Physiology and Pathophysiology of Apolipoprotein E receptor-2 splicing in Alzheimers disease

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USA

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Physiology and Pathophysiology of Apolipoprotein E receptor-2 splicing in Alzheimers disease

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NIH (NIA)

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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... Genetics... Neurodegenerative... Neurosciences

Research Abstract
PROJECT SUMMARY According to the most recent Alzheimer’s Association report, 2015 Alzheimer’s Disease Facts and Figures, one out of nine Americans over the age of 65 has Alzheimer’s Disease (AD) and an estimated 40-65% of them carry at least one copy of the ?4 allele of gene for a cholesterol transport protein, apolipoprotein E (ApoE). Despite being one of the highest risk factors for AD (second only to age), the mechanism by which ApoE4 increases AD occurrence is unknown. ApoE transports cholesterol to neurons via ApoE receptors, which are members of the low density lipoprotein (LDL) receptor gene family. Some of these ApoE receptors, i.e. LRP1, Apoer2, VLDL receptor (Vldlr), and Lrp4, are intrinsic components of central and peripheral synapses, where they serve as essential regulators of neurotransmission through cytoplasmic signaling and neurotransmitter trafficking. The progressive neurodegeneration in AD first presents as memory loss brought on by synaptic dysfunction. Amyloid-? (A?), the central component in the trademark plaques that build up in the brains of people with AD, are a product of the amyloid precursor protein, APP, and a likely source of this early dysfunction. We have shown previously that A?-induced synaptic suppression can be prevented through ApoE receptor activation and ApoE4 selectively impairs this synaptoprotective function by sequestering the ApoE receptor, Apoer2. Apoer2, an essential CNS ApoE receptor, is endogenously expressed in multiple alternatively spliced forms, indicating a physiological need for functionally diverse forms of the receptor. We have found that differential splicing of an extracellular O-glycosylation domain dramatically alters Apoer2 abundance, synaptic function and fear memory. Apoer2 can also modify the formation of A? through multiple interactions with APP that effect APP processing. Therefore, understanding the regulation and function of Apoer2 is central to understanding the mechanisms by which ApoE4 causes synaptic dysfunction in AD. Accumulating evidence has identified Apoer2 as a key regulator of synaptic homeostasis. In this application, we propose to investigate the consequences of the two main physiological splicing events of Apoer2 on gene expression, protein interactions, behavior and cognition. In Aim 1 we will employ Apoer2- deficient mice and mice expressing various splice forms of Apoer2 to explore how Apoer2 regulates gene expression. In Aim 2, we will explore the protein interactome of these Apoer2 isoforms and probe how the various ApoE isoforms affect their trafficking and signaling, as well as their ability to regulate APP processing. In Aim 3, we will explore how endogenous Apoer2 splice variants modify behavior and cognition and how they affect cognitive deficits in mice with human ApoE isoforms or A?-overproduction.

Lay Summary
PROJECT RELEVANCE Differential splicing and glycosylation of Apoer2 regulates cognition, memory and behavior. This has important implications for the pathogenesis of Alzheimer’s disease (AD), since Apoer2 and its ligand Reelin counteract the effect of A?, which causes the early synaptic dysfunction of AD. Understanding how Apoer2 regulates neuronal physiology opens a direct window into the pathogenesis of AD and may reveal novel therapeutic avenues.

Further information available at:

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Investments > €500k

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United States of America

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