Deconstructing the pathogenic effect of APP in memory circuits

https://neurodegenerationresearch.eu/survey/deconstructing-the-pathogenic-effect-of-app-in-memory-circuits/

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Country

USA

Title of project or programme

Deconstructing the pathogenic effect of APP in memory circuits

Source of funding information

NIH (NIA)

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15/07/2015

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid beta-Protein Precursor, Memory, Mosaicism, inhibitory neuron, neonatal brain

Research Abstract

? DESCRIPTION (provided by applicant): Genetic studies have demonstrated a central role for the amyloid precursor protein (APP) in Alzheimer’s disease, yet we do not understand at a cellular level how this protein contributes to disease. Endogenous APP is found in both

excitatory and inhibitory neurons, but whether it exerts greater impact on one than the other has not yet been examined. We lack even a fundamental grasp of whether disease-associated APP variants primarily affect the neuron in which they are expressed, or instead act on neighboring cells within reach of secreted fragments. To address these fundamental questions about the basic biology and pathogenic potential of APP, we have developed a set of model systems that combine precise spatial control over the cells in which APP is expressed with reversible temporal control over when it is active. We will use these models to test our central hypothesis that the impact of pathogenic APP depends on both the timing and location of its expression. Our studies are designed to answer three main questions. In the first aim, we will examine whether pathogenic APP causes distinct impairments in circuit function and cognitive performance when expressed in excitatory vs. inhibitory neurons. We have already characterized the behavioral and hippocampal deficits evoked by excitatory APP expression, and here will create and characterize a mouse model in which APP is limited to GABAergic interneurons for comparison. In our second aim, we will examine how the position of APP-overexpressing cells within the hippocampus affects transmission through the trisynaptic circuit. We will use stereotaxic viral injection to selectively express pathogenic APP within presynaptic CA3 or postsynaptic CA1 neurons to determine which side of the synapse APP acts from and on to impair synaptic transmission in the Schaeffer collateral pathway. Finally, in our third aim, we will determine whether pathogenic APP affects neuronal function through a cell-autonomous or cell-extrinsic manner. We will use viral mosaicism to produce two complementary expression patterns in which isolated APP-overexpressing cells are surrounded by wild-type neurons, or in which isolated wild-type cells are surrounded by APP-overexpressing cells, to test how neuronal physiology is altered by APP expression within the neuron compared to APP expression within its neighbors. By using the tet-off transgenic system to restrict the location of APP in each of these models, we gain the added flexibility to control when it is expressed. This feature will allo us to distinguish the effects of pathogenic APP on synapse formation during postnatal development from its impact on synapse maintenance and plasticity in the adult. Moreover, by acutely arresting pathogenic APP expression in either of these settings, we will identify which physiological or behavioral changes are dependent on continued production of APP/Aß and which are permanent consequences of past exposure.

Lay Summary

PUBLIC HEALTH RELEVANCE: This application studies how pathogenic forms of APP contribute to neuronal dysfunction in Alzheimer’s disease. Our experiments will clarify how the cellular source of APP influences its effect on synaptic transmission, circuit function, and cognitive behavior.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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