Dopamine-Induced Striatal Synaptic Plasticity

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Country

USA

Title of project or programme

Dopamine-Induced Striatal Synaptic Plasticity

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,620,722.94

Start date of award

19/10/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

hyperpolarization-activated cation channel, Synaptic plasticity, Corpus striatum structure, Dopamine, Acetylcholine

Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is caused by the degeneration of midbrain dopamine (DA) producing cells and results in motor and non-motor impairments. Congenital and acquired forms of Parkinsonism, caused by inherited defects in DA synthesis or brain injury and disease, also produce profound immobility and disability. The

hallmarks of Parkinsonism include bradykinesia, resting tremor, and postural instability that stem from a reduced supply of DA from the midbrain to the motor striatum, a brain structure required for motor control and cue-dependent learning. In turn, this loss of striatal DA prevents the normal spike-timing of the sparse population of tonically-active acetylcholine (ACh)-releasing interneurons (TANs) that provide the sole source of striatal ACh and are essential to many aspects of brain function. The resulting change in DA-ACh reciprocity contributes to the clinical symptoms and signs of Parkinsonism. Treatments that enhance DA availability or activate DA receptors incompletely restore motor function, become less successful over time, and are limited in efficacy due to induction of impulse control disorders and dyskinesias that are caused by neuroplasticity in TANs. Therefore, the precise targeting of ACh-releasing cells, while correcting for the decline in DA, would improve treatment and disability in Parkinsonism. TANs have been implicated in the pathophysiology of PD and treatment-dependent dyskinesias, but the mechanism whereby TANs participate in these movement disorders remains unclear. In this competing continuation, we will pursue an integrated series of molecular, electrophysiological, optical, and behavioral experiments in genetically engineered DA-deficient mice. Our goal is to show how DA deficiency promotes a long-lasting change in ACh release from TANs which contributes to motor features of Parkinsonism. We will test the hypotheses that 1) DA deficiency reduces autonomous firing in TANs by altering hyperpolarization-activated cation (HCN) channels that re-polarize the cell toward its resting membrane potential following each action potential; 2) DA replenishment provokes a paradoxical increase in TAN activity through DA and ACh auto-regulatory signal processing; and 3) DA deficiency produces plasticity in excitatory thalamostriatal inputs that contributes to the physiological and behavioral change. The central role of ACh in normal and abnormal movements has only recently been identified, despite clues from decades of empirical findings using anticholinergics. We now know that this is an important downstream response to DA deficiency. We will use innovative ways to measure transcribed mRNA and novel optical approaches to directly address alterations TAN function. These experiments provide a targeted molecular and circuit-level approach to cell-type specific effects which previous methods were not able to discern. By the end of this work, we will know the molecular and physiological mechanisms that regulate striatal ACh in DA deficiency and we will uncover pharmacological treatment targets that will improve DA-ACh reciprocity and motor function in children and adults with Parkinsonism.

Lay Summary

PUBLIC HEALTH RELEVANCE: The striatum is a cluster of cells within the brain that helps execute normal movements and establishes goal directed behaviors. The symptoms of Parkinson’s disease and other debilitating neuropsychiatric disorders are caused by abnormal dopamine and acetylcholine availability in the striatum. Our investigations will determine how dopamine can trigger lasting changes in acetylcholine and will generate new pharmacological targets and treatments for Parkinsonism and the dyskinetic motor movements that accompany treatment.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:

Parkinson's disease & PD-related disorders

Years:
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