

Molecular Mechanisms Underlying Mitochondrial Dynamics Abnormalities in Alzheimer Disease

<https://www.neurodegenerationresearch.eu/survey/molecular-mechanisms-underlying-mitochondrial-dynamics-abnormalities-in-alzheimer-disease/>

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Country

USA

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Molecular Mechanisms Underlying Mitochondrial Dynamics Abnormalities in Alzheimer Disease

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NIH (NIA)

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30/09/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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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

PROJECT SUMMARY/ABSTRACT Compelling evidence suggest that mitochondrial dysfunction is an early prominent feature in susceptible neurons in the brain of patients with Alzheimer's disease and plays a critical role in the pathogenesis of AD. Mitochondria are dynamic organelles that undergo continual fission and fusion events. Most recent studies from multiple groups including ours suggested a likely involvement of abnormal mitochondrial dynamics in AD brain. Indeed, overexpression of APP mutant or A β treatment induces profound mitochondrial fragmentation, ultrastructural deficits and altered distribution which are likely causally involved in A β -induced spine loss and synaptic abnormalities in hippocampal neurons. A β -induced changes in mitochondrial dynamics and distribution are also early events in animal models of AD. However, molecular mechanisms underlying A β -induced abnormal mitochondrial dynamics remains to be determined. Mitochondrial dynamics and function may be modulated by calcium signaling. Notably, a critical role of intracellular calcium dysregulation in the pathogenesis of AD has long been postulated. It is well established that A β oligomers induce a rapid and sustained increase in intracellular calcium in neurons which mediate A β -induced neuronal abnormalities including spine loss and synaptic dysfunction likely through the activation of calcium- dependent signaling molecules such as calpain and calcineurin. Importantly, our pilot study demonstrated that soluble A β oligomers induce elevation in cytosolic calcium which precedes mitochondrial fragmentation, and elevated mitochondrial calcium coincides with a wave of rapid decrease in mitochondrial length, suggesting that A β -induced aberrant calcium signaling is involved in the modulation of mitochondrial dynamics. This is likely through the modulation of mitochondrial fission/fusion proteins since our preliminary studies demonstrated that ADDLs caused reduction in DLP1/OPA1/Mfn1/2 and dephosphorylation of DLP1 at Ser637. Therefore, we hypothesize that A β - induced aberrant calcium signaling causes posttranslational changes (i.e., modifications and/or degradation) in mitochondrial fission/fusion proteins that leads to abnormal mitochondrial dynamics. To test this hypothesis, we will characterized the causal role of aberrant calcium signaling in mediating A β -induced mitochondrial fragmentation and abnormal mitochondrial transport/distribution in details both in vitro and in vivo. Our proposed studies will provide mechanistic insights into mitochondrial dynamic abnormalities in AD by linking two important deficits (i.e., calcium dyshomeostasis and mitochondrial dysfunction) involved in the pathogenesis of AD, which could serve as foundation for future drug development.

Lay Summary

PROJECT NARRATIVE It is suggested that defects in mitochondrial dynamics likely underlies mitochondrial dysfunction and synaptic/neuronal dysfunction in AD, however, molecular mechanism underlying abnormal mitochondrial dynamics in AD remains to be determined. The goal of this application is to understand the possible involvement of aberrant calcium signaling and its impact on posttranslational modifications on mitochondrial fission/fusion factors in AD models. Our findings will provide further support for targeting abnormal mitochondrial dynamics for future therapeutic development.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

Years:

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