Characterization of the Fidelity to PD of a Unique Rat Model

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Research Abstract
? DESCRIPTION (provided by applicant): Parkinson disease (PD), the second most prevalent neurodegenerative disorder of the elderly, is associated with movement and cognitive symptoms, and current pharmacological treatments result in transient symptomatic relief but are not disease-modifying. PD results from degeneration of dopaminergic neurons in the substantia nigra (SNPC), and loss of striatal dopaminergic function is undoubtedly the cause of the symptoms of PD. Current treatments for PD have been focused on augmenting dopamine levels

and include levodopa, dopamine agonists, and MAO-B inhibitors. Arguably the first biochemical deficits in PD, which arise before symptoms appear, are loss of parenchymal glutathione (GSH), the brain's major small molecule antioxidant, and elevation of its oxidized form (GSSG) (Chinta et al., 2006). This has led researchers to show that PD is associated with oxidative stress, though the cause of PD remains unknown. Familial PD cases have been linked to altered genes, among which is PTEN-induced putative kinase-1 (Pink-1). Genetic models of PD, mostly mice bearing mutations in PD-relevant genes, for unknown reasons do not have pathology or dopaminergic neuronal loss in the SNPC unlike PD patients. An ideal animal model of PD would display progressive loss of dopaminergic neurons, and formation of Lewy bodies, exhibit motor deficits, and also mimic non-dopaminergic characteristics of PD, i.e., loss of cognition and sense of smell (anosmia). It is thought that no mouse model of PD fulfills these criteria. Sage Labs (Horizon) has produced a Pink-1 knockout rat [PINK-1 KO] that exhibits progressive dopaminergic loss in the SNPC, moderate to severe motor deficits, and non-motor characteristics of PD, i.e., anosmia. At 8 months of age, abundant pathology in the SNPC and PD-relevant symptomology are present. This may be the only rodent model of PD that has PD-relevant pathology in the SNPC. It would be helpful to utilize this exciting novel biological tool or environmental studies relevant to environmental-gene interaction in the neurodegeneration associated with PD. However, this laudable goal is presently premature since this rat has not been fully characterized for goodness of fit to PD. Hence, to fill this critical need this R21 proposal will achieve the goal of characterizing this unique rat model of PD to test the overall hypothesis that this unique rat has high fidelity to PD in terms of pathology, biochemistry, and behavior. If this hypothesis is sustained by these studies, future investigations will employ this rat to probe gene-environmental interactions of relevance to PD.

Further information available at:

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