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The Role of Gut Microbiota in the Mechanism of Cognitive Impairment in the Elderly

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Abstract

With the aging in whole world, it has become a great challenge to explore the relationship between the cognitive and behavioral performance of senile dementia and the underlying pathology of the brain. Alzheimer's disease (AD) is a common age-related and progressive neurodegenerative disease characterized and one of the main causes of senile dementia. The pathogenesis and treatment mechanism of AD are not completely clear. In recent years, it has been found that the Gut microbiota (GM) disorder is related to nervous system diseases. The objective of this review is to summarize the etiology and pathogenyon the role of GM in the development of AD, metabolites of GM and the occurrence of AD, and GM, diabetes and occurrence of AD. Understanding the relationship between GM and AD will help provide possible interventions to improve the structure of GM and prevent AD through different treatments, and it may provide clinicians with a new and more effective way for early diagnosis, prevention and treatment of AD.

Keywords

Alzheimer's Disease, Cognitive Impairment, Gut Microbiota, Gut Microbiota-Brain Axis

1. Introduction

With the aging in whole world, it has become a great challenge to explore the relationship between the cognitive and behavioral performance of senile dementia and the underlying pathology of the brain. Alzheimer's disease (AD) is a worldwide neurodegenerative disease and one of the main causes of senile dementia, accounting for 50% to 70% of all senile dementia cases. Although the onset of AD is slow, the disease will worsen progressively, from initial short-term memory loss to behavioral problems such as language disorder and orientation

disorder, and gradually lose body function, resulting in death [1].

AD is related to neuronal injury and progressive synaptic dysfunction. Whether there is deposition of extracellular amyloid β (Aβ) and hyperphosphorylation of intracellular Tau protein which lead to neurofibrillary tangles is the pathological diagnostic criteria of the disease [2]. Amyloid precursor protein (APP) is a highly expressed normal transmembrane protein of neurons. In the process of cell metabolism, β and γ secretase cleavage into Aβ, Aβ aggregates outside the cell to form oligomers and fibers, and finally forms plaques [3]. Tau protein is a kind of intracellular microtubule binding protein. Hyperphosphorylation will cause the disintegration of microtubules and lead to axonal transport disorders [4]. The exact cause of AD is not clear, so far there is no effective cure for AD.

The human gut is an anaerobic bioreactor with a diverse population of microorganisms, including bacteria, yeast, archaea, viruses, protozoa, and parasites such as helminths, collectively known as microbiota, which occupy different niches of the mucosal surfaces in the gastrointestinal (GI) tract [5] [6]. The gut microbiota (GM) is numerous and rich in species, which have more than 10 000 species with a number of 10^{14} colonized in the intestinal tract of an adult. The GM is mainly composed of Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria [7], and other 2% microorganisms include Cyanobacteria, Fusobacteria, some fungi and viruses [4]. In general, these microorganisms are in dynamic equilibrium and maintain a mutually beneficial symbiotic relationship with the host. GM can degrade foods that are usually not digested, promote the absorption of nutrients, synthesize vitamins, participate in bile acid metabolism, affect lipase activity, thus affect the absorption and distribution of fat, promote the development of the immune system, maintain the normal function of the immune system, and inhibit the proliferation of pathogenic microorganisms [8].

GM is constantly changing. The species and number of GM bacteria are affected by the stage of human development, health status and food, resulting in flora dysbiosis. In the elderly, the diversity of bacteria decreased, and although Firmicutes and Bacteroidetes were still the main flora, but some potential pathogenic bacteria (such as Proteobacteria) increased and beneficial bacteria (such as Bifidobacterium) decreased. Flora dysbiosis is associated with a variety of diseases, including gastrointestinal diseases (irritable bowel syndrome, inflammatory bowel disease, etc.), metabolic diseases (obesity, hypertension, hyperlipidemia and diabetes, etc.), liver disease, cancer, chronic fatigue syndrome, behavioral and psychiatric diseases (such as autism and depression) [8]. Recent studies have shown that GM is also related to the onset of AD [4] [7] [9] [10] [11]. The GM of 85% AD patients is abnormal [12]. These diseases are accompanied by changes in GM. The important feature of AD is a decline in memory and cognition. A study has shown that memory disorders in mice were caused by high-fat diets or GM disorders caused by Citrobacter rodentium. The composition of microflora, toxin level and inflammatory response were also different in patients with liver cirrhosis with different cognitive abilities. Alcaligeneceae and

Porphyromonadaceae are positively correlated with the decline of cognitive ability [11]. By changing GM, such as GM transplantation, antibiotics or food, the state of the disease can be improved, and even the purpose of treatment can be achieved [8].

2. GM Participates in the Disease Process of AD

1) The basis of the interaction between GM and central nervous system (CNS): the gut microbiota-brain axis

The between brain and intestinal microflora communicate through the brain-visceral-sympathetic axis (gut microbiota-brain axis). The gut microbiota-brain axis consists of the CNS, neuroendocrine system, immune system, sympathetic nerve, parasympathetic nerve branches, intestinal nervous system and intestinal microflora [13]. There are three main ways of communication between the intestinal tract and the brain: afferent nerve fibers, neuroimmune regulation and the use of neuroendocrine pathways [14]. Intestinal microflora is involved in regulating many functions of the brain, for example, bacteria can regulate the activity of the peripheral nervous system and CNS through a variety of communication methods such as vagus nerve and adrenergic nerve; regulate the activation of the hypothalamic pituitary adrenal (HPA) axis, stimulate the HPA axis to release cortisol, and then control the activation of brain microglia; affect the release of cytokines and the migration of monocytes from the periphery to the brain; and produce neurotransmitters, neuropeptides and hormones etc., which affect the mental health of the host [15].

In addition, brain injury and different psychological states can affect the composition of GM and may induce diseases. For example, brain injury caused by stroke has been proved to change the composition of cecal flora in mice, which is characterized by a significant decrease in Prevodiaceae and an increase in the proportion of Enterococci, which is positively correlated with the severity of brain injury [16]. In patients with acute depression, the proportion of Bacteroides, Proteus and actinomycetes was higher, while the proportion of Firmicutes decreased significantly [17].

2) GM participates in the disease process of AD by affecting the stability of intestinal barrier

The increase of intestinal mucosal permeability is considered to be one of the mechanisms of abnormal gut microbiota—brain axis information transmission. Changes in GM can affect intestinal mucosal permeability and cause systemic and intestinal inflammatory reactions through ectopic bacteria and their metabolites. Lipopolysaccharide (LPS) can not only affect inflammatory response, but also affect intestinal mucosal permeability by affecting the tight junction of intestinal mucosal epithelial cells [18]. Anaerobic bacteria such as Bifidobacterium, Lactobacillus, and Clostridium tenuiformis are the dominant flora in the intestinal tract under physiological conditions, which can regulate the physiological function of the intestinal tract and inhibit the reproduction of pathogenic bacte-

ria. Enterobacter and enterococci are common pathogens in the intestinal tract. In the course of liver cirrhosis, the intestinal mucosal barrier is destroyed, enterobacteria and enterococci begin to multiply in large numbers, and translocate into blood circulation and ascites, participating in the occurrence and development of SBP and hepatic encephalopathy [19]. Under normal circumstances, cytokines cannot pass through the blood-brain barrier, but through the synthesis and release of pro-inflammatory cytokines and interleukin-6 (IL-6), it affects the brain to activate the HPA, thus affecting the nervous system [20].

3) GM participate in the disease process of AD through regulated inflammatory response

Researchers have been studying the possible causes of infections in neurodegenerative diseases for a long time. It has been reported that AD is associated with the infection of herpes simplex virus, spirochetes, chlamydia pneumoniae and fungi [21] [22] [23]. In APP/PS1 double transgenic mice, it was preliminarily observed that compared with the wild type control group, the Allobaculum and Akkermansia decreased, while Rikenellaceae increased [24]. Neuroinflammation is considered to be one of the main causes of pathological changes in neurodegenerative diseases [25]. Proinflammatory cytokines produced in CNS and peripheral nervous system regulate neuronal function and can cause pathological cell death [26]. Microglia cells play an important role in preventing and promoting neurodegenerative diseases, so it is reasonable to speculate that GM may affect these inflammatory diseases that lead to brain aging. The change of GM may promote the process of inflammation, which leads to neuroinflammation of AD. Some bacteria of GM can secrete large amounts of LPS and amyloid proteins, which may be the pathogenesis of AD in aging. The permeability of gastrointestinal epithelial cells and blood-brain barrier increases with age. It has been suggested that LPS and amyloid may directly or indirectly pass through protective physiological barriers such as the damaged gastrointestinal tract or blood-brain barrier, and then trigger cytokines or other small proinflammatory molecules that are normally transported [27] [28]. A recent study [29] reported that lipopolysaccharide from Bacteroides fragilis (BF-LPS) exposed to human major brain cells, and it is a potent inducer of proinflammatory transcription factor NF-kB (p50/p65) complex, which is known to trigger the expression of pathogenic pathways in inflammatory nervous system degeneration. The characteristic of the brain of patients with AD is that BF-LPS can further recognize TLR2, TLR4, CD14 microglial receptors and Aβ42. In addition, many intestinal bacteria also produce large amounts of amyloid protein, including Bacillus coli, Bacillus subtilis, Salmonella typhimurium, Salmonella entericus, Mycobacterium tuberculosis, and Staphylococcus aureus. Folding into Aβ through abnormal protein accumulation contributes to the pathological changes of AD [30]. It is speculated that functional amyloid produced by intestinal bacteria may be the source of protein misfolding in neurons and initiate innate immunity and activate neuroinflammation through cross-seeding [31].

4) GM affects AD through neurotransmitters

At present, many studies have shown that GM has changed in patients with AD, which may be involved in the pathogenesis of AD. Through the 16srRNA sequencing of 43 AD patients, it was found that at the classification level, the bacterial groups of AD patients were different from those of the control group, such as Bacteroides, actinomycetes, rumen cocci, spirochetes, selenomonas and so on, were significantly increased in AD patients. In addition, many bacteria can synthesize and release many neurotransmitters and neuroregulators themselves, and intestinal endocrine cells can secrete neuropeptides. All these suggest that intestinal microflora may be involved in the pathological development of AD [32] [33] [34]. Gram-positive bacteria such as Lactobacillus and Bifidobacterium can produce γ-aminobutyric (GABA) in the intestinal tract. GABA is an important inhibitory neurotransmitter in the human CNS [35]. The concentration of GABA in the nervous system is related to the concentration of GABA in the intestinal tract. If the number of Gram-positive bacteria such as Lactobacillus and Bifidobacterium in the intestinal tract decreases, the GABA in the intestinal tract will decrease, which will lead to a decrease in the level of GABA in CNS. However, GABA mediates neuroregulation and transmission of neurotransmitters, and if its level decreases, the dysfunction of the system can lead to cognitive disorders, such as AD. By autopsy comparison with individuals without AD, the levels of GABA in frontal lobe, temporal lobe and parietal lobe cortex of AD patients were decreased [36]. Serotonin (5-HT) plays an important role in the regulation of cognitive function. Selective 5-HT reuptake inhibitors can reduce the synthesis of Aβ in the brain, so increasing the level of extracellular level of 5-HT can reduce the formation of senile plaques, thereby reducing the risk of AD [37]. Candida albicans, Streptococcus and Escherichia coli synthesize more than 95% of the 5-HT in the intestine, while the blood 5-HT level of aseptic mice is about 60% lower than that of non-pathogenic mice with normal GM, but an increase in 5-HT concentration can be detected after GM reconstruction of aseptic mice [38]. Glutamate is an important excitatory neurotransmitter in human CNS. N-methyl-D-aspartate (NMDA) glutamate receptor plays an important role in normal learning and memory of the brain [39]. Through the observation and study of aseptic mice and mice fed with antibiotics, it was found that there was a correlation between NMDA receptor and GM, and the expression of NMDA mRNA and NMDA receptor level in the hippocampus of aseptic mice and mice given antibiotics decreased significantly [40].

In addition, the decrease of intestinal Lactobacillus will lead to a corresponding decrease in the level of acetylcholine (Ach) [41], and the decrease of Ach will lead to the dysfunction of cholinergic neurotransmitters in the cortex, which is the basis of cognitive impairment in patients with AD [42]. Brain-derived neurotrophic factor (BDNF), which blocks the accumulation of A β and tau proteins at synapses, was found to decrease in the brain and serum of patients with AD [43], and the expression of BDNF in the hippocampus of aseptic mice was also

lower than that of non-pathogenic mice with normal GM [44]. Increased levels of cyanobacteria in the intestine will produce too many neurotoxins, for example, β-N-Methylalanine-I-Alanine (BMAA) will interfere with the normal physiological activities of NMDA, and long-term exposure to BMAA will cause intracellular neuronal fiber tangles and Aβ deposition, increasing the risk of AD [45]. Clam toxin and Anabaena toxin-α can further cause neurological diseases with age and increase the risk of AD [46].

3. Metabolites of GM and the Occurrence of AD

1) GM affects animal behavior

GM has a great influence on the development of nervous system and animal behavior, for example, the aseptic mice have obvious anxiety symptoms and cognitive decline, but after the implantation of normal GM, the behavior and memory status of these aseptic mice return to the level of normal mice. This change is related to 5-HT receptor 1A and BDNF [4] [11]. BDNF is very important for the development and differentiation of nervous system and human cognitive function [47]. The content decreased in the brain and serum of patients with schizophrenia, anxiety and AD, as well as in aseptic mice. The decrease of BDNF in hippocampus and cerebral cortex caused by abnormal GM is related to progressive cognitive loss [4].

2) Protective and toxic effects of metabolites of GM

A variety of bacteria can produce 5-HT, adrenaline, dopamine, acetylcholine or GABA to play the role of hormone or neurotransmitter-like substances [48]. Lactobacillus, Lactococcus and Bifidobacterium can convert glutamate into GABA, and GABA is a major inhibitory neurotransmitter. The abnormality of its signal pathway is related to anxiety, depression [4] [49] and cognitive impairment including AD [50]. In addition, 3-indole propionic acid is the deamination product of tryptophan. And as a strong antioxidant, it can scavenge free radicals in plasma and cerebrospinal fluid and has preventive and therapeutic effects on AD. Clostridium sporogenes of GM can produce 3-indole propionic acid from tryptophan [48].

However, GM often produces large amounts of brain-toxic metabolites, including D-lactic acid and ammonia [51]. Bacteria that produce D-lactic acid increase in the feces of patients with chronic fatigue syndrome and neurocognitive impairment. Ammonia is usually converted into urea through the urease of bacteria, which is absorbed and detoxified by the liver. In liver cirrhosis, ammonia can enter the blood directly, causing hepatic encephalopathy [51]. The content of neurotoxic BMAA is increased in patients with AD, which is related to cyanobacteria of GM. BMAA can activate NMDA receptor, AMPA receptor and glutamate receptor 5 in motoneurons, which leads to the enhancement of oxidative stress and the decrease of antioxidant components such as glutathione (GSH), and in turn leads to neuronal apoptosis [52]. In addition, BMAA also appears in misfolded proteins, leading to inflammatory neurodegeneration and AD. Saxitox-

in and anatoxin-α produced by other cyanobacteria can increase the toxicity of BMAA [52]. With the increase of age and the decrease of intestinal endothelial barrier, stress, intestinal disease and lack of nutrition will increase the production of BMAA, leading to more serious neurological disorders [4].

3) GM and β-amyloid protein

Amyloid protein is formed by the aggregation of some insoluble protein molecules, which has a β-folding structure and is rich in lipoproteins. Abnormal accumulation and folding of amyloid proteins, especially Aβ_{42} and Aβ_{40}, bind to TLR2 receptors on the surface of microglia, activate cells, release inflammatory factors, and produce neuroinflammation, and in turn leads to AD. Some bacteria and fungi of GM produce large amounts of endotoxin, amyloid protein or their degradation. With increasing age, the permeability of intestinal epithelium and blood-brain barrier increases, and they enter the brain through the circulatory system. Fungal amyloid was found in the blood of patients with AD. It has been found that Streptomyces, Bacillus, Pseudomonas, Staphylococcus and Bacillus coli can secrete amyloid proteins. The precursor protein pathogen associated molecular model protein (PAMP) secreted by Bacillus coli is very similar to Aβ_{42} in structure and immunogenicity, and can bind to TLR2, which results in leading to the occurrence of AD [7] [27].

4. GM, Diabetes and Occurrence of AD

GM plays an important role in the glucose and lipid metabolism of the host. When the GM is dysbiosis, the endotoxin produced by bacteria will induce a low level of inflammation, leading to intestinal diseases such as irritable bowel syndrome [50]. Furthermore, Low-level inflammatory response is one of the causes of diabetes mellitus type2 (T2DM), hypertension, hyperlipidemia and cardiovascular disease, while T2DM or insulin resistance increases the risk of AD.

1) Short-chain fatty acids and inflammatory reaction

GM can degrade undigested plant polysaccharides into short-chain fatty acids (SCFA), which can be further oxidized and provide energy for the host, and the resulting SCFA can provide up to 10% to 15% energy. At the same time, SCFA also has a regulatory effect, affects cell proliferation and differentiation, and stimulates the secretion of hormones [8] [53]. SCFA has a protective effect on the intestinal barrier. When the number of bacteria producing SCFA decreases, the integrity of intestinal endothelium is impaired and inflammation is prone to occur [51] [53]. In diabetic patients, the bacteria that can ferment dietary fiber and produce SCFA decrease, while the content of TNF-α, IL-6, IL-8 and C-reactive protein in blood increases [51]. This increase is also related to endotoxins produced by bacteria. When Bifidobacterium bacteria reduce or eat a high-calorie diet for a long time, bacterial endotoxin can increase the permeability of intestinal mucosal barrier and cause inflammation [11] [53] [54].

2) AD is associated with insulin resistance and diabetes

When GM is maladjusted, the activity of lipoprotein lipase is enhanced, which

promotes the production of fat and the synthesis of triglycerides in the liver, and increases the energy intake from food, which leads to obesity and diabetes or insulin resistance [55]. The incidence of AD is higher in obese elderly, but AD can occur when people have a normal weight. After being fed a high-fat diet, the mice became obese and their GM changed. And after these altered GM were transplanted into normal mice, the normal mice without obesity appeared endotoxemia, neuroinflammation and cerebrovascular disorders, and cognitive and stereoscopic behavior also became abnormal. It is suggested that neurological symptoms can be weakened by changing GM, and GM can also cause behavioral and neurological disorders without obesity [56].

AD and T2DM have similarity and correlation. Insulin resistance is not only the cause of T2DM, but also an important risk factor of AD [57]. Patients with AD have symptoms of insulin resistance regardless of whether their blood glucose level is normal or not. Insulin resistance can promote the accumulation of amyloid protein, while the increase of amyloid protein is accompanied by the decrease of cognitive ability and the activation of GSK-3β in insulin signal transduction pathway [57]. The degree of insulin resistance in patients with AD is related to the decrease of their cognitive function, so AD can also be regarded as the result of insulin resistance occurring in the brain [53] [55].

Patients with diabetes are more likely to develop AD, especially in middle-aged patients with diabetes and in the elderly with borderline diabetes or impaired glucose tolerance [11]. Up to 80% of AD patients suffer from diabetes or glucose metabolism disorders [55]. Patients with diabetes often show low executive ability, information processing ability and visual memory function [58]. On the one hand, diabetes damages cerebral vascular function, affects insulin signal transduction and mitochondrial function in the brain, on the other hand, it changes the metabolism of amyloid protein and leads to more pathological changes [58] [59]. Coupled with the fact that AD, like T2DM, is associated with GM and inflammation, AD is considered to be type 3 diabetes [53] [55].

5. Intervention of AD by Regulating GM with Different Treatment Methods

1) Intervention of AD by transplanting fecal flora to regulate GM

In infancy, GM begins to colonize, and babies are exposed to maternal flora during delivery, which is very important in early life. GM affects brain function and is beneficial to the development of gastrointestinal tract and brain, and trains the body's immune system. Fecal microflora transplantation refers to the transfer of fecal microflora samples from healthy donors to AD patients or animals with AD. This method is a treatment to reconstruct healthy intestinal flora to improve neurological defects. It was found that the mice transplanted with fecal flora of AD patients showed significant cognitive impairment in object localization tests and object recognition tasks [60]. In addition, essential metabolites of the nervous system decreased, including γ-aminobutyric acid, taurine and valine

[60]. On the contrary, frequent transplantation of fecal flora from normal mice into mice with AD-like pathology with amyloid and neurofibrillary tangles ($ADLP^{APT}$) improved the formation of Aβ and neurofibrillary tangles (NFTs) and cognitive impairment in $ADLP^{APT}$ mice [61]. A study has shown that fecal flora transplantation between animals can transfer behavioral characteristics to each other [62]. Other studies have found that fecal flora transplantation reduces the abundance of Proteus and Ackerman in AD mice, and increases the abundance of Bacteroides [63]. Proteus is closely related to inflammation, and Bacteroides can promote the production of SCFA. As an important medium of intestinal-brain axis, SCFA has a protective effect on the nervous system [63]. SCFA has been shown to inhibit the aggregation of Aβ *in vitro* [64]. In addition, there is a positive correlation between Ackerman and hippocampal atrophy [65]. These bacteria can regulate the pathological changes of AD. Fecal flora transplantation is an effective measure to interfere with GM at present. It can be expected that transplanting fecal flora from healthy people into patients with AD to reduce the abundance of harmful flora and increase the abundance of beneficial flora is a potential strategy for the treatment of AD.

2) Intervention of AD by ingesting probiotics and prebiotics to regulate GM

Prebiotic refers to some organic substances which are not digested and absorbed by the host but can selectively promote the metabolism and proliferation of beneficial bacteria in the body, thus improving the health status of the host. Edible prebiotics contain dietary fiber that promotes the growth of intestinal flora, which is beneficial to the health of the host. Mice treated with the mixture of probiotics and prebiotics had higher levels of gastrointestinal hormones such as ghrelin, leptin, glucagon-like peptide-1 (GLP1) and insulin-stimulating peptide in plasma, among which ghrelin could counteract the memory impairment and synaptic degeneration of AD [66]. Leptin is a neurotrophic factor that exerts neuroprotective effects against Aβ oligomer-induced toxicity *in vitro* [67]. GLP1 participates in improving the cognitive activity of AD and the plasticity of hippocampal nerves, reducing the formation of Aβ [68]. Yang *et al.* [69] found that probiotic-4 (a probiotic preparation composed of multiple species of bacteria) could regulate the imbalance of intestinal flora and reduce the abundance of Proteus and Pseudomonas in aged SAMP8 mice for 12 weeks, thus improving memory impairment, brain neurons and synaptic damage. The mechanism is related to the inhibition of nuclear factor kappa B signal pathway mediated by Toll-like receptor 4 and retinoic acid inducible gene I. In addition, probiotic-4 also improves memory impairment associated with aging by inhibiting oxidative stress and neuroinflammation in the brain. The probiotic Bifidobacterium isolated from human GM can change the composition of GM in mice, especially the proportion of protein bacteria, reduce the level of LPS in feces and blood, inhibit the expression of Aβ in hippocampus, and slow down the rate of cognitive decline [70]. Chen *et al.* [71] have confirmed that probiotics rich in R13 (a prodrug of 7,8-Dihydroxyflavonoid) can reduce intestinal leakage and oxidative stress

in 5xFAD mice, and reduce the abundance of inflammatory protein bacteria, especially Helicobacter in the intestines of mice. R13 is used as a tropomyosin receptor kinase B (TrkB) agonist, and the mechanism of its treatment of AD lies in the direct activation of TrkB, up-regulation of brain-derived neurotrophic factor in CNS, and inhibition of intestinal CCAAT/enhancer binding protein β/asparagine endopeptidase signal transduction pathway. Probiotics and prebiotics show potential effects in delaying the progression of AD, and have less adverse reactions, and have a synergistic effect on re-colonization and restoration of GM when used with clinical drugs.

3) Intervention of AD by regulating GM with different dietary structure

Dietary structure plays a key role in regulating the composition of the GM. Depending on the dietary intake, the composition of the GM also changes in specific ways. Specific food and dietary patterns can affect the composition and abundance of different types of bacteria in the intestine, so as to maintain the balance of intestinal flora in the host. Long-term intake of high-fat diet leads to the imbalance of GM, induces inflammation, causes excessive activation of glial cells [72], and induces the secretion of inflammatory factors such as IL-1β, IL-6 and tumor necrosis factor-α. Inflammatory response mediated by these inflammatory factors can lead to Aβ and NFTs aggregation and accelerate the progress of AD [73]. The Mediterranean diet, which is mainly composed of fruits and vegetables, olive oil, legumes, red meat and wine, is rich in polyphenols and unsaturated fatty acids, which can restore the homeostasis of GM, reduce Aβ aggregation and contribute to the development of cognitive health [74] [75]. Dairy products fermented from fresh milk in Qinghai Tibetan area produce Lactobacillus, peptides and fatty acids in the production process, which plays a positive role in the prevention of dementia or cognitive impairment [76]. A study has shown that Tibetan fermented milk can reduce the abundance of mucus spirochetes in the intestinal tract of APP/PS1 mice, while mucus spirochetes are negatively correlated with cognitive function [77]. Long-term intake of Tibetan fermented milk can improve cognitive function, enrich the species of intestinal flora, reduce the level of Aβ in the brain, and delay the progress of AD [77]. Ketogenic diet can increase the abundance of intestinal beneficial flora (mucophil Ekman and Lactobacillus), reduce the abundance of intestinal proinflammatory flora (Desulphurization vibrio and Bacillus Zurich), and increase cerebral blood flow and p-glycoprotein transport on the blood-brain barrier to promote the clearance of Aβ [64] [78]. A healthy and nutritionally balanced diet is considered to have neuroprotective properties. Improper lifestyle and unbalanced diet are key exogenous factors in the development of AD. Diet as a non-drug therapy may become an effective way to prevent or delay the progress of AD.

4) Intervention of AD by intake of oligosaccharides to regulate GM

There is growing evidence that oligosaccharides can regulate the composition of GM. Sun *et al.* [79] studied the effects of fructooligosaccharides (FOS) on the AD of APP/PS1 mice. It was found that 6-week treatment with FOS could reverse the changes of GM, increase the abundance of Lactobacillus in the intes-

tines, reduce the abundance of Proteus, Helicobacter pylori and Vibrio desulfuriaceae, alleviate cognitive impairment, reduce Aβ deposition and improve neuropathological changes. Lactobacillus can reduce the production of Aβ by acting on GLP1, and improve the cognitive impairment of mice. Liu *et al.* [80] found that Mannose oligosaccharide can reshape GM and enhance the formation of neuroprotective metabolite SCFAs, reduce the aggregation of Aβ in the brain of 5xFAD transgenic AD mice, and alleviate the cognitive and behavioral impairment of AD mice. GV-971, a sodium mannan oligosaccharide extracted from algae, has been shown to improve cognition in a phase III clinical trial [81]. It can change the composition of intestinal flora, reduce the concentration of phenylalanine and isoleucine in feces and blood, and reduce Th1-related neuroinflammation in brain tissue, thus significantly reduce the activation of microglia and the levels of various proinflammatory cytokines, reverse cognitive impairment and inhibit the progression of AD [81]. The oligosaccharide component CA-30 extracted from Liuwei Dihuang decoction has been shown to regulate GM, rebalance GM-neuroendocrine immune regulatory network, and improve cognitive degradation in SAMP8 mice [82]. The above studies suggest that oligosaccharides can be used as a target to delay the progress of AD.

5) Intervention of AD through modulation of GM by compounds in plants

Some compounds from plants with anti-AD activity can regulate the composition of GM. It has been found that, in APP/PS1 mice, silymarin and its main active component silybin can change the composition of GM, alleviate memory impairment, reduce Aβ deposition in the brain, and delay the progress of AD [83]. Sun *et al.* [84] found that curcumin, a natural polyphenol isolated from turmeric, can reduce the deposition of Aβ in the hippocampus of mice and resist the progress of AD by regulating the composition of GM. In addition, ginsenoside Rg1 from plants can improve AD by changing the abundance of GM and reducing the production of tau protein [85]. These results suggest that substances derived from plant components may have a protective effect on patients with AD and may be an option for the treatment of AD.

6) Intervention of AD by exercise regulating GM

Exercise training can affect the occurrence of neurodegenerative diseases and can prevent and slow down the progress of AD. A study has shown that regular exercise for the elderly can not only slow down the decline of cognitive function, but also improve the level of Aβ protein and reduce the incidence of disease [86]. Exercise is called the regulator of GM, which promotes the health of the body by improving the richness of GM, increasing the abundance of beneficial microflora, and maintaining the balance of GM. Exercise can increase the diversity of GM and regulate the balance between beneficial flora and pathogenic bacteria. Recent evidence has shown that exercise can improve the cognitive function and histological markers of AD, reduce the level of GM that worsen the disease, and increase the abundance of SCAFs-producing flora [87]. In addition, Abraham *et al.* [88] found that running in APP/PS1 transgenic mice for 20 weeks could increase the abundance of Clostridium in the intestines of AD mice. Clostridium

could promote the production of butyrate, which as a component of SCFAs, could inhibit the formation of Aβ. The above studies suggest that the combination of exercise and medication is also a potential strategy for AD treatment.

7) Intervention of AD by regulating GM by circadian rhythm

Circadian rhythm refers to the regular cycle established by various physiological functions of organisms to adapt to the diurnal changes of the external environment, and circadian rhythm disorder may be one of the causes of AD. A study showed that the deposition of amyloid plaques composed of Aβ in the hippocampus of mice with circadian rhythm disorder accelerated the progress of AD [89]. Circadian rhythm can regulate the composition of GM, and the disorder of circadian rhythm can lead to intestinal barrier dysfunction and increase the abundance of Enterococci, but reduce the abundance of Lactobacillus yoelii [90]. In addition, circadian rhythm disorders can change the normal GM structure of the host, affect the metabolism of neurotransmitters, and lead to the occurrence of neurodegenerative diseases, which is consistent with the changes of GM structure in patients with AD [91]. Sleep interruption can promote the development of AD, and lack of sleep can induce Aβ aggregation in the brain of healthy individuals [92]. Therefore, regulating circadian rhythm is also an important factor in interfering with the progression of AD.

6. Conclusions

The healthy gastrointestinal tract which is in steady state in the body has normal and stable GM, which can provide nutrition and energy for the normal life of the body. GM affects human health and diseases, and regulates brain-gut interactions through the gut microbiota-brain axis. The onset of neurodegenerative diseases is closely related to GM and neuroinflammation, but the specific mechanism is not clear. GM can produce amino acids as a component of neurotransmitters that affect the activity of neurons in CNS. In addition, amyloid deposition, neurofibrillary tangles, GM and neuroinflammation have all been confirmed to play an important role in the pathogenesis of AD. At present, we can diagnose AD by imaging markers of brain structure and function, while in the future, we may combine the imaging findings of neuroinflammation and inflammatory markers for early diagnosis of AD, so as to facilitate timely intervention guidance for AD patients. It is also possible to find new methods for the treatment of patients with AD based on the changes of neuroinflammation and GM associated with AD, such as non-steroidal anti-inflammatory drugs used to treat neuritis and probiotics that improve intestinal microorganisms.

In general, GM may lead to AD through the combination of amyloid deposition, neurofibrillary tangles and neuroinflammation. In order to study the relationship between GM and AD, it is necessary to develop new methods to assist the clinical diagnosis of AD. Based on GM, it may provide clinicians with a new and more effective way for early diagnosis, prevention and treatment of AD. However, more evidences are needed to confirm these hypotheses. We also look

forward to using this as a breakthrough to bring hope to AD patients and their families.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Xu, R. and Wang, Q. (2016) Towards Understanding Brain-Gut-Microbiome Connections in Alzheimer's Disease. *BMC Systems Biology*, **10**, Article No. 63. https://doi.org/10.1186/s12918-016-0307-y

[2] Tremlett, H., Bauer, K.C., Appel-Cresswell, S., Finlay, B.B. and Waubant, E. (2017) The Gut Microbiome in Human Neurological Disease: A Review. *Annals of Neurology*, **81**, 369-382. https://doi.org/10.1002/ana.24901

[3] Hu, X., Wang, T. and Jin, F. (2016) Alzheimer's Disease and Gut Microbiota. *S cience China*: *Life sciences*, **59**, 1006-1023. https://doi.org/10.1007/s11427-016-5083-9

[4] Bhattacharjee, S. and Lukiw, W.J. (2013) Alzheimer's Disease and the Microbiome. *Frontiers in Cellular Neuroscience*, **7**, Article 153. https://doi.org/10.3389/fncel.2013.00153

[5] Cryan, J.F., O'Riordan, K.J., Cowan, C., *et al*. (2019) The Microbiota-Gut-Brain Axis. *Physiological Reviews*, **99**, 1877-2013. https://doi.org/10.1152/physrev.00018.2018

[6] Sonnenburg, J.L. and Sonnenburg, E.D. (2019) Vulnerability of the Industrialized Microbiota. *Science*, **366**, eaaw9255. https://doi.org/10.1126/science.aaw9255

[7] Hill, J.M. and Lukiw, W.J. (2015) Microbial-Generated Amyloids and Alzheimer's Disease (AD). *Frontiers in Aging Neuroscience*, **7**, Article 9. https://doi.org/10.3389/fnagi.2015.00009

[8] Tilg, H., Cani, P.D. and Mayer, E.A. (2016) Gut Microbiome and Liver Diseases. *Gut*, **65**, 2035-2044. https://doi.org/10.1136/gutjnl-2016-312729

[9] Hill, J.M., Clement, C., Pogue, A.I., *et al*. (2014) Pathogenic Microbes, the Microbiome, and Alzheimer's Disease (AD). *Frontiers in Aging Neuroscience*, **6**, Article 127.

[10] Alam, M.Z., Alam, Q., Kamal, M.A., Abuzenadah, A.M. and Haque, A. (2014) A Possible Link of Gut Microbiota Alteration in Type 2 Diabetes and Alzheimer's Disease Pathogenicity: An Update. *CNS & Neurological Disorders-Drug Targets*, **13**, 383-390. https://doi.org/10.2174/18715273113126660151

[11] Caracciolo, B., Xu, W., Collins, S. and Fratiglioni, L. (2014) Cognitive Decline, Dietary Factors and Gut-Brain Interactions. *Mechanisms of Ageing and Development*, **136-137**, 59-69. https://doi.org/10.1016/j.mad.2013.11.011

[12] Xiao, J., Li, S., Sui, Y., *et al*. (2014) *Lactobacillus casei-01* Facilitates the Ameliorative Effects of Proanthocyanidins Extracted from Lotus Seedpod on Learning and Memory Impairment in Scopolamine-Induced Amnesia Mice. *PLOS ONE*, **9**, e112773.

https://doi.org/10.1371/journal.pone.0112773

[13] La Rosa, F., Clerici, M., Ratto, D., *et al*. (2018) The Gut-Brain Axis in Alzheimer's Disease and Omega-3. A Critical Overview of Clinical Trials. *Nutrients*, **10**, Article No. 1267. https://doi.org/10.3390/nu10091267

[14] Westfall, S., Lomis, N., Kahouli, I., *et al*. (2017) Microbiome, Probiotics and Neurodegenerative Diseases: Deciphering the Gut Brain Axis. *Cellular and Molecular Life Sciences*, **74**, 3769-3787. https://doi.org/10.1007/s00018-017-2550-9

[15] Mayer, E.A., Tillisch, K. and Gupta, A. (2015) Gut/Brain Axis and the Microbiota. *Journal of Clinical Investigation*, **125**, 926-938. https://doi.org/10.1172/JCI76304

[16] Ghaisas, S., Maher, J. and Kanthasamy, A. (2016) Gut Microbiome in Health and Disease: Linking the Microbiome-Gut-Brain Axis and Environmental Factors in the Pathogenesis of Systemic and Neurodegenerative Diseases. *Pharmacology & Therapeutics*, **158**, 52-62. https://doi.org/10.1016/j.pharmthera.2015.11.012

[17] Dinan, T.G. and Cryan, J.F. (2016) Mood by Microbe: Towards Clinical Translation. *Genome Medicine*, **8**, Article No. 36. https://doi.org/10.1186/s13073-016-0292-1

[18] Dong, D., Xie, J. and Wang, J. (2019) Neuroprotective Effects of Brain-Gut Peptides: A Potential Therapy for Parkinson's Disease. *Neuroscience Bulletin*, **35**, 1085-1096. https://doi.org/10.1007/s12264-019-00407-3

[19] Wu, H., Chen, L., Sun, Y., Meng, C. and Hou, W. (2016) The Role of Serum Procalcitonin and C-Reactive Protein Levels in Predicting Spontaneous Bacterial Peritonitis in Patients with Advanced Liver Cirrhosis. *Pakistan Journal of Medical Sciences*, **32**, 1484-1488. https://doi.org/10.12669/pjms.326.10995

[20] Rieder, R., Wisniewski, P.J., Alderman, B.L. and Campbell, S.C. (2017) Microbes and Mental Health: A Review. *Brain, Behavior, and Immunity*, **66**, 9-17. https://doi.org/10.1016/j.bbi.2017.01.016

[21] Maheshwari, P. and Eslick, G.D. (2015) Bacterial Infection and Alzheimer's Disease: A Meta-Analysis. *Journal of Alzheimer's Disease*, **43**, 957-966. https://doi.org/10.3233/JAD-140621

[22] Agostini, S., Clerici, M. and Mancuso, R. (2014) How Plausible Is a Link between HSV-1 Infection and Alzheimer's Disease? *Expert Review of Anti-Infective Therapy*, **12**, 275-278. https://doi.org/10.1586/14787210.2014.887442

[23] Alonso, R., Pisa, D., Marina, A.I., *et al*. (2014) Fungal Infection in Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease*, **41**, 301-311. https://doi.org/10.3233/JAD-132681

[24] Harach, T., Marungruang, N., Duthilleul, N., *et al*. (2017) Reduction of Abeta Amyloid Pathology in APPPS1 Transgenic Mice in the Absence of Gut Microbiota. *cientific Reports*, **7**, Article No. 41802. https://doi.org/10.1038/srep41802

[25] Stephenson, J., Nutma, E., van der Valk, P. and Amor, S. (2018) Inflammation in CNS Neurodegenerative Diseases. *Immunology*, **154**, 204-219. https://doi.org/10.1111/imm.12922

[26] McCoy, M.K. and Tansey, M.G. (2008) TNF Signaling Inhibition in the CNS: Implications for Normal Brain Function and Neurodegenerative Disease. *Journal of Neuroinflammation*, **5**, Article No. 45. https://doi.org/10.1186/1742-2094-5-45

[27] Zhao, Y. and Lukiw, W.J. (2015) Microbiome-Generated Amyloid and Potential Impact on Amyloidogenesis in Alzheimer's Disease (AD). *Journal of Nature and Science*, **1**, e138.

[28] Kohler, C.A., Maes, M., Slyepchenko, A., *et al*. (2016) The Gut-Brain Axis, Including the Microbiome, Leaky Gut and Bacterial Translocation: Mechanisms and Pa-

thophysiological Role in Alzheimer's Disease. *Current Pharmaceutical Design*, **22**, 6152-6166. https://doi.org/10.2174/1381612822666160907093807

[29] Lukiw, W.J. (2016) Bacteroides Fragilis Lipopolysaccharide and Inflammatory Signaling in Alzheimer's Disease. *Frontiers in Microbiology*, **7**, Article 1544. https://doi.org/10.3389/fmicb.2016.01544

[30] Pistollato, F., Sumalla, C.S., Elio, I., *et al*. (2016) Role of Gut Microbiota and Nutrients in Amyloid Formation and Pathogenesis of Alzheimer Disease. *Nutrition Reviews*, **74**, 624-634. https://doi.org/10.1093/nutrit/nuw023

[31] Chen, S.G., Stribinskis, V., Rane, M.J., *et al*. (2016) Exposure to the Functional Bacterial Amyloid Protein Curli Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and *Caenorhabditis elegans*. *Scientific Reports*, **6**, Article No. 34477. https://doi.org/10.1038/srep34477

[32] Zhuang, Z.Q., Shen, L.L., Li, W.W., *et al*. (2018) Gut Microbiota Is Altered in Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease*, **63**, 1337-1346. https://doi.org/10.3233/JAD-180176

[33] Wang, X. and Quinn, P.J. (2010) Endotoxins: Lipopolysaccharides of Gram-Negative Bacteria. *Sub-Cellular Biochemistry*, **53**, 3-25. https://doi.org/10.1007/978-90-481-9078-2_1

[34] Fung, T.C., Vuong, H.E., Luna, C., *et al*. (2019) Intestinal Serotonin and Fluoxetine Exposure Modulate Bacterial Colonization in the Gut. *Nature Microbiology*, **4**, 2064-2073. https://doi.org/10.1038/s41564-019-0540-4

[35] Barrett, E., Ross, R.P., O'Toole, P.W., Fitzgerald, G.F. and Stanton, C. (2012) γ-Aminobutyric Acid Production by Culturable Bacteria from the Human Intestine. *Journal of Applied Microbiology*, **113**, 411-417. https://doi.org/10.1111/j.1365-2672.2012.05344.x

[36] Solas, M., Puerta, E. and Ramirez, M.J. (2015) Treatment Options in Alzheimer's Disease: The GABA Story. *Current Pharmaceutical Design*, **21**, 4960-4971. https://doi.org/10.2174/1381612821666150914121149

[37] Cirrito, J.R., Disabato, B.M., Restivo, J.L., *et al*. (2011) Serotonin Signaling Is Associated with Lower Amyloid-Beta Levels and Plaques in Transgenic Mice and Humans. *Proceedings of the National Academy of Sciences*, **108**, 14968-14973. https://doi.org/10.1073/pnas.1107411108

[38] Yano, J.M., Yu, K., Donaldson, G.P., *et al*. (2015) Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. *Cell*, **161**, 264-276. https://doi.org/10.1016/j.cell.2015.02.047

[39] Lakhan, S.E., Caro, M. and Hadzimichalis, N. (2013) NMDA Receptor Activity in Neuropsychiatric Disorders. *Frontiers in Psychiatry*, **4**, Article 52. https://doi.org/10.3389/fpsyt.2013.00052

[40] Neufeld, K.M., Kang, N., Bienenstock, J. and Foster, J.A. (2011) Reduced Anxiety-Like Behavior and Central Neurochemical Change in Germ-Free Mice. *Neurogastroenterology & Motility*, **23**, 255-264. https://doi.org/10.1111/j.1365-2982.2010.01620.x

[41] Lyte, M. (2013) Microbial Endocrinology in the Microbiome-Gut-Brain Axis: How Bacterial Production and Utilization of Neurochemicals Influence Behavior. *PLOS Pathogens*, **9**, e1003726. https://doi.org/10.1371/journal.ppat.1003726

[42] Hampel, H., Mesulam, M.M., Cuello, A.C., *et al*. (2018) The Cholinergic System in the Pathophysiology and Treatment of Alzheimer's Disease. *Brain*, **141**, 1917-1933. https://doi.org/10.1093/brain/awy132

[43] Mizukami, K., Ishikawa, M., Akatsu, H., *et al*. (2011) An Immunohistochemical Study of The serotonin 1A Receptor in the Hippocampus of Subjects with Alzheimer's Disease. *Neuropathology*, **31**, 503-509. https://doi.org/10.1111/j.1440-1789.2010.01193.x

[44] Carlino, D., De Vanna, M. and Tongiorgi, E. (2013) Is Altered BDNF Biosynthesis a General Feature in Patients with Cognitive Dysfunctions? *The Neuroscientist*, **19**, 345-353. https://doi.org/10.1177/1073858412469444

[45] Cox, P.A., Davis, D.A., Mash, D.C., Metcalf, J.S. and Banack, S.A. (2016) Dietary Exposure to an Environmental Toxin Triggers Neurofibrillary Tangles and Amyloid Deposits in the Brain. *Proceedings of the Royal Society B: Biological Sciences*, **283**, Article ID: 20152397. https://doi.org/10.1098/rspb.2015.2397

[46] Brenner, S.R. (2013) Blue-Green Algae or Cyanobacteria in the Intestinal Micro-Flora May Produce Neurotoxins Such as Beta-N-Methylamino-L-Alanine (BMAA) Which May Be Related to Development of Amyotrophic Lateral Sclerosis, Alzheimer's Disease and Parkinson-Dementia-Complex in Humans and Equine Motor Neuron Disease in Horses. *Medical Hypotheses*, **80**, Article No. 103. https://doi.org/10.1016/j.mehy.2012.10.010

[47] Yamada, K. and Nabeshima, T. (2004) Interaction of BDNF/TrkB Signaling with NMDA Receptor in Learning and Memory. *Drug News & Perspectives*, **17**, 435-438. https://doi.org/10.1358/dnp.2004.17.7.863702

[48] Wall, R., Cryan, J.F., Ross, R.P., *et al*. (2014) Bacterial Neuroactive Compounds Produced by Psychobiotics. *Advances in Experimental Medicine and Biology*, **817**, 221-239. https://doi.org/10.1007/978-1-4939-0897-4_10

[49] Kalueff, A.V. and Nutt, D.J. (2007) Role of GABA in Anxiety and Depression. *Depression and Anxiety*, **24**, 495-517. https://doi.org/10.1002/da.20262

[50] Gonzalez-Burgos, G., Fish, K.N., Lewis, D.A. (2011) GABA Neuron Alterations, Cortical Circuit Dysfunction and Cognitive Deficits in Schizophrenia. *Neural Plasticity*, **2011**, Article ID: 723184. https://doi.org/10.1155/2011/723184

[51] Galland, L. (2014) The Gut Microbiome and the Brain. *Journal of Medicinal Food*, **17**, 1261-1272. https://doi.org/10.1089/jmf.2014.7000

[52] Banack, S.A., Caller, T.A. and Stommel, E.W. (2010) The Cyanobacteria Derived Toxin Beta-N-Methylamino-L-Alanine and Amyotrophic Lateral Sclerosis. *Toxins* (*Basel*), **2**, 2837-2850. https://doi.org/10.3390/toxins2122837

[53] Bekkering, P., Jafri, I., van Overveld, F.J. and Rijkers, G.T. (2013) The Intricate Association between Gut Microbiota and Development of Type 1, Type 2 and Type 3 Diabetes. *Expert Review of Clinical Immunology*, **9**, 1031-1041. https://doi.org/10.1586/1744666X.2013.848793

[54] Daulatzai, M.A. (2014) Role of Stress, Depression, and Aging in Cognitive Decline and Alzheimer's Disease. *Current Topics in Behavioral Neurosciences*, **18**, 265-296. https://doi.org/10.1007/7854_2014_350

[55] Naseer, M.I., Bibi, F., Alqahtani, M.H., *et al*. (2014) Role of Gut Microbiota in Obesity, Type 2 Diabetes and Alzheimer's Disease. *CNS & Neurological Disorders-Drug Targets,* **13**, 305-311. https://doi.org/10.2174/18715273113126660147

[56] Bruce-Keller, A.J., Salbaum, J.M., Luo, M., *et al*. (2015) Obese-Type Gut Microbiota Induce Neurobehavioral Changes in the Absence of Obesity. *Biological Psychiatry*, **77**, 607-615. https://doi.org/10.1016/j.biopsych.2014.07.012

[57] Ho, L., Qin, W., Pompl, P.N., *et al*. (2004) Diet-Induced Insulin Resistance Promotes Amyloidosis in a Transgenic Mouse Model of Alzheimer's Disease. *The FASEB Journal*, **18**, 902-904. https://doi.org/10.1096/fj.03-0978fje

[58] Sato, N. and Morishita, R. (2014) Brain Alterations and Clinical Symptoms of Dementia in Diabetes: Aβ/Tau-Dependent and Independent Mechanisms. *Frontiers in Endocrinology*, **5**, Article 143. https://doi.org/10.3389/fendo.2014.00143

[59] Takeda, S., Sato, N., Rakugi, H. and Morishita, R. (2011) Molecular Mechanisms Linking Diabetes Mellitus and Alzheimer Disease: Beta-Amyloid Peptide, Insulin Signaling, and Neuronal Function. *Molecular BioSystems*, **7**, 1822-1827. https://doi.org/10.1039/c0mb00302f

[60] Doifode, T., Giridharan, V.V., Generoso, J.S., *et al*. (2021) The Impact of the Microbiota-Gut-Brain Axis on Alzheimer's Disease Pathophysiology. *Pharmacological Research*, **164**, Article ID: 105314. https://doi.org/10.1016/j.phrs.2020.105314

[61] Kim, M.S., Kim, Y., Choi, H., *et al*. (2020) Transfer of a Healthy Microbiota Reduces Amyloid and Tau Pathology in an Alzheimer's Disease Animal Model. *Gut*, **69**, 283-294. https://doi.org/10.1136/gutjnl-2018-317431

[62] Kundu, P., Stagaman, K., Kasschau, K., *et al*. (2022) Fecal Implants from *App*$^{NL\text{-}G\text{-}F}$ and *App*$^{NL\text{-}G\text{-}F/E4}$ Donor Mice Sufficient to Induce Behavioral Phenotypes in Germ-Free Mice. *Frontiers in Behavioral Neuroscience*, **16**, Article 791128. https://doi.org/10.3389/fnbeh.2022.791128

[63] Sun, J., Xu, J., Ling, Y., *et al*. (2019) Fecal Microbiota Transplantation Alleviated Alzheimer's Disease-Like Pathogenesis in APP/PS1 Transgenic Mice. *Translational Psychiatry*, **9**, Article No. 189. https://doi.org/10.1038/s41398-019-0525-3

[64] Ho, L., Ono, K., Tsuji, M., *et al*. (2018) Protective Roles of Intestinal Microbiota Derived Short Chain Fatty Acids in Alzheimer's Disease-Type Beta-Amyloid Neuropathological Mechanisms. *Expert Review of Neurotherapeutics*, **18**, 83-90. https://doi.org/10.1080/14737175.2018.1400909

[65] Li, B., He, Y., Ma, J., *et al*. (2019) Mild Cognitive Impairment Has Similar Alterations as Alzheimer's Disease in Gut Microbiota. *Alzheimer's & Dementia*, **15**, 1357-1366. https://doi.org/10.1016/j.jalz.2019.07.002

[66] Kim, S., Nam, Y., Shin, S.J., *et al*. (2020) The Potential Roles of Ghrelin in Metabolic Syndrome and Secondary Symptoms of Alzheimer's Disease. *Frontiers in Neuroscience*, **14**, Article 583097. https://doi.org/10.3389/fnins.2020.583097

[67] Calio, M.L., Mosini, A.C., Marinho, D.S., *et al*. (2021) Leptin Enhances Adult Neurogenesis and Reduces Pathological Features in a Transgenic Mouse Model of Alzheimer's Disease. *Neurobiology of Disease*, **148**, Article ID: 105219. https://doi.org/10.1016/j.nbd.2020.105219

[68] Dalile, B., Van Oudenhove, L., Vervliet, B. and Verbeke, K. (2019) The Role of Short-Chain Fatty Acids in Microbiota-Gut-Brain Communication. *Nature Reviews Gastroenterology & Hepatology*, **16**, 461-478. https://doi.org/10.1038/s41575-019-0157-3

[69] Yang, X., Yu, D., Xue, L., Li, H. and Du, J. (2020) Probiotics Modulate the Microbiota-Gut-Brain Axis and Improve Memory Deficits in Aged SAMP8 Mice. *Acta Pharmaceutica Sinica B*, **10**, 475-487. https://doi.org/10.1016/j.apsb.2019.07.001

[70] Lee, H.J., Lee, K.E., Kim, J.K. and Kim, D.H. (2019) Suppression of Gut Dysbiosis by *Bifidobacterium longum* Alleviates Cognitive Decline in 5XFAD Transgenic and Aged Mice. *Scientific Reports*, **9**, Article No. 11814. https://doi.org/10.1038/s41598-019-48342-7

[71] Chen, C., Ahn, E.H., Kang, S.S., *et al*. (2020) Gut Dysbiosis Contributes to Amyloid Pathology, Associated with C/EBPβ/AEP Signaling Activation in Alzheimer's Disease Mouse Model. *Science Advances*, **6**, eaba0466. https://doi.org/10.1126/sciadv.aba0466

[72] Saiyasit, N., Chunchai, T., Prus, D., *et al*. (2020) Gut Dysbiosis Develops before Metabolic Disturbance and Cognitive Decline in High-Fat Diet-Induced Obese Condition. *Nutrition*, **69**, Article ID: 110576. https://doi.org/10.1016/j.nut.2019.110576

[73] Lou, Y., Zhang, X., Du, W., *et al*. (2017) Therapeutic Effect of Bushen Jianpi Recipe on Mild and Moderate Alzheimer's Disease and Its Effect on Serum Levels of IL-1β, IL-6 and TNF-α. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, **26**, 1646-1649.

[74] Omar, S.H. (2019) Mediterranean and MIND Diets Containing Olive Biophenols Reduces the Prevalence of Alzheimer's Disease. *International Journal of Molecular Sciences*, **20**, Article No. 2797. https://doi.org/10.3390/ijms20112797

[75] Nagpal, R., Neth, B.J., Wang, S., Craft, S. and Yadav, H. (2019) Modified Mediterranean-Ketogenic Diet Modulates Gut Microbiome and Short-Chain Fatty Acids in Association with Alzheimer's Disease Markers in Subjects with Mild Cognitive Impairment. *EBioMedicine*, **47**, 529-542. https://doi.org/10.1016/j.ebiom.2019.08.032

[76] Ano, Y. and Nakayama, H. (2018) Preventive Effects of Dairy Products on Dementia and the Underlying Mechanisms. *International Journal of Molecular Sciences*, **19**, Article No. 1927. https://doi.org/10.3390/ijms19071927

[77] Liu, J., Yu, C., Li, R., *et al*. (2020) High-Altitude Tibetan Fermented Milk Ameliorated Cognitive Dysfunction by Modified Gut Microbiota in Alzheimer's Disease Transgenic Mice. *Food & Function*, **11**, 5308-5319. https://doi.org/10.1039/C9FO03007G

[78] Ma, D., Wang, A.C., Parikh, I., *et al*. (2018) Ketogenic Diet Enhances Neurovascular Function with Altered Gut Microbiome in Young Healthy Mice. *Scientific Reports*, **8**, Article No. 6670. https://doi.org/10.1038/s41598-018-25190-5

[79] Sun, J., Liu, S., Ling, Z., *et al*. (2019) Fructooligosaccharides Ameliorating Cognitive Deficits and Neurodegeneration in APP/PS1 Transgenic Mice through Modulating Gut Microbiota. *Journal of Agricultural and Food Chemistry*, **67**, 3006-3017. https://doi.org/10.1021/acs.jafc.8b07313

[80] Liu, Q., Xi, Y., Wang, Q., *et al*. (2021) Mannan Oligosaccharide Attenuates Cognitive and Behavioral Disorders in the 5xFAD Alzheimer's Disease Mouse Model via Regulating the Gut Microbiota-Brain Axis. *Brain Behavior and Immunity*, **95**, 330-343. https://doi.org/10.1016/j.bbi.2021.04.005

[81] Wang, X., Sun, G., Feng, T., *et al*. (2019) Sodium Oligomannate Therapeutically Remodels Gut Microbiota and Suppresses Gut Bacterial Amino Acids-Shaped Neuroinflammation to Inhibit Alzheimer's Disease Progression. *Cell Research*, **29**, 787-803. https://doi.org/10.1038/s41422-019-0216-x

[82] Wang J, Lei X, Xie Z, *et al*. (2019) CA-30, an Oligosaccharide Fraction Derived from Liuwei Dihuang Decoction, Ameliorates Cognitive Deterioration via the Intestinal Microbiome in the Senescence-Accelerated Mouse Prone 8 Strain. *Aging* (*Albany NY*), **11**, 3463-3486. https://doi.org/10.18632/aging.101990

[83] Shen, L., Liu, L., Li, X.Y. and Ji, H.F. (2019) Regulation of Gut Microbiota in Alzheimer's Disease Mice by Silibinin and Silymarin and Their Pharmacological Implications. *Applied Microbiology and Biotechnology*, **103**, 7141-7149. https://doi.org/10.1007/s00253-019-09950-5

[84] Sun, Z.Z., Li, X.Y., Wang, S., Shen, L. and Ji, H.F. (2020) Bidirectional Interactions between Curcumin and Gut Microbiota in Transgenic Mice with Alzheimer's Disease. *Applied Microbiology and Biotechnology*, **104**, 3507-3515. https://doi.org/10.1007/s00253-020-10461-x

[85] Wang, L., Lu, J., Zeng, Y., *et al*. (2020) Improving Alzheimer's Disease by Altering

Gut Microbiota in Tree Shrews with Ginsenoside Rg1. *FEMS Microbiology Letters*, **367**, fnaa011. https://doi.org/10.1093/femsle/fnaa011

[86] Brini, S., Sohrabi, H.R., Peiffer, J.J., *et al*. (2018) Physical Activity in Preventing Alzheimer's Disease and Cognitive Decline: A Narrative Review. *Sports Medicine*, **48**, 29-44. https://doi.org/10.1007/s40279-017-0787-y

[87] Mitchell, C.M., Davy, B.M., Hulver, M.W., *et al*. (2019) Does Exercise Alter Gut Microbial Composition? A Systematic Review. *Medicine and Science in Sports and Exercise*, **51**, 160-167. https://doi.org/10.1249/MSS.0000000000001760

[88] Abraham, D., Feher, J., Scuderi, G.L., *et al*. (2019) Exercise and Probiotics Attenuate the Development of Alzheimer's Disease in Transgenic Mice: Role of Microbiome. *Experimental Gerontology*, **115**, 122-131. https://doi.org/10.1016/j.exger.2018.12.005

[89] Kress, G.J., Liao, F., Dimitry, J., *et al*. (2018) Regulation of Amyloid-β Dynamics and Pathology by the Circadian Clock. *Journal of Experimental Medicine*, **215**, 1059-1068. https://doi.org/10.1084/jem.20172347

[90] Parkar, S.G., Kalsbeek, A. and Cheeseman, J.F. (2019) Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health. *Microorganisms*, **7**, Article No. 41. https://doi.org/10.3390/microorganisms7020041

[91] Deaver, J.A., Eum, S.Y. and Toborek, M. (2018) Circadian Disruption Changes Gut Microbiome Taxa and Functional Gene Composition. *Frontiers in Microbiology*, **9**, Article 737. https://doi.org/10.3389/fmicb.2018.00737

[92] Shokri-Kojori, E., Wang, G.J., Wiers, C.E., *et al*. (2018) β-Amyloid Accumulation in the Human Brain after One Night of Sleep Deprivation. *Proceedings of the National Academy of Sciences*, **115**, 4483-4488. https://doi.org/10.1073/pnas.1721694115