Presenilins in the hippocampal network and Alzheimers disease

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Country

USA

Title of project or programme

Presenilins in the hippocampal network and Alzheimers disease

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NIH (NIA)

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15/05/2001

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

presenilin, Perforant Pathway, mossy fiber, Hippocampus , familial Alzheimer disease

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common neurodegenerative disorder characterized by dementia and neurodegeneration. Mutations in the Presenilin (PSEN) genes account for >80% of all causative mutations identified in familial AD,

highlighting its importance in the pathogenesis of AD. Through the development and multidisciplinary analysis of a series of Psen mutant mice, we previously established that Presenilin (PS) is essential for learning and memory, synaptic function and neuronal survival. For example, presynaptic PS plays a selective role in neurotransmitter release and synaptic plasticity through the regulation of ryanodine receptors (RyRs) and RyR-mediated calcium release from the ER. Synaptic dysfunction has widely been considered to play a key role in AD pathogenesis, and the hippocampal network is particularly vulnerable in AD. However, published reports have largely focused on the hippocampal Schaffer collateral pathway, and rarely explored in the mossy fiber and the perforant path. Furthermore, inhibitory interneurons play an integral role in the regulation of neuronal networks, but it is entirely unknown whether PS plays a normal physiological role in interneurons. In this competing renewal application, we propose two Specific Aims to investigate the role of PS in the regulation of the hippocampal network and the pathogenic mechanism of familial AD. In Aim 1, we will determine and compare the role of PS in the tri-synaptic loop of the hippocampus. Specifically, we will determine the consequences of PS inactivation in mossy fiber and perforant synapses, relative to Schaffer collateral synapses, using acute hippocampal slices. We will also investigate the role of PS in inhibitory interneurons through the generation and analysis of interneuron-specific conditional double knockout mice. In Aim 2, we will investigate the role of PS in familial AD. Specifically, we will compare mouse neurons derived from knockin mice carrying the pathogenic PSEN1 L435F or C410Y mutation with human neurons derived from iPS cells carrying the same mutation, and will assess the effects of the mutation on ?-secretase activity, calcium regulation and synaptic function between the mouse and human neurons. The completion of the proposed study will provide mechanistic insight into PS function and dysfunction in excitatory and inhibitory neurons as well as its involvement in familial AD.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is the most common neurodegenerative disorder, and mutations in the Presenilin genes are the most common cause of the inherited forms of the disease. The hippocampus is particularly vulnerable in AD, and synaptic dysfunction is widely considered as the earliest pathogenic event. In this application, we propose to study the normal function of Presenilins in the hippocampal network and how the mutations cause familial AD. Completion of our proposed study will provide insights into AD pathogenesis and may identify novel therapeutic targets for AD.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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