Vesicular modulation of dopamine neuron toxicity

https://www.neurodegenerationresearch.eu/survey/vesicular-modulation-of-dopamine-neuron-toxicity/

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Country

USA

Title of project or programme

Vesicular modulation of dopamine neuron toxicity

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NIH (NINDS)

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17/11/2014

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

dopaminergic neuron, neurotoxicity, Dopamine, Parkinson Disease, Polychlorinated Biphenyls

Research Abstract

DESCRIPTION (provided by applicant): A major feature of Parkinson’s disease (PD) is the loss of dopamine-producing neurons in the substantia nigra pars compacta and the concomitant loss of dopamine in the striatum. While multiple processes likely contribute to the loss of dopamine

neurons, we argue that disruption of the proper storage and release of dopamine from vesicles plays a key role. This theory is supported by the literature, which demonstrates that improper storage of dopamine causes the formation of oxidative dopamine byproducts and toxic aldehydes that damages neurons. Evidence from genetic and toxicological studies of PD demonstrates that many insults converge on the dopamine vesicle to exert their deleterious effects. We hypothesize that vesicular function mediates dopamine neuron toxicity, such that increasing vesicle function will enhance dopamine storage and release and confer resistance to neurotoxicants, while decreasing vesicle function will have the opposite effect. Our laboratory has generated and characterized two unique mouse lines that allow us to test this hypothesis: a bacterial artificial chromosome-based transgenic mouse that overexpresses VMAT2 (VMAT2-HI) and a genetic knockout of the synaptic vesicle glycoprotein 2C (SV2C-KO), which was recently implicated in Parkinson's disease pathogenesis. Here, we provide preliminary data that clearly demonstrate that increased vesicular function is beneficial to the dopamine system and that SV2C is a novel regulator of dopamine uptake and release. Together, these findings provide the basis for the following aims. Aim 1: To determine the effects of variable VMAT2 or SV2C expression on vesicular dopamine storage and release dynamics. We will determine how these genetic manipulations alter vesicular dynamics, including the readily releasable pool. Aim 2: To determine if altered vesicular storage and release alters vulnerability of dopamine neurons in a model of PD. We determine the effect of reduced SV2C or increased VMAT2 on MPTP toxicity in aged mice, a classical and well-established model. Aim 3: To determine if altered vesicular storage and release of dopamine influences vulnerability to the PD-related toxicity of polychlorinated biphenyls (PCBs). We expect that our mice will show an inverse correlation between vesicle function and PCB-induced. In addition to the novel mouse lines generated in our laboratory we will use a suite of cutting-edge techniques in our studies, including optogenetic stimulation, fast-scan cyclic voltammetry, in vivo microdialysis, and CLARITY. Completion of these aims will establish a pivotal concept in neuroprotection: increasing vesicle function improves neurotransmitter signaling and opposes dopamine neuron toxicity. This suggests that modulation of synaptic vesicle function represents an innovative and unexplored opportunity for addressing dopamine neuron dysfunction and provides a foundation for new therapeutic approaches.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson's disease (PD) afflicts over one millions U.S. citizens and is caused by a combination of environmental and genetic factors. This proposal will examine how persistent environmental chemicals disrupt key processes of dopamine function, which may contribute to the development of PD. The results of these studies may provide a foundation for new approaches to prevent or treat the disease.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:

2016

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