ApoE isoform-specific therapy for Alzheimer disease

https://www.neurodegenerationresearch.eu/survey/apoe-isoform-specific-therapy-for-alzheimer-disease/

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Country

USA

Title of project or programme

ApoE isoform-specific therapy for Alzheimer disease

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NIH (NIA)

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4

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... Prevention

Research Abstract
DESCRIPTION (provided by applicant): The ?4 allele of the apolipoprotein E (APOE) gene is

the strongest genetic risk factor for late-onset Alzheimer's disease (AD) compared to the more common ?3 allele. Studies in animal models and humans suggest that apoE4 exhibits both loss-of-function and gain-of-toxic-function compared to apoE3. In regulating amyloid pathology, apoE4 is less efficient than apoE3 in mediating the clearance of amyloid-ß (Aß) peptides and is more dominant in promoting Aß aggregation. Outside the Aß pathway, apoE4 is also less efficient in transporting lipid and supporting synapses. These studies led to an important yet unanswered question as to whether it is better to increase or decrease apoE levels in AD therapy. As there have not been studies addressing the effects of modulating apoE expression in adult mice, we have developed new animal models that allow for inducible and cell-type specific expression of apoE3 or apoE4. To take advantage of these unique animal models, we have established biochemical, pathological, and behavioral analyses that distinguish apoE3- and apoE4-related phenotypes. Thus, the major goal of this proposal is to investigate how an increase or decrease of apoE3 or apoE4 expression with or without amyloid pathology affects apoE isoform-related functions, synapses and behavior. Our overall hypothesis is that decreasing apoE levels in APOE4 carriers and increasing apoE levels in APOE3 carriers respectively represent promising treatment and/or preventive strategies for AD. We propose three specific aims to test our hypothesis. In Aim 1, we will examine how over-expression of apoE3 or apoE4 at different ages and at different stages of amyloid pathology affects Aß metabolism, plaque deposition, synapses and behavior. These studies will be carried out in the background of apoE3-targeted replacement (TR) mice or apoE4-TR mice, without or with amyloid model APP/PS1 background. In Aim 2, we will investigate how down-regulation of apoE3 or apoE4 expression at different ages and at different stages of amyloid pathology affects Aß metabolism, plaque deposition, synapses and behavior. These studies will be carried out in the background of apoE knockout mice in the absence or presence of APP/PS1. Finally in Aim 3, we will assess how peripheral expression of apoE3 or apoE4 impacts brain Aß metabolism, plaque deposition, synapses, behavior and cardiovascular health. These studies will be carried out in the absence of apoE expression in the brain. Together, our studies will for the first time test how up-regulation or down-regulation of apoE isoforms in the adult brain or periphery at different ages and at different stages of amyloid pathology affects AD pathogenesis. Results from these studies will provide mechanistic insights for apoE-based AD prevention and therapy.

Lay Summary
Alzheimer's disease (AD) is the leading cause of dementia in elderly and a significant public health issue as our population ages; however, recent clinical trials targeting the amyloid-? pathway alone have not yield promising results. As a form of apolipoprotein E (apoE) called APOE4 is the strongest genetic risk factor for AD, we have developed new mouse models that allow for inducible and cell-type specific expression of apoE isoforms. By examining how changes in apoE expression in the brain or peripheral at different ages and at different stages of amyloid pathology affect AD-related phenotypes, our studies should establish critical guidelines by which apoE-based AD therapy can be effectively designed.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

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2016

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