In Vivo Imaging Alzheimers Disease Pathology with 2-Photon/Lifetime Microscopy

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Country

USA

Title of project or programme

In Vivo Imaging Alzheimers Disease Pathology with 2-Photon/Lifetime Microscopy

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 936,990.83

Start date of award

30/09/2015

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)... Bioengineering... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): This project aims to characterize the changes in calcium regulation and cerebral metabolism associated with Alzheimer's Disease (AD) using advanced microscopy. AD has a devastating impact on over 20 million people and their families worldwide, and the incidence rate is expected to double every 20 years. Understanding the mechanisms of AD-related deficits in calcium homeostasis and mitochondrial metabolism is important for developing new diagnostic criterion and effective preventative therapies. Optical microscopy permits non- destructive, measurement of metabolic markers with high spatial and temporal resolution in animal models of human pathologies. Two-photon / lifetime microscopy has recently proven useful for measuring absolute calcium concentration ([Ca]) and measuring the reduced form of the endogenous electron carrier nicotinamide adenine dinucleotide (NADH), reportedly allowing the distinction of NADH species involved in glycolysis from NADH species involved in oxidative metabolism, with unprecedented resolution. Through the use of novel dendritic Pd-porphyrin phosphors, cerebral oxygen partial pressure (pO2) in brain tissue and vasculature can also be measured with high resolution using two-photon microscopy. The central focus of this project is to use two-photon / lifetime microscopy to measure cerebral NADH, [Ca], and pO2 in vivo in an AD mouse model at different disease stages. Characterizing the relationship between these metabolic markers as the disease progresses in vivo will provide detailed insight into the complex metabolic alterations involved in AD pathogenesis. The specific aims of this project are: 1. Develop and validate methods and instrumentation for near-simultaneous 2P measurement of pO2, and either [Ca] or NADH species. A two-photon imaging system will be upgraded and validated to feature two excitation sources, four detection channels, and custom-written control software, enabling non-destructive measurement of cerebral metabolic indicators in vivo. 2. Apply the microscope to identify cerebral NADH species and validate their association with specific metabolic processes in healthy mice Fluorescence lifetime imaging enables resolution between specific enzyme-bound formulations of NADH. The specific nature of these enzyme bound formulations will be comprehensively evaluated and characterized. 3. Apply the microscope to characterize cerebral metabolism in the exposed cortices of transgenic mice modeling AD pathogenesis The technology and knowledge obtained from aims 1 and 2 will be utilized to evaluate and compare cerebral metabolism in vivo in APPswe:PS1dE9 transgenic mice representing distinct stages of AD progression. This project will yield insight into the mechanisms of AD pathogenesis with unprecedented detail, and it will facilitate the development of new therapeutic techniques widely applicable to the growing population of at-risk aging citizens.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal describes the exploration of cerebral metabolic changes in an animal model of Alzheimer's Disease (AD) using advanced microscopy techniques. Identifying the mechanisms by which brain cells meet energetic demand is important for understanding brain function and the progression of several neurodegenerative diseases like AD. Optical imaging is perhaps the only existing method to nondestructively measure brain tissue with subcellular resolution. This project will use two-photon/ lifetime microscopy to measure and correlate three distinct markers of cerebral metabolism and cellular signaling in vivo with high spatial and temporal resolution. The results will provide a more comprehensive understanding of the metabolic deficits brought about by AD progression, and they will guide development of new preventative strategies and drug screening techniques to mitigate the degradative effects of AD.

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