Synaptic toxicity of Huntington disease protein

https://neurodegenerationresearch.eu/survey/synaptic-toxicity-of-huntington-disease-protein/

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Huntington gene, Huntington Disease, Synapses, N-terminal, polyglutamine

Research Abstract

DESCRIPTION (provided by applicant): Synaptic toxicity of the Huntington's disease protein Huntington's disease (HD) is caused by polyglutamine (polyQ) expansion in the N- terminal region of huntingtin (htt). It is characterized by progressive neurodegeneration that preferentiall affects the medium spiny neurons in the striatum. Furthermore, polyQ expansion leads to ht becoming misfolded and aggregated in an age-dependent manner. Thus, HD and other aging-related neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, share the major features of late-onset and selective neurodegeneration, as well as age-dependent protein aggregation. Because of its well-defined genetic mutation and neuropathology, HD makes an

ideal system for investigating the pathogenesis of age-dependent neurodegenerative diseases. Moreover, numerous studies have shown that mutant htt can impair synaptic function, an early neuropathologic event that is also common in many other age-dependent neurological disorders. Despite the fact that mutant ht can affect a variety of synaptic functions, how exactly synaptic dysfunction contributes to HD neuropathology remains unclear. We also do not know how mutant htt can preferentially accumulate in the axons of medium spiny neurons in HD knock-in (KI) mice that express full-length mutant htt. Since it is medium spiny neurons that are mostly affected in HD, understanding the mechanism for this preferential accumulation is important to unravel the pathogenesis of HD and develop treatments for the early neuropathology of HD. We hypothesize that mutant N-terminal htt fragments may interact abnormally with axonal proteins to preferentially accumulate in axonal terminals of medium spiny neurons and affect synaptic function. To test these hypotheses, we have generated a novel transgenic HD mouse model that selectively expresses N-terminal mutant htt in axonal terminals. Using this HD mouse model, we will explore whether axonal terminal mutant htt can cause neurological symptoms and affect synaptic function, as well as identify the common pathological events that also occur in HD KI mice. We will then examine whether and how N-terminal mutant htt fragments can preferentially accumulate in axons and affect the function of medium spiny neurons by identifying the axonal proteins that may abnormally interact with mutant htt. These studies also have implications for our understanding of synaptic dysfunction in other age-dependent neurodegenerative diseases that are also caused by misfolded proteins.

Further information available at:

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