Mitochondrial ATP Synthase Dysfunction and Synaptic Stress in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/mitochondrial-atp-synthase-dysfunction-and-synaptic-stress-in-alzheimers-disease/

Principal Investigators

DU, HENG

Institution

UNIVERSITY OF TEXAS DALLAS

Contact information of lead PI
Country

USA

Title of project or programme

Mitochondrial ATP Synthase Dysfunction and Synaptic Stress in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,754,587.16

Start date of award

01/08/2016

Total duration of award in years

1

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

Research Abstract

Program Director/Principal Investigator (Last, First, Middle): Du, Heng Project summary: Increasing evidence has suggested that mitochondrial dysfunction plays a central role in the pathogenesis of Alzheimer's disease (AD) . Compromised synaptic mitochondrial capabilities in ATP production and calcium retention have been proposed to be underlying the early synaptic injury in A?-rich milieus. However, the detailed molecular mechanisms of such A?-potentiated synaptic mitochondrial deficits still remain elusive. The specific hypothesis behind this proposed study is that mitochondrial F1Fo ATP synthase dysfunction via oligomycin sensitivity conferring protein (OSCP) aberrations is a potential cause of synaptic mitochondrial defects, leading to synaptic failure in AD-relevant conditions. This hypothesis is firmly built on the following observations: First, Mitochondrial F1Fo ATP synthase plays a vital role in ATP generation ; and uncoupled F1Fo ATP synthase constitutes the molecular basis of mitochondrial permeability transition pore (mPTP) , the opening of which lowers mitochondrial ability to buffer calcium .Its dysfunction has been implicated in aging brain and AD; but the mechanisms are not well understood; Second, in preliminary studies we have found that mitochondrial F1Fo ATP synthase dysfunction is a prominent synaptic mitochondrial defect in an AD animal model overexpressing APP/A? (5xFAD mice); Third, our further studies on this enzyme in AD brains and synaptic mitochondria from 5xFAD mice have shown the selective loss of its OSCP subunit and the interaction of OSCP with A?. Furthermore, such OSCP alterations disrupt the integrity and function of mitochondrial F1Fo ATP synthase. Lastly, the restoration of OSCP expression mitigates A?-induced neuronal mitochondrial and synaptic dysfunction. In the proposed studies, we will adopt multiple tools including our newly generated neuron-specific OSCP overexpressing 5xFAD mice, a decoy peptide to inhibit OSCP/A? interaction as well as genetic OSCP down-regulation and apply multidisciplinary approaches of biochemistry, cell and molecular biology, electrophysiology and live cell imaging. We aim to firmly establish the link between OSCP aberrations and synaptic mitochondrial F1Fo ATP synthase deregulation in AD-relevant condition and determine its impact on the development of synaptic mitochondrial dysfunction (Specific aim1) and synaptic injury/cognitive impairments (specific aim2) in 5xFAD mice. Furthermore, we will address the mechanisms of A?-mediated mitochondrial OSCP deficiency (specific aim3). The positive findings will provide a novel mechanism of mitochondrial and synaptic defects in AD and shed light on the development of novel therapeutic strategies for the treatment of AD by the protection of OSCP. In addition, the results can be extended to further our understanding of mitochondrial dysfunction and synaptic failure in other neurodegenerative diseases which have Amyloid beta (A?) deposition, ATP deficiency, and/or mPT activation. OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015) Page Continuation Format Page

Lay Summary

Program Director/Principal Investigator (Last, First, Middle): Du, Heng Narratives This project addresses a novel mechanism of synaptic mitochondrial dysfunction and synaptic injury in AD-relevant conditions by aiming to determine the impacts of mitocondrial F1Fo ATP synthase deregulation via oligomycin sensitivity conferring protein (OSCP) aberrations on synaptic mitochondrial functions in an Alzheimer's disease (AD) animal model. The study will show the undetermined role of mitochondrial F1Fo ATP synthase dysfunction in the pathogenesis of AD by mediating ATP deficiency and the activation of mitochondrial permeability transition (mPT). In addition, the results will not only shed light to the development of a novel strategy for the treatment of AD, but also have positive impacts to further our understanding of mitochondrial dysfunction and synaptic failure in other neurodegenerative diseases which have Amyloid beta

(A?) deposition, ATP deficiency, and/or mPT activation. OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015) Page Continuation Format Page

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