Cellular and Molecular Medial Temporal Lobe Pathology in Elderly PreMCI subjects

https://www.neurodegenerationresearch.eu/survey/cellular-and-molecular-medial-temporal-lobe-pathology-in-elderly-premci-subjects/

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Country

USA

Title of project or programme

Cellular and Molecular Medial Temporal Lobe Pathology in Elderly PreMCI subjects

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,295,463.30

Start date of award

15/09/2013

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Frontotemporal Dementia (FTD)... Genetics... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): By 2050 older people at risk for cognitive decline are predicted to reach 13 million and health care costs are borne by individuals, their families, and society at large. The overall goal of the proposed project is determine the earliest cellular and molecular changes underlying the disconnection of the neuronal memory circuit within the medial temporal lobe (MTL), which degenerates in a highly predictable region-to-region pattern beginning prior to the onset of cognitive decline in the elderly. A growing literature implicated endosmal/lysosomal (E-L) dysfunction occur even before the formation of the classic pathologic AD lesion, the neurofibrillary tangle (NFT), composed of polymers of the microtubule-associated protein, tau. NFTs occur first in the transentorhinal cortex (TEC) then spread to the entorhinal cortex (EC) layer II and then to the hippocampal formation (HF) CA1 neurons of the MTL. Our group has shown that E-L rab GTPase genes are dysregulated in HPC CA1 neurons in MCI. Building on these findings, we propose to perform single cell expression profiling combined with site specific tau antibody neuronal labeling to test whether select rab GTPases are differentially regulated early during the evolution of TEC layer III NFTs prior to ether EC or HF prior to cognitive decline. We will examine whether select tau cytoskeletal isoforms and/or rab expression correlate with clinical diagnosis, memory tests specific to the MTL connectome, amyloid and apolipoprotein E genotype in preclinical AD. The project will characterize how pathology alters the neuronal environment at the mRNA expression level and provide new information on the complex mechanism(s) driving the molecular pathogenesis underlying MTL degeneration before clinical onset of dementia. This timely, novel and powerful approach will transform our understanding of the contributions of E-L expression to the vulnerability of MTL neurons in preclinical AD. The project is well positioned to lay the groundwork for a wide range of potential interventions that are truly distinct from approaches currently under investigation. I addition, the novel information gained about role that intraneuronal site-specific tau epitopes, E-L activation and amyloid pathology play in the vulnerability of MTL neurons may provide a panel of targets to better inform CSF tau based screening for dementia onset.

Lay Summary

PUBLIC HEALTH RELEVANCE: Cognitive decline and dementia associated with AD represent a major public health problem. Disease prevention provides the best long-term strategy to reduce the human and economic toll of AD. This timely study of preclincial AD molecular and cellular pathobiology could provide new knowledge critical to the development of novel drug therapies for dementia as well as impact public health policy needed to make the crucial difference for our aging population.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:

N/A

Database Tags:
N/A