Parkinson's Disease:

Part II. Cellular Basis of Medical Treatment

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Parkinson's disease has a variety of medical treatment options, most of which act on the dopaminergic systems of the basal ganglia. Especially under conditions of denervation, the physiology of basal ganglia neurotransmission is complex, and no single agent is sufficient to address all the motor, cognitive, and autonomic symptoms. For this reason, emerging treatments, such as neuroprotective drugs, restorative cell and gene-based approaches, and surgical options remain an essential complement to polypharmacy with the existing drugs.

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While the causes of Parkinson's disease (PD) and the underlying reasons for the dysregulation of motor, autonomic, and cognitive function are complex, the precipitating event on the cellular level appears to be clear: there is a loss of dopaminergic projections from the substantia nigra pars compacta to the striatum (i.e., the caudate nucleus and putamen).

Nigrostriatal dopaminergic neurodegeneration was first described in the mid-20th century by Dr. Oleh Hornykiewicz, who dissected autopsy specimens and described the neuropathologic characteristics of idiopathic PD. Working independently, Dr. Arvid Carlsson did seminal research that led to recognition of dopamine as an important neurotransmitter in the basal ganglia that is lacking in PD.

With the discovery of dopamine as a key neurotransmitter in the basal ganglia, it was realized that dopamine replacement represented a promising treatment for PD. The widespread introduction of levodopa (L-dopa) in the 1970s immediately helped many patients with their symptoms of akinesia, rigidity, and tremor. Yet, it quickly became apparent that L-dopa has serious side effects and limited long-term efficacy.

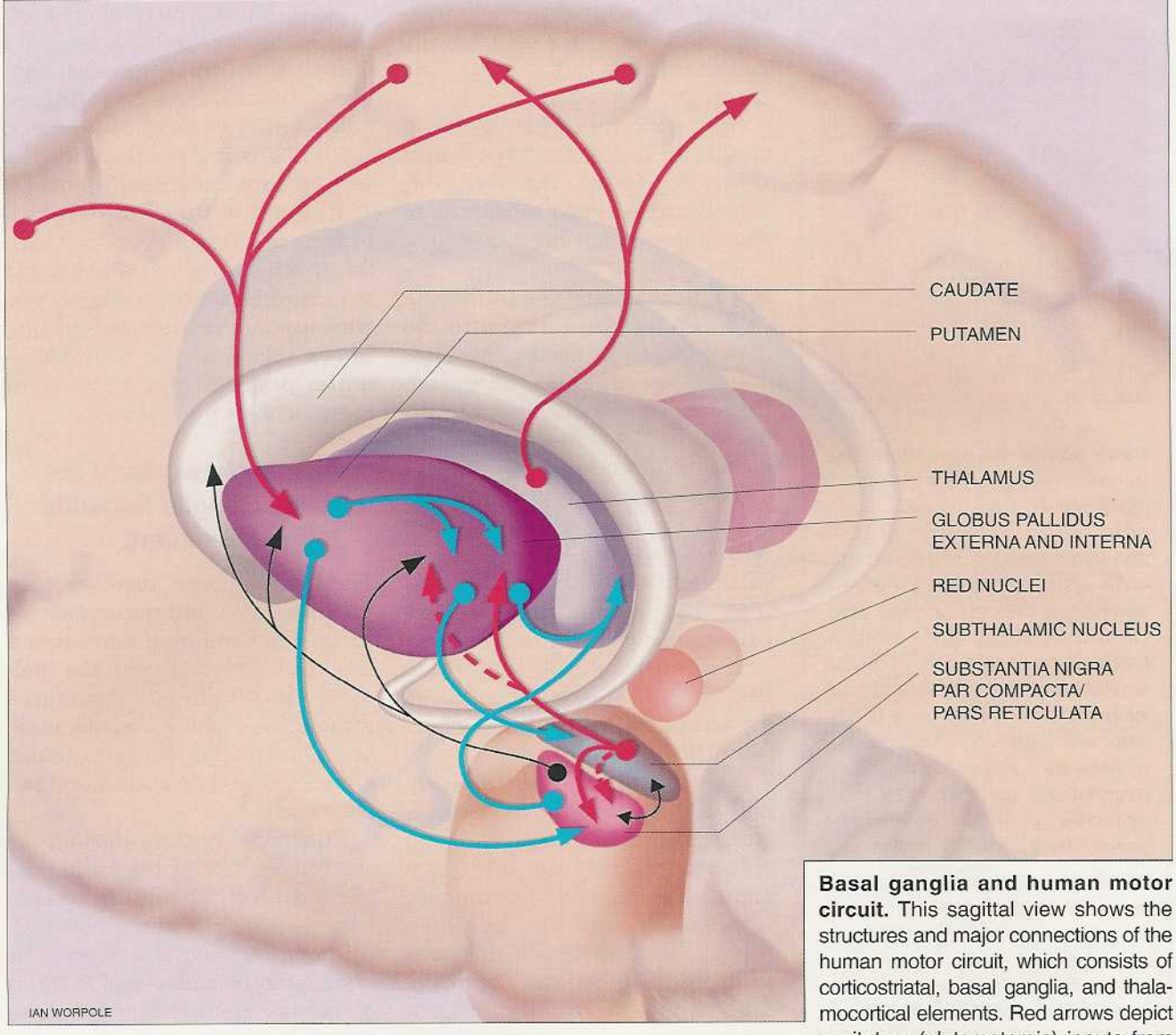
A variety of other drugs are currently available for use as adjuncts to standard L-dopa or surgical therapies. Unfortunately, none has proven superior to L-dopa monotherapy in terms of symptomatic relief, and all have significant side effects. At present, reformulations of existing drug classes, newer gene-based drug therapies, and novel methods of drug delivery such as neurosurgical depot administration may offer the best emerging drug options.

This article examines the disruption of dopaminergic transmission in the basal ganglia and reviews the agents currently used in the treatment of PD.

Dopaminergic Degeneration Occurs Primarily in the Basal Ganglia

Before the work of Hornykiewicz and Carlsson, it was apparent that motor systems, and the basal ganglia in particular, were involved in the pathogenesis of tremor and akinesia seen in PD, but the details of neurotransmission remained unclear. Striatal dopamine depletion occurs in PD due to a near complete loss of nigrostriatal afferent fibers. This depletion in dopamine is most pronounced in the postcommissural putamen, which is the sensorimotor territory.

In October 2000, Dr. Arvid Carlsson, along with Paul Greengard and Eric Kandel, was awarded a Nobel Prize for his work in elucidating the dopaminergic neurotransmitter system and its depletion in PD.



Basal ganglia and human motor circuit. This sagittal view shows the structures and major connections of the human motor circuit, which consists of corticostriatal, basal ganglia, and thalamocortical elements. Red arrows depict excitatory (glutamatergic) inputs from the cortex to basal ganglia, blue arrows depict inhibitory (GABAergic) connections among basal ganglia constituents, and black arrows depict dopaminergic efferents from the substantia nigra.

The globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr) are the principal output pathways of the basal ganglia to the thalamus, which projects back to the supplementary motor cortex to complete the circuit. Descending pathways (not shown) also exist between the thalamus and brainstem through the red nuclei, and fibers also pass from the substantia nigra and globus pallidus to the brainstem (nigroreticular and pallidoreticular tracts).

The essential neuropathologic feature of PD is the "Lewy body," named after the 20th-century German-American neurologist Dr. Friedrich Lewy. These intracellular proteinaceous aggregates are found in nigral and extranigral sites in monoaminergic and cholinergic neurons and throughout the autonomic nervous system.

Given their presence throughout the brain and in peripheral ganglia, not strictly within the dopaminergic system, the pathophysiology of PD is more diffuse than once thought. Recent evidence also suggests that Lewy bodies may first appear in extranigral, rather than nigral, sites.

Cellular degeneration in PD classically occurs in the ventral tegmental dopaminergic region of the midbrain and affects all areas that receive input from this region. This includes the striatum, amygdala, basal nucleus of Meynert, and frontal cortex, which may explain the disruption of motor as well as nonmotor systems.

The neuronal loss in the substantia nigra pars compacta (SNc) itself is often nonuniform and is usually most pronounced in the lateral ventral tier of the SNc. In comparison, in normal aging, the opposite pattern is seen, with the dorsal tier being primarily affected. In PD, the lightly melanized

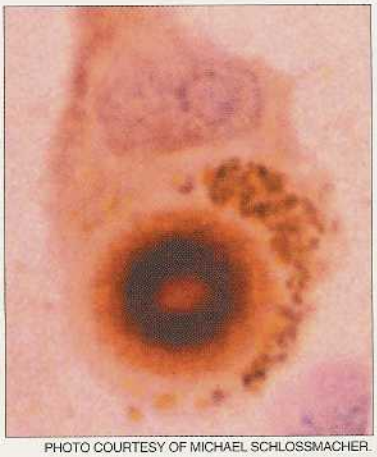


PHOTO COURTESY OF MICHAEL SCHLOSSMACHER.

Lewy bodies are intracellular proteinaceous aggregates found in nigral and extranigral sites in monoaminergic and cholinergic neurons and throughout the autonomic nervous system. Classical brainstem Lewy bodies are eosinophilic cytoplasmic inclusions with peripheral halos and dense cores, whereas cortical Lewy bodies are morphologically less well defined. Lewy bodies react with antibodies to cytoskeletal proteins such as neurofilament and neurotubulin, and also react to α-synuclein, ubiquitin, parkin, and paired helical filament epitopes.

Within the autonomic nervous system, Lewy bodies have been reported in the hypothalamus, Edinger-Westphal and dorsal vagal nuclei, intermediolateral columns, and sympathetic and parasympathetic ganglia. Outside the substantia nigra, Lewy bodies also may be found in the nucleus basilis of Meynert, locus coeruleus, raphe nuclei, thalamus, and cerebral cortex.

cells of the ventral tier preferentially degenerate, but more heavily melanized cells in the dorsal tier are spared.

The significance of this pattern of cell loss is unknown, but it may reflect cell-specific differences in gene expression and sensitivity to environmental insults.

Whereas the dopaminergic system is essential to the pathology of PD, nondopaminergic systems are also affected, including cholinergic transmission in the nucleus basilis of Meynert and the dorsal motor nucleus of the vagus.

The cholinergic system is mostly spared, however, and may in fact become overactive in the striatum relative to the dopaminergic system. This abnormality is the rationale behind symptomatic anticholinergic drug therapy in PD, to help balance the output of dopaminergic and cholinergic neurotransmission.

Noradrenergic transmission may be affected in the locus coeruleus, and there are decreased levels of serotonin in the substantia nigra, striatum, and hippocampus, which may underlie common behavioral syndromes in PD such as depression. Striatal neuropeptides may be decreased in parkinsonism, and opioid receptor binding in the putamen and thalamus is decreased in patients with dyskinesias, suggesting a reduced availability of these receptors under conditions of altered dopaminergic transmission.

Glutamate also is an important neurotransmitter in the corticostriatal pathway and in the "indirect" pathway through the subthalamic nucleus. Glutamate has been implicated in excitotoxicity through subthalamic nuclei connections.

Aside from dopamine, GABA is arguably the most critical neurotransmitter in the motor circuit, with very high concentrations found in efferents from the substantia nigra pars reticulata (SNr) and the globus pallidus.

As with motor processing in cerebellar Purkinje cells, the primary output signal from the basal ganglia to the thalamus is GABAergic and inhibitory, and this anatomic feature has implications for the pathogenesis and treatment of PD.

In terms of the relative contributions of various neurotransmitter systems to PD, it is important to recognize that these distinct systems are interrelated and changes in one region or one neurotransmitter pathway may affect other components of the system.

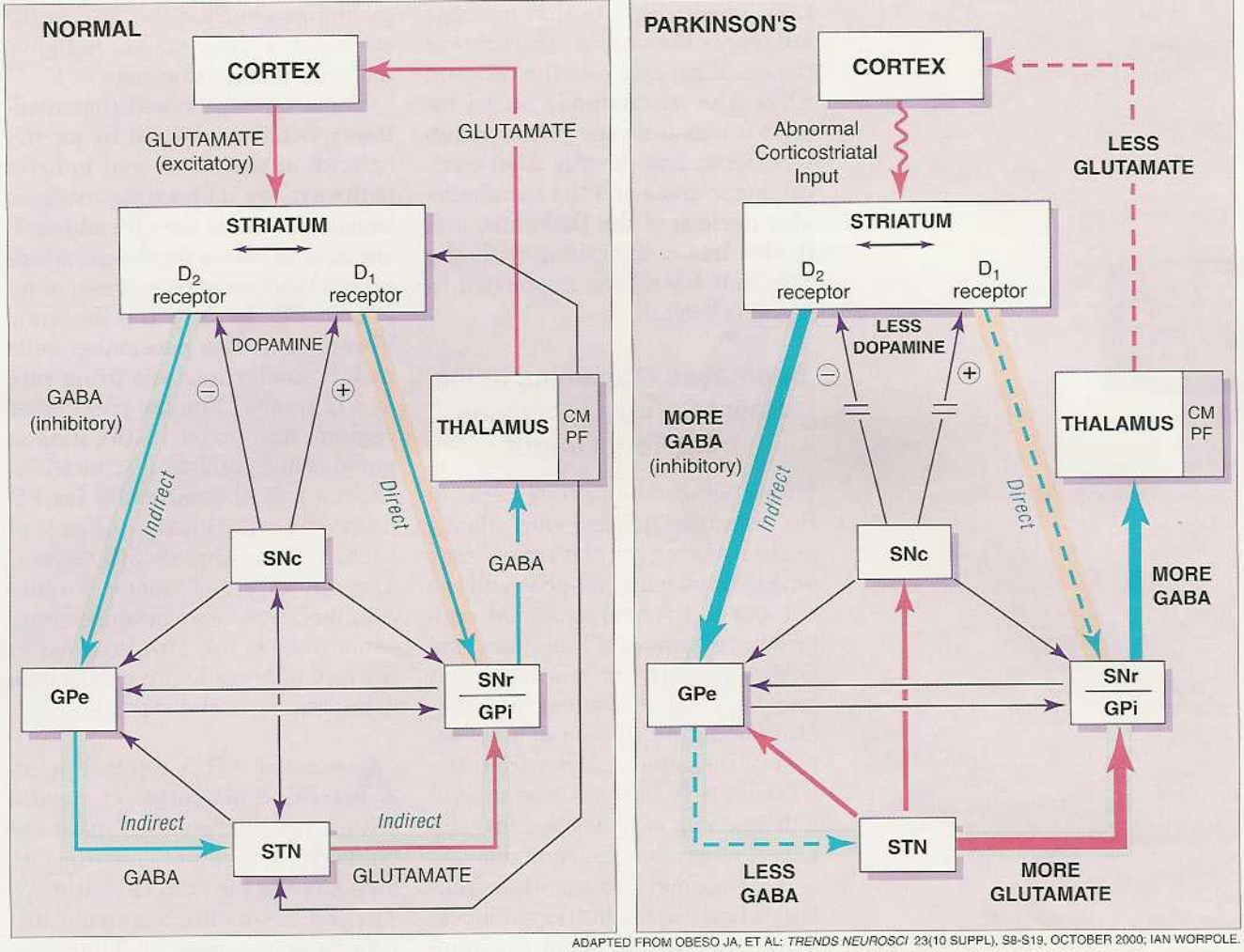
Neural Networks in the Basal Ganglia Regulate Movement

The basal ganglia, together with the cerebellum, are responsible for processing complex movements through connections with the thalamus. Basal ganglia structures include the caudate nucleus, putamen, globus pallidus, substantia nigra (SNr and SNc), and subthalamic nuclei.

Functional relationships among the components of the basal ganglia have been established by electrophysiologic recording, microdialysis, and ablation techniques. The system can be understood in terms of its basic input and output structures.

The main input structure of the basal ganglia is the striatum (i.e., caudate nucleus and putamen), which is the target for cortical afferent fibers from the sensorimotor cortex as well as dopaminergic fibers from the SNc. Corticostriatal projections terminate mainly in the putamen.

The primary basal ganglia output structure is the globus pallidus pars interna (GPi) and the SNr, which project to the thalamus and brainstem. Thalamic afferents from this region are directed to the ventroanterior, ventromedial, and centromedial nuclei of the thalamus, which in turn project to the cortex, putamen, and midbrain. There, they influence bulbar nuclei and the spinal cord.



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Connections among basal ganglia elements in the normal brain and in Parkinson's disease. This idealized representation represents a modern version of the "classical" basal ganglia schema as proposed by Albin, Young, and Penney and modified by others, such as Alexander and Crutcher, to include the "direct" and "indirect" pathways. Many other types of neurotransmitter connections are also present.

The "direct" pathway is believed to operate by exciting D_1 dopaminergic neurons in the striatum which project to the output structures of the GPi and SNr. In the indirect pathway, stimulation of D_2 receptors in the striatum leads to inhibition of neurons projecting to the globus pallidus externa (Gpe), subthalamic nucleus (STN), and then to the output structures.

In PD, dopamine depletion in the striatum leads to disinhibition of D_2-receptor-bearing neurons in the indirect pathway, producing increased inhibition of GPe and disinhibition of STN. The resulting overactivity in STN neurons leads to excess excitation of the GPi/SNr and overinhibition of the thalamocortical and brainstem motor centers. (CM, centromedian nuclei; PF, parafascicular nuclei [in thalamus].)

In the classical schema of basal ganglia neural networks as proposed by Albin, Young, and Penney in the late 1980s, motor input from the corticostriatal pathway reaches the basal ganglia output structures and thalamus via two parallel pathways, known as "direct" and "indirect." Recent cell tracing studies, however, have shown considerable connectivity and overlap between these two pathways, calling into question the role of the indirect pathway (as originally conceived) on basal ganglia output structures.

The "direct" monosynaptic pathway goes from the putamen to the GPi and SNr, whereas the "indirect" pathway passes through the globus pallidus externa and subthalamic nucleus. In addition, reciprocal connections exist between the globus pallidus externa and the GPi/ SNr that bypass the subthalamic nuclei.

Along with the globus pallidus externa, the subthalamic nucleus appears to be a particularly impor-

tant integrative site that strongly influences the output structures of the basal ganglia (i.e., the GPi and SNr). The subthalamic nuclei receive inputs from the globus pallidus externa and directly from cortical motor areas and the parafascicular nucleus of the thalamus, and it also has connections with the SNc that have been implicated in nigral cell death.

Decreased Dopamine in the Basal Ganglia Increases Inhibitory Output

Except for excitatory projections in the corticostriatal and subthalamic nucleus pathways, the connections among basal ganglia nuclei and the outputs to the thalamus and midbrain are primarily inhibitory and GABAergic. In the normal basal ganglia, the end result of nigrostriatal dopamine release is a reduction of inhibitory output from the GPi and SNr to the thalamus and a dampening of phasic cortical signals through the basal ganglia.

This normal process of disinhibition leads to facilitation of movements, due to increased thalamocortical signaling. Because output from the GPi and SNr to the thalamus is inhibitory, in parkinsonian patients a decrease in dopaminergic activity through the direct or indirect loop results in increased inhibitory output to the thalamus.

In PD, the subthalamic nucleus is markedly overactive due to decreased inhibition by the globus pallidus externa through the indirect pathway, which increases the excitatory drive upon the GPi and SNr and leads to increased GABAergic transmission from those output nuclei to the thalamus.

This increased tonic inhibitory activity helps to explain the akinesia and postural instability seen in PD, but it does not easily account for tremor. It is thought that an imbalance between the direct and indirect pathways is important in simultaneously promoting akinesia and tremor, which possibly includes altered modulatory dopaminergic influences from the SNc to the striatum, cortex, globus pallidus, and subthalamic nucleus.

Some have proposed that oscillatory behavior caused by an imbalance of the direct and indirect pathways, by unmasking intrinsic tremor circuits in the GPi and thalamus, is to blame for the paradoxical combination of tremor and akinesia in PD. In fact, the thalamic Vim nucleus has pacemaker cells with a similar intrinsic firing rate as PD tremor. Similar pacemaker regions may exist in the globus pallidus and subthalamic nuclei.

As surgical treatments for PD have shown, ablation of any of these regions can abolish tremor. The physiology of tremor is quite complex, however, because these same regions are also involved in the seemingly opposite phenomena of bradykinesia and rigidity.

As noted, PD is typified by increased activation of striatal output via the "indirect" pathway but decreased inhibition of the GPi and SNr via the "direct" pathway. The end result of this systemic disruption is increased inhibitory signaling to the thalamus through the output tracts of the basal ganglia. There is also a failure to modulate other parallel circuits, which can lead to the emergence of tremor, dyskinesias, and other paradoxical symptoms.

It is likely that compensatory changes occur in local gene expression in the striatum, globus pallidus, and subthalamic nuclei following the disruption in dopaminergic transmission and other neurotransmitter systems (e.g., cholinergic interneurons) that control accessory functions in the basal ganglia.

Inhibition of thalamocortical neurons in PD may render cortical motor areas less responsive to other inputs involved in the regulation of movement, also leading to bradykinesia or akinesia. Feedback loops within the cortex may be affected, and proprioceptive and spinal sensory input to the thalamus also may be abnormally processed.

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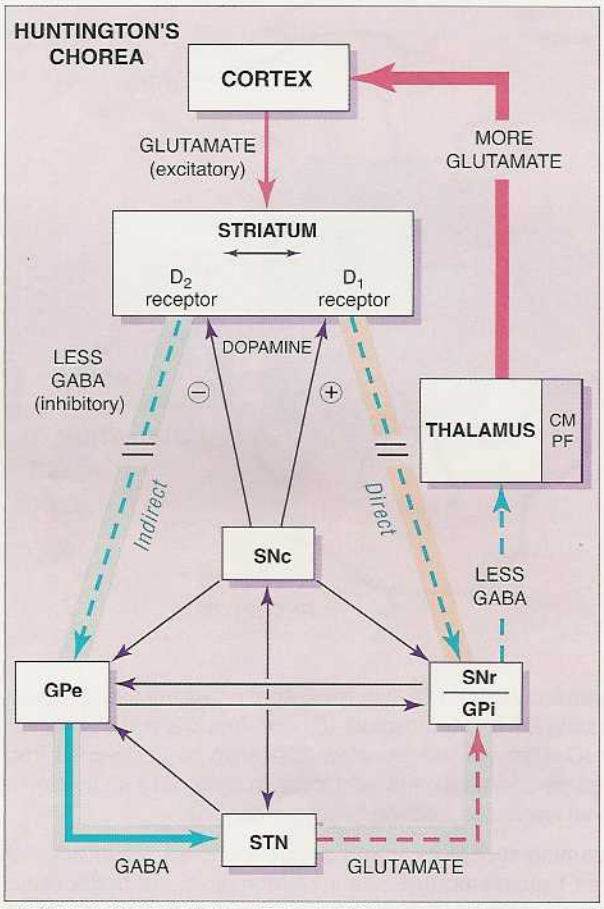
GABAergic Loss in Huntington's Disease Produces Excitatory Output

The abnormal basal ganglia circuit in Huntington's disease may offer additional insight into the abnormal circuits in PD. GABAergic cell death occurs throughout the striatum in Huntington's disease, due in part to amplified trinucleotide repeats in the Huntington's gene.

Striatal GABAergic depletion leads to a net downregulation of the subthalamic nuclei through the "indirect" pathway and a decrease of tonic excitatory transmission to the primary output nuclei (GPi/SNr). The "direct" pathway is also inhibited through loss of striatal GABAergic neurons, which would be predicted to exert a net disinhibitory effect on the output nuclei, but this pathway appears to be less important. The net result is that there is less inhibitory signaling from the output nuclei to the thalamus, leading to increased glutamatergic signaling and pronounced dyskinesias.

It is interesting that dyskinesias also occur as a common side effect of longstanding treatment with the dopamine precursor L-dopa in PD, which reflects long-term changes in striatal dopaminergic receptors. In PD, dyskinesias occur when drug dosing produces rapid fluctuations of dopaminergic signaling in an environment of striatal dopaminergic deafferentation and receptor sensitization. In managing dyskinesias, the thalamus may be the most relevant target for downregulation, whereas for akinesia, the inhibitory actions of other nuclei (e.g., the GPi/ SNr) on the thalamus need to be blocked.

Interestingly, ablative surgery in the GPi and subthalamic nuclei helps with dyskinesias in PD, which is paradoxical given the fact that removal of inhibitory GABAergic transmission from the GPi would be predicted to increase, rather than decrease, dyskinesias on the basis of the classical model of basal ganglia organization. One explanation is that there are limited zones in each of these regions that can effect akinesia and dyskinesia, and other regulatory pathways are probably also affected by interruption of the GPi.



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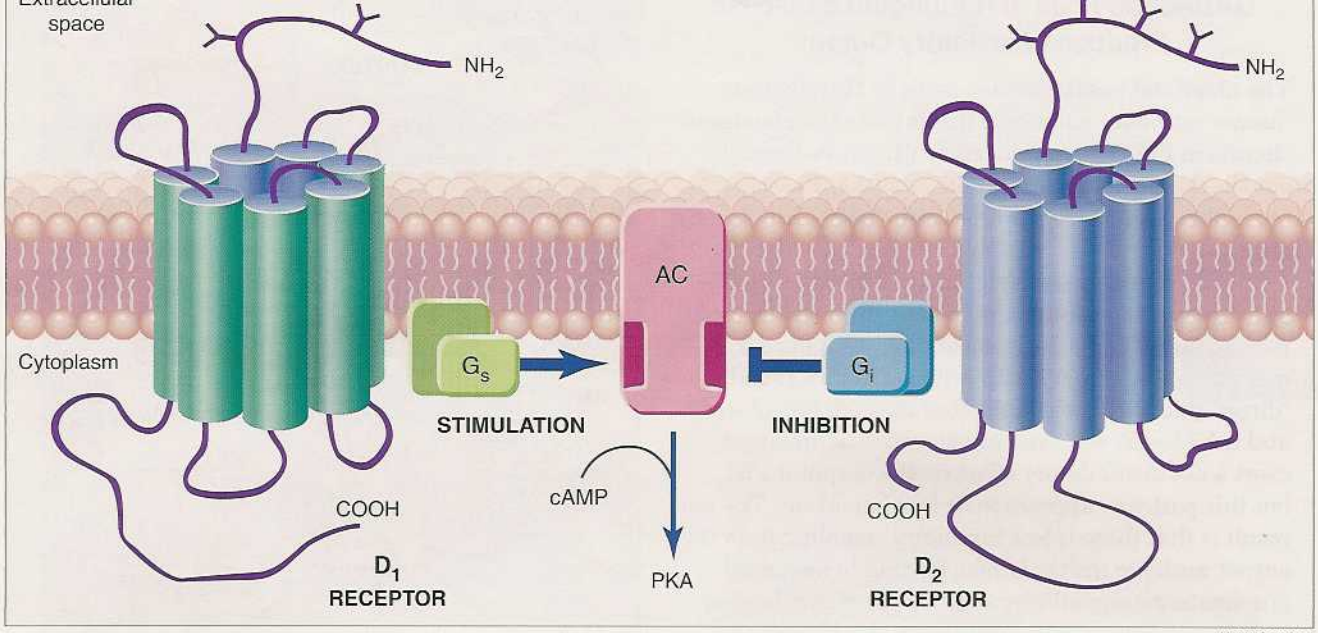
It is clear that the increase in tonic and phasic discharge in the thalamus in PD has complex and contradictory effects on motor output, given the simultaneous presence in many patients of lack of movement (akinesia) and uncontrolled movement (tremor and dyskinesia). This problem of system integration remains one of the primary unsolved features of PD.

Paradoxical Movement Disorders Involve Dopamine D_1 and D_2 Receptors

Dopamine receptors were functionally characterized starting in the 1970s, when it was discovered that two biochemically distinct receptor types exist that are coupled to the cAMP pathway of signal transduction. Since then, at least five classes of receptors have been identified in the brain, which nevertheless fall neatly into the two original categories of D_1-like and D_2-like types.

The genes for D_1 and D_2 receptors were isolated in the late 1980s, followed by the cloning of related receptors. The various dopamine receptor genes were found to share similarities of exon-intron structure with opsin genes, another class of G-protein-coupled receptor.

D_1-like receptors comprise D_1 and D_5 receptors, and D_2-like receptors comprise D_2, D_3, and D_4



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Dopamine D_1- and D_2-like receptors consist of five subtypes, including D1 and 5 receptors (D_1-like) and D2, 3, and 4 receptors (D_2-like). All five receptors appear to be descended from the same ancestral gene, and those in each class share similar but not identical dopamine-binding properties.

Dopamine receptors are G-protein-coupled receptors with seven transmembrane-spanning domains. The intracellular effector mechanisms depend largely on coupling to G_s-mediated stimulation or G_i-mediated inhibition of adenylate cyclase (AC), which initiates signal transduction via the cAMP cascade.

Recent evidence suggests that complex interactions may occur among G-proteins. This "membrane crosstalk" includes homodimerization of dopamine receptors, hetero- or oligomerization of dopaminergic and other receptors (e.g., somatostatin, serotonin, adenosine), and counter-regulatory effects on D_1 receptors by muscarinic ACh receptors which are coupled to G_i.

receptors. These subtypes have distinct localizations in the brain.

D_1-like receptors are found primarily on postsynaptic neurons in many brain regions, including the cortex, hippocampus, striatum, and thalamus. D_1 and D_5 receptors are coexpressed in the cortex and hippocampus, but the D_5 receptor is present alone in some areas. Conversely, D_1 receptors are expressed alone in areas such as the SNr. The functional significance of this expression pattern is unclear, but it may contribute to the long-term side effects of dopaminergic drugs.

The D_2 receptor is found in pre- and postsynaptic neurons in the striatum, cortex, amygdala, hippocampus, hypothalamus, SNc, and other regions. The related D_3 receptor is rare in the striatum, but is enriched in limbic areas and present in the SNc, ventral tegmentum, and cerebellum.

As presynaptic dopamine depletion gradually occurs in PD, the "direct" pathway neurons bearing postsynaptic D_1 receptors are downregulated. These D_1 neurons are positive for substance P and dynorphin, whereas a distinct pool of D_2 neurons is positive for preproenkephalin.

Levels of substance P, dynorphin, and D_1 receptors themselves are reduced in response to decreased signaling through the D_1 receptors. Conversely, D_2 receptors and levels of enkephalin are upregulated in "indirect" pathway neurons bearing postsynaptic D_2 receptors, due to loss of normal inhibition through the D_2 receptors.

When dopamine agonists are acutely applied as a treatment for PD, postsynaptic D_1 receptors may demonstrate a "supersensitive" or exaggerated response of the direct pathway, followed by an increase in neuropeptide production which

EFFECTS OF DOPAMINERGIC D_1 vs. D_2 RECEPTORS

Effect	D_1-like	D_2-like
Arachidonic acid	–	+
Na^+/H^+ exchange	–	+
L-type Ca^{2+} channel influx	+	–
K^+ efflux	?	+
Na^+,K^+-ATPase	–	–
Phospholipase C	+	?

eventually causes dampening of opioid autoreceptors, perhaps contributing to dyskinesias. On the other hand, striatal D_2 receptors could be downregulated in response to chronic treatment with dopaminergic agonists, causing a compensatory gradual increase in abnormal "indirect" pathway signaling.

It is also believed that the presence of D_2 autoreceptors on presynaptic neurons in the nigrostriatal tract may contribute to the erratic effects of dopaminergic drugs in the setting of the denervated striatum, by compounding the pulsatile stimulation that occurs when L-dopa is administered to this environment.

Because most presynaptic dopaminergic neurons are already compromised in PD, their ability to convert L-dopa (which has no activity of its own at dopamine receptors) to dopamine and to release it in a physiologic fashion is lost, and other cells, such as striatal astrocytes or nondopaminergic neurons, without the ability to store or regulate release of dopamine, are responsible for this pulsatile release.

Animal models have been used to clarify dopaminergic signaling. In the 6-OHDA rat model of PD, there is a compensatory upregulation of striatal D_2 receptors and downregulation of D_1 receptors, consistent with a loss of dopaminergic stimulation of postsynaptic neurons. Results from the MPTP primate model and from studies of human autopsy material appear to confirm these findings.

Interestingly, a D_2 receptor knockout mouse, which lacks the D_2 receptor but otherwise has normal nigrostriatal innervation, has a phenotype of akinesia resembling PD in humans. This activity is consistent with a disinhibition of the "indirect" pathway, along with an upregulation of the peptide neurotransmitter preproenkephalin.

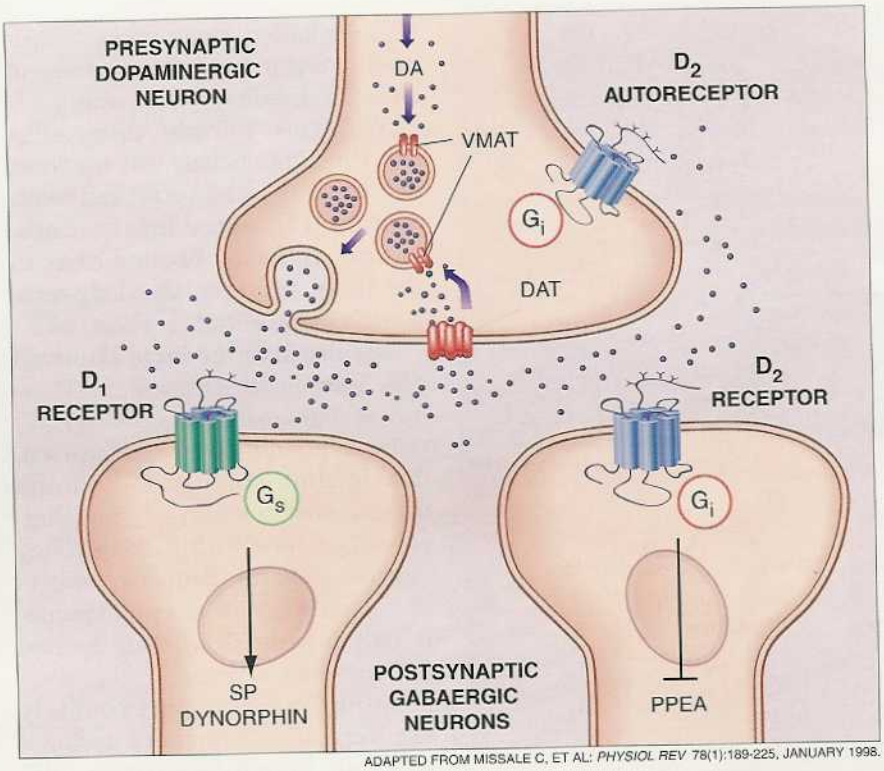
On the other hand, D_1 receptor knockout mice show an increase in locomotor activity consistent with inhibition of the "indirect" pathway, along with a decrease in substance P. Notably, D_1 knockout mice show no increase in locomotor response following treatment with the dopaminergic agonist cocaine, indicating that D_1 receptors are required for psychomotor stimulation acting at the D_2 receptors.

Finally, a dopamine transporter knockout mouse, which has chronically elevated levels of synaptic dopamine, demonstrates hyperactivity and compensatory downregulation of both D_1 and D_2 receptors on the genetic level.

Taken together, these observations suggest a complex pattern of regulation on the level of gene expression and neurotransmitter feedback loops, including adaptive changes on corticostriatal and nigrostriatal inputs.

L-Dopa Therapy Replaces Endogenous Dopamine

After the discovery of dopamine as a key neurotransmitter in the basal ganglia and recognition of its deficiency in PD, dopamine replacement was embraced as the most promising treatment for PD. The introduction of levodopa in the



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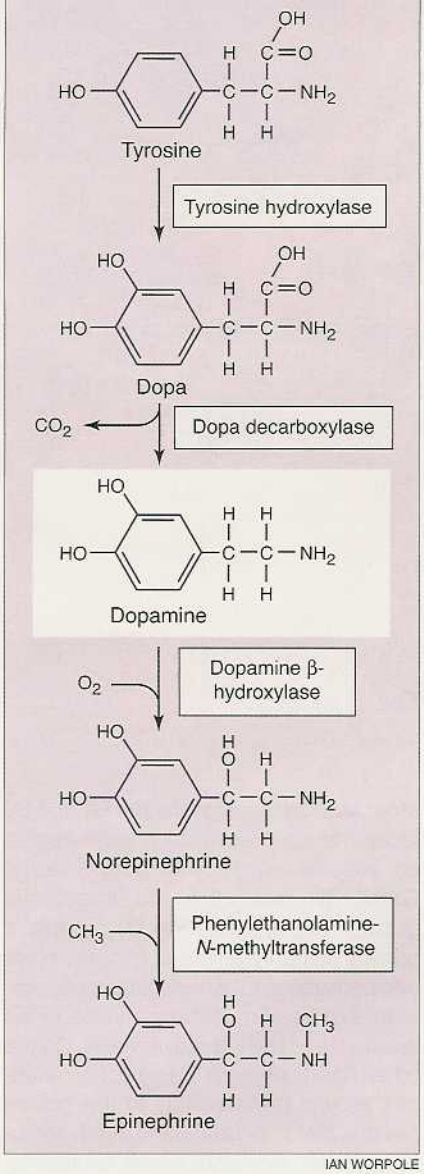
Most evidence suggests that D_1 and D_2 receptors are present to a large degree on separate groups of postsynaptic GABAergic neurons in the nigrostriatal circuit. Neurons bearing D_1 receptors project primarily to the substantia nigra (striatonigral) and, when stimulated, activate expression of the neuropeptides substance P (SP) and dynorphin. On the other hand, neurons bearing D_2 receptors project preferentially to the globus pallidus (striatopallidal), and when stimulated, these receptors inhibit expression of preproenkephalin-A (PPEA) and hence enkephalin. Alteration of these neuropeptide signals may have complex effects on GABAergic and glutamatergic autoregulation.

As shown in the opposite table, the effects of D_1-like and D_2-like receptors are essentially opposite and may involve a variety of different signaling pathways. Nevertheless, there is considerable evidence for D_1-like and D_2-like receptor synergism on the single-cell level. [DAT, dopamine transporter; VMAT, vesicular monoamine transporter.]



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Catecholamines are synthesized from the precursors tyrosine and dopa, which in turn are converted into the neurotransmitters dopamine, norepinephrine, and epinephrine. Because dopamine is rapidly degraded and does not readily cross the blood-brain barrier, it is necessary to use the precursor dopa (L-dopa) rather than dopamine for oral administration.

1970s afforded many patients dramatic relief from their symptoms of akinesia, rigidity, and tremor.

With this "miracle" drug, surgery, which previously was the most effective and widely practiced treatment for PD, moved into the background. It finally became clear in the 1980s, however, that long-term use of L-dopa entails serious risks.

Results from the large Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) trial, a prospective, randomized, double-blind study of L-dopa and other medications, typify the clinical experience with L-dopa. They suggest that the beneficial effects of L-dopa wear off in approximately half of patients who are treated for more than 2 years.

After 2 years, approximately one-third of patients have dyskinesias, one-fourth experience "off" states or freezing, and one-tenth suffer unpredictable motor fluctuations or "on/off" states. Other studies suggest that serious motor complications occur in 50 to 90% of patients who use L-dopa for 5 to 10 years (including who have delayed treatment with L-dopa or who initially used low doses).

In addition to the chronic symptoms, acute side effects may include nausea and vomiting (due to stimulation of dopaminergic receptors in the area postrema of the brainstem) and postural hypotension and sinus tachycardia (due to D_1 receptor activity). These symptoms are lessened somewhat with current L-dopa formulations, which include a dopamine carboxylase inhibitor (e.g., carbidopa) to minimize peripheral conversion of L-dopa to dopamine.

All symptoms of PD do not respond equally well to L-dopa. For example, gait instability is a major disabling symptom in later stages of PD, but L-dopa is not as effective for this as it is for akinesia or tremor. This suggests that the anatomic basis of gait instability may be distinct from that of akinesia, and other neurotransmitter systems and feedback loops are involved.

The "on/off" phenomenon, in which L-dopa administration produces increasingly sporadic and unpredictable effects, usually emerges several years after initiation of therapy, following a so-called honeymoon period of good response to L-dopa. At this point, many physicians simply increase the L-dopa dose.

However, an increase in dosage inevitably leads to other, more serious side effects including dyskinesias and motor fluctuations as well as nonmotor problems, such as confusion, delirium, and psychosis. This decreased responsiveness to L-dopa and the increased side effects are due in part to the progressive degeneration of presynaptic striatal neuronal terminals and their inability to properly store and release dopamine.

Newer formulations of L-dopa include an inhibitor of the dopa-decarboxylase enzyme, which increases the plasma levels and half-life of L-dopa and greatly reduces the amount of L-dopa required to produce a given response. The primary metabolic pathway for L-dopa involves dopa decarboxylase, which metabolizes about 70% of oral L-dopa to dopamine in the liver and intestine. Even with peripheral dopa-decarboxylase inhibitors, however, at best only 10% of oral L-dopa reaches the brain.

Another issue relates to the pharmacokinetics of L-dopa, with intermittent rather than continuous dosing providing suboptimal effects that may exacerbate the degeneration. Although controlled-release formulations can provide more "on" and less "off" periods, it generally becomes necessary to increase the dosage due to decreased bioavailability.

One possible solution is the continuous infusion of L-dopa or other drugs directly into the brain via surgically implanted catheters or polymeric systems. This produces less sporadic effects than simple oral dosing, but this strategy is invasive and not adequately tested.

It may be considered in the future as an adjunct to deep-brain stimulation or ablative surgery.

There is also controversy about the best time to start a patient on L-dopa therapy, given the fact that L-dopa has limited long-term utility. This question is complicated by the fact that L-dopa is the most effective agent for symptom relief, and it is difficult to withhold or withdraw a medication that has already offered relief to a patient.

Preliminary results from studies using dopaminergic agonists, such as pramipexole, appear to support a delay in initiating L-dopa therapy in patients with mild symptoms, while a trial of other drugs is tried. However, motor complications still develop ultimately in patients who delay treatment with L-dopa or who use low doses.

Other Agents May Delay the Need for L-Dopa Therapy

A variety of other drugs is currently available for use as adjuncts to standard L-dopa or surgical therapies. None of these drugs is superior to L-dopa monotherapy in terms of symptom relief, and all have significant side effects.

Anticholinergics are most useful in treating mild tremor, with akinesia and rigidity being less responsive. These drugs also can provide symptomatic relief for drooling due to dysphagia (they do this by decreasing production of saliva, although swallowing difficulties may worsen). Cholinergic neurons are disinhibited by the loss of dopaminergic neurons and act partly as antagonists to dopaminergic neurons. Thus, anticholinergics may help to balance the relative activity of these two classes of neurons.

Anticholinergics have many well-known side effects. Among these is a worsening of dementia, making these drugs relatively contraindicated in patients with psychiatric symptoms.

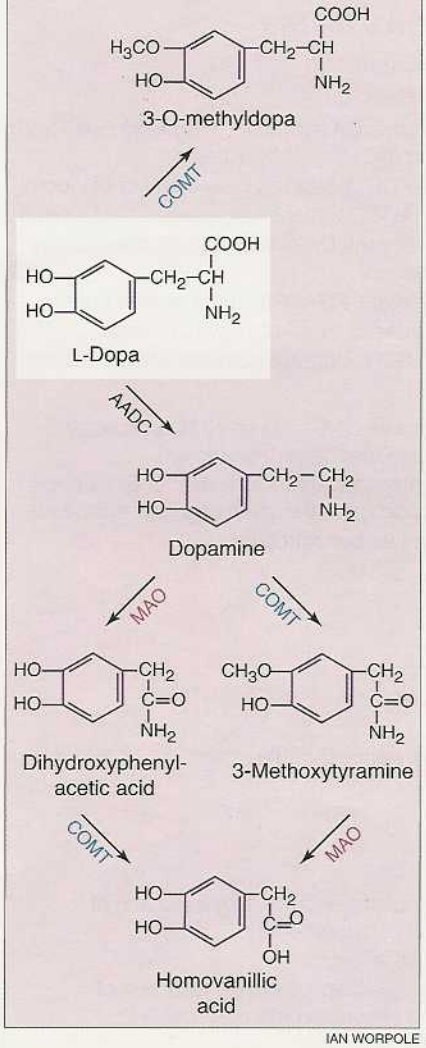
The antiviral drug amantidine also offers symptomatic relief of mild tremor, and it is used in early stages of PD primarily as monotherapy, though it may be effective in later stages in conjunction with L-dopa. The drug has several potential mechanisms of action, including anticholinergic effects, central release of dopamine, delay of dopamine reuptake, and NMDA glutamate receptor blockade. The antiviral action is not thought to contribute to its antiparkinson effect.

Another commonly used class of drugs is the catechol-O-methyl-transferase (COMT) inhibitors. These agents, which include entacapone and tolcapone, act on the secondary metabolic pathway of L-dopa, preventing conversion of L-dopa to 3-O-methyldopa.

ANTI-PARKINSON'S DRUGS

Agent	Mechanism or Effect
Dopamine Replacement	
L-Dopa	DA precursor, promotes DA synthesis, long-term use leads to "wearing off" effects, dyskinesia
Benserazide	Inhibits peripheral AADC, increases bioavailability of L-dopa
Carbidopa	Inhibits peripheral AADC, increases bioavailability of L-dopa
Selegiline	MAO-B inhibitor, increases DA availability; neuroprotective effects unestablished
Lazabemide	MAO-B inhibitor, increases DA availability; newer agent
Tolcapone	COMT inhibitor, increases bioavailability of L-dopa
Entacapone	Inhibits peripheral COMT, increases bioavailability of L-dopa
Anticholinergics	
Amantidine	Anticholinergic, promotes DA release, NMDA receptor antagonist (precise mechanism unknown)
Benzotropine	Blocks ACh R, counteracts striatal inhibition of DA effects and effects of drooling; may worsen cognitive symptoms
Trihexyphenidyl	Blocks ACh R, same as benzotropine
Biperiden	Blocks ACh R
Metixene	Blocks ACh R
Piroheptine	Blocks ACh R
Profenamine	Blocks ACh R
Dopamine-receptor agonists	
Ergot derivatives	
Bromocriptine	D_2 receptor agonist, partial D_1 antagonist
Cabergoline	D_2/D_1 agonist
Non-ergot derivatives	
Lisuride	D_2 agonist
Pergolide	D_2/D_1 agonist
Pramipexole	D_2/D_3 agonist, may cause apoptosis by induction of bcl-2 or inhibition of cytochrome *c*
Ropinirole	D_3 agonist with D_2/D_4 effects
Talipexole *	D_2/D_3 agonist, may affect apoptosis by induction of bcl-2 or inhibition of cytochrome *c*

* Talipexole is not approved in the US.
AADC, L-amino acid decarboxylase; AChR, acetylcholine receptor; DA, dopamine.



IAN WORPOLE

L-Dopa and dopamine are degraded through the effects of various enzymes. L-Dopa is metabolized in peripheral tissues by catechol-O-transferase (COMT) into 3-methyldopa, or in the brain, it is metabolized by amino acid decarboxylase (AADC) into bioactive dopamine. Dopamine is further degraded by COMT or monoamine oxidase (MAO), yielding the metabolites dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine, and homovanillic acid (HVA).

Because 3-O-methyldopa competes with L-dopa for transport into the brain, blocking its formation increases L-dopa uptake. COMT inhibitors decrease the plasma elimination of L-dopa and increase its half-life, allowing for lower dosages and more consistent plasma drug levels.

Clinical trials with COMT inhibitors have shown increased "on" and decreased "off" time, with improved motor functioning. Entacapone and tolcapone may be used as adjuncts to L-dopa in patients without dyskinesia, but concerns over hepatotoxicity have limited their wider usage.

Dopaminergic agonists are a large and diverse class that may be useful for patients with motor fluctuations or suboptimal benefit from L-dopa alone. These include older ergot drugs, such as bromocriptine (D_2 receptor agonist), and newer, non-ergot drugs.

Bromocriptine was originally developed to suppress prolactin release in prolactinoma due to natural antagonism between dopamine and prolactin, and it is still used for this purpose. It is sometimes used as monotherapy in PD, but patients invariably require L-dopa.

When bromocriptine is used in combination with L-dopa, it is possible to reduce the L-dopa dosage by about 40%, without an initial decline in therapeutic response. Motor fluctuations and "on/off" symptoms may be less frequent with a combined regimen, but these symptoms eventually emerge once L-dopa is initiated.

Like L-dopa, bromocriptine is not very effective in postural instability. Also, bromocriptine is not as effective as anticholinergics for tremor symptoms, and it can exacerbate dyskinesias.

Several clinical studies have compared L-dopa with the dopaminergic agonists. The ongoing CALM-PD study is examining L-dopa vs. pramipexole, and long-term data (>4 years) are becoming available. This study, as well as other randomized, double-blind studies, indicate that the side effects of dyskinesia and motor complications occur less often in the dopaminergic agonist group than in the L-dopa group. However, the overall response to treatment remains better in the L-dopa group.

Another study has shown that patients taking cabergoline with open-label L-dopa supplementation had the same risk for developing motor complications as those taking a stable dose of L-dopa without open-label supplementation.

Two additional large international studies have looked at early use of the dopaminergic agonists roprinirole and pergolide. They show that dopaminergic agonists are less efficacious on their own but do not cause dyskinesia as frequently and may delay the time to L-dopa administration. Once L-dopa is begun, however, there is no evidence that dopaminergic agonists alter the time to onset of L-dopa-associated side effects.

Thus, existing data suggest that while combined therapy with dopaminergic agonists may allow use of a reduced dosage of L-dopa initially (which is necessary for symptom relief), combined therapy does not prevent the ultimate development of long-term side effects. Patients with milder symptoms at disease onset also may benefit from such a delay in L-dopa if their symptoms are manageable with other drugs.

Monoamine Oxidase Inhibitors Prolong L-Dopa Bioavailability

MAO-B is involved in the main catabolic pathway of dopamine in the brain and accounts for the majority of inactivation of L-dopa. MAO-B activity is known to increase with normal aging but appears unaffected by PD.

The rationale for using selective MAO-B inhibitors in patients with PD is simply to prevent the breakdown of dopamine. Use of the nonselective, antidepressant MAO inhibitor drugs, which act on both

MAO-A and B, is contraindicated in PD, because these drugs can exacerbate the side effects of L-dopa, such as dyskinesia, psychiatric symptoms, and cardiac effects of catecholamines.

Selegilene, a selective irreversible MAO-B inhibitor, is used in combination with L-dopa and can increase "on" time. However, monotherapy with selegilene alone has not been shown to be effective.

Some data have suggested that MAO-B inhibitors, because of their ability to inhibit the effects of MPTP toxicity (prevent its oxidation to MPP+), may have a possible neuroprotectant effect, slowing disease progression. In theory, reduction of dopamine oxidation by MAO-B could reduce oxidative stress and production of reactive species. In vitro experiments have shown upregulation of some antioxidant and antiapoptotic molecules (e.g., SOD, bcl-2).

Interestingly, toxins in cigarette smoke are known to block MAO-B, which may explain why smokers appear to have a lower incidence of PD than nonsmokers (though they also tend to die earlier).

Some clinical studies have suggested a possible neuroprotective role for MAO-B inhibitors, including data from the DATATOP and SINDEPAR (Sinemet-Deprenyl-Parlodel) studies. However, use of MAO-B inhibitors does not stop disease progression in PD, and no well-controlled clinical trials have shown any neuroprotective effects aside from mild symptomatic relief. The benefit, if any, from MAO-B inhibitors appears to be mainly as an alternative to dopaminergic agonists or COMT inhibitors when used together with L-dopa.

The limited efficacy of drug-based treatments in use for PD today is due in part to the advanced stage of the disease by the time symptoms appear. At clinical presentation, 70% or more of the approximately 500,000 dopaminergic cells in the SNc may be dead, and nondopaminergic systems also are affected, including those in regions outside the basal ganglia (e.g., cerebral cortex). The disease gradually spreads beyond the SNc as the entire motor system is dysregulated.

Promising drug-based treatments in the future will include reformulations of existing drug classes to achieve more stable and specific effects of dopamine. For example, partial agonists may interact better with sensitized dopaminergic receptors, as occur in late PD. Also, they could avoid the problem of downregulation of receptors, as may occur with D_1/D_2 agonist treatment.

Also under study are newer gene-based drugs, which cater to an individual's underlying risk factors and extent of damage to the basal ganglia at diagnosis, and novel methods of drug delivery such as neurosurgical depot administration, which effect more stable dopaminergic stimulation. Some of these emerging treatments are described in the final part of this series.

SELECTED ANTI-PARKINSON'S DRUGS IN DEVELOPMENT

- Adenosine A_{2A} receptor antagonist (theophylline, KW-6002)
- Adrenergic α_2 receptor antagonist (JP-1730)
- Serotonin 1A receptor agonist + dopamine receptor antagonist (saritozan)
- Glutamate antagonist (riluzole, memantine)
- Cell signaling modifier (CEP-1347)
- Opioid (δ, κ) agonists (U-69)
- Opioid antagonists (naloxone)
- Immunophilins
- Minocycline
- Ganglioside mimetics

Part I of this review article, discussing the pathogenesis of Parkinson's disease, appeared in the November/December 2002 issue.

Part III covering the basis of surgical and emerging therapies, such as gene and cell-based approaches, will appear in the April 2003 issue.

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