Defective brain insulin signaling and memory impairment in Alzheimer’s disease.

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Compelling preclinical and clinical evidence supports a pathophysiological connection between Alzheimer’s disease (AD) and diabetes. Altered metabolism, inflammation and insulin resistance are key pathological features of both diseases. For many years, it was generally considered that the brain was insensitive to insulin, but it is now accepted that this hormone has central neuromodulatory functions, including roles in learning and memory, that are impaired in AD. However, until recently the molecular mechanisms accounting for brain insulin resistance in AD have remained elusive. We investigated the role of synaptotoxic Aβ oligomers in AD-associated defective insulin signaling and memory impairment using mice models of AD and macaques receiving Aβ oligomer infusions. We found that Aβ oligomers activate a proinflammatory pathway in the hippocampus and in the hypothalamus, resulting in eIF2α-P and neuronal insulin receptor substrate (IRS-1) inhibition. In the hippocampus, the effects of AβOs lead to synapse loss, and memory impairment while the effects of AβOs in the hypothalamus lead to impairment in peripheral glucose homeostasis. Bolstering insulin signaling protected the brain from the deleterious effects of Aβ oligomers in mice and macaques.