Remote ischemic conditioning for neuroprotection in vascular cognitive impairment

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Principal Investigators

HESS, DAVID C.

Institution

GEORGIA REGENTS UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Remote ischemic conditioning for neuroprotection in vascular cognitive impairment

Source of funding information

NIH (NIA)

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01/07/2015

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Vascular Cognitive Impairment, Carotid Stenosis, Leukoaraiosis, white matter damage, Bilateral

Research Abstract

? DESCRIPTION (provided by applicant): Dementia is a major threat to public health. Vascular dementia makes up to 20% of the cases of dementia and estimates of “”mixed dementia”” related to AD and vascular causes range up to 50% of cases of dementia. Vascular cognitive impairment (VCI) is the term that encompasses the clinical spectrum from mild cognitive dysfunction to vascular dementia. The NINDS Stroke Progress Review Group in 2012 cited “”prevention of vascular cognitive impairment”” as a major research priority. The pathological hallmark of VCI is white matter (WM) damage from ischemia in the periventricular regions and centrum semi vale. The imaging correlate of this WM damage is “”leukoaraiosis”” best detected by magnetic resonance imaging (MRI)/ Remote limb ischemic conditioning (RLIC) is the simple, inexpensive, and safe use of repetitive inflation of a blood pressure (BP) cuff on the arm or leg to protect distant organs such as the brain from ischemic injury. We now have exciting novel preliminary data after Bilateral Carotid Artery Stenosis (BCAS) in the mouse (model of VCI) that daily remote ischemic postcondtioning (RIPostC) using a BP cuff for 2 weeks increases CBF in a sustained fashion, improves cognitive performance, and reduces accumulation of amyloid-beta 42 protein (Aß42) in the brain. Our central hypothesis is that RIPostC therapy after BCAS will improve CBF and cognitive performance, and attenuate WM demyelination and brain atrophy during long-term follow up in young and aged animals, independent of sex. Our secondary hypothesis is that plasma nitrite and MRI imaging will be a useful tool to track these changes and detect responses to the therapy. Our specific aims are: Aim 1: Determine if short term (1 month) and/ or long-term (4-mo) RIPostC therapy after BCAS improves long- term (6-mo) cognitive performance, and reduces WM damage in young male mice. Our published data show that short-term (2-wks) RIPostC therapy after BCAS improves CBF and cognitive performance when assessed at 28 days. 2 In this aim, mice will be followed up for up to 6-mo for behavioral outcomes. Aim 2: Determine if RIPostC therapy (optimal duration from Aim 1) after BCAS improves CBF, long-term (6- mo) cognitive performance, and reduces WM damage, independent of sex in aged mice. Since leukoaraiosis is predominant in aged humans of both sexes and progresses with time, we will also test long-term RIPostC treatment after BCAS in aged animals of both sexes. Animals will be followed up for 6 months. Aim 3: Determine the utility of humoral and imaging biomarkers as a response to RIPostC in murine BCAS model: a) the “”circulating”” humoral biomarker, plasma nitrite and b.) MRI-diffusion tensor imaging (DTI) to elucidate WM damage, and Arterial Spin Labeling (ASL) to quantify CBF. This work is the FIRST STEP to translate RIPostC therapy to humans as a safe and inexpensive therapy for vascular cognitive impairment.

Lay Summary

PUBLIC HEALTH RELEVANCE: Dementia caused by vascular disease is a major cause of disability and there is no known treatment. This proposal is aimed at developing a safe, inexpensive treatment, the repetitive inflation and deflation of a blood pressure cuff on the limbs This treatment is called remote limb ischemic conditioning and we will test this treatment in young and old mice with partial obstruction of blood flow to the brain and see if it prevents worsening memory and brain damage.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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