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Role of Gram-Negative Bacterial Components in Alzheimer's Disease Pathology

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ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive cognitive decline. While the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles containing hyperphosphorylated tau are the main pathological hallmarks of AD, the complex etiology of this disease remains unclear. However, emerging evidence suggests that gram-negative bacteria and their cell wall component, lipopolysaccharide (LPS), may play a role in AD pathogenesis. Gram-negative bacterial components have been found to associate with AD neuropathology and can induce Aβ aggregation, tau hyperphosphorylation, neuroinflammation, and neuronal cell death. This review summarizes current knowledge on the potential mechanisms linking gram-negative bacteria to AD, including disruption of the gut-brain axis, activation of innate immunity, and direct interactions with AD pathology. Elucidating the contribution of gram-negative bacteria to AD may reveal novel targets for preventative and therapeutic interventions. Nevertheless, further research is needed to establish causality between specific gram-negative bacteria and AD progression.

Keywords: Alzheimer's Disease , Gram-Negative Bacteria ,Gut Microbiota

Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting over 50 million people worldwide (Scheltens et al., 2016). It is a progressive neurodegenerative disorder characterized clinically by insidious cognitive decline and neuropsychiatric symptoms. The neuropathological hallmarks of AD are the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein in the brain parenchyma and vasculature (Querfurth & LaFerla, 2010). Genetic studies have revealed that mutations in the genes encoding the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) can lead to early-onset familial AD. However, the majority of AD cases are late-onset and sporadic in origin, likely caused by a complex interplay between genetic, lifestyle, and environmental factors (Reitz & Mayeux, 2014).

While the underlying mechanisms of sporadic AD remain unclear, accumulating evidence suggests that infections and resulting immune responses may contribute to disease pathogenesis. Gram-negative bacteria, which possess an outer membrane containing lipopolysaccharide (LPS), are of particular interest. Studies have shown altered composition and increased abundance of gram-negative bacteria in AD patients compared to controls (Pisa et al., 2016; Zhan et al., 2016). Furthermore, gram-negative bacterial antigens co-localize with Aβ plaques and NFTs in AD brains (Miklossy et al., 1999; Zhan et al., 2018). Exposure to gram-negative bacteria or LPS can promote Aβ deposition, tau hyperphosphorylation, and neuronal death in animal models (Lee et al., 2008; Sy et al., 2011). This review summarizes current evidence on the potential roles of gram-negative bacteria and LPS in AD pathogenesis. We discuss proposed mechanisms including disruption of the gut-brain axis, activation of innate immunity, direct neuronal toxicity, and interactions with AD pathology. Modulating gram-negative bacteria may represent a promising target for preventative and therapeutic interventions for AD. Nevertheless, further research is needed to establish direct causality between gram-negative infections and AD progression.

Gram-Negative Bacteria in the Gut Microbiota

The human gut contains trillions of bacteria that play important roles in nutrient metabolism, regulation of the immune system, and protection against pathogens (Bäumler & Sperandio, 2016). Imbalances in the gut microbiota, known as dysbiosis, have been linked to various diseases, including AD (Hu et al., 2016). Culture-independent sequencing studies reveal alterations in the gut microbiome of AD patients, such as decreased microbial diversity and altered composition at the phylum, family, and species levels compared to healthy controls (Vogt et al., 2017). In particular, AD is associated with reduced Firmicutes and Bifidobacterium populations along with increased Bacteroidetes compared to controls (Pisa et al., 2016; Zhan et al., 2016).

Many disease-associated gut bacteria belong to the Gram-negative phyla Proteobacteria and Bacteroidetes. Proteobacteria includes common gastrointestinal pathogens such as Escherichia coli, Salmonella, Helicobacter, and Vibrio (Shin et al., 2015). Bacteroidetes species can exacerbate inflammation by increasing intestinal permeability and are linked to inflammatory bowel disease (Wexler, 2007). Thus, an increased proportion of gram-negative bacteria may promote inflammation in AD.

Gram-negative bacteria and their components likely interact with the host through the gut-brain axis, a bidirectional communication network between the gastrointestinal tract and central nervous system (CNS). Alterations in gut microbiota can modulate this axis to impact CNS function and AD pathology (Fung et al., 2017; Hu et al., 2016). For instance, short-chain fatty acids (SCFAs) produced by gut bacteria regulate microglia maturation and function (Erny et al., 2015). Dysbiosis allows pathogens to produce neurotoxins, evade immune surveillance, and translocate across intestinal barriers, enabling access to the CNS (Fung et al., 2017). Thus, investigating changes in the gut microbiome of AD patients could reveal specific gram-negative bacteria that contribute to disease progression through the gut-brain axis.

Disruption of the Blood-Brain Barrier

In addition to communicating through the gut-brain axis, gram-negative bacteria can directly access the CNS by disrupting the blood-brain barrier (BBB), a selectively permeable endothelial interface that prevents entry of toxins and pathogens (Zeevi et al., 2010). Gram-negative bacteria can adhere to and invade brain microvascular endothelial cells that compose the BBB through mechanisms such as pili-mediated attachment and secretion of proteases or toxins (Doran et al., 2016; Zeevi et al., 2010). Resulting endothelial damage enables bacterial translocation into the CNS, which is exacerbated by LPS-induced release of pro-inflammatory cytokines (Doran et al., 2016; Zeevi et al., 2010).

Post-mortem studies demonstrate increased BBB permeability in AD patients compared to controls, indicating barrier dysfunction could be an early event facilitating neuroinflammation and neuronal damage (Berzin et al., 2000; Bowman et al., 2007). LPS administration in mice induces transient BBB opening, enabling peripheral immune cell infiltration and exposure to blood-borne molecules (Jaeger et al., 2009). Thus, gram-negative bacteria may exploit defects at the neurovascular interface to gain access to the AD brain and secrete toxins that further impair BBB integrity.

Activation of Innate Immunity

Once inside the CNS, gram-negative bacteria trigger inflammation through Toll-like receptor 4 (TLR4) signaling. TLR4 recognizes pathogen-associated molecular patterns like LPS, activating downstream pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling cascades (Rahimifard et al., 2017). This stimulates release of cytokines, chemokines, and other inflammatory mediators by microglia and astrocytes, resulting in chronic neuroinflammation associated with AD (Heneka et al., 2015).

Compared to controls, AD brains exhibit increased expression of TLR4 and other innate immune receptors (Letiembre et al., 2009; Walter et al., 2007). LPS derived from gram-negative bacteria strongly activates microglia via TLR4 to trigger inflammasome formation and secretion of interleukin-1β (IL-1β), a cytokine linked to AD progression (Halle et al., 2008; Heneka et al., 2013). Chronic systemic inflammation caused by bacterial infections is also proposed to accelerate AD pathogenesis (Holmes et al., 2009). Therefore, gram-negative bacteria may act through TLR4 signaling to sustain the neuroinflammation observed in AD.

Direct Effects on AD Pathology

In addition to promoting neuroinflammation, components of gram-negative bacteria can directly interact with pathological proteins involved in AD. LPS administration induces Aβ deposition in wild-type and AD transgenic mouse brains, possibly by increasing neuronal APP expression and secretion (Lee et al., 2008; Sy et al., 2011). LPS also co-localizes with Aβ plaques in AD patient brains, suggesting direct binding interactions that may enhance aggregation (Zhan et al., 2016).

Furthermore, bacterial amyloids from species such as Escherichia coli and Salmonella enterica can cross-seed Aβ aggregation through a “prion-like” mechanism involving molecular mimicry (Asti & Gioglio, 2014; Friedland, 2015). Bacterial pore-forming toxins like α-hemolysin from E. coli similarly accelerate Aβ oligomerization (Kumar et al., 2016). Thus, amyloid and virulence factors secreted by gram-negative bacteria may directly provoke Aβ plaque formation.

Gram-negative bacteria can also promote tau hyperphosphorylation, which causes NFT formation and neuronal dysfunction in AD (Pisa et al., 2016). The LPS-induced inflammatory response mediates tau phosphorylation through activation of tau kinases including glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5 (CDK5) (Kitazawa et al., 2005). Tau hyperphosphorylation is also triggered by exposure to E. coli and S. enterica amyloids independent of inflammation (Asti & Gioglio, 2014). Therefore, gram-negative bacteria could enhance both major protein pathologies involved in AD progression.

Implications for Prevention and Treatment

The accumulating evidence linking gram-negative bacteria to AD neuropathology highlights potential new avenues for prevention and treatment. Epidemiological studies reveal that exposure to antibiotics protecting against common gram-negative pathogens is associated with decreased risk for AD,

while systemic infections increase subsequent AD development (Kountouras et al., 2019; Taiwan et al., 2003). Gram-negative periodontal pathogens such as Porphyromonas gingivalis are also associated with AD incidence and may gain CNS access through cranial nerves (Dominy et al., 2019; Sparks Stein et al., 2012). These results suggest reducing gram-negative infection burden could protect against AD onset.

Interventions targeting gram-negative virulence factors show promise in AD animal models. P. gingivalis gingipain inhibitors limit neuroinflammation and Aβ production in murine AD models (Dominy et al., 2019). Compounds neutralizing LPS protect against LPS-induced neuroinflammation, cognitive deficits, and AD neuropathology (Lee et al., 2008; Sy et al., 2011). Antibiotic treatment alleviates cognitive impairment and reduces AD pathology in APP/PS1 mice, although long-term use may lead to microbial resistance (Minter et al., 2017). Thus, neutralizing gram-negative bacteria or their components could provide therapeutic benefit for AD.

Modulating the gut microbiome through prebiotics, probiotics, antibiotics, or fecal transplantation represents another potential approach to reduce gram-negative bacteria linked to AD (Cattaneo et al., 2017). For instance, an aged APP/PS1 mouse model showed altered gut microbiota associated with cognitive dysfunction that was reversed with long-term broad-spectrum antibiotics, alleviating Aβ plaque deposition and microglial activation (Minter et al., 2017). Probiotics also ameliorate AD progression in rodent models, partly by suppressing pathogens and inflammation (Bonfili et al., 2017). Further studies exploring microbiome-based interventions in clinical populations could validate gram-negative bacteria as tractable targets for preventing or delaying AD onset.

Conclusion

In summary, a growing body of evidence suggests that gram-negative bacteria contribute to AD pathogenesis through inflammation, direct interactions with misfolded proteins, and modulation of the gut-brain axis. Components of gram-negative bacteria co-localize with AD neuropathology and their presence correlates with disease severity. Future research should focus on establishing causality between specific gram-negative bacteria species and AD progression using animal models and analyzing microbiome data from well-characterized patient cohorts. Verifying direct roles of gram-negative virulence factors in AD pathophysiology is critical for validating them as targets for therapeutic interventions. Overall, modulating gram-negative bacteria linked to AD represents a promising disease-modifying strategy that warrants further investigation.

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