Immediate-early intra-axonal signaling in neurodegeneration

https://www.neurodegenerationresearch.eu/survey/immediate-early-intra-axonal-signaling-in-neurodegeneration/

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Research Abstract

? DESCRIPTION (provided by applicant): Though the prevalence Alzheimer’s disease (AD) continues to increase, the mechanisms underlying disease pathogenesis remain to be elusive. In order to delay or prevent disease progression, it is important to understand the earliest pathogenic alterations that occur in AD brain. Characteristics of AD pathology include the

deposition of ß-amyloid (Aß) plaques and hyperphosphorylated tau tangles, though the pathophysiological relevance of these hallmarks in disease pathogenesis is unclear. The amyloid hypothesis suggests that oligomeric Aß peptides, toxic precursors of Aß plaques, play a causative role in neurodegenerative alterations observed in AD brains. Studies from brains of AD mouse models suggest that axonal exposure to Aß is sufficient to trigger neurodegeneration of the entire neuron, ultimately resulting in cell death. The role of intra- axonal signaling event in AD pathogenesis is further supported by studies in human AD brains showing that synaptic dysfunction precedes cell death. In our recently published study we demonstrate in vitro and in vivo that axonal Aß application does indeed induce neurodegeneration via local synthesis and retrograde transport of activating transcription factor 4 (ATF4), which is followed by ATF4-dependent pro-apoptotic changes in gene expression. Consistent with these findings, post-mortem brain tissues from AD patients exhibited higher frequencies of ATF4 mRNA and protein in axons and cell bodies compared to age-matched controls. My dissertation project is an organic extension of this study, which is primarily focused on the earliest intra-axonal signaling events that occur in response to Aß. My preliminary data shows that axonally applied Aß induces rapid Ca2+-dependent ribosomal activation, and inhibition of axonal protein synthesis and retrograde transport are both sufficient to block Aß-induced recruitment of Atf4 to axons. These findings are reminiscent of studies from the field of spinal cord injury, which show that axotomized peripheral neurons induce an immediate Ca2+ influx followed by rapid translation of resident mRNAs whose protein products play critical roles in retrograde injury signaling to the nucleus. Interestingly, RNA sequencing experiments of healthy hippocampal axons from our previous study reveal the presence of mRNAs encoding many of the proteins known to be involved in sciatic nerve retrograde injury signaling. Therefore, I hypothesize that, similar to injured axons of the peripheral nervous system, hippocampal axons challenged with Aß induce rapid Ca2+-dependent local translation of a retrograde signaling complex that informs cell bodies of a peripheral degenerative insult. The specific aims of this application to assess the role of immediate-early intra-axonal signaling induced by Aß will be: (i) to determine the mechanisms controlling Aß-induced immediate-early local protein synthesis and (ii) to demonstrate the rapid local synthesis of retrograde signaling complex components in response to Aß. These studies will provide insight into the earliest intra-axonal pathogenic signals induce by Aß, which can improve our understanding of how neurodegeneration spreads retrogradely throughout the brain.

Further information available at:

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