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NEUROCIRCUITRY OF PARKINSON'S DISEASE

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Recent progress in neuroscience research has led to major insights into the structure and function of the basal ganglia and into the pathophysiologic basis of Parkinson's disease (PD) and other movement disorders of basal ganglia origin (3,4,116,313,314). The availability of suitable animal models, such as primates rendered parkinsonian by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), has been crucial in this progress (17,57,173). In addition, the renaissance of stereotactic surgery for PD and other movement disorders has provided valuable neuronal recording and imaging data from human subjects. Newer genetic models, for instance mice that overexpress α-synuclein, should provide further insights into the genetic backdrop upon which PD develops. This chapter summarizes from a systems perspective the pathophysiologic concepts that have arisen from the animal models and from work in patients with PD.

ETIOLOGY AND PATHOLOGY IN PARKINSON'S DISEASE

Idiopathic PD is a disorder characterized by the cardinal signs of akinesia (impaired movement initiation and poverty of movement), bradykinesia (slowness of movement), muscular rigidity, and tremor at rest. The etiology of the disease is uncertain and likely multifactorial, with both genetic and environmental/toxic factors playing a role (see below; see refs. 279 and 287 for review). Idiopathic PD must be distinguished from a large number of other disorders ("atypical" parkinsonism, or "Parkinson-plus" syndromes) which share some of the features of PD but exhibit additional signs (for instance, signs indicative of upper motor neuron, cerebellar or oculomotor involvement). Among these disorders are, for instance, the multiple systems atrophies, progressive supranuclear palsy, and corticobasal ganglionic degeneration. These "atypical" forms of parkinsonism are associated with different and more widespread pathologic abnormalities than those seen in PD proper, and will not be dealt with further in this chapter.

The salient pathologic feature of idiopathic PD is relatively selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) that project to the striatum (99,137), and, to a lesser extent, to other basal ganglia nuclei such as the external and internal segments of the globus pallidus (GPe, GPi, respectively), the subthalamic nucleus (STN), and the substantia nigra pars reticulata (SNr) (99,137). Consistent with the early manifestations of motor dysfunction, in the early stages of PD, dopamine depletion is greatest in the sensorimotor territory of the striatum, the postcommissural portion of the putamen (157).

Although it appears that only a small minority of patients suffer from purely inherited forms of PD, investigations into the genetic mechanism that may underlie these cases are being very actively pursued in hopes of discovering pathogenetic mechanism for parkinsonism in general. Inherited forms of parkinsonism in fact have been known for many years (11,24,113,270,272), and it has been shown that specific forms of parkinsonism may be caused by different genetic mechanisms. For instance, in a large kindred with *autosomal-dominant* parkinsonism, the disorder was linked to genetic markers on chromosome 4 (PARK1) (233), and has subsequently been shown to be due to a mutation in the α-synuclein gene (215,234). α-Synuclein is one of the major components of Lewy bodies, i.e., eosinophilic inclusions in degenerating neurons in the SNc that have long been accepted as one of the pathologic hallmarks of PD (273). A form of *autosomal-recessive* juvenile parkinsonism is caused by a mutation in a gene on chromosome 6, called parkin (PARK 2) (160,192,286). Finally, *mutations in the mitochondrial DNA*, particularly those affecting complex I function, may also cause or contribute to PD (81,120,165, 203,248). An involvement of mitochondrial dysfunction in

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the development of some forms of parkinsonism is also suggested by findings indicating that the toxicity of MPTP may be due to its inhibition of the mitochondrial complex I enzyme reduced nicotinamide adenine dinucleotide (NADH) coenzyme Q1 reductase (58,120,197,247), and the recent discovery that systemic administration of the pesticide rotenone, a mitochondrial complex I inhibitor, induces striatal dopamine depletion in rats (33).

Overall, however, a *genetic predisposition* for environmental insults that lead to parkinsonism may be far more common than gene mutations that directly result in the disease (87,102,171,288,289). Epidemiologic studies have shown an association with rural living, well-water drinking, pesticide exposure, and wood-preservative use (70,163,236,237, 253). An interesting inverse relationship has been reported between PD and smoking (112,128,134,153,240). Among specific toxins that may contribute to PD are MPTP and other isoqinoline derivatives (172,197), organophosphate pesticides (38), and perhaps mitochondrial toxins such as rotenone (33).

ANATOMIC SUBSTRATE FOR CIRCUIT DYSFUNCTION IN PARKINSONISM

To understand how the relatively selective loss of dopamine in the basal ganglia leads to parkinsonism, it is necessary to consider in some detail the circuitry, molecular anatomy, and physiology of the basal ganglia and related structures.

The basal ganglia are a group of functionally related subcortical nuclei that include the neostriatum (composed of the caudate nucleus and the putamen), ventral striatum, GPe, STN, GPi, SNr, and SNc. These structures are anatomically related to large portions of the cerebral cortex, thalamus, and brainstem. The striatum, and, to a lesser extent, the STN, are the main entries for cortical and thalamic inputs into the basal ganglia. From these input nuclei, this information is conveyed to the basal ganglia output nuclei—GPi and SNr. Basal ganglia outflow is directed at a variety of targets, among them frontal areas of the cerebral cortex (via the ventrolateral and intralaminar thalamic nuclei), various brainstem structures (superior colliculus, pedunculopontine nucleus, parvicellular reticular formation), and the lateral habenular nucleus.

Input to the Basal Ganglia

The most abundant inputs to the basal ganglia are the topographically segregated corticostriatal projections (7,8,225). In primates, projections from the somatosensory, motor, and premotor cortices terminate in the postcommissural putamen, the motor portion of the striatum (97,98,167,168). Similarly, associative cortical areas project to the caudate nucleus and the precommissural putamen (110,254, 320–322) and projections from limbic cortices, amygdala, and hippocampus terminate preferentially in the ventral striatum, which includes the nucleus accumbens and the olfactory tubercle (9,121,166,242).

Cortical inputs also terminate in the STN (1,126,210). The corticosubthalamic projection is derived from the primary motor, prefrontal, and premotor cortices (1,126,167, 210). The segregation of cortical projections found in the striatum is also present in the STN. Thus, afferents from the primary motor cortex reach the dorsolateral part of the STN (126,210), whereas afferents from premotor and supplementary motor areas innervate mainly the medial third of the nucleus (126,168,210,212). The prefrontal-limbic cortices project to the ventral portion and the medialmost tip of the STN (1,27,126,193).

A second major group of inputs to striatum and STN arises from the intralaminar thalamic nuclei, the centromedian and parafascicular nucleus (CM/Pf). These nuclei have long been identified as major source of excitatory afferents to the basal ganglia (86,92,154,245,281,317). The projections to striatum and STN arise largely from different neurons in the parafascicular nucleus of the thalamus in rats (92, but see ref. 79). In primates, CM projects to the motor portions of putamen and STN, whereas Pf projects largely to the associative and limbic territories (208,244,245,265).

Other thalamostriatal inputs arise from the ventral anterior (VA), ventrolateral nucleus (VL), and possibly even the cerebellar-receiving areas of the thalamus (VPLo) (196, 265). These thalamostriatal projections are less well documented, and their functional significance is unclear. The available evidence indicates that these projections are much less prominent than the projections from the intralaminar nuclei.

Intrinsic Basal Ganglia Connections

The topographically segregated cortical information is conveyed from the striatum to the output nuclei of the basal ganglia (GPi and SNr). Striatofugal projections maintain the striatal organization into motor, limbic, associative, and oculomotor territories (8). The connections between the striatum and the output nuclei of the basal ganglia are thought to be organized into two distinct pathways, the so-called direct and indirect pathways (3,6,29). The direct pathway arises from a set of neurons that projects monosynaptically to neurons in GPi and SNr, whereas the indirect arises from a different set of neurons that projects to GPe (see ref. 106 for review). In deviation from this strict scheme, some striatofugal neurons may collateralize more extensively, reaching GPe, GPi, and SNr (226). GPe conveys the information it receives either directly or via the STN to GPi and SNr [and, as was recently shown, back to the striatum (159, 274)].

Several studies have demonstrated highly ordered and specific relationships between the neurons in GPe, STN, and GPi that constitute the indirect pathway (256,262,

266). Thus, populations of neurons within sensorimotor, cognitive, and limbic territories in GPe are reciprocally connected with populations of neurons in the same functional territories of STN, and neurons in each of these regions, in turn, innervate the same functional territory of GPi (256, 262), although additional, more divergent circuits may also exist (149,256,262,266).

The STN also provides a dense feedback projection to the GPe (35,52,205,216,256,258,264) and projections to the striatum (22,230,265), the SNc (158,261,264), the pedunculopontine nucleus (124,158,230), and the spinal cord (285). STN output is highly collateralized in the rat (77, 297), but is more specific in primates (27,122,230,256,297) (but see refs. 228 and 229).

The subpopulation of striatal neurons that gives rise to the direct pathway can be further characterized by the presence of the neuropeptides substance P and dynorphin, by the preferential expression of the dopamine D1 receptors, and by the fact that these neurons (as well as most striatal interneurons) appear to be the targets of thalamic inputs from the centromedian nucleus (231,260). The subpopulation that gives rise to the indirect pathway expresses preferentially enkephalin and dopamine D2 receptors (105,176, 283), and may be the principal target of cortical inputs (231,260).

Although the segregation of D1 and D2 receptors between the direct and indirect pathways is probably not as strict as initially proposed (2,282,283), it may still serve to explain the apparent dual action of dopamine, released from the nigrostriatal pathway arising in the substantia nigra pars compacta, on striatal output. Dopamine appears to modulate the activity of the basal ganglia output neurons in GPi and SNr by *facilitation* of transmission over the direct pathway and *inhibition* of transmission over the indirect pathway (104). The net effect of striatal dopamine release appears to be to reduce basal ganglia output to the thalamus and other targets (see below). This implies that a reduction of dopamine release as is seen in PD results in a net increase in basal ganglia output.

Output Projections of the Basal Ganglia

Basal ganglia output arises from both GPi and SNr. The segregation of GPi into a caudoventral "motor" portion and rostromedial associative and limbic areas (225) is maintained in the pallidothalamic projections (259). The motor territory of GPi projects almost exclusively to the posterior part of the ventrolateral nucleus (VLo in macaques), which in turn sends projections toward the supplementary motor area (SMA) (143,249,280), the primary motor cortex (MI) (135,136,143,148,152,213,241), and premotor (PM) cortical areas (135). The outflow from pallidal motor areas directed at cortical areas MI, PM, and SMA appears to arise from separate populations of pallidothalamic neurons (135), indicating that the motor circuit itself can be subdivided into subcircuits, each centered on specific cortical motor and premotor areas. Associative and limbic areas project preferentially to the parvocellular part of the VA and the dorsal VL nucleus (80,155,259), and may be transmitted in turn to prefrontal cortical areas (111,198), as well as motor and supplementary motor regions (68,143).

Other output projections from GPi arise mostly as collaterals from the pallidothalamic projection. Thus, prominent axon collaterals are sent in a segregated manner to the CM/Pf complex, which project to the striatum (see above), constituting one of the many feedback circuits in the basal ganglia–thalamocortical circuitry (259). Additional axon collaterals reach the noncholinergic portion of the pedunculopontine nucleus (PPN) (125,227,243,257,277), which gives rise to descending projections to pons, medulla, and spinal cord, and ascending projections to basal ganglia, thalamus, and basal forebrain (see ref. 144 for review).

Although the overlap between motor and nonmotor areas is probably greater in the SNr than in GPi (127), the SNr can be broadly subdivided into a dorsolateral sensorimotor and a ventromedial associative territory (78). By and large, projections from these areas target the same nuclei that also receive GPi output, but tend to terminate in different regions of these nuclei. Projections from the medial SNr to the thalamus terminate mostly in the medial magnocellular division of the ventral anterior nucleus (VAmc) and the mediodorsal nucleus (MDmc), which, in turn, innervate anterior regions of the frontal lobe including the principal sulcus (Walker's area 46) and the orbital cortex (Walker's area 11) in monkeys (140). Neurons in the lateral SNr project preferentially to the lateral posterior region of VAmc and to different parts of the MD. These areas of the thalamus are predominately related to posterior regions of the frontal lobe including the frontal eye field and areas of the premotor cortex, respectively (140). As is the case with GPi, SNr also sends projections to the noncholinergic neurons in the medial two-thirds of the PPN (117,243,271,277). Additional projections reach the parvicellular reticular formation, a region whose neurons are directly connected with orofacial motor nuclei (55,204,304), and the superior colliculus, which may play a critical role in the control of saccades (319). The latter projection is far more prominent in phylogenetically old animal species (amphibians) than in primates (189).

ROLE OF THE BASAL GANGLIA–THALAMOCORTICAL CIRCUITRY IN THE CONTROL OF MOVEMENT

At the most basic level, voluntary movements appear to be initiated at the cortical level of the motor circuit with output to brainstem and spinal cord, and to multiple subcortical targets, including the thalamus, putamen, and the STN. The exact nature of the information reaching either striatum

or the STN is not clear. Thus, studies of the electrophysiologic properties of corticostriatal projection neurons have shown that these neurons are different from corticospinal projection neurons (20,295) and tend to have slower conduction velocities and lower spontaneous rates, and are usually not responding to somatosensory input.

According to the current model of the functions of the basal ganglia–thalamocortical circuitry, activation of an ensemble of striatal neurons that give rise to the direct pathway leads to a reduction of inhibitory basal ganglia output from targeted neurons with subsequent disinhibition of related thalamocortical neurons (142). The net effect is increased activity in appropriate cortical neurons, resulting in a *facilitation* of the movement. In contrast, activation of the striatal neurons that give rise to the indirect pathway will lead to increased basal ganglia output and, presumably, to *suppression* of movement. Because the majority of neurons in GPi increase their firing rate with movement (103,202), the presumed increased suppression of unintended competing movements may be a particularly important role of the basal ganglia. Depending on the precise timing and anatomic connectivity, this dual action on movement could result in limiting the spatial or temporal extent of movements.

Clinical and experimental studies suggest that the basal ganglia play a role in specifying the amplitude or velocity of movement (14,46,59,74,142,296) or in maintaining postural stability during arm movements (142). The combination of information traveling via the direct and the indirect pathways of the motor circuit has been proposed to serve to either scale or focus movements (7,200,211). *Scaling* would be achieved by a temporal sequence of activity changes in the basal ganglia. Striatal output would first inhibit specific neuronal populations in GPi/SNr via the direct pathway, thus facilitating movement, followed by disinhibition of the *same* GPi/SNr neuron via inputs over the indirect pathway, leading to inhibition (“braking”) of the ongoing movement. In the *focusing* model, by contrast, inhibition of relevant pallidal/nigral neurons via the direct pathway would allow intended movements to proceed, whereas unintended movements would be suppressed by concomitant increased excitatory input via the indirect pathway in *other* GPi/SNr neurons (see discussions in refs. 145 and 309). Overall, the effect exerted by the two pathways in this case would be to further shape or sculpt the movement.

Both models are not entirely compatible with the available data. The focusing model, however, is difficult to reconcile with the fact that basal ganglia neurons become active after changes in cortex and thalamus are manifest (13,63, 73,75,103,202,293,294,309). Both models are at odds with the fact that although STN lesions (thus an interference with the indirect pathway) result in spontaneous dyskinesias, they do not directly disrupt or alter voluntary movements.

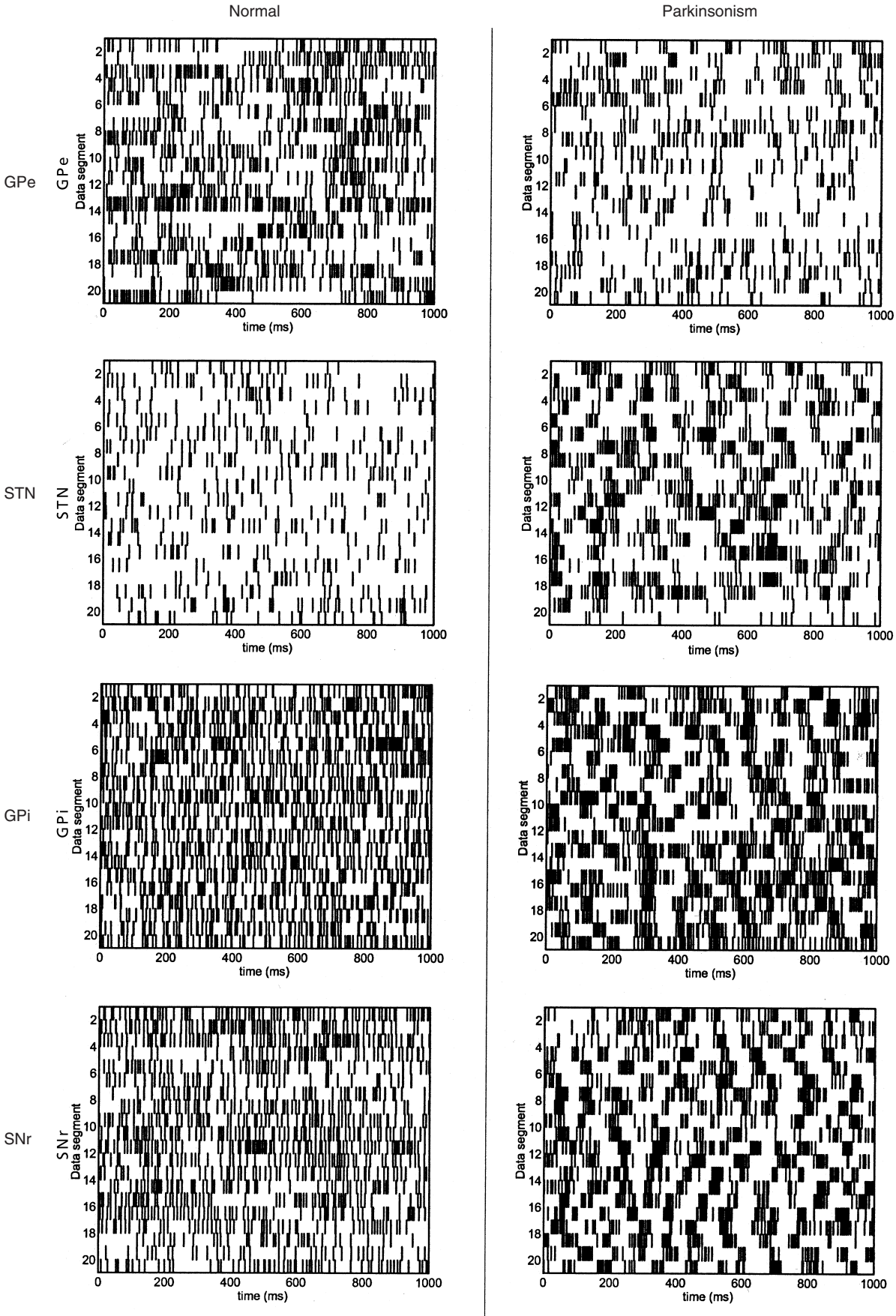
The view that the basal ganglia are involved in the direct control of ongoing movements is too simplistic. A multitude of other motor functions of the basal ganglia are strong candidates, such as a role in self-initiated (internally generated) movements, in motor (procedural) learning, and in movement sequencing (115,250,318). These can only be mentioned in passing here, but will probably gain greater prominence in future models of basal ganglia function.

CHANGES IN BASAL GANGLIA CIRCUIT ACTIVITY IN PARKINSONISM

Regardless of the precise causation of the disease, all of the proposed proparkinsonian mechanisms have in common interference with the synthesis, and release or action of dopamine in the basal ganglia as well as cortex and thalamus. The study of pathophysiologic changes in the basal ganglia that result from loss of dopaminergic transmission in the basal ganglia has been greatly facilitated by the discovery that primates treated with MPTP develop behavioral and anatomic changes that closely mimic the features of PD in humans (17,47,100,170).

Changes in the activity over striatopallidal pathways were first suggested by studies in MPTP-induced parkinsonism in primates that indicated that the metabolic activity (as measured with the 2-deoxyglucose technique) is increased in both pallidal segments (60,201,222,252). This was interpreted as evidence of increased activity of the striatum-GPe connection and the STN-GPi pathway, or, alternatively, as evidence of increased activity via the projections from the STN to both pallidal segments. It was then shown directly with microelectrode recordings of neuronal activity that MPTP-induced parkinsonism in primates is associated with reduced tonic neuronal discharge in GPe, and increased discharge in the STN and GPi, as compared to normal controls (see example recordings in Fig. 122.1) (31,39,94,

FIGURE 122.1. Raster displays of spontaneous neuronal activity recorded in different basal ganglia structures within the basal ganglia circuitry in normal and parkinsonian primates. Shown are ten consecutive 1000-msec segments of data from the external and internal segments of the globus pallidus (GPe, GPi, respectively), the subthalamic nucleus (STN), and the substantia nigra pars reticulata (SNr). The neuronal activity is reduced in GPe, and increased in STN, GPi, and SNr. In addition to the rate changes, there are also obvious changes in the firing patterns of neurons in all four structures, with a marked prominence of burstiness and oscillatory discharge patterns in the parkinsonian state. For further explanations, see text.


Normal
Parkinsonism
GPe
STN
GPi
SNr
GPe
STN
GPi
SNr
Data segment
time (ms)
0
200
400
600
800
1000
2
4
6
8
10
12
14
16
18
20

95,199). In parkinsonian patients undergoing pallidotomy it has also been shown that the discharge rates in GPe are significantly lower than those in GPi (83,182,284,302), as had previously been shown in the MPTP-primate model. Recently, we have shown that treatment with MPTP results also in changes of neuronal activity in the second output nucleus of the basal ganglia, the SNr (Fig. 122.1). These changes in activity are qualitatively similar to those occurring in GPi (312). In addition, loss of dopamine in the striatum should also lead to reduced activity via the inhibitory direct pathway. To date, this has not been directly demonstrated, however.

The changes in discharge rates in the subnuclei of the basal ganglia have been interpreted as indicating that striatal dopamine depletion leads to increased activity of striatal neurons of the indirect pathway, resulting in inhibition of GPe, and subsequent disinhibition of STN and GPi/SNr. The proposed pathophysiologic model of changes in the level of activity in the basal ganglia–thalamocortical motor circuit is summarized in Fig. 122.2.

The basal ganglia circuitry incorporates multiple negative and positive feedback loops that may play a prominent role in the development and maintenance of abnormal discharge in the basal ganglia output structures. Some of the primary feedback loops that may directly affect GPi activity involve intrinsic basal ganglia structures such as GPe and STN (the two pathways labeled *3* in Fig. 122.3), or structures outside of the basal ganglia, such as the thalamic nucleus CM (labeled *1* in Fig. 122.3), the PPN (labeled *2* in Fig, 122.3) (101,117,161,263), and the habenula (e.g., GPi → lateral habenula → raphe nuclei → SNc → striatum → direct, indirect pathway → GPi; not shown in Fig. 122.3). Positive

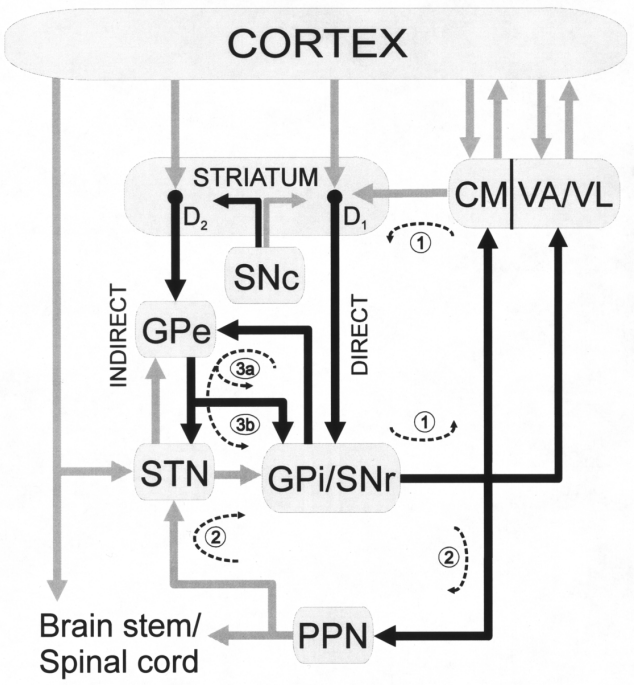


FIGURE 122.3. Simplified schematic diagram of the basal ganglia–thalamocortical circuitry under normal conditions. Inhibitory connections are shown as *filled arrows*, excitatory connections as *open arrows*. The principal input nuclei of the basal ganglia, the striatum, and the STN are connected to the output nuclei—GPi and SNr. Basal ganglia output is directed at several thalamic nuclei [ventral anterior/ventrolateral (VA/VL) and centromedian (CM)] and at brainstem nuclei [pedunculopontine nucleus (PPN) and others]. Some of the many important feedback connections are shown by the *dashed lines*. For further explanation of the model, see text.

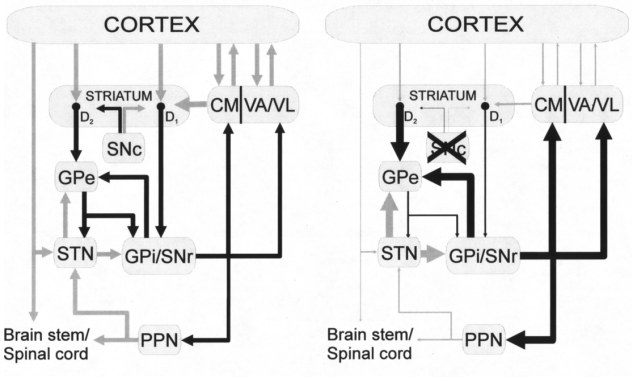


FIGURE 122.2. Model of the proposed rate changes in the basal ganglia–thalamocortical circuitry under normal (**left**) and parkinsonian conditions (**right**). In parkinsonism, dopaminergic neurons in the the substantia nigra pars compacta (SNc) degenerate, which results, via a cascade of changes in the other basal ganglia nuclei, in increased basal ganglia output from GPi and SNr. This, in turn, is thought to lead to inhibition of related thalamic and cortical neurons. In addition to the changes shown here, there are prominent alterations in discharge patterns (see text).

feedback loops, such as the one involving PPN and the STN (labeled *2*) and the pathway through CM and the putamen (labeled *1*) will tend to aggravate or enhance the abnormalities of discharge in the basal ganglia output nuclei associated with movement disorders, such as PD, whereas negative feedback circuits, such as a feedback involving CM and STN (not shown) will act to normalize neuronal discharge in the basal ganglia output nuclei. It is worth noting that via the CM nucleus, activity changes in the indirect pathway may influence the activity along the direct pathway. Thus, increased STN output in parkinsonism, by an action via GPi and CM, may result in a reduction of activity along the direct pathway.

The pathophysiology of early parkinsonism may differ from that of late parkinsonism in several aspect. For instance, increased STN output in early parkinsonism may have a compensatory function by increasing glutamatergic drive on SNc neurons. Thus, it has been shown that local injections of glutamate receptor blockers into the SNc significantly worsen motor signs in early stages of MPTP-induced parkinsonism (36,37), whereas such worsening is

no longer seen in later stages of the disease, probably reflecting loss of the majority of dopamine neurons in the SNc. At the same time, increased glutamatergic drive onto surviving SNc neurons may also be (excito-) toxic (239).

The reciprocal changes in activity in the indirect and direct pathways following dopamine depletion should both result in increased activity in GPi/SNr, and, subsequently, increased basal ganglia output to the thalamus and increased inhibition of thalamocortical neurons. The 2-deoxyglucose studies mentioned above demonstrated increased (synaptic) activity in the VA and VL nucleus of thalamus (60,201, 252), presumably reflecting increased inhibitory basal ganglia output to these nuclei. Consistent with this are positron emission tomography (PET) studies in parkinsonian patients that have consistently shown reduced activation of motor and premotor areas in such patients (42,48,54,88, 90), although no changes have been seen in the thalamus. Alterations of cortical activity in motor cortex and supplementary motor areas have also been demonstrated with single-cell recording in hemiparkinsonian primates (306).

The finding that SNr activity is also abnormal in parkinsonism is potentially important, because output from this nucleus reaches different cortical targets than output from GPi. For instance, the movement-related output from the SNr appears to reach predominately premotor areas, and could conceivably play a role in some aspects of akinesia (141). In addition, the SNr carries a substantial portion of the nonmotor circuitry of the basal ganglia. Abnormal SNr discharge may therefore be associated with some of the non-(limb)-motor abnormalities in parkinsonism, including oculomotor disturbances as well as cognitive, behavioral, and emotional disturbances.

Brainstem areas such as the PPN may also be involved in the development of parkinsonian signs. It has been shown that lesions of this nucleus in normal monkeys can lead to hemiakinesia, possibly by reducing stimulation of SNc neurons by input from the PPN, or by a direct influence on descending pathways (51,146,162,206). It remains unclear, however, whether the motor abnormalities seen after PPN inactivation in fact are related to parkinsonism or represent changes in the behavioral state or other disturbances that have no direct relation to PD. It is noteworthy that these animals do not manifest rigidity or tremor, which appear to be critically dependent on thalamic circuitry (see below).

It is important to realize that parkinsonism is a *network* disease. Changes that arise in any portion of the complex basal ganglia–thalamocortical circuitry will have significant consequences in all other areas of the network. This implies that the search for a parkinsonism-inducing "source" of abnormalities in the neuronal activity within the network may be futile, but suggests also that surgical or pharmacologic interventions at a variety of targets within the network could be successful. This can indeed be appreciated when considering the results of lesion studies in parkinsonian primates. One of the most important and dramatic in this regard was the demonstration that lesions of the STN in MPTP-treated primates reverse all of the cardinal signs of parkinsonism, presumably by reducing GPi activity (16,30, 119). Similarly, GPi and SNr inactivation have been shown to be effective against at least some parkinsonian signs in MPTP-treated primates (179,181,308,315).

Over the last decade, these results from animal studies have rekindled interest in functional neurosurgical approaches to the treatment of medically intractable PD. This was first employed in the form of GPi lesions (pallidotomy) (19,85,169,183,276,301) and, more recently, with STN lesions (108). In addition, high-frequency deep brain stimulation (DBS) of both the STN and GPi have been shown to reverse parkinsonian signs. The mechanism of action of DBS remains controversial. It appears most likely, however, that DBS and lesions act similarly in that both result in an overall reduction of basal ganglia output.

PET studies in pallidotomy patients performing a motor task have shown that frontal motor areas whose metabolic activity was reduced in the parkinsonian state became again active after the procedure (53,85), providing support for the concept of excessive pallidal inhibition of thalamocortical systems in PD, which, when eliminated, reverses the major parkinsonian signs. DBS of the STN and GPi have revealed similar changes with PET, further supporting this concept as well as the belief that DBS appears to act functionally like ablation.

The experience with inactivation or deep brain stimulation of the SNr is very limited at this point. There are no studies of the effects of (exclusive) lesioning of the SNr available, and one case report on the effects of (inadvertent) stimulation in the ventral STN/dorsal SNr area reported the appearance of psychiatric depression during episodes of stimulation (23). This clearly needs further study, but it seems that the SNr may not be a feasible target for surgical interventions, because of its prominent involvement in nonmotor functions, and possibly also because of the greater degree of overlap between the different functional territories in this nucleus (123,127,186).

Controversial Issues

It has long been clear that the aforementioned models of the pathophysiology of parkinsonism are too simplistic, and that they cannot explain many of the clinical and experimental features of the disease. Thus, although the results of lesions in parkinsonism seem at first glance easily explained by the above-mentioned rate-based model of parkinsonism, more detailed studies of the results of lesions in patients with parkinsonism have brought to light several important findings that are not compatible with the models. For instance, in contrast to the prediction of simple rate-based models, lesions of the "basal ganglia–receiving" areas of the thalamus (VA/VL) do not lead to parkinsonism and in fact are beneficial in the treatment of both tremor and

rigidity (45,109,220,290)). Similarly, lesions of GPi in the setting of parkinsonism lead to improvement in all aspects of PD without any obvious detrimental effects. Furthermore, they are, often in the same patient, effective against both parkinsonism and drug-induced dyskinesias (217, 235). In contrast to the abnormalities seen in parkinsonism, such dyskinesias are thought to arise from pathologic *reduction* in basal ganglia outflow (223,313), and thus should not respond positively to further reduction of pallidal outflow (190).

The assumption that parkinsonism may at least in part result from altered processing of proprioceptive input, abnormal timing, patterning, and synchronization of discharge that introduces errors and nonspecific noise into the thalamocortical signal may help to explain these seemingly paradoxical findings. Alterations in discharge patterns and synchronization between neighboring neurons have been extensively documented in parkinsonian monkeys and patients. For instance, neuronal responses to passive limb manipulations in STN, GPi and thalamus (31,95,199,299) have been shown to occur more often, to be more pronounced, and to have widened receptive fields after treatment with MPTP. There is also a marked change in the synchronization of discharge between neurons in the basal ganglia. Cross-correlation studies have revealed that a substantial proportion of neighboring neurons in the globus pallidus and STN discharge in unison in MPTP-treated primates (31). This is in contrast to the virtual absence of synchronized discharge of such neurons in normal monkeys (309). Finally, the proportion of cells in STN, GPi, and SNr that discharge in oscillatory or nonoscillatory bursts is greatly increased in the parkinsonian state (31,94,199,300, 302,311). Oscillatory burst discharge patterns are often seen in conjunction with tremor. The question of whether this is simply a reflection of tremor-related proprioceptive input or of active participation of basal ganglia in the generation of tremor is still unsettled (see below).

Conceivably, altered neuronal activity patterns in the basal ganglia may play an important role in parkinsonism. Thus, increased phasic activity in the basal ganglia may erroneously signal excessive movement or velocity to precentral motor areas, leading to a slowing or premature arrest of ongoing movements and to greater reliance on external clues during movement. Alternatively, phasic alteration of discharge in the basal ganglia may simply introduce noise into thalamic output to the cortex that is detrimental to cortical operations. The polarity and exact nature of the abnormal patterning and overall activity in the basal ganglia–thalamocortical pathways may determine the nature of the resulting movement disorder.

The foregoing discussion indicates that in patients with movement disorders it is not only the loss of basal ganglia contribution to movement that must be compensated for, but also the disruptive influence of the inappropriate basal ganglia output. The therapeutic benefits of GPi and STN lesions suggest that in patients with PD and other movement disorders the absence of basal ganglia input to the still intact portions of the basal ganglia–thalamocortical network is more tolerable than abnormal input. Near-normal motor function is still possible in these disorders once the abnormal basal ganglia–thalamocortical input is removed. It needs to be emphasized, however, that the surgical interventions do not necessarily normalize cortical motor mechanisms in parkinsonian subjects, but rather may allow the intact portions of the thalamocortical and brainstem system to more effectively compensate for the loss of the basal ganglia contribution to movement.

Another recent further challenge to the proposed pathophysiologic model of parkinsonism has arisen from histochemical studies on the amount of messenger RNA (mRNA) for GAD_{67}, one of the enzymes synthesizing γ-aminobutyric acid (GABA) in basal ganglia neurons. In contrast to GAD itself, which is found in neuronal cell bodies or terminals, the mRNA for the enzyme is thought to be contained exclusively in cell bodies. In these studies the GAD mRNA activity in a given nucleus is therefore taken as a parameter for the level of activity of GABAergic neurons in the nucleus under study. Experiments in parkinsonian primates have shown that, as expected from the above-mentioned model, GAD_{67} mRNA activity is increased in GPi neurons (131,132,269), and is reversed with levodopa administration. GAD_{67} mRNA activity in the GPi of humans with parkinsonism, however, was found to be similar to that in controls, possibly because these patients were chronically treated with levodopa (131,132). Some of the findings regarding GAD mRNA in GPe, however, are at odds with the above-mentioned model in which the activity of GABAergic neurons in GPe is decreased. In rats, primates and humans, GAD_{67} mRNA in GPe was either unchanged in the parkinsonian state or even increased (56,72,131,132,268). These results have been interpreted as evidence that GPe and GPi function may not be as tightly linked via the indirect pathway as proposed by the model outlined above, and that the observed activity changes in the basal ganglia may primarily be due to altered activity via the corticosubthalamic projection or dopaminergic inputs to STN itself, which, by changing STN activity, may cause the neuronal activity in both nuclei to increase, possibly due to a greater tendency of neurons to discharge in bursts (178). However, the consistent finding of significantly decreased GPe discharge in MPTP-treated animals (93,94,199) and patients with PD (83,182,284,302) is difficult to reconcile with the lack of change in GAD_{67} mRNA in GPe. Conceivably, GAD_{67}-mRNA levels may reflect something other than neuronal discharge rates (191,238), or may be greatly influenced by the emergence of burst discharges. In a recent study it was shown that GABA levels in the STN, which are at least in part reflective of GABA release from terminals of GPe axons, were reduced in MPTP-treated primates, as predicted by the above-mentioned model (267). This finding casts further

doubt on the assumption that GAD_{67}-mRNA levels are a reliable predictor of the activity along the GPe outflow pathways.

PATHOPHYSIOLOGY OF INDIVIDUAL PARKINSONIAN MOTOR SIGNS

Although the cardinal parkinsonian signs of tremor, rigidity, akinesia, and bradykinesia are generally all present in a given patient, they can occur independently of each other. For instance, patients with severe akinesia/bradykinesia do not necessarily exhibit tremor or rigidity, and severely akinetic patients may not experience significant bradykinesia or rigidity. This suggests that the different signs may depend on different pathophysiologic mechanisms, possibly involving different subcircuits of the larger motor circuit. The physiologic basis of the cardinal parkinsonian motor signs will be briefly considered in the following subsections.

Akinesia

Akinesia, the hallmark of PD, is characterized by a global impairment of movement initiation, affecting gross and fine movements as well as gait. In extreme cases, akinesia is experienced as freezing episodes, i.e., periods of complete motor block (107). Although there is some evidence that certain aspects of akinesia may be related to abnormal activity along the brainstem projections of the basal ganglia output nuclei (162), most authors attribute akinesia to changes in cortical processing, due to altered basal ganglia output to the thalamus. Freezing episodes may be the manifestation of temporary near-complete failure of compensatory mechanisms. This happens more often in late than in earlier stages of the disease, suggesting that the compensatory reserve of remaining intact thalamic, cortical, and brainstem circuits becomes smaller as the disease progresses.

As mentioned above, as a first approximation, overall discharge rates in the basal ganglia output nuclei have an impact on movement. GPi/SNr rates are determined by the amount of striatal dopamine, which in turn determines the balance between overall discharge in the direct and indirect pathways. There are many possible ways in which increased basal ganglia output could lead to akinesia. For instance, increased tonic inhibition of thalamocortical neurons by excessive output from GPi/SNr may reduce the responsiveness of cortical mechanisms involved in motor control. Increased tonic inhibition of thalamocortical neurons by increased basal ganglia output in parkinsonism may also render precentral motor areas less responsive to other inputs normally involved in initiating movements or may interfere with "set" functions that have been shown to be highly dependent on the integrity of basal ganglia pathways (6).

Akinesia may be a good example of a parkinsonian sign whose development appears to depend on discharge abnormalities in specific subcircuits of the motor loop. PET studies of cortical activation in akinesia-predominant parkinsonism suggest that the supplementary (SMA) and dorsal premotor areas are hypoactive in such patients (44,147). Moreover, pallidotomy results in increased metabolism in these areas in association with improvement in akinesia and bradykinesia (43,88,91,114,129,246). Further evidence for abnormal activity in these nuclei comes from studies of the Bereitschaftspotential (readiness potential), a slow negative cortical potential that precedes self-paced movements and is thought to reflect the neural activity in SMA (71). The early portion of the Bereitschaftspotential is smaller in parkinsonian patients than in age-matched controls (82,218), suggesting a deficit in the normal function of the SMA in the early stages of preparation for self-initiated movements. Akinesia may be thus related to abnormal discharge in a subcircuit whose activity may be to a large degree "preparatory" (5,12,40,61,148,251), interfering with the planning and early execution stages of movement. A disorganization of preparatory activity in SMA neurons was indeed identified with electrophysiologic methods in hemiparkinsonian primates (306).

One of the inconsistencies with the concept of akinesia as a consequence of increased inhibition of thalamocortical neurons is the finding that thalamic lesions per se do not appear to result in akinesia, as predicted by the model (but see ref. 49), although VA/VL lesions are effective in reducing rigidity and tremor. These findings argue against the view that increased tonic pallidal output and resulting inhibition of the neurons in the VA/VL nuclei is the sole or even the major reason for the development of akinesia. Alternatively, the fact that ventral thalamic lesions do not appear to influence akinesia may indicate that akinesia develops as a consequence of abnormally reduced activity in the intralaminar thalamic nuclei, or in the PPN with its descending brainstem projections. As discussed earlier, CM/Pf involvement may be the reason for the finding of prominent changes in cortical activity associated with akinesia, whereas involvement of the PPN is suggested by the finding that lesions of this structure result in poverty of movement (162, 206).

Bradykinesia

Although bradykinesia is usually associated with akinesia, as mentioned earlier, these two signs can be strikingly dissociated in some patients. The pathophysiology of bradykinesia may be closely associated with the postulated scaling function of basal ganglia output (see above) (25,305) and is probably also dependent on abnormal processing in prefrontal cortical areas that are strongly influenced by increased basal ganglia output. In normal monkeys, neurophysiologic studies and, more recently, PET studies investigating cerebral blood flow have described an influ-

ence of velocity/amplitude on the discharge of neurons in these premotor cortical areas (21,62,130,296).

Conceivably, abnormally increased phasic GPi/SNr output during movement may signal excessive speed and/or amplitude of ongoing movement, leading to a corrective reduction in cortical motor output (as mentioned above). PET studies, measuring cerebral blood flow in human parkinsonian patients investigated before and during deep brain stimulation of GPi, have revealed that stimulation that improved bradykinesia led to an increase in blood flow in the ipsilateral premotor cortical areas (69). A PET study has shown a significant correlation between movement speed and basal ganglia activation (296), and the loss of this in PD (Turner et al., personal communication). Thus there are several independent lines of evidence for the role of the basal ganglia motor circuitry in the scaling of movement and the disruption of this in diseases such as PD.

Rigidity

Parkinsonian rigidity is characterized by a uniform (''plastic'') increase in resistance to passive movements about individual joints. A ''cogwheel'' feature may result from superimposed, and usually subclinical, tremor (96). The pathophysiology of rigidity is elusive, but it has been suggested that altered basal ganglia output, mediated via the PPN and its output to the pontine nucleus gigantocellularis and the dorsal longitudinal fasciculus of the reticulospinal projection, may lead to increased inhibition of spinal Ib interneurons, which in turn may disinhibit α-motoneurons (50,76,139,175). Abnormalities of long-latency reflexes (LLRs) may also play a role in abnormal α-motoneuron excitability (26,174,291,292,316), although the velocity-independence of rigidity suggests that it is not a reflex phenomenon per se. The finding that rigidity can be abolished by interruption of the basal ganglia–thalamocortical circuit at multiple levels (STN, GPi, and thalamus) suggests that pallidal output leads to rigidity via the thalamocortical route rather than via brainstem projections.

Tremor

Parkinsonian tremor is typically a 4- to 5-Hz tremor at rest that is suppressed by voluntary movement. Parkinsonian tremor has been shown to be critically dependent on the integrity of the thalamic nucleus ventralis intermedius (Vim), which contains neurons that exhibit oscillatory discharge at the tremor frequency (177,214,219), although a tight correlation between oscillatory discharge and tremor is often not observed (28,221). Lesions of Vim have also been shown to abolish tremor (207). It has been proposed that thalamic oscillatory discharge may be induced by hyperpolarization of these cells induced by increased inhibitory basal ganglia output (224). This increases the likelihood that these cells will discharge in bursts (156,180,278). On the other hand, tremor may also arise from oscillatory discharge originating within the basal ganglia, based on the finding of oscillatory discharge patterns in the STN and GPi in parkinsonian patients and animals (31,84,150,284, 311). These oscillatory discharge patterns may arise from local pacemaker networks, such as a feedback circuit involving GPe and STN (232). It has also been speculated that intrinsic membrane properties of basal ganglia neurons are conducive to the development of oscillatory discharge (15, 34,209) in basal ganglia neurons themselves, or that they may contribute to the generation of oscillatory discharge in the thalamus (303,310,313), which may then be transmitted to the cortex. Finally, and perhaps most likely, oscillations throughout the entire basal ganglia–thalamocortical network may be tightly related to each other, so that no one oscillator can be identified as their sole source (187, 188).

Support for the concept that altered basal ganglia discharge either alone or as part of the basal ganglia–thalamocortical network is important in the pathogenesis of tremor comes from lesion studies showing that parkinsonian tremor in MPTP-treated African green monkeys and in patients with parkinsonism is significantly ameliorated by lesions of the STN and GPi (19,29,284,310). It has been suggested that loss of *extrastriatal* dopamine may contribute to the development of tremor, because primates in which MPTP treatment affects the dopamine supply to GPi (African green monkeys) tend to develop tremor, whereas species in which the dopamine supply to GPi is not as severely affected (Rhesus monkeys) rarely develop parkinsonian tremor (28). Furthermore, in a postmortem study it was found that the degree of dopamine loss in the striatum did not correlate with the extent of tremor in parkinsonian patients, whereas the degree of dopamine loss in the pallidum did (32). More direct evidence for a role of extrastriatal dopamine in the development of tremor is lacking, however.

It remains unclear which oscillation frequency within the basal ganglia in fact is related to tremor. Oscillatory discharge in the basal ganglia of MPTP-treated primates has been shown to occur in at least two different frequency bands—the 3- to 5-Hz range, and the 8- to 15-Hz range (28,31,310). Although, intuitively, discharge in the lower frequency range would be expected to be more directly related to tremor at the typical parkinsonian frequency range, there is some evidence that oscillations in the higher frequency range in fact may be an important determinant of tremor. Thus, in MPTP-treated animals in which tremor had been eliminated with STN lesions, oscillations in the 8- to 10-Hz range in GPi were also greatly reduced, whereas oscillatory discharge in the lower frequency band persisted (310). In addition, basal ganglia neurons in tremulous animals show considerable coherence in the 8- to 15-Hz range, but not in the 3- to 5-Hz range (28). A process by which 10-Hz oscillations could be transformed in the thalamus into 5-Hz oscillatory discharge has been proposed by Pare

et al. (224). However, even primate species that generally do not show tremor after MPTP treatment (i.e., Rhesus monkeys) develop 8- to 13-Hz oscillations in the basal ganglia output nuclei (28,31,199,312). The difference between monkeys with and those without tremor may therefore lie not in the presence or absence of oscillations, but rather in the degree of synchronization between neighboring neurons. For tremor to occur, significant synchrony with little phase difference in large neuronal assemblies may be required. Thus, in one study the phase shift distribution of oscillatory cross-correlograms of neighboring pallidal cells in MPTP-treated vervet monkey were tightly clustered around a 0-degree phase shift, whereas the oscillatory correlograms in the MPTP-treated rhesus monkey were more widely scattered between 0 and 180 degrees (28). It is tempting to implicate the motor subcircuit that is centered on the motor cortex in the pathogenesis of tremor, because tremor-related neurons are focused primarily in the most ventral portions of the sensorimotor GPi (118), a region that in the monkey has been shown to project (via the thalamus) to the motor cortex.

Nonmotor Symptoms of Parkinson's Disease

Besides the cardinal (and early) skeletomotor abnormalities, parkinsonism is also associated with oculomotor abnormalities, such as hypometric and slow saccades (41,138,184,185, 255,298,307), autonomic dysfunction, depression, anxiety, sleep disturbances, impaired visuospatial orientation and cognitive abnormalities (18,64,67,194,275). It is likely that at least some of these abnormalities rely on abnormal discharge in nonmotor circuits of the basal ganglia, which may be affected by dopamine loss in much the same way as the motor circuit. This is particularly true for oculomotor abnormalities that may directly result from dopamine depletion in the caudate nucleus (151,164). Similarly, some (20) of the cognitive and psychiatric disturbances seen in parkinsonian patients are reminiscent of syndromes seen after lesions of the dorsolateral prefrontal cortex (problems with executive functions) or of the anterior cingulate (apathy, personality changes), and may be the result of loss of dopamine in the dorsolateral or ventral caudate nucleus, respectively (65). Besides abnormalities in dopaminergic transmission in the striatum, several studies indicate that concomitant noradrenergic and serotoninergic deficiencies could contribute to the mood alteration in PD. For instance, cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindolacetic acid are reduced in depressed parkinsonian patients compared with nondepressed parkinsonian patients, and selective serotonin reuptake inhibitors are effective in treating parkinsonian depression (10,67,195). Finally, disturbance of the normal function of cortical–basal ganglia–thalamocortical circuits has also been implicated in the occurrence of obsessive-compulsive disease, as well as in Tourette's syndrome (66,89,133).

CONCLUSION

From the considerations above, a complex model of parkinsonism emerges in which relatively selective dopamine depletion in the striatum and other basal ganglia nuclei results in increased and disordered discharge and synchronization in motor areas of the basal ganglia–thalamocortical motor loops. Abnormal activity in one or more of the basal ganglia feedback loops may contribute to the development of parkinsonism. Individual parkinsonian motor signs appear to be caused by distinct abnormalities in basal ganglia discharge, and by involvement of specific subcircuits related to distinct cortical targets. It is probable that progressive loss of dopamine in nonmotor areas of the striatum and other basal ganglia nuclei may underlie the nonmotor abnormalities of PD. By contrast, drug-induced dyskinesias are characterized by decreased pallidal output. Differences in the balance between direct and indirect pathways, and in the degree of synchronization of discharge in the basal ganglia output nuclei must be invoked to explain the striking clinical differences between PD and the drug-induced dyskinesias and dystonia. A critical analysis of the effects of pallidal and thalamic lesions in hypo- and hyperkinetic disorders strongly suggests that the main features accounting for the different signs of movement disorders are the appearance of not only changes in discharge rate, but also altered discharge patterns, changes in the degree of synchronization of discharge, altered proprioceptive feedback, and ''noise'' in the basal ganglia output signal. It is proposed that both ablation and deep brain stimulation are effective in treating both hypo- and hyperkinetic disorders because they both remove the abnormal signals directed to the thalamus and brainstem, thus allowing these intact systems to compensate more effectively.

The current models of basal ganglia pathophysiology are incomplete and should be taken as a first draft of basal ganglia dysfunction in the different disease states. Most pertinently, changes in phasic discharge patterns, and new anatomic connections need to be better incorporated into any new concept of basal ganglia function and a greater emphasis placed on the manner in which thalamic, brainstem, and cortical neurons utilize basal ganglia output.

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