ApoE4 and mechanisms of diffuse white matter injury

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Country

USA

Title of project or programme

ApoE4 and mechanisms of diffuse white matter injury

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NIH (NIA)

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30/09/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

white matter injury, apolipoprotein E-4, white matter damage, sulfated glycoprotein 2, Diffuse

Research Abstract

Subcortical and periventricular white matter damage is a major cause of age-related cognitive impairment, but the mechanisms remain elusive. Although the association with small vessel disease leading to chronic ischemia is well recognized, the factors promoting white matter

damage are poorly understood. Located at the borderzone between separate arterial territories and supplied by terminal arterioles, the deep white matter is highly vulnerable to hypoxia-ischemia. ApoE is a lipid transport protein enriched in brain and present in three allelic variants (?2, ?3, ?4). Homozygosity for the ?4 allele (?4/?4) is the main genetic risk factor for Alzheimer's disease, but ApoE4 carriers also have increased risk for white matter lesions in the setting of both vascular cognitive impairment and Alzheimer's disease. ApoE4 carriers have reduced cerebral blood flow raising the possibility that cerebrovascular factors contribute their increased propensity to white matter damage. However, it remains unclear whether ApoE4 disrupts vital cerebrovascular mechanisms that assure adequate cerebral perfusion thereby promoting white matter ischemic injury. Perivascular macrophages, bone marrow derived cells closely apposed to the outer wall of cerebral arterioles, are enriched in ApoE receptors and are a powerful source of reactive oxygen species and proinflammatory mediators. Therefore, we hypothesize that ApoE4 promotes white matter damage by disrupting critical neurovascular mechanisms that assure adequate cerebral perfusion, an effect mediated by perivascular macrophages through oxidative stress and inflammation. Since TRPM2 channels are involved in macrophage activation and neurovascular dysfunction, we will also examine their role. We will test the following hypotheses: (a) ApoE4 disrupts vital homeostatic mechanisms regulating the cerebral microcirculation; (b) perivascular macrophages contribute to the dysfunction through TRPM2 channels and ApoE receptors; (c) ApoE4 exacerbates hypoxic-ischemic white matter damage, an effect mediated by perivascular macrophages. Studies are conducted in young and old mice of both sexes with targeted replacement of mouse ApoE with human ApoE3 or 4. White matter injury is produced in the corpus callosum by bilateral carotid artery stenosis. State-of-the-art approaches are used to study neurovascular regulation, including a novel 3-photon imaging method enabling us, for the first time, to simultaneously assess microvascular perfusion and damage in the white matter of the corpus callosum in vivo. These studies will provide insight into the mechanisms underlying the impact of ApoE4 on white matter damage, and may unveil new therapeutic targets for a leading cause of cognitive dysfunction.

Lay Summary

Diffuse white matter damage is a major factor underlying vascular cognitive impairment, the second major cause of dementia in the elderly, but the factors mediating the damage have not been fully established. This application, which is in response to an RFA on diffuse white matter injury, will investigate the role of ApoE in the damage to the white matter. The findings deriving from the proposed study will advance our knowledge of the factors causing white matter injury and will suggest new putative therapeutic targets to counteract the devastating cognitive impact of white matter damage.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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