Pathophysiology of APP in vivo

https://neurodegenerationresearch.eu/survey/pathophysiology-of-app-in-vivo/

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Country

USA

Title of project or programme

Pathophysiology of APP in vivo

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,809,913.76

Start date of award

01/03/2008

Total duration of award in years

9

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... Stem Cell Research... Stem Cell Research - Nonembryonic - Non-Human

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common form of age-related neurodegenerative disorder defined by the deposition of ?-amyloid (A?) peptides

which are generated from processing of the amyloid precursor protein (APP). Mutations or gene duplication of APP are causal for a subset of early onset AD, establishing its central role in AD pathogenesis. However, the vast majority of AD cases are late onset in which advanced age and the ?4 allele of the apolipoprotein E (ApoE) gene are established risk factors. Age is associated with many changes, one of them is adult neurogenesis, a process that generates functional neurons throughout life but its ability declines with age. Impaired adult neurogenesis in the hippocampus has been implicated in learning and memory decline associated with aging and in AD. Interestingly, ApoE has been shown to play multiple roles in adult hippocampal neurogenesis through both cell-autonomous and non cell-autonomous mechanisms the latter requires GABAergic interneurons and is differentially influenced by the ApoE3 and ApoE4 isoforms. Using various APP genetic mutants we created during the current funding cycle and as part of our long-standing research in understanding the APP pathophysiology, we uncovered a potent role of APP in mediating adult hippocampal neurogenesis and, remarkably, many of the phenotypes observed in APP mutant mice resemble those of ApoE mutants. The overarching goals of the renewal application are to decipher the cellular mechanisms of APP in adult hippocampal neurogenesis, to investigate the genetic and functional interactions of APP and ApoE, and to evaluate the effects of APP gene dosage and A? on APP/ApoE-mediated adult neurogenesis using the APP YAC genomic transgenic mice. These mice will allow us to elucidate the pathogenic mechanisms since both APP gene duplication and mutation are causal for AD. This proposal is highly innovative and significant in that it brings APP and ApoE, molecules that play critical roles in familial early-onset and “”sporadic”” late-onset of AD, togethe and addresses a question that’s directly relevant to aging and Alzheimer’s disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: The objective of the application is to investigate the interaction of APP and ApoE in adult neurogenesis and the contribution of this pathway to AD pathogenesis using novel and disease- relevant mouse models. It brings early- and late-onset AD together and will lead to the identification of cellular targets for therapeutic intervention.

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