Mint Adaptor Proteins in APP Binding and Processing

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Country

USA

Title of project or programme

Mint Adaptor Proteins in APP Binding and Processing

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,530,144.04

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01/02/2014

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Amyloid plaques, which consist of fibrillar amyloid-ß

(Aß) peptides, play a key role in Alzheimer's disease (AD) pathogenesis. It is well established that Aß is generated by sequential proteolysis of the amyloid precursor protein (APP) by ß- and ?-secretases, respectively. However, the cell biology and molecules controlling APP trafficking essential for Aß production in neurons are less defined. A key step in Aß generation is APP endocytosis that is mediated by the YENPTY sequence located in the cytoplasmic region of APP. Mints are adaptor proteins that are functionally important in regulating APP endocytosis and Aß production. We previously showed that the Mint adaptor proteins regulate APP endocytosis by directly binding to the YENPTY endocytic motif of APP, thereby influencing proteolytic processing of APP. The evidence that Mints are upregulated and found in Aß plaques in postmortem human AD brains supports a role for Mints in AD pathogenesis. Consistent with this finding, we showed that loss of any one of the three Mint proteins decreases Aß production in aging mice and mouse models of AD. These findings suggest that the APP-Mint interaction is a potential key therapeutic target to selectively reduce Aß production in AD. However, the mechanisms underlying the effects of Mints on APP binding and Aß production are unclear. Therefore, the overall goal of this research proposal is to understand Mint-dependent regulation of APP binding and processing. In Aim 1, we will determine the cell biology of APP trafficking and how Mints are essential for synaptic activity-induced APP endocytosis and Aß production. In Aim 2, we will investigate the effects of perturbing the APP-Mint1 interaction to decrease Aß production in both in vitro and in vivo mouse models. The identification of novel ways to modulate APP binding and Aß production will be an important tool that can lead to the development of alternative therapeutic strategies for treating AD. Through our structural studies, we found that autoinhibition of Mint1 regulates APP binding and processing; however, the molecular mechanism underlying Mint1 autoinhibition and the physiological relevance of this regulation in neurons are not known. In Aim 3, we will elucidate the biological mechanisms underlying Mint1 autoinhibition in regulating APP binding. A detailed delineation of the autoinhibitory mechanism regulating Mint1 binding to APP is an invaluable tool in exploring the critical routes to which it operates and a platform for future targeted therapeutics. The proposed research will provide new insights into understanding APP-Mint biology and the outcomes of this research are expected to have strong translational implications.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disorder characterized by progressive memory loss and cognitive decline. AD affects millions of people world-wide and the disease is becoming more prevalent as the population ages marking as a major public health concern. Therefore, the need for prevention and cure are urgent. The main neuropathological hallmark of AD is amyloid plaques that consist of aggregated amyloid peptides derived from the proteolytic cleavage of the amyloid precursor protein (APP). Understanding the cell biology and molecules controlling APP localization and processing is of great significance for the mechanistic understanding of AD. It will provide novel insights into AD pathogenesis and can lead to the development of novel therapeutic strategies for treating or preventing AD.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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