Mechanisms of A-Beta Oligomer Induced Synapse Dysfunction in Alzheimer’s Disease

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Country

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Mechanisms of A-Beta Oligomer Induced Synapse Dysfunction in Alzheimer’s Disease

Source of funding information

NIH (NIA)

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€ 2,826,374.31

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01/08/2010

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6

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

? DESCRIPTION (provided by applicant): In Alzheimer's disease (AD), an early causative role for Amyloid beta (A?) peptide is supported by pathology, by human genetics and by biomarker studies. More specifically, A? oligomers trigger a toxic cascade that impairs synaptic function and subsequently leads to Tau pathology and progressive cognitive dysfunction. Therapeutic efforts to intervene in the A? pathway have focused on the production or clearance of the peptide, and unfortunately have been disappointing so far. Additional validated targets for AD therapy are needed. Previously, we have studied the basis for A? oligomer (A?o) toxicity in neurons. Using an unbiased genome-wide screening method we searched for A? oligomer-specific binding sites expressed in brain, and identified PrPC. Amongst reported A?o binding sites, only PrPC was identified through an unbiased, genome-wide screen. In the previous grant cycle, we went on to define an A?o-PrPC-mGluR5-Fyn cascade that damages synapses in AD models. Here, we will pursue three aims to expand our knowledge of A?o synaptotoxic signaling, focusing on the PrPC-mGluR5 complex. First, we use conditional deletion of PrPC expression in AD transgenic mice, and show a role for A?o signaling via PrPC in the maintenance and progression of synaptic and memory impairments. Deleting PrPC rescues established deficits. This highlights the need to understand how specific residues in the natively unfolded segment of PrPC recognize oligomeric but not other forms of A? peptide to trigger synaptic symptoms. We will combine biochemical, mutagenesis and NMR analyses to provide molecular insight. Not only are PrPC and mGluR5 required individually for mouse transgenic phenotypes, but preliminary data show that they also interact genetically in linking A?o to intracellular signaling molecules and in generating mouse model synapse and memory loss. Importantly, while mGluR5 interacts with many intracellular polypeptides, PrPC is unique as an extracellular polypeptide interaction. We will examine the basis for the interaction of these two proteins, defining requisite domains and changes in quaternary structure. While we and later others observed that negative allosteric modulators of mGluR5 rescue A?o and AD transgene phenotypes, the therapeutic index is very narrow. Minor increases in dose interrupt endogenous Glu signaling and impair behavioral function. The optimal therapeutic compound would preserve endogenous mGluR5 signaling for Glu but block signaling from A?o-PrPC. Having identified a high potency Silent Allosteric Modulator with this profile, we propose to test its efficacy to bloc neuronal A?o signaling in neurons and in transgenic mice. Together these studies will provide insight into how the PrPC-mGluR5 transduction complex plays a central role in AD related signaling and explore a potential therapeutic approach.

Lay Summary

PUBLIC HEALTH RELEVANCE: Disease-modifying therapy for Alzheimer's disease is a massive unmet medical need. Research with Alzheimer models demonstrates that oligomeric forms of Amyloid beta peptide attack the neuron by binding to Cellular Prion Protein and triggering a signaling cascade of reactions. Steps in this cascade may provide new therapeutic targets for Alzheimer's disease. Here, we seek to characterize the timing and localization of this pathophysiological signaling cascade, delineate the molecular basis of signaling and develop means to target mGluR5 pharmacologically for AD.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

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