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Review

From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson disease

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Abstract

Despite remarkable advances, the relationship between abnormal neuronal activity and the clinical manifestations of Parkinson disease (PD) remains unclear. Numerous hypotheses have emerged to explain the relationship between neuronal activity and symptoms such as tremor, rigidity and akinesia. Among these are the antagonist balance hypothesis wherein increased firing rates in the indirect pathway inhibits movement; the selectivity hypothesis wherein loss of neuronal selectivity leads to an inability to select or initiate movements; the firing pattern hypothesis wherein increased oscillation and synchronization contribute to tremor and disrupt information flow; and the learning hypothesis, wherein the basal ganglia are conceived as playing an important role in learning sensory-motor associations which is disrupted by the loss of dopamine. Deep brain stimulation (DBS) surgery provides a unique opportunity to assess these different ideas since neuronal activity can be directly recorded from PD patients. The emerging data suggest that the pathophysiologic changes include derangements in the overall firing rates, decreased neuronal selectivity, and increased neuronal oscillation and synchronization. Thus, elements of all hypotheses are present, emphasizing that the loss of dopamine results in a profound and multifaceted disruption of normal information flow through the basal ganglia that ultimately leads to the signs and symptoms of PD.

Keywords: Parkinson's disease; Basal ganglia; Physiology; Human; Deep brain stimulation; Intraoperative; Oscillations

Contents

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1. Introduction

The basal ganglia (BG) are a group of subcortical nuclei involved in multiple-partly segregated parallel loops that modulate cortical activity (Alexander et al., 1986; Alexander and Crutcher, 1990; Alexander, 1994; Hoover and Strick, 1999). These loops share some common features in that they begin with convergent input from the cortex to the striatum (caudate and putamen) and then proceed through different pathways to the globus pallidus internus (GPi) or the substantia nigra pars reticularis (SNpr), which are the output nuclei of the basal ganglia. From there, the output nuclei project to the thalamus or other brainstem nuclei. A number of circuits have been characterized including oculomotor, prefrontal, limbic, and motor loops (Alexander and Crutcher, 1990). The nuclei involved in the motor loop include the striatum, globus pallidus, substantia nigra, subthalamic nucleus (STN), and the motor nuclei of the thalamus.

Concurrent with the tremendous increase in knowledge regarding basal ganglia structure and function, surgery for the treatment of refractory PD has undergone a dramatic evolution over the past 15 years. Laitenen's reintroduction of pallidotomy was followed by its widespread use for about 10 years (Laitinen et al., 1992; Alkhani and Lozano, 2001). More recently, pallidotomy has been almost completely replaced by subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) (Limousin et al., 1995; DBS Study Group, 2001; Krack et al., 2003; Rodriguez-Oroz et al., 2005). The major appeal of DBS therapy is that it is adjustable, reversible, and demonstrates therapeutic efficacy for many years (Rodriguez-Oroz et al., 2005). Consequently, in the United States, DBS therapy has almost completely replaced lesional surgery for the treatment of refractory PD (Eskandar et al., 2003).

From a scientific perspective, microelectrode recordings performed during DBS surgery provide a unique opportunity to directly record neuronal activity from the STN or GPi of human patients with PD. While recording from human subjects has limitations, it provides insights that are not available in other ways. The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) animal model of Parkinsonism has been invaluable in advancing our understanding of PD. However, the model is not a perfect match for idiopathic PD, and primates treated with MPTP are usually unable to perform complex behavioral tasks (Raz et al., 2000). This makes it difficult to evaluate neuronal activities during complex behaviors. In contrast, human subjects can be easily trained to perform intraoperative tasks and represent the true disease state.

This review will briefly present the current models of BG function and how they account for the symptomatology of PD. It will then outline the implications of intraoperative findings for specific models of BG function. What will become apparent is that no one-model adequately describes all the features of the basal ganglia dysfunction in PD. Rather, dopamine plays a critical role in multiple facets of basal ganglia function, and the loss of dopaminergic neurons results in derangements of firing rates, neuronal selectivity, and firing patterns of BG neurons, all of which contribute to the clinically observed manifestations of the disease.

2. Principal models

2.1. The standard "antagonist balance" model

The Standard Model suggests that there are two pathways through the BG—the direct and indirect pathways. Based on the polarities of the known connections, the direct pathway is thought to facilitate movements while the indirect pathway is thought to suppress movements (Fig. 1) (Albin et al., 1989; DeLong, 1990). The model posits that the effect of dopamine is different in the two pathways due to the presence of different dopaminergic receptors in striatal neurons (Albin et al., 1989). Dopamine is hypothesized to excite D1 receptors of the direct pathway

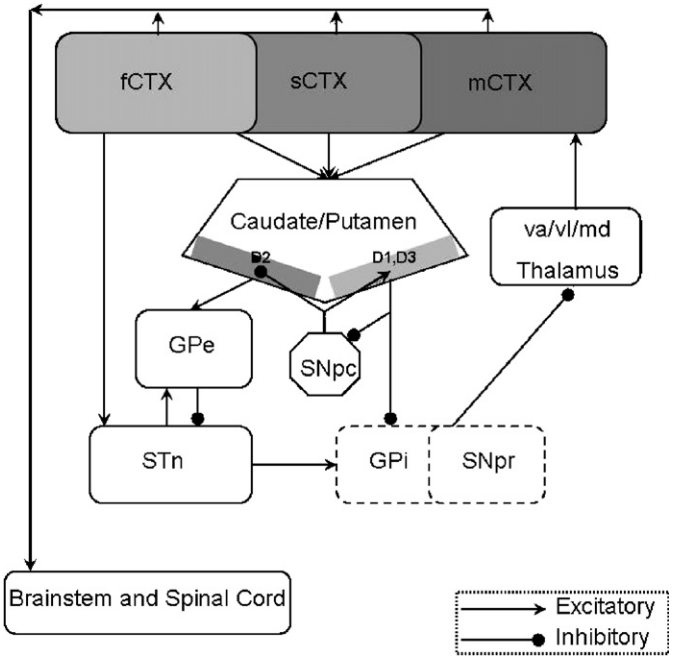

Fig. 1. A general schematic of the basal ganglia circuitry. fCTX = frontal cortex; sCTX = sensory cortex; mCTX = motor cortex; GPe = globus pallidus externus; GPi = globus pallidus internus; STN = subthalamic nucleus; SNpc = substantia nigra pars compacta; SNpr = substantia nigra pars reticularis; va = ventral anterior; vl = ventral lateral; md = medial dorsal.