Role of PS1 in neurodegeneration

https://www.neurodegenerationresearch.eu/survey/role-of-ps1-in-neurodegeneration/

Principal Investigators

BEREZOVSKA, OKSANA

Institution

MASSACHUSETTS GENERAL HOSPITAL

Contact information of lead PI
Country

USA

Title of project or programme

Role of PS1 in neurodegeneration

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,276,602.75

Start date of award

15/05/2014

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): Synaptic dysfunction and Aß accumulation are the key features of Alzheimer’s disease (AD) pathology. Numerous studies have shown that Aß can be produced in activity-dependent manner, and this correlates with synaptic vesicle exocytosis.

PS1/g-secretase is present at the synaptic terminals, and our preliminary data show that it changes its conformation rapidly and reversibly in concert with synaptic activity and calcium (Ca2+) influx. Presenilin 1 (PS1) is the catalytic component of ?-secretase, which liberates the C-terminus of Aß peptide, and thus determines both amount of Aß and which Aß species will be produced: Aß40 or the longer, highly fibrillogenic and neurotoxic Aß42. However, the cell biological mechanisms that control precision of the PS1/?-secretase cleavage site and local Aß production at the synapse remains unknown. PS1 phosphorylation by several kinases has been reported; however mechanistic effect of the PS1 phosphorylation remains unclear. Aim 1 will determine whether neuronal activity/Ca2+-induced phosphorylation of PS1/?-secretase represents the regulatory mechanism of PS1 conformation and function at the synapse. Furthermore, our recent proteomics screen of mouse brain lysates in the presence or absence of calcium identified two novel PS1 interacting proteins, synapsin1 (Syn1) and synaptotagmin1 (Syt1), that showed strong but opposing Ca2+-dependent profiles of binding to PS1. Syn1 anchors synaptic vesicles to actin filaments, but releases them after Ca2+-induced Syn1 phosphorylation. Syt1 acts as Ca2+sensor in neurotransmitter release. Aim 2 will explore whether, Ca2+ influx may function as a switch controlling PS1 conformation and interactions with Syn1 and Syt1. In addition, we will test if PS1 interactions with Syn1 and Syt1 modulate PS1/?-secretase and APP processing at the synapse in an activity-controlled manner. Aim 3 will validate physiological relevance of the newly found PS1 interaction with synaptic proteins in vivo by establishing if it is affected in aged and/or diseased brain, and whether these interactions can be manipulated pharmacologically. This study will provide mechanistic data for PS1 conformational changes, will explore novel PS1 interactions with synaptic vesicle machinery proteins, and will elucidate novel Aß-dependent and independent role of PS1 at the synapse. Understanding these issues is of high importance because manipulation of the PS1 conformation and synaptic interactions may translate into novel therapeutic strategies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is one of the most prevalent neurodegenerative disorders for which no cure is available. Due to the increased average population age, and thus increased number of affected individuals and associated tremendous healthcare coasts, AD has become an urgent public health concern in the U.S. By deciphering mechanisms underlying the pathogenesis we will be able to develop new therapeutics to prevent of halt the 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