Failure of metabolite clearance in a model of multi-lacunar infarcts

https://neurodegenerationresearch.eu/survey/failure-of-metabolite-clearance-in-a-model-of-multi-lacunar-infarcts/

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Country

USA

Title of project or programme

Failure of metabolite clearance in a model of multi-lacunar infarcts

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,628,022.02

Start date of award

15/05/2012

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Lacunar Infarctions, glymphatic system, Waste Products, Tracer, interstitial

Research Abstract

DESCRIPTION (provided by applicant): Unlike all other organs, the brain and spinal cord lack lymphatic vessels. Traditional thought has averred that the brain – despite having the highest basal metabolic rate of any organ – can function without such an organized network for the

removal of interstitial fluid-borne metabolic waste products. We questioned this position, seeking to define the pathways by which the brain removes the potentially toxic byproducts of cellular activity. Our preliminary analysis, based on in vivo two-photon imaging, shows that low molecular weight tracers delivered to the CSF circulate surprisingly rapidly through the mouse brain, and do so along a defined anatomical route. This consists of a para-arterial inflow path, an intra-parenchymal path of interstitial flow, and a para-venous outflow path. Within the interstitial space, astrocytes support convective fluid currents, as deletion of the astrocytic watr channel AQP4 sharply reduces tracer flow along these routes. Given the continuous movement of fluid along this pathway, and its critical dependence upon astrocytic fluid transport, we propose that this system – which we designate the 'glymphatic system' – subserves a function homologous to the peripheral lymphatic system, and is essential for the clearance of metabolic waste products from the CNS. We will test the provocative hypothesis that cognitive function in an experimental model of vascular dementia in part is suppressed by accumulation of metabolic waste products. This hypothesis is based on the observation that glymphatic transport is sharply reduced in a murine model of multi-lacunar infarcts, which results in widespread trapping of small tracers in the lesioned hemisphere. Aim 1 will use in vivo 2-photon microscopy to assess the spatial dynamics and temporal kinetics of fluorophore-tagged tracer clearance. By systematically comparing the effect of modifications of molecular sizes or surface charge upon tracer clearance, we will define the basic transport properties of the glymphatic system. Aim 2 will extend the preliminary finding that aged mice exhibit a striking decline in glymphatic system function, and evaluate the effect that age-related suppression of arterial wall pulsation and resulting loss of convective inflow along the para-arterial path has on glymphatic function. Aim 3 will extend the observation that intra-parenchymal fluid movement is reduced in a mouse model of multi-lacunar infarcts and evaluate whether aging cause an additional suppression of glymphatic clearance. Aim 4 will take advantage of inducible astrocyte-specific deletion of AQP4 transgenic mice and test the hypothesis that suppressing glymphatic transport in mice with multi-lacunar infarcts will impair their cognitive functions independently of the ischemic injury. To our knowledge, these studies represent the first attempt to systematically define the mechanisms involved in the clearance of metabolic waste products from the brain on a whole-organ level. The proposed studies will provide fundamental new insight into cognitive impairment in vascular dementia, and will likely also improve our understanding of the pathophysiology of brain injury following stroke and head trauma.

Lay Summary
The proposed studies will test the hypothesis that accumulation of metabolic waste products contributes to impairment of cognitive functions in a murine model of multi-infarct dementia.

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