

Impact of gut–brain interaction in emerging neurological disorders

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Abstract

The central nervous system (CNS) is a reservoir of immune privilege. Specialized immune glial cells are responsible for maintenance and defense against foreign invaders. The blood–brain barrier (BBB) prevents detrimental pathogens and potentially overreactive immune cells from entering the periphery. When the double-edged neuroinflammatory response is overloaded, it no longer has the protective function of promoting neuroregeneration. Notably, microbiota and its derivatives may emerge as pathogen-associated molecular patterns of brain pathology, causing microbiome–gut–brain axis dysregulation from the bottom-up. When dysbiosis of the gastrointestinal flora leads to subsequent alterations in BBB permeability, peripheral immune cells are recruited to the brain. This results in amplification of neuroinflammatory circuits in the brain, which eventually leads to specific neurological disorders. Aggressive treatment strategies for gastro-

intestinal disorders may protect against specific immune responses to gastrointestinal disorders, which can lead to potential protective effects in the CNS. Accordingly, this study investigated the mutual effects of microbiota and the gut-brain axis, which may provide targeting strategies for future disease treatment.

Key Words: Neuroinflammation; Blood–brain barrier; Microbiota; Gut–brain axis; Neurological disorders

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Core Tip: Neurological disorders are increasingly diagnosed globally owing to the disruption of the gut-brain axis. The impact of dysbiosis on the gut microbiota often plays a crucial role in disease pathogenesis. A thorough understanding of this complex relationship is essential for the development of new management strategies against various neurological disorders.

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INTRODUCTION

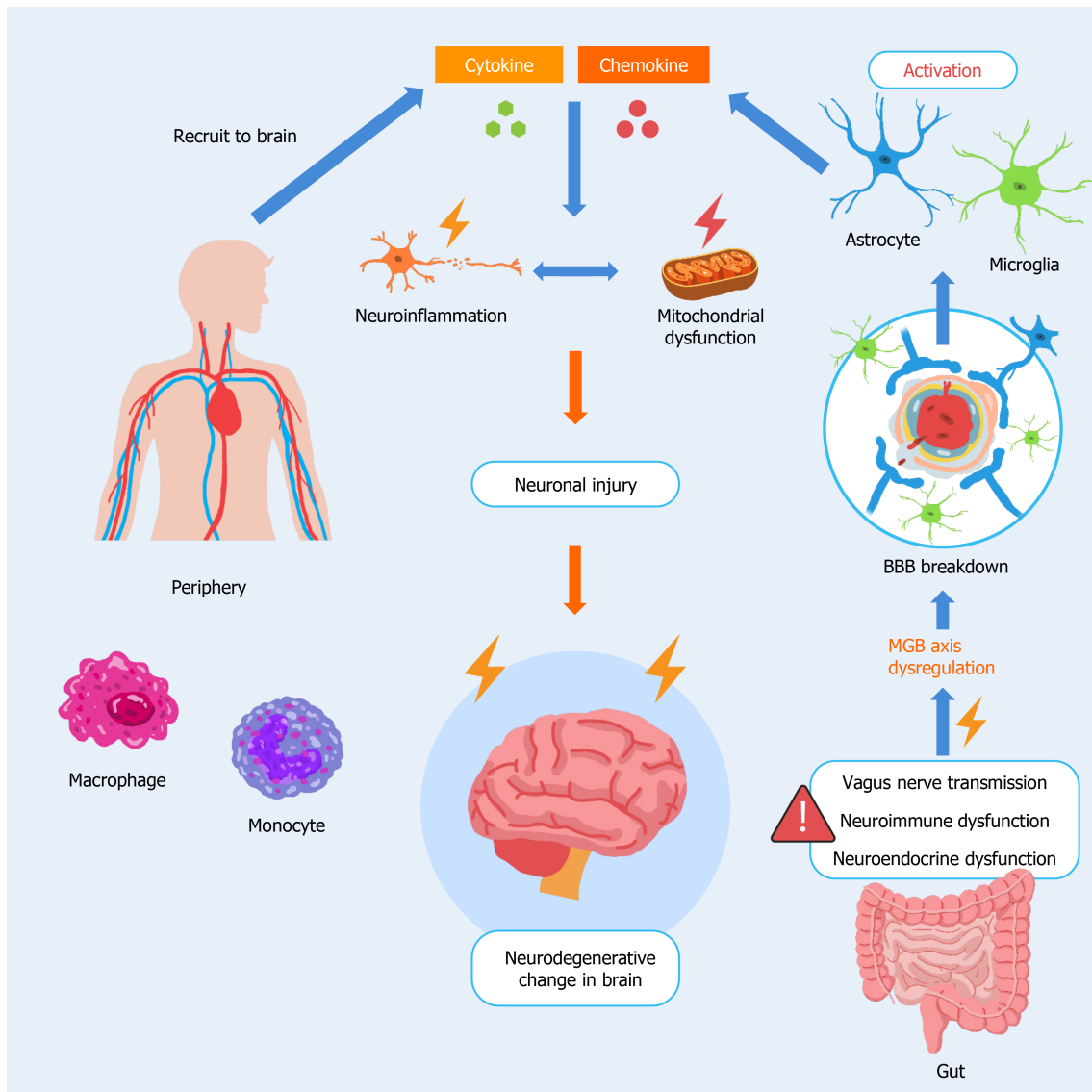
An increasing number of preclinical and clinical studies have provided evidence on how various neurological disorders result from an imbalance of the gut–brain interaction. A recent animal model study reported that gut-derived metabolites can substantially influence mouse behaviors[1]. Moreover, a multicenter randomized controlled trial performed by Korean investigators concluded that probiotics may help improve cognitive dysfunction in older adults[2]. In this editorial, we summarize and demonstrate the mechanisms of the complex gut–brain interaction in neurological disorders (Figure 1), providing a pivotal solution for scientists, researchers, and clinicians to protect the brain. Refined treatment schemes for gut disorders and related microbiota environments may be beneficial in improving the prognosis of neurological disorders such as Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, and diabetic neuropathy[3,4]. Considering the growing body of relevant literature, aggressive therapeutic strategies for gastrointestinal disorders may be implicated to protect the peculiar immune responses from the gastrointestinal disequilibrium that causes specific diseases of the nervous system. We believe that the gut–brain axis and balanced microbiota play a considerable role in a diverse spectrum of neurological disorders and can serve as a basis for future investigations.

ASTROCYTES

In the central nervous system (CNS), astrocytes, which are dedicated glial cells, are the majority, exceeding the number of neurons by a factor of five[5]. In embryology studies, astrocytes, similar to neurons, emanate from neuroepithelial precursors[6]. The presence of astrocytes in the CNS plays a critical role in its overall maintenance and homeostasis. The cardinal features of astrocytes include the buffering of potassium across the CNS, elimination and retrieval of glutamate, and maintenance of water equilibrium and osmotic pressure of the microenvironment. Furthermore, astrocytes are innate immune cells that can mediate neuroinflammatory responses in the CNS[7] and generate neurotrophins, such as brain-derived neurotrophic factors, and anti-inflammatory cytokines, such as interleukin 10[8].

MICROGLIA

Microglia are innate immune cells of the CNS that are embryologically derived from myeloid progenitor cells and are homologous to the macrophage series in the peripheral blood[9]. With their homology to macrophages, microglia function as immune pioneers in the CNS by promoting immune responses to stabilize and homogenize the microenvironment of the brain. Microglial activation may occur as an initial step in the neuroinflammatory response due to dysregulation of immune regulation in age-related neural diseases or abnormal folding/aggregation of proteins resulting from environmental or genetic factors. Stimulated microglia may trigger a more intense neuroinflammatory reaction *via* the reactivation of astrocytes. Through the microglia–astrocyte crosstalk, these two series of glial-derived



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Figure 1 Dysregulation of the microbiome–gut–brain axis contributes to the vicious amplification of neuroinflammatory circuits in the brain. Astrocytes, microglia (glial cells), and the blood-brain barrier (BBB) have supportive and defensive functions to ensure neuronal stability and maintain constancy in the brain. Through a neuroinflammatory response that is dominated by glial cells in the central nervous system, the neurological system is committed to preserve cell metabolism, repair, and renewal to maintain microenvironment homeostasis and integrity/long-term viability of the nervous system. In the event of microbiome–gut–brain axis dysfunction, the self-fulfilling regions of the brain are implicated and disturbed. The leakage of microbiota or microbial-derived intermediates from the gut likely causes a systemic immune response that affects the neuroendocrine system. These pathological factors may destabilize the brain directly from the gut *via* the vagus nerve. These factors may modify BBB permeability, causing a shift in peripheral immune cells toward the brain (originally blocked by the BBB), such as macrophages and monocytes. Meanwhile, glial cells are activated, and more proinflammatory cytokines and chemokines are secreted, inevitably leading to neuroinflammation and progressing to mitochondrial dysfunction. These events aggravate the neurodegenerative changes in the brain.

innate immune cells may mutually modulate the innate immune defense system of the CNS[10,11].

BLOOD-BRAIN-BARRIER

In combination with microvascular endothelial cells, pericytes, and basement membranes, the endfeet of astrocytes encircle the capillaries, resulting in an almost completely gapless blood-brain-barrier (BBB) *via* gap junctions. While the BBB allows the passage of a minor fraction of lipids or molecules with molecular weights less than 400 Da[12], it can prevent external substances, bacteria, or viruses from entering the brain through the peripheral blood circulation.

VICIOUS NEUROINFLAMMATORY CIRCUIT IN THE BRAIN AUGMENTED BY BOTTOM-UP INTERFERENCE OF THE MICROBIOME-GUT-BRAIN AXIS

With an excessive neuroinflammatory response to stress in the brain, the activation of astrocytes and subsequent reactive astrogliosis may contribute to alterations in BBB permeability[13]. Accordingly, owing to the compromise of this defense line between the peripheral system and brain, several proinflammatory cytokines and chemokines, which are released owing to glial activation, recruit peripheral innate immune cells, such as neutrophils, monocytes, macrophages, natural killer cells, and dendritic cells, to shift toward the brain[14]. During neuroinflammation in the CNS, innate and peripheral immune cells are excessively augmented, and glial cytokines/chemokines amplify the inflammatory signal, resulting in a vicious cycle. The neuroinflammatory response amplifies and progresses to mitochondrial dysfunction in the principal neurons or surrounding cells of the CNS, eventually leading to degenerative brain damage[15]. The pathological state of BBB permeability is involved in brain inflammation, resulting from the alternation of gut microbiota or lipopolysaccharides released from the intestine into the bloodstream[16]. This underlies the microbiome-gut-brain (MGB) axis and provides a rationale for the close relationship between an unhealthy gut and brain diseases. Dysbiosis, an abnormal composition in microbiota, may be caused by conditions such as aging[17], gastrointestinal diseases[18], and renal transplantation[19,20].

DISRUPTION OF GUT-BRAIN INTERACTION IN NEUROLOGICAL DISORDERS

In general, progressing from the bottom-up, the gut may interact with the brain *via* three main pathways. The vagus nerve innervates the brainstem and gut *via* a direct conduit. *Lactobacillus rhamnosus* (JB-1) affects the γ -aminobutyric acid (GABA) receptors in brain regions associated with mood and anxiety[21]. The aggregation of α -synuclein (Lewy bodies) disseminates from the enteric nervous system to the CNS, exacerbating the symptoms of patients with Parkinson's disease[22], since vagotomy eliminates the extent of pathogenesis. Predisposing factors that precipitate increased intestinal permeability, such as gastrointestinal inflammation or infection, may contribute to systemic inflammation caused by pathological antigens or dietary allergens. These pathogen-associated molecular patterns or proinflammatory cytokines may circulate toward the brain, causing subsequent cerebral inflammation. For example, short-chain fatty acids, which are microbial-derived intermediates, can penetrate the BBB, react with microglia, and subsequently trigger neuroinflammation in the brain[23]. Increased permeability of the intestinal barrier, resulting from high-fat consumption and long-term inflammation of the gastrointestinal tract[24], may lead to the distribution of lipopolysaccharides from the gut into the circulation, stimulating systemic inflammatory activation and eventual destruction of the BBB[25], along with inflammation-driven neurodegeneration in the brain. Furthermore, the metabolites produced by intestinal microbiota, analogous to hormones, affect the functioning of the neuroendocrine system in the brain *via* the systemic circulation, serving as the bottom-up signaling pathway involved in the MGB axis. For example, GABA, derived from *Levilactobacillus brevis* and *Bifidobacterium dentium* among the gut microbiota, can traverse the BBB[26] and may affect neurotransmission homeostasis, ultimately leading to neurodegenerative diseases.

CONCLUSION

The CNS, which is an immune-privileged site, maintains the equilibrium of the system through a supportive and defensive glial cell cohort that elicits neuroinflammatory responses. However, neuroinflammation, which is a double-edged sword, can be confronted by a load level that exceeds its protective capacity. The stress signals originating from the periphery likely interfere with the CNS, rendering neuroinflammation in the brain detrimental and disrupting the homeostasis of the neuroendocrine system. These warning signals from the gastrointestinal tract cause the dysregulation of the MGB axis. Thus, the future development of medical and molecular therapies must target the molecular focus from the gut to the brain.

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FOOTNOTES

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