OVEREXPRESSION OF APP AND CEREBROVASCULAR REGULATION

https://neurodegenerationresearch.eu/survey/overexpression-of-app-and-cerebrovascular-regulation/

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Country

USA

Title of project or programme

OVEREXPRESSION OF APP AND CEREBROVASCULAR REGULATION

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,666,706.42

Start date of award

01/06/1998

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

cerebrovascular, Amyloid beta-Protein Precursor, CD36 gene, Amyloid, overexpression

Research Abstract
DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the leading cause of dementia, and there is a pressing need to develop treatments to mitigate its enormous human and public health impact. Amyloid-ß (Aß) is a key pathogenic factor in AD, but its mechanisms

of action are not well understood. In addition to damaging neurons and glia, Aß also impairs vital neurovascular mechanisms that regulate the cerebral blood supply, thus increasing the brain's susceptibility to hypoxic-ischemic injury. Vascular dysfunction may also compromise brain Aß clearance, promoting the retention of the peptide and its damaging effects. During the previous funding period we have established that Aß exerts its deleterious vascular effects by engaging the Aß-binding scavenger receptor CD36. CD36, in turn, leads to the production of reactive oxygen species (ROS) by activating Nox2. However, the cells expressing CD36 on which brain Aß acts on the abluminal side of cerebral blood vessels to increase Nox2-dependent ROS production remain unknown and their elucidation may suggest novel targets for AD therapy. Resident brain macrophages, mainly perivascular macrophages (PVM), reside along the Aß clearance pathway, express CD36 and Nox2, and are in close contact with the outer vessel wall. Therefore, PVM are uniquely positioned to contribute to vascular oxidative stress and neurovascular dysfunction induced by brain Aß. The central hypothesis of this application is that CD36 in PVM participates in the deleterious vascular effects of Aß and in the long-term consequences of Aß overproduction. We will test the following specific hypotheses: (1) PVM are the cells on which brain Aß acts to induce vascular oxidative stress and dysfunction; (2) CD36 in PVM is responsible for these actions of Aß, and (3) CD36 in PVM contributes to the long-term consequences of Aß overproduction, including cognitive deficits and perivascular Aß accumulation. Our studies will use state-of-the-art methods to investigate neurovascular regulation in mice. Pharmacological approaches and bone marrow chimeras will be used to investigate the specific role of CD36 in PVM in Aß-induced oxidative stress, neurovascular dysfunction, and cognitive deficits.

Lay Summary

There is an urgent need to develop treatments for Alzheimer's disease (AD), the most common cause of dementia. We propose to investigate how the A? peptide, a key pathogenic factor in AD, damages cerebral blood vessels and contributes to the brain dysfunction underlying the dementia. We will focus on the role of perivascular macrophages and on the scavenger receptor CD36. The proposed studies may establish CD36 on perivascular macrophages as a new therapeutic target to counter the deleterious vascular effects of A? on the brain.

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