Role of apolipoprotein E in age and amyloid beta related neuronal dysfunction

https://www.neurodegenerationresearch.eu/survey/role-of-apolipoprotein-e-in-age-and-amyloid-beta-related-neuronal-dysfunction/

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Country

USA

Title of project or programme

Role of apolipoprotein E in age and amyloid beta related neuronal dysfunction

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

250102.7523

Start date of award

01/05/2015

Total duration of award in years

2

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): Apolipoprotein E is a major regulator of intracerebral lipid metabolism and has been implicated as an important actor shaping synaptic biology. In addition, more than two decades ago, the APOE4 allele was identified as the strongest genetic risk factor for the sporadic form of Alzheimer’s disease (AD). This K99/00 application proposes

to examine the complex impact of APOE in a neurodegenerative context, trying to disambiguate its role as a necessary catalyst of Aß neurotoxic effects in AD, while acting as a cholesterol and phospholipids carrier to the synapse and as a regulator of NMDAR-dependent calcium influx in a physiological context. Taking advantage of recently developed cutting-edge techniques such as awake in vivo multiphoton calcium imaging, array tomography, and synaptoneurosome purification with lipidomics assays to examine synaptic lipid content, I will interrogate the functional relevance of APOE towards Aß mediated neurotoxicity at the synapse. During the mentored phase of this award, I will address how APOE gene disruption is protective against Aß toxicity. Our preliminary data suggest that APOE null diminishes oligomeric Aß's effects on calcium dyshomeostasis, both in the setting of transgenic mice undergoing awake in vivo calcium imaging and in wild type mice exposed to biologically produce oligomeric Aß. To directly test the hypothesis that the beneficial effects of APOE null are due to disruption of APOE-Aß interactions, we will dissociate the APOE/Aß complexes in AD transgenic mice by intraperitoneal injection of a specific competitive inhibitor, Aß12-28P. Using a novel gene transfer approach by intravenous injection of AAV9, the independent phase will then restore the expression of the different APOE isoforms and evaluate how each variant modulate neuronal activity and synaptic integrity. We have already succeeded in transducing astrocytes brain wide after a single peripheral infusion of AAV9. We will then express APOE2, APOE3 and APOE4 in the brains of APOE-null or APP/APOE-null animals. We postulate that each variant will differentially shape APOE physiological functions and Aß neurotoxicity. In particular, we expect that APOE2 will act as a neuroprotective factor on the neural system and limit Aß synaptotoxicity, while APOE4 will be detrimental at the synapse. These experiments will lay the groundwork for my independent career. By learning structural and functional synaptic assays with Dr. Hyman (my mentor), combined with newly acquired biochemical -omics approaches with Dr. Gerszten (an expert in lipidomics and proteomics analyses) and modern gene transfer approaches with Dr. Breakefield, I will be in an excellent position to take advantage of emerging discoveries in neurodegenerative diseases and to launch an independent career to both carry out careful structural, functional, and biochemical phenotyping and to create and manipulate genetic models of neurological diseases.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A