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The Research Progress of Gut-Brain-Microbiome Axis in the Pathogenesis of Alzheimer's Disease

Zhiqiang Hao, Huiwen Yang, Feng Miao*

Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
**Corresponding author*

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Abstract: Alzheimer's disease (AD) is primarily caused by the pathological changes of tau induced by amyloid-beta (Aβ), which leads to a group of clinical syndromes characterized by cognitive impairment. In recent years, people have gradually realized the complex influence of the gut microbiome on the central nervous system (CNS), and the bidirectional communication between them plays a crucial role, which indicates that the gut microbiome may shape neural development, regulate neurotransmission, and affect behavior, making it a potentially operable target for improving neurodegenerative diseases. Therefore, this paper aims to discuss the molecular mechanisms of the microbiome-gut-brain axis on AD, summarize the new targets and methods of treating AD through the gut microbiome, with the hope of providing new theoretical basis for clinical treatment of AD.

1. Introduction

AD is a clinical syndrome characterized by progressive cognitive impairment in multiple domains or severe neurobehavioral symptoms that are severe enough to cause significant functional impairment in daily life [1]. AD is widely considered to be the most common type of dementia, accounting for 60% to 80% of all dementia cases, and the latest data indicates that the global prevalence of AD will increase by 2 times by 2050, while the increase in some developing countries may be higher, which may be related to the level of disease management. Current research shows that AD risk is 60%-80% dependent on genetic factors, with the APOE allele being the most strongly associated with the disease, of course, unhealthy diet and reduced physical activity, as well as lifestyle behaviors such as diabetes, cerebrovascular disease, and craniocerebral injury, are also major risk factors for AD [2]. The earliest stage of AD involves the accumulation of Aβ, which exhibits cytotoxicity, especially to neurons, promoting the formation of toxic oxygen free radicals that lead to calcium homeosta disturbance and neuron death. At the same time, in the final stage of the disease, Aβ induces the pathological spread of tau protein, leading to cell apoptosis. Currently, plasma detection of Aβ and phosphorylated tau protein has shown great prospects in clinical and research applications [3,4]. In addition, oxidative stress, inflammation, cholinergic changes, mitochondrial dysfunction, etc. are molecular mechanisms that cause changes, which are particularly evident in the amygdala, cingulate cortex, and prefrontal and temporal lobe cortical association areas [5]. The importance of the microbiome-gut-brain axis has long been recognized, and this axis is gaining increasing attention in the field of research on the biological and physiological basis of mental

illnesses, neurodevelopmental disorders, age-related diseases, and neurodegenerative diseases, as it interacts with the brain through multiple pathways [6]. Therefore, this article mainly summarizes the impact of the microbiota-gut-brain axis on AD, related targets and treatments, so as to provide a basis for further development of drugs targeting this target and delay the progression of AD.

2. The concept of the microbiota-gut-brain axis

Microorganisms have always been an important part of human life, and the human gastrointestinal tract is full of diverse microbial communities in the human body, among which Bacteroidetes and Firmicutes are the two most prominent bacterial phyla in healthy individuals, and more and more evidence reveals the two-way communication between the gut microbiota and the CNS, called the "microbiota-gut-brain axis", gut microbes regulate the immune system, vagus nerve, enteric nervous system (ENS) by producing neuroactive substances, metabolites and hormones, Neuroendocrine and circulatory systems [7,8]. There are extremely complex interactions between the microbiota and the brain, so understanding how microbes affect the physiology and behavior of the brain is important for the treatment of neurological diseases.

3. Effect of the microbiota-gut-brain axis on AD

3.1. Regulation of microbiota-gut-brain axis on microglia in the AD brain

Microglia are the major macrophages in the CNS, accounting for about 10% of cells in the adult mouse and human brains [9], and are of great significance for maintaining brain homeostasis, but they exhibit different phenotypes, namely pro-inflammatory (M1 type) and anti-inflammatory (M2 type) in different brain environments, and the activation of their phenotype is mainly associated with Toll-like receptor 4 (TLR4). In healthy humans, microglia are constantly changing their morphology to monitor the brain parenchyma while being able to remodel synapses during development, contributing to motor learning, memory, and engulfing dead cells [10]. In the early stages of AD, microglia are rapidly activated, like other phagocytes in the body, to engulf and remove pathogens and dead cell debris entering the central nervous system [11], alleviating brain damage, and microglia can also modify synapses, including establishing new connections with synapses or removing synapses [12], which is particularly important for AD patients and is likely to be a new target for improving the cognition of AD patients. However, when the excessive accumulation of Aβ and the formation of deposits lead to the overactivation of microglia, i.e., the transformation to the M1 type, the negative effects of this process on neurons are exacerbated, leading to a rapid progression of neurodegenerative changes in the patient's brain, leading to a deterioration in their overall health [13]. Therefore, it is of great significance to explore the effect of microbiota-gut-brain axis on microglia in the brain of AD for the treatment of AD.

Sequencing of the bacterial 16S rRNA gene in fecal samples from AD model mice and wild-type mice at different ages showed that the gut microbiota of the two mice was significantly different and significantly related to age, while compared with AD model mice without gastrointestinal microbiota (GF model mice), the deposition of Aβ pathology in the brain of GF model mice was reduced, but this effect was weakened after fecal bacterial transplantation (FMT) [14]. It has also been shown that FMT decreases hippocampal neurogenesis and brain-derived neurotrophic factor expression and increases p21 expression in adult mice in AD models, while microglia are activated, leading to pro-inflammatory cytokines (eg, tumor necrosis factor-α and interleukin-1β elevation), leading to memory impairment and promoting the development of AD [15]. Microglia also regulate the immune function of astrocytes and determine the phenotype of astrocytes. One of the potential links in bilateral gut-brain communication is tryptophan (TRP) metabolism. Trp enters the body by digesting proteins in

the intestine and finally crosses the blood-brain barrier (BBB) into the CNS. Upon arrival in the CNS, Trp acts on aryl hydrocarbon receptors (AHRs) to control astrocyte and microglial activation, and microglial AHR activation has a bidirectional effect: in the absence of AHR ligands, AHR knockdown inhibits microglial responses, leading to pro-inflammatory and neurotoxicity. In contrast, in the presence of AHR ligands, activation of AHR attenuates the pro-inflammatory function of LPS-induced microglia by reducing LPS-induced binding of AHR to inflammatory cytokines [16]. Thus, metabolites that affect the interaction between microglia and astrocytes may be key to the treatment of AD. TLRs are involved in microglial regulation, symbiotic colonization, maintenance of homeostasis, and integrity of the intestinal barrier. In addition to various gut bacteria and their excretions, Aβ is also a ligand for TLR, meaning that it can initiate inflammatory processes in the gut and brain, leading to the development of neurodegenerative diseases, including AD. First, various bacteria and intestinal metabolites can activate TLR4 and mediate Aβ-induced neurotoxicity, including the release of various inflammatory factors and chemokines, while AD mice with TLR4 deficiency showed a more beneficial side [17], and studies have confirmed that TLR2 deficiency enhances the phagocytosis and clearance of Aβ in cultured microglia and improves the learning ability of model mice [18]. Therefore, modulating the activation of TLR4 and TLR2 to promote Aβ clearance without activating neuroinflammation should be a promising therapeutic target for AD.

3.2. Regulation of BBB in the AD brain by the microbiota-gut-brain axis

BBB is mainly composed of capillary endothelial cells (EC), but also includes neurons, extracellular matrix, pericytes and astrocytes, which are connected by tight junction proteins, which control the passage and exchange of molecules and nutrients between the circulatory system and the brain parenchyma, and enable them to filter various bacteria and some harmful factors that are harmful to the center, which is of great significance for maintaining brain homeostasis [19]. The lack of physiological gut microbiota in germ-free mice results in reduced expression of tight junction proteins and higher BBB permeability compared to pathogen-free mice with normal gut microbiota, whereas these injuries can be reversed after FMT [20]. Excess saturated fatty acids and monosaccharides in the Western diet can induce intestinal dysbiosis by accelerating inflammation to trigger AD, and metabolic and systemic inflammation-induced BBB damage plays a central role in this process [21]. Polyphenolic antioxidants, including dietary phytolignans, modulate the gut-brain axis, which involves the conversion of these polyphenolic compounds into compounds with physiologically active and neuroprotective agents through gut bacterial metabolism, and when combined with nanoparticle-based blood-brain barrier (BBB)-targeted drug delivery, may prove to be effective agents for the treatment of various neurological disorders, including AD [22]. Dysbiosis of the gut microbiota impairs the integrity of the BBB by activating AHR signaling, thereby aggravating AD pathology [23]. The intestinal pro-inflammatory response of the periodontitis-associated salivary microbiota may induce intestinal barrier compromise and increased systemic inflammation, significantly reduce the expression of tight junction-related proteins ZO-1 and occludin, increase the permeability of the blood-brain barrier, and exacerbate the progression of AD [24].

3.3. Regulation of astrocytes in the AD brain by the microbiota-gut-brain axis

Astrocytes are the most abundant type of glial cell in the central nervous system, and based on the expression of a selected set of genes, two activation states of reactive astrocytes: A1 and A2, are defined, which exert neurotoxic and neuroprotective effects, respectively [25]. Helicobacter pylori adventitial vesicles can cross the blood-brain barrier and eventually reach the brain, where they can be absorbed by activating astrocytes through the complement C3-C3a receptor signaling pathway, which induce glial activation and neuronal dysfunction, ultimately leading to increased Aβ pathology

and cognitive decline [26]. IL-3 derived from astrocytes triggers IL-3R in microglia, resulting in increased microglial clearance of pathological debris, and reactive astrocytes also produce C3 through the Aβ-induced NF-kB pathway. The receptor C3R is abundantly present in microglia and binds to C3R to promote microglial phagocytosis [16]. LPS induces transcription of pro-inflammatory and cytotoxic pathways in astrocytes and disruption of tight junctions between cells, leading to further structural and functional alterations of BBB [27].

4. Treatments targeting the microbiota-gut-brain axis

At present, most treatment strategies for AD, such as cholinesterase inhibitors (donepezil, tacrine, and rivastigmine), NMDA receptor antagonists (memantine), and nonsteroidal anti-inflammatory drugs, are only effective in the treatment of mild to moderate AD [5], and some of these effects are unsatisfactory. Some antibiotics, probiotics, prebiotics, synbiotics, fecal microbiota transplantation (FMT), polyphenols, low-FODMAP diets, and nanotechnology-applied therapies that modulate the microbiome-gut-brain axis have been validated in animal experiments, but there are few clinically relevant studies, so clarifying the mechanism of intestinal microbiota in the occurrence and development of AD will help accelerate the development of new drugs for this target and provide more options for the treatment of AD.

4.1. Probiotics, prebiotics

Studies on probiotic-4 (i.e., a mixture of Bifidobacterium lactis, Lactobacillus casei, Bifidobacterium bifidum and Lactobacillus acidophilus) have found that probiotic-4 significantly alleviates the disruption of the intestinal and blood-brain barriers associated with aging, reduces interleukin 6 and tumor necrosis factor-α at the mRNA and protein levels, reduces plasma and cerebral lipopolysaccharide (LPS) concentrations, toll-like receptor 4 (TLR4) expression, and nuclear factor-κB (NF-κB) nuclear translocation, Regulates the phenotype of microglia, reduces inflammatory responses, and improves cognitive function in AD mice [28]. In the rat model, ethanol precipitation of fermented milk mediated by Lactobacillus Switzerland IDCC3801 reduced amyloid precursor protein β levels in vitro and significantly reduced Aβ levels, improving cognitive function in mice. The gut microbiota influences glutamate metabolism and reduces the glutamate metabolite 2-keto-glutamate, while gut bacteria containing glutamate racemase can convert l-glutamate to d-glutamic acid, and N-methyl-d-aspartate glutamate receptor (NMDAR) enhancers have been found to improve cognition in AD patients [29]. Genetic analysis showed that consumption of Bifidobacterium breve A1 inhibited amyloid-induced hippocampal inflammation and immune response genes, with beneficial effects on cognitive function in older adults with memory problems [30]. In an AD clinical trial in which subjects received probiotics containing Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum and Lactobacillus fermentum in disease-matched control subjects, or were not treated for 12 weeks, a significant increase in learning and memory measured with the Mini-Mini-Mental State Examination (MMSE) test was observed in the probiotic group compared to the placebo group, with a decrease in malondialdehyde, suggesting that probiotics can also improve patients' cognitive function by inhibiting oxidative stress [31]. The concept of prebiotics primarily refers to carbohydrate substances such as oligosaccharides and human milk oligosaccharides, and later extended to non-carbohydrate substances, mainly including polyunsaturated fatty acids (PUFAs), phenols, and phytochemicals. The biotic mannan-oligosaccharide (MOS) is one of the prebiotics derived from konjac and the outer membrane of the cell wall of bacteria, plants or yeast that remodel the gut microbiome and enhance the formation of neuroprotective metabolites short-chain fatty acids. MOS treatment at 8 weeks significantly improved cognitive function and spatial memory, while attenuating anxiety and obsessive-compulsive-like

behaviors in a mouse model of AD, reducing Aβ accumulation in the cerebral cortex, hippocampus, and amygdala, with the potential to be a novel microbiota-targeted therapy for the treatment of neurodegenerative diseases [32].

4.2. Chiral nanoparticles and various compounds

Chiral nanoparticles restored cognitive ability and ameliorated Aβ and hyperphosphorylated tau pathology in AD mice by altering gut microbiome composition and increasing the gut metabolite indole-3-acetic acid, and clinical trials have also found that indole-3-acetic acid in serum and cerebrospinal fluid is low in AD patients [33]. Flavonoids can inhibit the growth of harmful bacteria by destroying the lipid bilayer of the cell membrane of harmful bacteria or affecting the permeability of their cell membranes, and provide metabolic substrates for the intestinal microbiota to promote the growth of beneficial bacteria, thereby optimizing the structure of the intestinal microbiota, which interacts with the intestinal microbiota, and related metabolites may pass through the biological barrier to reduce the excessive phagocytosis and elimination of neuronal synapses caused by microglia, thereby achieving the purpose of preventing and treating cognitive impairment [34].

4.3. Diet, exercise therapy

Diet is a key determinant of gut bacterial assembly and genetic makeup. Specific foods and dietary patterns affect the composition and abundance of different types of bacteria in the gut, thus maintaining homeostasis in the host. The Eastern Mediterranean diet (MD), which includes a high consumption of fruits, vegetables, legumes, and grains, has long been described as a healthy dietary pattern. Higher MD slows the progression of AD and delays the onset of AD for 1.5 to 3.5 years [35]A 15-year study of more than 1,000 dementia-free elderly people, aged 60-80 years, showed that high consumption of milk and dairy products reduced the risk of dementia due to the abundance of saturated fatty acids and various minerals. However, more research is needed to determine how diet and its components affect the microbiota-gut-brain axis, and to describe whether the effects of diet on the microbiota drive changes in overall brain function.Irisin is a exercise-induced muscle factor that promotes neuroplasticity and cognitive function through BDNF signaling, and studies have found that the BDNF produced by irisin may mediate the positive effects of physical activity on some aspects of AD pathophysiology through the interaction between exercise and gut microbial ecosystem, neuroplasticity, anti-inflammatory signaling pathways, and neurogenesis [36], so a certain degree of aerobic exercise is beneficial for the prevention and recovery of AD.

4.4. Fecal microbial transplantation

Fecal microbial transplantation is the transfer of feces from a pre-screened donor into the gastrointestinal tract of a patient with the aim of increasing overall diversity and restoring the function of the gut microbiota. Currently, FMT is only recommended for the treatment of recurrent Clostridium difficile infection, and studies of central nervous system disease remain experimental [35]. Frequent transfer and transplantation of fecal microbiota from WT mice into AD model mice has improved Aβ, glial reactivity, and spatial learning in mice [37]. Most of the current AD-related FMT-related studies are animal trials, and there are only a few human clinical studies, most of which demonstrate promising results for FMT treatment in AD, which warrants further evaluation of FMT in preclinical and clinical studies. In the past, FMT methods have received considerable attention in both preclinical and clinical studies, and are likely to develop rapidly in the next decade.

5. Conclusion

Currently, defining a healthy microbiome can be a complex topic, as there are significant inter-individual differences in the gastrointestinal microbiome. When the gut microbiome becomes unbalanced due to dietary changes, drug use, lifestyle choices, environmental factors, and aging, it may potentially accelerate the progression of AD, and a clear causal relationship has been demonstrated in animal experiments. When the intestinal microbiota is unbalanced, it can directly or through its metabolites acting on microglia, brain endothelial cells, astrocytes, etc., which can affect Aβ deposition and tau pathological changes, and affect the process of AD. However, there is a small amount of evidence that it can affect the microbiota and play a therapeutic role in AD, and there is a lack of drugs that directly intervene in the intestinal flora to achieve the purpose of treatment, so it is necessary to further study the mechanism of the influence of intestinal microbes on AD in the future, so as to make the early prevention and treatment of AD more effective, delay the onset of AD, slow down the progression or reverse the disease, and reduce the burden on families and society.

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