Abeta Oligomers and Mechanisms of Neuronal Cell Death in Alzheimers Disease

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Research Abstract

? DESCRIPTION (provided by applicant): The long-term goal of the proposed study is to understand the disease-relevant toxic properties of the ß- amyloid peptide (Aß), which is strongly implicated in the etiology of Alzheimer’s disease (AD). The central hypothesis of this proposal is that the ability of Aß to damage membranes contributes to Alzheimer’s disease

pathology, and tau hyperphosphorylation, a hallmark of AD pathology, is a consequence of a neuronal response to membrane damage. We propose that neuronal cell death in AD is a result of chronic tau phosphorylation resulting from chronic membrane damage caused by oligomeric forms of Aß. This hypothesis is supported by our demonstration that single residue substitutions in Aß that block its ability to permeabilize membranes also render this peptide non-toxic in a variety of in vitro and in vivo models. Furthermore, preliminary studies reveal that primary neurons exposed to the membrane pore- forming toxin streptolysin O (SLO) show patterns of tau hyperphosphorylation very similar to that induced by exposure to Aß. We will test this hypothesis using primary neuronal cultures and a novel C. elegans model that enables us to visualize Aß-induced membrane repair in living animals. This model will allow us to better define the toxic Aß species by engineering informative Aß variants (including known familial AD mutations) and assaying their ability to induce membrane repair. Critically, this model will also allow us to genetically test the disease relevance of the membrane damage model by mutating worm orthologs of AD risk genes potentially involved in membrane repair (e.g., PICALM, BIN1, and CTNNA2), and determining if this alters Aß-induced membrane repair. These studies will be complemented by using primary hippocampal neurons to confirm tau phosphorylation as a component of membrane repair, and to determine where along the repair pathway this event occurs. Relevance: Identification of compounds that block Aß toxicity (rather than Aß accumulation) has been hindered by uncertainty regarding the toxic Aß species and its mechanism of action. The deposition of insoluble, hyperphosphorylated tau in AD is believed to be a downstream consequence of Aß accumulation, but the biological rationale for why this occurs has not been established. Our proposed studies can potentially provide new leads for the development of AD therapeutics, as well as explain the altered tau metabolism observed in a range of tauopathies in addition to AD.

Further information available at:

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