CEREBRAL AMYLOID ANGIOPATHY AND MECHANISMS OF BRAIN AMYLOID ACCUMULATION

https://www.neurodegenerationresearch.eu/survey/cerebral-amyloid-angiopathy-and-mechanisms-of-brain-amyloid-accumulation/

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Country

USA

Title of project or programme

CEREBRAL AMYLOID ANGIOPATHY AND MECHANISMS OF BRAIN AMYLOID ACCUMULATION

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 5,217,353.21

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01/02/2016

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Cerebral Amyloid Angiopathy, Amyloid, cerebrovascular, Cerebrovascular Physiology, Blood Vessels

Research Abstract
? DESCRIPTION (provided by applicant): The small vessels of the brain play key roles in both age-related vascular cognitive impairment and clearance of the ß-amyloid peptide (Aß). Cerebrovascular deposition of Aß as cerebral amyloid angiopathy (CAA) sets up a potentially self-reinforcing mechanistic loop in which CAA-related vascular injury and dysfunction lead to reduced Aß clearance and progressively worse Aß deposition, CAA, and Alzheimer disease pathology. We propose a systematic, multidisciplinary analysis of the mechanisms underlying Aß-related cerebrovascular injury, vascular dysfunction, and impaired perivascular clearance in human CAA and transgenic mouse models. Specific experiments, each designed to translate from mouse models to reliably diagnosed human CAA, focus on the effects of CAA on cerebral small vessel compliance, physiologic reactivity, and their relationship to focal brain lesions (SA1), the effects of altered physiology on Aß clearance and accumulation (SA2), and the effects of CAA on gene expression in cerebrovascular endothelium and smooth muscle (SA3). The proposal builds on the applicants' long record of successful mutual collaborations and their internationally recognized expertise and leadership in noninvasive detection and analysis of human CAA, real-time measurement of vascular structure and physiology in living transgenic mouse models, and molecular analysis of cerebrovascular gene expression in control and disease states. The proposal also builds on a wide range of cutting-edge methodologic advances such as ultrahigh-field functional MRI, serial molecular Aß imaging, intravital multiphoton microscopy, vasculomic analysis, and laser-capture microdissection of post-mortem tissue. Successful completion of the proposed highly translational experiments will determine Aß's vascular effects at the molecular, single-vessel, and whole-brain levels, establish their relevance to clinical disease, and yield entirely new and promising approaches to interrupting the vicious cycle of vascular injury and reduced Aß clearance key to the propagation of CAA and Alzheimer's disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: We propose to study the cycle by which amyloid deposits in the small blood vessels of the brain can produce a vicious cycle of blood vessel injury, impaired blood vessel function, reduced clearance of amyloid out of the brain, and further amyloid buildup. These studies will be performed in both mouse models of disease (which are much easier to study and allow observation of individual blood vessels) and human subjects diagnosed with amyloid deposition in blood vessels (who can give the best indication of whether findings from animals will apply to the actual disease). The ultimate goal of these multidisciplinary studies is to identify candidate treatments for blocking the vicious cycle of progressive amyloid deposition and brain injury in Alzheimer's disease and vascular cognitive impairment, two major threats to our aging population.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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