

Influence of apoE on LRP1 function and Beta-Amyloid Transport Across the BBB

<https://neurodegenerationresearch.eu/survey/influence-of-apoe-on-lrp1-function-and-beta-amyloid-transport-across-the-bbb/>

Principal Investigators

BACHMEIER, CORBIN

Institution

ROSKAMP INSTITUTE, INC.

Contact information of lead PI Country

USA

Title of project or programme

Influence of apoE on LRP1 function and Beta-Amyloid Transport Across the BBB

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,416,024.77

Start date of award

01/08/2012

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Cerebrovascular... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is the sixth leading cause of death in the United States and is characterized by the formation of neurofibrillary tangles and the deposition of beta-amyloid (A β) proteins in the brain. A β accumulation in the brain is a key factor in AD pathogenesis and is a predictor of cognitive impairment. A β reducing strategies in AD have primarily targeted A β production mechanisms which, to this point, have been largely unsuccessful in clinical trials. Evidence now suggests that the excessive accumulation of A β in the AD brain is not due to aberrant A β production, but the result of impaired A β removal from the brain. Thus, targeting clearance-related pathways may prove most effective in attenuating A β accumulation in the AD brain. The blood-brain barrier (BBB) transporter primarily responsible for the brain elimination of A β is the low density lipoprotein receptor-related protein 1 (LRP1). One of the ligands with which LRP1 interacts is apolipoprotein E (apoE) and possession of the E4 allele represents the strongest genetic risk factor for AD. However, the role of apoE in the exchange of A β across the BBB is not clearly defined. Several studies in cell culture have shown a stimulation of A β internalization in the presence apoE, while others have reported apoE is disruptive to A β clearance across the BBB. In our preliminary studies we sought to clarify the role of apoE in the BBB clearance of A β . Our studies and the work of others indicate that when apoE is bound to A β , the transport of A β across the BBB is dramatically attenuated. However, for the first time, we demonstrate that unbound apoE in the brain can facilitate A β BBB clearance in an isoform-specific manner (apoE3 >> apoE4). At the BBB level, few studies have investigated the influence of apoE isoforms on LRP1 function, in particular LRP1 shedding (i.e., formation soluble LRP1, which is nonfunctional and does not transcytose A β). In apoE4 transgenic mice and AD patients carrying the E4 allele, we observe elevated LRP1 shedding in the brain compared to apoE3 genotypes. When combined with our in vivo A β BBB transit data, our preliminary studies demonstrate an inverse relationship between LRP1 shedding and A β transport across the BBB, one that is apoE genotype-specific. We hypothesize that apoE4 is less efficient than other apoE isoforms in preventing LRP shedding, which leads to reduced A β clearance across the BBB. Our preliminary findings also show that modulation of LRP1 internalization leads to enhanced LRP1 shedding and reduced A β transport across an in vitro model of the BBB. Since LRP1 internalization and transcytosis are essential steps in eliminating A β from the brain, we will examine the effect of apoE isoforms on LRP1-mediated internalization and subcellular trafficking of A β in the BBB. Overall, the current proposal will investigate several potential mechanisms to elucidate the apoE- dependant differences we observe in LRP1 shedding and A β transit across the BBB. These studies will improve our understanding of the relationship between apoE and LRP1 in AD and may provide new treatment modalities for this disease.

Lay Summary

Alzheimer's disease (AD) is now the sixth leading cause of death in the United States — affecting millions of people. This proposal will investigate the contribution of a novel pathway to the progression of AD with the purpose of identifying new treatment strategies for this 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