Mechanisms of alpha-synuclein accumulation in traumatic brain injury (R21 NS094908 Resubmission)

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Research Abstract

? DESCRIPTION (provided by applicant): Traumatic brain injury (TBI) has been considered a causative factor for Parkinson’s disease (PD) based in case-control studies and brain injury has been suggested to facilitate ?syn aggregation and PD development. This notion is further

supported in an experimental study showing that ?syn expression and aggregation increased transiently following TBI in aged mouse brain. In addition, the exposure of mice to the pesticide paraquat, combined with TBI, resulted in triple the risk of the mice developing Parkinsonian symptoms, and ?syn has been found to be increased in the CSF of patients with severe head trauma, indicative of secondary neuropathologic events occurring after injury. Despite these intriguing data, the exact mechanism(s) underlying brain injury-induced aggregation of ?syn remain elusive. Our preliminary data suggest that extracellular ATP (eATP) is released from injured cells and can facilitate ?syn aggregation. Here, we propose to investigate the release of eATP from damaged neural tissue in vivo as a trigger for alpha-synuclein aggregation following TBI. We will explore this novel hypothesis in three coordinated aims. In aim 1 we will use an innovative eATP reporter probe coupled with real-time in vivo imaging to determine if eATP levels increase post-TBI. In aim 2 we will investigate if cellular degradation pathways are modulated by TBI using an original brain tissue recovery method. In aim 3, we will examine the contribution of P2X receptors to alpha-synuclein aggregation following TBI and eATP release in vivo. The high-risk nature of the hypothesis makes the R21 mechanism ideal for further exploration. If successful, the experiments described in this proposal will advance our knowledge of mechanisms of protein aggregation following TBI and TBI-induced PD.

Further information available at:

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