STALLED CAPILLARY FLOW: A NOVEL MECHANISM FOR HYPOPERFUSION IN ALZHEIMER DISEASE

https://neurodegenerationresearch.eu/survey/stalled-capillary-flow-a-novel-mechanism-for-hypoperfusion-in-alzheimer-disease/

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Country

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Title of project or programme

STALLED CAPILLARY FLOW: A NOVEL MECHANISM FOR HYPOPERFUSION IN ALZHEIMER DISEASE

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,503,532.11

Start date of award

15/05/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias

(AD/ADRD)... Brain Disorders... Cerebrovascular... Dementia... Neurodegenerative... Neurosciences... Vascular Cognitive Impairment/Dementia

Research Abstract
? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is characterized by a loss of cognitive function caused by the dysfunction and death of neurons and other cells in the brain. This cell injury is largely due to the toxic effects of aggregates of amyloid-beta (Aß), whch accumulates into dense plaques in the brain. There is also increased brain inflammation, mediated by reactive oxygen species (ROS) produced by cells stressed by Aß aggregates, suggesting that Aß aggregates create a toxic microenvironment that could affect many functions. Research in humans and in animals suggests that brain blood flow is reduced in AD by ~30%. Although it likely contributes to cognitive impairment and disease progression, no physiological explanation for this hypoperfusion has emerged. Chronic in vivo two-photon excited fluorescence microscopy was used to study cerebrovascular blood flow in mouse models of AD. While no blood flow disruption in cortical arterioles or venules were observed, blood flow was found to be stalled in an average of 1.8% of cortical capillaries in mouse models of AD, as compared to 0.25% in wild type controls ($p< 0.005$). These capillary stalls appeared early in disease progression, before any amyloid deposition. Because one stalled capillary reduces flow in several downstream vessels, even ~2% of capillaries stalled could have a large impact on brain blood flow. Indeed, when leukocytes were depleted in AD mice and the fraction of capillary stalls dropped to near zero, brain blood flow improved by ~30%, suggesting that capillary stalling may cause brain hypoperfusion in AD. About 80% of the capillary stalls were caused by leukocytes that plugged a capillary segment, suggesting increased vascular inflammation in the AD brain as the mechanism that leads to capillary stalling. These data suggest a working model to explain the origin of hypoperfusion in AD: Aß accumulation leads to increased production of ROS that stresses endothelial cells and leads to increases in inflammatory receptors on the vessel lumen. This vascular inflammation causes leukocytes to adhere and plug capillaries, resulting in decreases in perfusion. This blood flow deficit could contribute to dementia independently of the direct effects of Aß and could also accelerate Aß aggregation by decreasing clearance of Aß monomers. In this proposal, this leukocyte plugging of capillaries in mouse models of AD is carefully characterized and then three important hypotheses are tested: First, that leukocyte adhesion occurs at sites of vascular inflammation that result from endothelial activation by ROS. Second, that the collective effect of the capillary plugs is to substantially reduce global cerebral blood flow and that blocking leukocyte adhesion can improve flow. Third, that eliminating capillary plugs and improving blood flow will lead to an acute improvement in cognitive performance and that chronically blocking capillary plugging over time will lead to decreased amyloid burden and chronically improved cognitive performance. The hypothesis that brain hypoperfusion in AD is due to leukocyte plugging in capillaries is both novel and supported by preliminary data, and directly suggests therapeutic targets that are complementary to anti-amyloid approaches.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is no explanation for the reduced brain blood flow observed in Alzheimer disease patients, although this reduction may contribute to cognitive deficits and likely accelerates disease progression. We recently found that individual brain capillaries are plugged by white blood cells in mouse models of Alzheimer disease, and we now propose to investigate the mechanism leading to these capillary stalls and to quantify the impact of the stalls on overall brain blood flow. These capillary stalls are a likely mechanism for the

decreased blood flow in AD, and this work could lead to novel therapies that improve cognitive function and slow Alzheimer’s disease progression.

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