ANATOMY, PHYSIOLOGY, AND PHARMACOLOGY OF THE BASAL GANGLIA

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Voluntary movement is regulated by complex feedback loops that involve the cortex, the thalamus, and the basal ganglia; a group of five interconnected nuclei in the basal forebrain. The basal ganglia consist of the caudate and putamen, the internal and external segments of the globus pallidus (GPI and GPe), the subthalamic nucleus (STN), and the substantia nigra (SN). The caudate and putamen together constitute the striatum, the primary input structure of the basal ganglia. The striatum receives two major inputs, a massive excitatory glutamatergic input from most areas of the cerebral cortex, and a dopaminergic input from the substantia nigra pars compacta (SNC). In addition, the striatum receives inputs from the amygdala and thalamus (glutamate) and the raphe (serotonin). The principal output nuclei of the basal ganglia are the substantia nigra pars reticulata (SNr) and GPI (entopeduncular nucleus [EP] in rodents). The output nuclei of the basal ganglia, SNr and GPI, tonically inhibit the ventral anterior and ventral lateral motor nuclei of the thalamus, thereby reducing excitatory thalamic innervation of cortical motor areas. Movement occurs when the thalamus is disinhibited, facilitating excitation of cortical motor areas resulting in increased motor output to the brain stem and spinal cord.

Human movement disorders with underlying pathology in the basal ganglia provide the most compelling evidence supporting a role of the basal ganglia in regulating motor function. Two examples at the extremes of the continuum are Parkinson's disease with its severe hypokinesia and Huntington's disease with its choreiform-type hyperkinesia. The motor symptoms associated with these disorders are the consequence of the degeneration of specific populations of neurons in different basal ganglia.
structures: dopamine neurons of SNC in Parkinson’s disease\(^{34}\) and striatal output neurons in Huntington’s disease.\(^{46}\) Pathology within structures of the basal ganglia not only serves to highlight the contribution of this system in regulating motor function, but also provides the basis for a variety of animal models for these human diseases.\(^{15,65}\)

**BASAL GANGLIA CIRCUITRY**

An elegant model of basal ganglia circuitry, put forth a decade ago, posits that voluntary movement is regulated by the activity of two opposing pathways which connect the striatum to the output nuclei of the basal ganglia (SNr/GPi) (Figure 1).\(^{1,2}\) The “direct pathway” consists of a distinct population of striatal projection neurons, which send an inhibitory gamma-aminobutyric acid (GABA) projection directly to the SNr/GPi output nuclei. In contrast, the “indirect pathway” consists of a separate population of striatopallidal neurons, which send an inhibitory GABAergic projection to the GPe. These external pallidal neurons, in turn, send a GABAergic projection to the STN, which sends an excitatory glutamatergic projection to the SNr/GPi output nuclei. The SNr/GPi output nuclei send an inhibitory GABAergic projection to the motor nucleus of the thalamus, which sends an excitatory glutamatergic projection to cortical motor areas. The SNr also influences oculomotor function through projections to the superior colliculus and dorsal medial thalamus.\(^{45}\)

The influence of the direct and indirect pathways on cortical control of motor behavior can be predicted, based on the circuitry of the basal ganglia (see Figure 1). Activation of these two pathways exerts opposite effects on the activity of the output nuclei of the basal ganglia, and thereby produces antagonistic effects on thalamocortical activity.\(^{15,65}\) For example, activation of the direct pathway leads to GABA-mediated inhibition of SNr/GPi leading to an increase in motor behavior caused by disinhibition of the thalamus. In contrast, activation of the indirect pathway leads to GABA-mediated inhibition of the GPe, attenuating the activity of GABAergic pallidal neurons, thereby disinhibiting the STN. Disinhibition of the STN leads to glutamate-mediated excitation of the SNr/GPi, increased inhibition to the thalamus, and decreased motor activity. In summary, activation of the direct pathway inhibits SNr/GPi while activation of the indirect pathway excites SNr/GPi. Therefore, voluntary movement is mediated by a balance between the activity of these two opposing pathways which determines whether or not the basal ganglia issue instructions for motor activities to proceed.

Recent anatomical evidence supports an added degree of complexity of basal ganglia circuitry that extends beyond the direct and indirect pathways. Most notably, these findings highlight additional roles for two indirect pathway nuclei: the STN and GPe (see Figure 1). Current models of basal ganglia circuitry include a more independent role for the STN, since this nucleus also receives direct inputs from cortical motor areas, intralaminar thalamus, SNC, and raphe.\(^{49,66}\) The STN itself projects to the GPe, striatum, SNC, as well as projecting to the basal ganglia output nuclei, SNr/GPi.\(^{49,61}\) Recent evidence suggests that the GPe does not simply serve as a link between the striatum and the STN. The GPe itself sends direct projections to the GPe/SNr and the reticular nucleus of the thalamus,\(^{49,61}\) suggesting that this nucleus is in a position to regulate basal ganglia function through circuits that are distinct from the indirect pathway.

It is a matter of some controversy as to how synaptic information that passes through the basal ganglia is processed. One theory suggests that there is significant convergence of synaptic inputs, which results in a progressive funneling of information. There is a significant reduction in neuronal densities from the striatum (10^6–10^7 neurons) to the output nuclei GPe/EP (10^5–10^6 neurons),\(^{49,61}\) and this observation, together with the large dendritic arbors of pallidial neurons,\(^{52}\) lends support to the convergence of striatal inputs onto a limited number of postsynaptic neurons.\(^{49,61}\) However, a second theory suggests that synaptic information remains largely segregated and is processed by separate, parallel pathways within the basal

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**Figure 1.** The circuitry of the basal ganglia. A, Model of basal ganglia circuitry from 1990, which highlights the direct and indirect pathways. B, Current model of basal ganglia circuitry, which includes connections between GP, STN, and other nuclei. Projections from SNC and thalamus to STN are not shown. Shaded arrows = excitatory pathways; solid arrows = inhibitory pathways. SNC = substantia nigra pars compacta; GP = globus pallidus; STN = subthalamic nucleus; SNr/GPi = substantia nigra pars reticulata/globus pallidus internal segment; Glut = glutamate; DA = dopamine; ENK = enkephalin; SP = substance P. (Adapted from Burke RE, Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13:266, 1990; with permission from Elsevier Science).
This theory is supported by recent electrophysiologic evidence in primates using multiple simultaneous recordings of pallidal neurons. Dopamine denervation in these animals abolishes this segregated processing, thereby suggesting that dopamine plays a significant role in regulating the flow of information through the basal ganglia.

**BASAL GANGLIA PHYSIOLOGY**

The neurons in the basal ganglia display a range of basal physiologic firing rates and demonstrate distinct changes in neuronal firing relative to motor activity. Most striatal projection neurons display very low spontaneous activity with membrane potentials that fluctuate between a slightly depolarized “up-state” and a hyperpolarized “down-state”. Striatal neurons demonstrate significant increases in their firing rate prior to movement, caused by the release of glutamate from corticostriatal neurons. In contrast, pallidal neurons display one or two types of spontaneous bursting activity, with firing rates that either increase or decrease in relation to motor activity. Neurons in the STN display moderate basal activity and generally increase their firing rate prior to movement. Dopaminergic neurons of the SNc display low spontaneous activity, which is not correlated with motor activity. In contrast, neurons of the basal ganglia output nuclei, SNr/GPi, demonstrate high basal firing rates with excitatory drive from the STN. SNr/GPi neurons either increase or decrease their firing rate after movement has begun, supporting the notion that the output of the basal ganglia does not play a significant role in movement initiation. Furthermore, the electrophysiologic response of individual SNr/GPi neurons is often complex and likely reflects integration of synaptic information both from the direct and indirect pathways.

**NEUROTRANSMITTER AND RECEPTOR LOCALIZATION**

The primary neuronal cell type in the striatum is the medium spiny neuron, so named because of the size of its cell body (12–20 micrometers in diameter) and the presence of spines on its dendrites. These medium spiny neurons account for 90%–95% of striatal neurons, and constitute the striatal projection neurons. Other populations of striatal neurons include large, aspiny cholinergic interneurons, as well as separate populations of interneurons that contain GABA or the neuropeptide somatostatin. Staining for certain neurochemical markers results in the definition of two distinct anatomical compartments in the striatum: patches (striosomes) and matrix. High densities of mu opioid receptor binding and low levels of acetylcholinesterase staining define patches (striosomes), whereas the surrounding matrix is defined by high levels of the calcium binding protein, calbindin. Neurons in these compartments have distinct afferent and efferent relationships with other structures in the basal ganglia. For example, patch and matrix compartments receive cortical inputs from neurons that reside in separate zones of layer V with deeper neurons projecting to patches and more superficial neurons projecting to matrix. Likewise, separate zones of dopaminergic neurons in the SN project to patches and matrix and, in turn, striatal output neurons project to distinct regions in the SN, with the patch neurons projecting to SNc and matrix neurons projecting to SNr.

Both the direct and indirect striatal output pathways arise from separate populations of medium spiny neurons that share morphological similarities. All medium spiny neurons contain the inhibitory neurotransmitter GABA but each striatal output pathway co-expresses different neuropeptides. Direct pathway (striatonigral) neurons contain the neuropeptides substance P and dynorphin, while indirect pathway (striatopallidal) neurons contain enkephalin. These output neurons are evenly distributed throughout the striatum and to patch and matrix compartments. Medium spiny neurons also have extensive axon collaterals that are thought to participate in synaptic interactions both within and outside of the striatum.

Direct and indirect pathway neurons express different dopamine receptor subtypes, with D1 receptors localized to striatonigral neurons and D2 receptors localized to striatopallidal neurons. An estimated 5% of striatal projection neurons express both D1 and D2 receptors, but this low estimate has been the subject of controversy. D1 and D2 dopamine receptors have been cloned, but unlike D1 and D2 receptors they are not appreciably expressed in the dorsal striatum. Dopaminergic D1 and D2 receptor subtypes modulate striatal neuropeptide expression in opposite ways: D1 receptor subtypes with D1 stimulation necessary to maintain basal levels of substance P and dynorphin in striatonigral neurons, and D2 stimulation tonically inhibiting enkephalin synthesis. Conversely, depletion of striatal dopamine content by a neurotoxic lesion or treatment with dopamine antagonists decreases levels of substance P and dynorphin but increases enkephalin levels in the striatum.

Striatal neurons express a variety of different neurotransmitter receptors, which reflect the neurochemical diversity of the inputs to this structure. Both NMDA and non-NMDA ionotropic glutamate receptors, as well as several subtypes of metabotropic glutamate receptors, are expressed by striatal neurons with variations observed in the type of ionotropic receptor subunit or metabotropic receptor subtype expressed in medium spiny neurons and striatal interneurons. Three subtypes of muscarinic cholinergic receptors are expressed in striatum. The m1 and m4 receptors are found in both cholinergic interneurons and medium spiny neurons, with only 40% of striatopallidal neurons expressing the m4 receptor. Cholinergic interneurons express m2 muscarinic receptors, as well as D2 dopamine receptors and, to a smaller extent, D1 dopamine receptors. A1 and A2a adenosine receptors are differentially expressed in medium spiny neurons with A1 receptors co-localized with D1 receptors in striatonigro-entopeduncular neurons and A2a receptors and D2 receptors co-expressed in striatopallidal neurons. Functionally, each adenosine receptor subtype appears to oppose the effects of its co-localized dopamine receptor subtype.
GLUTAMATE–DOPAMINE INTERACTION

The cortical input to the striatum is massive and topographically ordered, with sensory and motor cortices projecting to putamen, associative cortex projecting to caudate and rostral putamen, and limbic cortical areas projecting to the ventral striatum. Release of glutamate by cortical neurons has a uniformly excitatory effect on striatal neurons. Therefore, most theories of basal ganglia function propose that glutamate drives striatal activity and dopamine modulates this activity by shifting the balance between hyperkinesia and hypokinesia. Ultrastructural evidence suggests that glutamate and dopamine interact at the level of synaptic inputs to medium spiny neurons (Figure 2). Excitatory cortical and thalamic afferents synapse mainly onto the heads of dendritic spines of medium spiny neurons, whereas nigrostriatal dopamine neurons synapse primarily onto the shafts of the same dendritic spines. These findings are consistent with the notion that dopaminergic synapses are in an anatomical position to modulate glutamatergic input to medium spiny neurons.

Glutamate released by corticostriatal neurons activates both striatopallidal and striatonigral neurons. Consequently, glutamate stimulates motor behavior through excitatory effects on the direct pathway and inhibits motor behavior through excitatory effects on the indirect pathway. In contrast, dopamine promotes motor behavior by its action on both the direct and indirect pathways, since dopamine excites striatonigral neurons expressing D1 receptor and inhibits striatopallidal neurons expressing D2 receptors. Therefore, similar to glutamate, dopamine promotes motor activity in the direct pathway but, unlike glutamate, dopamine also promotes motor behavior in the indirect pathway through D2-mediated inhibition of striatopallidal neurons. Consequently, in the absence of dopamine, striatopallidal neurons become hyperactive since the excitatory influence of glutamate is no longer balanced by dopamine. Attempts to counter this imbalance by administration of glutamate antagonists produces variable, dose-dependent results, although glutamate antagonists can more reliably potentiate the motor effects of L-dopa in the dopamine depleted system.

Although dopamine acting on both striatal output pathways promotes motor activity, the information conveyed by these pathways is slightly different. While D2 agonists are more potent than D1 agonists in stimulating motor behavior, simultaneous activation of both D1 and D2 receptors is necessary for the strongest motor response in the intact basal ganglia. In contrast, following dopamine denervation, D1 and D2 dopamine receptors appear to function more independently with significant motor activity observed following administration of either D1 or D2 selective agonists, however, even in the dopamine depleted system, D1 and D2 synergism is still noted.

ACETYLCHOLINE–DOPAMINE INTERACTION

Although cholinergic interneurons comprise only 1%–2% of the total neuronal population in the striatum, these interneurons possess extensive projections and large dendritic fields. Cholinergic interneurons synapse directly onto medium spiny neurons with synaptic contacts found on spines, dendrites, and cell bodies. Cholinergic interneurons themselves receive input from the thalamus/cortex (glutamate), medium spiny neurons (GABA/substance P), and SNc (dopamine). Cholinergic neurons express both NMDA and non-NMDA glutamate receptors and appear to be especially sensitive to the excitatory effects of glutamate.

Dopamine differentially regulates striatal cholinergic function with stimulation of D1 receptors increasing, and stimulation of D2 receptors decreasing acetylcholine release. These responses occur through D1 and D2 receptors expressed by cholinergic interneurons as well as through D1–mediated substance P release from striatonigral axon collaterals. A balance between acetylcholine and dopamine has been recognized as necessary for normal striatal function, thereby suggesting that acetylcholine usually opposes the effects of dopamine. Consistent with this notion, muscarinic antagonists can potentiate D1 responses or partially substitute for D2 dopamine receptor stimulation. Early pharmacotherapies for PD using cholinergic antagonists aim to restore this acetylcholine–dopamine balance.
SUMMARY

The basal ganglia influence cortical control of voluntary movement by regulating the activity of the motor nuclei of the thalamus. Since the output nuclei of the basal ganglia tonically inhibit the thalamus, the basal ganglia exert their motor promoting effect through a disinhibition of the thalamus. The striatum (caudate-putamen) serves as the input structure of the basal ganglia receiving afferents primarily from the cortex and SNc. Striatal projection neurons form the direct and indirect pathways, which transmit information to the SNr/GPi output nuclei. Based on recently delineated connections between GP, STN, and other structures of the basal ganglia, there appear to be several indirect pathways. Analysis of neuronal densities suggest that there is a significant degree of synaptic convergence in the basal ganglia; however, there is also evidence supporting separate, parallel pathways of information flow. Striatal neurons display very low levels of spontaneous activity, whereas the output nuclei, SNr/GPi, have high basal firing rates, which provide tonic inhibition to the thalamus. While striatal neuronal firing increases prior to movement, the activity of SNr/GPi is more complex and reflects integration of inputs from both the direct and indirect pathways. The striatum can be divided into two separate anatomical compartments, called patch and matrix, each of which maintains distinct afferent and efferent relationships with other brain nuclei. All striatal projection neurons contain the inhibitory neurotransmitter GABA, but each striatal output pathway also contains distinct neuropeptides. Different dopamine receptor subtypes are expressed by the separate populations of striatal output neurons with D1 receptors on striatonigral neurons and D2 receptors on striatopallidal neurons. Receptors for glutamate, acetylcholine, and adenosine are also present in the striatum, with variations observed in their expression in striatal output neurons and cholinergic interneurons. Glutamate and dopamine directly influence striatal output neurons through synaptic inputs onto distinct portions of their dendrites. Glutamate and dopamine both promote motor behavior through excitatory effects on the direct pathway, but provide antagonistic effects on the indirect pathway since dopamine inhibits striatopallidal neurons. Cholinergic interneurons also regulate the activity of striatal output neurons and balance the influence of dopamine.

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**NEUROBEHAVIORAL ASPECTS OF MOVEMENT DISORDERS**

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With the motor symptoms, cognitive, behavioral, affective, and psychiatric changes occur in varying degrees in almost all movement disorders. Movement disorders differ in their clinical and pathologic characteristics; and they also differ in their neurobehavioral presentations. Quantitative and qualitative differences in neuropsychologic and neuropsychiatric symptoms have important implications for the diagnosis and management of movement disorders. Cognitive and neurobehavioral changes that occur early in the course of illness, for example, are important for distinguishing between the diagnoses of Parkinson's disease (PD) and progressive supranuclear palsy. It is recognized that dopamine replacement is less efficacious and pharmacologic management of symptoms is more difficult in patients with PD who develop dementia. Such patients show lowered motor responsiveness and increased confusion and psychosis when administered dopaminergic agents. PD patients with dementia also tend to have a more rapid progression of illness, higher mortality, and earlier death. Additionally, cognitive impairments and psychotic symptoms contribute to the burden of caregivers, and these problems lead to institutionalization even more often than the motor impairments of patients with PD and other movement disorders.

A review of all the different neurobehavioral syndromes associated with movement disorders is beyond the scope of this article. To highlight some commonalities and differences among movement disorders, the article focuses on two syndromes PD and Huntington's disease (HD) that are representative of the two major classes of movement disorders. Parkinson's disease is the most common and best studied of the akinetic-rigid group of movement disorders. This group of disorders

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