AMPK in Alzheimers Disease-Associated Synaptic Failure and Memory Deficits

https://neurodegenerationresearch.eu/survey/ampk-in-alzheimers-disease-associated-synaptic-failure-and-memory-deficits/

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Contact information of lead PI
Country

USA

Title of project or programme

AMPK in Alzheimers Disease-Associated Synaptic Failure and Memory Deficits

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 834,787.16

Start date of award

01/09/2015

Total duration of award in years

4

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... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Lack of mechanistic understanding hampers our search for solid therapeutic targets on Alzheimer’s disease (AD), the most common form of dementia in the elderly and one of the leading causes of death across all ages. Current disease modifying strategies based on the Amyloid beta (A?) hypothesis, such as A? antibody immunotherapy, have met with limited success. Meanwhile, the downstream signaling pathways of A? as well as A?-independent mechanisms are being actively pursued as potential targets for AD therapy. One such potential mechanism is via regulation on the AMP-activated protein kinase (AMPK), a central cellular energy sensor and signaling transducer integrating a number of signaling pathways implicated in synaptic plasticity, learning and memory. Moreover, AMPK activity is stimulated during oxidative stress which is known to play a role in AD pathogenesis. The goal of this project is to understand the role of AMPK in AD pathophysiology and to develop therapeutics that can reverse impairments due to AMPK dysregulation. Driven by the preliminary data, the central hypothesis is that restoring normal AMPK activity will improve multiple aspects of pathophysiology in APP/PS1 AD model mice. Four specific aims are formulated to test this hypothesis as described in the following. The first two aims are to be performed during the mentored phase (K99): Aim 1 is to determine how AMPK signaling is regulated in AD model mice and whether aberrant AD-related autophagy can be rescued by restoring AMPK activity; Aim 2 is to determine whether pharmacologically inhibition of AMPK activity reverse synaptic plasticity impairments and memory deficits displayed by AD model mice. And with this information in hand, I will then move on to the other two aims to be achieved during the independent phase (R00): Aim 3 is to determine whether genetic reduction of AMPK activity prevents synaptic and behavioral defects in AD model mice; and Aim 4 is to determine the AD-related cellular and molecular abnormalities that are corrected in APP/PS1/AMPK?2(+/-) double mutant mice. Findings derived from this project will potentially provide important insights into identification of novel therapeutic targets for AD and other related cognitive syndromes such as frontotemporal lobe dementia. Furthermore, the research project and career development components of this K99/R00 application will provide critical training for the applicant to become a successful independent investigator who can integrate these knowledge and techniques to improve our understanding of neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The molecular signaling mechanisms underlying AD pathogenesis is not well understood which hampers our ability to search for solid therapeutic targets. This project may help understand the role of a potential important signaling pathway related to AD etiology and translate into novel therapeutic targets for AD and related cognitive syndromes. PUBLIC HEALTH RELEVANCE: Effective therapy or disease modifying strategy is still not available for Alzheimer’s disease. This project will help understand the role of AMPK signaling in AD pathogenesis and may translate into novel therapeutic targets for AD and related cognitive syndromes.

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