Mechanisms Underlying Tau45-230-Induced Neuronal Degeneration

https://www.neurodegenerationresearch.eu/survey/mechanisms-underlying-tau45-230-induced-neuronal-degeneration/

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Country

USA

Title of project or programme

Mechanisms Underlying Tau45-230-Induced Neuronal Degeneration

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NIH (NIA)

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01/09/2015

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5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, tau Proteins, tau aggregation, Nerve Degeneration, tau function

Research Abstract

? DESCRIPTION (provided by applicant): The mechanisms underlying tau pathology in neurodegenerative diseases have not been completely elucidated. However, a growing body of

evidence suggests that tau posttranslational modifications, other than phosphorylation, might play an important role in those mechanisms. Recently, we have shown that one of such modifications is calpain-mediated tau cleavage. This cleavage leads to the generation of the 17 kDa tau45-230 fragment in the context of Alzheimer's disease (AD) and other tauopathies. In addition, our data indicated that this fragment induced progressive degeneration in cultured hippocampal neurons. Conversely, conditions that prevented the generation of this fragment were associated with enhanced neuronal survival in central neurons. Furthermore, increased neuronal death, synapse loss, and behavioral abnormalities have been detected in transgenic mice expressing tau45-230. Together, these data provide evidence indicating that tau cleavage into this neurotoxic fragment is a conserved molecular pathogenic pathway of neurodegeneration. On the other hand, the mechanisms by which tau45-230 induces degeneration and cell death remain unknown. Based on our preliminary results, we hypothesize that tau45-230 could exert its neurotoxic effects through a dual mechanism: 1) tau45-230 could modulate the aggregation of full-length tau inducing the formation of smaller and more toxic aggregates; and 2) tau45-230 could interfere, either as a monomer or as small aggregates, with full-length tau's biological functions. To test these hypotheses, we propose to: 1) assess the presence and toxicity of tau45-230 aggregates in brain samples obtained from AD and other tauopathy subjects; 2) determine to what extent tau45-230 modulates full-length tau aggregation; and 3) identify the mechanisms by which tau45-230 alters tau function in central neurons. These experiments will be performed by means of a combination of techniques including: Western blot analysis, immunocytochemistry, in vitro polymerization assays, aggregate purification, homologous recombination techniques, microtubule-binding assays, live cell microscopy, and cell viability assays. These studies could lead to the identification of a novel molecular pathway of degeneration. In addition, they could provide useful for the diagnosis, prevention, and eventually the treatment of AD and other tauopathies.

Lay Summary

PUBLIC HEALTH RELEVANCE: The long-term goal of this project is to study a novel and poorly understood mechanism underlying neuronal degeneration. This mechanism involved the cleavage of the microtubule-associated protein tau by calpain leading to the generation of a neurotoxic fragment. Obtaining this information could provide useful tools for the diagnosis, prevention, and eventually the treatment of Alzheimer's disease and other tauopathies.

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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