

ApoE and LRP1 in brain insulin signaling and glucose metabolism (Competitive Renewal)

<https://www.neurodegenerationresearch.eu/survey/apoe-and-lrp1-in-brain-insulin-signaling-and-glucose-metabolism-competitive-renewal/>

Principal Investigators

BU, GUOJUN

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI

Country

USA

Title of project or programme

ApoE and LRP1 in brain insulin signaling and glucose metabolism (Competitive Renewal)

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,471,674.31

Start date of award

01/12/2009

Total duration of award in years

8

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... Dementia... Diabetes... Endocrine System... Neurodegenerative... Neurosciences... Nutrition

Research Abstract

? DESCRIPTION (provided by applicant): APOE4 is the strongest genetic risk factor for Alzheimer's disease (AD); however, how apoE4 predisposes people for the risk for AD is still not clear. Clinical studies have shown that APOE4 carriers, both as healthy adults or with dementia, have lower cerebral glucose metabolism and increased neuroinflammation, conditions that are also common in individuals with diabetes. Interestingly, diabetes and impaired insulin signaling are linked to the pathogenesis of AD. Supporting these, a recent clinical trial with insulin intranasal spray in AD patients has yielded positive results in preventing cognitive decline and this has led to a new national plan for a Phase II/III trial. Thus, there is an urgent need to understand the function and regulation of brain insulin signaling and glucose metabolism in preclinical models. In the previous funding cycle and during the preliminary stage of this project, we found that apoE and its major receptor LRP1 regulate the metabolism of both lipid and glucose in the brain. Specifically, using in vivo microdialysis techniques, we found that brain glucose metabolism is impaired in APOE4-targeted replacement (TR) mice and in Lrp1 neuronal knockout mice. We also found that LRP1 interacts with insulin receptor (IR) and regulates insulin signaling and glucose metabolism in a manner that depends on the function of glucose transporter 4 (GLUT4). Impaired insulin signaling and chronic neuroinflammation were further exacerbated in the APOE4 mice by either amyloid- β ($A\beta$) pathology or a loss of neuronal LRP1. Thus, our goal for this renewal project is to study the molecular and cellular mechanisms by which apoE4 synergizes with pro-inflammatory cytokines and $A\beta$ to impair neuronal insulin signaling and glucose metabolism and test whether a restoration of insulin signaling in APOE4-TR mice allows a rescue of APOE4-related AD phenotypes. We hypothesize that apoE4 impairs neuronal insulin signaling and glucose metabolism in a manner that depends on the functions of apoE receptor LRP1 and glucose transporters, and that neuroinflammation and $A\beta$ further exacerbate these events in aging and AD. We propose three Specific Aims to test our hypothesis. In Aim 1, we plan to dissect the mechanisms by which apoE4 impairs neuronal insulin signaling and glucose metabolism in vitro in neurons, in vivo in APOE-TR mice, and in human brains. In Aim 2, we will examine how pro-inflammatory cytokines and $A\beta$ synergize with apoE4 in reducing neuronal insulin signaling and glucose metabolism. In Aim 3, we plan to test whether brain administration of insulin or insulin-sensitizing drug metformin, or a restoration of apoE4 expression and lipidation rescues impaired glucose metabolism, reduces apoE4-associated neuroinflammation, and improve synaptic functions and cognition. These studies will not only address the underlying mechanisms of impaired insulin signaling and glucose metabolism in APOE4 carriers and AD patients but will also test therapeutic potentials targeting insulin and apoE pathways.

Lay Summary

PUBLIC HEALTH RELEVANCE: Diabetes and Alzheimer's disease (AD) are growing health concerns that affect a large population of our aging society. Interestingly, diabetes is also a risk factor for AD. The strongest genetic risk factor for AD is APOE4, which promotes conditions common to diabetes and AD, including impaired insulin signaling and chronic inflammation. Thus, the goal of this project is to reveal how APOE4 synergizes with other pathogenic pathways to increase the risk for AD and how we can target these pathways for therapy.

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