Molecular pathways leading to neurodegeneration in vivo

https://neurodegenerationresearch.eu/survey/molecular-pathways-leading-to-neurodegeneration-in-vivo/

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Country

USA

Title of project or programme

Molecular pathways leading to neurodegeneration in vivo

Source of funding information

NIH (NIA)

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€ 2,186,949.54

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15/04/2015

Total duration of award in years

2

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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Prevention

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease is the leading cause of dementia

in the elderly, and because the number of at risk individuals is rapidly increasing, AD represents a major health crisis. At this point, while a number of key insights and clinical tools have arisen there are still no effective treatments to prevent or reverse the disease. The genetics of AD have led to a simple and plausible hypothesis of disease progression: amyloid-ß, a known cytotoxic peptide that forms both small diffusible and large insoluble aggregates, leads to neurodegeneration and AD. This simple hypothesis has led to myriad studies using high concentrations of synthetic amyloid peptide that is almost impossible to work with from a chemical biology standpoint, and absolutely leads to cell toxicity in every cell based assay used. Indiscriminate use of synthetic amyloid preparations have confounded the field, for the most part hampering and not helping research progress in AD. It is clear now that the progression of disease is a much more complex process. AD is a multifactorial disease that must include a spectrum of cellular and molecular events that change over time. Therefore, while it is impossible to ignore that Aß is somehow central to the disease, there is a clear need to determine the sequence of events in physiologically relevant models that will identify age sensitive treatment strategies. There are other key tenets of disease progression that are central, but still not clearly defined. It is well established that oxidative stress, mitochondrial alterations, and calcium dyshomeostasis are key molecular components on the pathway to cell death. However, there is no consensus as to whether these events are related, causal, or reflective of the disease. Therefore, we aim to systematically evaluate the temporal sequence of these molecular and cellular events in the living brain of the most thoroughly characterized transgenic mouse models of AD to identify the contribution of these factors, the causality of these factors, and the appropriate timing of these factors in the course of the disease to inform multifactorial therapeutic strategies based on duration and extent of progression. We will test the hypothesis that Aß leads to neurodegeneration through a pathway involving calcium dyshomeostasis, ROS generation, and mitochondrial dysregulation. To test this hypothesis, we will develop tools to image each of these endpoints in the living brain of APP mice using multiphoton microscopy that in and of themselves will be broadly useful to the neuroscience community. Finally, we will explore interventions to identify therapeutic pathways that ultimately will lead to treatments for Alzheimer’s disease in patients.

Lay Summary
PUBLIC HEALTH RELEVANCE: This proposal aims to develop tools to investigate the temporal sequence and causal links between amyloid pathologies of Alzheimer’s disease, mitochondrial structure and function, reactive oxygen species, and calcium dysregulation. Techniques developed will exploit intravital imaging of the intact mouse brain in transgenic models of disease to examine physiologically relevant endpoints. The goal is to identify pathways and develop time-sensitive therapeutic approaches to treat Alzheimer’s disease.

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