Oxidative DNA Damage And Its Processing

https://www.neurodegenerationresearch.eu/survey/oxidative-dna-damage-and-its-processing/

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Country

USA

Title of project or programme

Oxidative DNA Damage And Its Processing

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 763,738.53

Start date of award
Total duration of award in years

24

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... Genetics... Neurodegenerative... Neurosciences

Research Abstract

Oxidative lesions are removed from DNA primarily via the base excision repair (BER) pathway. BER is carried out through four enzymatic steps, but it is now clear that several other proteins modulate BER efficiency through protein-protein interactions and posttranslational modifications. We and others identified several protein interactions for the core BER enzymes. Oxidative DNA damage is implicated in brain aging, neurodegeneration and neurological

diseases. Damage can be created by normal cellular metabolism, which accumulates with age, or by acute cellular stress conditions, which create bursts of oxidative damage. Thus we are exploring mechanisms to stimulate DNA repair pathways since we believe elevated DNA repair capacity may thwart cell death and improve cellular metabolism and could limit age associated degeneration. Brain cells have particularly high basal levels of metabolic activity and use oxidative damage repair mechanisms to remove oxidative damage from DNA and dNTP pools and nevertheless DNA damage accrues with normal aging. Accumulating DNA damage and loss of robust DNA repair pathways with age may contribute to neurological dysfunction. In part, neurodegeneration may arise in individuals that lack BER DNA repair because in non-proliferating cells it is essential and disruption of these processes impact mitochondrial fitness which in turn compromises cellular energetics and cell survival. Recently, we found that loss of DNA glycosylase endonuclease 8-like 1 (NEIL1) in mice causes deficits in spatial memory retention. Furthermore, we found that there is a significant loss of NEIL1 enzyme levels and its activity in postmortem Alzheimer's disease brains. Interestingly, the expression levels of Neil1 messenger RNA are higher in the olfactory bulb compared with other areas of the brain. Olfaction in mice is a central brain function that involves many central nervous system pathways. Thus, we studied the effect of complete loss of Neil1 gene on olfactory function. We explored olfactory function in mice with 3 different behavioral tests namely, olfactory sensitivity, performance, and buried food tests. Neil1 KO mice performed poorly compared with wild-type mice in all 3 tests. Our data indicate that loss of Neil1 causes olfactory function deficits supporting our previous findings and that normal brain function requires robust DNA repair. Changes in olfactory are often seen early in the development of AD and other neurodegenerative conditions, therefore we are pursuing whether our other DNA repair deficient mouse model also possess olfactory functional deficits. Elucidation of mechanism that contributes to olfactory degeneration may have particular relevance for many neurodegenerative diseases including Alzheimer's and Parkinson's disease.

Lay Summary
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