Molecular Basis of Synaptic Suppression by ApoE

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Principal Investigators

HERZ, JOACHIM J

Institution

UT SOUTHWESTERN MEDICAL CENTER

Contact information of lead PI
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Molecular Basis of Synaptic Suppression by ApoE

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Long-Term Depression, Metabotropic Glutamate Receptors, Apolipoprotein E, apolipoprotein E-4, Protein Tyrosine Phosphatase

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a progressive neurodegenerative disease marked by the accumulation of amyloid plaques and neurofibrillary

tangles. Overexpression or mutations of the amyloid precursor protein (APP) gene create soluble amyloid-beta (A?) oligomers, which are the toxic particles that alter synaptic plasticity y decreasing long-term potentiation (LTP, a paradigm for learning and memory) and enhancing long-term depression (LTD, a paradigm for forgetfulness). This suggests that the synaptic dysfunction found early in AD is A?-driven. Interestingly, the most important genetic risk factor n the pathogenesis of AD is Apolipoprotein E (ApoE) ?4 genotype. Carriers of the ?4 allele of ApoE (ApoE4) are at increased risk for AD compared with those carrying the more common ?3 allele (ApoE3), whereas the ?2 (ApoE2) allele decreases the risk. One mechanism by which ApoE4 promotes AD involves a propensity for impaired clearance and increased aggregation of ?-amyloid; however, that alone may not fully explain the origins of the synaptic dysfunction, which begins long before the amyloid plaques become prominent indicators of blooming AD. Work from our laboratory has revealed how ApoE4 dampens postsynaptic efficacy by impairing Reelin signaling and vesicular trafficking of ApoE and glutamate receptors. Reelin, a ligand for the ApoE receptors Apoer2 and Vldlr, physiologically strengthens the synapse and counteracts A?-induced synaptic suppression by promoting the phosphorylation, and thus reducing the endocytosis, of glutamate receptors. ApoE4 impairs ApoE receptor recycling along with the associated glutamate receptors, thereby diminishing synaptic strength. A? oligomers cause endocytosis of AMPA receptors and synaptic suppression at least in part through Class 1 mGluR-dependent LTD-inducing mechanisms. A? oligomers and the drug DHPG (Dihydroxyphenylglycine) activate mGluRs and increase the tyrosine phosphatase activity of striatal-enriched tyrosine phosphatase (STEP), which dephosphorylates and thereby induces AMPA and NMDA receptor endocytosis. By contrast, Reelin activates Src Family kinases (SFKs), which phosphorylate ionotropic glutamate receptors and block their endocytosis. What remains unclear is how Reelin, ApoE isoforms and ApoE receptors interact with the LTD-inducing postsynaptic machinery to balance synaptic strength through local protein synthesis and in particular GluA1-4 and STEP expression. In this proposal we will investigate whether Reelin alters mGluR- LTD, and whether reduction of Reelin signaling by the AD-promoting ApoE4 isoform enhances mGluR-LTD and the expression of Ca2+-permeable, excitotoxicity-promoting GluA2-lacking AMPAR during aging. Our specific aims will address the roles of Reelin and ApoE isoforms on 1) regulation of mGluR-LTD and AMPA receptor trafficking, 2) induction of LTD and postsynaptic protein translation of FMRP (Fragile X Mental Retardation Protein), Arc and STEPa, and 3) interaction with APP and ?-amyloid at the synapse. Our results will define the roles of Reelin and ApoE isoforms as modulators of A?-induced synaptic suppression.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer`s disease (AD) is the most common form of dementia, marked by early and progressive decline in cognition. Amyloid plaque and neurofibrillary tangles are the hallmarks of the disease. Apolipoprotein E (ApoE) ?4 genotype is the most important risk factor for AD. In this proposal, we aim to explore the molecular basis by which ApoE4 impairs synaptic function. Elucidation of these underlying mechanisms is essential for the development of novel and effective therapeutic approaches.

Further information available at:

Types:
Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
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