Endothelial function of amyloid precursor protein

https://neurodegenerationresearch.eu/survey/endothelial-function-of-amyloid-precursor-protein/

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Country

USA

Title of project or programme

Endothelial function of amyloid precursor protein

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,953,612.84

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11/04/2016

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid beta-Protein Precursor, cerebrovascular, peripheral blood vessel, brain endothelial cell, Cerebrovascular system

Research Abstract

? DESCRIPTION (provided by applicant): Amyloid precursor protein (APP) is best known for its critical role in pathogenesis of Alzheimer’s disease (AD). Relevant to this application, APP is

abundantly expressed in the cerebrovascular endothelium under physiological conditions. APP is also expressed in endothelium of peripheral blood vessels but apparently at significantly lower levels than in the cerebral circulation. Strong evolutionary conservation supports the concept that APP plays an important but yet poorly defined physiological role(s). Indeed, the exact role of endothelial APP in cerebrovascular/cardiovascular homeostasis is unknown. To start bridging this gap in the existing literature, we performed extensive preliminary studies in cultured human brain microvascular endothelial cells (BMECs) and mice with genetically modified expression of APP. Next generation RNA sequencing (RNA-Seq) was employed to determine differential gene expression between control human BMECs and APP-deficient BMECs. Most notably, significant down-regulation of endothelial nitric oxide synthase (eNOS) expression was detected in APP-deficient cells. Moreover, in isolated cerebral arteries derived from APP-knockout mice, endothelium-dependent relaxations were significantly impaired. Endothelial dysfunction was associated with reduced production of NO and cyclic GMP thereby providing important in vivo evidence to suggest that intact expression and processing of APP is required for normal endothelial function. Intriguingly, only cerebral blood vessels (large arteries and microvessels) were adversely affected by the loss of APP as we did not detect significant alterations in endothelium-dependent vasomotor function in the peripheral blood vessels. Metabolism of APP was significantly impaired by aging thereby increasing vulnerability of the cerebral circulation to aging-induced endothelial dysfunction. Based on these findings we formulated following central hypothesis: endothelial APP subserves an essential protective function in endothelium of the cerebral circulation. To test this hypothesis we propose three specific aims: 1) Define molecular mechanisms and signal transduction pathways responsible for cerebrovascular endothelial function of APP, 2) Identify contributions of APP to cerebrovascular homeostasis in vivo, and 3) Determine the role of APP in cerebrovascular aging. Studies proposed in this application represent the first attempt to define physiological cerebrovascular function of APP. Successful completion of the proposed studies will identify molecular mechanisms responsible for vasoprotective properties of endothelial APP. This will have immediate impact on clinical efforts to preserve and protect healthy cerebrovascular tree in patients at risk for development of cerebrovascular disease and dementia including AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Endothelial cells provide inner lining of blood vessels that is essential for normal blood circulation. In the brain, impairment of vascular endothelial function plays an essential role in initiation and progression of vascular disease. High levels of amyloid precursor protein (APP) are detectable in endothelium of the brain blood vessels yet the endothelial function of APP is unknown. Our proposed experiments are designed to define function of APP in the cerebral circulation. We will also examine functional importance of APP in blood vessels of other organs. Our preliminary findings suggest that APP is critically important for normal function of brain circulation. Moreover, we have evidence that aging impairs cerebrovascular function of APP thereby increasing vulnerability to vascular injury. Since, diseased blood vessels in the brain predispose to development of cognitive decline and Alzheimer’s disease, we will determine how APP function in blood vessel wall could be utilized in preservation of healthy arteries in the brain.

Further information available at:

Types:

Investments > €500k

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United States of America

Diseases:
Alzheimer's disease & other dementias

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