# Endothelial Dysfunction In The Cerebral Circulation

https://www.neurodegenerationresearch.eu/survey/endothelial-dysfunction-in-the-cerebral-circulation/

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**Country**

USA

**Title of project or programme**

Endothelial Dysfunction In The Cerebral Circulation

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 2,065,424.77

**Start date of award**

01/01/2012

**Total duration of award in years**

2

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

Peroxisome Proliferation, NOS3 gene, endothelial dysfunction, Cerebrovascular Circulation, amyloid precursor protein processing

**Research Abstract**

ABSTRACT In the cerebral circulation, endothelial dysfunction caused by decreased biological activity and/or biosynthesis of nitric oxide (NO) is principal mechanism responsible for initiation

and progression of vascular disease. Epidemiological studies established strong association between vascular disorders and incident Alzheimer's disease (AD). However, the molecular mechanisms linking cerebrovascular disease and AD are unknown. Our recently published findings (Circulation Research, 107:1498-1502, 2010) and preliminary experiments identified previously unrecognized role of endothelial NO in modulation of amyloid precursor protein (APP), ß-secretase (BACE1) and amyloid-ß peptide (Aß). Pharmacological or genetic inactivation of endothelial nitric oxide synthase (eNOS) causes up-regulation of APP and BACE1, leading to increased production of Aß. Moreover, we have preliminary evidence suggesting that activation of peroxisome proliferation-activated receptor-?(PPAR?) exerts beneficial effect on endothelial function by enhancing production of NO. Moreover, activation of PPAR? prevents amyloidogenic processing of APP. Based on these finings we formulated following central hypothesis: impairment of endothelial function in the cerebral circulation plays a critical role in initiation and progression of AD pathology. To test this hypothesis we propose three specific aims: 1) Determine the molecular mechanisms that underline the effects of eNOS/cGMP signaling on expression and processing of APP, 2) Define the role of PPAR? in cerebrovascular endothelial function and processing of APP and 3) Assess the role of eNOS/cGMP signaling in initiation and progression of AD pathology. Cultured human brain microvascular endothelial cells will be used to study signal transduction pathways responsible for NO effects on generation of Aß. These studies will be followed by in vivo testing of the proposed hypothesis in genetically modified mice including eNOS, nNOS-, and iNOS-deficient mice, ?1 or ß1 isoform of soluble guanylate cyclase-deficient mice, and endothelial specific PPAR?-defcient mice. To determine the role of eNOS in onset and progression of AD we propose to cross eNOS-deficient (eNOS-/-) mice with murine models of AD. Created AD mice lacking eNOS will provide new and unique models of AD relevant to study contribution of endothelial dysfunction to development of amyloid pathology. Functional, biochemical and morphological analyses will be preformed on microvessels and neuronal tissue. We anticipate that successful completion of the proposed studies will define the role of eNOS/cGMP signaling and activation of PPAR? in production of Aß. We expect the results of our proposed studies will establish cerebrovascular endothelium as a critical target in the prevention of AD thereby directing and concentrating therapeutic focus on the cerebral circulation.

**Lay Summary**

Project Narrative: Dysfunction of endothelial cells (inner lining of the brain arteries) is believed to play an important role in initiation and progression of Alzheimer's disease. The long-term goal of the studies proposed in this application is to determine the mechanisms underlying alterations in function of brain blood vessels that could contribute to development of Alzheimer's disease. We propose to create new experimental models of Alzheimer's disease which will be very useful in studies designed to determine contribution of diseased arteries to development of the cognitive impairment. In addition, these models will be employed in testing novel therapies for prevention and treatment of Alzheimer's disease.

**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