Mitochondrial degrading enzyme, synaptic mitochondrial function in AD mouse model

https://www.neurodegenerationresearch.eu/survey/mitochondrial-degrading-enzyme-synaptic-mitochondrial-function-in-ad-mouse-model/

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Country

USA

Title of project or programme

Mitochondrial degrading enzyme, synaptic mitochondrial function in AD mouse model

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,732,659.63

Start date of award

15/08/2014

Total duration of award in years

3

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Mitochondrial and synaptic dysfunction is an early pathological feature of Alzheimer’s disease (AD) affected brain1-7. Recent studies have highlighted the role of mitochondrial Abeta in AD pathogenesis. A progressively accumulates in mitochondria of AD brain and transgenic AD mice overexpressing Abeta. Notably, accumulation of mitochondrial Abeta precedes extracellular Abeta deposition in AD brain, which is consistent with the early onset of loss of synapses and synaptic and mitochondrial damage. Thus, accumulation of mitochondrial Abeta may be an initiating pathological event leading to mitochondrial and neuronal perturbation. Human PreP (hPreP) located in brain mitochondria, is a novel mitochondrial Abeta degrading enzyme. Our recent studies indicates that the proteolytic activity of hPreP was significantly reduced in Abeta-rich mitochondria from AD-affected brain and transgenic AD mice overexpressing APP/Abeta, suggesting that hPreP may potentially be of importance in preventing amyloid pathology of AD through its degradation and clearance of mitochondrial Abeta. However, the effects of PreP on amyloid pathology and mitochondrial and synaptic degeneration in Abeta milieu have not yet been disclosed. In our pilot studies, we observed the reduction of Abeta accumulation in mitochondria and cerebral cortex by increased PreP activity in Tg mAPP mice. We hypothesize that impaired function of PreP protease contributes to chronic mitochondrial Abeta accumulation relevant to developing amyloid pathology of AD, leading to mitochondrial and synaptic degeneration, thus, clearance of mitochondrial Abeta by PreP may be of importance in the pathology of AD. The goal of this proposal is to gain new insight into the role of PreP in AD pathogenesis, focusing on mitochondrial Abeta accumulation/clearance, amyloid pathology, synaptic mitochondrial properties, oxidative stress, synaptic function, utilizing a novel genetically manipulated transgenic mouse models and neuronal culture with altered PreP levels and proteolytic activity in Abeta-rich environment [(increased expression of neuronal PreP, inactive mutant PreP with catalytic base Glu(78) in the inverted zinc-binding motif replaced by Gln, lacking enzyme activity, and genetic deficiency of neuronal PreP in AD-type transgenic mice overexpressing Abeta). The outcomes of the project would also support that PreP might be a potential therapeutic agent for limiting mitochondrial and cerebral amyloid accumulation thereby halting AD progression.

Lay Summary

PUBLIC HEALTH RELEVANCE: The aim of this project is to investigate an unexplored role of mitochondrial Abeta degrading enzyme (PreP) in mitochondrial amyloid pathology leading to synaptic mitochondrial and synaptic degeneration relevant to the pathogenesis of Alzheimer’s disease. The outcomes of the proposed studies would also support that PreP might be a potential new therapeutic agent for eliminating and limiting mitochondrial and cerebral amyloid accumulation thereby halting progression of Alzheimer’s disease.

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