Dissecting the Toxicity of Glial and Neuronal Expression of APP in the Brain

https://www.neurodegenerationresearch.eu/survey/dissecting-the-toxicity-of-glial-and-neuronal-expression-of-app-in-the-brain/

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Country

USA

Title of project or programme

Dissecting the Toxicity of Glial and Neuronal Expression of APP in the Brain

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,226,917.43

Start date of award

15/03/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid beta-Protein Precursor, Neuroglia, Toxic effect, Neurons, Brain

Research Abstract

? DESCRIPTION (provided by applicant): Over the last several years, much effort has been devoted to studying the role of Amyloid Precursor Protein (APP) in Alzheimer’s disease (AD).

One of the key goals has been to understand the precise role of APP in AD. APP is clearly involved in the pathogenesis of AD. For instance, the first gene mutation identified as a cause for autosomal dominant form of AD is in the APP gene. Similarly, duplication for the APP gene is a risk factor for developing AD. APP is expressed both in neurons and glia, and while much work has been directed towards understanding its role or processing in neurons, the importance or the relevance of expression and the processing of APP in glia has not been examined. Thus, we know very little about the role of APP in glia in the development of AD. We have developed a robust APP-gain of function (APP-GOF) model in the Drosophila brain. We can express this specifically in glial cells or neurons. When we expressed APP in glia and compared to neuronal expression, we found differences in both the pattern of deposition of APP, processing of APP, and lethality induced by such expressions. We further found that the lethality strictly correlated with a specific processed peptide other than Abeta; the level of which increased with the co-expression of human BACE and resulted in a greater lethality compared to APP expression alone. These main results led us to formulate experiments to dissect the role of APP, its processing and toxicity when expressed in glial cells, and compare this with APP in neurons. Thus, our specific aims are: 1) Analyze the processing and the lethal effects of expression of APP in glial cells, 2) Analyze the effects of expression of processed peptides of APP in glia and neurons in the brain, and 3) Perform a conditional genetic screen for recessive modifiers of APP-GOF. We believe that these aims when completed, will contribute significantly to our understanding of the role played by APP in glia and its contribution to the development of the neuropathology and the disease. These studies will also likely identify new players in the APP-mediated pathway(s).

Lay Summary
PUBLIC HEALTH RELEVANCE: This grant examines the role of APP and its processed peptides on glial cells, and the impact of expression of APP in glial cells on the brain using the model organism Drosophila. It also explores a novel recessive genetic screen for identifying modifiers of APP-over-expression.

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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