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Review Article in Biology

Examining the Influence of Gut Microbiota on the Progression of Alzheimer's Disease

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Abstract: Alzheimer's disease is the most common type of dementia affecting at least 27 million people. Recent connections have been observed between gut microbiota and brain health, highlighting the connection of the microbiota-gut-brain axis. Moreover, it has been shown that gut microbiota dysbiosis can affect Alzheimer's pathology through the upregulation of NLRP3 inflammasome. Additionally, diet was shown to contribute to either a neural protective role or result in the progression of Alzheimer's disease. The gut microbiota metabolites trimethyl amine oxide and select short-chain fatty acids were found to induce NLRP3 inflammasome recruitment, ultimately resulting in further aggravation of Alzheimer's disease. In this review, we examined the influence the gut microbiota has on Alzheimer's disease progression.

Keywords: Alzheimer's disease, gut microbiota, microbiota-gut-brain axis

1. Introduction

Alzheimer's disease (AD) was first discovered in 1906 by German physician Alois Alzheimer. Despite allowing temporary improvement, there is no known treatment that can stop or reverse its progression. Currently, AD affects at least 27 million people and is the most prevalent type of dementia accounting for 60 to 70% of all dementia cases (Ferreira et al., 2014) (Ballard et al., 2011). In addition to the high financial cost to society, this disease also has a detrimental effect on patients' families. Characterized by cognitive impairment, Alzheimer's disease (AD) is a central degenerative disease. The major contributing factors of AD are hypothesized to be the formation of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs). This is marked by the misfolding of Aβ peptides forming insoluble dense plaques outside and around the neurons. These polymerized Aβ peptides entangle nerve cells, resulting in the progressive loss of neural tissue(De-Paula et al., 2012). Moreover, hyperphosphorylation of Tau protein has been shown to result in the NFTs associated with AD (Mudher & Lovestone et al., 2002). Increasing evidence indicates inflammation may contribute to AD development and progression. Individuals with AD have elevated levels of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 in their brains. This inflammation is proposed to lead to the accumulation of plaque aggregates and tau hyperphosphorylation resulting in neuronal loss (Kinney et al., 2018). As a result of the accumulation of the inflammatory factors, microglia can become activated and nerve cells undergo inflammatory apoptosis, ultimately leading to loss of memory and cognitive ability in patients (Balducci et al., 2017) (Kobayashi et al., 2018).

Gut microbiota (GM) consists of a large population of commensal microorganisms (bacteria, archaea, fungi, viruses) in the human intestine (Shen et al., 2020). The intestinal microbiota is a complex ecosystem that supports a dynamic ecological balance in the body (Wang & Wang et al., 2016). There are more than 100 trillion bacterial cells in the human gut of which belong to about 1,000 different bacterial species.

Beyond the host's enzymes, this microbiological community possesses a large and diverse set of metabolic enzymes capable of showing a vast array of metabolic activities in the gut (Guinane & Cotter et al., 2013). GM plays a key role in human health by affecting metabolic and gastrointestinal health, giving rise to further reaching influences on the development of many diseases (Hills et al., 2019).

Through the lymphatic and vascular systems, gut microbiota produces substances, most notably monoamines and amino acids, that can affect the activity of central neurons (Wekerle et al., 2016). Furthermore, gut bacteria respond to neurotransmitters sent by the brain (Calsolaro & Edison et al., 2016) (Briguglio et al., 2018). This bidirectional relationship between the gut microbiota and the central nervous system (CNS) is a result of chemical substances crossing the blood-brain barrier or the nervous system interacting with the intestine (Angelucci et al., 2019). This link from the GM to the CNS is generally referred to as the "microbiota-gut-brain axis". The gut and brain connection consist of communication between the gut to the enteric nervous system (ENS), which the ENS then communicates with the CNS (Thangaleela et al., 2022). Moreover, recent research has highlighted the importance of this relationship by showing GM disorders can cause and influence CNS diseases (Zhu et al., 2021). Herein we will examine the influence of GM on AD development and look at the potential nutritional rationale. Furthermore, implementing treatments and prevention of AD that utilize this relationship will be discussed.

2. Relationship between AD and GM

2.1. Neural inflammation resulting from GM of AD patients

The dysbiosis of the GM composition has been shown to contribute to the development and progression of many diseases including inflammatory bowel disease, type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease events. Moreover, GM alterations have been shown to influence CNS disorders such as autism, depression, Parkinson's disease, multiple sclerosis, and Alzheimer's disease (AD)(Jiang et al., 2017). It was found in APP/PS1 double transgenic mice, an AD mouse model commonly used, that the microorganisms to the phyla Firmicutes, Verrucomicrobia, Proteobacteria, and Actinomycetes are significantly decreased, while Bacteroides and Tenericutes are significantly increased in the progression of AD (Harach et al., 2017). These results show that there is a connection between GM and AD progression.

Research has shown that inflammation may be a major contributor to AD progression and development. In AD, pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 are upregulated in the brain, resulting in tau hyperphosphorylation and plaque accumulation (Kinney et al., 2018). One mechanism of initiating this inflammatory response is through inflammasome NLRP3 expression. NLRP3 inflammasome detects uric acid and ATP release from damaged cells, at which point the complex initiates the inflammation response through the cytokine cascade. The NLRP3 system increases the brain's proinflammatory factors such as IL-1β and IL-18. A key mechanism of this process is the activation of cysteine-containing aspartate-specific proteases 1 (Caspase-1), which further facilitates the aggregation of innate immune cells and initiates the inflammatory response cascade, resulting in AD pathology progressing more rapidly (Falcão et al., 2017) (K. Wang et al., 2017). Neuroinflammation is mainly triggered by this mechanism; however, GM has not been consistently implicated in neuroinflammation. In AD patients, NLRP3 expression in the intestinal tissue is significantly higher than in the general population (Pang et al., 2017). Whether abnormal NLRP3 expression is associated with inflammation and AD-related neuroinflammation, however, needs to be investigated further.

To probe this question a study by Shen et. al aimed to look at the inflammatory response and neurobiological impairments that arose from mice given fecal microbiota transplants (FMT) from AD patients (Shen et al., 2020). In this study APP/PS1, double transgenic mice were given FMT from either a

healthy donor or an AD patient, with an antibiotic-treated mouse as a negative control. Mice with FMT from AD patients showed a significant increase in expression of NLRP3 in the intestinal tissue relative to the mice that received FMT from a healthy patient and the negative control. This translated to increase expression of proinflammatory factors caspase-1, IL-1β and IL-18 in the peripheral blood of mice. The inflammatory response was shown to carry through the CNS resulting in microglia cell expression in the hippocampus, advancing the progression of AD. Moreover, cognitive impairment was more severe in mice receiving FMT from AD patients.

NLRP3 inflammasome activity and other inflammatory factors were significantly upregulated in AD mice after FMT from AD patients. A rise in related inflammatory factors was also observed in the peripheral blood of mice (Shen et. al., 2020). In AD patients, GM activates the intestinal NLRP3 inflammasome to promote intestinal inflammation. Inflammatory factors reach the brain tissue through circulation, activating microglia and promoting an inflammatory response in the hippocampus, this cascade causes AD to progress more rapidly. However, there is still much work to be done on identifying the exact microbes responsible for promoting NLRP3 inflammatory response. In follow-up studies, it was shown SCFA supplemented diet resulted in an increase in NLRP3 expression and, ultimately, neural inflammation hallmarks (Ruan et al., 2021). This would indicate diets that facilitate the production of SCFA's would promote AD progression.

2.2. P. gingivalis infection results in Aβ plaques

By assessing the accumulation of Aβ peptide and the production of proinflammatory cytokines in rodents orally infected with P. gingivalis (Pg) and the performance in spatial memory-dependent tasks, studies have established the association between Pg and AD-related cognitive decline (Díaz-Zúñiga et al., 2020). Moreover, rats fed Pg showed an increase in neural inflammation, and the development of Aβ plaques was observed in these mice (Chi et al., 2021). When the GM of the rats that were orally dosed with Pg was analyzed it showed lower levels of Parabacteroides gordonii and Ruminococcus callidus than the control group, but higher levels of Mucispirillum schaedleri. These results indicate the Pg infection that initiates Aβ plaque pathology originates from GM dysbiosis.

Figure 1. Healthy rats fed *P. gingivalis* display Aβ plaques

3. Nutritional effects on GM and AD

The most influential factor in maintaining a healthy GM is diet. With the recent studies showing the link between GM and AD, it is no surprise that several studies have demonstrated that a healthy diet may contribute to improvement in AD symptoms. For example, diets such as the Mediterranean diet (MeD), Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), all of which are plant-based diets, were shown to enhance cognitive scores in patients aged 40 years or older (Solfrizzi et al., 2017) (Tsivgoulis et al., 2013) (van den Brink et al., 2019). These diets influence the GM and ultimately the metabolites that are produced and influence the host. The most notable metabolites that have an effect on AD include short-chain fatty acids (SCFA), trimethylamine oxide (TMAO), and polyphenols.

3.1. Short Chain Fatty Acids

Highly fibrous foods, such as fruits, veggies, legumes, and whole grains encourage the production of short chain fatty acids. Anaerobic gut bacteria produce SCFAs by saccharolytic fermentation of complex-resistant carbohydrates such as sugar alcohols, resistant starch, and polysaccharides from plant cell walls. The fermentation of carbohydrates and amino acids also produces SCFA. Approximately 500–600 mmol of SCFAs are produced in the gut through fermentation of 50–60 g carbohydrates. SCFAs can also be produced by fermenting amino acids (Nogal et al., 2021).

SCFA plays a critical role in brain health. Braniste et al. have demonstrated that germ-free (GF) mice have reduced levels of tight junction proteins including claudin and occludin, which leads to a more permeable blood-brain barrier (BBB) from fetal life onwards. This shows that SCFAs influence the BBB function. The BBB can be reconstituted by re-colonizing the GM with a complex microbiota or monocolonizing with SCFA-producing bacteria. It has also been shown that SCFAs can alleviate cognitive impairment caused by AD, such as isoflurane exposure, scopolamine, and radiation. Lee et al. found that radiation-induced downregulation of phosphorylated cAMP response element binding protein (p-CREB)/brain-derived neurotrophic factor (BDNF) expression was reversed by sodium butyrate (Lee et al., 2019).

Suggesting that they may be useful in the treatment of AD, SCFAs appear to be effective in treating cognition in AD, tau pathologies, and neuroinflammation. Currently, SCFA concentrations in the body are primarily regulated by three types (Qian et al., 2022). First, the in vivo concentration of SCFAs can be regulated by oral or intravenous supplementation of SCFAs. SCFAs can modify the pathological effects of Aβ in various ways. Oral sodium butyrate treatment reduces Aβ levels in the brains of 5xFAD mice early in the disease development (Fernando et al., 2020). A second approach would be to rebuild healthy homeostasis of gut microbes through fecal transplants or probiotics (LeBlanc et al., 2017). Producing butyrate, Clostridium butyricum can enhance cognitive performance, diminish Aβ deposition, and inhibit neuroinflammation by inhibiting microglial activation and proinflammatory cytokine release (Sun et al., 2020). Lastly, high levels of SCFAs can be produced by transplanting wild-type mouse feces into APP/PS1 mice (Sun et al., 2019). Eating prebiotics or eating a healthy diet can increase the proportion of metabolic substrates that are converted into SCFAs (Gibson et al., 2017).

There are competing perspectives on the role SCFA plays in AD pathology. Researchers have found that SCFAs regulate Aβ and tau pathologies. According to clinical studies, Aβ levels are positively correlated with serum acetate and valerate concentrations and negatively with butyrate (Marizzoni et al., 2020). AD mice fed a mixture of SCFAs sodium acetate, sodium propionate, and sodium butyrate, showed to stimulate double-negative T cell (DNT) differentiation, promoting NLRP3 inflammasome activation in the intestine and further downstream neuroinflammation. AD-related inflammation may be signaled by SCFAs-DNTs-NLRP3(Ruan et al., 2021). While this may seem contrary to other studies it is noted that the

SCFA mixture used in this study contained sodium acetate which had been previously shown to enhance AD pathology, and, thus, is most likely SCFA responsible for initiating the inflammatory response.

3.2. Trimethyl Amine Oxide

TMAO is a bacterial metabolite that is derived from choline, betaine, and L-carnitine. It has been shown to cause inflammation (Yang et al., 2019). To produce TMAO, gut microbes convert ingested precursors (e.g., choline and L-carnitine) into trimethylamine (TMA), at which point hepatic flavin monooxygenase 3 (FMO3) in the liver converts it to TMAO (Brunt et al., 2021) (Z. Wang et al., 2011). Choline and L-carnitine are mostly found in animal-derived foods, including meat or eggs, while betaine is mostly found in plants and shellfish (Jonsson & Bäckhed et al., 2017).

A significant correlation has been found between TMAO and cognitive decline and the progression of AD (Li et al., 2018; Vogt et al., 2018). It has been demonstrated that TMAO causes neuroinflammation and astrocyte activation that affects cognitive function (Brunt et al., 2021). Oxidative stress and NLRP3 inflammasome activation could also be induced by TMAO, resulting in enhanced inflammatory cytokines release (Boini et al., 2017).

3.3. Polyphenols

Polyphenols are chemical compounds, a group of phytochemicals found in several drinks such as green and black teas and red wine, and several foods such as fruits, vegetables, chocolate, olive oil, and plants (Watson et al., 2018). Noteworthy that polyphenols and their metabolites may enhance the intestinal barrier integrity and thus decrease local and systemic inflammation. For example, gallic acid, which is a bacterial-derived metabolite of anthocyanins, was shown to decrease Aβ deposition, and reduce neuroinflammation and oxidative stress in the brain of AD mice (Mori et al., 2020).

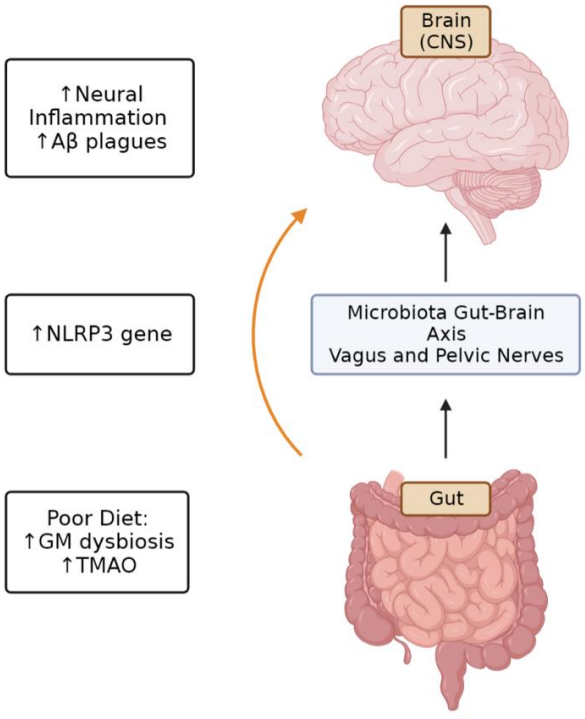

Figure 2. Relationship between GM and AD progression

4. Conclusions

In the United States, more than 5 million people suffer from AD. AD is marked by the accumulation of Aβ plaques and Tau tangles in the brain. A variety of substances produced by the gut microbiota can affect the activity of the central neurons, which could have repercussions on behavior via the lymphatic system and vascular systems. In our gastrointestinal ecosystem, the gut microbiota consists of a complex community of microbacteria whose alterations affect not only gut disorders, but also disorders of the central nervous system, including AD.

It was shown that fecal transplants from AD patients caused neural inflammation in mice through the recruitment of the NLRP3 inflammasome in the gut epithelial cells. Through the microbiota-gut-brain axis the brain's proinflammatory factors are upregulated resulting in the progression and development of AD. Moreover, it was also shown in P. gingivalis infections resulting in the development of Aβ plaques. This was later shown to result from the same mechanism of GM dysbiosis resulting in neural inflammation.

There is overwhelming evidence that a healthy plant-based diet can ameliorate AD symptoms. Diet affects AD development by influencing the metabolites produced by the GM during digestion. The most significant metabolites in AD progression are SCFA, TMAO, and polyphenols. TMAO and select SCFA, most likely acetate, showed the same increased the expression of the NLRP3 and neural inflammation. Together these reveal the metabolic products of the gut microbiota and the physiological response causing the advancement of AD. In contrast, polyphenols and select SCFAs, such as sodium butyrate, have been shown to have neural protective effects against AD.

Through these studies, a clear link between the GM and AD progression has been established through the NLRP3 inflammatory response. However, the role SCFA plays in this neural inflammatory response is still debated. Future work to look at specific SCFA's to parse out the particular molecules that cause the inflammatory response would be beneficial to the field.

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