Dopamine modulation of synaptic plasticity and integration in the striatum

https://www.neurodegenerationresearch.eu/survey/dopamine-modulation-of-synaptic-plasticity-and-integration-in-the-striatum/

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USA

Title of project or programme

Dopamine modulation of synaptic plasticity and integration in the striatum

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,627,105.50

Start date of award

01/04/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Synaptic plasticity, Corpus striatum structure, Dopamine, Synapses, Parkinson Disease

Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a debilitating neurodegenerative disorder that disrupts proper motor movement and behavior. Motor

movement is regulated by the striatum, which integrates excitatory inputs in the form of glutamate from the cortex and thalamus. While it is known that excitatory inputs to the striatum are specifically affected in PD, it has been difficult to precisely parse out whether cortical or thalamic inputs are responsible for these aberrant adaptations. Recent methodological advances in the field now provide the unique opportunity to directly examine if cortical and thalamic excitatory inputs are differentially modulated in PD, and what the mechanisms of these changes are. In this proposal, we employ the use of genetically modified mice and virus injections to allow for selective expression of blue-light activated channels (channel rhodopsin) in either corticostriatal (CS) or thalamostriatal (TS) terminals to the striatum. By simultaneously activating specific excitatory terminals and performing whole-cell patch clamp on identified principle striatal cells, our experiments will provide for a high-resolution assessment of the differential effects of CS and TS activation on striatal neurons. Combined with 2-photon laser microscopy, calcium imaging, glutamate uncaging and mouse genetics, this proposal aims to provide a unique, multi-faceted approach to study the excitatory connections in the basal ganglia, and the mechanisms of how PD states alter these connections. Based on our compelling preliminary findings, we propose the following three specific hypotheses: 1) The long-term plasticity of glutamatergic synapses in the striatum are differentially regulated based on pre-synaptic cell type (CS vs TS) and not post-synaptic cell targets, 2) CS and TS terminals input onto different regions of striatal neuron dendrites, causing for differential non-linear integration, and 3) Activation of different DA receptors and chronic dopamine depletion will result in bi-directional modulation of synaptic integration through specific downstream pathways. Our novel findings on synaptic plasticity and non-linear integration suggest that the study of striatal input compartmentalization is critical in understanding normal and aberrant striatal function. These studies will close this gap in our knowledge of striatal integration and create a new window into our understanding of PD, potentially providing better tools and novel therapeutic targets for the disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) affects 7-10 million people worldwide, and its debilitating motor disturbances are attributed to abnormal striatal excitatory transmission. While it is known that dopamine loss in PD changes excitatory integration within the motor nuclei of the brain, this proposal harnesses powerful new technologies to examine specifically which excitatory inputs are affected and precisely how they are altered. Results from these studies aim to create a clearer picture of how PD alters the brain, ultimately providing potentially new therapeutic avenues for the disease.

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

Database Tags:
N/A