Differences in Gut Microbiota as a Potential Factor in Alzheimer's Disease Development

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ABSTRACT

Considering that humans consist of more non-human species than cells, it is critical to understand the impact of the microbiome on diseases. As Alzheimer's disease becomes a more and more pressing issue, it may be possible to combat it or slow its progress by understanding how alterations in the gut microbiome, which can influence functions in the brain in a variety of ways, affect its development.Gut bacteria can produce neurotransmitters such as melatonin, gamma-aminobutyric acid, histamine, and acetylcholine, which can contribute or antagonize neuroinflammation and neurofibrillary tangles. It is best to balance beneficial bacteria with harmful bacteria. Additionally, using probiotics and altered diets can serve to change gut microbiome composition and influence Alzheimer's disease development. It is important to understand microbiome-cell interactions and utilize that information to create new therapeutic strategies for Alzheimer's disease through forms like diets, probiotics, and interventional procedures.

Introduction and Background Research

Alzheimer's disease (AD) is a neurodegenerative disorder resulting in dementia, loss of independence, and death from an amalgamation of conditions from a weakened body. It appears as cognitive and physical impairment (Henley et al., 2015). Neurofibrillary tangles formed of hyperphosphorylated tau protein and plaques formed of amyloid-β protein are characteristic of AD. Studies have shown that the dysregulation of neural functions, like disruption of kynurenic and serotonin pathways, is present in Alzheimer's disease (Sochocka et al., 2018). Such interferences can be caused by various metabolites that penetrate the blood-brain barrier (BBB). Conversely, metabolites moving through the BBB can positively impact the progression of AD. A transgenic murine model of AD demonstrated improved learning and memory with an increased sodium butyrate treatment (Govindajaran et al., 2011).

It is suggested that humans contain the same number of microorganisms as human cells, and for this reason, looking inwards is critical. The gut microbiome, specifically, has been shown to contribute to the body's interaction with pathogens, vitamin biosynthesis, regulation of bone density, and much more (Giau et al, 2018). Literature suggests that intersections of the gut and the brain, like the hypothalamic-pituitary-adrenal axis (HPA) is a prominent route of communication. Developmental research shows that the importance of the microbiome is important as early as gestation (Das & Nair, 2019). In murine models, interactions between gut microbiota and the developing human has been shown to influence HPA axis development. Additionally, gut microbiota could affect the activity of neurotransmitter systems in various brain regions, impacting motor control and anxiety in adult life (Calvani et al., 2018).

Studies involving germ-free (GF) mice demonstrated that the gut microbiome is affected at different times and that the effects are specific to sex. Gut microbiome depletion is found *in utero* development in males, and during adulthood for females (Calvani et al., 2018). Ethnicity, region, and sex appear to be important epigenetic factors in microbiome health and composition. The male brain appears to be more vulnerable to microbiota-induced results, according to animal studies (Jaggar et al., 2020). The GF mice showed that increased myelination in the prefrontal

cortex could be reversed by colonization of certain microbiota after birth (Calvani et al., 2018). There is ample evidence supporting the role of the gut microbiome on the human body, especially in brain functions.

Effects of Products of the Gut Microbiome on Alzheimer's Disease

Metabolites that disrupt brain functions can be created by the gut microflora, which contains up to 95% of the human microbial population. The intestinal mucosal lymphoid tissue contains a majority (70%-80%) of the immune system of the body, which stays in close proximity to the gut bacteria and therefore is affected by fluctuations in the gut microbiome. Such bacteria produce neurotransmitters such as melatonin, gamma-aminobutyric acid, histamine, and acetylcholine, which could lead to inflammation within the brain (Sochocka et al., 2018).

Various studies have shown that changes in the gut microbiome are associated with AD pathology. One such study used rRNA-sequencing of DNA found in the fecal matter of AD-diagnosed and not diagnosed individuals. AD patients demonstrated a reduced richness (according to the abundance-based coverage estimator) in microbiome composition. Compared to the control group matched by age and sex, 14 OTUs were more abundant and 68 OTUs were less abundant in AD patients, where OTU is an operational taxonomic unit cluster of rRNA sequence reads. Research by Vogt et al showed a decrease in the phylum *Firmicutes*, which makes up to 80% of all gastrointestinal tract bacteria, a decrease which is also associated with obesity and type 2 diabetes. Diabetes and insulin resistance have been shown to increase risk of Alzheimer's disease. The study also showed a decrease in *Bifidobacterium* in AD patients, a genus correlated with decreased intestinal permeability and decreased inflammation in the gut, as well as an increase in phylum *Bacteroidetes*, and such bacteria have a membrane made of lipopolysaccharide (LPS), which can release pro-inflammatory cytokines (IL6, IL10, IL12p40, IL17A, IL22, IL23p19, TNFα) when translocated from the gut to circulation. Studies involving LPS also show that injection into transgenic and wild-type AD mice increases amyloid deposition and neurofibrillary tangles (Vogt et al. 2017).

Chronic gut inflammation may lead to increases in amyloids, lipopolysaccharides, and serum amyloid A (SAA), which could leak from the gut and increase levels of pro-inflammatory cytokines. This could allow for amyloid proteins to more easily cross the blood-brain barrier as the cytokines alter RAGE, LRP-1 receptors, and tight junctions, making the barrier more permeable. Cytokines that are able to reach the brain may signal toll-like receptors 2/1. CD14, and NF-κB, which play a role in neurodegeneration. Additionally, bacterial species such as Lactobacillus and Bifidobacterium metabolize glutamate to produce γ-aminobutyric acid (GABA), and alterations in the gut microbiome could lead to alterations in GABA which is linked to cognitive impairment, anxiety, depression, and Alzheimer's disease (Pistollato et al. 2016). E. coli LPSs have been shown to be abundant in neocortical and hippocampal extracts from an AD brain, correlating with research that LPS induces pro-inflammatory signaling in primary human neurons (Zhao et al. 2017). Catecholamines, hormones produced by adrenal glands, have been shown to be produced by a wide range of bacteria, especially dopamine which can be used to treat Alzheimer's disease (Patterson et al., 2014).

Gut microbiome-derived endotoxins are generally components of the cell wall of Gram-negative bacteria. When they diffuse, they can induce fever, hemorrhage, leukopenia, and other systemic effects. *B. fragilis* toxin (BFT) has been shown to disrupt epithelial cells of the gastrointestinal tract by cleaving the synaptic type-1 transmembrane adhesion protein E-cadherin, and has been shown to affect pathology of autism spectrum disorder. It has been observed that BFTs affect the function and strength of synapses, through amyloid peptide-dependent changes in synaptic adhesion, which disrupts signaling between neurons (Zhao et al. 2017).

Studies suggest that lymphoid follicles are key sites of prion accumulation in the small intestine, which further facilitates interaction between the gut microbiome and AD brain pathology. Prions are misfolded β-sheet forms of proteins which have been shown to be aggregated in AD brains and result in cascades of neurodegenerative pathways. Prion misfolding from its normal PrPC form to its pathological form PrPSc has been one of the leading investigated causes of Alzheimer's disease. Bacteria in the gut can induce amyloid-beta oligomerization, which again changes the shape of a prominent protein in the brain and promotes aggregation (D'Argenio & Sarnataro, 2019).

Alterations Made to Gut Microbiome and its Effects

Changes to the microbiome might be the answer to increased and decreased Alzheimer's disease progression. A study conducted on melanoma patients demonstrated that a favorable microbiome composition correlated with enhanced T-cell responses and tumor control. This established a relationship between the microbiome composition and health to immune response and disease progression, which can be applied again to Alzheimer's disease (Hylander & Repasky, 2019).

Choline is critical for signaling, repair, and transport through the cell membrane as well as membrane function and structure. It is integral to the synthesis of acetylcholine, identified earlier as contributing to inflammation in the brain, and to methylation and gene expression, where studies involving DNA methylation in AD indicate a direct association between the two (D'Aquila, 2020). Choline is metabolized into trimethylamine (TMA), and then into trimethylamine N-oxide (TMA) and it is then distributed to organs. High TMA and TMAO levels are shown to correlate with a high *Firmicutes/Bacteroidetes* ratio. Western diets, which contain regular consumption of pork meat, liver, and eggs, contain large amounts of choline. As the Western animal-based diet correlates with elevated TMAO levels and choline levels, it could lead to heart disease from TMAO accumulation as well as neural inflammation (Arias et al., 2020).

Omega-3 fatty acids affect the gut microbiome as well. Omega-3 polyunsaturated fatty acid (PUFA) supplements showed increases in *Bifidobacterium* and *Oscillospira* genera, and a reduction of *Coprococcus* and *Faecalibacterium* genera. There was an increase in butyrate-producing genera after the PUFA supplementation, where butyrate is one of the most abundant short-chain fatty acids in the gut lumen as a product of fermentation by dietary fibers by microbiota. Butyrate is linked to anti-inflammatory properties, so omega-3 fatty acid supplementation is a viable indirect solution to inflammation (Costantini et al., 2017).

The vegan diet, which excludes any products made out of animals, results in a different nutrient income, including fruits and vegetables. The vegan diet appears to result in less gut microbiome changes, with omnivores demonstrating a greater change as animal-biased diets have increased levels of fecal bile acids which act in composition-altering metabolic and inflammatory pathways. Enterotyping demonstrated that an increased *Prevotella* to *Bacteroides* ratio was present in people with a vegan diet as opposed to a Western meat-based diet (Jaggar et al., 2020). *Prevotella* provides anti-inflammatory properties in diseases like arthritis and multiple sclerosis (Tomova et al., 2019). Persons who have human immunodeficiency virus (HIV) have shown gut microbiomes that have less biodiversity, with increased bacteria of clade *Desulfovibrionaceae* and decreased bacteria of clade *Clostridia*, resulting in up to a five-fold excess risk of metabolic syndromes that could produce neurotransmitter chemicals that could cross the blood-brain barrier (Gelpi et al., 2020).

Treatments for the Gut Microbiome to Improve AD Progression/Development

Change in diet is one of the fastest ways to induce a change in the gut microbiota and improve health in patients with Alzheimer's disease. For example, a diet containing saturated fat, processed foods, and carbohydrates would reduce microbiota diversity, as a meat-based diet would do, and lead to neuroinflammation and cognitive impairment. The Mediterranean diet could create a positive impact as it promotes the flourishing of preventative bacteria. Lactic acid bacteria and bifidobacteria have also been shown to improve pathology in CNS-related diseases (Bonfili et al., 2020). Because diets have been so prevalent in gut microbiota modulation, dietary manipulation, especially through probiotics, prebiotics, and a change in consumption have been investigated as possible treatments for Alzheimer's disease (Marques et al., 2014).

The bacteria *L. plantarum* could be stimulated through probiotics and supplements. *L. plantarum MTCC1325* improves behavior activity and learning skills by stimulating the cholinergic neurotransmitter in the cerebral cortex and hippocampus, counteracting the effects of D-galactose-induced Alzheimer's disease, where D-galactose is converted into galactitol and accumulates in cells where it generates reactive oxygen species that lead to intracellular damage and mitochondrial dysfunction. *L. plantarum NDC 75017* works to recover learning and memory-related injuries by reducing mitochondrial dysfunction (Marques et al., 2014). Increasing probiotic milk intake could also serve as a treatment measure, as lactobacilli in the gut will produce metabolic products that increase calcium ion levels and

stimulate intracellular signaling (Morris, 2018). In a murine model, the treatment group was given SLAB51 probiotic formulation containing bifidobacteria and LAB, influencing key metabolic hormones of Alzheimer's disease and in-flammatory cytokines, counteracting morphological symptoms of the disease like brain weight reduction and decline of cortical regions (Bonfili et al., 2017).

Manually adjusting the microbiota is viable as a potential treatment. The practice of fecal microbiota trans-plantation has also been suggested as a form of therapy. A series of three randomized controlled trials has shown a cure rate of 90% or higher in extra-intestinal disease, and could be used in creating a favorable environment to slow or cease AD development or progression (Groot et al., 2017). Additionally, using probiotic supplements could aid in stabilizing the *Firmicutes:Bacteroidetes* ratio, along with repopulating important species to protect against inflammation like *L. plantarum* (Magne, 2020).

Conclusion

Considering that humans consist of more non-human species than cells, it is critical to understand the impact of the microbiome on diseases. As Alzheimer's disease becomes a more and more pressing issue, it may be possible to combat it or slow its progress by understanding how alterations in the gut microbiome, which can influence functions in the brain in a variety of ways, affect its development. Inflammatory conditions (neurological, autoimmune, and malignant) are now demonstrating a common characteristic of altered microbial populations (Proal et al., 2017). It is important to understand microbiome-cell interactions and utilize that information to create new therapeutic strategies for Alzheimer's disease through forms like diets, probiotics, and interventional procedures.

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