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Symposium

Symposium: What Does the Microbiome Tell Us about Prevention and Treatment of AD/ADRD?

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Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRDs) are broad-impact multifactorial neurodegenerative diseases. Their complexity presents unique challenges for developing effective therapies. This review highlights research presented at the 2024 Society for Neuroscience meeting which emphasized the gut microbiome's role in AD pathogenesis by influencing brain function and neurodegeneration through the microbiota–gut–brain axis. This emerging evidence underscores the potential for targeting the gut microbiota to treat AD/ADRD.

Introduction

Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRDs) are among the leading causes of death in the United States, creating a significant health, economic, and societal burden for patients, caregivers, and society at large (Wong, 2020). AD/ADRDs are late onset, multifactorial, progressive, and terminal neurodegenerative diseases characterized by impaired cognition and behavior, memory loss, and dementia. The pathophysiological hallmarks of AD include the aggregation and spread of hyperphosphorylated tau proteins and amyloid-(Aβ) plaques accumulation in the brain, which lead to neuroinflammation, neuronal loss, and neurodegeneration (Ballatore et al., 2007; Sexton et al., 2024). AD and ADRDs—including frontotemporal dementia (FTD), Lewy body dementia, and other brain disorders—share many cognitive and physiological pathologies. These characteristics are observed beyond AD, representing a host of tau-mediated neurodegenerative disorders and dementias. Despite its significant health impact, clinical relevance to a broad scope of disorders, and prolific research investment, AD etiology is not completely understood.

Genes such as apolipoprotein E (*APOE*) and triggering receptor expressed on myeloid cells 2 (*TREM2*) are risk factors for late-onset AD; however only a small number of AD cases are caused by autosomal dominant mutations in amyloid precursor protein (*APP*), presenilin (*PSEN*) 1/2 (Guerreiro et al., 2013; Perkovic and Pivac, 2019). Most cases are believed to result from interactions between the genome and the exposome—nonheritable environmental factors such as diet, microbes, lifestyle, socioeconomic status, and environmental exposures (Tamiz et al., 2022). Peripheral influences on brain health are important to understand AD complexity and heterogeneity toward the development of effective treatments. Symbiotic microbes live in the gastrointestinal tract and are referred to as the gut microbiota. The gastrointestinal tract hosts ∼70% of the body's immune cells, >100 million enteric neurons, and ∼40 trillion bacteria (Yoo and Mazmanian, 2017). This colocalization of a myriad of immune, neural, and bacterial cells creates complex interactions regulating human health across all systems, including the central nervous system (Schroeder and Backhed, 2016). The bidirectional communication between the gastrointestinal tract and the brain suggests that the gut microbiota impacts brain function and influences neurodegenerative processes in AD (Erny et al., 2015; Thion et al., 2018; Kling et al., 2020; Spichak et al., 2021; Chandra et al., 2023). Furthermore, genetic overlap between AD and gastrointestinal disorders suggests an interaction between the gut microbiome and genetics in AD pathogenesis (Adewuyi et al., 2022). A better mechanistic understanding of how the microbiome influences AD/ADRD onset and progression is leading toward new molecular targets for drug development and the potential use of pre- and probiotics as an added therapeutic intervention.

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This review describes the current understanding of how the microbiome, genetics, and the nervous system interact to influence AD, neurodegeneration, and neuroinflammation. Talks presented at the 2024 Society for Neuroscience meeting highlighted the importance and implications of the gut microbiome in AD. This review is divided into three sections. The first discusses the role of the gut microbiome and its metabolites in disease pathogenesis. The second examines implications of the gut microbiome in experimentation: primarily, the importance of well-designed studies to consider the gut microbiome–brain axis and how the gut microbiome impacts the reliability of animal models. The third section highlights microbiome-based interventions for treatment and management of AD. Research presented on AD and the microbiome has broad implications for many neurodegenerative diseases, tauopathies, and ADRDs which present conserved pathophysiological patterns.

The Microbiome and Neurodegeneration

Gut dysbiosis

A mutualistic and balanced relationship between microbiota and the host (eubiosis) supports human health, while dysbiosis, or disruptions to microbial communities, is linked to disease. Gut bacterial communities differ between AD patients and cognitively normal individuals (Hung et al., 2022; Chen et al., 2023). Similar findings have been found in individuals with mild cognitive impairment (MCI), suggesting that shifts in microbiome composition and metabolism may contribute to dementia progression, possibly through impaired adult hippocampal neurogenesis (Sheng et al., 2021). In AD patients, the relative abundance of the bacterial phylum *Firmicutes*, which produces essential metabolites, is lower whereas the proinflammatory taxa *Bacteroidetes* is higher (Cattaneo et al., 2017; Murray et al., 2022; Grabrucker et al., 2023). Additionally, the relative abundance of serotonin-transporting bacterium *Turicibacter* spp. decreases in cohorts of AD patients in an age-dependent manner (Vogt et al., 2017). Animal models that recapitulate human AD display similar microbiome and microbial metabolic profiles. For example, the relative abundance of *Turicibacter* spp. decreases with age in the transgenic Aβ mouse model, 5xFAD, when compared with wild-type animals (Dunham et al., 2022). Further, the microbiota composition of hAβ-KI (late-onset AD) mouse models differed from 3xTg-AD (early-onset AD) mouse models and from wild-type controls, driven primarily by dissimilar abundance of *Romboutsia ilealis* and *Turicibacter* species (Dunham et al., 2024).

In AD, the hippocampus is one of the first brain regions affected (Braak et al., 1993). Although still debated, the hippocampus is host to a population of neural stem cells in the dentate gyrus subfield, which generate new neurons throughout the lifespan in a process of neural plasticity called adult hippocampal neurogenesis (Kempermann et al., 2015; Kozareva et al., 2019). Adult-born neurons integrate into the hippocampal circuitry required for episodic memory functions such as pattern separation, one of the initial cognitive impairments in aging AD patients (Moreno-Jimenez et al., 2019; Tobin et al., 2019; Salta et al., 2023; Lazarov et al., 2024). Expounding the role of the gut microbiota in adult hippocampal neurogenesis, germ-free mice devoid of microorganisms and antibiotic treatment experiments in rats have shown decreased adult hippocampal neurogenesis and associated AD behavior (Ogbonnaya et al., 2015; Nicolas et al., 2024).

Fecal microbiota transplantation is the transfer of a microbial community from a donor to a recipient host, and is a tool to establish causal relationships between altered microbiomes and the host's physiological or pathological condition. Fecal transplantation from AD patients into microbiota-depleted young rats increased the abundance of harmful *Desulfovibrio* bacteria compared with control rats receiving fecal samples from healthy subjects (Grabrucker et al., 2023). Notably, the gut microbiota from AD patients caused memory deficits in the recipient rats. In particular, impairments in pattern separation were observed coupled with reduced adult hippocampal neurogenesis and an altered caecal and hippocampal metabolome. These results suggest that *Desulfovibrio* may be a compositional gut microbiome signature for AD cognitive status. Similar results have been observed in preclinical studies where fecal microbiota transplantation from an AD transgenic mouse model resulted in memory and adult hippocampal neurogenesis impairments in healthy control mice (N. Kim et al., 2021). These studies demonstrate that AD's symptoms are transferred to a healthy organism via the gut microbiota and suggest that AD pathogenesis is a converging cellular process impacted by circulatory and gut-mediated factors, including microbe-derived metabolites (Maruszak et al., 2023).

Microbial-derived metabolites

Gut microbiota secrete bioactive metabolites into the bloodstream, including neuroactive molecules that modulate host brain function. Metabolomics (study of metabolites) allows for the simultaneous detection of compounds that may be involved in disease pathology and progression and provides a snapshot of the individual overall metabolic state. Bacteria-derived metabolites are associated with biological pathways altered in AD such as peripheral immunity, adult hippocampal neurogenesis, and cognitive decline (Hernandez-Benitez et al., 2012; Gebara et al., 2015; MahmoudianDehkordi et al., 2019; Nho et al., 2019; Baloni et al., 2020; Jia et al., 2020; Grabrucker et al., 2023; Schweickart et al., 2023; Seo et al., 2023). Though causative mechanisms have not yet been described, shifts in microbiome composition are associated with metabolic neurodegenerative processes (C. S. Kim, 2024). Bioavailability and metabolism of various metabolites have been experimentally associated with AD/ADRD, including biosynthesis of tryptophan, short-chain fatty acids (SCFAs), trimethylamine *N*-oxide (TMAO), neurotransmitters like histamine, GABA, serotonin, dopamine, indole-containing compounds, and branched-chain amino acids (Bravo et al., 2011; Pedersen et al., 2016; Toledo et al., 2017) Human hippocampal progenitor cells exposed to serum (containing circulatory metabolites) from AD patients resulted in a decrease in proliferation and differentiation of the progenitor cells; these in vitro neurogenic readouts correlated with cognitive screening scores and key gut microbial species of the AD patients (Maruszak et al., 2023).

Neuroinflammation and neurodegeneration in AD are influenced by SCFAs, which affect Aβ plaque pathogenesis, modulate plaque neurotoxicity, and mediate anti-inflammatory signaling in vitro (Ho et al., 2018). Notably, SCFAs are reduced in the blood of AD patients with brain Aβ pathology (Marizzoni et al., 2020). Additionally, gut SCFA production alters microglial response to plaque burden in the AD brain by modulating expression of disease-associated microglial genes such as *TREM2*, *APOE*, and others involved in activation or suppression of the neuroinflammation-neurodegeneration pathway (Erny et al., 2021; Huang et al., 2023). Specific mechanisms involved in glial modulation are unknown; SCFAs may regulate glial function after entering the brain via epigenetic and mitochondrial

metabolic mechanisms (Erny et al., 2021). These results support previous reports implicating the brain innate immunity (i.e., glia) in the development of Aβ and tau pathology and neurodegeneration (Shi and Holtzman, 2018; Shi et al., 2019).

Serotonin, carnosine, several phosphatidylcholines, and phenylacetone are differentially abundant in AD mouse model biosamples (5xfAD and APP transgenic mice) when compared with wild-type animals (Kimball et al., 2016; Dunham et al., 2022). Serotonin is a neurotransmitter regulating brain function, cognition, and mood (Aaldijk and Vermeiren, 2022; Goncalves et al., 2022; Baker et al., 2024). Consistent with shifts in microbiota, the serotonin system is altered in MCI and AD (Smith et al., 2023a,b). Peripheral serotonin bioavailability, and neurotransmitter metabolism more broadly, is regulated in the intestine by bacteria species, including *Turicibacter* spp. (Fung et al., 2019). Although 90% of the human body's serotonin is gut derived, serotonin secreted to the periphery does not cross the blood–brain barrier (El-Merahbi et al., 2015; Dunham et al., 2022). The influence of microbial serotonin on and its mechanistic relationship with pathogenesis in the brain is complex and requires further investigation.

The gut microbiome–brain axis is also altered in mood disturbances such as depressive episodes, anxiety, and aggression, which are common behavioral presentations of neurodegenerative pathology (Grossberg et al., 2020). Altered gut microbial composition, bacteria-derived metabolites, and intestinal symptoms are linked to neuropsychiatric disorders inlcuding anxiety and depression (Brydges et al., 2021; MahmoudianDehkordi et al., 2022). Altogether, these findings suggest that the gut microbiota impact the CNS beyond the secretion of proinflammatory or immune mediators into the periphery but through modulation of neurotransmitter metabolism and other neuroactive molecules such as secondary bile acids. Thus, bacteria-derived metabolites may serve as biomarkers for AD pathology and could be used as a noninvasive screen for progression of diseases.

Experimental Considerations

Among other environmental factors, microbiota significantly influence AD/ADRD and should be considered in preclinical research. Reliable animal models and effective study designs are essential to identify the complex biological networks defining the gut microbiome–brain axis in AD/ADRD (Vogt et al., 2017). Most animal studies of neurodegenerative disease do not consider the microbiome, despite emerging clues about the role of microbial exposures on disease onset and progression. For example, timing of neurological symptoms onset and lifespan are modified whether pathogen-free conditions are used (Figueroa-Romero et al., 2019), phenotypes are lost in animal models when moving to new facilities, and phenotypes differ between cages or facilities (Servick, 2016). These suggest that microbial exposures interact with biological processes and genetic factors triggering neuronal pathology.

Cage effects

Cohoused animals share strong microbial features, similarly to how humans share microbes within households (Song et al., 2013). Cage-dependent microbiome and metabolomic signals often outweigh those related to genotype or disease progression and should be carefully considered in study design (Ericsson et al., 2018). Across microbiome studies, individual and family-related microbiome variance is greater than other factors, such as disease state. "Cage effects" can obscure results, especially in animals like mice, where these effects account for up to 80% of microbiome variance and 20% of metabolite variance (Dunham et al., 2022). In addition, mice are coprophagic rodents; they obtain essential nutrients by eating feces from their cages. This fecal microbial self-reinoculation affects mouse gut microbial composition. Co-housing experiments have demonstrated that healthy animals can develop AD-like phenotypes via coprophagic exposure to mice with AD (Wang et al., 2019). Thus, reducing animal density and treating the cage as the unit of replication will reduce experimental variance and will improve the reproducibility of the microbiome in neurodegeneration animal studies (Bogatyrev et al., 2020; Ericsson and Franklin, 2021; Russell et al., 2022).

Animal models and treatments

The conditions in which laboratory animal models are raised suggest that microbial exposure influences AD pathology, progression, and lifespan. AD transgenic gnotobiotic mice—animals born and raised in sterile conditions—or antibiotic-treated animals present decreased Aβ brain pathology, reduced glial reactivity, and altered immune response compared with wild-type mice (Minter et al., 2016; Harach et al., 2017). Although antibiotics are widely used to perturb the commensal gut microbiome in animal models, behavioral off-target effects such as water and food consumption should be considered (Bongers et al., 2022).

New animal models are emerging to better recapitulate human conditions and to improve the validity and translatability of AD preclinical studies to humans. The wildling mice are natural microbiota-based models, which have shown to better resemble human immune responses than the conventional laboratory mice (Rosshart et al., 2019). Humanized AD/ADRD wildling mice could offer better understanding on how environmental conditions impact the gut microbiome–brain axis in AD/ADRD.

Genome and sex-specific effects

Investigating the interplay between metabolomics and the microbiome in AD has uncovered gene- and sex-dependent differences, shedding light on how these factors together influence disease progression and biological processes. Dunham and colleagues used shotgun metagenomic sequencing and untargeted metabolomics to show that female hAβ-KI mice (late-onset AD) harbored distinct microbiomes when compared with their age- and sex-matched wild-type counterparts (Dunham et al., 2024). Eighteen percent of the microbiome variance was attributable to genotype, and the differences were largely driven by the increased abundance of several low abundance microbes (2% relative abundance or lower), as well as a single high-abundance *Muribaculum* species, which was significantly depleted in female hAβ-KI mice. Conversely, the male hAβ-KI microbiomes were indistinguishable from control mice.

Neurodegenerative disease mouse models differ by sex in their presentation of pathology and their response to experimental treatments. Pathological phenotypes of female mice from amyloidosis and tau pathology models respond to microbiome perturbations and antibiotic treatment dissimilarly to their male counterparts when compared with wild-type mice (Dodiya et al., 2019; Chandra et al., 2023; Seo et al., 2023). In addition, ovariectomy to females decreases Aβ pathology and plaque-associated microglia. These observations implicate the complex interaction between sex-specific hormonal modulations, gut microbiota dynamics, and pathology (Saha et al., 2024). Future studies combining ovariectomy and antibiotics in different AD animal models may clarify the differential response to antibiotics in the tau- and Aβ-mediated neurodegeneration.

Seo and colleagues investigated whether the gut microbiota regulates tau-mediated neurodegeneration by interacting with APOE isoforms. AD is the most common of tauopathies, presenting with tau-associated neurodegeneration comparable with other primary tauopathies, including frontotemporal dementia (FTD) and Pick's disease, primary supranuclear palsy (PSP), and corticobasal degeneration (CBD). The gut microbiota structure in tau-mediated neurodegeneration is affected by apolipoprotein E (APOE) isoforms, the strongest genetic risk factors for AD (Shi et al., 2017; Tran et al., 2019; Parikh et al., 2020). Manipulation of the gut microbiota in a mouse model of tauopathy expressing P301S human mutant tau and different forms of human APOE revealed a significant microbial contribution to tauopathy. Under germ-free conditions (those devoid of microorganisms), tau-mediated neurodegeneration was blocked. Following short-term antibiotic treatment during early life, Seo et al. observed a drastic reduction of AD pathological hallmarks, such as neuroinflammation, hyperphosphorylated tau, and severe brain atrophy in male mice carrying *APOE3*, but not *APOE4*. Notably, these phenotypic effects of early life antibiotics were not observed in females. In addition, when supplementing SCFAs to adult germ-free P301S/APOE4 mice, reactive glial phenotype and gene expression, tau pathology, and neurodegeneration increased (Seo et al., 2023). These observations suggest that the gut microbiota may play an essential role in modulating tau-mediated neurodegeneration and the severity of the pathology is altered depending on APOE genotype and by sex.

Finally, interactions between microbial produced metabolites, microbiota, AD pathology, and sex have been observed in the APOE4*TREM2 and hAB-KI AD animal models, which exhibit different levels of amino acids, glycerophospholipids, acylcarnitines, secondary bile acid, taurodeoxycholic acid, and peptides in a sex-dependent manner (Dunham et al., 2024; Pandey et al., 2024). Sex-dependent metabolite biomarkers may also facilitate early AD diagnosis.

Microbiome-Based Interventions for AD/ADRD

Incomplete etiology of most neurodegenerative diseases halts the development of efficient therapies. Current strategies for treating AD include targeting abnormal protein formation by using pharmacological modulation of tau microtubules and hyperphosphorylation and Aβ plaque clearance (Pardo-Moreno et al., 2022). However, none of these strategies have proven effective in humans, perhaps due to the complex pathophysiology of the disease and other unknown factors beyond biochemical abnormalities with tau and Aβ. Clinical and preclinical studies suggest that the gut microbiota could serve as a therapeutic strategy to slow the progression of AD and other tauopathies (Seo et al., 2023). Approaches to shift the microbiome composition from dysbiosis to eubiosis in AD/ADRD include antibiotics, prebiotics (beneficial foods), probiotics (live beneficial organisms), and postbiotics (metabolites; Seo and Holtzman, 2024).

Antibiotic treatment has been suggested as a potential therapy for AD. A recent epidemiological study analyzing public health insurance data in Germany reported that antibiotics decreased the likelihood of developing dementia (Rakusa et al., 2023). However, there are reports indicating that antibiotic treatment is associated with cognitive impairment (Ye et al., 2024). Thus, a better understanding of the microbes and pathways altered by antibiotics is needed.

Fecal microbiota transplantation is an emerging approach for restoring gut microbiota in neurodegenerative disease (Ghezzi et al., 2022). A case study reported that an AD patient receiving a fecal microbiota transplant from a healthy donor to treat *Clostridioides difficile*, an infection of the gastrointestinal tract, presented with attenuated AD symptoms (Hazan, 2020). Refinement of fecal microbiota transplantation to optimize and prolong engraftment efficiency and mitigate risk of side effects from potential transmission of detrimental microbiota will offer therapeutic strategies for intervention in AD. In addition, microbiome composition can be altered by diet. The modified Mediterranean ketogenic diet and curcumin intake shift gut microbial composition in AD patients, resulting in improved cerebrospinal fluid AD biomarker profiles, modulation of gamma-aminobutyric acid (GABA) metabolism, and restoration of bile acid pool. Dietary interventions, including antioxidants and anti-inflammatory rich diets, reduced caloric intake, and supplementation of gut-derived fatty acids, are noninvasive means to positively influence metabolic profile, gut microbiota, and health in those at risk for AD (Nho et al., 2019; Dilmore et al., 2023; Ross et al., 2024).

Conclusion

The gut microbiome–brain axis significantly impacts AD/ADRD pathogenesis, the study of neurodegeneration, and the development of prospective therapeutics for neurodegenerative diseases. First, the microbiome is associated with neurodegenerative mechanisms; gut dysbiosis is linked to AD with compositional characteristics correlating to pathophysiology and neurogenesis. Second, microbiomes are a significant confounding factor and promising target in the study of neurodegenerative disease mechanisms in animal models. Microbiota variation confers cage effects and significantly influences AD animal research outcomes. Robust animal models that consider microbial exposure, genetic factors, diet, and sex-specific responses are essential for replicating and translating human disease mechanisms and testing treatments. Third, therapeutic strategies targeting the gut microbiome, such as fecal microbiota transplantation and dietary changes, show promise in modulating AD by restoring microbial balance.

Novel tools analyze how the microbiome interacts with other biological systems. Resources like the Human Microbial Metabolome Database (MiMeDB) are essential for identifying key interactions between microbes and metabolites, providing valuable support for AD/ADRD research (Wishart et al., 2023). Initiatives such as the AD Metabolomics Consortium (ADMC) and the AD Neuroimaging Initiative (ADNI) are using advanced technologies to map metabolic dysregulation in AD, offering new insights into disease mechanisms and potential treatments (Wishart et al., 2023).

Continued exploration of the gut microbiome's role in pathogenesis and methods for microbiota reconditioning will advance the study and treatment of AD/ADRD. Understanding biochemical connections between the gut, brain, and other organs will progress effective interventions in the fight against debilitating neurodegenerative diseases. More mechanistic research is needed to fully understand the complex interactions between microbiota, microbial metabolism, and disease-related molecular targets. Collaborative efforts across various fields, including neurology and microbiome research, are crucial for advancing our understanding and developing innovative interventions for AD/ADRD.

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