Presenilins and neuronal calcium dyshomeostasis

https://neurodegenerationresearch.eu/survey/presenilins-and-neuronal-calcium-dyshomeostasis/

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Country

USA

Title of project or programme

Presenilins and neuronal calcium dyshomeostasis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,101,811.01

Start date of award

15/08/2013

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

presenilin, Calcium, Presenile Alzheimer Dementia, Endoplasmic Reticulum, Alzheimer's Disease

Research Abstract

DESCRIPTION (provided by applicant): The broad, long-term objective of the project is to understand the importance of neuronal calcium (Ca2+) signaling in pathogenesis of Alzheimer’s

disease (AD). Presenilins are transmembrane proteins localized to endoplasmic reticulum (ER). Missense mutations in presenilins account for 40% of familial AD (FAD) cases. Many FAD mutations in presenilins have been also linked to abnormal endoplasmic reticulum (ER) calcium (Ca2+) signaling. The main aim of the current proposal is to understand the connection between mutations in presenilins, dysregulation of neuronal ER Ca2+ signaling and synaptic loss and dysfunction in AD. Specifically, we will focus on testing the novel hypothesis that defects in ER Ca2+ signaling may lead to destabilization of “”mushroom spines”” widely considered to be physical units for memory storage by attacking these aims:. 1. To investigate the importance of postsynaptic store-operated calcium (SOC) entry pathway downregulation in loss of mature synaptic spines in AD. Our preliminary data suggest that the increase in neuronal ER Ca2+ levels leads to a compensatory downregulation of neuronal store-operated Ca2+ entry pathway (nSOC). We discovered that the downregulation of nSOC occurs due to reduced expression of STIM2 protein, a master regulator of nSOC. We propose that reduction in synaptic nSOC causes destabilization and eventual elimination of mushroom spines, leading to loss of memories in FAD and aging brains. This hypothesis will be tested in experiments with PS1-FAD mouse model and STIM2 conditional knockout mouse model. 2. To investigate the connection between dysregulation of neuronal activity and destabilization of LTP- induced mature synaptic spines in AD. Our preliminary data indicate that appropriate pattern of neuronal activity is criticl for maintenance of mature “”mushroom spines””. We further discovered that abnormal ER Ca2+ signaling causes disruption of this pattern in PS1-FAD neurons. We will perform a series of experiments aimed at dissecting the connection between ER Ca2+ homeostasis, neuronal activity pattern and stability of mushroom spines in AD neurons. We will evaluate a crucial role of intracellular Ca2+ stores and SK family of Ca2+-activated potassium channels in this process. 3. To analyze the cross-talk of amyloid and calcium pathways for AD pathogenesis. Abeta42 oligomers influence neuronal Ca2+ signaling and neuronal activity via variety of pathways. In this aim we will investigate if some of the Ca2+-related targets and pathways explored in SA1 and SA2 may also apply to models of amyloid synaptotoxicity. These experiments will be performed with in vitro model of Abeta42 synaptotoxicity and with recently generated APP-KI mouse model of AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed project will have direct and immediate relevance for public health. Alzheimer’s disease (AD) is a major cause of dementia in the elderly and an enormous health problem. The experiments described in the grant are aimed at testing specific hypothesis regarding pathogenesis of AD and will provide information critical for eventual development of the cure.

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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