NOVEL EXPERIMENTAL PLATFORM FOR PRODOMAL PARKINSONS DISEASE

https://www.neurodegenerationresearch.eu/survey/novel-experimental-platform-for-prodomal-parkinsons-disease/

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NOVEL EXPERIMENTAL PLATFORM FOR PRODOMAL PARKINSONS DISEASE

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Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a movement disorder whose hallmark motor symptoms arise due to loss of dopaminergic innervation of the striatum. Motor symptoms include slowed movement, decreased coordination, and gait abnormalities. These symptoms typically do not present until dopamine levels in the striatum have been reduced by 70-80%. Clinically, this means that patients who seek medical help at the onset of motor symptoms have likely been living with chronically low levels of dopamine for years. This

early phase of the disease, when dopamine levels are pathologically low but motor symptoms have not yet presented, is called the prodromal phase, and is likely the optimal period in which to administer therapies. However, most research utilizing animal models of parkinsonian motor impairments investigates circuit dysfunction only in late stages of depletion, after severe motor dysfunction has already occurred. These animal models have greatly advanced our understanding of the synaptic and circuit-level changes present in massively dopamine depleted animals, but we still know very little about the progression of circuit dysfunction, or compensatory plasticity leading up to the appearance of motor impairments, an understanding that may be critical to halting disease progression before it becomes incurable. The primary goal of the proposed research is to study the progression of circuit dysfunction and compensation leading up to the appearance of motor deficits using a novel dopamine depletion paradigm where the onset and progression of dopamine loss can be tightly controlled. In Aim 1, we will conduct a nonbiased, high throughput screen for brain areas showing differential activation in mice gradually depleted over weeks to months, relative to acutely depleted mice. Brain areas showing differential activity in acutely vs. gradually depleted animals will identify potential sits of compensatory plasticity, providing a foundation for future studies of the cellular and synaptic mechanisms of network adaptations during prodromal PD. In Aim 2, we will validate our model by comparing patterns of brain activity in gradually depleted mice to those observed in an established genetic model of PD, Thy1-?Syn, where ~40% of dopamine is lost by age 14 months. Brain areas showing common changes across both models will reveal the most promising sites of disease-relevant plasticity. Finally, in Aim 3, we will use cutting-edge electrophysiological approaches to record neural activity in candidate brain areas over the duration of our gradual depletion paradigm. These experiments will identify neural correlates of network compensation leading up the appearance of motor deficits. Combined, these results will provide novel insights into the location and progression of compensatory plasticity during prodromal PD, and will lay the foundation for future studies of the cellular and synaptic basis of adaptive plasticity in disease.

Further information available at:

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