Prokineticin 2 and Neuroinflammatory Mechanisms

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Research Abstract
DESCRIPTION (provided by applicant): Neuroinflammation is now recognized as a key degenerative mechanism in several neurodegenerative diseases including Parkinson's disease (PD). The severity of neuronal damage caused by neuroinflammatory stress is dependent on the degree of dysregulation of inflammatory and anti-inflammatory pathways in brain. Most studies to date are focused on identifying major pro-inflammatory pathways that are activated during neuroinflammatory insult. Understanding the anti-inflammatory mechanisms associated

with various stages of brain inflammation will provide new insights into disease processes associated with neurodegenerative diseases. In this proposal, we aim to delineate a novel anti-inflammatory protective response in the nigrostriatal dopaminergic neurons mediated by the recently discovered mammalian protein homolog of mamba snake venom: Prokineticin-2 (PK2). Unexpectedly, we observed a dramatic up-regulation of PK2 protein and its release from dopaminergic neuronal cells during inflammatory TNF¿ insult. Further observation of increased PK2 expression in nigral dopaminergic neurons in an animal model of PD as well as in the nigral samples from postmortem PD patients provides credence for the clinical significance of our findings. Interestingly, recombinant PK2 significantly protected against apoptotic neuronal cell death and TH positive dopaminergic neuronal loss induced by neuroinflammatory insults. Surprisingly, PK2 treatment also promoted migration of both astrocytes and microglial cells. Therefore, in this proposal, we intend to expand our preliminary observations by pursuing the following specific aims: (i) To characterize the PK2 induction, release and function in dopaminergic neurons following inflammatory insults in primary cell culture and animal models, (ii) To determine the effect of PK2 induction on astroglial and microglial migration and function following inflammatory stimuli, (iii) To investigate the molecular mechanisms of PK2 up-regulation in neuronal cells, and (iv) To demonstrate the neuroprotective effect of PK2 in primary cell culture and animal models of PD. Cellular, molecular and neurochemical approaches will be used to delineate these specific aims. Together, understanding the role of PK2 up-regulation and release during inflammatory stress in dopaminergic neurons will not only provide new insights about neurodegenerative mechanisms underlying nigral dopaminergic degeneration but may also yield novel therapeutic strategies for treatment of Parkinson’s disease.

Further information available at:

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