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Basal Ganglia Mechanisms in Action Selection, Plasticity, and Dystonia

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Abstract

Basal ganglia circuits are organized to selected desired actions and to inhibit potentially competing unwanted actions. This is accomplished through a complex circuitry that is modified through development and learning. Mechanisms of neural plasticity underlying these modifications are increasingly understood, but new mechanisms continue to be discovered. Dystonia, a movement disorder characterized by involuntary muscle contractions that cause abnormal postures and movements. Emerging evidence points to important links between mechanisms of plasticity and the manifestations of dystonia. Investigation of these mechanisms has improved understanding of the action of currently used medication and is informing the development of new treatments.

Introduction

Vertebrate animals have complex motor repertoires that increase in complexity throughout phylogeny. The motor repertoire in human beings is especially complex. As the motor, and indeed the entire behavioral repertoire becomes more complex, the potential for conflict among competing movements or behaviors increases in a non-linear manner. Effective execution of volitional movements requires efficient selection of which action(s) to perform. Perhaps more important is the efficient simultaneous inhibition of competing actions. During development from the neonatal period, through childhood and adolescence, and continuing through adulthood, new motor patterns emerge and new skills are learned. Each newly acquired skill creates an additional potential competitor to already existing patterns, with a plethora of new potential conflicts. Thus, the ability to select and maintain motor patterns while simultaneously inhibiting competing patterns must also change through development and learning.

Action selection and inhibition occurs in a context-dependent and rule-based manner⁽¹⁾. However, the rules sometimes change and motor behavior must adapt to those changes⁽²⁾. For example, someone who has grown up in North America has learned to look to the *left*

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Competing Interests Statement

The author has no relevant competing interests.

for cars before crossing the street. If that person travels to the United Kingdom, she must now suppress that automatic response and look to the *right* for oncoming traffic. The newly learned pattern must be suppressed again in favor of the previously learned pattern when she returns to North America. Thus, efficient switching among actions and among action-rule associations is also required⁽³⁾.

Basal Ganglia Circuits in Selection and Inhibition of Competing Actions

The basal ganglia are thought to play a central role in selection and inhibition of competing actions^(4–8). This concept is informed by the organization of basal ganglia circuits, the action of individual neurons and groups of neurons within those circuits, and the effect of lesions and disease affecting the basal ganglia on motor control and behavior^(7–10).

The basal ganglia include the striatum (caudate, putamen, nucleus accumbens), the subthalamic nucleus (STN), the globus pallidus (internal segment - GPi; external segment - GPe), and the substantia nigra (pars compacta – SNpc; and pars reticulata - SNpr). Each nucleus has specific cell types, receives different patterns of input, and has different synaptic organization⁽⁸⁾. The striatum and STN receive the majority of the inputs from outside the basal ganglia, most of which emanate from the cerebral cortex. The striatum has the most complex synaptic organization of the basal ganglia components, and it is within the striatum that most plasticity probably occurs. The bulk of outputs from basal ganglia arises from GPi and SNpr and are **inhibitory** to thalamic nuclei, superior colliculus, and the pedunculopontine area of the brainstem. Thus, the output of the basal ganglia is inhibitory to posture and movement pattern generators. The inhibitory output neurons fire tonically at high frequencies (70 – 80 spikes/s at rest)⁽¹¹⁾. Thus, the output of the basal ganglia is analogous to a braking system (Mink, 1996).

When a desired action is initiated by a particular motor pattern generator in the cerebral cortex or brainstem, basal ganglia output neurons projecting to that generator decrease their discharge, thereby removing tonic inhibition and “releasing the brake” on that generator. Basal ganglia output neurons projecting to other motor pattern generators, that are involved in competing actions, increase their firing rate and thereby apply the “brake” to those generators. In this manner, competing actions are prevented from interfering with the one(s) selected. The result is the focused selection of desired actions and surround inhibition of competing actions. Disruption of the ability to facilitate desired movements and inhibit unwanted movements results in slow voluntary movements (parkinsonism), abnormal involuntary movement (chorea, dystonia, tics), or both^(7, 9, 12).

Historically, much of the focus of basal ganglia research has been on motor control and the movement disorders resulting from basal ganglia injury. However, there is no doubt that basal ganglia circuits are also critically involved in cognitive and affective processes. These topics are beyond the scope of this review, but are the subject of several recent studies and reviews^(13–15).

Basal Ganglia Plasticity and Learning in Motor Control

There is substantial for involvement of the basal ganglia in different types of learning⁽¹⁶⁾. Most work has focused on two areas: the learning of goal-directed actions and the learning of habits⁽¹⁷⁾. The concept of goal-direct learning requires reinforcement of the result of the action by some form of reward signal. Habit learning is the establishment of more automatic responses independent of contingent reward. There is evidence in the rodent for segregation of circuits for goal-directed learning from those involve in habit formation within the striatum^(18, 19). There is also evidence for a role of the basal ganglia in goal-directing learning that ultimately leads to the formation of habits and the performance of behavioral routines once they are learned^(18, 20, 21).

The synaptic mechanisms underlying plasticity in striatum are several and are complex. They include modulation of cortio-striatal synaptic strength by dopamine, acetylcholine, and other neuromodulators, calcium-mediated changes in synaptic efficacy, and other mechanisms of long-term potentiation and long-term depression including those mediated by coordinated activity of inputs to striatal project neurons^(22–24). In addition to striatal projection neurons, there is evidence for use-dependent modulation of striatal interneuron activity. Among the most important mechanisms, and those most relevant for clinical care, are those modulated by dopamine, acetylcholine, or both.

The effect of dopamine on the strength and plasticity of striatal projection neuron response to cortical inputs is one of the most studied processes in the basal ganglia. From studies of dopamine receptor genetic knock-out mice^(25, 26), to more recent optogenetic studies of selective activation⁽²⁷⁾ there have been consistent findings of an important function of dopamine in modulating synaptic plasticity. Nigrostriatal dopamine neurons fire in relation to behaviorally significant events and reward⁽²⁸⁾. The activity patterns of these neurons change as the task becomes learned and when novel stimuli or events are introduced. This behaviorally-contingent release of dopamine modifies the strength of corticostriatal synapses and changes the excitability of striatal projection neurons^(29–31).

Acting through muscarinic receptors, acetylcholine also plays an important role in the plasticity of striatal activity. Cholinergic interneurons fire in relation to behaviorally significant events^(32, 33) and have task-dependent influence on striatal projection neruons⁽³⁴⁾. They act in concert with the nigrostriatal dopamine system to influence the excitability and responsivity of the projection neurons⁽³⁵⁾. Activation of M1 muscarinic receptors leads to long-term potentiation of striatal projection neurons, which enhances performance of mice in a dorsolateral striatum-dependent learning task⁽³⁶⁾. Activation of M4 muscarinic receptors promoted long-term depression of corticostriatal glutamatergic synapses and blocks dopamine D1-receptor dependent long-term potentiation⁽³⁷⁾.

Aberrant Plasticity and Learning in Dystonia

Dystonia is a movement disorder characterized by involuntary, sustained or intermittent muscle contraction causing abnormal, often repetitive, movements, postures, or both⁽³⁸⁾. Dystonia results from multiple causes, but the clinical syndrome of dystonia has important

commonalities regardless of etiology. One characteristic clinical feature of dystonia is “task specificity”. Task specificity refers to the phenomenon that dystonic muscle contractions may occur in one task, but not in other tasks that use exactly the same muscles. For example, a patient may have difficulty walking forward but not backward. Or a patient with writer’s cramp may have difficulty writing, but not knitting or playing the piano. This phenomenon has led to the idea that dystonia might be due to aberrant use-dependent brain plasticity brought on by high repetition of highly skilled tasks^(39–41). A converse, but related idea is that individuals with dystonia have underlying aberrant neural plasticity that puts them at risk to develop dystonia in one or more body parts without the requirement for highly constrained repetition^(42–44). Regardless of whether aberrant plasticity results from the dystonia or whether aberrant plasticity is the underlying substrate for dystonia, a link between dystonia and abnormal neural plasticity is fairly well accepted.

In certain forms of dystonia, there is evidence for abnormal neural plasticity. In adult-onset focal dystonias, there is strong physiologic evidence for enhanced excitability^(44–46) or for loss of normal surround inhibition in motor cortex^(47–50), or both. Additionally, there is evidence that individuals who carry a gene mutation associated with development of dystonia but who *do not* manifest dystonia themselves, have impaired motor sequence learning⁽⁵¹⁾. Thus, abnormal neural plasticity is likely to be necessary, but not sufficient for the development of dystonia.

Additional data on neural plasticity in dystonia come from animal models of dystonia. In a transgenic knock-in rodent model of dystonia, there is consistent evidence for abnormal plasticity at corticostriatal synapses that relates to both dopaminergic and cholinergic mechanisms^(52–54). Those abnormalities can be reversed, at least in part, with M1 receptor blockade⁽⁵²⁾. In the *dtsh* hamster, a phenotypic model of paroxysmal dystonia, the M4-preferring antagonist tropicamide provided reduction in dystonic attacks either alone or in combination with the M1 antagonist, trihexyphenidyl⁽⁵⁵⁾. Finally, in a DYT11/SCGE mouse model of myoclonus-dystonia syndrome, there is impaired long-term depression at corticostriatal synapses that is restored after inhibition of adenosine 2A receptors⁽⁵⁶⁾. Thus, there is likely to be a variety of different mechanism underlying altered plasticity in different forms of dystonia. Each of these mechanisms is a potential therapeutic target.

In summary, the functions of basal ganglia in selection and inhibition of potentially competing actions are influenced by development and learning, often through use-dependent plasticity. The mechanisms underlying neural plasticity in the basal ganglia have been the target of much research and understanding is increasing substantially. These mechanisms are relevant for understanding the mechanisms of many forms of dystonia. Furthermore, they are promising targets for future therapy development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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