Characterization of ApoE4 Induced Phospholipid Dysregulation in AD Pathogenesis

https://www.neurodegenerationresearch.eu/survey/characterization-of-apoe4-induced-phospholipid-dysregulation-in-ad-pathogenesis/

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Country

USA

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Characterization of ApoE4 Induced Phospholipid Dysregulation in AD Pathogenesis

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NIH (NIA)

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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... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract
DESCRIPTION (provided by applicant): The ApoE4 genotype is the strongest genetic risk factor for developing AD. However, the mechanisms that underlie this link between ApoE4 genotype and AD are not well understood. Objective/Hypothesis: the objectives of this proposal are to understand the molecular underpinnings of the association between ApoE4 genotype-specific changes in brain phospholipid homeostasis and ApoE4 increased susceptibility to develop late-onset AD. Our preliminary data indicate that the levels of PI(4,5)P2 are reduced in postmortem human brain tissues of ApoE4 carriers, in the brain of ApoE4 homozygous knock-in (KI) mice, and in primary neurons expressing ApoE4 alleles, if compared to ApoE3 counterparts. The expression of synaptojanin 1 (synj1) that dephosphorylates PI(4,5)P2 reducing its levels, is elevated in ApoE4 brains. Our recent observations demonstrate that synj1 reduction (with subsequent elevation of PI(4,5)P2 levels) can accelerate endosomal/lysosomal degradation of A?nd ameliorate cognitive deficits in AD transgenic mice. In this proposal we are testing the hypothesis that ApoE genotype is a critical determinant of brain phospholipid homeostasis and that the ApoE4 isoform is dysfunctional in this process (increased synj1 expression and reduced PIP2 levels). As a consequence, ApoE4 impairs A?learance through endosomal/lysosomal degradation pathway, accelerates cognitive decline, and disrupts synaptic functions. These ApoE4-induced changes in the cascade of aberrant molecular events lead to long-term neurodegenerative process and AD development. Rationale/Experimental Design: In this application, we will study whether reducing synj1 thus normalizing brain phospholipid metabolism can rescue ApoE4-related neuropathological changes by utilizing mouse models of synj1 haploinsufficiency with human ApoE4 or E3 homozygous KI background in studies that assess: 1) AD-related cognitive dysfunction (aim 1.1); 2) AD-related biochemical changes such as A?learance and ApoE secretion (aim 1.2 and 1.3); 3) AD related morphological changes and synaptic phospholipid homeostasis (aim 2); 4) molecular mechanisms underlying ApoE isoform specific changes in synj1 expression/PIP2 homeostasis (aim 3). Relevance/Impact: The proposed studies in this application will be the first mechanistic studies that link ApoE4 genotype-specific changes in brain phospholipid homeostasis to ApoE4 increased susceptibility to develop AD. These studies may uncover new therapeutic options for the treatment of AD targeting at ApoE4 pathogenic nature.

Lay Summary
PUBLIC HEALTH RELEVANCE: Our project represents the first mechanistic studies that link ApoE4 genotype-specific changes in brain phospholipid homeostasis to the ApoE4-dependent increased susceptibility to develop late-onset Alzheimer disease. These studies may uncover new therapeutic options for the treatment of Alzheimer disease patients with ApoE4 genotype.

Further information available at:

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United States of America

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