Pathogenic tau promotes tau induced neurotoxicity as a result of reduced nuclear calcium

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Abstract

As a central signaling transducer, calcium ions (Ca^{2+}) are integral to basic neuronal processes including membrane excitability and neurotransmitter release from the synapse. In addition, nuclear Ca^{2+} regulates cAMP response element-binding protein (CREB)-dependent transcription, and thus plays a central role in shaping the transcriptome. As a master regulator of both signal transduction and transcription, Ca^{2+} levels must be maintained within narrow limits to avoid significant effects on nervous system function. In the current study, we find that reduction of baseline nuclear calcium levels contributes to neuronal death in the context of tauopathies, a group of neurodegenerative disorders including Alzheimer’s disease that are pathologically defined by deposits of tau protein in the brains of affected individuals. Starting with an unbiased, bioinformatic approach using RNA-sequencing data from postmortem human Alzheimer’s disease brain tissue, alongside mouse and Drosophila models of primary tauopathy, we find that Ca^{2+}-dependent transcription is reduced compared to controls. In the adult Drosophila brain, we find that transgenic expression of human tau causes an age-dependent reduction of baseline nuclear Ca^{2+} levels. Mechanistically, we demonstrate that tau-induced depletion of nuclear Ca^{2+} in the Drosophila models occurs via reduced CREB-dependent expression of the Drosophila large-conductance, calcium-activated-K^+ big potassium (BK) channel homolog, Slowpoke. Genetic and pharmacologic manipulation of nuclear calcium and BK channels modifies tau-induced neurodegeneration in vivo, suggesting that nuclear calcium and BK channel dysfunction causally mediate tau-induced neurotoxicity. Taken together, our studies identify reduction of nuclear Ca^{2+} as a downstream mediator of tau-induced neurotoxicity, and nuclear Ca^{2+} as a critical regulator of neuronal survival.

Nuclear calcium is reduced in tau transgenic Drosophila

Pathogenic tau reduces CREB levels in tau transgenic Drosophila

Reduced expression of Slowpoke induces aberrant cell cycle activation in tau transgenic Drosophila

Rescue of Slowpoke channel activity reduces neurotoxicity and improves nuclear calcium levels in tau transgenic Drosophila

Conclusions

In order to better understand what role Slowpoke plays in regulating the changes in calcium that we observe in the presence of pathological tau, it will first be necessary to determine if the induced release of calcium from endoplasmic reticulum stores, via the ryanodine receptors, is hampered by the reduction of Slowpoke that we observe in tau transgenic animals. Answering this question will greatly advance our knowledge on the effects pathological tau has on calcium levels during disease progression and lead to potential therapeutic targets for Alzheimer’s disease and related tauopathies.

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