Commentary

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The potential role of the brain–gut axis in the development and progression of Alzheimer's disease

Guisheng Zhou[1], You Yin[2], Xiaoyu Huan[1], Yu Zhuang[1], Shiyu Xu[1], Jiashuai Liu[1], Shijia Liu[3], Jin'ao Duan[1]

[1]Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, and Jiangsu Key Laboratory for High Technology Research of TCM Formulae, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China;
[2]Department of Neurology, Changzheng Hospital, Navy Medical University, Shanghai 200003, China;
[3]Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, Jiangsu Province, China

INTRODUCTION

Alzheimer's disease (AD) is a classic chronic progressive degenerative disease of the central nervous system (CNS). Although the pathogenesis of AD remains unclear, several molecular mechanisms have been proposed in view of the major neuropathological features, including the abnormal increase in amyloid-β (Aβ), excessive phosphorylated tau proteins, imbalance in Ca^{2+} homeostasis, oxidative stress, imbalance in neurotransmitters, and brain atrophy.[1] However, none of the above mechanisms by itself elucidates all the histopathologic and multifactorial molecular changes described in AD.

BRAIN–GUT AXIS

The AD drugs were developed based on the above hypothesis, and of these, the US Food and Drug Administration (FDA) has approved only six drugs for the treatment of AD.[2] However, the 2021 World Alzheimer's Report stated that these approved AD drugs mainly improved symptoms and none of them could slow or stop disease progression.[2] The failure of the explored drugs in clinical trials has revealed gaps in the understanding of AD pathology, which requires a reassessment of AD pathogenesis from a different cognitive perspective.

Gut microbiota could affect the brain function and behavior through the brain–gut axis (BGA), with bidirectional interactions via top-down and bottom-up regulations.[1] BGA mediates the crosstalk between the brain and the gut, mainly through the following pathways. The vagus nerve transmits information to the CNS regarding intestinal osmolarity, mechanical distortions of the intestinal mucosa, and the presence of bacterial products.[3] In this way, the brain controls many functions of the gut and sends relevant signals to the thalamus and cortical areas. The communication between the gut and the brain is mainly through the exchange of signals between the gut microbiota and multiple nervous systems.[4] The intestinal mucosa and the blood–brain barrier (BBB) allow the passage of some cytokines, neurotransmitters, and neurotoxic substances synthesized by the gut microbiota, which affects the functions of brain and gut.[5] Thus, BGA is regarded as a multifunctional complex network in which the central, peripheral, immune, and endocrine systems are all involved in its bidirectional regulation.

THE BOTTOM-UP REGULATION OF BGA

Many studies have highlighted BGA in the pathophysiology of AD, and it is involved in the progression of AD through various pathways. BGA is considered as a new target for the treatment of AD. Gut microbial compositions of AD patients are characterized by high proinflammatory microbial levels and low distribution of

Address for Correspondence:
You Yin, Department of Neurology, Changzheng Hospital, Navy Medical University, 415 Fengyang Road, Huangpu District, Shanghai 200003, China.
E-mail: yinyou179@163.com

Shijia Liu, Affiliated Hospital of Nanjing University of Chinese Medicine, No. 155 Hanzhong Road, Qinhuai District, Nanjing 210029, Jiangsu Province, China.
E-mail: 3toyfy0039@njucm.edu.cn

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anti-inflammatory microorganisms, which lead to local inflammation, increased gastrointestinal permeability, abnormal secretion of neurotoxic metabolites, and impairment of BBB function.[5] Additionally, high abundance of *Bacillus subtilis*, *Streptococcus* spp., *Escherichia coli*, and *Staphylococcus aureus* in AD patients is strongly associated with the production of Aβ and lipopolysaccharides (LPS).[5,6] Aβ oligomers are first found in the gastrointestinal tract and migrate bottom-up to the brain.[5,6] Once Aβ is produced in the gut, it easily enters the systemic circulation and accumulates in the brain due to increased permeability of the intestinal wall.[7] The accumulation of Aβ produced by gut microbiota in the brain triggers many downstream events such as the activation of NF-κB and the upregulation of proinflammatory microRNA-34a, which in turn downregulates the expression of triggering receptor expressed on myeloid cells 2.[7] The excess LPS activate the hypothalamic-pituitary-adrenal (HPA) axis, which not only affects the brain function, but also leads to further changes in gut microbial compositions and gut barrier permeability. LPS binding to CD14 of Toll-like receptor 4 (TLR-4) expressed on microglia induce immune responses similar to those observed in the microglia of AD patients.[1] Then, TLR-4 activates astrocytes, releases proinflammatory cytokines, causes oxidative stress, and induces the accumulation of Aβ in the brain. Finally, it is noteworthy that Aβ or LPS produced by the gut microbiota promote the release of proinflammatory factors and inhibit the synthesis of anti-inflammatory factors, exacerbating neuroinflammation and promoting the development of AD.

Gut microbiota release various metabolites such as short-chain fatty acids (SCFAs), neurotransmitters, and vitamins. SCFAs could regulate intestinal barrier function, improve the immune system, and affect the CNS function.[8] Butyrate is a beneficial SCFA that plays a role in learning, memory, and promoting the growth of neurons.[8-10] Serotonin (5-HT), a neurotransmitter, is mainly synthesized in the gastrointestinal epithelial enterochromaffin cells.[10] *Lactobacillus* and *Bifidobacterium* convert glutamate to produce γ-aminobutyric acid (GABA).[10] The dysfunctions of GABA signaling are linked to cognitive and memory impairment, while the disorder gut microbiota regulated tryptophan metabolism via kynurenine pathway to produce lower level of 5-HT, affecting the availability of 5-HT in the nervous systems.[7] Gut cyanobacteria produce a neurotoxin of β-*N*-methylamino-l-alanine, which interacts with *N*-methyl-d-aspartate receptor to cause some of the pathological features of AD.[7] Additionally, the dysregulations of gut microbial-derived vitamins are also associated with AD.[11] Both *Bacteroidetes* and *Fusobacteria* could secrete a certain amount of vitamin B1, which is involved in the metabolism of glutamate and GABA. However, an abnormal level of vitamin B1 leads to excessive glutamate or decreased acetylcholinergic and GABAergic neurotransmission, causing excitatory toxicity of neurons.[11] The dialog and function realization between the gut and the brain is mainly affected by the gut microbial-derived metabolites, and this bottom-up interaction of BGA quietly participates in the development of AD.

THE TOP-DOWN REGULATION OF BGA

The brain could regulate BGA and influence the gut function and microbial compositions. This top-down regulation includes both direct pathway and indirect pathway.[3] The sympathetic nerves, parasympathetic nerves, and HPA axis form a system that mediates the effects of emotional states on the body. Activation of this system might alter the intestinal environment, produce different intestinal immune responses, affect the formation of intestinal mucus layer, and thus directly or indirectly alter microbial compositions. Stress and aging activate intestinal gliocytes and mast cells, thereby increasing the intestinal permeability and ultimately making it easier for bacteria to enter the gut epithelium and trigger an immune response in the gut mucosal layer.[5] The top-down regulation of BGA in the pathological state of AD leads to enhancement of intestinal permeability, activation of inflammatory response, and an increase in proinflammatory gut microbiota, further worsening the AD symptoms.

CLINICAL IMPLICATIONS OF AD BASED ON BGA

The disruption of gut microbiota promotes the production of Aβ and activates inflammatory signaling pathways, which in turn affect the brain function and behavioral activity via BGA. The probiotics and prebiotics could counteract the dysbiosis of gut microbiota, and these approaches were clinically studied as effective alternatives for treating cognitive disorders.[7-9,12] Mediterranean diet could enhance the abundance of butyrate-producing gut microbiota, improve colon functions, reduce intestinal permeability, and increase the anti-inflammatory ability of AD patients.[9]

Antibiotics have also attracted some attention and could be combined with specific probiotics to play a synergistic role in the treatment of AD.[4] Recently, based on the theory of BGA, sodium oligomannate (GV-971) was developed for treating AD and received conditional approval in China to improve cognitive function.[13] The clinical trial demonstrated that GV-971 significantly improved cognition with sustained improvement across all observation periods of a 36-week trial.[14]

BGA is involved in the progression of AD. However, most existing studies have explored the possible interactions between BGA and cognitive functions in animal models and lacked comprehensive analysis of gut microbial compositions and functions in a large cohort of clinical samples. Future studies need to consider that the gut microbial compositions in BGA are influenced by many confounding factors such as ethnic differences, dietary habits, smoking, and medication. To explore the applications of the newly discovered probiotics, further studies are needed on the safety of specific probiotics and their exact effects on cognitive function.

CONCLUSION

BGA plays important roles in the progression of AD, which has challenged the previous view that the etiology of AD is mainly concentrated in the brain. The bottom-up regulation of BGA is mainly realized by gut microbiota. Disrupted gut microbiota significantly affect the inflammatory mechanisms of AD, leading to neuroinflammation, neuronal damage, and neuronal death. Disturbed gut microbiota could promote neurodegeneration of AD by upregulating the processes of neuroinflammation, changing intestinal and BBB permeability, and affecting the formation of SCFAs, neurotransmitters, vitamins, Aβ, and other metabolites. The top-down regulation of BGA in the pathological state of AD leads to enhanced intestinal permeability, active inflammatory response, and increased proinflammatory gut microbiota, further aggravating the symptoms of AD. The probiotics and healthy dietary patterns could improve the cognitive function and reduce inflammation in subjects with cognitive impairment. Therefore, in-depth understanding of the anti-dementia mechanism of prebiotics by regulating BGA would help scientists to develop new therapeutic strategies for AD.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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