Calcineurin and inflammatory signaling processes in aging and Alzheimers Disease

https://neurodegenerationresearch.eu/survey/calcineurin-and-inflammatory-signaling-processes-in-aging-and-alzheimers-disease/

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Country

USA

Title of project or programme

Calcineurin and inflammatory signaling processes in aging and Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,351,322.94

Start date of award

01/12/2005

Total duration of award in years

10

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)... Biotechnology... Brain Disorders... Dementia... Gene Therapy... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): The experiments in this project use innovative gene delivery techniques and a multipronged approach to assess the fundamental role of astrocyte activation in neurologic function in an intact mouse model of Alzheimer's disease (AD). Studies use adeno-associated virus vectors (AAV) bearing the astrocyte-specific promoter Gfa2 to target the protein phosphatase calcineurin (CN) and NFAT transcription factors in astrocytes of wild-type and APP/PS1 mice. AAV-Gfa2 vectors are bilaterally delivered to the hippocampus at different ages/disease stages and mice are assessed on different AD biomarkers. In Aim 1, cognitive status is assessed using the active avoidance task, while synaptic function is evaluated using hippocampal slice electrophysiology and Western blot measures of synaptic proteins. In Aim 2, hippocampal glutamate regulation is investigated using ceramic enzyme-based microelectrode arrays and measures of glutamate transporter levels. In Aim 3, levels of glial activation and neuroinflammation are determined with immunohistochemical (IHC) analyses and assessment of cytokine levels using Multiplex ELISAs. In Aim 4, IHC is used to determine the extent of Aß deposition, while ELISAs are used to quantify levels of Aß40 and Aß42 in soluble and insoluble hippocampal tissue fractions, and Westerns used to assess BACE protein expression. AAV-Gfa2 vectors encode either potent inhibitors or activators of CN/NFAT signaling and therefore will determine the necessity and sufficiency of this astrocytic pathway in driving and/or maintaining neurologic dysfunction in AD mice. These studies provide a highly novel approach to the study of activated astrocytes and could have a major impact on the development of treatment strategies for AD and other neurodegenerative conditions.

Lay Summary

Increasing evidence implicates activated astrocytes in a variety of neurodegenerative conditions, including Alzheimer's disease (AD). However, these cells are difficult to target selectively with therapeutics. In this project, we use cutting-edge adeno associated virus vectors to selectively prevent astrocyte activation and improve neurologic function in intact AD model mice. This approach could emerge as a new treatment strategy for AD and other neurodegenerative disorders.

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

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