ApoE receptor pathways and abeta metabolism

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Country

USA

Title of project or programme

ApoE receptor pathways and abeta metabolism

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,446,655.96

Start date of award

01/05/2006

Total duration of award in years

11

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Amyloid-? (A?) peptide accumulation and aggregation in the brain lead to synaptic dysfunction and neurotoxicity. Increasing evidence indicates that impaired A? clearance is an early and central pathogenic event in Alzheimer’s disease (AD).

Our long-term goal is to understand the molecular and cellular pathways by which A? is either cleared from the brain or accumulated to form toxic aggregates. A? clearance and aggregation are regulated by A? chaperones and cell surface receptors. Apolipoprotein E (apoE) is a major A? chaperone and cholesterol carrier in the brain. Of the three apoE isoforms in humans (E2, E3, E4), the ?4 allele of the APOE gene is the strongest genetic risk factor for AD. Mounting evidence indicates that both apoE and apoE receptors, members of the low-density lipoprotein receptor (LDLR) family, play important roles in A? clearance, aggregation and toxicity. During our previous funding period, we have delineated the specific roles of a major apoE receptor, the LDLR-related protein 1 (LRP1), in neuronal A? uptake and trafficking. We found that neuronal LRP1 functions together with cell surface heparan sulfate proteoglycan (HSPG) to mediate A? uptake, trafficking and eventual delivery to lysosomes. Conditional knockout of Lrp1 in neurons in adult mice leads to increase A? accumulation and amyloid plaque deposition. Interestingly, while apoE3 promotes A? degradation, apoE4 facilitates A? accumulation and aggregation in the lysosomes. Finally, we found that the apoE receptor LRP1 and HSPG also play important roles in A? metabolism by astrocytes. Based on these observations, our overall hypothesis is that apoE and apoE receptor LRP1 and HSPG play critical roles in A? uptake and trafficking to lysosomes by neurons and astrocytes, and that the efficiency of A? clearance is differentially regulated by apoE isoforms. Thus, our overall goal for this competitive renewal application is to use both in vitro and in vivo models to systematically dissect how apoE isoforms and apoE receptors regulate A? clearance, aggregation and toxicity. We propose three specific aims to test our hypothesis. In Aim 1, we will use primary cultured neurons and astrocytes to analyze the specific roles of apoE isoforms and apoE receptors in A? endocytic trafficking to lysosomes, its degradation, aggregation and toxicity. In Aim 2, we will use in vivo microdialysis technique to assess the roles of apoE isoforms and apoE receptors in brain A? clearance. In Aim 3, we will use conditional knockout mouse models to examine the roles of apoE receptors in A? aggregation and pathology. Together, our proposed studies will likely provide insight into the mechanisms underlying A? clearance and aggregation pathways in the brain and uncover how apoE isoforms and apoE receptors regulate these events in AD.

Lay Summary

PROJECT NARRATIVE: Mounting evidence indicates that impaired clearance of amyloid- ? (A ?) peptide in the brain is a major pathogenic event in Alzheimer’s disease (AD), which is the leading cause of dementia in the elderly. A ? clearance is regulated by its chaperone apolipoprotein E (apoE), with an isoform (apoE4) being a strong risk factor for AD. In our previous funding period, we identified an apoE receptor-mediated A? clearance pathway. The goal of this renewal proposal is to delineate the molecular and cellular pathways by which apoE isoforms and apoE receptors regulate A? clearance, aggregation and toxicity. Our studies should provide insights into why apoE4 is a strong risk factor for AD and will likely define apoE and apoE receptors as novel diagnostic tools and targets for AD therapy.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

Years:
2016

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N/A

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