COGNITION AND ALZHEIMER'S DISEASE

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P. GINGIVALIS–LPS-INDUCED NLRP3 INFLAMMASOME ACTIVATION DRIVES AD PATHOLOGIES
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Alzheimer’s disease (AD) is the leading cause of dementia among older adults. AD is characterized by amyloid-β deposition, abnormal hyperphosphorylation of tau leading to the formation of neurofibrillary tangles, and neuroinflammation. Porphyromonas gingivalis, the keystone-pathogen of periodontitis, is being increasingly linked with AD and Alzheimer’s disease-related dementias (ADRD). Poor oral health is common in older populations, and literature suggests that oral health correlates with prevalence of ADRD. NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-mediated IL-1β is significantly involved in periodontal diseases. However, the exact mechanism by which NLRP3 inflammasome is regulated in response to pathogenic bacteria remains unclear. We hypothesized that P. gingivalis-LPS may be responsible for the neuroinflammation via TLR4 activation and its downstream caspase-1, caspase-3 or caspase-4/5/11 dependent cell signaling. Our results suggest that P. gingivalis accelerated the induction of NLRP3. Furthermore, NLRP3/Caspase-1/Caspase-4/5/11 dependent IL-1β production may contribute to the dysregulated neuroinflammatory response in AD pathogenesis.

A MECHANISM OF ACTION OF HUMAN-ORIGIN PROBIOTIC COCKTAIL IN ATTENUATING ALZHEIMER'S DISEASE PATHOLOGY
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Alzheimer’s disease (AD) is a detrimental public health problem affecting millions of older adults in the USA alone, with no or limited treatment options. Emerging evidence indicates the pivotal role of gut microbiota in AD pathology, but mechanisms remain largely unknown. Also, microbiome modulators like probiotics are proven beneficial in preventing AD with little understanding of their mechanisms. Therefore, we investigated how a microbiota metabolite-short-chain free fatty acid receptor-2 (FFAR2) signaling in the intestine affects AD pathology in brain using intestinal FFAR2 knock-out APP/PS-1 mice; as well as determined if a human-origin-probiotic cocktail exhibits its actions via FFAR2 signaling. We measured changes in the microbiome, permeability in gut and blood-brain barriers (BBB), neuroinflammation, AD pathology, and cognitive behaviors. Results showed, the mice lacking FFAR2 in their intestine exacerbated AD pathology by developing abnormal changes in gut microbiome and intestinal permeability, which in turn promotes permeability in BBB and neuroinflammation. It’s also promoting microglia activation linked with increased Aβ accumulation and cognitive decline. It’s interesting to note that probiotic cocktail feeding reversed these abnormalities in AD mouse models. Further, this probiotic cocktail showed its mechanism in both FFAR2-dependent and independent manner. Overall, our findings indicate that the microbiome sensing mechanism FFAR2 signaling participates in regulating the gut-brain in AD pathology, and a human-origin probiotic cocktail improves the abnormal changes in the microbiome-intestinal & BBB permeability-neuroinflammation axis to ameliorate AD pathology. Thus, FFAR2 agonism and probiotic therapy can be viable options to prevent/ delay the risk of AD progression in older adults.