Dynamin-Related Protein 1 and Mitochondrial Fragmentation in Alzheimers Disease

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Country

USA

Title of project or programme

Dynamin-Related Protein 1 and Mitochondrial Fragmentation in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,829,942.20

Start date of award

30/09/2012

Total duration of award in years

6

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): The long-term goal of our proposed research is to understand molecular basis of mitochondrial dysfunction Alzheimer's disease (AD) in pathogenesis and to develop neuroprotective strategies to delay or prevent the onset of AD. Increasing evidence suggests that amyloid beta (Ab), hyperphosphorylated tau and mitochondrial structural and functional abnormalities are critically involved in the loss of synapses and cognitive decline, in patients with Alzheimer's disease (AD). Several lines of evidence suggests that Ab and hyperphosphorylated tau are directly responsible for causing mitochondrial dysfunction and oxidative stress in AD pathogenesis. 1) Several studies found Ab and N-terminal tau in mitochondrial membranes and causing mitochondrial dysfunction in neurons affected by AD; 2) recent studies found increased mRNA and protein levels of the mitochondrial fission genes and decreased fusion genes in AD postmortem and transgenic mouse models and cell-lines that express Ab, causing abnormal mitochondrial dynamics; 3) several other studies found that Ab reduces total motile mitochondria, impairs mitochondrial axonal transport, particularly anterograde transport; inhibits synaptic ATP production; and causes synaptic degeneration in AD neurons and 4) further, GTPase protein, Drp1 interacted with Ab and hyperphosphorylated tau in neurons from AD patients and transgenic mouse models of Ab and tau. These findings lead to the hypothesis that the interaction of Drp1 with Ab and hyperphosphorylated tau triggers mitochondrial fission by enhancing Drp1 enzymatic activity and causes excessive mitochondrial fragmentation, and ultimate neuronal dysfunction selectively in AD neurons. The objectives of our application are 1) to determine whether Drp1 interactions with Ab and hyperphosphorylated tau increases with disease progression and pathogenesis; 2) further how such interaction affects Drp1 enzymatic activity and mitochondrial morphology, distribution and function in AD neurons; 3) in addition, whether partial loss of Drp1 decreases Ab and hyperphosphorylated tau-induced mitochondrial fragmentation, neuronal damage and synaptic dysfunction. The outcome of the proposed experiments in this application, will provide new insights in understanding the physiological relevance of interactions Drp1 with Ab, and phosphorylated tau in AD progression and pathogenesis and the outcome may have implications to develop mitochondrial therapeutics to reduce Ab and hyperphosphorylated tau-induced pathologies in AD patients.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mitochondrial dysfunction is a major hallmark of Alzheimer's disease (AD). Mitochondria play an important role in neurons and maintain the balance of mitochondrial fission and fusion. The objective of the proposed research is to determine whether Drp1 interactions with amyloid beta and with hyperphosphorylated tau affect Drp1 enzymatic activity and alter mitochondrial morphology, distribution, and function in AD neurons, and whether partial loss of Drp1 decreases amyloid beta and hyperphosphorylated tau-induced mitochondrial fragmentation, neuronal damage, and synaptic dysfunction.

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