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Review

The Influence of the Gut Microbiota on Alzheimer's Disease: A Narrative Review

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Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease that tends to occur in the elderly. The main symptom is hypomnesia. More and more older people are suffering from this disease worldwide. By 2050, 152 million people worldwide are expected to have AD. It is thought that the aggregation of amyloid-beta peptides and hyper-phosphorylated tau tangles contribute to AD. The microbiota-gut-brain (MGB) axis appears as a new concept. The MGB axis is a collection of microbial molecules produced in the gastrointestinal tract that influence the physiological function of the brain. In this review, we discuss how the gut microbiota (GM) and its metabolites affect AD in different ways. Dysregulation of the GM has been shown to be involved in various mechanisms involved in memory and learning functions. We review the current literature on the role of the entero-brain axis in the pathogenesis of AD and its potential role as a future therapeutic target in the treatment and/or prevention of AD.

Keywords: Alzheimer's disease; human gut microbiota; neurodegenerative disease; neurotransmitters; neuroinflammation

1. Introduction

The microbes that live in the human gut include bacteria, eukaryotes, and viruses. These microbes modulate human health by regulating the function and development of the immune system [1]. Gut microbiota (GM) affect nutrient absorption/metabolism, and influence brain development and neurogenesis. The pathway connecting the GM to the brain is called the "microbiota-gut-brain (MGB) axis" [2]. The MGB axis is mediated by various microbial molecules produced in the gastrointestinal tract, which can then infiltrate many organs, even the brain [3]. In recent years, more and more attention has been paid to the influence of the MGB axis on the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Recent preclinical and clinical studies have reported the latest advances in the study of the brain-enteric axis and neurodegenerative diseases [4–6]. Approximately 70–80% of immune cells are found in the gut. Mediators derived from the gut microbiome, including short-chain fatty acids (SCFAs) and other metabolites, lipopolysaccharides (LPS), and neurotransmitters, can affect neuro-immune interactions and the pathways by which these interactions may occur [7]. There is a complex bidirectional interaction between the intestinal microbiome and AD [8]. More than 80% of PD patients have various severe gastrointestinal symptoms [9]. The genetic susceptibility to PD may be related to the ecological imbalance in the intestinal microbiome [10]. The MGB axis can influence motor, mental, and cognitive symptoms as well as weight loss in HD [11].

In this review, we focus on the close association between AD and the MGB axis. In addition, we provide a figure to show the possible mechanism between the GM and AD (Fig. 1). By 2050, 152 million people worldwide are expected to have AD [12]. The main characteristics of AD are amyloid-beta (Aβ) plaques and neurofibrillary tangles, which are caused by the hyperphosphorylated tau protein. Amyloid precursor protein (APP) is a highly conserved multifunctional protein expressed in neurons and glial cells. Aβ is a polypeptide produced by the hydrolysis of APP [13]. Other features of AD include neuroinflammation, impairment of calcium balance/energy metabolism and vascular degeneration [14]. Studies have shown that the human GM is associated with cognitive behavior, and that alteration of the human GM influenced the development of AD [15]. The role of GM in AD is summarized in Table 1 (Ref. [13,16–28]).

2. GM and Inflammation in the Gastrointestinal Tract

Immune system dysregulation is a major feature of AD [29,30]. GM have been found to play a role in influencing amyloid plaque deposition [31]. Neuronal injury is a common pathological manifestation of AD. The occurrence of innate immune responses in the central nervous system (CNS) usually results in neuronal damage [32]. The cap-

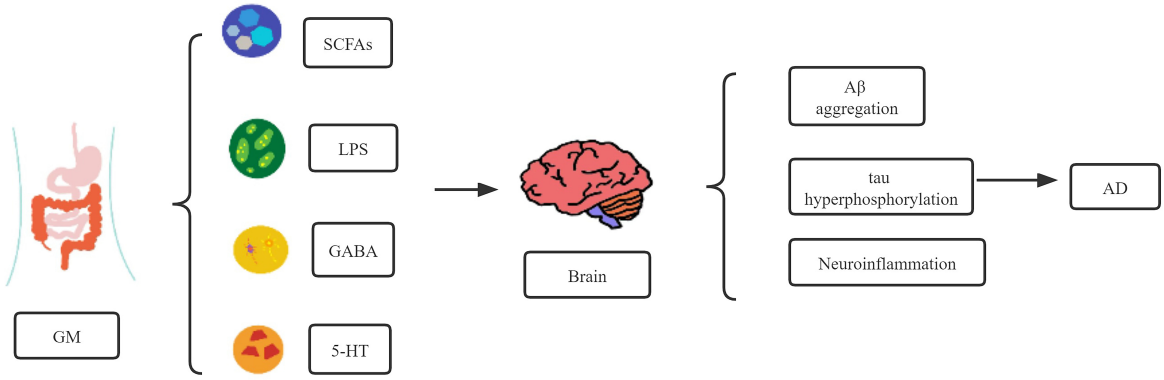

Fig. 1. GM affects the mechanism of AD. The imbalance of GM affects the lack of GM diversity. GM release metabolic substances that can be transferred to the brain through the MGB axis. These substances can directly or indirectly cause Aβ aggregation, tau hyperphosphorylation and neuroinflammation in the brain. GM may contribute to the pathogenesis of neurological diseases such as AD.

Table 1. The role of GM in AD.

Name of Microorganisms	Role in AD	Research	Year	Reference
Bacteroides fragilis	Inflammation The release of proinflammatory cytokines	Human 16S rRNA gene sequencing	2016 2021	[16,17]
Actinobacteria	Inflammation	Human 16S rRNA gene sequencing	2017	[18,19]
Firmicutes	Anti-inflammatory effects Neuroprotective effects	Human 16S rRNA gene sequencing	2012 2017	[18,20]
Helicobacter pylori	Aβ aggregation Inflammation	Human CSF and serum anti-Helicobacter pylori IgG concentrations measurement	2009 2019	[13,21]
Escherichia coli	Deposit amyloid tau phosphorylation	Human DNA sequencing, Immunohistochemical staining	2005 2016	[22,23]
Porphyromonas gingivalis	Neuroinflammation	Animal qRT-PCR, immunohistochemistry	2018	[24]
Akkermansia muciniphila	5-HT levels in the hippocampus	Animal Serotonin measurement	2020	[25]
Bifidobacterium	Reduce the expression of inflammatory cytokines	Feeding animal model	2017	[26]
Lactobacillus	Reduce neuroinflammation	Reduce neuroinflammation	2018 2020	[27,28]

illary endothelium, astrocyte terminal foot and basement membranes are the morphological basis of the blood-brain barrier (BBB). LPS can be found in a large proportion of the human gastrointestinal tract [33]. Many amyloid and immunogenic mediators are also produced by the GM [34]. GM and its products travel to the blood circulation of the brain *via* a cytokine cascade [35]. The permeability of the gastrointestinal mucosa and the BBB is greater among older people, which contributes to the deposition of Aβ in the brain. Immune cells detect Aβ and control the release of inflammatory cytokines [36]. These findings strongly suggest that the GM have a significant effect on neuroinflammation and contribute to the process of neurodegeneration.

2.1 GM Effect on Brain and Immune System

GM play a role in the metabolism of nutrients and support immunity. The intestinal mucosa plays a vital role in resisting pathogens [37]. More and more evidence suggests a complex relationship between the gut and the CNS. Visceral signals from the gut affect the CNS *via* the vagus nerve; in turn, the brain directs signals to regulate the function of the gut. This two-way communication is termed the MGB axis [38]. GM significantly affect the physiological function and behavior of the brain through three pathways of the MGB axis (immune, neuroendocrine and vagal pathways) [15]. The enteric nervous system (ENS) is made up of various types of neurons. The brain receives information from neurons near the spine and intestine that is transferred by spinal and vagal afferent nerves [39]. As the ENS is the communication channel between the GM and the CNS, there is a vital connection between the GM and the physiological activity of the brain [40]. GM develop and regulate the body's immune system; at the same time, the immune system also affects the composition of the GM. Normal physiological functions in the brain, such as the development of the nervous system, the transmission of signals between nerves, and the activation of the CNS immune system, are affected by the GM through changes in microglia and astrocytes. The integrity and permeability of the BBB are also related to the GM [41]. The immune system plays a role in the formation of the brain's physical structure and its response to inflammation [32]. Intestinal

inflammation and leakage of the intestinal barrier may be caused by the imbalance of the GM. The efflux of incompletely digested food, microorganisms, endotoxins, and immune factors may be the cause of chronic systemic inflammation. The intestinal barrier is permeated mainly by incompletely digested food molecules [42]. The development of a majority of chronic diseases is accompanied by an overactive immune system, which is often associated with immune system overload. The overloading of the immune system can be caused by a chronic inflammatory reaction of the intestinal mucosa, such as neurodegenerative diseases [43]. However, the effect of probiotics on Aβ plaque load is minimal. There is also little association between glial proliferation and probiotic-regulated GM. Most evidence supports an important manifestation of extra-encephalic diseases in biological abnormalities mediated by intestinal dysfunction [44]. Increased AD-related neuroinflammation has been associated with GM-induced activation of peripheral inflammasome. An increase in inflammasomes in the brain has been found to result in an imbalance in the GM of young and old AD mice [45].

2.2 Microglia and AD

Microglia are non-neuronal cells. The maturation and function of microglia are influenced by host intestinal microbes [46]. When the GM decrease, microglia develop defects and cannot mature [47]. Acetate is an important GM metabolite that stimulates microglia to mature [48]. Microglia activation increased after SCFAs supplementation in germ-free (GF) mice [49]. LPS produced by the GM increased the inflammatory response of microglia and promoted the activation of microglia [50]. The increase of Clostridium and Bacillus in the intestinal tract decreased the expression of IB4 binding and β3 tubulin, damaged the vagal afferent pathway, and activated microglia [51].

The production of pro-inflammatory cytokine/chemokine microglia is the main manifestation of advanced AD-related chronic neuroinflammatory pathology. In humans and animal models of AD-like pathology, enhanced levels of associated inflammatory cytokines are detected in the early stages of AD [52]. Microglia are the main source of Complement component 1q in the brain [53]. The innate immune response mediated by CNS-resident microglia plays an important role in neuroinflammation in AD. Therefore, microglia may play an important role in regulating neurodegeneration [54]. In the presence of aging or genetic predisposing factors, tau pathologically induces abnormal activation of microglia, resulting in the accumulation of toxic amyloid proteins; in turn, the activated microglia promote the spread of tau pathology by phagocytic synapses and secreting neurotoxic cytokines [55]. Bacterial products or metabolites from the GM modulate microglia maturation, morphology and function, such as SCFAs [47,56]. Microglia have an active role in synaptic formation [57]. In addition to plaques, microglia and immune-related pathways are also the focus of interest in AD. They may be early mediators of synaptic loss and dysfunction in AD [58]. GM dominate the development, maturation and activation of microglia. Activated microglia are involved in brain development and homeostasis [59]. However, activated microglia can serve as a source of inflammatory mediators, as well as phagocytosis of regulating synapses that contribute to AD [55]. The number of microglia in cortical gray and white matter was increased in postmortem AD cases. Furthermore, microglial proliferation was increased in AD and correlated with the severity of AD [60]. Microglia also degraded some of the tau species released from the brains of AD patients [61]. Microglia participated in the process of AD. Studies have shown that the decrease of microglia inhibited the proliferation of tau cells. In addition, neuronal death might be related to astrocytes regulated by microglia. In the pathogenesis of AD, activated microglia play a role in the activation of acute microglia that enhanced phagocytosis and clearance, thereby reducing Aβ accumulation. In addition, neurotoxicity and synaptic damage can occur through the triggering of a number of pro-inflammatory cascades, which is often associated with chronic activation of microglia [62]. Reactive microglia can drive the development of tau pathology in mice with the deletion of the microglial fractalkine receptor (CX3CR1) [63]. Microglia play an important role in the spread of tau protein and neurotoxicity in the brain [64]. CX3CR1 deficiency is associated with the deterioration of AD-related neurons and the exacerbation of cognitive deficits. CX3CR1 is thought to be a key pathway by which abnormally activated microglia lead to AD-related cognitive deficits [65]. Older people and mice are more prone to brain damage and even neurodegeneration. This is because microglia grow slowly with age, leading to a reduction in surrounding tissue, impaired synaptic contact, and poor recovery from injury [66]. Studies have found that brain inflammation associated with AD-like pathology could be alleviated in the APPswe/PS1ΔE9 mouse model by lifelong choline supplementation. This might be related to the fact that choline reduces the expression of activated microglia [67].

Using single-nucleus RNA-seq, a group of disease-associated astrocytes was found in a mouse model of AD [68]. The A1 neurotoxic phenotype describes mouse astrocytes after exposure to a specific cytokine secreted by microglia of LPS [69]. The formation of A1 neurotoxic reactive astrocytes is a fundamental pathological response of the CNS, which is associated with LPS-induced neuroinflammation, acute CNS injury, and all neurodegenerative diseases. A1 reactive astrocytes are induced by classical activated neuroinflammatory microglia. A1 reactive astrocytes have many normal astrocyte functions that are decreased, such as synaptic functions, phagocytic capacity and neurovirulence. A1-activated astrocytes account for a large proportion of AD in central neurodegenerative regions

[70]. In AD mouse models, microglia-mediated reactive astrocyte transformation was blocked by repeated subcutaneous administration of NLY01, a long-acting glucagon-like peptide-1 receptor agonist. Neuronal activity was maintained, and spatial learning and memory were improved [71]. Following CNS injury, astrocytes and microglia produced a large number of mutually regulated signaling molecules. More research is needed to understand how microglia and astrocytes act on neurons in AD environments [72].

2.3 BBB

The BBB is a barrier that separates the CNS from the peripheral blood circulation [73]. The BBB is composed of cerebral vascular endothelial cells, astrocytes of the perivascular foot, basement membrane and perivascular cells [74]. Tight junctions are expressed in the vascular endothelial cells, preventing polar molecules from passing freely between the blood and the brain [75]. The BBB breakdown is thought to be an early biomarker of cognitive dysfunction in humans [76]. It separates nerve cells from immune system cells. BBB dysfunction during AD influences Aβ clearance and activated glial cells, and facilitates the recruitment of leukocytes in the brain. Therefore, the BBB assists in the generation and maintenance of chronic inflammation during AD [77]. Current studies show that intestinal flora can affect the BBB through the vagus [78] and immune system [79]. Metabolic substances produced by intestinal flora, such as SCFAs, also affect the function of the BBB. SCFAs or metabolites produced by the GM affect the BBB permeability. When C. *tyrobutyricum* or B. *thetaiotaomicron* were colonized separately in the gut of GF adult mice, the BBB permeability was reduced. *C. tyrobutyricum* produces butyrate, and *B. thetaiotaomicron* mainly produces acetate and propionate [80]. Propionate protects the BBB from oxidative stress by inhibiting pathways associated with nonspecific microbial infection through a CD14-dependent mechanism [81]. The antibiotic-treated mice showed intestinal disorders and increased expression of tight junction protein 1 and occludin mRNA in the amygdala. The expression of tight junction proteins in the frontal cortex, striatum and hippocampus of GF mice was decreased [82].

There is evidence that deterioration of the BBB morphology and function occurs in many neurodegenerative diseases and is considered a marker of cognitive decline [83]. One study confirmed greater BBB permeability in GF mice than in GM normal disease-free mice. In addition, SCFAs or metabolites produced by the GM reduced BBB permeability [80]. The basement membranes cover the brain capillary endothelial cells of the BBB, and the pericytes and astrocytes end foot surround the BBB neurovascular unit. The ability of the BBB to regulate the exchange of molecules between blood flow and the brain parenchyma, determines homeostasis of the CNS. Therefore, BBB dysfunction may be involved in the pathogenesis of several neurological diseases, including AD [84]. Researchers observed an approximately 4.2-fold increase in Aβ load in AD individuals. Inadequate coverage of pericapillary cells in the brain led to increased Aβ accumulation in the hippocampus of AD patients compared to controls [85]. The Chinese medicine, Rehmannia, may maintain the integrity of microvessels in the brain, decrease the BBB permeability, increase Aβ clearance in the brain, and improve daily activity and function in AD mice [86]. Increased inflammation in the CNS was associated with damage to the BBB, which led to infiltration of immune cells into the brain [87]. Disruption of the BBB led to the flow of neurotoxic blood debris, cells and microbial pathogens into the brain, secondary to associated inflammation and immune responses, which could lead to a variety of neurodegenerative diseases [88]. There is a close GM- mediated relationship between the intestinal barrier and the BBB. Intestinal disorders could lead to increased permeability of the hippocampus, which is involved in learning and memory processes. Some blood-derived molecules could cross the BBB at this time, further exacerbating intestinal inflammation [89]. The integrity of the BBB was compromised by translocated bacteria and secreted pro-inflammatory cytokines, which also induced neuro-inflammatory cascades [43]. A study showed that the BBB in patients with mild cognitive impairment manifested an increased permeability to small molecules, such as water. The permeability of the BBB to water is related to AD markers in cerebrospinal fluid (CSF) [90]. The breakdown of the BBB begins in the hippocampus and could lead to cognitive impairment [91]. Brain capillary damage was found in older adults with early cognitive impairment and was associated with parietal cell damage and disruption of the BBB in the hippocampus [76].

These studies provide evidence that the human GM influence the development of the immune system through primary immune cells. Brain microglial activation, neuroinflammation, neuronal apoptosis and Aβ deposition are more severe in older individuals [92]. Dysfunction caused by increased BBB permeability also increases inflammation. GM disorders lead to a diseased state and promote systemic inflammation.

3. Metabolites of the GM in the CNS

The two-way communication between the CNS and GM plays a vital role in human health. There is growing evidence that a variety of metabolites secreted by the GM affect the human brain and behavior, and can even affect the cognitive performance of patients with neurodegenerative diseases [93]. Metabolites such as LPS and SCFAs have the ability to regulate hormone release produced by the GM and can therefore influence cerebral function [94].

3.1 LPS

Endotoxins can cause or contribute to neurodegenerative changes. Neurodegenerative diseases can be triggered by the interaction of endotoxins with different aggregators, which is related to the promotion of the aggregation of Aβ and tau proteins by endotoxins [95]. Bacteroides, such as Bacteroides fragilis, are the largest phylum of Gram-negative bacteria in the human GM. They have the potential to secrete pro-inflammatory neurotoxins, including surface LPS [17]. LPS, the major glycolipid of the outer membrane in gram-negative bacteria, are a potent and powerful endotoxin that could bind to cell surface receptors and induce the secretion of pro-inflammatory cytokines [96], resulting in systemic inflammation [18]. The immune system's response is highly sensitive to LPS. Sepsis and septic shock can be caused by high concentrations of LPS. Sepsis is a risk factor for cognitive impairment and the development of AD [97]. Therefore, LPS are often used to model neuroinflammation associated with neurodegeneration [98]. The gram-negative facultative anaerobe Bacteroides fragilis secrete pro-inflammatory LPS. Aβ levels in the brain and the permeability of the BBB are increased by LPS in an AD mouse model. The increase of LPS is consistent with findings in AD patients [99]. LPS are present in the cell walls of all gram-negative bacteria and may play a role in the development of AD [100]. LPS can bind to some blood proteins and be transported to different parts of the body. LPS can bind to receptors at the blood-brain interface *via* lipoprotein transport [101]. There is evidence that LPS accumulates gradually in the neuronal parenchyma in AD and appears to preferentially bind to the peripheral nucleus of neurons [102]. Photoelectron microscopy showed that LPS antibody staining and amyloid fibrils might be present in the same location [103]. Compared to age-matched controls, LPS levels were higher in AD patients. LPS and Aβ were co-localized in amyloid plaques and blood vessels in AD patients, suggesting that LPS are associated with AD pathology [22]. Intracellular molecules could be activated by LPS. The expression of a large number of inflammatory mediators was altered by the action of LPS on its receptors. Neurodegenerative processes might be driven by LPS-induced inflammation. Pathological regression of neurodegenerative changes can be induced by activation of cells by stimulating the immune system with low doses of LPS [98].

The loss of connections between synapses could lead to cognitive deficits. During neuroinflammation, synaptic proteins can be altered by co-activated pro-inflammatory markers and associated cytotoxic products. Altered synaptic proteins are harmful to neurons [104]. Peripheral injection of LPS could induce learning and memory impairments in mice, which is attributed to the microglia-induced synapse damage [105]. When hippocampal dysfunction occurs, such as a reduction in the number of contact zones and the size of postsynaptic densities, it results in a decrease in hippocampal-dependent learning and memory performance [106]. LPS could act directly within brain tissue to disrupt synapses in hippocampal slice cultures, which were dependent on microglia and IL1β [107].

3.2 SCFAs

SCFAs are the main metabolite of mammalian intestinal dietary fiber by microbial anaerobic fermentation. They have important physiological functions for the human body, and are sources of energy and act as signaling molecules. SCFAs are absorbed effectively by the intestinal mucosa and recognized by specific receptors [108]. SCFAs are not digested and absorbed in the small intestine [109]. Acetate, propionate, and butyrate are the most abundant SCFAs in humans [56]. Butyrate is produced mainly by the gram-positive anaerobes Roseburia and Faecalibacterium (previously Fusobacterium) [110]. SCFAs affect the function of the peripheral nervous system and CNS in different ways [111]. In radiation-induced cognitive impairment models, hippocampal phosphorylated cAMP-responsive element binding protein and brain-derived neurotrophic factor expression were reduced by butyrate, and cognitive impairment was subsequently improved [112]. The GM that produced select SCFAs could reduce the formation of toxic soluble Aβ aggregates. Lap Ho *et al.* [113] also found that SCFAs interfered with the formation of toxic soluble Aβ aggregates. These results suggest that SCFAs in the gut are likely to protect against the development of AD. In a prospective observational study, the composition of the fecal microbiome in patients with encephalitis was compared with that of healthy controls. They observed GM disruption in encephalitis patients and decreased levels of fecal SCFAs [114].

Butyrate plays an important role in the human gut. It is the primary source of energy for the colonic epithelial cells and maintains the intestinal barrier and regulates intestinal immunity. Haran *et al.* [115] demonstrated that butyrate producing species were decreased and taxa was increased in elderly individuals with AD compared to those without dementia. Sun *et al.* [116] found that cognitive impairment in APPswe/PS1dE9 transgenic mice could be improved by fecal microflora transplantation therapy. The brain deposition of Aβ was also reduced in AD mice. We hypothesized that increasing SCFAs butyrate could improve the process of AD. As a histone deacetylase inhibitor, butyrate can improve memory in AD mice by restoring histone acetylation [117].

Functional amyloid peptides and immunogenic mediators, such as LPS, can be produced by the GM. The physiological processes of the bacterial cell surface are closely related to the amyloid peptide in bacteria. The structure and biophysical properties of this amyloid peptide were similar to those of human pathological amyloid [118]. SCFAs can also influence the CNS by modulating microglia [119]. SCFAs are important metabolites secreted by the human GM. SCFAs levels in feces of AD were lower than normal values.

The presence of SCFAs has a positive effect on reducing the occurrence of AD.

4. GM Affects AD through Neurotransmitters

The microbiota can synthetize the neurotransmitters and neuromodulators. However, it is unknown whether it can produce the neuropeptide-like compounds [120]. Microbiota homeostasis can influence complex neurodegenerative disorders through neurotransmitters [121]. Studies have shown that the GM influences neurotransmitter, synaptic, neurotrophic signaling systems and neurogenesis in GF mice [122]. GM affect the MGB through immune, neuroendocrine and direct nerve mechanisms. The central, peripheral, hormonal and immune systems have bidirectional communications due to the MGB axis. GM alter the activity of neurons by producing neuromodulators and neurotransmitters, as well as amino acid metabolites. Studies have demonstrated that variations in the composition of the GM could result in behavioral abnormalities, but surprisingly, few results were found about direct cause-and-effect relationships between the GM and behavioral abnormalities. Another plausible hypothesis is that the GM can lead to the generation of neurotoxic substances in the brain. Increasing evidence has demonstrated that intestinal dysbiosis may participate in the development of AD [123].

Neurotransmitters transmit signals throughout the brain and regulate some of physiological functions of the brain. The synthesis and release of 5-hydroxytryptamine (5-HT) and γ-aminobutyric acid (GABA) by the GM play an important role in this process [124].

4.1 GABA

GABA is the main inhibitory neurotransmitter. Studies have shown that GABA can be produced by the human GM, such as Lactobacillus and Bifidobacterium [125]. Lactobacillus brevis and Bifidobacterium dentium are the most efficient GABA producers among the strains that have been tested [125]. Both lactobacillus inoculation and lactic acid treatment significantly increase the GABA level in the hippocampus of mice [126]. Commensal Bifidobacterium dentium produces GABA through glutamate decarboxylase catalyzed by the decarboxylation of glutamate [127]. GABA is a non-protein amino acid synthesized by dependent glutamic acid decarboxylase (GAD) through irreversible α-decarboxylation of l-glutamate [128]. The changes of intestinal microbiota are related to the changes of glutamate metabolism in the gastrointestinal tract. *Campylobacter jejuni* can activate glutamate synthesis, and then affect the metabolism of glutamate [129]. Glutamic acid decarboxylation synthesizes GABA, which is stored in synaptic vesicles by vesicular GABA transporters. GABA transaminase is a key substance responsible for eliminating and metabolizing GABA [130].

Studies have shown that GABA is not only present in neurons, but also in astrocytes. GABA in astrocytes can release and activate GABA receptors in neighboring neurons [131]. However, GABA is not present in normal astrocytes. Diseased astrocytes become reactive and produce GABA around amyloid plaques [132]. The mode of GABAergic glial cell delivery is altered in the AD mouse model. The upregulation of GABA released by astrocytes can bind to extra-synaptic associated GABA receptors and strongly inhibit synaptic function, ultimately leading to memory and cognitive impairments in AD [133]. Recent evidence indicates that the primary inhibitory neurotransmitter GABA in the brains of AD patients was different from that of a group of non-AD patients, and was mainly distributed in the frontal, parietal, temporal cortex and hippocampus regions [134]. High GABA levels of reactive astrocytes in the dentate gyrus were associated with the development of AD in mouse models (5xFAD), and increased the incidence of tension suppression and memory deficits [135]. Early neuropathological changes from AD were mostly confined to the loss of excitatory glutamatergic pyramidal neurons and synaptic connections in the hippocampus and temporal cortex. The balance between excitatory and inhibitory signals was important for normal cognitive function and memory formation within the hippocampus and cortex, and was needed to be carefully maintained [136]. Part of the risk of cognitive and memory loss came from loss of excitatory glutamate pyramidal neurons and synaptic connections. The GABA levels of CSF decreased significantly, and synaptic loss correlated with memory loss in AD patients [137]. Both GABA and 5-HT can be synthesized and released by the GM. These molecules have important physiological roles in the brain. They act as neurotransmitters or precursors of neurotransmitters and control neuron activity [124]. Glutamate, acting at N-methyl-d-aspartate receptors primarily in peri-synaptic astrocytes, can impair function in AD. The downregulation of vesicular glutamate transporters is related to the abnormal APP expression in AD patients. Glutamate uptake/recycling mechanisms are disrupted by toxic Aβ, and therefore glutamate availability increased. AD-associated excitotoxicity and neurodegeneration might be caused by the increased supply of glutamate. Hippocampal GABA/glutamate ratios are regulated by the human GM [129]. As to why abnormal production and aggregation of Aβ could lead to cognitive dysfunction in AD patients and mice, it may be because the function of GABA inhibitory interneurons was affected, causing abnormalities in the transmission of signals between neurons [138]. These studies strongly suggest that human GM have an important role in AD.

4.2 5-HT

The human GM can determine the production of 5-HT through its metabolites. Entero-endocrine cells are found throughout the intestinal mucosal epithelium. They are specialized hormone-secreting cells, consisting of an array of

different cell types that receive stimulation from the luminal and the basolateral surfaces and secrete a combination of more than 20 hormones [139]. Chemical messengers involved in messaging, such as 5-HT, and serotonin, interact with the GM [140]. The rate-limiting enzyme tryptophan hydroxylase 1 (TPH1) found in entero-chromaffin cells of the gut produces more than 90% of the 5-HT in humans [141]. Studies in GF mice have shown that GM is necessary for the development of the central serotonergic system [142]. SCFAs enhance the expression of the enzyme TPH1 mRNA by interacting with EC cells. EC cells use TPH1 to synthesize 5-HT [143]. In human EC cell models, butyrate enhanced Tph1 transcription in mice by inducing ZBP-89, a zinc finger transcription factor [141]. Tryptophan is a central precursor in the synthesis of 5-HT. Tryptophan is produced by the GM. The peripheral tryptophan is able to cross the BBB, where it is involved in 5-HT synthesis [144]. It was found that gut Firmicutes Clostridium sporogenes could decarboxylate tryptophan to tryptamine. Tryptamine enhances the inhibitory response of cells to serotonin [145]. Kynurenine and its metabolites are an important pathway in tryptophan metabolism. Indoleamine 2,3-dioxygenase is a rate-limiting enzyme responsible for the initiation of the Kyn metabolic pathway [146]. L. plantarum treatment can increase 5-HT in the human gut [147]. GM play a key role in enhancing colon and serum 5-HT levels by inducing and reversibly promoting 5-HT in colonic entero-chromaffin cells. Gastrointestinal motility and platelet function are significantly affected by the microbiota-dependent effects on 5-HT [148].

5-HT can affect dopaminergic neurons in several ways, which is vital to the ENS [149]. Studies have found that the occurrence of AD in humans could be delayed and alleviated by most selective serotonin reuptake inhibitors [150]. Serotonin content significantly decreased in the temporal and frontal cortex and was altered in the CSF [151]. A connection between 5-HT and AD showed that citalopram acted as a selective serotonin reuptake inhibitor (SSRI) that increased serotonin levels in AD neurons. Citalopram-treated APP mice exhibited improved cognitive behavior [152].

Memory retention and the ability to learn depend on the serotonergic system. 5-HT-related receptors, such as 5-HT1, 5-HT4, 5-HT6 and 5-HT7 receptor classes, have unique abilities to enhance cognition [150]. In patients with severe AD, the density of the 5-HT2A receptors in the brain was lower than that in the control group, specifically in the frontal and temporal cortex. Despite the effects of choline acetyltransferase activity and the presence of behavioral symptoms, there was an association between the loss of the 5-HT2A receptor and cognitive decline [153]. Burke *et al*. [154] reinforced the relationship between depression, APOE ϵ4, and the development of AD. An emerging theory is that the use of antidepressants, usually SSRIs, such as tetracyclic serotonin antagonists, might reduce the deleterious effects of AD [154]. Aβ levels in mouse interstitial fluid could be reduced by administration of several SSRI antidepressants and by direct injection of 5-HT into the hippocampus [155].

In addition to AD, there is a strong association between the gut-brain axis and neurodegenerative diseases, such as PD and HD.

5. The Association between Parkinson's Disease (PD) and the GM

PD is the second most common neurodegenerative disease. It is estimated that the prevalence of PD will reach nearly 1,238,000 cases by 2030 in the United States alone [156]. PD is characterized by the absence of dopaminergic neurons in the substantia nigra and the presence of misfolded alpha-synaptic nucleoproteins (Lewy bodies) [157]. Motor symptoms of PD include tremor, tetanus, bradykinesia, and postural abnormalities [158]. The gut microbiome interacts with the autonomic and CNS through a variety of pathways including ENS and the vagus nerve [159]. The metabolites of the GM may induce intestinal inflammation and even PD [160]. One study demonstrated that motor function was impaired in mice treated with the SCFA mixture [161]. Fecal SCFAs concentrations were significantly reduced in PD patients [162], and Bifidobacteriaceae, Christensenellaceae, Tissierellaceae, Lachnospiraceae, Lactobacillaceae, Pasteurellaceae and Verrucomicrobiaceae families were all significantly decreased [163]. Intestinal microbiota can exacerbate motor deficits in Parkinson disease (PD) [164]. GM are also related to the Linchuan phenotype of PD. Compared to healthy controls, the prevalence of the Prevotellaceae bacteria family in PD decreased. Compared to patients with tremor-dominant PD, patients with postural instability and gait difficulty phenotypes had a higher abundance of the Enterobacteriaceae family of bacteria [165]. However, several studies demonstrated that dietary intake of polyphenols might inhibit neurodegeneration and PD progression [166].

6. The Association between Huntington's Disease (HD) and the GM

HD is an inherited neurodegenerative disorder that can cause progressive movement disorders, psychiatric symptoms, and cognitive impairment. In most cases, it occurs in mid-adulthood [167]. The atrophy of the striatum and cerebral cortex is the main cause of motor symptoms of HD. HD is caused by expansion of CAG repeats in the Huntingtin gene. Intestinal flora can affect the occurrence of HD. HD patients develop intestinal disorders [168]. Changes in the composition of the GM were observed in men with HD. In addition, plasma acetate levels were elevated in male Huntington's mice in the early and late stages of the disease [169]. In the R6/2 mouse model of HD, the relative abundance of Bacteroidetes increased and that of Firmicutes decreased. In addition, R6/2 mice showed increased intestinal

permeability [170]. The 16S V3-V4 rRNA sequencing results of fecal samples were used to express the intestinal microbiome. The HD gene expansion carrier groups significantly reduced the intestinal microbiome richness. In obvious HD gene expansion carriers, low abundance of E. hallii was strongly associated with the severity of motor symptoms and the proximity time of disease onset [171]. A comparison of longitudinal fecal microbiome data from early 4 weeks to 12 weeks of wild-type and HD mice confirmed the presence of intestinal ecological disorders in HD mice. Reductions in plasma concentrations of propionate and butyrate were also observed in HD mice, but were not significant [172].

With more and more research, we found that the GM may be a new breakthrough in the treatment or prevention of AD. The positive intervention effect of probiotics and prebiotics on AD has been gradually discovered.

7. Probiotics and prebiotics in AD

Probiotics and prebiotics can regulate neuroinflammation and improve cognitive function *via* the brain-gut axis [12]. Accumulating clinical evidence suggests that the therapeutic potential of probiotics in AD is generated through a variety of mechanisms [173]. One study found improved cognitive function in AD patients treated with probiotics [174]. Probiotic-4 (a probiotic preparation) significantly improved memory deficits in the brains of older senescence-accelerated prone 8 (SAMP8) mice and significantly reduced intestinal barrier damage and inflammation in older SAMP8 mice [175]. SLAB51 (a novel formulation of lactic acid bacteria and bifidobacteria) was treated in 3xTg-AD mice at the early stages of AD. This study demonstrated the beneficial effect of probiotics in AD subjects. Probiotics could improve the loss of middle brain weight and the reduction of cortical areas in AD mice [176]. This study demonstrated that the nonviable Bifidobacterium breve strain A1 and acetate could partially improve the behavioral defect of AD model mice [177]. Tryptophan-related dipeptides can prevent cognitive decline, inhibit the inflammatory response of microglia and enhance the phagocytosis of Aβ in AD mice [178].

Prebiotic is the name given to substrates selectively used by host microorganisms to confer health benefits. Several different food components are considered to be prebiotics, including resistant starch (RS), insulin, fructooligosaccharides (FOS), galactooligosaccharides, and xylo-oligosaccharides [179]. FOS have been found to improve memory in AD animals. FOS not only improve oxidative stress and inflammatory disorders, but also regulate the synthesis and secretion of neurotransmitters [26].

8. Discussion

This review describes the importance of bidirectional communication between the gut and brain for AD. There is increasing evidence that the GM have an important role in the pathogenesis of nervous system diseases. The human gut has a complex bacterial composition. Changes in the species and number of the GM have a huge impact on the brain through the MGB axis, leading to neuroinflammation and neurodegeneration through different pathways, and even promoting the possibility of AD. The MGB axis is the bridge between the human gut and the brain, involving neural, endocrine, and inflammatory mechanisms. The immune system, brain development and behavior are influenced by the GM. Their metabolites and neurotransmitters have different effects on the body. These studies suggest that gut dysbiosis may be related to Aβ deposition and neuroinflammation.

Inflammatory infections have the potential to act as the triggers for neurodegenerative processes, primarily by disrupting the function of the immune system, causing excessive synthesis and accumulation of Aβ resulting in chronic inflammation in the brain. The occurrence and development of local and systemic inflammation in the human body are closely related to disorders of the GM. Under the influence of the GM, the permeability of the BBB increases, and different bacteria, viruses and their neuroactive products are more likely to invade the brain, resulting in neuro-inflammatory reactions. The metabolites and neurotransmitters that the GM produced can modulate important processes, including microglia maturation and activation, nerve inflammation and the BBB permeability. Microglia activated by inflammation have a greater chance of turning astrocytes into reactive astrocytes. Proinflammatory cytokines can be secreted by the microglia and astrocytes, and the persistent deposition of Aβ, further contributes to neurodegeneration. LPS, produced in the GM, are also associated with inflammation. SCFAs levels in feces are decreased in AD patients. SCFAs can interfere with the formation of Aβ polymers. GM are closely related to neurotransmitter biosynthesis in the brain. Changes in the composition of the GM affect the biosynthesis and metabolism of neurotransmitters or their precursors. GM and its metabolites are implicated in impaired memory and learning as well as dysfunctional signaling by GABA. 5-HT can affect the development and survival of brain neurons and reduce Aβ levels. While several studies have demonstrated a link between the GM and AD, the exact mechanism remains unclear.

Author Contributions

J-TY, X-YY and X-GW planned and conducted the review. J-TY, X-WX and C-YJ collected the data and drafted the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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