Mechanisms transducing insulin and insulin resistance in the hippocampus

https://neurodegenerationresearch.eu/survey/mechanisms-transducing-insulin-and-insulin-resistance-in-the-hippocampus/

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Country

USA

Title of project or programme

Mechanisms transducing insulin and insulin resistance in the hippocampus

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,754,466.06

Start date of award

01/05/2016

Total duration of award in years

1

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... Prevention

Research Abstract

? DESCRIPTION (provided by applicant): The goal of this proposal is to prevent and treat the cognitive and neural impairment associated with impaired brain insulin signaling. Such signaling is now recognized as central to the impact of both type 2 diabetes (T2DM) and Alzheimer's disease (AD), which is now commonly characterized as 'type 3 diabetes' [1, 2]. Work in our lab, funded by the grant of which this is a renewal, showed that insulin is a key component of hippocampal metabolism and memory processes and that systemic insulin resistance impairs both hippocampal metabolism and cognitive function [3-6]. However, little is known about the molecular mechanism(s) by which insulin regulates cognitive and neural processes. Similarly, the clinical fact that T2DM causes cognitive impairment is well-established, but not understood at a cellular or molecular level. Several clinical studies have shown a clear link between T2DM and development of AD [7-16]; conversely, AD patients show reduced hippocampal insulin signaling that accompanies hypometabolism and abnormal accumulation of beta-amyloid (A?). Several in vitro studies suggested that insulin and A? oppose each other at a molecular level [17-24]; recent in vivo work from our lab showed that administration of oligomeric A? to the hippocampus caused rapid cognitive impairment, reduced glucose metabolism, and impaired translocation of the insulin-regulated glucose transporter GluT4 [6]: this closely resembles hippocampal insulin resistance. Further, our animal model of diet-induced T2DM causes elevation of hippocampal amyloid [25]: a key hypothesis presented here is that this causes T2DM-associated cognitive impairment as well as the elevated risk of dementia. Understanding insulin's modulation of hippocampal processes, and how this modulation is impaired by insulin resistance and/or A?, is central to developing treatment for T2DM and/or AD. Long-term, the public health goal of this work is to identify therapeutic targets for prevention and treatment of brain dysfunction in T2DM and AD. The experiments proposed here build on the successful progress during this grant's first funding period. We will determine the molecular effectors by which insulin, and conversely insulin-resistance, impact hippocampal function. As part of this, we will directly manipulate candidate effectors, supported by preliminary data, including GluT4 and multiple forms of A?. The second aim, again emerging from strong preliminary data, is to investigate the different involvement of insulin and downstream effectors in distinct stages of hippocampal memory processing.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project seeks to understand the role of insulin in the hippocampus, which will also guide prevention and treatment of both Alzheimer's disease and Type 2 diabetes.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
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Database Categories:
N/A

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