Para-Vascular Basis of Small Vessel Disease

https://www.neurodegenerationresearch.eu/survey/para-vascular-basis-of-small-vessel-disease/

Principal Investigators

NEDERGAARD, MAIKEN

Institution

UNIVERSITY OF ROCHESTER

Contact information of lead PI
Country

USA

Title of project or programme

Para-Vascular Basis of Small Vessel Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,518,621.10

Start date of award

30/09/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Abstract Among adult dementias, a large proportion are either due to or associated with small vessel disease (SVD) of the brain. The incidence and prevalence of SVD, which may be anticipated by aging, hypertension and diabetes, is on the rise, and causally linked to the rising incidence of dementia and age-related neurological disability. Despite the fact that diagnostic MRI can track SVD progression during a premanifest period and potential therapeutic window of years to decades, no treatments are yet available. The pathophysiology of SVD is presently poorly understood. A widening of perivascular spaces (PVS) and white matter hyperintensities

on neuroimaging are strongly associated with SVD. The perivascular expansion in SVD appears to correspond structurally with the perivascular spaces of the glymphatic system, our recently described system of glial-mediated lymphatic-like convective flow that directs interstitial fluid fluxes in the brain. The glymphatic system is analogous to the lymphatic system in peripheral tissues, which clears excess interstitial fluid and waste products from the brain. Glymphatic fluid transport pathways circulate cerebrospinal fluid (CSF) which exchanges with interstitial fluid (ISF), and relies on the aquaporin-4 (AQP4)-defined water channels in astrocytic endfeet to achieve parenchymal entry. Astrocytic endfeet effectively enclose the vasculature and thereby create a network of interconnected donut-shaped tunnels around the brain's arteries, capillaries, and veins. The existence of an astrocyte-enclosed perivascular space is recognized as a unique anatomical feature of the CNS, but its functional importance has only recently become apparent. Since a hallmark feature of SVD is the structural remodeling of the perivascular space, we here propose to ask, based on a compelling set of preliminary observations, if an increase of glymphatic fluid exchange plays an essential role in SVD pathobiology. The proposed studies will address the following questions: Aim 1 will map glymphatic activity in several experimental rodent SVD models, including CADASIL, hypertensive rats and mice (SHR and BPH/2J mice). Aim 2 will use MRI to assess the roles of blood pressure fluctuations, glymphatic influx or efflux, and BBB permeability on glymphatic transport and pathological fluid accumulation in SHR and controls. Aim 3 will test the hypothesis that interventions which promote normal glymphatic function will slow myelin loss and the cognitive impairment in SVD. The experiments will directly correlate the benefits of anti-hypertensive treatment, exercise, and insomnia treatment with improvements in glymphatic transport. To our knowledge, this application constitutes the first formal study focused on glymphatic functions and the perivascular space in SVD. The proposed studies will address key gaps in our understanding of SVD. Our hope is to provide novel mechanistic insight into the pathological events that leads to myelin loss in SVD.

Lay Summary
PROJECT NARRATIVE We propose to determine the role of the `glymphatic system' in small vessel disease (SVD) – a common type of dementia which evolves slowly and typically first manifests in old age. Our goal is to understand how dysfunction of the glymphatic system contributes to myelin loss and dementia in SVD. The novel studies will be performed in three rodent models, where SVD evolves slowly and most closely mimics the human condition.

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