Role of Systemic Amylin Dyshomeostasis in Alzheimers Disease

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Country

USA

Title of project or programme

Role of Systemic Amylin Dyshomeostasis in Alzheimers Disease

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NIH (NIA)

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15/09/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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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

Abstract We propose that an early and possibly treatable contributor to the multifactorial etiology

of Alzheimer’s disease (AD) involves dyshomeostasis of amylin, a pancreatic hormone that crosses the blood brain barrier and has amyloidogenic properties similar to those of the ?-amyloid (A?) peptide. This hypothesis is supported by recent work from our lab and others showing large amylin deposits in brains of AD patients. Moreover, we found >4-fold higher brain amylin level in ApoE4 carriers, particularly in patients with type-2 diabetes, suggesting a link of the accumulation of amylin in the brain with ApoE and metabolic risk factors. Using rats expressing human amylin in the pancreas and amylin knockout, we found that the brain amylin accumulation is likely promoted by elevated blood levels of oligomerized amylin via the interaction with plasma low density lipoproteins and causes neuroinflammation and neurologic deficits. Here, we propose to test these ideas. Planned studies will determine physiological and functional changes in the brain using a rat model expressing human amylin in the pancreas and appropriate controls (Aim 1). We will specifically identify therapeutic targets to reduce amylin-induced cytotoxicity in the brain. Pharmaceutical interventions will reinforce mechanistic insights while also informing on mechanisms that underlie the brain amylin accumulation and potential functional effects in humans. Human studies will elucidate amylin-APOE and amylin-A? interactions contributing to AD pathology (Aim 2). Here, we collaborate with the University of Kentucky AD Center, which has a large repository of brain, plasma and cerebrospinal fluid specimens from clinically well-characterized subjects. We also collaborate with the Queen Square Brain Bank for Neurological Disorders of the University College of London and Medical Research Council of King’s College London which provided for this project brain specimens from early onset familial AD patients (PSEN1 and APP mutation carriers). These brain specimens will be used to elucidate a potential relationship between the brain amylin accumulation and AD-type of plaque, i.e., early onset familial AD (associated with increased A? oligomerization) vs. late onset AD (attributed to the impaired A? clearance). To further elucidate the pathobiology of amylin-A? interaction, we crossed the “human” amylin expressing rat with the TgF344-19 rat model of AD. The successful completion of this project offers the potential to refining diagnosis and tailoring specific therapies to modify/ delay/ prevent brain injury and cognitive decline in aging and metabolic disorders.

Lay Summary

Narrative We have recently discovered that, in addition to plaques laden with ?-amyloid, brains of Alzheimer’s disease patients contain large deposits of amylin, an amyloidogenic hormone secreted from the pancreas. In this research project, we propose to use human tissue, clinical data, transgenic animals and cell models to 1) decipher mechanisms of brain amylin pathology in humans, 2) determine the impact of amylin deposition on the neurovascular unit, and 3) test clinically relevant therapies to modify/ reduce/ prevent amylin-mediated deleterious effects in the brain. The successful completion of this project offers the potential to refining diagnosis and tailoring specific therapies to modify/ delay/ prevent cerebrovascular injury and cognitive decline in aging and metabolic disorders.

Further information available at:

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Investments > €500k

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United States of America

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