The Gut Microbiome in Alzheimer's Disease: Research Progress and Perspectives

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment, with typical pathological processes involving β-amyloid deposition, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction. In recent years, the gut microbiota, residing in the intestine, has attracted increasing attention for its influence on AD pathology through the gut-brain axis (GBA). Studies have demonstrated decreased gut microbial diversity in AD patients. Gut dysbiosis may contribute to AD pathogenesis by disrupting the blood-brain barrier, activating microglia, exacerbating neuroinflammation, and promoting Aβ deposition. Moreover, microbial metabolites and microglial activation have been identified as critical mediators in AD pathology. Although microbiota-targeted strategies such as probiotics and dietary interventions have shown partial therapeutic potential, their clinical efficacy remains limited by individual heterogeneity, mechanistic complexity, and insufficient standardization. Future research should integrate multi-omics technologies and longitudinal cohorts to elucidate the causal mechanisms of the gut-brain axis in AD progression, thereby facilitating the development of microbiome-based diagnostic and therapeutic strategies.

Keywords: Alzheimer's Disease; Gut-brain Axis; Gut Microbiota; Neurodegenerative Disease; Neuroinflammation.

1. Introduction

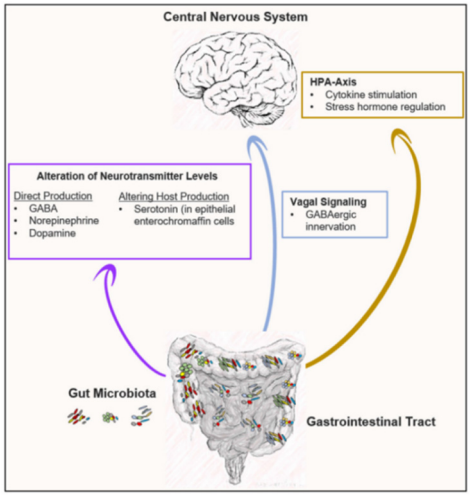

Figure 1. Mechanisms of the gut-brain axis[4]. Gut microbiota can influence brain activity through multiple pathways

Alzheimer's disease (AD) is a neurodegenerative disorder with pathological hallmarks of progressive cognitive impairment. Its main clinical symptoms include memory decline, behavioral changes, and gradual loss of daily living abilities. With the global trend of population aging, the incidence of AD is rising annually. By 2030, the number of dementia patients worldwide is projected to reach 78 million [1], posing challenges to healthcare systems and society at large across economic, ethical, policy, and cultural dimensions. The classical pathological features of AD involve Aβ deposition, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction[2], reflecting its high complexity. In recent years, the gut-brain axis has emerged as a research frontier in

neurodegenerative diseases. Dysbiosis of the gut microbiota may participate in AD pathogenesis by modulating microglia, activating inflammatory factors, impairing Aβ clearance, and increasing blood-brain barrier permeability[3]. Although numerous studies have revealed potential associations between gut microbiota and AD, the precise mechanisms and microbiome-based therapeutic strategies remain to be fully elucidated.

The potential association between the gut microbiome and the nervous system not only provides a novel theoretical perspective on the pathogenesis of Alzheimer's disease (AD), but also opens up new avenues for its prevention and treatment. Research on interventions based on constructing a bidirectional gut–brain axis regulatory system may not only improve the cognitive function and quality of life of AD patients[5], but also offer potential targets for future personalized and precision therapies for AD, carrying significant clinical value[6].

This paper will first introduce the basic concepts of the microbiota-gut-brain axis, then discuss the role of the gut microbiome in AD pathology, including its impact on neuroinflammation, Aβ deposition, and the blood-brain barrier. Subsequently, current interventions such as dietary modification, probiotics, and fecal microbiota transplantation will be summarized, with an evaluation of their clinical efficacy [7]. Finally, the review will highlight future research directions and potential therapeutic targets, offering new perspectives for AD treatment and intervention.

2. Gut Microbiota

2.1 Diversity of the Gut Microbiome

The gut microbiota is a complex ecosystem colonizing the intestine, comprising beneficial, harmful, and neutral microbes. More than 1,000 microbial species inhabit the adult human gut, with an estimated total of up to 10^{14} cells [8], weighing approximately 1.2 kg, and containing a gene pool about 150 times larger than the human genome. These microbes are involved in numerous physiological and biochemical processes. For instance, beneficial bacteria such as Lactobacillus can facilitate digestion, synthesize vitamins, regulate immune function, and inhibit the growth of pathogenic bacteria. By contrast, harmful bacteria such as Clostridium difficile may trigger intestinal infections and inflammation. Collectively, these findings underscore the essential role of the gut microbiome in human health.

Figure 2. Simplified classification of gut microbes. The human intestinal environment harbors diverse microbial species, including both beneficial and harmful bacteria.

2.2 How the Gut Microbiome Participates in Life Processes

Due to its remarkable diversity, the gut microbiome regulates multiple physiological functions of the host via microbial metabolites, immune modulation, and signal transduction with the nervous system. For example, in immune regulation, short-chain fatty acids (SCFAs) such as butyrate can induce bone marrow monocytes to differentiate into a tolerogenic phenotype [9]. The gut microbiota can also influence the differentiation of hematopoietic stem and progenitor cells (HSPCs), thereby

shaping the production of immune cells[10]. In addition, pattern recognition receptors (PRRs) on intestinal epithelial cells can recognize microbe-associated molecular patterns (MAMPs) from the microbiota, triggering immune responses[10]. For instance, Toll-like receptors (TLRs), a type of PRR, can induce chemokine and cytokine production upon activation, thereby modulating host immune activity[10].

Metabolically, the gut microbiome is deeply involved in nutrient processing, being one of the most metabolically active sites in the body. Gut microbes encode numerous carbohydrate-active enzymes that break down complex carbohydrates into SCFAs[11]. These metabolites not only supply energy for microbes themselves but are also absorbed by host cells, contributing to energy metabolism and regulation of intestinal barrier function.

At the same time, the gut microbiota establishes a bidirectional regulatory network with the nervous system through the gut-brain axis (GBA). This axis modulates brain activity in multiple dimensions by promoting immune responses, influencing the integrity of the blood-brain barrier (BBB), and shaping neurophysiological processes[12].

2.3 Pathological Consequences of Gut Microbiome Dysbiosis

Host health depends to a large extent on microbial homeostasis in the gut. Dysbiosis may directly or indirectly lead to diseases such as diabetes, obesity, inflammatory bowel disease (IBD), and certain neurodevelopmental disorders. For instance, metagenomic studies of IBD patients have shown significantly reduced gut microbial diversity, with decreased abundance of beneficial bacteria (e.g., Bifidobacterium) and increased abundance of harmful bacteria (e.g., Clostridium difficile)[13]. This imbalance compromises the intestinal mucosal barrier, increases gut permeability, and allows harmful microbes and their metabolites to enter the circulation, eliciting systemic inflammation.

Other studies suggest that gut dysbiosis may contribute to neurological disorders via a "gut-inflammation-neurodegeneration" pathway. Specifically, large-scale microbial imbalance can impair BBB integrity and activate microglia, triggering neuroinflammatory diseases[2]. Additionally, dysbiosis may lead to accumulation of neurotoxic metabolites that promote Aβ deposition, tau hyperphosphorylation, and neuronal dysfunction, directly damaging the function of neurons[14]. Furthermore, small molecules and hormones derived from dysbiotic microbiota, although unable to cross the BBB directly, may act indirectly via peripheral immune activation or vagus nerve signaling, thereby aggravating neuropathology.

3. Alzheimer's Disease

3.1 Pathological Progression of Alzheimer's Disease

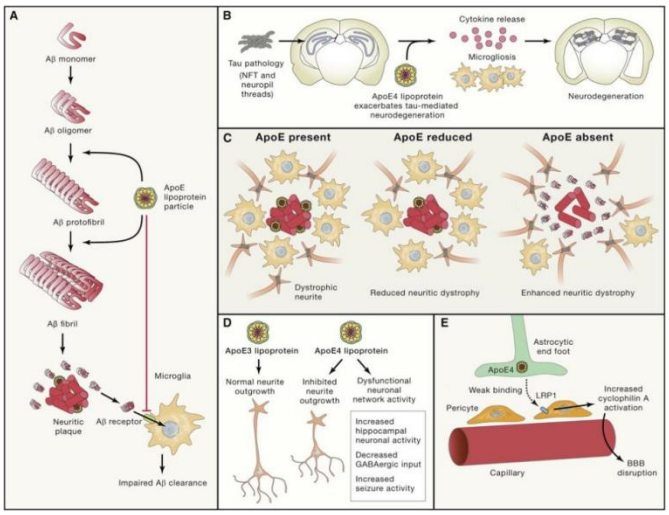

Figure 3. Mechanisms of AD pathogenesis [15]. This involves Aβ deposition, tau hyperphosphorylation, and apolipoprotein E (ApoE)-related synaptic dysfunction.

AD is a neurodegenerative disorder with progressive cognitive decline as its core clinical feature. Multiple hypotheses coexist to explain its pathology. The hallmark pathological features include excessive Aβ deposition, abnormal phosphorylation of microtubule-associated tau protein, chronic neuroinflammation, and synaptic dysfunction.

Aβ accumulation is a defining pathological marker of AD. Aβ peptides are derived from amyloid precursor protein through the abnormal cleavage by secretases. Under pathological conditions, soluble Aβ peptides undergo oligomerization and aggregation, impair synaptic signaling, and eventually form insoluble neurotoxic plaques, leading to widespread neuronal death.

Tau protein, a microtubule-associated protein, normally undergoes reversible phosphorylation to regulate microtubule stability. In AD, tau phosphorylation is markedly elevated, especially at certain amino acid residues (e.g., tyrosine and threonine)[14]. This aberrant phosphorylation alters tau conformation, causing its aggregation into intracellular neurofibrillary tangles (NFTs). The accumulation of NFTs disrupts neuronal function and induces cell death. Recent studies suggest that soluble tau assemblies may act as earlier pathological drivers preceding NFT formation [16].

Synaptic dysfunction in AD results from multiple synergistic neurotoxic mechanisms. Aβ oligomers accumulate in dendritic spines, inducing abnormal internalization of N-methyl-D-aspartate receptors (NMDARs), thereby weakening synaptic transmission. Consequently, synaptic dysfunction is considered the most direct cellular basis for cognitive decline in AD patients [17].

Neuroinflammation in AD is multidimensional and self-amplifying, involving oxidative stress, cytokine networks, and interactions with neuropathological features such as NFTs [18]. Neuroinflammation forms a vicious cycle: cellular damage triggers inflammation, and inflammation in turn exacerbates cellular damage. For example, TNF-α promotes reactive oxygen species (ROS) generation, further activating inflammatory signaling pathways [18]. Such cyclical inflammation may be more amenable to intervention in early disease stages but becomes increasingly uncontrollable at later stages.

3.2 Immune Cells in the Central Nervous System

Although neurons are the principal cellular components of the nervous system, the central nervous system (CNS) also contains various glial cells. Microglia, the only resident immune cells in the CNS, account for approximately 10-20% of all glial cells. In their resting state, microglia continuously survey the neural microenvironment to maintain homeostasis and regulate synaptic function through synaptic pruning[19]. When stimulated by factors such as Aβ deposition, microglia become overactivated and release harmful mediators, including pro-inflammatory cytokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS), thereby driving neuroinflammation[20]. Neuropathological studies reveal that microglia in the brains of AD patients are markedly activated, underscoring their close involvement in AD progression.

In early AD, microglia predominantly exhibit a neuroprotective M2 phenotype, relying on oxidative phosphorylation to clear Aβ deposits. However, as the disease progresses, microglia shift toward a glycolysis-dependent M1 phenotype, with impaired Aβ clearance capacity[21]. At the same time, activated microglia produce abundant pro-inflammatory cytokines and facilitate intercellular transmission of misfolded proteins (e.g., tau and Aβ) via exosomes, accelerating neurodegeneration [20].

Moreover, brains of AD patients exhibit upregulated expression of inflammatory cytokines and genes. For instance, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) not only exert direct neurotoxicity but also suppress insulin-degrading enzyme, thereby hindering Aβ clearance and exacerbating deposition[22].

In summary, sustained microglial activation is a key “ignition switch” for AD-related neuroinflammation. Increasing evidence suggests that such activation is not solely triggered by endogenous damage-associated molecular patterns (DAMPs) within the CNS. Gut microbiota can transmit exogenous signals to brain-resident microglia through two parallel pathways: some microbes synthesize or release bacterial amyloids structurally homologous to Aβ or tau, which cross-seed with

host proteins to form highly toxic oligomers, inducing chronic inflammation. Lipopolysaccharide (LPS), detected in AD patients with increased BBB permeability, can directly bind to the TLR4-CD14 complex on microglia, amplifying NF-κB-mediated pro-inflammatory cascades while inhibiting Aβ phagocytosis [23]. These bidirectional signaling pathways between gut microbiota and microglia constitute a critical bridge linking peripheral dysbiosis with central AD pathology, laying the foundation for microbiome-based therapeutic strategies.

4. Microorganisms in the Pathological Progression of Alzheimer's Disease

4.1 Characteristics and Mechanisms of the Gut Microbiome in Alzheimer's Disease

In recent years, research on microbial involvement in AD pathogenesis has made significant progress. Multiple studies have suggested that oral microbes, gut microbiota, and certain pathogens may contribute to AD pathology through diverse mechanisms [24]. Among these, the gut-brain axis, highly influenced by the gut microbiome, has yielded breakthrough findings.

The gut-brain axis plays a crucial regulatory role in AD pathogenesis. Metagenomic studies consistently reveal marked alterations in gut microbiota composition in AD patients, particularly reduced microbial abundance [25]. Additionally, the levels of microbiota-derived metabolites, such as SCFAs, are significantly decreased, potentially aggravating AD pathology through multiple mechanisms. These include enhancing Aβ plaque deposition, inducing metabolic dysfunction, and dysregulating microglial activity. These findings provide cutting-edge theoretical evidence for understanding the role of the gut microbiome in AD.

4.2 The Bidirectional Gut-Brain Axis

The concept of the gut-brain axis was first introduced in 2004 by Sudo and colleagues, based on germ-free mouse models[26]. It was defined as a dynamic bidirectional signaling pathway connecting the intestine and the central nervous system (CNS) via neural, endocrine, and immune routes [27]. With advancing research, this concept evolved into the "gut-microbiota-brain axis," which is now recognized to participate in the pathophysiology of neurodegenerative diseases through neural, endocrine, and immune dimensions.

The vagus nerve is the primary neural pathway linking the gut to the CNS, and its signaling mechanisms have been extensively studied. Microbial metabolites can specifically activate enteroendocrine cells or enterochromaffin cells in the gut [28], stimulating the release of neurotransmitters such as cholecystokinin, which in turn activate vagal afferent fibers [29]. These signals are relayed via the nucleus tractus solitarius to the limbic system, ultimately influencing mood and cognitive functions [30].

Microbe-host co-metabolites also play a central role in endocrine signaling. For instance, SCFAs can cross the BBB and upregulate brain-derived neurotrophic factor (BDNF) [31]. Similarly, tryptophan metabolism, which is strongly influenced by gut microbiota, produces indole derivatives and serotonin precursors that act on the CNS via the portal circulation, thereby modulating neuronal function [32].

The immune-mediated link between the gut microbiota and CNS involves a cascade of responses. Gut dysbiosis disrupts intestinal barrier integrity, allowing LPS to enter circulation[33]. LPS subsequently activates peripheral immune cells[33], inducing the release of pro-inflammatory cytokines[34], which in turn influence CNS function through multiple routes. Animal studies confirm that antibiotic-induced dysbiosis significantly suppresses hippocampal neurogenesis, whereas microbiota restoration or anti-inflammatory treatments can reverse these pathological effects[35].

Despite progress, several key scientific questions remain unresolved. First, some microbial species detected in AD patients are also present in healthy individuals[36]. Thus, establishing gut microbes as reliable AD biomarkers requires stricter validation. For example, reduced abundance of faecalibacterium prausnitzii has been positively correlated with Aβ deposition, but longitudinal studies are needed to confirm its temporal stability[37]. Second, gut microbiota composition varies

significantly with diet, lifestyle, and medication, introducing high individual heterogeneity and complicating study design and interpretation.

Nevertheless, the potential roles of gut microbiota in AD pathogenesis offer promising therapeutic perspectives. Clinical evidence suggests that microbiota-targeted interventions, such as probiotics, can effectively reshape gut microbial structure, improve cognitive function, and alleviate neuroinflammation in AD patients[24]. With continued research, future studies may further uncover the complex interplay between gut microbiota and AD pathology, leading to microbiome-based diagnostic tools and therapeutic strategies.

5. Challenges and Perspectives

This review has systematically summarized the widely recognized pathological mechanisms of AD and the multidimensional roles of the gut microbiome in modulating AD pathophysiology through the microbiota-gut-brain axis. It has also explored the therapeutic potential of microbiota-based interventions. However, several key challenges remain:

First, most existing evidence is correlation-based, and causal relationships between gut microbiota and AD progression still require confirmation through prospective cohort studies and rigorous animal models. Second, the regulatory mechanisms of the microbiota-gut-brain axis are highly multidirectional and dynamic, with microbial metabolites exerting pleiotropic effects via multiple targets, making mechanistic dissection challenging[38]. Third, gut microbiota abundance displays significant inter-individual heterogeneity, which not only affects comparability across studies but also complicates the development of standardized microbial diagnostic biomarkers [39]. In terms of therapeutic translation, although microbiota-targeted interventions have shown neuroprotective effects in animal models, their clinical efficacy remains inconsistent. For example, a synbiotic formulation of lactobacillus producing indole-3-lactic acid (ILA) combined with inulin improved cognitive function in AD mice[40], yet its effectiveness in clinical settings remains to be validated, highlighting the need for more precise intervention strategies.

Looking ahead, research in this field urgently requires a multidisciplinary approach. Integration of multi-omics technologies, such as metagenomics and metabolomics, combined with machine learning algorithms, holds promise for constructing more accurate microbiota-AD association models [39]. From a translational perspective, well-controlled longitudinal intervention studies are needed, with a focus on specific microbial strains or metabolites that modulate AD pathology [41]. Progress in this direction will not only deepen the understanding of AD mechanisms but may also open new avenues for the prevention and treatment of neurodegenerative diseases.

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