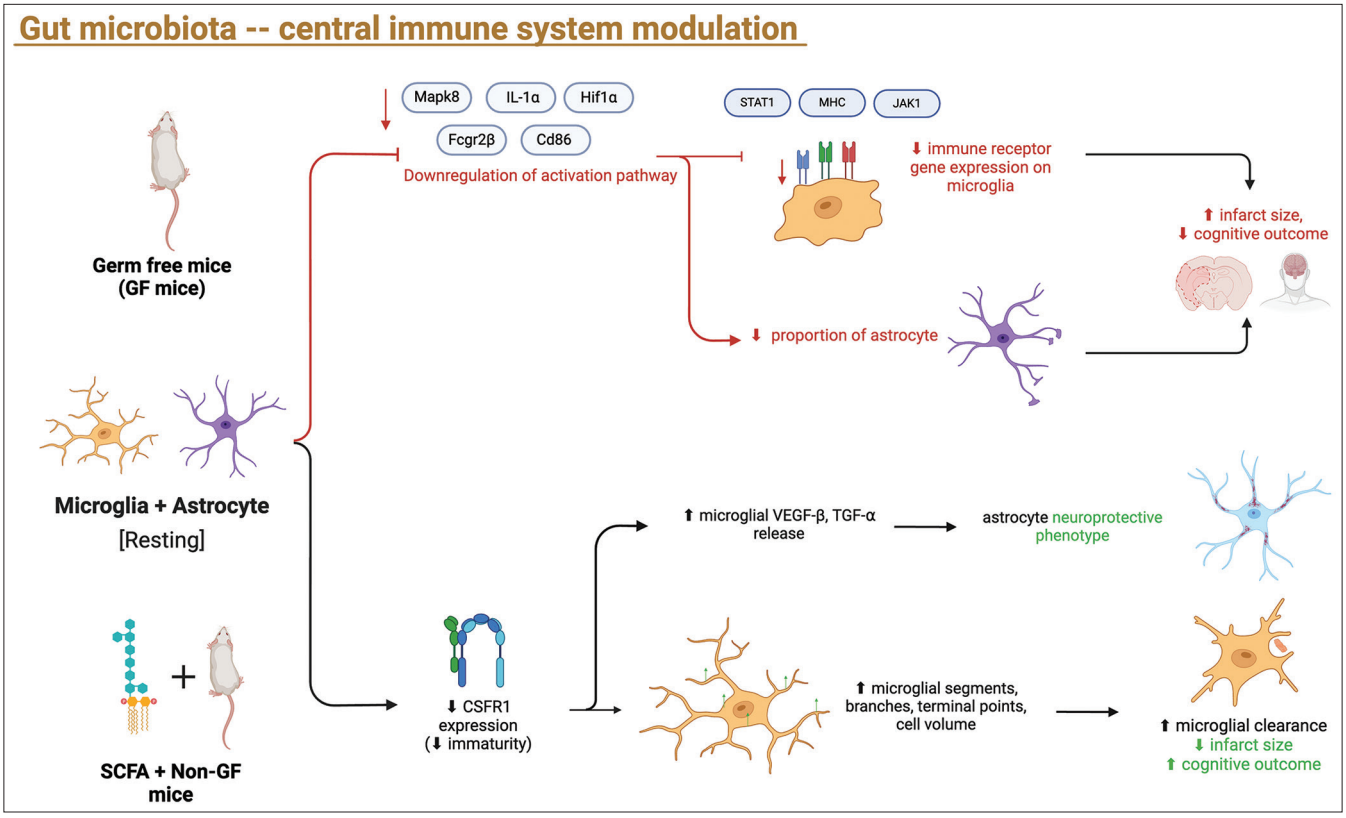

Figure 1: The gut-brain axis' major central immune system pathways which contribute to stroke outcomes. In germ-free mice, microglial activation pathways such as mitogen-activated protein kinase 8 and interleukin-1α are downregulated, which decreases the number of functional astrocytes, leading to worsened cognitive outcomes in stroke. On the other hand, short-chain fatty acid treated with nongerm-free mice causes reduced CSFR1 expression with bone marrow and spleen cells, improving microglial clearance.

offer new therapeutic insights, as astrocytes can also play neuroprotective roles by alleviating oxidative stress, releasing neurotrophic factors, and reducing cerebral edema.[28,56,66,71,77]

Peripheral immune systems

Activation of the central immune system by DAMPs alters the BBB function. Instead of excluding peripheral immune cells, the BBB facilitates the infiltration of neutrophils, lymphocytes, and monocytes with the brain parenchyma, where they typically aggregate around the area of infarcted tissue [Figure 2].[73,78]

Neutrophil

One of the principal recruited cell types is circulating neutrophils, which undergo several migration phases before ultimately crossing the endothelium through paracellular or transcellular mechanisms to travel to areas of necrotic tissue.[10,26,46] Although these myeloid cells primarily have a pro-inflammatory role, they may also switch to an anti-inflammatory phenotype in response to IL-4 released from damaged neurons. Neutrophils stimulate, upon signaling from IL-4, the release of trophic factors and mediate peroxisome proliferator-activated receptor (PPAR)-γ-dependent phagocytosis.[44,77]

Gut microbiota regulates neutrophil production under normal physiological conditions. Antibiotic-treated and GF models show a substantial decrease in neutrophil numbers in both adults and neonates. GF mice have decreased levels of circulating LPS within their bloodstream, reducing available LPS to bind with TLRs and nucleotide oligomerization domains (NODs) and downregulating TLR4/Myd88 signaling cascade responsible for producing granulocyte colony-stimulating factor.[11,54] Gut microbiota, therefore, aids in the priming of neutrophils for a robust response to inflammatory stimuli. Neutrophils isolated from GF mice have lower levels of myeloperoxidase activity and chemotactic ability than those from conventional mice.[48,74] This priming has a trade-off effect: it enhances pathogen clearance and amplifies neutrophil-mediated end-organ damage. In stroke, this results in greater brain parenchymal loss and increased infarct size.[39]

T cells

As one of the most implicated immune cell types in stroke pathophysiology, T lymphocytes infiltrate the BBB similarly to neutrophils through selectin-mediated adhesion, rolling, and transmigration of the endothelium.[17] T-cell infiltration can occur through three main routes: the BBB, choroid plexus, or meninges.[17] CD3+ T cells have been detected in animal models within the first 24 h of middle cerebral artery occlusion (MCAO), reaching a peak level 3–5-day poststroke and persisting even after 7 days.[68]

T cells can mediate poststroke inflammation through both antigen-dependent and antigen-independent mechanisms. Antigen-independent T-cell responses occur first, involving the peripheral infiltration of crucial stroke neuroinflammatory T cells, including CD3+, CD4+, γδ, CD8-, and regulatory T (Treg) cells.[27,75] These cells collectively increase the secretion of TNF-α, IL-21, and IL-17, which enhance the infiltration of Th1 cells in promoting neuronal autophagy and inducing microglial phenotype change toward an inflammatory phenotype.[27,75] These changes occur within the first 3 days of T-cell infiltration into the stroke infarct area. After day 14, antigen-dependent T-cell responses are observed at later stages, involving CD8+ T cells[41,57] and Treg cells[61,62] through direct cytotoxicity of granzyme B and amphiregulin secretion, respectively.[41,57] These result in further neuronal apoptosis and inhibition of astrogliosis, worsening stroke outcomes.

As shown above, gut microbiota plays an important role in T-cell priming. Stroke-induced gut dysbiosis triggers T-cell polarization toward proinflammatory Th17 and Th1 cells in the Peyer's patches of transplanted GF mice due to the upregulation of cytokines IL-17 and interferon-gamma.[62] Activation of these T cells coincides with an increase in cerebral pro-inflammatory gene expression, and labeling studies of Peyer's patches confirm that these peripheral-activated T cells were recruited as a result of the release of central cytokines with subsequent infiltration of ischemic hemispheres.

Treg cells form a critical subset of T cells that assume a key role in modulating the transition from inflammatory to neuroprotective effects. They account for 5–10% of the peripheral CD4+ T-cell population and are characterized by the expression of transcription factor forkhead box protein P3 (FoxP3). Depletion of Treg cells in animal studies leads to expansion of infarct size and uncontrolled neutrophil and T-cell activation. Conversely, fecal matter transplant (FMT) has improved clinical outcomes in stroke models by increasing the number of FoxP3+ Treg cells.[16,62] Similarly, studies using antibiotics to induce alterations in intestinal flora in mice with ischemic brain injury have shown an increase in FoxP3+ Treg cells (neuroprotective) and a reduction in IL-17 γδ T cells (neuroinflammatory) in the lamina propria and intraepithelial layer of the small intestine.[6,7] Immunofluorescence studies have identified that these IL-17 γδ T cells aggregate in the meninges and the choroid plexus 16 h after MCAO induction, which are the primary sites of peripheral T-cell migration into the CNS. The neuroprotective effect is likely mediated by IL-10 secretion from Treg cells, which suppresses the IL-17 γδ T cells.[6,7]

In contrast, FMT improves clinical outcomes in the MCAO stroke model through an observed increase in the number of FoxP3+ Treg cells.[50,62] Similar effects are observed in studies using antibiotics to induce alterations in intestinal flora in ischemic brain injury mice. In antibiotic-treated mice models, there is an increase in FoxP3+ Treg cells and a reduction in IL-17+ γδ T cells in the lamina propria and intraepithelial layer of the small intestine.[6] Through immunofluorescence studies, these IL-17+ γδ T cells aggregate in the meninges and the choroid plexus 16 h after MCAO induction, two primary sites of peripheral T-cell migration into the CNS. The neuroprotective effect is likely mediated by IL-10 secretion from Treg cells suppressing IL-17+ γδT cells.[6]

Monocytes

After T cells, monocytes are the subsequent cell type mediating the acute inflammatory phase of ischemic stroke, entering the brain within the first 24 hours and reaching its maximum level within 3–5 days.[5,7] In particular, a specific pro-inflammatory monocyte expressing LPS receptor CD14 and Fc gamma receptor III is implicated in the formation and propagation of vascular events precipitating in acute ischemic stroke.[30,65] Within human clinical studies, a significant increase in the number of such inflammatory subsets of monocytes has been correlated with the progression and severity of brain infarction.[35,61] The same clinical study revealed that the major factor determining the levels of CD14++ Cd16+ monocyte was the TMAO concentration present within the patient's blood, with a dose-dependent relationship observed.[35,61] These activated pro-inflammatory monocytes mediate neuroinflammation through the secretion of high levels of inflammatory cytokines, including TNF-α, while also increasing the endothelial adhesion molecule levels, allowing for greater monocyte infiltration into the damaged brain parenchyma.[35,61] The two main microbiota taxa associated with TMAO production are *Prevotella* and *Peptococcaceae*,[36,59] with FMT of these taxa causing a direct increase in the risk of thrombosis and atherosclerosis leading to downstream ischemic stroke events.[78,79]

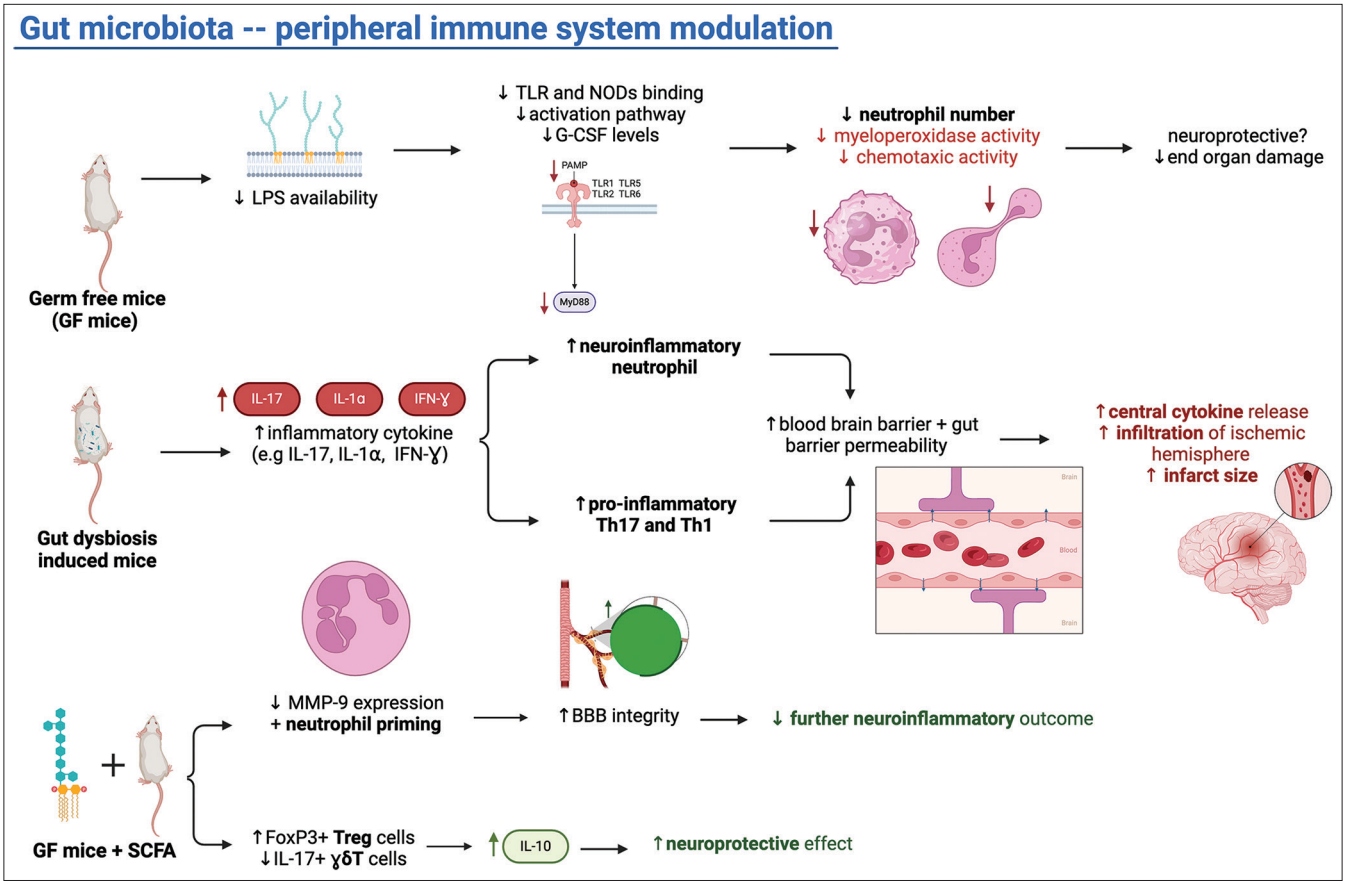

Figure 2: A complex interaction exists between the brain-gut axis and peripheral immune cell components. Germ-free mice models show a decrease in inflammatory pathway activations, reducing the level of neutrophil priming crucial for the clearance of cellular debris. The gut dysbiosis effect upregulates the presence of inflammatory neutrophils and T cells, further worsening the disrupted blood–brain barrier's patency and adversely affecting stroke clinical outcomes. These effects are contrasted with nongerm-free mice or supplement-treated mice. Upregulation of neuroprotective cells and anti-inflammatory cytokines play important roles in limiting the extent of stroke damage.

Therapeutics

Therapeutic strategies modulate the gut-brain axis based on the 3 a forementioned metabolite pathways in the gut-brain axis: LPS, SCFA, and TMAO. Some of these interventions achieve protective effects by reducing ictal or recurrent ischemic events, while other interventions reduce neuroinflammatory cascades following ischemic stroke to improve poststroke prognosis [Figure 3].

LPS pathway

High LPS levels are associated with systemic inflammatory states that precipitate procoagulant states, increasing ischemic stroke risk.[25] However, a phenomenon known as preconditioning, where low doses of LPS exposure are given before cerebral ischemia, is neuroprotective in stroke models by improving stroke outcomes.[25] The reason for this phenomenon is due to the recruitment of Ly6C^{hi} neuroprotective monocyte population, along with the upregulation of additional neuroprotective factors such as IL-10, inducible nitric oxide synthase, and CCR2 within monocytes crucial for neuroprotection.[25] These factors collectively increase the ischemic tolerance of rats treated with LPS priming, thus improving cognitive outcome poststroke.[25] The same study also found that exposure of monocytes to LPS for only 2 h is already sufficient to induce protective effects, which suggests its potential to be used as a cell-based therapy to reduce the chances of recurrent stroke.[25]

Probiotics, consumed live bacterial cultures, have therapeutic benefits for stroke patients associated with improved poststroke outcomes and shorter hospital stays, especially when combined with enteral nutrition.[76,77] Key probiotic strains associated with improved stroke outcomes in animal models include *Bacillus licheniformis, Lactobacillus,* and *Clostridium Butyricum*. Probiotics interact with gut-associated lymphoid tissues (GALTs) situated at the lower parts of the gastrointestinal tract, such as Peyer's patches and lymphoid cells. Microbial-associated molecular patterns present, such

as LPS, within probiotics interact with specific PRRs on the surface of antigen-presenting cells of GALT.[77] This results in down activation of the inflammatory signaling cascade and reduction in neuro-inflammatory factors, including TNF-α and IL-6. Moreover, probiotics also help to improve intestinal flora imbalance rates by reducing the risks of major stroke complications such as lung, gastrointestinal, and urinary tract infections.[77] The immunomodulatory effects of probiotics are not restricted to the LPS. Further investigation is warranted to explore specific bacterial strains' effects and verify whether probiotics demonstrate similar efficacy within human studies.

SCFA pathway

Another important therapeutic pathway is SCFAs, primary metabolites produced by the gut microbiota. SCFA supplements are beneficial in managing stroke outcomes in both early and later phases.[14,78]

Adequate fiber consumption, a quotidian dietary intervention, acts as a preventative measure to reduce the incidence of stroke by encouraging microbiota fermentation to produce SCFAs.[49] Based upon a meta-analysis of 8 cohort studies conducted in the United States, Northern Europe, Australia, and Japan, total dietary fiber intake is inversely associated with the risk of ischemic stroke, achieving an almost 10% reduction in the relative risk of stroke events.[53] The effects of such reduction are also particularly notable, with a shift toward a high-fiber diet for as little as 2–3 weeks, effectively shifting the gut microbiota toward a neuroprotective phenotype of a high *Prevotella*-to-*Bacteroides* ratio.[53] During the microbial fiber fermentation process, this results in the acidification of the gut microbiota through the release of SCFA compounds, including acetate, propionate, and butyrate.[71] These SCFA compounds would then bind to major receptors, including GPR41/43/109A, G-coupled proteins found on immune cells. Such binding would then mediate downstream effects, including the suppression of pro-inflammatory HDAC and nuclear factor-κB (NF-κB).[71] Overall, the downregulation of these pathways results in a reduction in the number of peripheral mononuclear cells, inflammatory macrophages, and dendritic and Treg cells, all of which are inflammatory cells implicated with worse ischemic stroke outcomes.[71]

Another major therapeutic strategy acting upon the SCFA pathway is FMT. Systematic reviews based upon preliminary animal studies have concluded that FMT, rich in butyric acid, has been effective in reducing infarct volume and associated cerebral edema, survival rates, and neurological and behavioral outcomes while also reducing blood lipid levels and risk of further thrombosis.[52] The mechanism of action for the therapeutic effect of butyric acid is due to its ability to activate PPARs, which are important nuclear hormone receptors regulating the gut-brain axis, mediating downstream reduction (NF-KB) pro-inflammatory signaling.[52] In addition, the butyric acid also acts upon the gastrointestinal system by reducing pathogenic bacterial strains, including *Bacteroides*, *Klebsiella,* and *Haemophilus*, while enriching beneficial bacterial strains, including *Lactobacillus, Butyricicoccus,* and *Megamonas.*[52] Through repairing the leaky gut barrier and reductions within inflammatory signaling pathways, butyrate SCFAs can achieve neuroprotective effects leading to improved poststroke outcomes.

Besides FMT, direct supplementation of SCFA compounds is an alternative strategy that could be used to manage the gut concentrations of SCFA compounds.[52] Direct butyrate supplementation, when administered within mice stroke models, improves neurological outcomes while reducing the volume of cerebral infarction and cerebral edema. Sodium butyrate (NaB), particularly in animal models, reduces the expression and release of inflammatory cytokine IL-1β and IL-18 from ischemic regions. The mechanism behind this action is similar to that of fibers by acting as an HDAC inhibitor while stimulating the production of neuroprotectant insulin-like growth factor 1 (IGF-1) from peripheral tissue sites such as the liver and spleen.[51,74] NaB also further offers a neuroprotective effect due to increased expression of GPR41, PI3K, and phosphorylated Akt, which are important cell survival pathways that attenuate neuronal apoptosis after ischemic stroke strokes.[78]

Another effective SCFA supplementation that has shown promising results is liposome-encapsulated acetate (LIPA). LIPA was shown to modulate chronic neuroinflammatory events, preventing expansion of post infarct size.[78] Mice treated with LIPA excited improved motor and cognitive outcomes, with lower levels of circulating pro-inflammatory M1 microglia-secreting inflammatory mediators. Instead, they had higher concentrations of anti-inflammatory, neuroprotective M2 microglia secreting anti-inflammatory cytokines such as IL-10, IGF-1, and nerve growth factor,[78,79] thus protecting the ischemic penumbra from additional insult from secondary injury cascade. The mechanism of this acetate supplementation is through the hyperacetylation of H3K9. This downregulates the expression of a broad range of inflammatory cytokine expression of TGF-β, IL-4, IL-6, and NF-κB signaling cascade, proven factors that worsen neuroinflammatory events in stroke patients.[64,79]

Both FMT and SCFA have shown clinical promise in the treatment of other conditions, but the effects of specific strains of microbiota remain unknown. To support its role in the clinical management of ischemic stroke, we suggest future studies to investigate its long-term effects, which would provide a foundation for its implementation in clinical trials.

Trimethylamine N-oxide (TMAO)

Elevated plasma TMAO levels from TMA-producing gut bacteria are seen in patients with moderate-to-severe

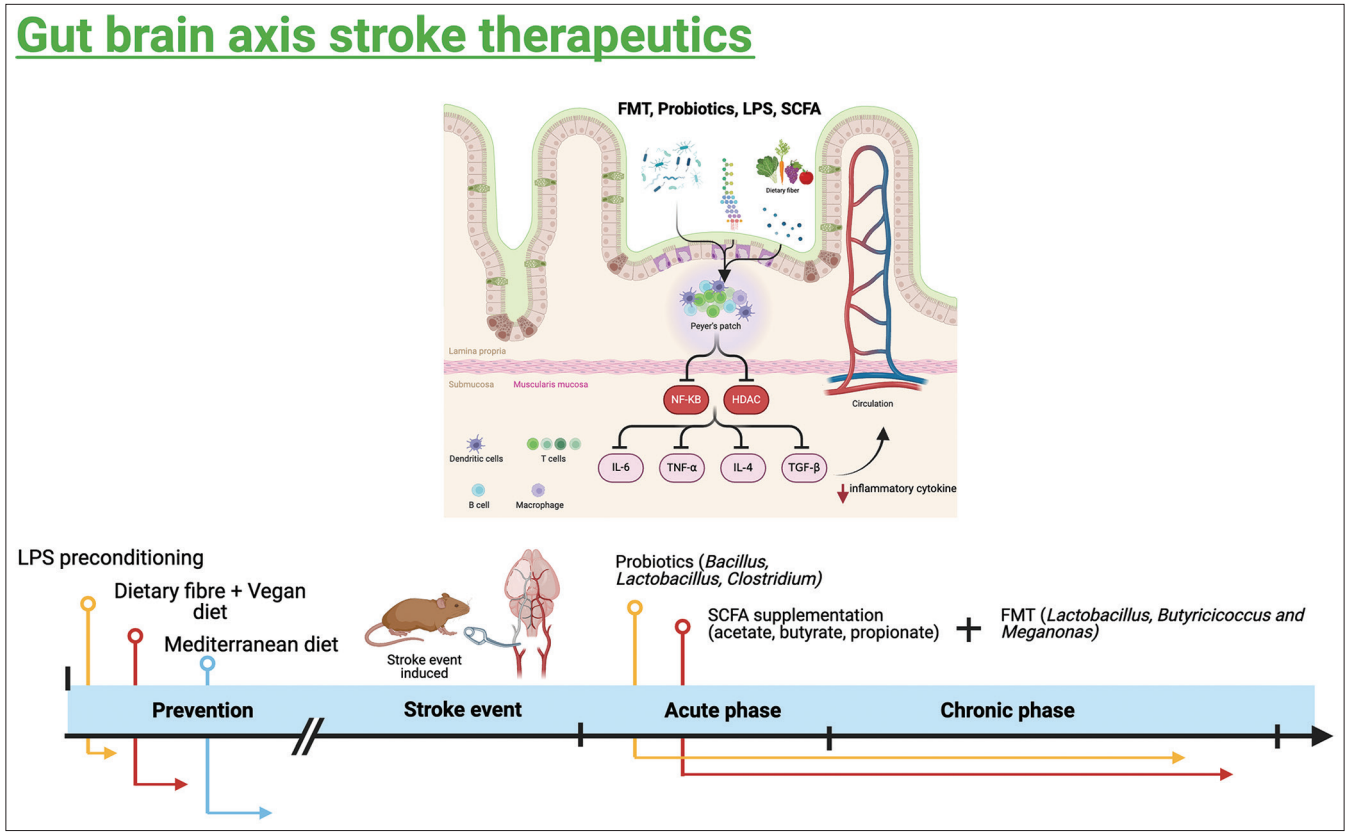

Figure 3: Lipopolysaccharide preconditions and dietary changes act as preventative measures, reducing the chance of ischemic stroke by reducing the overall level of systemic inflammation. Probiotics, short-chain fatty acid supplementation, and fecal matter transplant can be used in the acute and chronic poststroke phase by acting upon key gastrointestinal lymphoid tissue to reduce inflammatory pathways such as nuclear factor-κB and histone deacetylase and lower systemic levels of inflammatory cytokines. This reduces neuroinflammatory events and limits the severity of stroke outcomes.

ischemic stroke.[78,80] One possible cause is TMAO's contribution to the development of atherosclerosis, whereby higher levels cause increased plaque formation from an accumulation of cholesterol and other lipids.[79,80]

Atherosclerosis is a major risk factor for stroke, as it can reduce cerebral blood flow and increase the risk of embolic events. As TMAO is a product formed by dietary choline and carnitine metabolism, modification of the levels of these two metabolites may lead to improved stroke outcomes.[21,40,42] Intriguingly, elevated levels of TMAO have been demonstrated by two independent clinical studies to be associated with lower risks of strokes and recurrent strokes due to its neuroprotective effects. This is contrary to what we would have expected since carnitine consumption would lead to increased TMAO production. However, this was attributed to the fact that neither of these studies had data on the impact that gut microbiota had on L-carnitine and TMAO levels, which is a major limitation.

On the other hand, dietary interventions have seen success in reducing circulating TMAO levels. This includes a vegan diet, which showed a rapid decrease in TMAO levels from baseline within 8 weeks, and also with improvements seen in lipid profile markers.[2] Another diet that has also seen success is the Mediterranean diet, which, although is rich in TMAO, appears not to have an impact on affecting plasma TMAO concentrations.[18,40] This is the case as it only changes the composition of gut bacteria, such as increasing levels of *Prevotella* and *Firmicutes*, bacteria known to be beneficial to the human body and reduce stroke risk. Interestingly, although ketogenic diets have been well established to be able to change the composition of the gut microbiota, to our knowledge, there is yet to be published literature investigating the exact association between ketogenic diet, TMAO levels, and stroke risk.[34]

CONCLUSION

The gut-brain axis is a complex and dynamic system critical in stroke pathophysiology. The gut microbiota produces key metabolites such as LPS, SCFA, and TMAO, which are involved in maintaining normal homeostatic brain functions.

However, growing evidence suggests that disruption in the levels of these metabolites can lead to immune pathway dysregulation affecting both the central and peripheral immune systems, thereby exacerbating stroke outcomes. Interventions targeting gut microbiota composition and its metabolites offer promise in mitigating stroke-related damage. However, the exact importance of the gut-brain axis in these interventions is not yet fully understood. Further research is needed to elucidate the precise mechanisms associated with these therapies and to translate these findings into effective clinical interventions. In summary, the gut-brain axis represents a promising area of research for improving our understanding and treatment of stroke.

Ethical approval

The Institutional Review Board has waived the ethical approval for this study as it is retrospective and qualitative in nature without unique patient identifiers.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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