Mechanisms of resistance to cognitive decline in AD

https://neurodegenerationresearch.eu/survey/mechanisms-of-resistance-to-cognitive-decline-in-ad/

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Country

USA

Title of project or programme

Mechanisms of resistance to cognitive decline in AD

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NIH (NIA)

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01/09/2013

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4

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)... Behavioral and Social Science... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most severe

neurodegenerative dementia for which there is currently no cure. Abundant deposition of amyloid beta (A?) plaques and the presence of neurofibrillary tangles of hyper-phosphorylated tau protein are the two CNS lesions that, concomitant with synaptic disruption and preponderant insulin resistance, hallmark the onset and progression of AD. Some individuals, however, remain cognitively intact despite the presence of substantial AD neuropathology. The existence of these unusual cases (which we termed Non-Demented with Alzheimer's Neuropathology, NDAN) reveals that there is a natural way for the human brain to resist the neurotoxic events that normally lead to cognitive demise in AD. It follows that understanding the molecular mechanisms involved in such resistance would reveal a very effective target for treatment of cognitive decline in AD. Achieving this knowledge is the overarching goal of our research. We present compelling preliminary results supporting the hypothesis that NDAN individuals remain cognitively intact because A? oligomers do not bind to, and therefore, do not disrupt post-synaptic elements owing to increased insulin sensitivity that impacts the make-up of the PSD proteome rendering A? oligomer docking unlikely. The goal of this application is to establish that, as compared to demented AD, cognitive integrity of NDAN cases is collectively marked by a) molecular evidence of synaptic integrity; b) absence of A? oligomers from post-synaptic elements; c) increased insulin sensitivity; d) unique PSD proteome signature. We will test this hypothesis by pursuing the following three specific aims: 1) To demonstrate the presence (or absence) of A? oligomers at synapses in the hippocampus and cortex of AD and NDAN brains as a function of synaptic welfare, insulin sensitivity and cognitive competence; 2) To determine the existence of a causal link between sustained insulin signaling and the ability of synapses to reject the disfunctional binding of A? oligomers; 3) To determine and contrast the protein make-up of the PSD in control, AD and NDAN cases and in wt mice treated with the insulin sensitizing drug PTZ. Results will characterize the NDAN human synapse which is capable of escaping disruptive targeting by A? oligomers and maintaining increased insulin sensitivity and establish a molecular signature underscoring a causal relationship between sustained insulin signaling and the ability of synapses to reject detrimental A? oligomer binding. This new knowledge is necessary to lay solid foundations for the identification of potential pharmacological targets for the development of new, effective treatments for AD. We propose a multidisciplinary approach that brings together a uniquely qualified team of experts in neuronal molecular signaling in AD (Taglialatela), CNS electron microscopy (Carlton), behavior in APP Tg mouse models (Dineley), proteomics (Wiktorowicz), AD histopathology (Woltjer) and AD clinical aspects (Quinn).

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed research is relevant to public health because the discovery of mechanisms allowing resistance to A? toxicity and associated cognitive dysfunction is ultimately expected to drive the development of an effective therapy for AD, thus improving these patients' health while driving down the societal cost for their care, which is expected to increase to unbearable proportions by the year 2050. Thus, the proposed research is relevant to the part of NIH's mission concerned with fostering creative discoveries and their application to advance the Nation's capacity to protect and improve health.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

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Alzheimer's disease & other dementias

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