How interconnections between the gut microbiome and the brain influence Alzheimer's disease susceptibility and progression

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Abstract

Alzheimer's disease is a neurodegenerative disorder that causes memory decline over time. The human gut is colonized with millions of microscopic organisms that can communicate with the brain. Recently research has established a gut-brain axis between these two organs, and this communication link has been implicated in neurodegenerative diseases such as Alzheimer's disease. Given the mounting evidence that the gut-brain axis impacts Alzheimer's disease progression, the gut brain-axis may also have therapeutic potential. In this review, we discuss recent research that highlights the impact of the gut microbiome on Alzheimer's disease using mouse models and human fecal samples. We hope that increased knowledge of the gut-brain axis expands our understanding of Alzheimer's disease and leads to the advancement of future treatments.

Introduction

Alzheimer's disease (AD) is a type of neurodegenerative disease that causes memory decline over time. AD is the most common form of dementia, with an estimated 6.9 million Americans age 65 and older living with AD (Alzheimer's Disease Facts and Figures, 2024). People with this disease often require around the clock care and help with daily tasks, sanitary tasks, and other necessities. Additionally, caregivers of people with AD provide care for a longer duration than caregivers of people with other types of conditions, thus showing the far-reaching impacts of the AD (Katzman, 1986). Family and friends are often the ones caring for these people and since this care is long term, caregivers' mental and physical health is also affected (Alzheimer Society of Canada, 2024). While there are special nursing homes for AD patients, these facilities require staff with specialized training and there are concerns about whether the majority of the residents with AD or cognitive impairment receive the comprehensive care they need (Gaugler et al. 2014). Despite AD quickly becoming a major healthcare crisis, the causes and progression of AD are still not well understood, thus hampering any efforts to find effective treatments.

One of the main hallmarks of AD are the presence of extracellular protein deposits of amyloid beta (A□) plaques. These plaques are formed from the aberrant processing of a protein called amyloid precursor protein, and plaques are typically found in brain regions such as the hippocampus and cortex (O'Brien et al. 2011). These regions are crucial for memory and cognition (National Institute on Aging, 2024). The abnormal levels of A□ aggregates damage the communication between neurons, especially at synapses, which are critical for processing information and memory formation (Zhang et al. 2022). A□ plaques can also trigger chronic inflammation by activating immune cells such as microglia and astrocytes (Kinney et al. 2018). In the healthy brain, these glial cells try to clear away debris and maintain homeostasis (National Institute on Aging, 2024). However, they often fail in AD, which can lead to the release of proinflammatory cytokines and reactive oxygen species (Wang et al. 2015). This persistent inflammation damages surrounding neurons and further promotes disease progression.

A□ also contributes to the formation of another protein aggregate called tau. These intraneuronal tangles consist of hyperphosphorylated tau protein. Tau is a protein typically found on microtubules within neurons (Zhang et al. 2021). Microtubules are hollow, tube-like structures that help support the shape of a cell (National Cancer Institute, 2011). Neuronal microtubules are critically important for early developmental stages of the neuron and throughout life. This structure allows for the neuron to maintain its proper shape, to support axonal and dendritic

transport, and to accommodate shape changes such as alterations in dendritic morphology that may correspond with cognitive plasticity (Baas et al. 2016). Tau function involves helping the microtubules stabilize under normal physiological conditions (Avila et al. 2004). This healthy tau is beneficial because without it, the microtubules wouldn't be able to function (BrightFocus Foundation, 2024). However, tau protein can ultimately become hyperphosphorylated and form tangles. These tangles start in the brainstem, which connects the brain to the spinal cord. From the brainstem, they spread upward toward the entorhinal cortex and hippocampus, which are areas in the brain that are key to memory (BrightFocus Foundation, 2024). The build-up of these tangles causes a blockage within the neuronal transfer system, which causes microtubule instability and damages the synaptic communication between neurons, ultimately resulting in neuron death (Zhang et al. 2021).

The current treatments that have been approved by the U.S. Food and Drug Administration (FDA) for AD are anti-amyloid antibodies. These antibodies, donanemab and lecanemab, are the first disease modifying therapies that have been shown to reduce AD clinical symptoms (Van Dyck et al. 2023; Sims et al. 2023). These medications work by teaching the immune system to reduce the amount of amyloid protein in the brain (Cumming et al. 2023). Donanemab is an intravenous (IV) infusion therapy that is delivered every four weeks (Alzheimer's Association, 2024). By slowing down the progression of A□ accumulation Donanemab provides patients with more time to participate in daily life and live independently. In a similar manner, lecanemab (Leqembi) is an anti-amyloid antibody that lowers A□ in the brain and reduces cognitive and functional decline in people living with early AD (Alzheimer's Association, 2024). Although these drugs have proven to be beneficial, there are still some drawbacks to them. Side effects of these antibodies include fever, flu-like symptoms, nausea, vomiting, dizziness, changes in heart rate and shortness of breath. They may also cause serious side effects such as brain swelling or brain bleeding which can be fatal (Mayo Clinic, 2024). Time will tell if these anti-amyloid therapies are effective at widespread AD treatment and patient improvement.

While A□ and tau are the classic contributing factors to AD, recent studies have shown that the gut microbiome may play a crucial role in the development of this disease as well. The gut microbiome is an ecosystem in a person's gut that harbours trillions of microscopic organisms. These microorganisms include over a thousand species of healthy gut bacteria (gut flora), as well as viruses, fungi, and parasites. This ecosystem is unique to each individual person as it's developed through diet and environmental exposures. The range at which the gut microbiome assists the body is through physiological functions such as strengthening gut integrity or shaping the intestinal epithelium, harvesting energy, and protecting against pathogens and regulating host immunity (Thursby et al. 2017). It also helps provide essential capacities for the fermentation of non-digestible substrates like dietary fibres and endogenous intestinal mucus. This fermentation supports the growth of special microbes that produce short chain fatty acids (SCFAs) and gases (Valdes et al. 2018).

The gut microbiome interacts with many different parts of the body, including the brain, thus forming the gut-brain axis. In the past fifteen years, there has been an emergence of the gut microbiota as one of the key regulators of brain function. These two communicate through various parts of the body including the immune system, tryptophan metabolism, the vagus nerve, and the enteric nervous system. This communication also involves microbial metabolites such as short-chain fatty acids, branched chain amino acids, and peptidoglycans (Cyran et al. 2019). The brain and gut communicate various emotional, physical, and practical matters. The

body has more nerve cells in the gut than in any other part of the body which is why more information passes through these two organs than any other part of the body. This connection between the two have gained more traction in fields investigating the biological and physiological basis of neurodegenerative disorders. This new found discovery sparks the possibility that the gut may be another influencing factor towards neurodegenerative diseases such as AD. This connection is worth studying to further gain a better understanding about the disease and increase the therapeutic options. This review presents recent studies investigating the influence of gut microbes on AD based on data from animal studies and available clinical observations.

Elucidating the Impact of Gut Microbiome Alterations on Alzheimer's Disease Pathology using the APP/PS1 Transgenic Mouse Model

APP/PS1 mice are double transgenic models whose genomes have been specifically engineered to express multiple human mutations associated with familial Alzheimer's disease, enabling researchers to study disease mechanisms and potential therapeutic interventions (Sasaguri et al. 2017). This model specifically has been generated by crossing the well-established APP mutant line, Tg2576, with a line expressing mutant PSEN. These mice begin to develop many fibrillar Aβ deposits in the cerebral cortex and hippocampus at about six months of age. The plaque pathology is not only accelerated, but enhanced in the double transgenic mice, with Aβ deposits eventually occupying a large area of the neocortex and hippocampus by 16 months. There is a substantial increase in plaque-associated astrocytes and microglia, suggesting an overall increase in neuroinflammation between the ages of six and 16 months of age (Alzforum, 2024). With these alterations, the mice are able to mimic certain aspects of AD which allows researchers to discover more about the disease (Tai et al. 2021).

Researchers used the APP/PSI mouse model in their study to investigate therapeutic options towards AD. They investigated this by administering icariin (ICA) to the mice. This drug is an active ingredient extracted from *Epimedium* species and has shown promising signs towards AD treatment (Liu et al. 2023). Researchers tested their cognitive function using the Morris Water Maze (MWM) test and molecular structures using hematoxylin-eosin staining. RNA gene sequencing was also conducted on fecal samples to analyze the gut microbiome (GM) composition. This study found that the ICA injection improved cognitive dysfunction in APP/PS1 mice and typical AD pathologies in the hippocampus of the APP/PS1 mice, such as better latency in the MWM and preservation of nerve cells in the hippocampus, which is critical for learning and memory. The analysis also discovered that the ICA treatment altered the GM by increasing beneficial bacteria such as *Akkermansia* which is associated with blood lipid and blood glucose metabolism and decreasing pro-inflammatory species like *Alistipes,* which is associated with a higher fat diet. These findings indicate that ICA can possibly be a therapeutic option towards AD (Liu et al. 2023).

Research by Traini et al. (2024) demonstrated that prebiotics significantly impact AD progression by using APP/PS1 mice to comprehensively evaluate how probiotic and prebiotic interventions affect multiple disease parameters, including cognitive performance, intestinal mucus secretion, circulating Aβ levels, and gut microbiota composition. Male and female mice were treated with a multi-extract of fibers and plant complexes containing fruit oligosaccharides for six months starting at the age of two months. Fecal pellets were then extracted from the mice and then tested and processed for a total DNA extraction, which was then used to profile the gut microbiome. The results of this study show that the treatment was able to enhance the

performance of the rotarod test. The fourth and eighth months demonstrated that the motor coordination of the mice was unchanged in both sexes. However, between the first and third trials, with an increase in the latency of the first fall and a reduction in the total number of falls during the trials, indicating that the mouse's performance improved. In the Barnes maze test, the study found that both male and female groups showed a progressive reduction in their latency to find the escape hole, and the first five days represented the effective period of learning. In a marble burying test, the number of marbles buried by each mouse was low and comparable among all of the groups. This result demonstrated the absence of innate anxious behaviors or the presence of stressors in the environment. The application of these behavioral tests that investigated different types of brain performance showed that APP/PS1 mice, at the two ages, suffered from learning and memory deficits but did not present motor disorders or anxiety. The deficits were also prevented by the treatment with a mixture of prebiotics and probiotics, likely shaping the functions exerted by the gut microbiome. Furthermore, the treatment was effective in preventing the reduced mucus secretion of the intestinal epithelium and the increase in blood levels of Aβ, thus further suggesting the existence of the components of the microbiome–gut–brain axis, strengthening the role of the complex cross-talk occurring along the gut–brain axis and providing evidence about how modulation of the gut MB might translate into the improvement of AD pathology.

Researchers also used the APP/PS1 mice to explore the impact of periodontitis-related salivary microbiota on AD hallmarks. This study collected saliva samples from patients with periodontitis and healthy individuals. The salivary microbiota from the humans was then delivered via oral gavage to APP mice for two months. This study revealed that the salivary microbiota composition in patients with periodontitis was significantly changed compared with healthy individuals, with the enrichment of periodontal pathogens such as *Treponema, Porphyromonas*, and *Fusobacterium*. This study also suggested that the gut-brain crosstalk plays a crucial part in the event and development of AD. They conducted this by demonstrating through continuous gavage of periodontitis-related salivary microbiota in the transgenic mice. This resulted in gut microbial dysbiosis, intestinal pro-inflammatory responses, and intestinal barrier impairment, subsequently leading to the exacerbation of systemic inflammation. Gut-associated lesions were consistent with impaired cognitive function, increased Aβ accumulation, and neuroinflammation in the mice, suggesting that the periodontitis-related salivary microbiota may aggravate AD pathogenesis through bidirectional gut-brain communication. Notably, the results of this study show that periodontitis-related salivary microbiota exposure disturbed intestinal homeostasis by altering the gut microbiota and affecting the intestinal immune status in the AD mouse model, suggesting a role for oral examination in the treatment of AD (Lu et al. 2022).

Elucidating the Impact of Gut Microbiome Alterations on Alzheimer's Disease Pathology using the 5xFAD Transgenic Mouse Model

5xFAD mice are a transgenic mouse model like APP/PSI mice. However, this model is different from the APP/PSI mice because 5xFAD mice express human APP and PSEN1 transgenes (Alzforum, 2024). At three months of age, 5xFAD mice display prominent Aβ deposition, particularly in the hippocampus and cortex. Additionally, they have high levels of microgliosis and astrogliosis, in addition to impairments in spatial working memory and a decrease in anxiety that emerges between 3 to 6 months old (Oakley et al. 2006).

One study using 5xFAD mice treated these mice with antibiotics or probiotics containing *L.acidophilus* and *L.rhamnosus* for 14 weeks (Guilherme et al. 2021). The aim of this research was to explain the effect of a changed gut microbiome on pathological hallmarks of AD. The mice received food and water with the antibiotic mixture at the age of four weeks and this lasted up to 18 weeks. Behavior and disease pathogenesis were measured by nest building capability and plaque deposition, which is where they discovered that the nest building improved in the antibiotics-treated mice. These animals additionally displayed reduced plaque load in the hippocampus. They also discovered a change in the gut microbiome, as antibiotics significantly reduced viable commensals, while probiotics transiently increased *Lactobacillaceae.* This study provides evidence that antibiotics might create a beneficial effect on AD pathology and the subsequent drop in the influx of Aβ. This also demonstrates the complexity of studies on the involvement of the microbiota in non-gut disorders.

Microbial strains are a group of organisms that belong to the same species, but have unique genetic characteristics not found in other members of that species. These strains have helped facilitate identifying new species (Surat, 2018). In one study, researchers used a multi-omics approach to identify specific microbial strains and metabolites that could potentially mitigate amyloidopathy in 5xFAD mice. The models were orally administered the strains and then were maintained for 16 weeks (Kim et al. 2024). They then conducted a non-targeted metabolomic analysis that explored a wide range of metabolites and captured the overall metabolic changes under conditions with and without bacterial administration. By administering six strains they discovered that compared to 5xFAD control group, soluble Aβ-42 was significantly reduced in the cerebral cortex of mice treated with three microbial strains, namely, *S. thrm., L. reut., and L. lact*., suggesting that these species affect Aβ pathology in the brain. The researchers also discovered that the levels of Trp and ILA were relatively increased in the plasma of the group administered with the effective strains, which prevented both Aβ accumulation and cognitive impairment in the 5xFAD mice. This study also evaluated pro-inflammatory and anti-inflammatory cytokines in the plasma from microbial-administered mouse groups, including WT and 5xFAD mouse control groups. Pro-inflammatory cytokines were observed at lower levels in the effective groups *S. thrm.*, *L. reut.*, and *L. lact.*, potentially correlating to the reduced levels of soluble Aβ-42, as well as in the untreated 5xFAD mice. In contrast, pro-inflammatory cytokines were relatively higher in the non-effective groups that showed no changes in the soluble Aβ level and 5xFAD control group. This suggests that inflammation in the 5xFAD mouse groups treated with *S. thrm*, *L. reut*, and *L. lact* was reduced compared to the 5xFAD control group, transitioning to a level similar to that of WT. In conclusion, this research discovered that ILA may reduce inflammation and remove Aβ through microglia, implying an important role for indole-producing bacteria in AD patients.

Another study (Mezö et al. 2020) used 5xFAD mice to explore how the GF (germ-free) housing conditions and/or antibiotics (ABX) help reduce hippocampal Aβ pathology associated with neuronal loss. In order to conduct this study mice were housed under specific pathogen-free (SPF) conditions. In order to deplete microbiota, mice were treated orally via drinking water with a mixture of antibiotics (ABX). Researchers then conducted a DNA extraction, 16S rRNA sequencing and computation analysis of caecal contents from 4 months old SPF and ABX-treated 5xFAD mice. The research conducted found a significant reduction in species richness in ABX-treated 5xFAD mice and WT littermates. SPF mice showed robust hippocampal Aβ pathology at early (4 months) and later disease stages (10 months). This resulted in neuronal loss and memory deficits that were caused by the absence of gut

microbiota. RNA-seq analysis of hippocampal microglia uncovered distinct microbiota-dependent gene expression patterns including genes attributed to phagocytosis and complement signalling, which is beneficial in disease. Further, they found genes ascribed to AD-linked activation of microglia such as *Cst7*, *Clec7a*, *Apoe* and *Itgax* being expressed in a microbiota-dependent manner, which was lower in ABX mice and is not beneficial in terms of this disease. In conclusion, this study provided a better understanding of gut-microglia connection and the treatment of microglia-mediated CNS diseases.

Elucidating the Impact of Gut Microbiome Alterations on Alzheimer's Disease Pathology using fecal matter samples

Stool (feces/fecal matter) is made up of undigested food, bacteria, mucus, and cells from the lining of the intestines (National Cancer Institute, 2011). Stool contains trillions of microbes living inside our gut and could be beneficial when looking to treat or alter the microbiome.

One of the many diseases that have discerned similarities in fecal matter is AD. In one study researchers performed a bacterial 16S ribosomal RNA (rRNA) gene sequencing of DNA isolated from fecal samples to characterize the gut microbial communities in individuals with and without a clinical diagnosis of dementia due to AD (Schoch et al. 2012). The gene sequencing performed in this study is a sequencing method used to identify and compare bacterial diversity, from complex microbiomes or environments that are difficult to study. The researchers discovered that across all 40 participants, they observed generally consistent trends between bacterial relative abundance and CSF biomarkers of AD pathology. The study discovered that CSF p-tau and p-tau/Aβ-42 correlated with the gut microbiome of the AD participants that had decreased microbial diversity compared to control participants.

Similar to the previous research paper, Jung and colleagues extracted DNA from human feces to identify gut microbial alterations associated with preclinical AD (Jung et al. 2022). They did this by comparing cognitively normal (CN) older adults with cerebral Aβ deposition (Aβ+ CN) and those without cerebral Aβ deposition (Aβ− CN). There were 78 CN participants between 65 and 90 years of age included in this study. Stool samples were collected and underwent 16S rRNA gene PCR amplification, sequencing, and processing to extract the DNA from the feces. They identified a total of 227 fecal microbiome genera and 333 species in the participants. The five most abundant genera were *Bacteriodes*, *Prevotella*, *Faecalibacterium*, *Unclassified Lachnospiraceae*, and *Coprococcus*. Among the five genera that were decreased in the Aβ+ group were *CF231*, *Victivallis*, *Enterococcus*, *Mitsuokella* and *Clostridium*. Considering all the potential links between the genera, pathophysiological changes, inflammatory or metabolic changes may mediate the relationship between the microbial changes researchers found Aβ increase in preclinical AD. In conclusion, this study's findings suggest that specific alterations of gut bacterial taxa are related to preclinical AD and may be helpful for screening the preclinical AD.

Another group tried to identify specific gut bacterial taxa associated with preclinical AD (Ferreiro et al. 2023). They conducted this study by examining cognitively normal individuals with and without preclinical AD to determine whether cognitively normal individuals with preclinical AD may have an AD-associated dysbiotic gut microbiome. This study also investigated whether specific microbiome characteristics in stool samples correlated with preclinical AD status or established AD biomarkers. Spanning through three years, stool samples were collected from the participants and processed for bacterial DNA. The DNA extracted from the stool revealed microbial pathways that are associated with preclinical AD.

The microbial pathways most associated with preclinical AD are L-arginine, L-ornithine, and 4-aminobutanoate, which all have succinate as a bacterial metabolite. Succinate is largely known as an intermediate of the tricarboxylic acid cycle. It's also a bacterial metabolite produced in the gut that has been associated with obesity. This intermediate succinate is a major precursor for the short-chain fatty acid (SCFA), which has been found to be elevated in symptomatic individuals with AD and in AD mouse models. This study also discovered that distinct *Bacteroides* species were highly associated with preclinical AD and healthy groups (*Bacteroides intestinalis* and *Bacteroides caccae*, respectively). In summary, this study reports global and specific differences in the gut microbiome at the preclinical stage of AD.

Discussion

The articles discussed in this review are all crucial to furthering our understanding of the gut-brain axis. These new studies reveal aspects and contributions that were previously unknown about AD and could lead to new therapeutic targets. For example, icariin might be a promising therapeutic intervention in the future (Liu et al. 2023). Given that the current therapeutic options available for AD have varying levels of effectiveness, (Mayo Clinic, 2025), researching new therapeutic targets, such as the gut microbiome, are crucial for working towards a cure. Another possible therapeutic option that has been mentioned throughout this review could include prebiotics and probiotics such as inulin/FOS as a possible way to decrease AD hallmarks (Guilherme et al. 2021). Not only are the reviewed papers useful for discovering a potential AD treatment, but they are also good for scientists to learn from and discover new aspects of AD. For example, Jung and colleagues used fecal matter for characterizing the gut microbial communities and even suggested that specific gut bacterial taxa alterations are related to preclinical AD (Jung et al. 2022). This suggests that these changes may precede cognitive decline and signify that further inspection of the gut microbiome during preclinical AD screening may be helpful.

Although there are numerous benefits to gut-brain axis research, there are also some limitations. Some limitations are the time it will take to logistically plan and start testing these primary discoveries on humans in the clinic, in addition to the translatability of these studies to humans. Although the APP/PSI and 5xFAD mice model major aspects of human AD, the results may not be the same in humans as it is in the mice. These models often lack the widespread presence of other pathological features that define AD including neuronal loss and most importantly, neurofibrillary tangle development (Drummond et al. 2017). Another limitation regarding these studies is that their range of methods used are limited. One group stated that the scope of their study was limited because they only used one analytical method to detect the fecal and serum metabolites (Liu et al. 2023). Given these limitations, further research should be done to help confirm whether the beneficial or detrimental effects of the microbiomes found in mice are also present in humans. In future studies, multiple analytical methods should be used to widen the scope of the studies. Another aspect that should be in future studies is longer research periods in order to fully rule out the relationship the gut microbiome and the brain have. The progressive nature of AD can challenge the conclusion of trials, which is why longer trials are beneficial for capturing definitive clinical outcomes (Liu et al. 2023). Overall, more research on how the gut microbiome is related to AD should be conducted to help better understand the gut-brain axis and find more therapeutic options.

Conclusion

Alzheimer's disease (AD) is a progressive brain disorder that deteriorates memory. The human gut is colonized with millions of microbial species and has been shown to communicate with the brain. This gut-brain axis is a two way communication system that has been increasingly linked to neurodegenerative disease such as AD. The complex interplay between the gut-brain axis and Alzheimer's disease pathophysiology remains partially elusive, representing a critical frontier for neurodegenerative disease research and therapeutic development.In this review, we discussed recent studies that have investigated different aspects of the gut brain axis connection to AD, with the hope that further research will be able to provide a better understanding about the disease and the connection to the gut microbiota. A deeper understanding of the gut-brain-axis could pave the way for innovative approaches to treating AD.

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