Cholesterol and Sphingolipid Metabolism in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/cholesterol-and-sphingolipid-metabolism-in-alzheimers-disease/

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Country

USA

Title of project or programme

Cholesterol and Sphingolipid Metabolism in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,523,394.50

Start date of award

15/08/2010

Total duration of award in years

7

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)... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): The goal of the current application is to provide more

evidence at the cell culture and intact animal levels to support the characterization of acyl-CoA: cholesterol acyltransferase1 (ACAT1) as a potential new therapeutic target for Alzheimer's disease (AD) treatment. ACAT1 is an enzyme that catalyzes the conversion of free cholesterol to cholesterol esters, and that plays an important role in cholesterol homeostasis in systemic tissues and the brain. Previously, our laboratory showed that in a mouse model for AD, gene knockout (KO) of Acat1 decreased amyloidopathy and rescued cognitive deficits. During the last cycle of this grant, we showed that adeno-associated viruses expressing microRNAs targeting Acat1 delivered directly to the brains of symptomatic AD mice decreased the levels of brain amyloid-beta and full-length human amyloid precursor protein to levels similar to complete genetic ablation of Acat1. We also showed that in microglia and neurons, Acat1 gene KO or an ACAT1-specific inhibitor K604 stimulated autophagosome formation and transcription factor EB-mediated lysosomal proteolysis, thereby resulting in an increase in lysosomal Aß1-42 degradation. The enhancing effect of ACAT1 blockage on autophagy was independent of mammalian target of rapamycin (mTOR) signaling and the endoplasmic reticulum stress response. These results suggest that ACAT1 blockage in microglia and neurons may be effective in the treatment of AD. To provide more evidence at the cell culture and in vivo levels to support the therapeutic potential of ACAT1 blockage, we propose two specific aims in the current application: Specific Aim 1: To test the hypothesis that ACAT1 blockage increases autophagosome formation by altering the cholesterol-rich/ceramide-rich domain within the mitochondrial- associated membrane. Specific Aim 2: To test the hypothesis that ACAT1 blockage in microglia and neurons delays neuronal cell loss and memory deficits in AD. Relevance The outcome of this application will offer evidence to support a potential new therapeutic approach to target ACAT1 in microglia and neurons for AD treatment.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is a major neurodegenerative disease. Currently, there is no cure for AD. Acyl-CoA: cholesterol acyltransferase1 (ACAT1) is an enzyme that plays an important role in cholesterol homeostasis in many tissues, including the brain. Recent evidence from our laboratory shows that blocking ACAT1 activity can ameliorate brain cells that are affected by AD. This application seeks to provide more evidence at the cell culture level and the intact animal level to support the characterization of ACAT1 as a potential new therapeutic target for AD treatment.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
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