Processing Of Oxidative Stress In Alzheimer

https://neurodegenerationresearch.eu/survey/processing-of-oxidative-stress-in-alzheimer/

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Title of project or programme

Processing Of Oxidative Stress In Alzheimer

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

231374.3119

Start date of award
Total duration of award in years

20

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

We are testing the hypothesis that the accumulation of oxidative DNA damage contributes to neuronal dysfunction seen in neurodegenerative diseases by utilizing multiple model systems like transgenic mice, cultured cells and C. elegans. We are focusing on Alzheimer’s disease (AD) since this is the most prevalent form of dementia in people 65 years or older. The base excision repair (BER) pathway repairs oxidative DNA damage, such as base modifications, which occur spontaneously or as a result of attack by reactive oxygen species (ROS). DNA polymerase Beta (PolB) is responsible for the DNA synthesis step in the BER pathway, which can be rate limiting. Previously we bred the 3xTg AD mouse to our DNA Polymerase Beta heterozygous mouse (PolB) to create a new mouse model, 3xTgAD/PolB+/- that displayed

several important new features that the parental AD mouse model did not. We observed elevated cell death markers, altered ABeta deposition, greater mitochondrial dysfunction and worse memory and learning. These added features make the new mouse model more similar to the AD presentation seen in humans. Together, our work and others suggest that deficiencies in BER enzymes might contribute to the accumulation of oxidative damage in both nuclear and mitochondria DNA of AD patients and contribute to disease progression. There is an urgent need for effective therapies for treating or managing AD. We postulate that depletion of intracellular NAD+, persistent activation of PARP1 and low sirtuin activity could be impacting AD disease pathology. PARP1 activation contributes to neurodegeneration and high levels of PAR are reported in brains of AD patients and tissues from AD mice. Furthermore, other NAD+ metabolizing enzymes, like SIRT1, displays lower activity in AD patients than in age-matched controls. We have measured lower NAD+ levels in our 3xTg AD/PolB mice and are therefore testing whether modulation of NAD+ using NAD+ precursor supplements can ameliorate AD features in our mouse model.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A