Apolipoprotein E in Alzheimers Disease: Molecular Mechanism

https://www.neurodegenerationresearch.eu/survey/apolipoprotein-e-in-alzheimers-disease-molecular-mechanism/

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Country

USA

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Apolipoprotein E in Alzheimers Disease: Molecular Mechanism

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NIH (NIA)

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15/04/2015

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2

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... Stem Cell Research... Stem Cell Research - Induced Pluripotent Stem Cell... Stem Cell Research - Induced Pluripotent Stem Cell - Human... Stem Cell Research - Nonembryonic - Non-Human

Research Abstract

? DESCRIPTION (provided by applicant): Apolipoprotein (apo) E4 increases the risk and lowers the age of onset for Alzheimer's disease (AD) in a gene dose-dependent manner. In most clinical studies, apoE4 carriers account for 60-75% of all AD cases, highlighting the importance of apoE4 in AD pathogenesis. Remarkably, the lifetime risk (LTR) estimate of developing AD by the age of 85 is ~60-70% for people with two copies of the apoE4 allele (~2% of the population) and ~30% for those with one copy of the apoE4 allele (~25% of the population), but is only ~10% in those with two copies of the apoE3 allele. Thus, apoE4 is considered a major gene, with semi-dominant inheritance, for AD. Although many hypotheses have been advanced, the exact mechanisms underlying the pathogenic actions of apoE4 remain unclear. This proposal builds on four novel findings from our studies of mouse models or human induced pluripotent stem cell (hiPSC)-derived neurons expressing different apoE isoforms. First, in apoE4-KI mice and mice expressing a neurotoxic apoE4 fragment, apoE4 and its fragment cause age- and tau-dependent impairment of GABAergic interneurons in the hilus of the hippocampus, and the extent of the impairment correlates with the extent of learning and memory deficits. Second, this apoE4-induced interneuron impairment also impairs adult hippocampal neurogenesis in mice. Third, the GABAA receptor potentiator pentobarbital rescues both the impaired neurogenesis and the deficits in learning and memory in apoE4-KI mice and apoE4 fragment transgenic mice. Fourth, apoE4 displays increased proteolysis and causes GABAergic interneuron death in hiPSC-derived neuronal cultures. These findings strongly suggest that apoE4 and its neurotoxic fragments cause hilar GABAergic interneuron impairment, contributing to learning and memory deficits and AD pathogenesis. The goal of this project is to determine how apoE4 impairs hilar GABAergic interneurons and how this process leads to spatial learning and memory deficits. Specifically, we will determine whether and how apoE4-induced impairments of GABAergic interneurons in the hilus of the dentate gyrus contribute to learning and memory deficits (Aim 1); explore the mechanisms by which apoE4 impairs hilar GABAergic interneurons (Aim 2); and determine whether and how apoE4 impairs human GABAergic interneurons derived from isogenic hiPSC lines with different apoE genotypes (Aim 3). These studies, involving in vitro, in vivo, and hiPSC approaches, will provide insights into the roles of apoE4 in both health and disease and may identify new therapeutic targets for apoE4-associated neurodegenerative disorders, particularly AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The goal of this project is to determine how human apolipoprotein (apo) E4, the major genetic risk factor for Alzheimer's disease (AD), impairs hilar GABAergic interneurons and how this process leads to spatial learning and memory deficits. The proposed studies will provide insights into the roles of apoE4 in both health and disease and may identify new therapeutic targets for apoE4-associated neurodegenerative disorders, particularly AD.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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