Toxicant-induced synaptic dysfunction and neurotoxicity in Parkinson disease

https://neurodegenerationresearch.eu/survey/toxicant-induced-synaptic-dysfunction-and-neurotoxicity-in-parkinson-disease/

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Contact information of lead PI
Country

USA

Title of project or programme

Toxicant-induced synaptic dysfunction and neurotoxicity in Parkinson disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 790,255.96

Start date of award

09/09/2016

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
DESCRIPTION (provided by applicant): Our long term goal is to study the mechanisms of neurodegeneration induced by environmental toxicants, genetic mutations and potential gene-environment interactions to gain insights into the pathogenesis of Parkinson’s disease (PD). Advances in the genetics of PD have highlighted the critical role of mitochondrial dynamics (fission / fusion / movement) in neuronal function and survival. However, because monogenic

familial PD represents only a small fraction of PD cases, it is critical to determine whether perturbed mitochondrial dynamics also plays a role in the nigrostriatal damage induced by environmental neurotoxicants. Most of these exogenous toxic molecules cause mitochondrial dysfunction either directly by blocking mitochondrial respiration, or indirectly through oxidative stress. Based on our preliminary data, this proposal will utilize two complementary toxicant-based animal models of nigrostriatal neurodegeneration: A) The herbicide paraquat (PQ) induces cell death primarily through oxidative stress. B) The pesticide/insecticide rotenone directly inhibits mitochondrial function. We hypothesize that whether excessive mitochondrial fission and dysfunction is induced directly by blocking mitochondrial respiration (rotenone) or indirectly by oxidative stress (PQ), promoting mitochondrial fusion will attenuate pre-synaptic dysfunction and neurotoxicity seen in these animal models. In Aim 1, we will investigate the impact of promoting mitochondrial fusion in the PQ mouse and rotenone rat models. Because PQ does not induce striatal damage in regular mice, we will use our novel mutant mice with deletion of the organic cation transporter 3 (Oct3-/-) to create a PQ animal model with damage in both nigra and striatum, as well as to enhance relevance to human gene-environment interactions because OCT3 variants have been associated with PD. Small molecule and gene-based approaches will be used for manipulation of mitochondrial fission/fusion machinery. Both neurorestorative and neuroprotective effects of these strategies will be determined in animals with pre-existing lesions and with active neurodegeneration. Striatal mitochondrial function, evoked striatal dopamine release in freely moving animals, synaptic function using electrophysiology, motor function and the integrity of the nigrostriatal pathway will be analyzed. In Aim 2, we will investigate the mechanisms by which PQ and rotenone induce mitochondrial fission and why blocking this process is protective. Where relevant, both animal models and cell cultures will be used. A wide range of state-of-the art equipment/techniques such as 3-dimensional electron microscopy, laser capture microdissection, the Seahorse extracellular flux analyzer and amperometry will be used to quantify alterations in levels of proteins/genes of interest specifically in nigral dopaminergic neurons, mitochondrial trafficking/morphology/function and synaptic density/function. Accomplishment of these aims will provide critical information regarding how toxic insults impact nigrostriatal pathway through perturbed mitochondrial dynamics and offer insights into a potential novel therapeutic target for PD.

Lay Summary

PUBLIC HEALTH RELEVANCE: In the United States alone, about one million people have Parkinson’s disease (PD) and 50-60,000 new cases of PD are diagnosed each year. The causes of PD in most of these cases remain unknown; however, environmental factors have been implicated. The focus of this grant is of two-fold: First, to elucidate the mechanisms by which exogenous environmental relevant toxicants induce neurotoxicity through perturbed mitochondrial function and second, to identify potential novel therapeutic strategies for PD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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