Synaptic Transmission, Plasticity and Integration in the Subthalamic Nucleus

https://neurodegenerationresearch.eu/survey/synaptic-transmission-plasticity-and-integration-in-the-subthalamic-nucleus/

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Country

USA

Title of project or programme

Synaptic Transmission, Plasticity and Integration in the Subthalamic Nucleus

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,464,558.72

Start date of award

01/04/2001

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
DESCRIPTION (provided by applicant): The debilitating motor symptoms of akinesia, bradykinesia and rigidity in Parkinson’s disease (PD) are intimately related to changes in the frequency and pattern of neuronal activity in the reciprocally connected GABAergic external globus pallidus (GPe) and glutamatergic subthalamic nucleus (STN) and associated cortico-basal ganglia-thalamocortical networks. In idiopathic and experimental PD the GPe and STN

exhibit hypo- and hyperactivity, respectively, and abnormal synchronous, rhythmic, burst firing. Following acute loss of substantia nigra dopamine neurons in experimental models of PD abnormal STN activity emerges slowly and intensifies gradually until it reaches a stable maximum after 2-3 weeks. This process suggests that adaptive changes in cellular and network properties contribute to the development of parkinsonian STN activity. Because the GPe potently regulates the frequency and synchronization of STN activity and can generate rebound burst firing in the STN, GPe-STN transmission was compared in control and 6-hydroxydopamine-lesioned rodents using electrophysiological, molecular and anatomical approaches. These studies revealed that 2-3 weeks after loss of dopamine the GPe-STN projection had strengthened considerably through proliferation of synaptic connections. This alteration could therefore be a major contributor to the emergence of abnormal GPe-STN activity in PD. Here we propose to study the timecourse, nature, underlying mechanisms and functional consequences of alterations in GPe-STN transmission that follow the loss of dopamine. We propose to apply cellular physiology to measure GPe-STN synaptic function and dysfunction; anatomical approaches to define the structural and molecular bases of GPe-STN synaptic plasticity; 2-photon laser scanning microscopy and optogenetics to define the sources of Ca2+ that trigger synaptic plasticity; viral vector, molecular and biochemical approaches to define the underlying molecular mechanisms and enable us to manipulate GPe-STN transmission. We propose 4 Specific Aims: Aim 1. Determine the timecourse and nature of alterations in GPe-STN synaptic transmission in experimental PD. We hypothesize that alterations in GPe-STN transmission are correlated with the development of parkinsonian STN activity; Aim 2. Determine the triggers leading to potentiation of GPe-STN synaptic transmission in experimental PD. We hypothesize that hyperactivation of STN glutamate receptors and/or Cav channels leads to the potentiation of GPe-STN synaptic transmission in experimental PD; Aim 3. Determine the cellular and molecular mechanisms underlying the potentiation of GPe-STN synaptic transmission. We hypothesize that hyperactivation of STN glutamate receptors and/or hyperactivity of STN neurons leads to an increase in intracellular Ca2+, which activates signaling cascades that mediate synaptic potentiation and proliferation; Aim 4. Determine the impact of chronic dopamine depletion on action potential-dependent inhibition of STN neurons. We hypothesize that the autonomous activity of GPe-STN neurons is not altered by dopamine depletion and that GPe-STN inhibition is increased through potentiation of GPe-STN connectivity.

Lay Summary
In Parkinson’s disease a small brain region called the subthalamic nucleus exhibits a characteristic, abnormal pattern of activity, which if corrected by medication or deep brain electrical stimulation greatly improves movement. The emergence of this abnormal pattern of activity is associated with alterations to the inputs of the subthalamic nucleus. We propose to study the mechanisms underlying these alterations and to determine whether they can be prevented for therapeutic benefit.

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