Glymphatic function in a transgenic rat model of Alzheimers disease

https://neurodegenerationresearch.eu/survey/glymphatic-function-in-a-transgenic-rat-model-of-alzheimers-disease/

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Country

USA

Title of project or programme

Glymphatic function in a transgenic rat model of Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,318,549.54

Start date of award

01/09/2014

Total duration of award in years

3

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... Cerebrovascular... Dementia... Diagnostic Radiology... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): All neurodegenerative diseases, including Alzheimer’s

disease (AD) are associated with the accumulation of misfolded protein aggregates. The brain lacks the lymphatic drainage system that peripheral tissues rely on for macroscopic waste removal; however we recently discovered a brain-wide system that subserves this role. We named it the ‘glymphatic’ pathway, because it is dependent on aquaporin 4 (AQP4) water channels expressed in a highly polarized pattern on astroglial processes surrounding blood vessels. As much as 60% of soluble A? proteins are cleared from the interstitial space along the glymphatic pathway and clearance is sharply reduced in a murine AD model [expressing mutant human amyloid precursor protein (APPsw) and presenilin 1(PS E9)] when compared to age-matched wildtype mice. The proposed studies will utilize the first rodent AD model-transgenic APPsw/PS E9 rats-that replicates all the hallmarks of AD in humans, including amylodosis, reactive astro- and microgliosis, and progressive neuronal loss. HYPOTHESES: (1) Dysfunction of the glymphatic system in young, middle aged and old rats caused by oxidative stress and mislocation of AQP4 contributes to vascular amyloid deposition in APPsw/PS E9 rats. (2) Glymphatic transport can be quantified brain-wide using clinically relevant magnetic resonance imaging (MRI) in live rodents by minimally invasive lumbar administration of contrast agents. (3) Young (6 months) and middle-aged (16 months) APPsw/PS E9 rats that by MRI imaging are identified as those that exhibit the most severe decline in glymphatic clearance are at higher risk of developing AD pathology, detected as cognitive decline, and oxidative stress and amyloidosis, when they reach old age (26 months). Aim 1: Using CSF tracers and optical imaging, we will correlate glymphatic decline locally with the severity oxidative stress, astro- an microgliosis, loss of polarized perivascular AQP4, amyloid burden, and neuronal loss as a function of age in APPsw/PS E9 and wildtype rats. Aim 2: Establish a clinically relevant rodent imaging platform for evaluation of glymphatic pathway function using minimally invasive techniques using clinically relevant magnetic resonance imaging (MRI) combined with minimally invasive administration of paramagnetic contrast via lumbar intrathecal space. Aim 3: Using the glymphatic diagnostic MRI test developed in Aim 2, we will test the hypothesis that glymphatic pathway dysfunction in 6 and 16 months old APPsw/PS E9 rats predicts the severity of cognitive decline and amyloid burden in the same rats at 26 months. These studies will take advantage of the known interanimal variability of disease progression in APPsw/PS E9 rats to define whether failure of glymphatic function contributes to AD pathology. These studies present the first attempt to apply MRI imaging to track glymphatic dysfunction in normal aging and in AD. Clinical translation of the MRI imaging platform may allow similar questions to be asked in humans and permit tracking of interventional therapeutic approaches intended to slow AD progression.

Lay Summary
PUBLIC HEALTH RELEVANCE: This project will test the hypothesis that age-related decline in glymphatic clearance precedes and contributes to cognitive decline and amyloidosis in wild type rats and in a transgenic rat model of Alzheimer disease. The project will take advantage of the complementary expertise of two laboratories (MRI and optical imaging) that have successfully collaborated in the past.

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

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