The Basal Ganglia and Disorders of Movement: Pathophysiological Mechanisms

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The basal ganglia are part of a neuronal network organized in parallel circuits. The “motor circuit” is most relevant to the pathophysiology of movement. Abnormal increment or reduction in the inhibitory output activity of basal ganglia give rise, respectively, to poverty and slowness of movement (i.e., Parkinson’s disease) or dyskinesias.

The basal ganglia (BG) are a group of nuclei located subcortically (Fig. 1). The term BG has no precise anatomic limitation and includes the corpus striatum (caudate nucleus and the lenticular nucleus, which includes the putamen and the globus pallidus) and other subcortical allied nuclei such as the subthalamic nucleus (STN), the substantia nigra (SN) [consisting of the pars compacta (SNc) and pars reticulata (SNr)], and, more recently, the pedunculopontine tegmental nucleus (PPTg). Currently, the putamen and caudate are together referred to as the striatum. Dysfunction of the BG traditionally has been associated with the so-called extrapyramidal system and “extrapyramidal syndrome,” both of which are obsolete and inaccurate terms, rapidly disappearing from both the anatomic and clinical scenarios.

The normal BG

The BG are part of a complex network of neuronal circuits organized in parallel to integrate activity from different cortical regions (2). Five cortico-BG-thalamo-cortical loops have been defined: 1) motor, 2) oculomotor, 3) associative, 4) limbic, and 5) orbitofrontal. In addition, the BG are intimately interconnected with brain stem nuclei such as the locus ceruleus (noradrenergic), raphe nuclei (serotonergic), and the reticular formation.

The “motor circuit” (Fig. 2) is most relevant to the pathophysiology of movement. This circuit is somatotopically organized throughout the loop, so that the leg is represented dorsally, the face ventrally, and the arm in between (2). Movement-related neurons are found mainly in the posterolateral region of the BG. This organization has been well defined in the monkey, and it is also probably true in humans. Cortical motor areas (area 4, the premotor cortex, and the supplementary motor area) as well as the primary somatosensory cortex send glutamatergic (excitatory) axons to the posterolateral putamen, where they synapse mainly with GABAergic medium spiny neurons. The release of glutamate following cortical activation is regulated by nigrostriatal dopaminergic terminals. The medium spiny GABAergic cells are projection neurons directed to the main output nuclei of the primate BG, that is, the internal segment of the globus pallidus (GPi) and the SNr.

There are two main striato-GPi/SNr circuits. Neurons in the “direct pathway” establish a monosynaptic, inhibitory connection from the putamen to GPi/SNr; these neurons are biochemically characterized by containing mainly D1 dopamine receptors and coexpressing the peptides substance P and dynorphin (8). Neurons in the “indirect pathway” send their GABAergic axons to the external segment of the globus pallidus (GPe), which connects with the STN, which in turn projects to the GPi/SNr. The STN uses glutamic acid as a neurotransmitter and therefore exerts an excitatory effect on the GPi/SNr and to other brain stem nuclei that are connected with the STN (i.e., PPTg and SNc).

Striatal neurons in the “indirect pathway” are chemically characterized by expressing mainly D2 dopamine receptors and the peptide enkephalin. The output of the motor circuit from the GPi/SNr is inhibitory and is directed to the ventrolateral thalamic nucleus (“motor thalamus”) and to the PPTg. Output neuronal activity in the GPi/SNr is thought to be under a dual control mechanism. Thus increased activity in the direct pathway gives rise to inhibition or pauses of neuronal firing in the GPi/SNr, leading to disinhibition of their projection nuclei (i.e., thalamus, PPTg, superior colliculus, etc.). On the contrary, activity in the indirect pathway leads to increased excitation of the STN and augmented inhibition from the GPi/SNr onto their projection nucleus (1, 6).

In addition, the “motor loop” has several “internal” or “closed” loop circuits, which seem designed to modulate and regulate the excitability of the BG themselves (9, 17). Several circuits may be recognized: 1) the centromedian/parafascicular (CM–Pi)–thalamic nuclei–striatum–GPe–CM–Pi circuit, which is probably a positive feedback loop leading to increasing neuronal activity; 2) the CM–Pi–STN–GPe–CM–Pi circuit, which is probably a negative loop leading to reduced neuronal activity; 3) the STN–GPe–STN circuit, which is an excitatory–inhibitory loop with “autostabilizing” characteristics; 4) the STN–GPe/GPi dual projection, which is an “open” but interconnected loop by which the STN might induce excitation and inhibition of the same GPi neurons within <5 ms; and 5) the
primary motor cortex (area 4)–STN–GPi–motor thalamus–area 4 loop, which is perfectly suited to provide inhibitory feedback signaling to the cortex and probably very relevant for the termination of movement (17).

The dopaminergic system innervates all BG nuclei and probably exerts a powerful modulatory control of the above-summarized circuits. The mesencephalic dopaminergic system stems from three main cellular groups known as areas A8, A9, and A10. The A8 group refers to the retrorubral area (RRA), the A9 group to the SN, and the A10 group to the ventral tegmental area (VTA). Mesencephalic dopaminergic neurons are now divided according to their topographical distribution and chemical characteristics (8). Neurons in the dorsal tier of the SN mesencephalic region (including some SN cells, VTA, and RRA) are loosely spaced and are positive for calbindin D$_{28k}$ but contain relatively low levels of dopamine transporter and tyrosine hydroxylase. These neurons project mainly to the limbic and associative areas of the striatum. On the other hand, cells from the ventral region of the SN mesencephalic region, which are calbindin D$_{28k}$ negative but rich in dopamine transporter, give rise to the major dopaminergic projection to the motor regions of the BG (8). Two different types of axonal projections have been recently distinguished (18): 1) neurons with a long axon traveling directly to the striatum and emitting no collaterals, which mainly innervate specific zones of the striatum known as “patches” or striosomes; and 2) neurons producing axons that are profusely arborized and mainly innervate extrastriatal nuclei such as the GPe, GPe, STN, and even the thalamus. The latter type of cells in the ventrolateral tier of the SN, which appear arranged in columns penetrating into the SNr, seems to be the first to degenerate in Parkinson’s disease (PD).

**Origin of motor disorders secondary to BG diseases**

Movement disorders comprise a large variety of motor manifestations, not all of which are necessarily due to dysfunction of the BG. Equally, BG dysfunction may be associated with nonmotor manifestations such as attention deficit, depression, mania, etc. In addition, the origin and pathophysiological basis of some movement disorders are presently ill defined. For instance, the tics of Gilles de la Tourette, the involuntary movements associated with chronic neuroleptic treatments (“tardive dyskinesias”), or the restless leg syndrome, all of which are sensitive to dopaminergic drugs, are commonly thought to have a BG origin, but this assertion has not been directly proven. In this section, we shall discuss the pathophysiological basis of the major clinical conditions known to arise as a consequence of BG dysfunction, namely PD and dyskinesias such as chorea-ballism or dystonia. In a simplistic way, one can view these BG disorders as opposite poles of normal movements. On the one hand are PD and related conditions (“parkinsonian” syndromes), in which there is poverty and slowness of movement. On the other hand, dyskinesias, like chorea-ballism or dystonia, are characterized by excessive and inappropriate motor activity. The former is thought to depend on increased inhibitory activity of motor cortical and brain stem areas (Fig. 2B) and the latter on abnormal neuronal signaling from the BG to the thalamus and cortex (Fig. 2C).

**PD**

**Clinical summary.** The cardinal features of PD are poverty of movement (hypokinesia), slowness of movement (bradykinesia), rigidity, and tremor at rest. While standing or walking, patients with PD exhibit a characteristic picture. The trunk and knees are flexed, the length of the stride is reduced, but the number of steps is increased and the patient appears to propel him/herself forward, finally losing equilibrium. The major pathological characteristic of PD is loss of melanized neurons in the SNc and the presence of intracellular inclusion aggregates known as Lewy bodies. Neuronal loss in the SNc produces a marked deficit of dopamine content in the striatum, which is particularly overt in the dorsolateral region of the putamen, thus impinging directly onto the motor circuit. Reduced dopaminergic innervation in patients with PD may now be assessed in vivo by using positron emission tomography (Fig. 3).

**Pathophysiology.** The pathophysiological hallmark of the parkinsonian state is increased neuronal activity in the output nuclei of the BG (GPi/SNr) leading to excessive inhibition of the thalamocortical and brain stem motor systems (Fig. 2B). Dopamine deficiency leads to reduced inhibition of GABAergic striatal neurons in the indirect pathway and decreased facilitation of GABAergic neurons in the direct pathway neurons (8–10). Reduced inhibition of neurons in the indirect pathway leads sequentially to overinhibition of GPe, disinhibition of STN, and increased excitation of GPi/SNr. Decreased activation of neurons in the direct pathway reduces its inhibitory influence on GPi/SNr and contributes to their excessive output activity. Considerable evidence supports the model
of parkinsonism (Table 1). Studies in the rat with unilateral lesion of the nigrostriatal projection with the neurotoxin 6-hydroxydopamine and in monkeys with lesion of the SNc with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have conclusively shown increased D2 receptor and preproenkephalin mRNA expression in striatal neurons of the indirect pathway and reduced D1 receptors, substance P, and dynorphin mRNA expression in striatal neurons of the direct pathway. Hyperactivity of the STN and GPi in MPTP-treated monkeys has been demonstrated by several techniques (3, 15) such as 2-deoxyglucose uptake as a marker of synaptic afferent activity, in situ hybridization of cytochrome oxidase I mRNA as a measure of cellular mitochondrial activity, glutamic acid decarboxylase mRNA as a measure of GABA activity, and, more importantly, by recording neuronal activity before and after dopamine depletion (Table 1). Furthermore, lesions of the STN and Gpi in MPTP-treated monkeys has been demonstrated by several techniques (3, 15) such as 2-deoxyglucose uptake as a marker of synaptic afferent activity, in situ hybridization of cytochrome oxidase I mRNA as a measure of cellular mitochondrial activity, glutamic acid decarboxylase mRNA as a measure of GABA activity, and, more importantly, by recording neuronal activity before and after dopamine depletion (Table 1). All of these data provided substantial evidence that neuronal activity is increased in the STN and Gpi and have served as the basis for a revitalization of surgical treatments in PD designed to reduce excess neuronal activity in these output nuclei of the BG.

**Dyskinesias**

**Clinical summary.** There are three main types of dyskinesias with a recognized BG origin: 1) Chorea is characterized by an irregular concatenation of involuntary movements, producing a “dancing-like” clinical picture (hence the term Saint Vitus’ dance applied to people with Sydenham’s chorea). When the movements are of larger amplitude involving the proximal joints the term “ballism” is applied. Thus chorea and ballism represent the same category of dyskinesias, differing mainly in the severity and amplitude of the movements. Huntington’s disease is the most common cause of chorea in patients, whereas vascular (i.e., stroke) lesion of the STN is the main etiology of ballism, usually taking the form of hemiballism. 2) Dystonia is characterized by prolonged (0.5–5 s) muscle spasms, involving agonist and antagonist muscles, which twist the body into typical postures. Focal lesions of the BG, particularly those involving the putamen or Gpi, are associated with focal dystonia. 3) Levodopa-induced dyskinesias (LID), caused by chronic treatment with levodopa, induce a variety of dyskinetic movements in patients with PD. These involuntary movements include chorea, dystonia, stereotypical repetitive movements of the legs, etc. They can be completely eliminated by either suppressing dopaminergic replacement therapy or by a focal, restricted lesion of the Gpi (pallidotomy), thus establishing LID’s origin within the BG.

**Pathophysiology.** The essential characteristic of dyskinesias is the presence of involuntary motor activity contaminating and impairing the execution of normal motor commands. Chorea-ballism and LID consist of the abnormal release of fragments of normal movements, whereas dystonia could be understood as an exaggeration of the normal postural mecha-
nisms. Chorea-ballism is classically understood as the result of reduced activity in the STN/GPi pathway (5) and decreased firing in GPi output neurons (Fig. 2C), the opposite of what is seen in parkinsonism. In accordance with the classic model of BG pathophysiology (1, 3, 6), choreic dyskinesias appear following reduced inhibitory activity in the striatum/GPe projection, which produces augmented activity of the GPe, which in turn results in overinhibition of the STN; this, in turn, leads to hypoactivity of the GPi. Decreased inhibitory output from BG neurons leads to unrestrained thalamocortical drive and the appearance of dyskinesias.

LID in PD was thought to occur through a similar mechanism (4). This set of events is supported by electrophysiological studies showing increased neuronal activity in GPe and decreased neuronal firing in GPi during apomorphine-induced dyskinesias in MPTP monkeys and PD patients (7, 13). However, the notion that GPi hypoactivity is the primary mechanism responsible for the development of dyskinesias contrasts with a well-established finding in monkeys and human patients, which is that pallidotomy abolishes dyskinesias (13). Pallidotomy is arguably the most radical approach to reducing GPi neuronal output, which, according to the classic model of the BG, should lead to the abnormal release of involuntary movements (1, 6).

The ant dyskinesia effect of pallidotomy has led to revision of the pathophysiology of dyskinesias, which cannot be understood as the result of GPi hypoactivity only but instead must be seen as due to abnormal firing patterns in BG output neurons (13, 15, 16). We believe that the firing pattern in GPi neurons is a signaling code that conveys information to the motor areas for the correct selection and execution of movement patterns (17). The neuronal firing pattern is comprised of a number of factors, which include degree and duration of bursting activity, length of interpotential pauses, and degree of temporal and neuronal synchronization, in addition to firing frequency. GPi output to the cortex cannot simply be analyzed in terms of the firing rate of any given set of neurons, nor by the overall rate of discharge. It is the code or pattern of GPi neuronal activity transmitted to the cortex that signals for the facilitation/inhibition of normal and abnormal movements. Pallidotomy abolishes this pattern and therefore eliminates dyskinesias. Similarly, the parkinsonian state is not simply explained by neuronal hyperactivity of the BG. A large body of clinical and experimental evidence supports this view. Thus the categories of movements that are abnormal in PD (for example, automatic and simple movements like arm swing and eye blink, automatic but complex muscle contractions such as those involved in walking, simultaneous and sequential movements, etc.) are too vast and heterogeneous to be explained by a single mechanism like neuronal hyperactivity.

Conclusions

The clinical manifestations and pathophysiological features of the BG cannot be understood as the result of dysfunction of a simple, unidirectional system that transfers information based solely on a firing-rate code. The normal BG is currently considered to be a highly organized network, with operational characteristics that simulate a nonlinear dynamic system. Different parts of the network may become activated depending

TABLE 1. Evidence supporting the role of increased neuronal activity in the STN and GPi as major pathophysiological features of the parkinsonian state

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| In MPTP monkeys          | "In situ" hybridization studies show increased GABA synthesis and mitochondrial energy production, increased neuronal firing in STN and GPi, decreased neuronal firing in GPi during apomorphine-induced dyskinesias in MPTP monkeys and PD patients (7, 13). However, the notion that GPi hypoactivity is the primary mechanism responsible for the development of dyskinesias contrasts with a well-established finding in monkeys and human patients, which is that pallidotomy abolishes dyskinesias (13). Pallidotomy is arguably the most radical approach to reducing GPi neuronal output, which, according to the classic model of the BG, should lead to the abnormal release of involuntary movements (1, 6). The ant dyskinesia effect of pallidotomy has led to revision of the pathophysiology of dyskinesias, which cannot be understood as the result of GPi hypoactivity only but instead must be seen as due to abnormal firing patterns in BG output neurons (13, 15, 16). We believe that the firing pattern in GPi neurons is a signaling code that conveys information to the motor areas for the correct selection and execution of movement patterns (17). The neuronal firing pattern is comprised of a number of factors, which include degree and duration of bursting activity, length of interpotential pauses, and degree of temporal and neuronal synchronization, in addition to firing frequency. GPi output to the cortex cannot simply be analyzed in terms of the firing rate of any given set of neurons, nor by the overall rate of discharge. It is the code or pattern of GPi neuronal activity transmitted to the cortex that signals for the facilitation/inhibition of normal and abnormal movements. Pallidotomy abolishes this pattern and therefore eliminates dyskinesias. Similarly, the parkinsonian state is not simply explained by neuronal hyperactivity of the BG. A large body of clinical and experimental evidence supports this view. Thus the categories of movements that are abnormal in PD (for example, automatic and simple movements like arm swing and eye blink, automatic but complex muscle contractions such as those involved in walking, simultaneous and sequential movements, etc.) are too vast and heterogeneous to be explained by a single mechanism like neuronal hyperactivity. Conclusions The clinical manifestations and pathophysiological features of the BG cannot be understood as the result of dysfunction of a simple, unidirectional system that transfers information based solely on a firing-rate code. The normal BG is currently considered to be a highly organized network, with operational characteristics that simulate a nonlinear dynamic system. Different parts of the network may become activated depending

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STN, subthalamalic nucleus; GPi, interior globus pallidus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SNr, substantia nigra pars reticulata.
on circumstances. For instance, in the early stages of learning, a complex task is executed by relying on the associative prefrontal cortex and the anterior BG (11). However, as the sequence becomes routine, premotor and primary motor areas and the posterior BG are predominantly engaged in the task (11). The nigrostriatal dopaminergic system plays an essential modulatory role during this learning process (14, 19). Adjusting to different aspects of behavior is an essential characteristic of the BG-cortical network.

We believe that the dopaminergic system and the internal BG circuits are designed to maintain the stability of the motor control network (9, 17). Dopamine depletion destabilizes the network and leads to abnormal neuronal activity in several BG loops. Surgical lesions of the STN or GPi reestablish a certain level of equilibrium by eliminating major sources of instability in the network. Interruption of such circuits is not accompanied by overt motor deficits because of the widespread and nonserial organization of the BG motor system but could lead to motor defects under special circumstances in which critical components of the network are required. Dyskinesias may be seen as the pathological expression of one fundamental function of the BG, which is to facilitate specific motor acts while inhibiting the majority of other possible actions.

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