Mechanisms of abeta induced dysfunction in hippocampal neuronal circuitry

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Principal Investigators

KOO, EDWARD H.

Institution

UNIVERSITY OF CALIFORNIA SAN DIEGO

Contact information of lead PI
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USA

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Mechanisms of abeta induced dysfunction in hippocampal neuronal circuitry

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

neuronal circuitry, Amyloid beta-Protein, Amyloid beta-Protein Precursor, postsynaptic neurons, Hippocampus

Research Abstract
DESCRIPTION (provided by applicant): Synaptic loss or dysfunction is believed to be one of the

major factors responsible for the memory and cognitive deficits seen in Alzheimer’s disease (AD), the most common age-related neurodegenerative disorder. According to the amyloid cascade hypothesis, the gradual accumulation in brain of amyloid ¿-peptide (A¿), derived from the amyloid precursor protein (APP), is hypothesized to trigger the cascade of events that lead to AD. The mechanisms by which A¿ may initiate these events, which include synapse loss or synaptic dysfunction, are unclear. Recent studies suggested that both amyloid deposition in extracellular space and intracellular neurofibrillary degeneration, the two hallmarks of AD, may progress in a trans-synaptic or anterograde fashion. That is, the spread of AD pathology in brain, as must occur as the disease develops, expands in a manner that is suggestive of neuron-to-neuron progression. If true, this suggests that A¿-induced synaptic injury should be initiated by the presynaptic neuron to alter function of the postsynaptic neuron. Indeed, we have recently obtained preliminary data that support this concept. Specifically, impairment of synaptic plasticity is present only when A¿ is derived from the presynaptic neuron but not in the reverse situation. These novel observations were obtained from transgenic mice that restrict APP expression preferentially to CA3 or CA1 neurons of the hippocampus. These transgenic mice therefore provide the unique opportunity to ask key questions related to neuronal function or dysfunction caused by local production and release of A¿ in brain. These questions cannot be addressed with existing transgenic mice where there is pan-neuronal expression of APP at high levels or the recently developed mice with expression restricted to entorhinal cortex. This application will examine the degree to which injury to synaptic function or neuronal circuits develops with respect to the neuronal population where A¿ is produced. Specifically, we will utilize transgenic mice with spatial and temporal control of APP expression directed to neurons in CA1, CA3, or dentate gyrus by using transgenic mouse lines that express Cre recombinase in CA1, CA3, or dentate gyrus granule cells, respectively. In addition, we will test the reversibility of synaptic and circuit dysfunction in these mouse lines as well as in the original tTA/tet-APP line. Two Aims are proposed: 1) we will explore whether behavior, biochemical, and morphological changes accompany the impairment in synaptic plasticity initiated by A¿ released from pre- vs. postsynaptic neurons and whether these functional changes become irreversible with age and 2) assess neuronal dysfunction in these mice by measuring field potentials and place cell firing patterns. Collectively, results from these studies using selective and reversible APP expression in subregions of the hippocampus will provide fresh insights into A¿-induced neuronal dysfunction in vivo.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal explores the mechanisms by which amyloid b-protein (A?) induces synaptic injury in brain using innovative animal models. According to the amyloid cascade hypothesis of Alzheimer’s disease (AD), the buildup of A? peptides in brain initiates the cascade of events to result in AD pathology. Therefore, by providing new insights into how A? damages synapses and causes impairment in synaptic function in the early phases of AD, results from our study may lead to more effective treatments for a disease that is increasing rapidly in our aging population.

Further information available at:

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Investments > €500k

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United States of America

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