Alzheimers Abeta, apolipoproteins and blood-brain barrier

https://www.neurodegenerationresearch.eu/survey/alzheimers-abeta-apolipoproteins-and-blood-brain-barrier/

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Contact information of lead PI
Country

USA

Title of project or programme

Alzheimers Abeta, apolipoproteins and blood-brain barrier

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,760,955.96

Start date of award

01/09/1995

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Lipoprotein Receptor, Apolipoproteins, Amyloid beta-Protein, Pericytes, Amyloid

Research Abstract

DESCRIPTION (provided by applicant): In this competing renewal, we propose to continue collaborative studies between the Zlokovic and the Holtzman labs aimed at understanding cellular and molecular mechanisms underlying apolipoprotein E (apoE) effects on the

cerebrovascular system, particularly on the blood-brain barrier (BBB), and how these effects contribute to development of neuronal dysfunction and neurodegeneration. Our focus is on apoE/low density lipoprotein receptor related protein-1 (LRP1) interactions in brain capillary endothelium and pericytes that form the BBB in vivo. We propose to study isoform-specific differences in apoE/LRP1 interactions and consequences between apoE4, which is a major genetic risk factor for Alzheimer's disease (AD), and apoE3, which carries a significantly lower risk for AD. Within the neurovascular unit, apoE is produced mainly by astrocytes which allow direct binding, uptake, and signal transduction of astrocyte-derived apoE with cell surface LRP1 expressed in the neighboring pericytes and endothelial cells. LRP1 is a key apoE receptor and an important Alzheimer's amyloid b-peptide (Ab) clearance receptor. Recent studies have suggested that apoE/LRP1 signal transduction in pericytes is important for cerebrovascular integrity. In AD and AD models, LRP1 expression in brain microvessels that form the BBB is significantly reduced. Whether reduced LRP1 expression at the BBB and the resulting diminished apoE-Ab and apoE interactions with LRP1 can initiate Ab, cerebrovascular and neurodegenerative disorders remains, however, unknown. To address these questions we will use new mouse lines with partial or complete LRP1 deletion from endothelium or pericytes generated from conditional Lrp1 mice (Lrp1lox/lox) and crossed with i) 5xFAD (PS/APP);TRE mice with targeted replacement of human apoE gene (TRE) to study Ab-dependent effects, or ii) TRE mice alone to study Ab- independent effects. We will use state-of the art methods to study Ab metabolism, optical imaging methods to study BBB and neurovascular functions ex vivo and in vivo, behavioral tests and methods to study neuronal function and structure. We will determine the effects of LRP1 partial and complete deletion from endothelium and pericytes on Ab pathology, vascular and neurodegenerative changes in aging 5xFAD;TRE3 mice (AIM 1) and 5xFAD;TRE4 mice (AIM 2), and on BBB integrity and neuronal function and structure independently of Ab in aging TRE3 mice (AIM 3) and TRE4 mice (AIM 4). The proposed studies will investigate for the first time the role of diminished LRP1 expression at the BBB, particularly in pericytes and endothelial cells, on apoE isoform- specific effects on disease onset and progression including effects on Ab metabolism and pathology, BBB integrity and neuronal dysfunction and degeneration. We expect that these new findings will establish LRP1 and its Ab-dependent and Ab-independent interactions with apoE in brain endothelium and pericytes as major new therapeutic targets for AD-associated Ab, cerebrovascular and neurodegenerative disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: The annual health care costs for neurodegenerative disorders range in excess of a hundred billion dollars. Sadly, we do not have cure yet for any of these diseases. Understanding cellular and molecular mechanisms underlying effects of apolipoprotein E (apoE) on the cerebrovascular system and how these effects may contribute to development of neuronal dysfunction and neurodegeneration will have profound implications for our understanding of Alzheimer's disease pathogenesis and may ultimately guide the development of new therapeutic approaches for this devastating brain disorder.

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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