Role of Tau Cleavage in Tauopathy

https://neurodegenerationresearch.eu/survey/role-of-tau-cleavage-in-tauopathy/

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Country

USA

Title of project or programme

Role of Tau Cleavage in Tauopathy

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NIH (NIA)

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, tau Proteins, CASP2 gene, synaptic function, Dendritic Spines

Research Abstract

This project aims to validate a novel drug target for tauopathies ¿ a group of incurable neurodegenerative conditions that includes Alzheimer¿s disease (AD). My lab previously used transgenic mice to assay the biological activity of the microtubule-binding protein tau, which aggregates to form neurofibrillary tangles, a cardinal feature of tauopathies. We discovered that cognitive dysfunction in rTg4510 mice expressing the P301L tau variant (tauP301L), linked to

frontotemporal dementia, begins prior to neuron loss and occurs independently of neurofibrillary tangles or insoluble tau. Cognitive function improves when soluble transgenic tau is reduced (SantaCruz et al., Science, 2005). These results implicated some form of soluble tau in impairing cognition. Next, we showed that tauP301L and pseudo-hyperphosphorylated wild-type tau (tauEPWT) mislocalize to dendritic spines, which results in decreased synaptic transmission due to the reduction of glutamate receptors in the spines (Hoover et al., Neuron, 2010). These data suggested a mechanism by which pathological forms of tau disrupt synaptic function. In the current application, we show that a specific modification of either tauP301L or tauEPWT is necessary and sufficient for tau to mislocalize to spines. We also show that the specifically modified form to tau is elevated in the brains of patients with Mild Cognitive Impairment and AD. Here, we propose to test the hypothesis that the specifically modified form of tau disrupts synaptic function and impairs cognition in tauopathies. The successful completion of our goals will enable us to lay the biological foundation for discovering drugs that may block tau-related neurotoxicity in Alzheimer¿s disease and other tauopathies. This project intends to improve both our understanding of the processes that initiate AD and our ability to treat it in its earliest stages, by determining whether specific forms of tau interfere with neurotransmitter receptor trafficking in dendritic spines and memory function. Since these abnormal processes occur prior to the loss of neurons, these pathogenic tau species could become a target for therapies aimed at preventing tauopathies from developing into progressive, fatal dementias. If successful, the work could benefit millions of people.

Lay Summary
Project Narrative The central focus of this proposal explores how to fill a knowledge gap – the identification of specific tau species disrupting neural and brain function. The identification of such molecular entities will enable us to lay the biological foundation for discovering drugs that may block tau- related neurotoxicity in Alzheimer’s disease and other tauopathies. This project intends to improve both our understanding of the processes that initiate AD and our ability to treat it in its earliest stages, by determining whether specific forms of tau interfere memory function and with neurotransmitter receptor trafficking in dendritic spines, the principal loci of synaptic plasticity underlying learning and memory. Since this abnormal process occurs prior to the loss of neurons, these pathogenic tau species could become a target for therapies aimed at preventing tauopathies from developing into progressive, fatal dementias. If successful, the work could benefit millions of people in America and the world.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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