Synaptic Depression: Focus on Cdk5 Signaling

https://neurodegenerationresearch.eu/survey/synaptic-depression-focus-on-cdk5-signaling/

Principal Investigators

ZHU, J. JULIUS

Institution

UNIVERSITY OF VIRGINIA

Contact information of lead PI
Country

USA

Title of project or programme

Synaptic Depression: Focus on Cdk5 Signaling

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,572,880.73

Start date of award

20/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Cyclin-Dependent Kinase 5, synaptic depression, Synapses, Alzheimer's Disease, Amyloid beta-Protein

Research Abstract
? DESCRIPTION (provided by applicant): The previous investigation has revealed a pivotal role for cyclin-dependent kinase 5 (Cdk5) in synaptic plasticity, behavior and cognition, but also raised a fundamental question on how Cdk5 signaling regulates synaptic plasticity and behavior. To address this question, we examined Cdk5 signaling at hippocampal CA1 synapses in rat

cultured slices and intact brains. We found that Cdk5, which is activated upon association with its neuron-specific regulatory subunit p35, depressed transmission using a homeostatic mechanism. Surprisingly, Cdk5 depressed transmission rapidly within 15?30 min. This result distinguishes Cdk5 from all known homeostatic transmission regulators (e.g., A? and Arc) that act in the time windows from hours to days. Moreover, we overexpressed p25, a cleavage product of p35 and more potent activator of Cdk5, in intact animals. Chronic overproduction of p25, seen in Alzheimer's patients, induced the concurrent reduction in synapse density and increase in synaptic size, the hallmark early synaptic pathology of Alzheimer's disease. This result designates p25 as the first molecule capable of inducing the characteristic synaptic pathology of the disease. Together, our preliminary data suggest a novel rapid transmission homeostasis at central synapses and a new mechanism for the early pathogenesis of Alzheimer's disease. Based on our preliminary findings, we propose to investigate how Cdk5 signaling regulates a novel rapid synaptic homeostasis at central synapses using a hippocampal cultured slice preparation (Aim 1). We expect that the investigation will define the synaptic role of Cdk5 signaling, and suggest a new molecule target (and strategy) for preventing the rapid status epilepticus. We also plan to extend the study into intact animals to examine how chronic overproduction of p25, seen in Alzheimer's patients, induces the characteristic early Alzheimer-like synaptic pathology and cognitive impairments (Aim 2). We expect that the examination will reveal a new mechanism for the pathogenesis of Alzheimer's disease, and establish an animal model for the pathogenesis. Finally, we will explore pharmacological and genetic manipulations that may reverse the synaptic pathology and cognitive impairments in the animal model (Aim 3). We expect that the exploration will develop alternative therapeutic options for Alzheimer's disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal is designed to test two novel hypotheses that physiological cyclin-dependent kinase 5 (Cdk5) signaling controls a novel rapid homeostasis at central synapses, and that chronic p25 overproduction-stimulated pathological Cdk5 signaling can induce the characteristic Alzheimer- like early synaptic pathology. We expect that the findings from this application will help to understand a mechanism that prevents the rapid status epilepticus, and suggest a feasible therapeutic intervention for 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