Mechanisms of age-dependent nigral neuron loss in PINK1 knockout rats

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Mechanisms of age-dependent nigral neuron loss in PINK1 knockout rats

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Parkinson's disease & PD-related disorders

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PINK1 gene, parkin gene, , ,

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a frequent cause of neurodegeneration, disability and premature mortality in older adults. Loss of dopaminergic

neurons in the substantia nigra is the primary neuropathological hallmark of PD. There are currently no treatments proven to slow down the progressive nigral cell loss in PD, which causes increasing severity of the clinical symptoms. The recent linking of human mutations in genes such as Parkin, DJ-1, and PINK1 to recessively inherited forms of PD provides new opportunities to discover pathogenic mechanisms and to develop and test neuroprotective therapies in animal models with nigral cell loss based on mechanisms physiologically relevant to human parkinsonism. We have pursued this strategy for over a decade using knockout (KO) mice. For unknown reasons, Parkin KO, DJ-1 KO and PINK1 KO mice do not reproduce the nigral cell loss that occurs in humans bearing loss-of-function mutations in these genes. We and others identified mitochondrial dysfunction (respiratory chain defects) in KO mice, Drosophila and cultured cells, suggesting that this is a common and perhaps early event in the mechanism by which loss-of-function mutations in these genes cause nigral cell loss. However, the lack of nigral cell loss precludes using nigral cell loss as an outcome measure to directly test this and other potential key pathogenic mechanisms in Parkin KO, DJ-1 KO or PINK1 KO mice. Recently developed PINK1 KO rats show age-dependent nigral cell loss beginning at age 6 months and reaching 50% by age 7 months. The age-dependent nigral neuron loss in PINK1 KO rats makes it possible for the first time to test the leading candidate pathogenic mechanisms such as mitochondrial impairment and diminished Parkin-mediated mitochondrial autophagy directly in a mammalian brain that reproduces this central neuropathological feature of PD. We propose to use PINK1 KO rats to achieve the following interrelated specific aims which have been chosen because of their significance for therapeutic development: 1) To identify mechanisms by which PINK1 deficiency leads to nigral cell loss in the rat, 2) To characterize Parkin as an inhibitor of age-dependent nigral cell loss in PINK1 KO rats and 3) To stimulate the mitochondrial respiratory chain as a potential therapy for PD. We expect to contribute a systematic characterization of PINK1 KO rats as an apt test bed for therapeutic development by testing the principal hypothesis that PINK1 deficiency diminishes Parkin-mediated degradation of impaired mitochondria and the second main hypothesis that respiratory chain stimulation via dietary intake of methylene blue is neuroprotective in PINK1 KO rats. We have previously shown that methylene blue prevents neurodegeneration in the rotenone rat PD model. The use of this novel rat model of nigral cell loss is innovative and the proposal will significantly impact the understanding of PD by shifting emphasis to disease mechanisms present in PD brain tissue selected for their strong therapeutic potential. The knowledge gained from our study will be broadly applicable to diseases associated with mitochondrial dysfunction and neurodegeneration.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD), which is caused by unknown factors or by mutations in genes involved in mitochondrial biology, is intractable and can only be alleviated by life-long palliative efforts, which constitutes an important health problem. Testing the mechanisms connecting progressive nigral neuronal loss and molecular events in PD tissue, such as mitochondrial impairment, fulfills the NIH mission by uncovering new fundamental aspects of brain function and by facilitating the development of potential therapies aimed at brain cell protection by restoring mitochondrial function.

Further information available at:

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Investments > €500k

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