2022 IMPACT CIRCLE

Project Title

A synaptic maintenance mechanism to rescue cognitive decline in the elderly using Alzheimer's disease as an accelerated aging model

Investigator(s) and collaborations: Tara Tracy, PhD

Unmet Need/Primary Question:

Cognition progressively declines with age in neurodegenerative diseases. There is an urgent need for new therapeutic approaches to rescue the underlying dysfunction in the brain that causes cognitive decline in aging and disease. The synapses on neurons are critical for normal cognition and the encoding of new memories. Impaired synapse function plays a key role in driving cognitive decline in age-related disease. We propose a synaptically targeted approach as a new direction to reverse age-related cognitive decline by repairing and rescuing synapse function, potentially re-stabilizing a key pathway for memory formation.

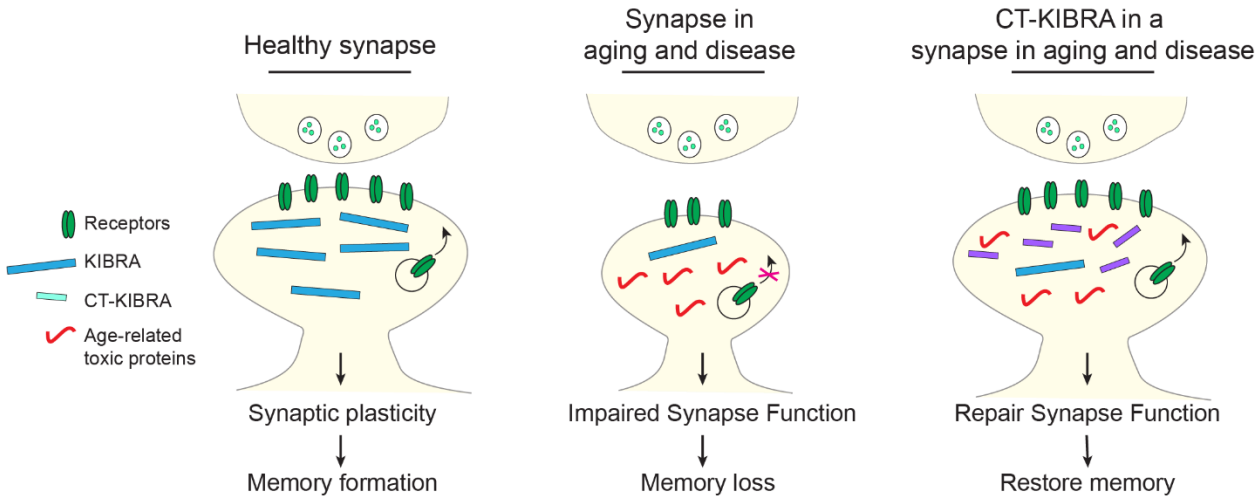
Novel Hypothesis: We hypothesize that a peptide derived from the KIBRA protein, called CT-KIBRA, is sufficient to restore synapse function of neurons in the brain and reverse cognitive decline in aging and in Alzheimer's disease.

Project Proposal: The Tracy Lab found that memory impairment in age-related neurodegenerative disease is linked to the loss of a protein at synapses in the brain called KIdney/BRAin (KIBRA). This KIBRA protein is required for synaptic plasticity, which is the dynamic modulation of synapse strength that enables the formation of new memories in the brain. The loss of KIBRA protein inhibits synaptic plasticity and leads to memory impairment associated with Alzheimer's disease. We found that the expression of a small C-terminus fragment of the KIBRA protein, called CT-KIBRA, in cultured neurons can reverse the synapse dysfunction caused by toxic tau protein in Alzheimer's disease. Viral-based expression of CT-KIBRA in the brain of an Alzheimer's disease mouse model also reversed memory loss. Our findings in mice suggest that CT-KIBRA can repair synapse function and protect them against toxicity in the brain during aging. Based on these findings we now propose a preclinical study to develop and test the efficacy of a CT-KIBRA peptide as a new therapeutic approach to reverse memory loss in aging and age-related disease. Our goal for this proposal is to establish a foundation for the potential therapeutic efficacy of a CT-KIBRA peptide for dementia. In this first step to understand the relevance of this peptide and mechanism in the aging brain, we will

monitor the impact of treatment with the CT-KIBRA peptide on Alzheimer's disease related phenotypes in neuron cultures and in a mouse model of Alzheimer's disease. Future work would consider the effect of CT-KIBRA in normal aging and prophylaxis.

Description of Potential Impact:

Cognitive aging is a major public health problem with over 13 million Americans estimated to develop dementia by midcentury threatening to triple the $200 billion currently spent on dementia care annually. There is a critical need for treatments of dementia to improve quality of life and healthy aging. Our research on the KIBRA protein could lead to the development of a new therapeutic approach targeting the KIBRA pathway to maintain synapse function with age and extend the years of intact cognition throughout lifespan.



CT-KIBRA repairs synapse function in age-related disease by restoring the synaptic plasticity that is critical for the formation of new memories. At healthy synapses, KIBRA protein promotes the insertion of neurotransmitter receptors to enhance synapse strength during synaptic plasticity and memory formation. In age-related disease including Alzheimer's disease, there is an accumulation of toxic proteins, such as tau, in neurons and reduced levels of KIBRA protein at synapses. Our findings suggests that expression of CT-KIBRA in neurons can re-establish synaptic plasticity and ameliorate memory loss caused by toxic tau protein.