CELLULAR CHANGES ALTERING SYNAPTIC CONNECTIVITY IN PRECLINICAL AD

https://www.neurodegenerationresearch.eu/survey/cellular-changes-altering-synaptic-connectivity-in-preclinical-ad/

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Country

USA

Title of project or programme

CELLULAR CHANGES ALTERING SYNAPTIC CONNECTIVITY IN PRECLINICAL AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,404,568.81

Start date of award

01/06/2013

Total duration of award in years

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... Prevention

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) manifests severe pathological

changes in the CNS including increased levels of amyloid, hyperphosphorylated tau, and synaptic loss. Synaptic dysfunction is a hallmark of the disease that associates with the cognitive ability and level of dementia during the progression of AD. It is unclear why synaptic numbers are reduced in the early stages of AD and how it is linked to other features of the pathology. We believe that oxidative damage and microtubule/actin changes are early events in the progression of AD and underlie synaptic dysfunction. Increasing evidence suggests that the medial temporal lobe (MTL) is the earliest regions of the brain affected and may provide important clues to the progression of the disease. Our hypothesis is that multiple different cellular changes occur in the MTL initiating the loss of synaptic plasticity resulting in a declinein cognition and the onset of clinical AD. The proposed experiments will evaluate changes in this brain region in regards to synaptic proteins, oxidative stress, and structural proteins. Studies ar carried out on short post mortem samples from longitudinally followed individuals with detailed cognitive testing. Individuals with amnestic mild cognitive impairment (aMCI) will be compared to individuals that clinically show no cognitive impairment (NCI). The NCI group is further classified as individuals with very low pathology (LP- NCI) or high (AD levels) of histopathology (HP-NCI). Current literature suggests that HP-NCI represents individuals with preclinical AD. Aim one assess the direct relationship between different key synaptic proteins and oxidative stress in the MTL. Aim two probes whether or not NADPH-oxidase (NOX) activity and its subunits change during the disease progression and how it associates with changes in synaptic proteins and soluble A beta. The NOX enzyme is normally expressed throughout the central nervous system and is a key non-mitochondrial source of free radicals. The third aim explores whether or not key cytoskeletal proteins, such as the actin binding protein cofilin and tau, increase in the MTL and alters different levels of key synaptic proteins. Successful completion of the proposed studies will reveal new insights into the mechanisms underlying the very early stages in the progression of AD and contribute to the development of rational therapies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Understanding cellular changes that occur in the early progression of AD will help to develop novel biomarkers for early detection. In addition it will help in designing specific novel therapies to slow or perhaps prevent the progression when detected early. The proposed studies are directly relevant to the mission of the NIA to support research aimed at understanding the cellular and clinical processes of dementia.

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