Sphingolipids and Inflammation in the Development and Progression of Alzheimers

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Country

USA

Title of project or programme

Sphingolipids and Inflammation in the Development and Progression of Alzheimers

Source of funding information

NIH (NIA)

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€ 1,330,681.65

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01/09/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): The pathophysiological brain changes associated with Alzheimer's disease [AD] begin decades before clinical symptoms. Although recent advances have led to a preclinical biomarker model of AD pathogenesis (first amyloid-beta [Aß] pathology, second neurodegeneration, and lastly cognitive symptoms), the mechanisms that underlie these pathological changes remain unknown, impeding the identification of potential biomarkers and treatment targets. Previous studies of blood or CSF biomarkers have mostly employed clinical outcomes (i.e., cognitively normal [CN], mild cognitive impairment [MCI] and AD. However, clinical phenotypes are heterogeneous. Thus, categorizing individuals by their clinical phenotype alone will include a mixture of individuals with varying types and severities of brain pathologies (e.g., Aß pathology, neurodegeneration, vascular disease). The overarching goal of this project is to determine the temporal relationship between plasma and CSF sphingolipids (e.g., ceramides, sphingomyelins), in vivo measures of Aß pathology (Aß imaging, CSF Aß) and neurodegeneration (FDG-PET hypometabolism, hippocampal atrophy, CSF tau), and clinical endpoints. As inflammation is associated with AD, and is intimately interrelated with sphingolipids, we will also determine whether inflammatory processes (e.g., TNF-? and IL-6) modify the associations between sphingolipids and in vivo AD pathology. While previous studies have examined many plasma and CSF biomarkers with limited success, the study of sphingolipids is uniquely promising and highly innovative. First, cellular and animal studies demonstrate direct links between sphingolipids and measures of Aß pathology and neurodegeneration. Reducing Aß-associated increases in ceramide levels prevents neurodegeneration. Second, we consistently demonstrate that high levels of plasma sphingolipids predict cognitive decline among individuals who are CN, MCI, and AD. The next logical step is to determine the cross-sectional and longitudinal associations between the sphingolipids and in vivo evidence of AD pathology. For example, we will determine whether individuals with both abnormal Aß and elevated ceramides develop more neurodegeneration and cognitive decline compared to individuals with abnormal Aß and low ceramides. To accomplish our goals we will utilize a longitudinal collection of cognitive endpoints and in vivo measures of Aß pathology and neurodegeneration from individuals enrolled in the population-based Mayo Clinic Study of Aging [MCSA] and the Mayo Clinic Alzheimer's Disease Research Center. Together these longitudinal studies have accumulated over 2,375 visits with Aß imaging, FDG-PET, and MRI scans on 1,617 unique individuals, and more than 1,085 CSF samples from 870 unique individuals, providing an ideal resource to test our hypotheses. The proposed research will further our understanding of the interrelationship between plasma and CSF sphingolipids, the development and progression of AD pathology, and the emergence and progression of clinical symptoms. This work will contribute to the identification of new treatment strategies for delaying, or possibly preventing, AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The brain changes associated with Alzheimer's disease begin several years before cognitive changes; there is currently no cure for the disease. This study will use resources from the Mayo Clinic Study on Aging and the Mayo Clinic Alzheimer's Disease Research Center to examine sphingolipids and inflammatory markers in relation to the development and progression of the brain changes and memory loss associated with Alzheimer's disease. Our results are important for developing biomarkers to predict who will develop Alzheimer's disease and for identifying new treatment targets.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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