The regulation of beta-amyloid sensitivity and Alzheimers related impairments by PP2A

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Country

USA

Title of project or programme

The regulation of beta-amyloid sensitivity and Alzheimers related impairments by PP2A

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,605,504.59

Start date of award

15/02/2015

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Protein Phosphatase 2A Regulatory Subunit PR53, Amyloid beta-Protein, Amyloid beta-Protein Precursor, Alzheimer's Disease, Impairment

Research Abstract
? DESCRIPTION (provided by applicant): Our poor understanding of the genetic and

environmental factors and the mechanisms by which they produce the cognitive and behavioral impairments that characterize Alzheimer’s disease stands as a critical barrier to identifying effective preventative measures and treatments for Alzheimer’s disease. This project seeks to address this gap in our understanding by examining the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer’s disease patients. PP2A is regulated by multiple mechanisms including post-translational methylation of the C-terminus of the catalytic subunit. This methylation is controlled by a dedicated methylesterase, PME-1, and a dedicated methyltransferase, LCMT-1. To perform these studies, we will alter PP2A activity in vivo by manipulating PME-1 and LCMT-1 expression using multiple lines of genetically modified mice. By altering PP2A methylation, the subunit composition and substrate specificity of the mature enzyme will be altered, thereby increasing or decreasing its ability to dephosphorylate Alzheimer’s disease relevant substrates. The following specific aims will be pursued: 1) Test the hypothesis that reduced PP2A methylation promotes the development of Alzheimer’s disease related impairments by increasing sensitivity to beta- amyloid. 2) Test the hypothesis that over expressing LCMT-1 or reducing PME-1 expression protects against Alzheimer’s disease related impairments by decreasing sensitivity to beta- amyloid. 3) Test the hypothesis that PP2A controls beta-amyloid sensitivity by regulating APP phosphorylation at Thr668. These aims will be addressed through a combination of behavioral, electrophysiological, and biochemical techniques. In summary, findings derived from these studies will identify the mechanisms whereby PP2A and its downstream targets may affect the development of Alzheimer’s disease by controlling sensitivity to beta-amyloid. Furthermore, they will suggest developing interventions that target this pathway as an effective new therapeutic approach for the disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: In the vast majority of cases, the cause of Alzheimer’s disease is unknown, and in no case is an effective disease-modifying treatment available. Our poor understanding of the genetic and environmental factors and the mechanisms by which they produce the cognitive and behavioral impairments that characterize Alzheimer’s disease, stands as a critical barrier to identifying effective preventative measures and treatments for Alzheimer’s disease. The project will seek to address this gap in our understanding by examining the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer’s disease patients.

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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