Six different *LRRK2* mutations have been linked to PD, with Gly2019Ser being the most common. The mechanism responsible for cell death with this mutation is not known but is thought to involve changes in kinase activity with altered phosphorylation of target proteins (including autophosphorylation) and possibly lysosomal dysfunction. Kinase inhibitors can block toxicity associated with *LRRK2* mutations in laboratory models, and there has been much interest in developing drugs directed at this target. However, kinase inhibitors are likely to be toxic, the physiologic role of *LRRK2* is not known, and the large majority of PD patients do not carry a *LRRK2* mutation.

Mutations in *PINK1* and *parkin* have implicated mitochondrial dysfunction as a possible cause of PD. Recent studies suggest a role for parkin and PINK1 proteins in the turnover and clearance of damaged mitochondria (mitophagy), and mutations in *parkin* and *PINK1* cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of parkin. This is a particularly attractive target because postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons.

Thus, evidence is accumulating that genetics plays an important role in both familial and "sporadic" forms of PD. It is anticipated that better understanding of the pathways responsible for cell death caused by these mutations will permit the development of more relevant animal models of PD and targets for the development of neuroprotective drugs.

PATHOPHYSIOLOGY OF PD

The classic model of the organization of the basal ganglia in the normal and PD states is provided in Fig. 449-5. With respect to motor function, a series of neuronal circuits or loops link the basal ganglia nuclei with corresponding cortical motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on the activity of the output pathway. The output of the basal ganglia provides inhibitory (GABAergic) tone to thalamic and brainstem neurons that in turn connect to motor systems in the cerebral cortex and spinal cord that control motor function. Physiologically, decreased neuronal activity in the GPi/SNr is associated with movement facilitation and vice versa. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network. The basal ganglia and similar cortical loops are now thought to also play an important role in regulating normal behavioral, emotional, and cognitive functions.

In PD, dopamine denervation with loss of dopaminergic tone leads to increased firing of neurons in the STN and GPi, excessive inhibition of the thalamus, reduced activation of cortical motor systems, and the development of parkinsonian features (Fig. 449-5). The current role of surgery in the treatment of PD is based on this model, which predicted that lesions or high-frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features.

TREATMENT PARKINSON'S DISEASE

LEVODOPA

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by Carlsson demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients and suggested the potential benefit of dopaminergic replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, a precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting due to activation of dopamine receptors in the area postrema that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet), whereas in

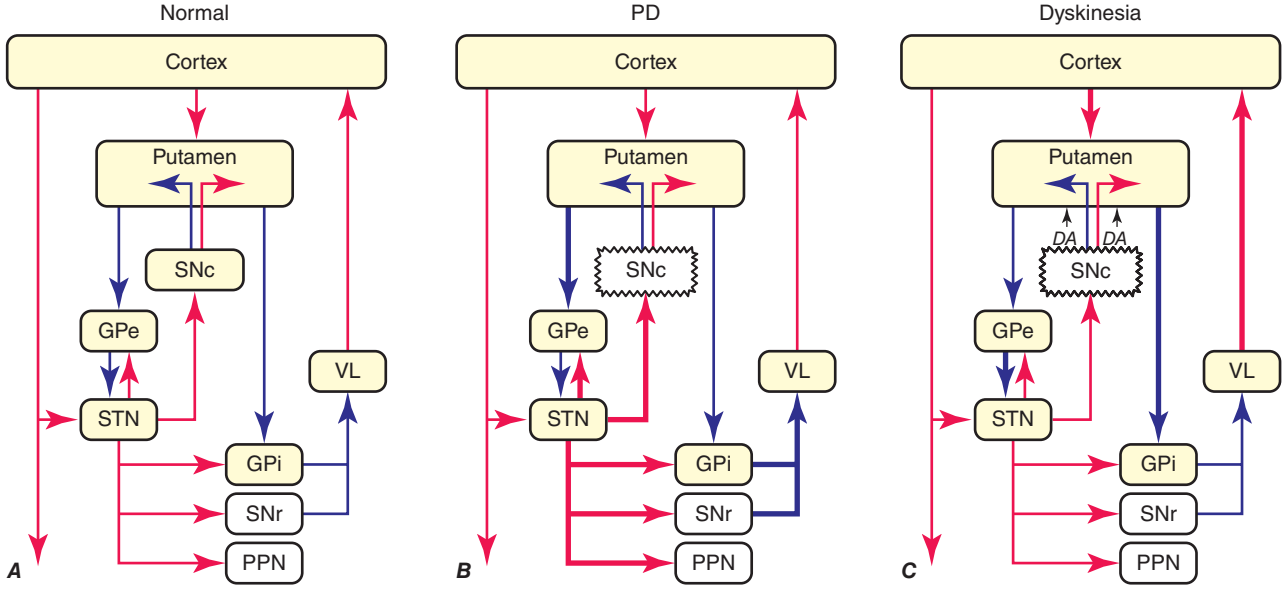

FIGURE 449-5 Basal ganglia organization. Classic model of the organization of the basal ganglia in the normal (***A***), Parkinson's disease (PD) (***B***), and levodopa-induced dyskinesia (***C***) state. Inhibitory connections are shown as *blue arrows* and excitatory connections as *red arrows*. The striatum is the major input region and receives its major input from the cortex. The GPi and SNr are the major output regions, and they project to the thalamocortical and brainstem motor regions. The striatum and GPi/SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPi and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions, resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct because lesions of the GPi ameliorate rather than increase dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia. DBS, deep brain stimulation; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventrolateral thalamus. *(Derived from JA Obeso et al: Trends Neurosci 23:S8, 2000.)*