MAEVE: Microbiota mediated flavonoid metabolites for cognitive health

ABSTRACT

Globally, populations are aging thereby increasing healthcare burden, overall cognitive impairment, and dementia including Alzheimer's disease (AD). The lack of effective treatments makes it essential to develop new strategies for healthy cognitive aging, including interventions to slow or prevent cognitive decline. A traditional Mediterranean diet, rich in polyphenols (PPs), may prevent or delay the onset of cognitive dysfunction in older adults, preserving healthy brain structure and function, and lowering the risk of AD. These effects, mediated in part by gut microbiome-derived PP metabolites, highlight the role alterations in the brain-gut microbiome system play in neurodegeneration. Moreover, high levels of circulating phenyl-γ-valerolactones, neuroprotective compounds, exclusively produced by gut microbiota from flavan-3-ol-rich foods (e.g., cocoa, tea, berries) are associated with delaying the onset of cognitive dysfunction in older adults. Intake of such PPs can also change gut microbial composition and function, altering the physiology of the host's secondary bile acid (BA) pool, affecting regulatory and signaling functions in the brain as well as cognitive decline and AD. We hypothesize that, in older adults with enhanced AD risk, dietary intake of PPs maintains healthier brain features and cognitive function, and that this beneficial effect is mediated by gut microbiota metabolites of PPs and BAs. In this multi- PI application by leaders in the field of brain-gut microbiome interactions, we will conduct a year-long, multi-center randomized double-blind placebo-controlled study in 300 older adults in the United States (validation sample of 100 from Northern Ireland) who are at enhanced risk of developing AD. Coupled with this, behavioral interactions will be investigated with a murine fecal microbiome transplant model incorporating samples from high AD risk participants on a high PP supplement compared to a placebo. We will apply multiple complementary approaches: meta and transcriptomic interrogation of the gut microbiome, targeted/untargeted metabolomics for microbiota- derived metabolites, multimodal brain imaging, assessment of cognitive function and inflammatory status, and advanced bioinformatic techniques for data integration. The hypothesis is addressed as follows: Aim A: Identify the protective effects of high intake of supplementary dietary PPs on brain and cognitive parameters in high AD- risk participants. Aim B: Determine the effect of PP intake on the microbiome, inflammatory, and AD biomarkers in high AD risk participants. Aim C: Explore causal relationships between PP intake and gut microbial metabolites, inflammatory and AD markers, brain parameters, and cognitive function. Aim D: Utilize a reverse translational approach to identify changes in mouse brain and behavior by PP-induced alterations in the human gut microbiome. Ultimately, we will establish the protective effects of regular dietary PP intake on cognitive function and on brain-gut microbiome interactions, ideally allowing the development of effective dietary regimes to prevent or delay the onset of AD in at-risk elderly, thereby reducing cognitive decline and healthcare costs.

RELEVANCE TO PUBLIC HEALTH

This study will provide new information about how regular dietary polyphenol intake in the elderly population at risk of Alzheimer's disease (AD) will help maintain cognitive function and brain health. Specifically, it tests the hypothesis that polyphenol intake beneficially alters the brain-gut-microbiome system and healthier cognitive function. A better understanding of how polyphenols contribute to alterations in the brain and gut microbial metabolites in older adults with enhanced AD risk could lead to novel therapeutic strategies tailored to support healthy cognitive aging and reduce risk of disease.