Abnormal Mitochondrial Dynamics and Mitochondrial Dysfunction in Alzheimers Dise

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Contact information of lead PI
Country

USA

Title of project or programme

Abnormal Mitochondrial Dynamics and Mitochondrial Dysfunction in Alzheimers Dise

Source of funding information

NIH (NIA)

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01/07/2013

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

mitochondrial dysfunction, Mitochondria, Alzheimer's Disease, OPA1 gene, Dynamin

Research Abstract

DESCRIPTION (provided by applicant): Multiple lines of evidence indicate that mitochondrial dysfunction plays a critical role in the pathogenesis of Alzheimer disease; however, the

underlying molecular mechanism and its role in AD pathogenesis remain poorly understood. Mitochondria are dynamic organelles that undergo continuous fission and fusion. Our recent in vitro studies suggest that abnormal mitochondrial dynamics likely contributes to mitochondrial dysfunction and synaptic/neuronal dysfunction in AD. Based on these studies, we hypothesized that impaired balance in mitochondrial fission/fusion plays a critical role in the pathogenesis of AD by causing excessive mitochondrial fragmentation and redistribution as well as causes mitochondrial ultrastructural defects and dysfunction which in turn adversely affects neuronal functions including synaptic dysfunction and cognitive/behavioral deficits in AD. However, due to the limitation of in vitro cell culture models, it remains to be determined whether it is mitochondrial fragmentation or elongation that occurs in vivo since swollen mitochondrial in AD or APP mice may demonstrate increased size and/or length. Moreover, it also remains to be determined whether abnormal mitochondrial dynamics is causally involved in mitochondrial/synaptic dysfunction and cognitive deficits in APP mice in vivo. Our preliminary results demonstrated mitochondrial dysfunction, fragmented mitochondria, and decreased expression of mitochondrial fission/fusion proteins in the hippocampus of 3 month-old CRND8 APP transgenic mice, suggesting an altered mitochondrial dynamics early in the disease process. More importantly, we were able to enhance mitochondrial fusion in vivo by overexpressing Mfn2 expression in hippocampus, which enables us to address these critical gaps in our knowledge in vivo. Therefore, we propose to cross these Mfn2 mice with CRND8 APP transgenic mice and determine how normalization of mitochondrial dynamics will affect mitochondrial function, and neuronal/synaptic dysfunction and pathological/behavioral/cognitive deficits in CRND8 mice. The goal is to obtain a definite answer on the involvement of mitochondrial fragmentation or elongation in APP mice and to determine the causal role of mitochondrial dynamics in mitochondrial/neuronal dysfunction and cognitive/behavioral deficits in AD mouse models, which will also serve as a proof-of-concept study for Mfn2-directed therapy for AD. To complement the in vivo studies, we will determine the causal involvement of abnormal mitochondrial dynamics in Abeta-induced mitochondrial/neuronal function and further pursue mechanisms underlying Abeta-induced changes in mitochondrial dynamics and how Mfn2 overexpression rescues Abeta-induced mitochondrial deficits.

Lay Summary
PUBLIC HEALTH RELEVANCE: The balance of mitochondrial fission/fusion is critical for mitochondrial distribution and function which affects synaptic/neuronal function in AD cell models. In this application, we propose to investigate the causal involvement of mitochondrial fragmentation and abnormal distribution in the pathogenesis of AD in vivo and explore the underlying mechanisms.

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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