Synaptic Interactions of Aβ(1-42) and Pyroglutamate-modified Aβ(pE3-42) Oligomers

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Alzheimer's disease (AD) is a uniquely human disease involving progressive loss of neuronal synapses and deposition of insoluble Aβ and tau pathologies coupled to symptoms of cognitive decline progressing to dementia. Memory impairment in AD is related to synaptic loss in the neocortex and limbic system. The human AD brain contains highly stable soluble assemblies of Aβ and a high proportion of Aβ chemical modifications, especially pyroglutamate which are much less prevalent in other species. The progression of cognitive symptoms in humans with AD is related to the soluble oligomeric content of the brain, rather than to the insoluble Aβ deposits. Physiological concentrations of human sequence Aβ oligomers selectively bind to a subset of excitatory, primarily glutamatergic synapses in both human and murine brain causing glutamate excitotoxicity leading to neuronal death. They bind to synaptosomes isolated from human and murine brain and to cultured primary cortical and hippocampal neuronal synapses from murine and human brain. We hypothesize that the pyroglutamate modifications of Aβ oligomers (N3(pE)-42 oligomers) in AD result in increased oligomer stability, longer and different interaction with synaptic receptors, and enhanced disruption of synaptic signaling systems. We will determine the stability and compare the binding of unmodified and (N3(pE)-42 oligomers to synaptosomes isolated from mouse brains, neuronal cultures, and brain tissue slices. Proximity ligation technology and flow cytometry will be employed to identify binding partner receptors and pathways impacted in synaptic endings. The disruption of electrophysiology and particularly long-term potentiation will be measured in mouse neuronal cultures and brain sections to elucidate pathways affected by unmodified and pE-modified Aβ oligomers.