Neuronal diversity in globus pallidus: from molecular profiling to function in voluntary movement

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Keywords
Research Abstract

Parkinson’s disease (PD), which is caused by the degeneration of dopamine neurons in the substantia nigra pars compacta affects more than 6.3 million people worldwide and is characterized by bradykinesia, rigidity and resting tremor. The Basal Ganglia (BG) are a group

of subcortical nuclei involved in motor control and movement related disorders. A model proposed more than 20 years ago has greatly improved our understanding of the anatomo-functional organization of this macrocircuit in health and disease states. This model posits that cortical information is processed by this network via two distinct routes, namely the “direct” and “indirect” pathways which exert opposite effect on motor execution. The direct pathway involves GABAergic striatal projection neurons, called medium spiny neurons (MSN) which directly inhibit the output of the network, namely the substantia nigra pars reticulata (SNr) and the internal portion of the globus pallidus (GPi), which release the motor thalamus for their constant inhibitory drive and thus favor movement execution. On the other hand, the indirect pathway involves MSN neurons which project to the external portion of the globus pallidus (GPe). Striatal inhibition of the GPe favor the disinhibition of the subthalamic nucleus, the only glutamatergic structure of the network, which thus excites the SNr/GPi complex, promotes inhibition of the motor thalamus and prevents motor programs execution.
In the model, the GPe, is considered as a monolithic entity which simply relays striatal information downstream to the output of the network. Our group has shown the existence of two molecularly distinct neuronal populations in GPe of dopamine-intact rat, called prototypic (PROTO) and arkypallidal (ARKY) GPe neurons. These results suggest a division of labor and call for a re-evaluation of the place of this nucleus in the BG circuitry, its role in the orchestration of both normal and abnormal activities in the BG and ultimately of its function in the control of voluntary movement.
The main objective of NEURODIVGP is to demonstrate a correlation between the presence of a single specific neuronal marker and the electrophysiological properties of GPe neurons in order to define specific subpopulations and understand their function in the control of voluntary movement. For success, anatomical experiments, in vitro electrophysiology combined with optogenetics, neuronal track-tracing studies and in vivo electrophysiology coupled with optogenetics in anaesthetized and behaving animals will be carried out. The use of cre-lox strategy (cre-on and cre-off expression) in transgenic mice is the most suitable approach to specifically dissect the role of the main pallidal neuronal populations in the orchestration of motor behavior. These original developments will involve a close relationship between the groups of Drs J. Baufreton (coordinator), N. Mallet (partner #1) and C. Herry (partner #2).
We propose to complete 5 specific aims (SA) to elucidate neuronal diversity in GP and its role in normal and pathological operations of the BG network:
SA 1: Determine the molecular specifications of PROTO and ARKY populations of GPe neurons and the correlation with specific intrinsic electrophysiological properties
SA 2: Unravel the functional connectome of GP-TI and GP-TA neurons, to reveal the specific wiring of these 2 populations with the other nuclei in BG
SA 3: Determine the consequences of dopamine-depletion on the excitability of GP-TI and GP-TA neuronal populations
SA 4: Determine the role of GP-TI and GP-TA in the propagation of neuronal oscillatory activity in the BG network in healthy and disease states
SA 5: Manipulate the neuronal activity of GP-TI and GP-TA neurons in vivo to understand their role in motor behavior and to restore movement in animal models of Parkinson disease

Lay Summary
Further information available at:

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