The Gut-brain axis: the role of gut microbiome in Alzheimer's disease

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Abstract. Alzheimer's disease is one of the most severe and wide-spread neurodegenerative diseases in the world. WHO estimates that more than 47 million people (8.1% of women and 5.4% of men over the age of 65) are currently living with dementia. Despite the long history and wide impact in humans of AD, the disease remains in mist. Until now, we cannot determine which factors cause AD and how to find a cure. There is several hypotheses about the pathogenesis of AD, of which cholinergic hypothesis and Nucleic acid oxidation hypothesis are two of the most insightful ones. Besides, increasing evidence suggests the intimidate role of gut microbiome in the development and mitigation of Alzheimer's disease. The bidirectional link between the gut and the brain is note-worthy, offering a potential insight to future investigation on AD. To fully understand the role of gut microbiome in process of Alzheimer's disease, this review illustrates pathogeneses of AD and the procedure of several important pathogenetic factors like high blood pressure, diabetes and aging should be discussed. Further application of gut microbiome can be a drug target for AD: scientists extract a chemical called sodium oligomannate for balancing gut microbiome to treat mild to moderate AD.

Key words: Alzheimer's disease, gut-brain axis, gut microbiome, pathogenesis, sodium oligommanate, diabetes.

1. Introduction

Alzheimer's disease (AD) is dementia that slowly damages memory, cognition and behavior, is a typical and common neurodegenerative disease happening mostly in elders. About 60 to 80% of dementias in older people can be attributed to AD. In the US, an estimated 10% of people ≥ 65 have Alzheimer disease. The number of individuals with Alzheimer's disease increases with age: for people at age 65 own a percentage of about 3%, whereas the percentage rocket 5 times to 17% for people aging at 75 to 84. Then the rate nearly doubled for people older than 85, about 32% [1]. The attack rate among the world population varies in regions. Data in China shows that people aged 65-74 have an incidence of AD of 4.8% and then goes up to 15% among people from 75-84; for people older than 85, the rate of incidence in China is about 25%, a little bit lower than in USA [2]. Partly because women have longer life expectancy, the difference in sex hormone and life experience to men, Alzheimer's disease is twice as common among women as among men.

The development of AD can be divided into three stages: early stage, middle stage and the late stage. Patients who experience early stage of Alzheimer's disease show symptoms consist mainly of rapid forgetting, no shift in rule-based strategies and visuospatial attention loss. The length and symptoms of early-stage AD may vary from person to person, but, on average, the early stage often stays for 2 years, then it turns to the middle stage, where patients suffer from more drastic and influential symptoms. For instance, they may notice abnormal memories loss, especially for working memory and long-term memory, awareness loss, and spatial memory compromised happening to them. The middle stage is the longest of three, which lasts up to four years at most. After the middle stage comes the last stage where patients suffer from severe sensory processing loss, hallucinations, motor loss and speech loss, then it deteriorates to basic function loss, including swallowing, speech, movement. Unfortunately, the causes of AD are complicated and remain unclear. This review systematically introduces the pathogenesis of AD and gut microbiome-brain axis bidirectional interaction, as well as discusses the relationship between gut microbiota and AD.

2. Pathogenesis of AD

The pathogenesis of AD can be treated from two aspects, macroscopically and microscopically. The former includes widespread cortical atrophy, as can be detected most significantly in the hippocampus as well as the temporal lobe, which are in charge of critical cognitive functions. Microscopically, the brain region that is affected shows signs of inflammation, neurofibrillary tangles (NFTs) and amyloid plaques (Aß), two typical neurological changes in the brain. Neurofibrillary entanglements in neural cellular bodies are defined as aggregations of abnormal tau protein and neurofilaments. This character may be important because it has shown a correlation between the density of NFTs and the clinical symptoms. Neurotic plaques are related neurofibrillar changes that happen in AD patients' brains. Extra neuronal aggregates of A-protein are present in Amyloid plaques. Neurotic and diffuse plaques are both types of plaque. The main component of diffuse plaques is A-protein, meaning that it can be used as a potential signal of AD. Although A is the main component of neurotic plaques, tau in the dystrophic neurites is also a main figure in AD as dystrophic neurites are commonly observed in neurodegenerative diseases.

There are also several hypotheses of the pathogenesis of AD, such as cholinergic hypothesis and Nucleic acid oxidation hypothesis. The cholinergic hypothesis notes that loss of cholinergic nerves in the cerebral cortex is an early pathogenic event associated with cognitive impairment in AD patients. The initial proposal of the cholinergic hypothesis suggests that the cognitive decline with advanced age and AD is largely attributed to malfunction of acetylcholine in neurons. As the result, major treatment and direction of drug development of AD has been using this idea as a basis thus far. However, recent investigations into patients experiencing mild cognitive impairment or early-stage AD have raised doubts about the validity of this hypothesis and questioned the reasoning behind utilizing cholinomimetics for treating the disorder, particularly in its initial phases. These challenges need to be considered within a broader framework that acknowledges various existing abnormalities related to both aging and AD in terms of cholinergic function. Findings from studies conducted on elderly individuals, patients with AD (both pre- and post-mortem), and animal experiments suggest a range of irregularities in processes of cholinergic neurons, including choline transportation changes, abnormal release of ACh, expression of nicotinic receptors, and neurotrophic support may contribute to the exacerbation of cognitive impairments during the course of disease and aging. Furthermore, these cholinergic abnormalities might also play a role in abnormal cognitive issues as well as the formation of toxic neurotic plaques characteristic of AD. Then, it can be assumed that drug development and treatment based on cholinergic strategies may become a valid and promising approach for AD.

Nucleic acid oxidation in Alzheimer disease refers to:1) the accumulation of Aβ accelerates nucleic acid oxidation and vice versa and 2) the early stage of fibrosis in tau is shown to be related to neurotoxicity caused by nucleic acid oxidation in neurons. Emerging evidence suggests a strong link between the pathophysiology of Alzheimer's disease and the presence of oxidative stress. Reactive oxygen species, specifically the hydroxyl radical, have been found to inflict damage on nucleic acids as well as other cellular macromolecules. Neurons possess intricate certain mechanism to defend their longevity since they are irreplaceable and long-lasting throughout an organism's lifespan. However, in individuals with Alzheimer's disease, there is an observed accumulation of oxidized nucleic acids indicating either heightened oxidative stress or reduced capacity for repairing such damage. The hypothesis proposing metal-catalyzed hydroxyl radicals as potent mediators of cellular injury encompasses all categories of macromolecules and plays a central role in comprehending the pathogenesis of Alzheimer's disease (AD).

3. Gut microbiome-brain axis bidirectional interaction

Somehow counterintuitive, actually our brain and gut are connected, scientists call this connection "the gut-brain axis". The gut nervous system is so active and important that it is sometimes called "the second brain." Gut-brain axis a two-way dialogue between the two organs, the brain and the

gut[3]. A key link between them is the vagus nerve, the 10th nerve of the twelve pairs of cranial nerves and also the main nerve of Peripheral Nervous System (PNS)[4]. After the spinal cord, it is the biggest nerve in the body and put simply it makes it possible for brain and gut to communicate or transform information to each other. In fact, 80 to 90% of nerve fibers in the vagus nerve are going from the gut to the brain. The thought-provoking role of the gut-brain axis may be primarily because of the significance of gut microbiota. Approximately a thousand different species of microbiota reside in our gut. Recent studies have also revealed a reciprocal link between the gut and the brain, wherein the central nervous system (CNS) impacts the ENS, through autonomic pathways by triggering the muscle tissues in the intestine. The pathway transmits signals from the brain to regulate various functions of the digestive tract, including permeability, secretion, motility, and immunity. Conversely, the intestinal microbiome can affect brain function through sensory signaling pathways and by releasing biologically active substances. Multiple research studies have provided evidence on the correlation between alterations in dietary patterns, utilization of antibiotics, and the existence of pathogenic microorganisms with the occurrence of intestinal dysbiosis. Consequently, these factors can contribute to cognitive impairments in individuals.

Regarding the role that a gut bacteria can play in the gut-brain axis, the connection between bacteria and neurotransmitters should be noted. The neurotransmitter called serotonin can affect people's mood and feelings of happiness and pleasure. The bacteria in your gut produce more than 90% of the serotonin found in your body. Enterococcus spp., Streptococcus spp., Lactobacillus plantarum, Morganella morganii and Klebsiella pneumonia are among various bacteria species that are capable of synthesizing serotonin. The 1714 serenitas culture has been shown to activate stress coping centers and reduce levels of stress hormone. It acts by becoming part of the gut microbiota that are involved in the gut brain axis. Besides, a growing body of evidence indicates the significant figure played by the gut microbiome for its use in signaling in neurotic immune system. Studies using germ-free mice consistently demonstrate negative impacts on the development of neurons and processes related to neurological diseases related to degenerative factors, often due to disruptions in the process of signaling with the gut microbiome.

4. Relationship between gut microbiota and AD

Growing agreement says that the gut microbiota is playing the key part in keeping balance in the gut and prevent various disease and disorders in CNS by keeping its composition. Certain bacteria in the human gut are able to synthesis acid and toxins[5]. This substance can penetrate the intestinal mucosa to interact with APOE genes, and thus incur inflammation responses in neurons, thereby having an impact on the overall health of the brain and functions of immune system, potentially risking neurodegenerative diseases.

As mentioned above, the gut microbiome is becoming as a hopeful target for AD drug treatment. Further application of gut-brain axis can be seen from a new drug called Sodium oligomannate.

As the main component of sodium oligomannate, oligomannate was firstly extracted by a Chinese scientist called Meiyu Geng. She wished to figure out the potential link between the gut flora and neuroinflammation through activation of microglia, a non-neuron cell common in CNS. Extract of a brown algae species, oligomannate obstruct the production of abnormal aminoamides and enables filtration of glial cell across blood brain barrier. A bran-new perspective in regard of the pathogenesis of AD has been generated by Geng and her team: neuroinflammation caused by microbial disorders in gut.

A mouse model of AD has provided evidence for connection between the progression of AD and the gut microbiome. In this model, an imbalanced gut microbiota disrupted the metabolism of amino acids, leading to elevated levels of certain basic amino acids which facilitated the proliferation of cells that penetrate brain tissue stratums and thus induced neuroinflammation. Ultimately, these processes contributed to the development and advancement of AD pathology. A study observed a notable reduction of Aβ accumulations in the brains of mice bred in a sterile environment compared

to those individuals from the control group under normal environment. Additionally, when microbiota from the intestines of CONVR-APPPS1 mice bred conventionally were introduced into the intestines of sterile-bred mice, it resulted in an elevation of Aβ deposits within the CNS. Conversely, fecal matter transplantation from WT mice did not lead to a significant increase. Meanwhile, an altered or disrupted composition of gut microbiota called dysbiosis contributes to neurodegenerative disease like AD or PD. For instance, C57BL/6 mice under stressful situation and infection caused by a type of bacteria showed memory disorders. In contrast, Swiss-Webster mice raised in a sterile environment without any postnatal exposure to intestinal bacteria showed deficits in spatial and working memory even without infection or stress[6]. This was accompanied by decreased expression of brain-derived neurotrophic factor (BDNF), a neurotrophic highly involved in plasticity of synapses[]. Interestingly, it has been found that patients with Alzheimer's disease have decreased level of BDNF in their brains and serum (Michalski et al., 2015). However, increased levels of BDNF were discovered in the central amygdala of sterile mice by Neufeld et al. They also observed a decrease in mRNA expression for the serotonin receptor and the NR2B subunit of the NMDA receptor in the dentate fascia region. As previously mentioned, cognitive impairment has been positively correlated with reduced serotonin precursor in the tryptophan pathway. Additionally, there is a significant correlation between gut microbiota. For instance, Ruminococcus abundance was negatively associated with indole-3-pyruvate presence—a compound involved in tryptophan pathway. Indole-3-pyruvate progressively increased from amnestic mild cognitive impairment to Alzheimer's disease patients as it is a precursor for ligands of aryl hydrocarbon receptor signaling pathway. Therefore, regulating gut microbiota composition may be an effective approach to treating Alzheimer's disease.

Moreover, recent studies show the casual link between diabetes and AD by affecting the pathological aging of the brain, thus causes Alzheimer's-like changes such as deposition of Aß and NFTs. People with diabetes are more prone to Alzheimer's, which may partly because dysregulated glucose metabolism and hyperinsulinemia (in this case, also refers to insulin resistance). Increased Aß production has been observed as a consequence of upregulation of AßPP induced by insulin resistance. Given the significant role that diabetes plays in predisposing individuals to Alzheimer's disease, researchers investigated whether inducing experimental type 2 diabetes through obese diets in SAMP8 mice (a mouse model having accelerated aging), would lead to pathological brain aging. The findings revealed that diabetic mouse models showed changes similar to what can be seen from early-stage AD, including increased levels of cerebral amyloid-β and memory deficits. These results suggest that these SAMP8 mice could serve as a metabolic model for studying AD. Further research has shown that the resistance of insulin solely cannot adequately explain the changes similar to AD happen in mice, unless accompanied with aging, the key factor for AD: study in which high fat diet-induced T2DM in young C57BL/6J mice did not produce AD-like pathology.

On the other hand, the persistent intake of saturated fats and sugar in one's diet results in the development of resistance to insulin and thus obesity[7]. That can lead to a range of metabolic complications including syndrome in respect to metabolism and type II diabetes mellitus. Changes in gut microbiome have been linked with alterations in insulin level and disruptions in the metabolism of glucose. For example, Karlsson et al found reductions in certain species of Clostridium, similar to the findings of Larsen et al. Additionally, they observed an increase in Lactobacillus species and positively associated between fasting glucose levels and Clostridium species. Meanwhile, Qin noted a decrease in bacteria that produce butyrate among individuals suffering from diabete, such as Roseburia intestinalis, Eubacterium rectale and Roseburia inulinivorans. Furthermore, they identified an increase in bacterial genes associated with oxidative stress within this group. Both the diabetes and AD are related to gut microbiome, referring to a potential cause-and-effect pathway. It gives insight to hypothesize that unhealthy diet affects insulin and glucose metabolism through gut microbiome, leading to diabetes and AD-like changes in brain. With the further exacerbation caused by age and other uncleared factors, the fact that elders are more prone to be caught in AD is explained and makes sense. The gut's microbiome is becoming a potential and hopeful target for mild to

moderate AD treatment. Further application of gut-brain axis can be seen from a new drug called Sodium oligomannate.

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5. Conclusion

To put in a nutshell, Alzheimer's disease is a complicated and tough enemy to people. This review mainly discusses several critical factors and characteristics of AD. This issue can only be handled by taking a broad and divergent perspective. The focus on bacteria within human body has a great potential to offer significant insight to the cure of AD through the above-mentioned homeostasis. Besides, from the previous elaboration, basic diseases especially diabetes and high blood pressure, may be significant in the development of AD through involving formation of neuroinflammation and deposition of Aß. Future studies and drug development should be investigating specific bacteria and the interaction between them in the gut and the cognitive effects on patients of lowering blood glucose earlier in life. Personalized treatment modalities tailored to individual patients' genetic profiles, such as pharmacotherapy or lifestyle modifications, are envisioned to be developed. Scientific investigations have demonstrated the potential benefits of modulating gut microbiota through probiotics and dietary interventions on immune system function, inflammation regulation, and even cognitive processes. But it must notice that microbiota is multi-factored affected by diet and lifestyle.

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