

Immune regulation of the gut-brain axis and lung-brain axis involved in ischemic stroke

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Abstract

Local ischemia often causes a series of inflammatory reactions when both brain immune cells and the peripheral immune response are activated. In the human body, the gut and lung are regarded as the key reactional targets that are initiated by brain ischemic attacks. Mucosal microorganisms play an important role in immune regulation and metabolism and affect blood-brain barrier permeability. In addition to the relationship between peripheral organs and central areas and the intestine and lung also interact among each other. Here, we review the molecular and cellular immune mechanisms involved in the pathways of inflammation across the gut-brain axis and lung-brain axis. We found that abnormal intestinal flora, the intestinal microenvironment, lung infection, chronic diseases, and mechanical ventilation can worsen the outcome of ischemic stroke. This review also introduces the influence of the brain on the gut and lungs after stroke, highlighting the bidirectional feedback effect among the gut, lungs, and brain.

Key Words: enteric glia cells; gut microbiota; gut-brain axis; immune response; inflammation; ischemic stroke; lung-brain axis; microglia

Introduction

Ischemic stroke is an acute cerebrovascular disease caused by cerebral artery occlusion. Although this disease has a great impact on public health, its exact etiological and pathological process are not directed and precise (Pluta et al., 2021). Currently, researchers believe that a complex series of neuropathological events such as excitotoxicity, oxidative stress, neuroinflammation, apoptosis, immune response, acidosis, and mitochondrial damage result in brain damage in ischemic stroke (Wang et al., 2021a, 2022b; Zhu et al., 2022; Zhu and Wan, 2023). Severe changes in local circulation lead to the accumulation of cell debris, and extensive infiltration of immune cells in the brain tissue also induces the secondary progression of cell injury. However, there is no single answer to the mechanisms of ischemic stroke, because of which there is considerable ambiguity regarding the direction of stroke treatment (Xiong et al., 2018). Despite alternative treatments such as thrombus removal to allow tissue reperfusion, the limited treatment window and inadequate response lead to the poor prognosis of many patients.

Ischemia of the local brain tissue has been regarded to cause significant inflammation and has been studied in the past (Cuenca-López et al., 2010). Rather than concentrating on restricted inflammation alone, recent studies are now carrying out systematic level analyses, because of increasing concerns about the relationship between the central nervous system (CNS) and the enteric nervous system. Once inflammation occurs in the human body, the whole immune system of the relative tissue of the organism undergoes activation and rapidly participates in the inflammatory immune response.

From the perspective of the brain, resident glial cells act as the main immune defense by eliminating injured or necrotic parts (Singh et al., 2016), while the intestinal tract and lung also assist the process via additional pathways, by translocation of immune cells and changing the central response through some metabolites (Wang et al., 2021b). This notion follows the popular concept of the gut-brain axis and lung-brain axis found by scholars. Therefore, this review attempts to rationalize the basic understanding of the immune mechanism of ischemic stroke and summarize the detailed role of the gut-brain axis and lung-brain axis in the inflammatory-immune response.

Search Strategy

The articles used in this review were retrieved through an electronic search of the PubMed database from 2013 to 2023. The search was performed using

the following key terms: Ischemic Stroke (MeSH Terms) AND ((Brain-Gut axis (MeSH Terms) OR lung (All fields)). To achieve a comprehensive search, we did not restrict the search terms for inflammation or immunity. We expanded the search range by changing the words ischemic stroke to brain (All fields) or nervous system (All fields). The results were further screened based on the title and abstract, which contained immune response or inflammation-related information.

The Immune Mechanism of Ischemic Stroke

Targeting the immune system

Recently, a series of relatively completed studies and reviews have highlighted the pathological process of cerebral ischemia with respect to the immune system (Gerganova et al., 2022; Wang and van de Pavert, 2022; Wicks et al., 2022). The core issues addressed are increased permeability of the blood-brain barrier (BBB) and subsequent cytoplasmic and nuclear events (Di Napoli et al., 2011). The brief problems caused by these two events include the production of inflammatory mediators, activation and infiltration of brain-resident and peripheral immune cells, and the release of damage-associated molecular patterns (DAMPs) by dying neurons, which contribute to the formation of an inflammatory environment (Zeng et al., 2022). The above-mentioned inflammatory cascades are always activated immediately after the pathological process of ischemic stroke and present for several days or weeks. To better understand the role of the gut-brain axis, we briefly emphasize on the different characteristics of each immune phase in ischemic stroke (Figure 1).

Innate immune response

DAMP, brain antigens, microglia and astrocytes initiate immune response by recognizing dsDNA and oxidative stress as the cytokines (Xu et al., 2019; DeLong et al., 2022). Normally, microglia dynamically supervise changes in brain homeostasis and can be activated to eliminate cellular debris and release abundant cytokines, neurotransmitters, or other molecules to save both neurons and synapse functions (Borst et al., 2021). Previous studies have fully distinguished the roles between M1 and M2 phenotypes, and suggested that M2 microglia are the earliest cell type to be activated when the stroke occurs (Sumbria et al., 2012; Li et al., 2018; Umahara et al., 2018). While some studies have confirmed the proinflammatory role of M1 microglia at the beginning of ischemic stroke, it should be made clear that such discrepancy probably depends on the primary ischemia condition, reperfusion time,

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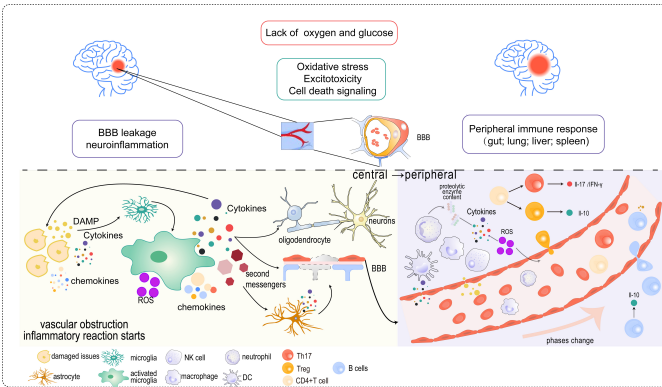


Figure 1 | BBB leakage, neuroinflammation, and related peripheral signaling pathways of immune response involved in ischemic stroke.

Because of lacking oxygen and glucose, the brain initiates a series of reactions such as oxidative stress. These reactions will cause BBB leakage and subsequent neuroinflammation. DAMPs released by damaged issues will promote the activation of microglia and stimulate them to release various elements such as cytokines, chemokines, second messengers, and ROS. Such materials have different effects at different times when triggering the peripheral immune cells to respond. Created with Adobe Illustrator 2019. BBB: Blood-brain barrier; DAMP: damage-associated molecular patterns; IFN- γ : interferon- γ ; IL-17: interleukin-17; IL-10: interleukin-10; ROS: reactive oxygen species.

lesion location, and research time (Neher et al., 2013; Alawieh et al., 2018). Additionally, another essential role of microglia is the interaction with endothelial cells, astrocytes, and oligodendrocytes (Xu et al., 2020). Activated microglia will induce A1-reactive astrocytes *in vitro* and *in vivo* by releasing interleukin (IL)-1 α , tumor necrosis factor- α (TNF- α), and complement component subunit 1q (Liddelow and Barres, 2017). This study also showed that astrocytes reduce brain damage and downregulate neuroinflammation, as it is vitally important to reconstruct the BBB and maintain the stability of central neurons (Pekny et al., 2016). Other studies have reported that astrocytes interact with microglia by secreting chemokines to stimulate the microglia and participate in its phenotype alteration and later ischemic inflammation (Inose et al., 2015).

The subacute phase of ischemic stroke is more complicated than innate one. Damaged neurons release IL-4, and via interferon regulatory factor 4 signaling, myeloid cells recruited from the periphery in the acute period transition from a naive condition to anti-inflammatory state (Zhao et al., 2015, 2017). However, a few days after the initial injury, some neurons will also promote the production of proinflammatory monocyte-derived macrophages and then activate proapoptotic signals by releasing ATP and Fas ligands (Meng et al., 2016). In particular, microglia can directly or indirectly damage neural structures in the chronic phase by interacting with various adhesion molecules that migrate to the ischemic injury site including the immunoglobulin superfamily (e.g., intercellular cell adhesion molecule-1) and inflammatory cytokines produced by white blood cells (Murray et al., 2013; Gülke et al., 2018). Furthermore, astrocytes will promote or hinder functional rehabilitation and regeneration of neuronal axons (Xu et al., 2020).

Adaptive immune response

Some brain-derived antigens such as S100b belong to the mutagenic family and are so named because of the solubility in 100% saturated solution of ammonium sulfate at neutral pH. S100b can stimulate the production of T and B cells to increase the amount of proinflammatory factors in acute ischemic stroke (Choi et al., 2021). Additionally, T cells infiltrate the brain 3–4 days after infiltration by monocytes and neutrophils; in rodent models of stroke, regulatory T cells (Tregs) accumulate within 24 hours (Yilmaz et al., 2006). When facing new antigens such as myelin basic protein, sensitized circulating T cells will mainly participate in the response, and different kinds of T cells will play distinct roles (Bornstein et al., 2001). For instance, Th1 plays a vital role in ischemic stroke by releasing pro-inflammatory cytokines (IL-2, IL-12, TNF- α). While Th17 secretes IL-17 to promote inflammation, Th2 can secrete IL-4, IL-5, IL-10, and IL-13 to play an important role in neuro-protection (Wu et al., 2021). By contrast, Tregs secrete IL-10 to hinder the production of pro-inflammatory cytokines and have profound influences on inflammation resolution and stroke recovery (Wu et al., 2021).

Similar to T cells, B cells also migrate to the brain after ischemic stroke. A deficiency of B cells is known to worsen functional outcomes and histological damage, especially after transient cerebral ischemia (Ren et al., 2011). A study even showed that a lack of B cells led to an increase in activated microglial neutrophils, macrophages, and T cells to further facilitate the proinflammatory state (Ren et al., 2011). One beneficial function of B cells is the release of IL-10. However, further studies are needed regarding the role of B cells, particularly in the different phases of ischemia. As B cells change, they alter the T-cell response in stroke recovery. Additionally, DAMP-mediated activation of Toll-like receptors (TLRs) also stimulates B cells by increasing the expression of costimulatory molecules to further promote activation and autoimmunity (Zera and Buckwalter, 2020).

Notably microglia also engaged in the promotion of T-cell differentiation, and distinct M1/M2 microglia will lead to opposite effects, which have been well documented in previous reviews (Coughlan et al., 2005; Park et al., 2006). Astrocytes also have tight interactions with T cells, and they can secrete IL-15, which increases the concentration of CD8⁺ T cells and natural killer (NK) cells to worsen brain injury (Lee et al., 2018b). In addition to IL-15, astrocytes also increase the levels of IL-17 (Ito et al., 2019), IL-33, and chemokines with the CC motif 1 (CCL1). IL-33 is thought to promote the proliferation of Tregs, and CCL1 levels increase when combined with chemokines with the CC motif 8 Tregs that secrete a vascular endothelial-derived growth factor ligand in the chronic phase of stroke. Tregs also regulate IL-6 and the signal transducer of activators of transcription pathways and ameliorates neurological deficits (Ito et al., 2019).

Extra immune cells

With knowledge of the roles of the common brain resident glia and peripheral innate and adaptive immune cells (DeLong et al., 2022), a recent study are focusing on the innate lymphoid cell (ILC) family that have been shown to migrate towards ischemic stroke lesions and elicit protective and recovery functions (Wang et al., 2023). This family includes the NK cells and ILC type 1, 2, and 3 cells, and the study speculated that through BBB, C-X-C motif chemokine12-C-X-C chemokine receptor type 4 axis expressed by ischemia brain will mainly recruit NK and ILC1s to move to stroke region and improve experiment models' motor movement (Wang et al., 2023). By contrast, IL-17A secreted by ILC will promote lesion enlargement, and a study revealed that IL-10 will restrict that signaling (Piepke et al., 2021).

Another new study reported that CD8⁺CD122⁺CD49dlo T regulatory-like cells (CD8⁺ TRLs) and its function of earliest infiltration in the animal brain to weaken inflammation after ischemic stroke (Cai et al., 2022); furthermore, its primary role is to suppress the proliferation of effector T lymphocytes and proinflammatory effects to maintain the immune homeostasis. This study also explored the function of CD8⁺ TRLs, which is implemented by releasing IL-10 and research discovered a material named epidermal growth factor-like transforming growth factor will assist the function of IL-10 (Cai et al., 2022).

Immune mechanism through the gut-brain axis

In current years, scientists have found that the gut-brain axis displays a vital link between the gut and cerebral ischemia (Pluta et al., 2021). Previously, researchers found that the brain, which has neural circuits, neurotransmitters, and receptors, can influence the movement, secretion, and immune function of the intestinal tract, and in stroke or transient brain ischemia patients, there is considerable dysbiosis of the gut microbiota. Remarkably, after a stroke, up to 50% of patients will experience gastrointestinal complications, including constipation, gastrointestinal bleeding, fecal incontinence, and dysphagia, which are associated with poor stroke prognosis (Camara-Lemarroy et al., 2014).

From the immune aspect, the intestinal tract is rich in immune cells that accounts for more than 70–80% of the whole-body related immune system (Li et al., 2019). Researchers are interested in multiple functions of gut microbes such as regulating brain development, immune regulation, antagonism, anticancer activity, and physiological nutrition (Cerf-Bensussan and Gaboriau-Routhiau, 2010; Human Microbiome Project Consortium, 2012). Specific to the gut-brain axis, studies have focused on the following mechanisms: the immune system, the gut microbiota metabolism pathway, the intestinal mucosal barrier and BBB, the neuroanatomical pathway, and the hypothalamic-pituitary-adrenal (HPA) axis neuroendocrine pathway (Wang et al., 2022a). Notably, all these pathways could interact and commonly act from an immune point of view, so deciphering the basic mechanisms of inflammatory signaling along the gut-brain axis is critical to our understanding of neuroimmune communication and should aid the development of immunomodulatory therapies for gastrointestinal and neurological diseases (Figure 2).

Immune system

In the intestinal tract, the first-line of immune cells are the macrophages, neutrophils, dendritic cells (DCs), NK cells, and ILCs (types 1–3). While the kinds of adaptive immune cells depend on DC-dependent antigen presentation, some T and B cells also migrate to the brain through these processes (Rojas et al., 2019). The activation and action of all these cells are secondary to the stimulation of the central inflammatory response in ischemic stroke. From the perspective of the immune system, the gut microbiota plays a great role in the maturation of the intestinal mucosal immune system by promoting the formation of gut-associated lymphoid tissue, IgA-producing B cells, T-helper (Th) 17 cells, and innate lymphoid cells (Camara-Lemarroy et al., 2020; Pröbstel et al., 2020). The acute response of the intestinal tract after stroke onset and the subsequent chronic process are described in the following sections:

Acute progressive stage

Under ischemic stroke, the rapidly progressive inflammatory response triggers the peripheral immune response, and the intermediate bridge involves the damaged tissue, brain glial cells (especially microglia), and a series of cytokines, DAMPs, and chemokines released by them. Studies have found that a subset of meningeal NK cells in the gut produce interferon (IFN)- γ , and these cells stimulate brain astrocytes that express lysosomal protein LAMP1 and the death receptor ligand TRAIL (Giovannoni and Quintana, 2020; Sanmarco et al., 2021), along with circulating immune cells moving to the damaged area and upregulating and activating adhesion molecule

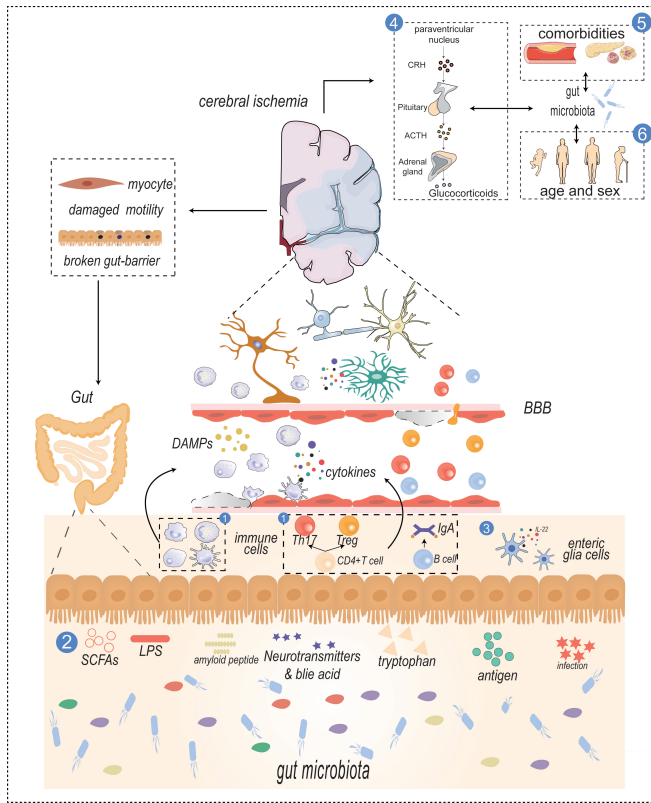


Figure 2 | The gut-brain axis in ischemic stroke.

① Immune cells including NK cells, neutrophils, and adaptive immune cells stimulated by cytokines or brain-derived antigens will circulate in the blood and cross the BBB to take part in neuroinflammation. ② Gut metabolites, except LPS which is a membrane component of gut microbiota, SCFAs, and tryptophan are generated by specific gut microbiomes that contribute to various effects like the activation of astrocytes or microglia. ③ Gut enteric cells release IL-22 to form a bidirectional communication and maintain the gut barrier integrity. ④ HPA axis plays an important role in ischemic stroke. Gut microbiota can affect the release of hormones, and hormones can also affect the composition of gut microbiota. ⑤ and ⑥ Comorbidities, age, sex, plaque formation in atherosclerosis, and insulin resistance in diabetes are related to gut microbiota, and the composition of gut microbiota is also different in different ages and sex. These factors are related to the onset of ischemic stroke. The prominent influences of interfering gut myocytes and gut barrier caused by the brain are drawn on the left. Created with Adobe Illustrator 2019. ACTH: Adrenocorticotropic hormone; BBB: blood-brain barrier; CRH: corticotropin-releasing hormone; DAMP: damage-associated molecular pattern; HPA: hypothalamic-pituitary-adrenal; IgA: immunoglobulin A; IL-22: interleukin-22; LPS: lipopolysaccharide; NK cells: natural killer cells; SCFA: short-chain fatty acid; Th17: T helper type 17 cell; Treg: regulatory T cell.

family-activated interactions between lymphocytes, leukocytes, endothelial cells, and platelets. Neutrophils, as the most important leukocytes, produce inflammatory cytokines such as IL-1 β , IFN- γ , IL-17, matrix metalloproteinase-9, and C-C motif chemokine 2 (Qin et al., 2022). They can also generate ROS, initiate the complement system, and mediate their high proteolytic activity to cause direct or indirect damage to the neural structures (Nathan, 2006). The whole process is inseparable from the role of the gut microbiome. Recent studies have suggested that gut microbes have the following influence. First, they change circulating cytokines and cause brain inflammatory reactions. Many studies have shown that both the intestinal microbiota and mucosal cells can regulate the activation of immune molecules that affect the CNS, including the proinflammatory factors IL-8 and IL-1 and the anti-inflammatory factors IL-10 and TGF- β (Shi et al., 2017; Kayama et al., 2020). Second, they shape the maturation and homeostasis of the microglia, which is important for the regulation of CNS development, such as myelination and neurogenesis in the adult brain and maintenance, and play an immune surveillance role in the brain by participating in information transmission and clearing cellular debris (Abdel-Haq et al., 2019). When microglia are lacking, their function in the phagocytosis of amyloid and tau protein that accumulates after ischemia is restricted (Endres et al., 2022). Third, as an important component of gram-negative microbes, lipopolysaccharide (LPS) combines with lipopolysaccharide or other microbial-related molecules with Toll-like receptors, which are one of the intestinal mucosal pattern recognition receptors (Siebler et al., 2008). This process activates some immune cells such as DCs, neutrophils, and macrophages, and then produces proinflammatory cytokines like IL-1 α , IL-1 β , TNF- α , and IL-6, to cross the BBB and affect brain function (Camara-Lemarroy et al., 2020). These conditions will further influence the outcome of the brain if it experiences an ischemic attack. Fourth, under the influence of the gut microbiota, some immune cells in the intestinal tract will migrate to the brain and play reverse roles to exacerbate inflammatory outcomes (Wastyk et al., 2021).

Chronic phase

Apart from brain-resident immune cells, there is still a wide repertoire of leukocytes in the meningeal layers such as T cells, B cells, and type 2 innate lymphoid cells (Alves de Lima et al., 2020). Although the core function of meningeal immune cells has not been clarified, gut microbiota have been shown to influence the migration of these cells to the brain. An earlier study showed that these cells participate in response to injury or infection. Meningeal T cells can assist cognitive function by releasing IL-4 and IFN- γ in the CNS (Alves de Lima et al., 2020). They communicate with astrocytes to induce Th1 and Th17 cell responses through the secretion of IL-12 and IL-23 or to restrict Th17 cell activity and stimulate IL-10-producing T cells through the secretion of IL-27 (Giovannoni and Quintana, 2020).

Ischemic stroke alters the gut microbiota composition, and this environment leads to the inner-gut proliferation of Th1 and Th17 cells accompanied by the migration of monocytes and intestine-derived T cells to the ischemic brain tissue, thereby aggravating neuroinflammation (Singh et al., 2016). Normally, CD4⁺ T cells are the main lymphocytes in the intestinal tract and mediate various kinds of host immune protection and homeostasis, and such responses are realized through the differentiation of T cells into Th1, Th2, Th17, and Tregs which are induced by the metabolites of gut microbiome (Shale et al., 2013). Furthermore, different kinds of immune T cells act differently, and conversion between T cells, such as Th17 cells and Tregs, is represented by relevant chemokine or cytokine expression. Low expression levels of TGF- β , IL-23, or IL-6 induce the differentiation of naive T cells into Th17 cells, while high expression levels of TGF- β induce Tregs (Gagliani et al., 2015). In this process, gut microbes are phagocytosed by DCs, which in turn are stimulated to release cytokines. Some bacteria will also promote CD8⁺ T cell intestinal microbes and reduce some adaptive cells such as Th17 cells. This process may lead to immune defects, but at the same time, it will definitely reduce the rates of some diseases, such as autoimmune conditions, which may play a role in the reduction of ischemic stroke (Stubbe et al., 2013). Specific cytokine combinations, biogeography, and the microbial environment are the three main ways that microbiota influence the formation of T cell subsets. For example, by expressing a critical regulator of the Th1 differentiation program, T-bet stimulates Th1 cells to secrete IFN- γ under the influence of IL-12, IL-18, and IL-23; by contrast, Th2 cells are formed under the influence of IL-4 or IL-5, express GATA-binding protein 3, and secrete IL-5 and IL-13 (Gev-Zatorsky et al., 2017). In addition, the majority of microorganisms that have the ability to invade epithelial cells can be phagocytosed by DCs, which can also stimulate DCs to release inflammatory cytokines such as TNF- α and IL-6 and bind to OX40 (a tumor necrosis factor receptor) and IL-12. These signals preferentially polarize Th1 cells (Brown et al., 2019). $\gamma\delta$ T cells are a group of cells with primitive innate immune functions that are predominantly located on the surface of the intestinal epithelium (Prinz et al., 2013). Following an imbalance in the gut microbiota, $\gamma\delta$ T cells can secrete large amounts of IL-17, which can cause chemokine production by peripheral monocytes and neutrophils and then exacerbate ischemic brain injury (Shichita et al., 2009). Effector T cells can induce enterogenous ischemic brain injury, but Tregs can exert adverse effects (Liesz et al., 2015). Tregs play a neuroprotective role by secreting IL-10 to inhibit IL-17⁺ $\gamma\delta$ T cells (Liesz et al., 2009). However, Tregs seem to not enter the brain parenchyma during the acute stroke phase, indicating that the beneficial effects of Tregs are achieved on the peripheral immune system instead of damaged brain tissue (Li et al., 2013). The detailed and exact mechanism of how the brain motivates peripheral immune cells to move to the CNS still needs to be explored.

The function of B cells cannot be neglected when intestinal stimulators such as antigens occur in the gut, as they promote the differentiation of B cells into plasma cells that secrete immunoglobulin A and control luminal microbes to prevent association (Rojas et al., 2019). When facing an attack, massive intestinal IgA-positive plasma cells will relocate into the brain and spinal cord to relieve neuroinflammation (Pröbstel et al., 2020). Although studies have found that this process is mediated by IL-10, the detailed signals have not been identified. Anatomically, researchers regard them as adjacent to dural venous sinuses to protect the CNS from the invasiveness of peripheral pathogens (Fitzpatrick et al., 2020).

Gut metabolites

Microbes in the gut synthesize neurotransmitters, short-chain fatty acids, and bile acids that enter the bloodstream, similar to brain cells and microglia in the CNS. Here, we have listed five terms of metabolites largely studied by recent researches.

Short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, are produced by specific microbes. SCFAs have a significant effect on the CNS in the following ways: First, SCFAs bind to the G protein-coupled receptors (e.g., GPR41 and GPR43) and act as signal molecules to activate specialized immune cells (Kim et al., 2013). The process involves a response to an acute infection or abnormal regulatory mechanism; consequently, this results in increased intestinal permeability and absorption of active metabolites (Sorboni et al., 2022). Second, SCFAs attenuate neuroinflammation by inhibiting the translocation of LPS to brain tissue. Third, SCFAs also regulate the apoptosis of neurocytes and cerebral neurotransmitters and modulate immunoinflammatory responses mediated by the microglia. Fourth, such materials may be absorbed into circulation and cross the BBB to exert their biological effects (Dang and Marsland, 2019; Sorboni et al., 2022). Differences in bacterial species are associated with SCFA production (Table 1).

al., 2007), studies have indicated the influence between the comorbidity—diabetes and ischemic stroke—from the perspective of the gut-brain axis.

Thus far, there is a relevant mechanism showing the complicated pathways among intestinal microflora, intracranial atherosclerosis, and innate and adaptive immune cells with cerebral injury after ischemic stroke (de la Cuesta-Zuluaga et al., 2018).

In epidemiological terms, diabetic patients have a 1.8–6 times higher risk of ischemic attack (Bäckhed et al., 2005). It is clear that hyperglycemia is another risk factor independently associated with ischemic stroke, and the key factor is insulin resistance. It has been found that an imbalance of the microbiota in the gut will lead to lower insulin levels, cause insulin resistance, and subsequently increase blood glucose levels (Qin et al., 2012). Once the microbiota show dysbiosis, it will initiate an inflammatory reaction, and some inflammatory factors will lead to insulin resistance by affecting the insulin signaling pathway. The chronic inflammatory response is a vital pathogenic characteristic of insulin resistance. The introduction of LPS into the circulation increases the production of proinflammatory cytokines that induce serine phosphorylation of insulin receptor substrate 1 in the muscle and adipose tissue, blocking insulin signaling pathways and leading to insulin resistance (Saad et al., 2016).

Age and sex dependence

Compared with young adults, older people have different patterns of gut microbes: the variety of bacteria and probiotics as well as SCFAs decrease, but facultative anaerobic bacteria increase, and dominant species change (Ling et al., 2022). A stroke pathology study revealed that aged mice (20 months) have reduced infarct volumes, but usually these animals have much worse functional outcomes than young mice (2.5 months) (Shin et al., 2015). One possible association is that in aged individuals' bodies, there probably exists a "primed" inflammatory environment as well as chronic systemic inflammation, which leads to the exacerbation of the poststroke inflammatory response. This is just one aspect of the influence of aging on stroke. It is well known that substantial synaptogenesis and neural development occur in the first 3 years of childhood development. At the same time, the gut microbiota also undergoes a process of maturation and forms a similar structure to the adult intestinal microbiota (Yatsunenkov et al., 2012). Although there are fewer types of gut microbes in the early years of the human body, the types and numbers of gut microbiota need to increase to resist disturbances with increasing age, and interactions between the host and gut microbiota have occurred since long in the process of growth and development. Hence, it is evident that in younger children, interruption of the intestinal microbiota may be involved in its association with the brain, in turn promoting CNS diseases.

Influences focusing on the intestinal tract after ischemic stroke

Another aspect of the brain-gut axis focuses on the influences caused by cerebral ischemia. Normally, the tract is innervated by both intrinsic and extrinsic nerves, wherein the latter one includes neurons of the sympathetic and parasympathetic system (Uesaka et al., 2016). A study showed that these efferent fibers will maintain gut microbiota as well as the integrity of the mucosal barrier and affect its tight junctions (Crapser et al., 2016). Another previous review introduced some pathways of the interactions between the brain and gut such as the autonomic nervous system, CNS, stress system (HPA-axis), corticotropin-releasing factor system, and the intestinal responses involving the intestinal barrier, luminal microbiota, and intestinal immune response (Cryan et al., 2019). Additionally, current studies have come up with the gut connectome which mainly focus not only on the direct effects of CNS such as using stress mediator-induced virulence genes and the secretion, motility, permeability, and immunological defense of the enteric nervous system to interrupt gut microbiota but also on the indirect modulation of the intestinal barrier induced by the autonomic system (Osadchiv et al., 2019). Currently, the study about diseases of the gastrointestinal tract gather in inflammatory bowel disease (Fairbrass et al., 2022) and irritable bowel syndrome (Jacobs et al., 2021), the bidirectional communication between brain and gut are getting increasing attentions.

Same to above mention, a clinical trial has revealed an accompany of cerebral ischemic diseases and gastrointestinal symptoms and gut dysbiosis. This study also revealed the gut influences caused by the ischemic brain, which are listed as follows (Zeng et al., 2019). (1) Cerebral ischemia will disturb the intestinal microbiota and gut metabolites, as reported by an experiment that showed that ischemic stroke is associated with less *Butyrivibrio*, *Lactobacillus*, *Prevotella*, *Meganona*, and *Alloripetovella*, but more of opportunistic pathogens such as *Proteus*, *Alistipes*, *Klebsiella*, *Fusobacterium*, *Haemophilus*, *Shuttleworthia*, and *Papillibacter* (Chen et al., 2019d). (2) Stroke will cause increased gut permeability and a leakage of microbiota that can translocate to the lung, brain, and liver to provoke systemic immune response and whole-body infection (Stanley et al., 2016). (3) Acute brain injury also induces severe gastrointestinal paralysis and damages intestinal motility which will cause the microbiota antigen to be presented to gut immune cells to initiate whole body and neuronal inflammation (Candelario-Jalil and Paul, 2021). (4) An ischemic stroke will repeatedly lead to former affects (gut dysbiosis, intestinal motility, and impaired intestinal barrier function) though the catecholaminergic stress response in the gut (Iadecola et al., 2020). (5) The effects induced by cerebral ischemia display age-related differences. Animal experiments indicated that young stroke models will change the gut microbes compare to aged models (Spychala et al., 2018). Another research formally identified that though stroke can cause indifferent alteration in both young and aged mice, the aged animals tend to be more susceptible to sepsis and immune dysfunction

(Crapser et al., 2016). In summary, considering hypoxia-ischemia contributes to neurofunctional and gastrointestinal disorders, diseases other than inflammatory bowel disease, such as gut microbiota dysbiosis, necrotizing enterocolitis, and tumorigenesis of the colorectal carcinoma are also cause for concern (Yang et al., 2022). Hence, it is essential to further illustrate the interaction between brain tissues and the gastrointestinal tract.

Immunological mechanisms of the brain-lung axis

The pulmonary complications of ischemic stroke have been largely studied in recent years, and many studies have highlighted the pathological mechanisms of respiratory environment interrupting the outcome of ischemic stroke (Pelosi et al., 2011; Hannawi et al., 2013; Smith et al., 2015). In the following sections, we have listed the immune or immune-related interactions between the brain and lung.

The influences to CNS caused by the lung

Early in 1998, Johnston et al. suggested after-stroke pneumonia will cause brain injury. Recently, a study discovered respiratory infection will alter the permeability of the BBB to large molecules and immune cells and induce CNS inflammation (Bohmwald et al., 2021). The influences to central nervous system caused by the lung involve that rats with chronic pulmonary infection showed invasion of the CNS by increased circulating inflammatory markers such as TNF- α and matrix metalloproteinase-9 to exacerbate neuronal cell death (Chen et al., 2019a, b). Acute lung injury (ALI) also led to brain dysfunction and lung tumors create several antigens to attack brain and caused undifferentiated autoimmune encephalitis (Bickenbach et al., 2009; Kazarian and Laird-Offringa, 2011), which indicated immune system plays an essential role in the lung communicating with the brain tissue.

Respiratory tract infections are a prominent inflammatory response of the body and it will increase the risk of ischemic stroke (Violi et al., 2014). A previous review reported that the activation of tissue factor and platelet are the key steps for activating the clotting system and pro-inflammatory stimulus, and LPS induction is necessary for this process (Aras et al., 2004; Berthet et al., 2012). From the aspect of the risk factors of ischemic stroke, recent studies have focused on chronic obstructive pulmonary disease (COPD) (Austin et al., 2016) and ambient air pollution (Verhoeven et al., 2021; Kulick et al., 2023). COPD is known to directly and independently increase the risk of stroke due to systemic inflammation and increase oxidative stress so that promoting cerebral vascular dysfunction (Austin et al., 2016). A current Rotterdam study included patients with COPD or restrictive lung functions and showed more lacunar infarcts and poor global cognitive function (Xiao et al., 2022). Moreover, the dual risk factors of aging and smoking also produce vascular impairments indirectly driven by the NADPH oxidases (Iida et al., 2008; Mayhan et al., 2008). The effects of ambient air pollution involve the local and subsequent global inflammation contributed by inhalation pollutants and autonomic respiratory reflex arcs which has been elucidated in previous studies (Verhoeven et al., 2021; Kulick et al., 2023).

As patients with severe brain damage are often put on mechanical ventilation (MV) for airway protection, and the influences acted by MV on cerebral ischemia brain have been studied for more than 10 years (Pelosi and Rocco, 2011). Except for ventilator-associated lung injury, regardless of previous lung diseases, MV will interrupt the brain though induced neutrophil infiltration and release inflammatory markers to increase neuron activations in many CNS areas to activate brain responses, alter regional cerebral perfusion, and activate the autonomic system (Pelosi et al., 2005). A recent study also indicated that MV provokes the deleterious effect on the hippocampus through a TRPV4-ATP-P2X signaling in lung tissue to cause MV-related cognitive disorders (González-López et al., 2019). Notably, with respect to other CNS diseases, scientists have significantly discovered the brain-lung interaction engaging in the lung microbes which induced LPS to cross the BBB and influence the brain-resident microglia to initiate type I interferon signaling pathways to restrict experimental autoimmune encephalomyelitis in animal models (Hosang et al., 2022). Such results provide a promising direction for future studies related to the lung microbiota and its immune roles in ischemic stroke.

The influences to lung caused by the CNS

Heuer noted that acute intracranial hypertension will augment lung injury and pointed out the interactive role (Heuer et al., 2011). A recent review has settled the crosstalk between the brain and lung and made a detailed introduction of the complications after acute brain damages, which mainly concentrated on ventilator-associated pneumonia, acute respiratory distress syndrome, and neurogenic pulmonary edema (Mrozek et al., 2020). To understand the lung influences that caused brain damage, particularly in cerebral ischemia, a summary involving the immune mechanisms related to neuroanatomy, endocrinology, HPA-axis, metabolites (Santos Samary et al., 2016), aging, and MV follows.

Neuroanatomical pathway: Stroke can directly destroy the vagus nerve and damage its endings distributed in the lung (Li et al., 2023). Besides the function of swallowing, the vagus nerve also participates in cholinergic anti-inflammatory pathways to reduce systemic inflammation, while also inducing immunosuppression in the lung and increasing the risk of bacterial pneumonia (Li et al., 2023).

Immune pathway: BBB destruction is the key event after ischemic stroke and it mediates the release of some necrotic substances such as high mobility group box 1—receptor for advanced glycation end signal—to inhibit the

peripheral immune response and cause post-stroke-associated pneumonia (Kim et al., 2018). In addition, injured brain tissue will initiate proinflammatory response with producing abundant inflammatory cytokines (IL-1, IL-6, IL-8, TNF) (Ott et al., 1994). In post-ischemia stroke experiment, animal models displayed diffuse alveolar damage and ultrastructural damage and the protein levels of proinflammatory mediators were documented among lung, brain and plasma, but the phagocytic ability of macrophages reduced (Samary et al., 2018).

Endocrine pathway and sympathetic nervous system regulation: In addition to the immune reaction, the maintenance of whole immune response and the two-hit mechanism is incomplete without significant stimulation of the sympathetic nervous system and endocrine reaction. Initial sympathetic discharge stimulates systemic inflammatory response (Mascia, 2009) and cooperates with the release of catecholamines to create a systemic inflammatory environment (first hit) that will make the lung more susceptible to “the second hit” such as sepsis, MV, or surgery (Mascia, 2009). Complete pathways and their effects have been illustrated in previous reviews, which have highlighted the release of the neurotransmitter norepinephrine and peripheral lymphopenia to cause impaired monocytes and shift from Th1 to Th2 (Prass et al., 2003; Walter et al., 2013). Though this process will protect the brain from further injury, pneumonia will neglect the shift and cover Th1 autoimmune response against CNS antigens (Prass et al., 2003; Winklewski et al., 2014).

HPA axis: Due to the effects of stress and inflammatory response after trauma, the HPA axis in acute brain injuries is involved in pulmonary dysfunction. Once the HPA axis is activated by inflammatory mediators such as IL-6, it will protect the peripheral organs by initiating the compensatory anti-inflammatory response syndrome throughout the body to delete inflammatory responses (Offner et al., 2002). Furthermore, endogenous glucocorticoids stimulate anti-infectious immunity (Rhen and Cidlowski, 2005).

Aging: Through lung imaging, scientists have revealed impaired pulmonary intravascular neutrophil function after stroke, and this fact is exacerbated by aging, which results in worse neutrophil antibacterial responses and increased risk of stroke-associated infection (Wen et al., 2022).

The effects caused by SARS-CoV-2 infection

A study identified that severe acute respiratory syndrome coronavirus (SARS-CoV-2) could reach the brain through the lung epithelium (Iroegbu et al., 2020). In past pandemics, researches have indicated that the SARS-CoV-2 infection will largely increase the risk of ischemic stroke (Beyrouti et al., 2020), resulting in poorer prognosis and higher mortality than infection with other respiratory viruses. In recent years, scientists have proposed various reasons and pathways to explain the mechanisms including activating HPA axis led by upregulated cytokines, SARS-CoV-2-related hypercoagulability, bacteremia induced by the usage of MV (Huang et al., 2020; Wang et al., 2020), and the molecules hypoxia-inducible factor-1a (Francisiová et al., 2021). While based on the study of damaged tricompartamental model of lung parenchyma oxygenation (alveolus, bronchial artery, and pulmonary artery) in SARS-CoV-2 infection, a case study reported that some pulmonary vein clots forming in the special pulmonary intravascular thrombotic lesions may embolize to the brain, thereby broadening the recognition of the fundamentals of ischemic stroke occurring with SARS-CoV-2 infection (Meaney et al., 2022). By contrast, other research has shown that the development of stroke will increase the risk of SARS-CoV-2 infection though promoting the expression of its receptor angiotensin-converting enzyme (ACE) 2 in the lung (Singh et al., 2021). Taken together, SARS-CoV-2 infection enhances the understanding of the dual interaction between respiratory system disorders and cerebral ischemia, and the responses of the lung may be more profound than those of the gastrointestinal system. **Figure 3** presents a brief summary of the gut-brain-lung axis.

Gut-Lung Interaction

As patients with inflammatory bowel disease often show an increased prevalence of COPD, and respiratory infection always accompanies gastrointestinal symptoms, the gut-lung axis in ischemic stroke and other diseases have been studied to reveal several mechanisms including alteration of gut/lung mucosa barrier permeability, bacterial translocation and abundance changes, movement of T cells, phenotype polarization of local macrophages, metabolites (SCFAs) and ACE2 receptors (Mahadeva et al., 2000; Ekblom et al., 2008).

Studies have shown that in both ischemic and hemorrhagic stroke, disruption of intestinal structure and increased barrier permeability will cause gut bacteria to disseminate to the lung and induce gut-derived lung infection (Wen et al., 2019; Zhang et al., 2021a). Another study showed significant alteration in the tight junctions of intestinal structure with downregulated zonula occludens-1, a key protein of the tight junction complex, and production of TNF- α that was more obvious in aged mice (Wen et al., 2019). Such effects finally lead to prominent differences that increase microbiota cultivated in the lung compared to other organs like the liver or spleen (Wen et al., 2019). These findings will further clarify the suitable intervention timing of secondary pulmonary infection in stroke patients (Zhang et al., 2021a).

Another mechanism involves inhibition of $\gamma\delta$ T cells movement. This will alleviate the effects led by social isolation to cerebral ischemia and stroke-associated pneumonia from small intestine. Because it will limit $\gamma\delta$ T cells to release the pro-inflammatory cytokines such as IL-17A, IL-22 and facilitate

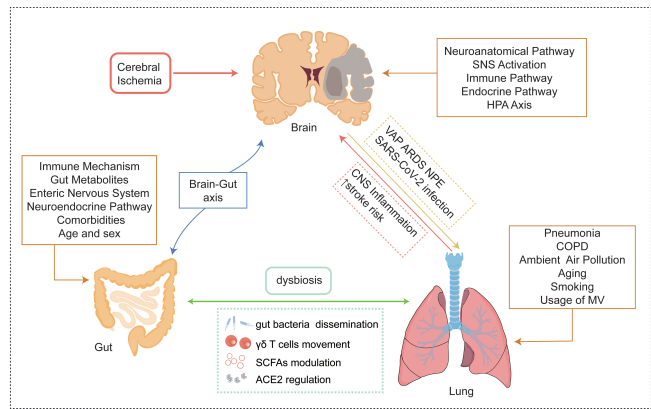


Figure 3 | The lung-brain axis and gut-lung axis in ischemic stroke.

Ischemic stroke will cause a series of pulmonary complications through neuroanatomical and other pathways. In turn, the lung influenced by pneumonia and COPD and many other issues will in the end lead to CNS inflammation and increase the risk of stroke and poor outcomes. The above section has introduced the brain-gut axis' different mechanisms, and the interaction between the gut and lung involves gut microbiota translocation, $\gamma\delta$ T cells movement, and metabolite changes such as SCFAs and ACE2. Created with Adobe Illustrator 2019. ACE2: Angiotensin-converting enzyme 2; ARDS: acute respiratory distress syndrome; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation; NPE: neurogenic pulmonary edema; SCFAs; short-chain-fatty acids; VAP: ventilator-associated pneumonia.

dysfunction of the gut-lung axis (Xie et al., 2023). Additionally, LPS will aggravate the immune damage of the lung when dysregulating intestinal microflora; increased immune response to local LPS and, in turn, LPS-induced lung injury will provoke a low-grade gut inflammation in acute injury. Such roles of LPS will be inhibited by mesenchymal stem cells to decrease the CD8⁺ T-cells and enhance barrier function (Xu et al., 2021b).

Moreover, gut microbiome metabolite SCFAs have also been reviewed to play dual roles in the lung and are distributed from the intestine to other organs throughout the portal venous system, and SCFAs also become the potent modulators for host immune response among the gut and the lung and the CNS (Ney et al., 2023). The COVID-19 pandemic resulted in extensive research on the functions of ACE2, wherein the link between gut dysbiosis and pulmonary hypertension was hypothesized to cause leaky gut and pathological events in the lung (Oliveira et al., 2020; Sharma et al., 2020b). Considering some probiotics may express ACE2, there is a potential advantage of the lung interrupting the intestine and influencing the gut transporters and communication between gut epithelial and its microbiota (Sharma et al., 2020a).

In addition, diseases from other systems such as nontuberculous mycobacterial infection (Kim et al., 2022), cancer (Lu et al., 2021), bronchopulmonary dysplasia (Ran et al., 2021), and toxic exposure (Zhang et al., 2023a) have identified the current knowledge regarding the interaction and bi-directional responses between the gut and the lung.

Perspectives

Based on the above detailed review and expectation from clinical practice, we go on to list three dimensions concentrating on the different phases of ischemic stroke on the brain-gut axis or brain-lung axis.

Key open questions: therapeutic time windows are now being considered to improve clinical outcome (Zhang et al., 2023b). First, enhancing the control of the risk factors at pre-stroke and post-stroke; second, reducing infarct size and complications at the acute phase; and third, preventing recurrence and promoting recovery at the subacute phase of stroke. These three main points provide practical ideas for future studies. When it comes to the brain-lung axis, studies related to lung microbiomes and stroke is limited and needs further research.

Potential targets and route: Considering the current studies focusing on the roles of EGCs in the regeneration of the enteric nervous system and its relative feasibility compared to microglia cells, the application of enteric glial cells in central nervous system regeneration after ischemic stroke may be a promising field. Furthermore, the dietary therapy targeted regulating gut microbiome and its metabolites, and the usage of antibiotics and prebiotics are waiting for more convincing results. Apart from diet and medication, the latest study has discovered electroacupuncture and induced pluripotent stem cell-derived small extracellular vesicles (Zhang et al., 2023b) modulating the gut microbiome to have significant and accurate effects on ischemic stroke, which provoke more physical or cellular strategies for substantial benefits. Other measures focusing on triggering receptor expressed on myeloid cells 1 and natural materials targeting SCFAs are all potential fields (Roselli and Huber-Lang, 2019; Guo et al., 2023). As for the lung-brain axis, early detection of acute lung injury through clinical signs and measurements of extravascular pulmonary fluid as well as brain injury by measuring specific markers can

help optimize ventilation settings and even contribute to the overall clinical management of critically ill patients. A recent study identified that molecules used in the lung can restrict brain injury after ischemia reperfusion and systemic inflammation activation, which indicates lung inflammation is the potential target for stroke treatment.

Key hurdles: Focusing on the BBB leakage and subsequent pathological procedures, past studies neglect the occurrence of other barriers like the gut vascular barrier and choroid plexus vascular barrier that provide potentially attractive targets (Carloni and Rescigno, 2022). Furthermore, the replicability of previous study results focusing on fecal transplant gavage or intestinal flora transplantation still remain the core problems for scientists, and researchers are also required to differentiate between aged persons and an aged gut microbiome. Some hurdles arise from the brain-lung axis contain the effects of anesthetic used on model bronchus, ischemic models (local or diffuse), results deduced to human, indirect effects of topical drugs on intracranial pressure and so on. The hurdles existing in the brain-lung axis include the effects of anesthetic used on model bronchus, ischemic models (local or diffuse), results deduced to human, and indirect effects of topical drugs on intracranial pressure.

In conclusion, there are close relationships between ischemic stroke and the gut or lung from the perspective of immune responses, gut microbiome, and lung sympathetic nervous system activation. Promotion of systemic inflammation is the core aspect that regulates the interaction between the brain and two peripheral organs. The dependent association between the brain and other organs provide requires continuous exploration. In the future, we look forward to more studies on the brain and peripheral tissues, especially the intestine and lung, of ischemic stroke, and hope that more effective treatment measures can be studied and applied to clinical practice to improve the clinical outcome of patients.

This review has some limitations. First, this review only focuses on the single role of the immune mechanism in disease progression, ignoring the influence of other mechanisms on immune function, thus resulting in the contents of this article being superficial, without in-depth details to explore the specific molecular pathways among the brain, gut, and lung. In addition, this article does not comprehensively summarize the current treatment measures of the gut-brain axis and lung-brain axis, the role between different measures, efficacy, and clinical significance, which have a direct significance for clinical practice. This article only briefly introduces some current targets and research gaps. In addition, in the brain-lung axis section, we did not make a detailed distinction between ischemic stroke and hemorrhagic stroke, rather only generalized the immune mechanisms underlying ischemic stroke.

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