Role of Cyclophilin D in Abeta- induced synaptic injury

https://www.neurodegenerationresearch.eu/survey/role-of-cyclophilin-d-in-abeta-induced-synaptic-injury/

Principal Investigators

YAN, SHIRLEY SHIDU

Institution

UNIVERSITY OF KANSAS LAWRENCE

Contact information of lead PI
Country

USA

Title of project or programme

Role of Cyclophilin D in Abeta- induced synaptic injury

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,410,550.46

Start date of award

01/07/2010

Total duration of award in years

7

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... Translational Research

Research Abstract

Mitochondrial and synaptic dysfunction is an early pathological feature of Alzheimer’s disease

(AD) affected brain. The underlying mechanisms and strategies to repair it remain unclear. Recent studies have highlighted the role of mitochondrial Aß and early synaptic mitochondrial defects in AD pathogenesis. The early synaptic mitochondrial damage suggests that AD neurons may have already suffered harm for years, which may help explain the limitations to current amyloid hypothesis. Thus, strategies that suppress/attenuate AD- and Aß-induced mitochondrial toxicity in addition to Aß levels in the brain and improve cognitive function are critical for preventing and/or halting AD at a very early stage by improving mitochondrial function. Cyclophiiin D (CypD) plays a central role in opening the mitochondrial membrane permeability transition pore (mPTP) leading to cell death. CypD- mediated mPTP potentiates Aß- and oxidative stress-induced mitochondrial, synaptic, and cognitive dysfunction in the AD mouse model. Abrogation of CypD results in persistent life-long protection against Aß toxicity in an AD mouse model, suggesting that CypD is a potential target of the drug development for AD therapy. However, a direct link of CypD to AD-derived mitochondrial defects remains elusive. It is unclear whether CypD-potentiated mPTP and signal transduction contribute to AD-related mitochondrial defects including alterations in mitochondrial morphology, dynamics, and function, how CypD regulates mitochondrial dynamics, and whether blocking CypD rescues AD mitochondrial injury. To explore the mechanism associated with AD-specific mitochondrial defects, we have recently generated transmitochondrial cytoplasmic hybrid (cybrid) neuronal cell lines with incorporated platelet mitochondria from MCI, AD, and cognitively normal aged-matched subjects into mitochondrial DNA {mtDNA)-depleted neuronal cells. These human AD cybrid neuronal lines recapitulate mitochondrial structural and functional changes observed in AD. We found increased expression of CypD in MCI and AD cybrid cells. Importantly, blockade of CypD expression or inhibiting CypD activity restored mitochondrial morphology, dynamics (fusion/fission balance) and function in AD cybrid cells. We hypothesize that CypD-mediated mPTP alters mitochondrial distribution/morphology and function, balance of mitochondrial dynamics, which is likely to underlie AD-related mitochondrial and synaptic defects. Blockade of CypD will have a protective effect on mitochondrial and synaptic injury. The overall goal of this project is to gain new insight into the role of CypD in AD specific mitochondrial defects and to explore/validate a new class of small molecule CypD inhibitor for rescuing mitochondrial and cognitive dysfunction. The outcomes of this project will have a significantly high impact on the AD research field by identifying new targets for preventive and therapeutic intervention.

Lay Summary

RELEVANCE {See instnJctions); The overall goal of this project is to gain new insight into the role of CypD in AD specific mitochondrial defects and to explore/validate a new class of small molecule CypD inhibitor for rescuing mitochondrial and cognitive dysfunction. We will utilizing novel transmitochondrial MCI and AD cybrid neuronal cell lines, novel CypD transgenic mice, and the disease phenotypes of AD mouse model producing Aß in neurons to,evaluate the biological activity of small molecule CypD inhibitor.

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