NEURONAL RECEPTORS OF SOLUBLE b - AMYLOID OLIGOMERS AND THE MECHANISMS OF PATHOGENESIS OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is characterized by a profound inability to form new memories and by progressive cognitive dysfunction. Accumulating evidence indicates that soluble oligomers of the β-amyloid peptide (Aβ?are the proximal neurotoxins responsible for early synaptic dysfunction, memory loss and, ultimately, neuronal degeneration in AD. However, the mechanisms by which Aβ oligomers attack neurons are only beginning to be elucidated. There are no effective treatments for AD and the development of novel therapeutic approaches will critically depend on a detailed understanding of the molecular/cellular basis of toxicity, including identification of the receptors that mediate the neuronal impact of Aβ. Using a combination of phage display of peptide libraries and other biochemical/cell biological approaches, we have identified components of a neuronal receptor complex that appears to mediate Aβ-induced neuronal dysfunction and toxicity. Recent studies will be discussed demonstrating the interaction with Aβ and functional deregulation of specific neuronal receptors/pathways that play critical roles in synaptic plasticity and memory, including nicotinic acetylcholine, NMDA and insulin receptors, and the Wnt/Frizzled/β-catenin signaling pathway. These results support the notion that nicotinic, glutamate and insulin receptors, as well as the Wnt receptor Frizzled, are early targets of Aβ-induced neuronal dysfunction in AD and provide a basis for the rational development of novel therapeutic approaches for this devastating disease.