Voltage-Dependent Anion Channel and Neurodegeneration in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/voltage-dependent-anion-channel-and-neurodegeneration-in-alzheimers-disease/

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Country

USA

Title of project or programme

Voltage-Dependent Anion Channel and Neurodegeneration in Alzheimers Disease

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NIH (NIA)

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15/05/2014

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4

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

DESCRIPTION (provided by applicant): The long-term goal of the proposed research is to understand the role of the voltage-dependent anion channel 1 (VDAC1) protein in Alzheimer's disease (AD) pathogenesis. Recent studies using postmortem AD brains, brain tissues from 6-, 12-, and 24-month-old AbetaPP transgenic mice, and primary neurons from AbetaPP and tau mice revealed that age, amyloid beta (Abeta)-, and phosphorylated (phospho) tau-induced mitochondrial dysfunction and oxidative stress are key factors involved in neuronal dysfunction in AD pathogenesis. Researchers have reported that Abeta is associated with mitochondria localized at synapses and with synaptic damage and mitochondrial dysfunction. Preliminary research revealed that VDAC1, located in the outer membrane of mitochondria, was higher in the cortical tissues from AD patients and was also higher in the cerebral cortices of the 6-, 12-, and 24-month-old AbetaPP mice. Research also revealed VDAC1 interacting with Abeta and phospho tau in the AD postmortem brains and in the cerebral cortices from APP, APPxPS1, and 3xAD.Tg mice. Mitochondrial functional analysis indicated increased free radicals, lipid peroxidation levels, and fission-linked GTPase activity, and decreased cytochrome oxidase and ATP levels in the APP transgenic mice. Preliminary research also indicated that Abeta-induced activated glycogen synthase kinase 3beta (GSK3beta) reduced hexokinases 1 and 2, and enhanced VDAC1 phosphorylation, leading to defects in mitochondrial structure/function. However, the links between Abeta and VDAC1 and between phospho tau and VDAC1 are unclear, and the relationship between GSK3beta and VDAC1 phosphorylation to mitochondrial dysfunction are unclear. One hypothesis is that Abeta and phospho tau interact with VDAC1, which disrupts the transport of proteins/metabolites, resulting in defects in oxidative phosphorylation and in ATP synthesis. Another hypothesis is that a partial deficiency of VDAC1 maintains the mitochondrial pore activity in neurons producing Abeta and phospho tau, which in turn reduce mitochondrial dysfunction/synaptic damage in AD neurons. The proposed research objective is to determine the role of VDAC1 in mitochondrial dysfunction in relation to Abeta and phospho tau in AD pathogenesis. To this end, the proposed specific aims are: 1) to determine the physiological relevance of the interactions between VDAC1 and Abeta, and between VDAC1 and phosphorylated tau in relation to VDAC1 phosphorylation and hexokinase reductions in AD neurons, 2) to determine whether reduced VDAC1 maintains mitochondrial pore activity and mitochondrial function in neurons producing Abeta and 3) phosphorylated tau. The outcomes of the experiments for these aims will provide new insights into the physiological relevance of increased levels of VDAC1 and its interactions with Abeta and phosphorylated tau in AD pathogenesis~ and will provide critical information that can be used to develop therapies for reducing Abeta- and phosphorylated tau-induced mitochondrial damage and neuronal dysfunction in AD patients.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mitochondrial dysfunction is an early and prominent feature of Alzheimer’s disease (AD) pathogenesis, but the precise mechanism underlying this dysfunction is still not well understood. The objectives of the proposed research are to determine the physiological relevance of the interactions between mitochondrial outer membrane protein, voltage-dependent anion channel 1 and amyloid beta/phosphorylated tau in AD neurons~ to determine whether partial reduction of voltage-dependent anion channel protein 1 maintains mitochondrial pore activity and mitochondrial function in neurons producing amyloid beta and phosphorylated tau. The outcomes of the proposed experiments will provide critical information that can be used to develop therapies for reducing amyloid beta- and phosphorylated tau-induced mitochondrial damage and neuronal dysfunction in AD patients.

Further information available at:

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Investments > €500k

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United States of America

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