A novel dual hit model of environmental risk factors for Parkinsons Disease

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Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is devastating neurological disorder that affects ~7 million people globally.41 Its etiology is unclear, but both genetic and environmental factors are contributors. Gut dysfunction may be involved; e.g., there is an upregulation/aggregation of a-synuclien (a-syn) in the enteric nervous system prior to a clinical diagnosis of PD. As aggregated a-syn within nigral dopaminergic neurons is a brain hallmark of

those who die with PD, gut a-syn may provide a `preclinical' biomarker for this disease. Abuse of the psychostimulant methamphetamine (meth) increases the chance of subsequently developing PD above non-abusers by 76%.8,9 Given that the number of meth users worldwide has recently surged to 33 million,56 these findings predict that the incidence of PD may also surge in the near future, especially in rural regions where meth is a popular abused drug. The biological link between meth abuse and PD is not known and thus therapy that reduces this risk does not exist. The link is difficult to study in humans due in part to the lengthy delay that ofte occurs between meth abuse and the diagnosis of PD. To help decifer the link, we will study a rat model of human drug-taking for which we are experts, meth self-administration (SA). We have revealed that meth SA results in mild `subclinical' PD-like pathology in the gut and brain. To indicate if meth abuse can promote the development of PD, we will challenge these rats with a sub-threshold environmental insult (i.e., low doses of rotenone) that when sufficiently robust, can induce PD-like pathology. The overall objective of this R21 proposal is to identify gut/brain pathological factors that underlie the increased risk to develop PD that are imposed by meth abuse. The central hypothesis is that meth SA renders animals vulnerable, so that a mild environmental insult that normally would not result in PD-like state is now sufficient to induce PD-like motor deficits, and PD-like brain and gut pathology. We predict that discovering proteins engaged in this potentiation will provide insights for biomarkers and therapeutic targets. This hypothesis will be tested in two Specific Aims. For Aim 1, we will use rats to determine rotenone treatments that induce PD-like motor deficits and tissue pathology as well as one that is sub-threshold to these effects. We will measure factors that are altered by meth and rotenone, e.g., dopaminergic lesions, mitochondrial stress, and a-syn. In Aim 2, we will determine if meth SA increases vulnerability for PD-like consequences. Accordingly, we will ascertain if a sub-threshold dose of rotenone in rendered sufficient in meth SA rats to induce PD-like motor deficits and brain/gut pathology. The proposed research is innovative for the studies present a new and substantially different way of mechanistically linking meth abuse and PD. The research is significant because it will substantially enhance our understanding of meth abuse as a risk factor for PD. Outcomes will form the foundation of an R01 application for multidisciplinary, mechanistic evaluations of meth exposure that enhance the vulnerability for developing PD and will determine which mechanisms have potential as therapeutic targets.

Further information available at:

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