White matter hypoxia in a novel model of MMP-mediated inflammation in SHR/SP

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Contact information of lead PI
Country

USA

Title of project or programme

White matter hypoxia in a novel model of MMP-mediated inflammation in SHR/SP

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,514,338.53

Start date of award

01/09/2003

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

white matter damage, subcortical ischemic vascular disease, Vascular Cognitive Impairment, Matrix Metalloproteinases, artery occlusion

Research Abstract

DESCRIPTION (provided by applicant): Subcortical ischemic vascular disease (SIVD), which is

the major form of vascular cognitive impairment (VCI), is common in the elderly due to the prevalence of small vessel disease secondary to hypertension, diabetes, and the metabolic syndrome. There is strong evidence that the white matter damage in SIVD is related to a neuroinflammatory response, and NIH has emphasized the need for animal models to be used to develop new treatments. The long-term goal is to use a novel animal model of white matter damage in spontaneously hypertensive/stroke prone rats (SHR/SP) to define the pathophysiology and to test drugs that could be translated into clinical trials. The SHR/SP animal model was developed by the PI during the prior grant, and is based on strong preliminary data, showing the major role of matrix metalloproteinases (MMPs) that are induced by hypoxia. The animal model for SIVD uses SHR/SP rats that are fed a Japanese Permissive Diet (JPD) at 12 weeks of age and subjected to a unilateral carotid artery occlusion (UCAO). The central hypothesis is that hypertension induces hypoxia in the deep white matter, driving a molecular cascade that begins with production of hypoxia inducible factor-1? (HIF-1?) and leads to expression of MMPs, disruption of the BBB, vasogenic edema, oligodendrocyte death, and ultimately behavioral dysfunction. The rationale of the proposed research is to determine the factors involved in the progressive damage to the white matter, and to use that understanding to test potential treatments. This hypothesis will be tested with three specific aims: 1) Determine the role of hypoxia in white matter damage in chronically hypertensive rats by using electron paramagnetic resonance (EPR) to measure ptO2 with lithium phthalocyanine (LiPc) microcrystals implanted stereotactically into the corpus callosum, and to correlate the impact of hypoxia on the structural changes in white matter with multimodal MRI; 2) Determine the molecular events occurring in the hypoxic white matter that lead to oligodendrocyte death and to determine the relationship of white matter ptO2 to damage to the cerebral capillaries; and 3) To test potential therapeutic agents to reduce white matter damage and improve behavior by interfering with the neuroinflammatory response that leads to oligodendrocyte death. EPR/MRI will be used to noninvasively monitor injury and recovery along with biochemical and behavioral end-points. These studies are innovative because they use EPR to monitor oxygen and multimodal MRI to show white matter damage along with biochemical and behavioral testing to completely characterize the mechanisms of damage, and to allow the course of the injury to be followed in the same animal over several months. The significance is that this novel animal model for VCI provides a means to test potential therapies for a common dementing illness in the elderly and that results from these studies could be translated into clinical trials.

Lay Summary

PUBLIC HEALTH RELEVANCE: Vascular cognitive impairment (VCI) is a major disease of the elderly that has been identified by NINDS Program Review Groups (PRG) as a major area of research emphasis. The 2011 Stroke PGR specifically identified the need for animal models to study the disease and to test therapies. This proposal will utilize a unique animal model to test the hypothesis that hypoxia-driven neuroinflammation is the cause of the white matter damage; monitoring hypoxia with electron paramagnetic resonance (EPR) and white matter damage with MRI, biochemical, and behavioral measures will fully characterize the pathological processes involved, providing a mechanistic, hypothesis-driven approach to develop novel therapies for VCI.

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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