Neurotransmitters and Disorders of the Basal Ganglia

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The basal ganglia are a group of subcortical nuclei which are components of modular circuits involved in many cortical functions. They have received considerable attention from basic scientists and clinicians alike because of their prominent involvement in movement disorders, a spectrum of diseases including disorders which are characterized by poverty of movement (hypokinetic disorders), as well as disorders characterized by excess movement (hyperkinetic disorders). It has become clear in recent years that most basal ganglia disorders are not restricted to motor disturbances, but involve cognitive and emotional features as well.

ANATOMY AND PHYSIOLOGY OF THE BASAL GANGLIA

The basal ganglia are parts of larger circuits. The basal ganglia are a group of related subcortical nuclei, including the neostriatum (caudate nucleus and putamen), the ventral striatum, the external and internal segments of the globus pallidus (GPe, GPi, respectively), the subthalamic nucleus (STN), and the substantia nigra pars reticulata and compacta (SNr, SNC, respectively). These structures are components of circuits involving portions of the cerebral cortex, thalamus and brain stem (Fig. 46-1, left). Based on their cortical site of origin, these loops can be grouped into skeletonotor, oculomotor, associative, and limbic based on their connectivity and presumed functions.

Due to its relevance to an understanding of movement disorders, the 'motor circuit' has received the most attention. This circuit is centered on somatosensory, motor and premotor cortices, which send projections to the 'motor portions' of striatum. The connections between the striatum and the basal ganglia output nuclei (Gpi/SNr) are organized into direct and indirect pathways [1]. The direct pathway is a monosynaptic projection between striatum and Gpi/SNr, while the indirect pathway is a polysynaptic connection that involves intercalated neurons in GPe and STN. Some striatofugal neurons may also collateralize more extensively, reaching GPe, Gpi/SNr and STN. Other 'motor'-related inputs to striatum and STN arise from the intralaminar thalamic nuclei, i.e. the centromedian and parafascicular nuclei (CM/Pf).

Basal ganglia output is directed from Gpi and SNr to the thalamus. Movement-related basal ganglia output projects from Gpi almost exclusively to the ventrolateral nucleus of the thalamus which, in turn, projects to the primary motor cortex, the cortical supplementary motor area, and other premotor cortical areas. Movement-related output from SNr terminates in the ventral anterior and in
the mediodorsal nuclei of thalamus, which, in turn, innervate premotor (and prefrontal) regions of the frontal lobe. GPi and SNr also project to noncholinergic neurons in the pedunculopontine nucleus (PPN) in the brainstem, and to CM/Pf. Additional projections from the SNr reach the superior colliculus. This connection may play a critical role in the control of saccades and orienting head and eye movements.

**Multiple neurotransmitter systems are found in the basal ganglia.** The basal ganglia contain most of the classical neurotransmitters, and many additional neuropeptides which may participate in the modulation of information transfer in the basal ganglia. Some of the more important systems will be discussed in the following paragraphs.

**GABA is the predominant intrinsic transmitter of the basal ganglia.** Inhibition and disinhibition are considered to be the most important modes of information transfer in the basal ganglia. Ninety-five percent of all neurons in the striatum are GABAergic medium spiny neurons. These neurons are the striatal output neurons. The medium spiny neurons which give rise to the direct pathway also contain substance P or dynorphin as a co-transmitter, while those striatal output neurons that give rise to the indirect pathway contain enkephalin as a co-transmitter. Most striatal interneurons, as well as neurons in GPe, GPi and SNr are also GABAergic. Because striatal and GPe efferents end in the SNr, GPe and GPi, GABA is found in high concentrations in these nuclei (Fig. 46-2).

Two GABA receptor subtypes have been characterized as GABA-A and GABA-B (see Ch. 16). GABA-A receptors are inhibitory ionotropic receptors (forming a chloride channel whose conductance is rapidly modulated by ligand binding), found mostly on postsynaptic membranes. GABA-B receptors are pre- and postsynaptic G-protein-coupled receptors.

**Glutamate.** Inputs to the basal ganglia, from the cortex, PPN and CM/Pf, as well as intrinsic projections from the STN, utilize glutamate as a neurotransmitter (Fig. 46-1).

Glutamate receptors are grouped into ionotropic and metabotropic receptors (mGluRs). Ionotropic glutamate receptors, i.e. NMDA, kainate and AMPA receptors, are present throughout the basal ganglia, and are mostly located postsynaptically. They are the primary receptors used for information transfer from cortex to striatum and STN, and STN output. In the striatum, these receptors may be involved in learning, through long-term potentiation (LTP) and long-term depression (LTD). In addition to the ionotropic glutamate receptors, there are eight different types of metabotropic glutamate receptors (mGluR1–8) which are classified into three groups based on their genetic and pharmacologic properties. These receptors are present at striatal and extrastriatal sites (Ch. 15).
FIGURE 46-2 Concentrations in the basal ganglia in brains from normal controls and from patients with Parkinson's. (A) Glutamate, aspartate and GABA. Values are presented as mean ± SEM. Thalₐ, anterior thalamus; Thalₐᵥ, ventral lateral thalamus; Thalₐₜ, ventral anterior thalamus; Thalₐₚ, medial thalamus; Thalₐₜ, centromedial thalamus; STN, subthalamic nucleus; GPₐ, lateral globus pallidus; GPₐₚ, medial globus pallidus; Nₐ, nucleus accumbens; Put, anterior putamen; CNₐ, tail of caudate nucleus; CNₐₕ, body of the caudate nucleus; CNₐₗ, head of caudate nucleus; SNₐ, substantia nigra pars reticulata; SNₐₗ, substantia nigra pars compacta; Gₚ, precentral gyrus; Gₚₗ, postcentral gyrus; fr Ctx, frontal cortex.

(Continued)
Acetylcholine. Most of the acetylcholine in the basal ganglia is found in the striatum, as the neurotransmitter of the large spiny interneurons, which account for about 3% of all striatal neurons. Both muscarinic and nicotinic cholinergic receptors are found in the striatum. Postsynaptic muscarinic receptors may inhibit transmitter release from glutamatergic terminals, whereas nicotinic receptor activation may enhance transmitter release.

Dopamine. Dopamine is present in high concentration in the striatum (Fig. 46-2), in densely arborized terminals of projections that originate in the SNC. Neurons in the
ventral tegmental area contribute to the dopamine supply to the ventral striatum as well as the cortex. Perhaps the most important site of extrastriatal dopamine release is the SNr, where the transmitter is released from dendrites of SNC neurons.

Dopamine synthesis in dopaminergic terminals (Fig. 46-3) requires tyrosine hydroxylase (TH) which, in the presence of iron and tetrahydropteridine, oxidizes tyrosine to 3,4-dihydroxyphenylalanine (levodopa, L-DOPA). Levodopa is decarboxylated to dopamine by aromatic amino acid decarboxylase (AADC), an enzyme which requires pyridoxyl phosphate as a coenzyme (see also in Ch. 12).

Dopamine acts on G-protein-coupled receptors belonging to the D1-family of receptors (so-called 'D1-like receptors', or D1Lrs, comprised of D1- and D5-receptors), and the D2-family of receptors ('D2-like receptors', or D2Lrs comprised of D2-, D3- and D4-receptors). D1Lrs stimulate adenylyl cyclase activity and, possibly, also phosphoinositide hydrolysis, while D2Lrs reduce adenylyl cyclase activity. In the striatum, D1Lrs are predominately associated with medium spiny neurons of the direct pathway, while D2Lrs have been found as autoreceptors on dopaminergic terminals, as heteroreceptors on cholinergic interneurons, and on indirect pathway neurons. In the SNr, D1Lrs are located on terminals of the direct pathway projection, while D2Lrs appear to function as autoreceptors.

The actions of dopamine are terminated through presynaptic reuptake. Some of the dopamine is then re-incorporated into vesicles, while the rest is metabolized (Fig. 46-3). Dopamine and its O-methyl derivative are both subject to the action of monoamine oxidase (MAO), a flavoprotein present in the outer membrane of the mitochondria. MAO exists in two forms: MAO type A (MAO-A) is predominantly present in catecholaminergic neurons, while MAO type B (MAO-B) predominates in serotonin-containing neurons and in astrocytes. Products of the MAO reaction include the aldehyde corresponding to the amine substrate, hydrogen peroxide and ammonia. Most of the aldehyde undergoes further dehydrogenation to form, in the case of dopamine, DOPAC, which is the substrate for catechol-O-methyltransferase (COMT), to generate homovanillic acid (HVA).

The basal ganglia are involved in multiple functions. The motor circuit of the basal ganglia has received the greatest attention from researchers, because of its perceived involvement in movement disorders. Due to the modular organization of the basal ganglia, many of the findings discussed below for the motor circuit may be applicable to other circuits as well.

A basic understanding of basal ganglia function can be gleaned from considering the effects of cortical activation on excitatory (glutamatergic) and inhibitory (GABAergic) projections in the basal ganglia (Fig. 46-1). Voluntary movements appear to be initiated at the cortical level of the motor circuit. Activation of the direct pathway neurons in the striatum will inhibit basal ganglia output neurons, which, in turn, will disinhibit related thalamocortical neurons, and ultimately facilitate movement. In contrast, activation of indirect pathway neurons in the striatum will lead to increased basal ganglia output and, presumably, to suppression of movement. Because most GPi neurons

**FIGURE 46-3** Synthesis and metabolism of dopamine. MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; HVA, homovanillic acid; DOPAC, 3,4-dihydroxyphenylacetic acid.
increase their firing rate with movement, the main role of the basal ganglia motor circuit is to inhibit and to stabilize the activity of the thalamocortical neurons.

The basal ganglia motor circuit may also play a role in the control of the amplitude or velocity of movement, and may focus movements, allowing intended movements to proceed while suppressing other movements (see discussion in ref. [2]). The basal ganglia have also been implicated in self-initiated (internally generated) movements, procedural learning, and movement sequencing [e.g. ref. 3]. Learning may involve modifications of the strength of glutamatergic synapses onto medium spiny neurons in the striatum through dopamine–glutamate interactions which are timed to salient external events. It is thought that phasic dopamine release in the striatum signals whether or not reward-related phenomena in the environment are present. These dopamine signals may affect LTP and LTD at corticostriatal synapses (see also in Ch. 53).

**DISORDERS THAT INVOLVE BASAL GANGLIA DYSFUNCTION**

**Parkinson's disease (PD) is a hypokinetic movement disorder.** PD manifests itself in most patients with prominent movement abnormalities, including a 4–6 Hz tremor at rest, muscular rigidity, slowness of movement (bradykinesia), and a failure of movement initiation (akinesia). Many of these signs are initially unilateral, but later progress to involve the opposite side. Depression occurs in up to 50% of patients. PD is a progressive disorder. Non-motor signs and symptoms, such as autonomic insufficiency and disturbances of gait and posture, develop later, along with psychiatric, cognitive and sleep complications.

Between 5 and 24 new cases per 100,000 persons are reported each year (20.5 per 100,000 in the USA). The prevalence of the disease is 57–371 patients per 100,000 persons worldwide (300 per 100,000 for the USA and Canada). With the increasing age of the population, a four-fold increase in the prevalence of PD is expected over the next 20 years. The age of onset differs substantially between patients (average age of onset is 62 years). Young-onset patients commonly suffer from one of the genetic forms of the disease (see below). Males appear to be affected slightly more frequently than females.

Several environmental factors may have an impact on the occurrence of the disease. Living in rural areas, drinking well water, pesticide exposure and head trauma are associated with an increased risk of developing PD, while caffeine consumption, taking nonsteroidal anti-inflammatory medications, and smoking appear to protect from it.

**Pathology.** The earliest degenerative changes in PD occur in structures outside of the basal ganglia [4], in the olfactory bulb, and brainstem structures, such as the dorsal motor nucleus of vagus, the locus coeruleus and the raphe nuclei. The prominent motor abnormalities in PD appear to arise in large part from degeneration of neurons in the SNC, with resulting loss of dopamine in the basal ganglia. Degenerating dopaminergic cells leave characteristic cosinophilic inclusions in their wake, the so-called Lewy neurites and Lewy bodies. Recent studies have also shown that low-level inflammatory responses may accompany the loss of dopaminergic cells, and may contribute to cell death. Recent imaging studies have suggested that the striatal dopamine concentrations steeply decline, preceding the onset of clinical Parkinsonism, which is usually only seen when more than 70% of striatal dopamine is lost.

In early phases of PD, dopamine loss affects primarily the posterior putamen (the striatal motor area) but later spreads to involve other nigrostriatal regions. In later stages, more widespread dopamine loss and neuronal degeneration in non-dopaminergic systems, such as the locus coeruleus and the raphe nuclei may account for some of the non-motor aspects of PD.

**Etiology.** Most cases of PD are 'sporadic' and appear to arise from a combination of genetic predisposition and environmental or toxic factors. Purely genetic forms of the disease probably account for less than 10% of cases, but the risk of family members of an affected patient to develop PD is significantly increased even in 'sporadic' PD. Cells in the SNCs are among the most vulnerable cells in the brain due to a relative deficiency in neuroprotective factors, such as the antioxidant glutathione, and because they are exposed to a high level of oxidative stress due to the presence of dopaminergic metabolism and other factors. This environment may render these neurons particularly vulnerable to nonspecific genetic or environmental insults that, by themselves, would not be sufficient to induce cell death in other cells. Interestingly, many of the factors known to be involved in neuronal damage in PD appear to interfere with the cell's ability to eliminate damaged or mutated proteins through the ubiquitin proteasome system [5].

One example of a genetically determined form of Parkinsonism, which results directly in degeneration of dopaminergic neurons are mutations of the gene coding for α-synuclein [6]. α-Synuclein is a normal brain protein that is found in synaptic vesicles and membranes along axons and terminals in many neurons. Mutated α-synuclein tends to aggregate as the result of a conformational change of the molecule from its usual unfolded, soluble form into a β-sheeted sheath. Aggregated α-synuclein is a prominent component of Lewy bodies.

The mechanism by which the mutated α-synuclein produces toxicity is not clear, but it is thought that the mutated protein forms fibrils, and the oligomers or fibrils formed from this protein exert a toxic gain of function leading to disruption of proteasomal function and the formation of Lewy bodies. However, as evidenced by the
discovery of several families in which triplication of the α-synuclein gene leads to four normal copies of the gene associated with autosomal dominant Parkinson's disease, overproduction of normal α-synuclein may also be causal. Dopaminergic neurons appear particularly sensitive to toxic effects of excessive or fibrillar α-synuclein. Other mutated genes possibly associated with autosomal dominant parkinsonism include UCHL1, NR4A2 and synphilin-1 (see ref. [7]).

A number of genetic mutations have been associated with autosomal recessive juvenile Parkinson's disease (ARJP). The most frequent of these is the gene PARK2, coding for parkin, which accounts for about half of patients with juvenile onset, below the age of 40. Parkin is an E3 ubiquitin ligase that is necessary for ubiquitination of proteins for their subsequent degradation in proteasomes. Loss of function of the mutated enzyme may result in failure to direct its substrates to the proteasomal system for degradation. Of interest is that Lewy bodies are not found in these subjects. Other genes for which there is strong evidence of linkage to ARJP include DJ-1 (PARK7) and PINK1 (PARK6). DJ-1, which is translocated to the outer mitochondrial membrane under conditions of oxidative stress, is therefore thought to have a role in protecting neurons from oxidative stress. PINK1 encodes a putative serine/threonine protein kinase. PINK1 is located primarily in mitochondria, and evidence from cell cultures suggests that PINK1 protects cells from stress-induced mitochondrial damage and apoptosis. At present, there is no postmortem neuropathologic information regarding the DJ-1 and PINK1 mutations. While the mentioned genetic mutations all lead to parkinsonism with progressive bradykinesia, rigidity, tremor and levodopa-responsiveness, the biochemical processes are different. Key questions related to all of the genetic mutations found are:

- Why is the dopaminergic system so uniquely vulnerable to their effects?
- What are the relationships of Lewy body formation, proteasomal protein degradation and mitochondrial dysfunction to parkinsonism (see ref. [8] for a detailed review).

Animal models. A variety of models can be employed to disturb dopaminergic functions in the brain. Attempts to model parkinsonism by treatment with the dopamine-depleting agent reserpine, or with dopamine-receptor blockers are fairly nonspecific. Models produced by dopaminergic toxins are more faithful reproductions of the pathology of the human disorder. In rodents, injections of 6-hydroxydopamine (6-OHDA) into the SNC, or treatment with mitochondrial complex I inhibitors, such as rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can be used to cause oxidative damage to dopaminergic neurons. Genetic models of parkinsonism in rodents are based on overexpression of α-synuclein. In primates, the most faithful model in terms of behavioral and pathological changes is produced by treatment with MPTP.

Pathophysiology. Metabolic and microelectrode recordings of neuronal activity in animal models of parkinsonism show that spontaneous neuronal discharge in STN, GPe and SNr is increased, as compared with normal controls, neuronal discharge in GPe is decreased (Fig. 46-4). These results and the known anatomical connections between the different structures have been used to develop a circuit model of parkinsonism (Fig. 46-1, right) in which striatal dopamine loss results in reduced activity in the direct pathway, resulting in disinhibition of the basal ganglia output nuclei. Striatal dopamine loss also results in greater inhibition of GPe, and, consequently, in disinhibition of STN and GPI. The net effect of these changes is an increase in basal ganglia output to brainstem and thalamus, which has been postulated to result in greater inhibition of thalamocortical neurons, and to reduce the responsiveness of brainstem and cortical mechanisms involved in motor control. Brainstem areas such as the PPN may also be involved in the development of akinesia, most likely secondary to excessive inhibitory input from GPI and SNr.

Additional support for this model comes from inactivation studies. For instance, GPI or STN lesions have been shown to reverse all the cardinal motor signs of parkinsonism, presumably by reducing the inhibitory basal ganglia output. However, some results of these lesion studies are not compatible with the simple model shown in Figure 46-1. Thus, surprisingly, lesions of the 'basal ganglia-receiving' areas of the thalamus (VA/VL) do not lead to parkinsonism, and lesions of GPI do not result in excessive movement. These findings suggest that the simple model shown in Figure 46-1(right) may not accurately describe all of the circuit abnormalities in PD.

Other factors that may play a role include specific alterations in information processing, alterations in discharge patterns and changes in the level of synchronization between neighboring neurons. All of these changes have been documented in parkinsonian patients undergoing electrophysiologic recording in the context of neurosurgical treatment of PD, or in animal models of the disorder, but it remains unclear whether there is a causal relationship between any of these abnormalities and the appearance of specific parkinsonian motor signs. The strongest argument for this can be made in the case of a relationship of tremor to the frequently seen oscillatory burst activity in the basal ganglia. However, it has proved to be extremely difficult to identify a single source of oscillatory discharge in the basal ganglia-thalamocortical circuitry.

Within the basal ganglia, abnormal oscillations may arise from changes in local pacemaker networks, through loss of extrastriatal dopamine, or as the result of intrinsic membrane properties of basal ganglia neurons. Increased inhibitory basal ganglia output may also act to induce
extracellular clear during movement. Any alteration of discharge rate of ongoing movements and its greater rate on cerebellar motor error is leading to a growing of prominent extracellular signals. Excitatory movement of recorded to pre- and post-synaptic inputs in deep brain stimulation (DBS) leads to oscillatory discharge in the basal ganglia. Thus, plasma oscillatory output to cortex. Besides normal certain aspects of pharmacokinesia may be related to oscillatory discharge in the thalamus. Which may then be oscillatory discharge in the thalamus, which may then be

![Image of neural activity patterns](image_url)

**FIGURE 4.6.4** Activity changes in the basal ganglia in Parkinsonism. The data are shown as separate discharge, where each individual line represents a single neural discharge. Each discharge shows 20 consecutive 100 ms segments of data from GPi, STN, and GPi. The neural activity is reduced in GPi, increased in STN and GPi, in addition to the rate changes. Over the course of the study, 100 ms segments of data from GPi, STN, and GPi show oscillatory output to cortex. Besides normal certain aspects of pharmacokinesia may be related to oscillatory discharge in the thalamus, which may then be oscillatory discharge in the thalamus, which may then be
in the basal ganglia may also simply introduce noise into thalamic output to the cortex that is detrimental to cortical operations.

**Pharmacotherapy.** The currently available treatments for PD are symptomatic, and do not alter the course of the disease. The earliest treatment that is still in limited use today, is with the anticholinergic medications, such as trihexyphenidyl or benztropine. These drugs are useful, particularly for tremor. However, their use is often problematic because of unpleasant side-effects, such as memory disturbances, blurred vision, sedation, dry mouth, or urinary retention, particularly in older patients.

After its introduction in the early 1960s, oral dopamine replacement therapy quickly became the mainstay of treatment of the disorder. The first agent to be introduced was the dopamine precursor levodopa, an amino acid which is metabolized into dopamine both peripherally and centrally. It quickly became apparent that the peripheral conversion into dopamine results in gastrointestinal and autonomic side-effects which significantly limit the usefulness of this agent. This problem was partially remedied by combining levodopa with peripheral blockers of dopa-decarboxylase (carbidopa or benserazide). These combination treatments have had an enormous impact on the outlook for patients with PD, greatly ameliorating many of the clinical features of the disorder and virtually normalizing life expectancy. More recently, blockers of another enzyme which is involved in peripheral metabolism of levodopa, catechol-O-methyl-transferase (COMT), was added to the therapeutic arsenal. The two available COMT-inhibitors, tolcapone and entacapone, are particularly useful in patients who suffer significant motor fluctuations with 'wearing off' of the drug effects, by slowing the metabolism of levodopa. However, problems with liver toxicity forced almost complete withdrawal of tolcapone from the market. The key to the effectiveness of the inhibitors, both carbidopa and entacapone, is that they do not cross the blood–brain barrier, so that their effects are strictly peripheral.

Levodopa therapy has a number of troubling side-effects. The most prevalent short-term problems include nausea and autonomic disturbances, such as orthostatic hypotension, and nausea. However, more troublesome are the development of motor fluctuations (wearing off and failed responses to dosing), drug-induced dyskinesias, and hallucinations. These are the primary reasons why many physicians delay the use of this agent. It also remains a theoretical possibility that levodopa may contribute to the degeneration of dopaminergic cells through free radical production. The results of recent trials suggest, however, that levodopa treatment does not hasten the clinical progression of the disease.

The most important alternatives to levodopa therapy are direct-acting dopamine receptor agonists, such as ropinirole, pramipexole, or pergolide (Fig. 46-5). A number of studies have shown that use of these agents may help to delay the need for use of levodopa/carbidopa. This has prompted the recommendation that dopamine receptor agonists should be used as first-line agents in patients with PD. It appears that these agents may also have a mild neuroprotective effect, which has further bolstered the case for their early use as monotherapy. Because the agonists have a longer half-life than levodopa and carbidopa, they are also often useful in later stages of the disease, when the response to levodopa and carbidopa may become erratic. Another dopamine agonist, apomorphine, has recently reached the market. This agent is only available in injectable form, and has a very short half-life. Its main use is in 'rescue' from episodes of unpredictable worsening in the severity of parkinsonian signs (sudden freezing episodes), sometimes seen in patients with long-standing PD.

The side-effects of agonists are similar to those of levodopa, including nausea, hallucinations and dyskinesias. Although also described for levodopa, recent studies have shown that daytime sedation with sudden 'sleep attacks' is a significant side-effect of these compounds. In addition, pergolide is an ergot derivative, and, like other ergot compounds, may result in ergotism, and may rarely induce cardiac fibrosis and valvular lesions. Ropinirole and pramipexole, both non-ergot compounds, do not have these side-effects.

**Neuroprotective treatments.** The first controlled clinical trial for neuroprotection in PD evaluated the MAO-B inhibitor selegiline and vitamin E vs. placebo control. Selegiline was selected on the premise that PD might be caused by an (unknown) environmental toxin, akin to MPTP, which requires an MAO-B dependent toxification step [9]. The initial studies with this medication were complicated by the fact that selegiline also has modest symptomatic effects, which were not completely accounted for in the washout phase of these experiments. Although this drug remains in wide use, its neuroprotective benefit remains controversial. It is now thought that mechanisms independent of its MAO-B-blocking actions may contribute to its (rather modest) neuroprotective actions. Initial use of dopamine receptor agonists such as ropinirole or pramipexole appear to be effective in reducing the development of dyskinesias.

Coenzyme Q-10, an agent that may help to augment mitochondrial function, has been shown in preliminary trials to slow progression in loss of activities of daily living in PD.

Based on recent insights into the pathogenesis and pathophysiology of PD, a large number of additional compounds have been suggested for neuroprotection in this disease. Drugs that reduce α-synuclein aggregation or inhibit apoptosis (propargylamine, caspase inhibitors), antioxidants (glutathione enhancers, tocopherol, flavonoids), anti-inflammatory drugs (nonsteroidal anti-inflammatory agents, inhibitors of cyclo-oxygenase-2), as well as glutamate receptor antagonists, given in an effort to reduce excitotoxicity, may all serve to provide some level of neuroprotection. In addition, trophic factors and agents to protect mitochondrial function have also been proposed as neuroprotective agents. Conceivably, cocktails of such drugs may
be used to provide effects beyond those achievable with single-drug approaches. Finally, in a remarkable series of studies it has been shown, in rodents, that physical exercise can reduce the effects of neurotoxins that induce parkinsonism such as MPTP and 6-OHDA. These effects may be due to exercise-induced production of trophic factors.

**Surgical therapy.** After 5–10 years, many patients reach a state in which antiparkinsonian drugs are no longer adequate because of the development of intractable motor fluctuations and dyskinesias. For these patients, neurosurgical approaches can be highly beneficial. Neurosurgical procedures were, in fact, widely used in the 1950s and 1960s, but were essentially abandoned with the introduction of levodopa therapy. Following promising results from studies that demonstrated reversal of parkinsonian motor signs through lesioning of the STN in MPTP-treated monkeys [10], there has been renewed interest in surgical treatments of parkinsonism. This was first employed in the form of GPI lesions (pallidotomy) (e.g., ref. [11]). Subsequently, high-frequency deep brain stimulation (DBS) of both the STN and GPI has been shown to reverse parkinsonian signs in a manner similar to ablation. Multiple mechanisms may contribute to these effects, for instance, inhibition of STN neurons through depolarization block, activation of inhibitory afferents, or true activation of STN efferents to the pallidum. Follow-up studies in patients who have been treated with these procedures have demonstrated that although the disease continues to progress in patients with lesions or DBS, patients get significant symptomatic benefit, which may last in excess of five years.

Thalamotomy and thalamic DBS, while effective against parkinsonian tremor, have been largely abandoned since they do not treat akinesia or bradykinesia. Interventions at the level of the STN or GPI are effective against akinesia, bradykinesia rigidity, tremor, as well as disabling drug-induced dyskinesias and dystonia.
throughout the use of modern imaging techniques and microelectrode guidance, these procedures have a higher success rate and a lower incidence of serious complications. Similar to other neurosurgical procedures, they may induce hemorrhage, infection, or cognitive problems (probably due to ‘collateral’ damage from probe passage through frontal areas), or stroke-like symptoms due to vascular or mechanical damage.

In developed countries, ablative procedures have largely been replaced by DBS, because the latter are equally effective or somewhat superior to ablation, are less invasive, and are reversible and adjustable. In addition, bilateral pallidal lesions have an increased risk of causing speech and swallowing dysfunction, while bilateral DBS procedures can be done without significantly increased risk. However, the stimulators require battery replacements, are prone to mechanical lead difficulties and sometimes require frequent adjustment of stimulation parameters.

One of the persistent paradoxes in basal ganglia research remains that these invasive procedures seem to have very little effect on motor performance in normal animals. Thus, no clear motor deficits and only subtle cognitive side-effects have been demonstrated. Mood disturbances, such as depression or manic episodes have been described particularly after STN DBS procedures, but are also relatively uncommon. It appears that the brain can tolerate or compensate for a lack of basal ganglia function much more readily than for the abnormal basal ganglia output that occurs in PD. In fact, although the mechanism of action of DBS is controversial, it now appears that it may act by replacing the abnormal output of the basal ganglia with a more tolerable pattern of discharge.

**New treatment options.** A variety of new treatment options are currently under development, and may become available in the near future. Among these are transdermal application of short-acting dopamine agonists. Selective D1-receptor agents, such as dihydrexidine also offer promise. In addition, non-dopaminergic treatments are under development.

One of the most promising treatments in this category is targeting the A2A adenosine receptor (A2ARs). A2ARs are expressed with the greatest abundance in the striatum, but are also found in other nuclei of the basal ganglia. The majority of striatal A2AR receptors appear to be postsynaptic, on dendrites of medium spiny neurons that give rise to the ‘indirect’ pathway. They may promote GABAergic signaling in these neurons, thus functionally opposing D2-receptor activation. Another important anatomical feature is that many dendrites carrying A2ARs appear to be contacted by glutamatergic terminals, suggesting that A2AR stimulation may facilitate cortical glutamatergic excitatory input to striatal neurons. In Parkinsonism, abnormalities of glutamatergic transmission in the striatum have been linked to the development of dyskinesias. Because of these anatomical and pharmacologic features, the use of A2AR antagonists has become a strategy for treating parkinsonism. Experiments in rodents and primates, and preliminary studies in humans, have shown that an A2AR antagonist (KW-6002) potentiates and prolongs the antiparkinsonian response to low-dose levodopa, and attenuates the induction and expression of dyskinesias and other motor response fluctuations that occur in response to dopaminergic stimulation (e.g. ref. [12]).

There is also substantial interest in drugs that target the glutamatergic system. Initial attempts have focused on antagonists that block ionotropic glutamate receptors. Preclinical and clinical studies with these medications (such as MK-801 or remacemide) have yielded mixed results, mostly because of substantial side-effects due to the fact that such glutamate receptors are ubiquitously distributed throughout the central nervous system [13]. More recently, metabotropic glutamate receptors have emerged as potential targets for therapeutic interventions. These compounds have the advantage of being relatively selectively located in specific basal ganglia loci, so that side-effects may be less likely to occur than with the ionotropic glutamate receptor ligands.

Finally, other surgical procedures are also being tested. For instance, there has been a long history of using cell transplants in parkinsonian patients. Initial transplantation studies have focused on the use of dopaminergic adrenal or fetal mesencephalic donor tissues. Owing to the mixed results of recent studies investigating the use of such grafts in parkinsonian patients, these procedures remain experimental. A particular problem that has become apparent is the appearance of transplantation-induced dyskinesias, which may be the result of unregulated dopamine release from the transplanted tissue [14]. Because of ethical and efficacy concerns, it is likely that graft procedures will increasingly rely on stem cells or encapsulated genetically modified cells, which may offer the opportunity to regulate the graft’s dopamine production.

**Huntington’s disease is a hyperkinetic movement disorder.** Huntington’s disease was described in 1872 by George Huntington, a general practitioner from Pomeroy, Ohio, who described a Long Island family with a hereditary form of chorea. The term chorea refers to involuntary, arrhythmic jerky movements of the limbs. Early in the disease process, the chorea is often a focal phenomenon, and may manifest itself as increased blinking, grimacing, or fidgetiness. Later, it progresses to involve multiple body parts, reaching its maximum within 10 years, when it is gradually replaced by bradykinesia and rigidity, i.e. symptoms reminiscent of PD. Besides the relentless development of chorea, prominent non-motor disturbances such as depression, behavioral disturbances, and cognitive impairments are also seen, and often represent the most significant source of disability for these patients and their families. Many patients have additional, symptoms such as weight loss and autonomic dysfunction.

Men and women are equally affected with a prevalence of 5–10 per 100,000 people [16]. There are distinct geographic
and ethnic differences in the prevalence of Huntington's disease, with the highest prevalence reported in the Western European population. The disease usually manifests itself after the third decade of life, although juvenile cases have been reported. Most patients die as the result of medical complications of the disease, usually 15–20 years after symptom onset.

Pathology and pathophysiology. Pathologic studies have shown widespread neuronal degeneration throughout the cortex, basal ganglia, thalamus and brainstem. Of these, striatal areas seem to be particularly affected [17]. Striatal degeneration first involves enkephalin-containing output neurons, i.e. a group of cells projecting to GPe. This may lead to reduced inhibition of GPe neurons and, subsequently, to increased inhibition of STN neurons, decreased facilitation of GPe output and disinhibition of thalamocortical neurons. Huntington's disease shares the reduction of basal ganglia output to the thalamus with other 'hyperkinetic' disorders, such as hemiballism, a disorder that most often arises from a stroke in the STN. In later stages of Huntington's disease, however, inhibitory striatal output neurons to GPe begin to degenerate, which may result in disinhibition of GPe neurons and development of parkinsonian features.

Striatal degeneration in Huntington's disease goes far beyond the motor portion of this structure. In fact, the earliest and most prominent anatomic and radiologic features of Huntington's disease are in the caudate nucleus. The involvement of basal ganglia–thalamocortical associative and limbic circuits may contribute to the prominent psychiatric and cognitive abnormalities in this disease. Patients also suffer widespread neural degeneration in non-basal-ganglia structures, including cortex, thalamus and brainstem, which may also play a significant role in the disease.

Genetic and molecular aspects of the disease. Huntington's disease results from a mutation of a highly conserved gene on the short arm of chromosome 4 and is transmitted in an autosomal dominant fashion (see ref. [18]). The gene codes for the cytosolic and nuclear protein huntingtin, which is associated with microtubules and synaptic vesicles, and which is widely expressed throughout the nervous system, and in non-neuronal tissues. Huntingtin appears to serve a critical function early in development. It may have a role in axonal transport, and may be involved in processes countering apoptosis.

Huntington's disease is a prototypical trinucleotide repeat disorder (see also Ch. 39 and Box 46-1 for disorders due to polyglutamine repeat mutations) [19] in which a short DNA fragment consisting of repeated segments of the trinucleotide sequence CAG greatly expands, resulting in expansion of a polyglutamine sequence in the related gene product. Within a given family, the age of onset of the disease tends to drop from one generation to the next (anticipation), at least in part due to further expansion of the CAG repeat sequence.

The process by which expansion of polyglutamine sections within the huntingtin protein results in the neuropathology of Huntington's disease remains unknown, but probably represents a toxic gain of function. Mutated huntingtin tends to form proteolysis-resistant aggregates, probably because of the formation of cross-links between its polyglutamine sections (Fig. 46-6), but it is unclear whether these aggregates are toxic, or whether they simply represent a metabolic end-product. Mutant huntingtin also increases the expression of caspase-1, which may, through caspase-3 activation, trigger apoptosis. Huntingtin may also act to impair proteasomal function and may lead to transcriptional dysregulation. Mutant huntingtin is also associated with changes in activation of various associated proteins, such as huntingtin–associated protein 1 (HAP1), and huntingtin–interacting proteins, which, in turn, may have far-reaching consequences in terms of intracellular transport pathways, the cellular Ca2+-homeostasis and other phenomena. Finally, problems with mitochondrial energy metabolism have also been identified in Huntington's disease.

Animal models. Early animal models of the disease were directed at mimicking the loss of striatal neurons in Huntington's disease, by injections of neurotoxins into the striatum [20]. Thus, striatal injection of excitatory neurotoxins, such as kainic acid, a rigid analog of glutamate, causes destruction of intrinsic GABA-containing and cholinergic neurons, but spares glia and afferent axons. Affected neurons are those which possess receptors for excitatory amino acid neurotransmitters. Quinolinic acid, a tryptophan metabolite found in brain and other tissues, has a more restricted neurotoxicity, which fairly closely mimics the chemical pathology of early Huntington's disease.

Injections of the neurotoxin 3-nitropropionic acid, an irreversible inhibitor of complex II of the mitochondria respiratory chain, induce selective striatal degeneration similar to that observed in Huntington's disease. Genetically modified animals which express either full-length mutant human huntingtin gene, or sections of the 5' end of this gene, which contains the CAG expansion, mimic many of the pathologic and some of the behavioral features of the disease.

Symptomatic treatment. The chorea of Huntington's disease responds (partially) to treatment with neuroleptics, which, through blockade of D2 receptors, may help to increase basal ganglia output to more normal levels. Dopamine-depleting agents, such as reserpine or tetra- benzine have also been used. At best, these agents are only moderately effective and they should only be used if the chorea truly interferes with activities of daily living or produces social embarrassment. Neuroleptics and
dopamine-depleting agents need to be discontinued in the late akinetic-rigid stage of the disease, because these agents may aggravate parkinsonian symptoms.

Non-motor signs of the disorder are also treatable with symptomatic medications. The frequent mood disorder can be treated with standard antidepressants, including tricyclics (such as amitriptyline) or serotonin reuptake inhibitors (SSRIs, such as fluoxetine or sertraline). This treatment is not without risks in these patients, as it may trigger manic episodes or may even precipitate suicide. Anxiety responds to benzodiazepines, as well as to effective treatment of depression. Long-acting benzodiazepines are favored over short-acting ones because of the lesser abuse potential. Some of the behavioral abnormalities may respond to treatment with the neuroleptics as well. The use of atypical neuroleptics, such as clozapine is preferred over the typical neuroleptics as they may help to control dyskinesias with relatively few extrapyramidal side-effects (Ch. 54).

Finally, it is of utmost importance to provide help with the many social problems these patients and their families and care-givers suffer. At this time there is no proven therapy to prevent the disease; however, genetic testing of patients at risk of the disease, particularly unaffected family members is available. It has been shown that knowing the results of the test helps those at risk of carrying the Huntington gene mutation, regardless of the actual outcome of the test.

Neuroprotective and restorative treatment strategies. Huntington’s disease is a disease with a known and testable gene defect, which produces symptoms late in life. This constellation of clinical features makes this disorder an almost ideal candidate for the development of neuroprotective treatments. Various avenues for this have been suggested. Thus, it is known that a continuous influx of the mutant protein is required to maintain inclusions and symptoms, raising the possibility that blockade of the process of polymer formation, which depends on the action of transglutaminases, may be an effective treatment of Huntington’s disease. In transgenic mice, use of the competitive transglutaminase inhibitor cystamine extended survival after the appearance of abnormal movements. Various disaccharides (such as trehalose) also inhibit polyglutamine-mediated protein aggregation and may improve motor dysfunction and increase survival in transgenic animals.

Other potential approaches involve the use of antiapoptotic treatments, such as caspase-1 inhibitors or HDAC inhibitors which may interfere with the transcriptional dysregulation seen in Huntington disease. Both approaches have resulted in encouraging results in animal experiments. The use of growth factors has also been suggested as possible treatment for Huntington’s disease.

Finally, cellular transplantation approaches have also been tried. These therapies are aimed at replacing the striatal neurons. However, in view of the widespread pathology, it remains doubtful that this disorder can be treated successfully with these interventions.

Wilson’s disease is a disease of copper accumulation. Wilson’s disease is an autosomal recessive disorder characterized by the accumulation of copper in liver and brain [21]. Hepatic involvement may result in liver cirrhosis and hepatic cancer. The deposition of copper in the basal ganglia results in a variety of movement disorders, including
tremor, dyskinesias, dystonia and rigidity, as well as behavioral and cognitive abnormalities.

Other organ systems are also involved in the disease. Thus, one of the most striking physical findings in Wilson's disease is the appearance of 'Kayser–Fleischer' rings at the periphery of the cornea. They represent copper deposits, and are seen in about 60% of all patients with Wilson's disease, and in all patients with neurologic manifestations (Fig. 46-7). Less-common signs of the disease are azure lunulae of the fingernails, copper accumulation in joints, resulting in chondrocalcinosis and osteoarthritis, renal hypercalcioria and nephrocalcinosis, perhaps due to a concomitant tubular defect in calcium reabsorption, and cardiomyopathy.

A diagnosis of Wilson's disease should be considered in younger patients presenting with a movement disorder, and in patients of any age who present with a combination of hepatic and neurologic abnormalities. Patients may also first present with behavioral or psychiatric manifestations. The diagnosis should be confirmed by an ophthalmologic assessment to detect Kayser–Fleischer rings, by studies to detect reduced serum levels of the copper-binding protein ceruloplasmin (see below) and elevated urinary copper excretion, and by liver biopsy, if indicated. Imaging techniques such as brain MRI scans to demonstrate basal ganglia abnormalities, cerebral atrophy, and subcortical-matter abnormalities, or echocardiography are also useful.

Several clinically distinct forms of Wilson's disease have been described. Thus, a relatively mild, late-onset form of the disease, has been described in Jewish patients from Eastern Europe. These patients usually present with the neurologic signs of the disease. In contrast, the more common early-onset (childhood) forms of the disease often present first with liver problems, followed by neurologic manifestations.

Molecular, pathophysiologic and genetic aspects. The worldwide prevalence of Wilson disease is estimated to be approximately 3 per 100,000 persons (e.g. ref. [22]).

The disease results from mutations within the ATP7B gene on the short arm of chromosome 13 [23, 24]. This gene encodes a protein which appears to be involved in copper transport coupled with the synthesis of ceruloplasmin and other cuproproteins.

Adults require 1–2 mg of copper per day, and eliminate excess copper in bile and feces. Most plasma copper is present in ceruloplasmin. In Wilson's disease, the diminished availability of ceruloplasmin interferes with the function of enzymes that rely on ceruloplasmin as a copper donor (e.g. cytochrome oxidase, tyrosinase and superoxide dismutase). In addition, loss of copper-binding capacity in the serum leads to copper deposition in liver, brain and other organs, resulting in tissue damage. The mechanisms of toxicity are not fully understood, but may involve the formation of hydroxyl radicals via the Fenton reaction, which, in turn initiates a cascade of cellular cytotoxic events, including mitochondrial dysfunction, lipid peroxidation, disruption of calcium ion homeostasis, and cell death.

Animal models. There are several animal models for Wilson's disease which may prove useful for the study of copper metabolism, ceruloplasmin functions, and the pathophysiology of Wilson's disease. One of these models is the Long–Evans Cinnamon rat, a genetically authentic model of Wilson's disease, in which the animals develop hepatitis and liver carcinoma, associated with abnormally high hepatic copper, which can be prevented by treatment with copper-chelating agents. Genetic mouse models have also been studied. Thus, homozygous null mutants for the Wilson's disease gene display a gradual accumulation of copper in liver (resulting in liver cirrhosis), kidney, brain, placenta and lactating mammary glands. However, other features of the phenotype of these animals do not resemble Wilson's disease, but rather suggest a copper-deficiency state. Finally, copper toxicosis, an autosomal recessive disorder in dogs, is also thought to be a genetically faithful model of Wilson's disease.

Treatment. Since the 1950s, the treatment of Wilson's disease has relied on chelating agents [25]. Early attempts to use BAL or EDTA for this purpose were unsuccessful, but penicillamine, triethylene tetramine dihydrochloride (tiendrine), and tetraethylenemolybdate, all in combination with a low-copper diet, have proved to be effective, and result in the urinary excretion of large amounts of copper. The use of penicillamine is complicated by the fact that it may induce a transient worsening of neurologic function due to rapid mobilization of copper, and also has other side-effects, such as the development of nephrosis. Tetraethylenemolybdate is an effective alternative with fewer side-effects [26]. In cases in which the dose was rapidly escalated, however, bone marrow suppression or liver function abnormalities have been described.

In addition, treatment with zinc acetate helps to reduce serum copper levels. Zinc acetate is a relatively nontoxic agent which blocks intestinal copper uptake and induces
hepatic metallothionein. It has a slow onset of action compared to penicillamine. Zinc treatment has also been used to prevent the onset of symptoms of Wilson's disease in patients who had been shown to be at risk (for instance, through genetic testing).

In cases in which drug treatment management is not successful, liver transplantation can be used. This is a highly effective treatment to correct the hepatic and metabolic problems, but neurologic symptoms and signs are often irreversible.

Dystonia is characterized by sustained muscle contractions. In patients with dystonia, normal movements are disrupted by cocontraction of agonist and antagonist muscles, and by excessive activation of inappropriate musculature (overflow), leading to abnormal postures and slow involuntary twisting movements, which are often associated with movement execution.

Etiology and classification. Dystonia may arise from a variety of disease processes, the majority of which involve the basal ganglia. Dystonia can be classified as a generalized or focal disorder. The most common forms of dystonia are focal in nature (e.g., spasmodic torticollis, blepharospasm, writer's cramp, etc.) and occur in adults, while many of the childhood dystonias are generalized.

Dystonia can also be classified as 'primary' or 'secondary'. In children and young adults, one of the main forms of 'primary' dystonia (i.e., dystonia without a clearly defined pathologic basis) is idiopathic torsion dystonia. The disease is autosomal dominant, occurring with high frequency (1 per 23,000 live births) in Ashkenazi Jews [27]. The penetrance, however, is only 30%. The disorder is caused by a genetic defect in the DYT1 gene on the short arm of chromosome 9 which codes for the ATP-binding protein torsin A. Torsin A is present throughout the brain, but is enriched in SNc neurons, suggesting a role in dopaminergic transmission. It is located primarily in the nuclear envelope. The disease often begins in childhood or adolescence with involuntary posturing of the limbs, and tends to generalize within a few years.

More than a dozen other determined forms of dystonia have been described. They differ in their mode of inheritance, and the genes involved. A detailed description of these disorders is beyond the scope of this chapter.

Dystonia due to identifiable structural or biochemical abnormalities ('secondary' dystonia) often occurs weeks or months after strokes or other focal lesions, which commonly involve the basal ganglia, but may also involve the thalamus or cerebellum. Dystonia is also seen in children with cerebral palsy and in patients with abnormalities of dopaminergic transmission. For instance, dystonia may develop in the context of Parkinson's disease, either as an early parkinsonian sign, or in response to dopaminergic drugs. A particularly interesting inherited disease results in a combination of dystonia and parkinsonian features at a young age, which responds dramatically to treatment with low-dose levodopa ('dopamine-responsive dystonia').

These patients suffer from a genetic defect of dopamine synthesis, caused by reduced GTP cyclohydrolase activity. This enzyme is rate-limiting in the biosynthesis of tetrahydrobiopterin, a cofactor of the dopamine-synthesizing enzyme tyrosine hydroxylase (see Fig. 40-2).

Pathophysiology. Research into the pathophysiology of primary dystonia has demonstrated that this disorder is associated with widespread loss of inhibition and a loss of specificity in sensorimotor maps at the cortical level. The notion that dystonia may result from aberrant plasticity in susceptible individuals is also indirectly supported by the observation that the beneficial effect of neurosurgical interventions for dystonia, such as pallidotomy or DBS, is typically delayed for several weeks or months.

In cases in which dystonia results from lesions affecting the striatum or its dopaminergic supply, such lesions may affect the affinity or number of dopamine receptors in the unlesioned portion of the striatum, or may lead to reorganization of striatal topography. This will eventually result in altered activity in the basal ganglia output structures. Recent PET studies and results of single-cell recording in human patients with dystonia have suggested a combination of activity changes in the direct and indirect pathways (see below).

Pharmacologic studies suggest that abnormalities in both the indirect and direct pathway contribute to dystonia. Thus, D2LR antagonists have a substantial potential for inducing dystonia, presumably by increasing striatal outflow to GPe via the indirect pathway, whereas D1-receptor antagonists may be beneficial in this regard, presumably by reducing striatal outflow to GPi along the direct pathway. By inference, these data suggest that a relative increase in the activity along the direct pathway (compared to that along the indirect pathway) may strongly contribute to dystonia. Increased activity along the direct pathway may be due to activity changes in feedback loops that regulate GPe activity, for instance the pathway through CM. Interestingly, it has been reported that thalamic lesions were most effective against dystonia if they included the CM nucleus (Fig. 46-1).

Agonist/antagonist co-activation in dystonia may primarily reflect a defect in segregation of 'channels' passing through the basal ganglia output nuclei, i.e. an increased degree of synchronization. The development of dystonia would also depend on the presence of low overall discharge rates in the basal ganglia output nuclei, permitting excess movement. The degree of synchronization is probably determined for the most part by the presence or absence of dopamine in the striatum, but could also be explained by extrastriatal dopamine loss, for instance at the level of the STN. Given the differential effects of dopamine D1 and D2 receptor antagonists in the production of dystonia, the phenomenon of synchronization is likely to be primarily a function of abnormal discharge in the indirect pathway.

Lack of segregation could affect smaller channels within motor subcircuits or could lead to synchronized activity
between different subcircuits. The latter possibility has been favored by the results of recent PET studies in dystonic patients, which have demonstrated widespread changes in the activity of prefrontal areas. Physiologic studies have also provided evidence that dystonia is associated with increased excitability of motor areas (particularly the SMA), probably due to widespread decrease in cortical inhibition.

Treatment. Treatment for dystonia is for the most part symptomatic, except in rare instances where known mechanisms are present and specific therapies are available. The available treatments include support and rehabilitation, pharmacotherapy and, in some cases, functional neurosurgery. Sensory retraining in humans with focal dystonias has resulted in a substantial recovery of function in some patients.

Pharmacotherapy. Anticholinergic drugs, such as trihexyphenidyl, are the most effective forms of treatment for generalized primary dystonia. The use of these medications is often limited by side-effects, such as constipation, dry mouth, blurred vision and urinary retention, as well as impaired short-term memory, confusion and hallucinations. Benzodiazepines, including clonazepam or diazepam, are also effective for dystonia, alone or in combination with anticholinergics. Dosages are raised slowly until benefits are obtained or side-effects, including sedation, ataxia and confusion, prevent further escalation. Baclofen, a GABA-B-receptor agonist, is also effective for treating both focal and generalized dystonia. Relatively high doses are required (60–100 mg); however, side-effects are often limiting. A baclofen pump for intrathecal infusion may be helpful for such cases. Dystonia involving the legs and trunk is most responsive to this form of therapy. Unfortunately, sustained benefits are not the rule, and complications are not infrequent. Dopamine-depleting agents, such as tetra-
benzamine or reserpine may also be helpful. Dopaminergic drugs are occasionally beneficial in both generalized and focal dystonias, but the most dramatic effects are seen in individuals with DRD, who experience a dramatic and sustained improvement with even a small dose of levodopa. Paradoxically, a fair percentage of patients with generalized dystonia (and craniocervical dystonia) respond to DA antagonists, such as haloperidol or pimozide. Sometimes, the combination or 'cocktail' of tetrabenazine, pimozide and trihexyphenidyl is reported to be effective.

In general, the response of focal dystonias to drug treatments with systematically applied drugs is unsatisfactory. However, focal dystonias (or generalized dystonias with prominent focal symptoms) respond dramatically to botu-
linum toxin injected into the affected muscle groups. The agent acts by preventing fusion of synaptic vesicles with the synaptic membranes in axonal terminals, thereby preventing the release of transmitter into the synaptic cleft. If injected into muscle, this affects mostly cholinergic transmission at neuromuscular junctions, resulting in dose-dependent weakness of the injected muscle. Repeated injections are required every two to five months. A problem with this form of treatment is that some patients develop resistance to the toxin after several injections, usually due to an immune reaction which results in the development of antibodies against the toxin. In these cases, different botulinum toxin serotypes can be used.

Surgical approaches. Prior to the introduction of botuli-
um toxin, peripheral denervation procedures, such as dorsal or anterior cervical rhizotomy and selective peripheral denervation, were commonly performed, primarily for the treatment of cervical dystonia. These are now performed far less frequently, generally in patients with cervical dystonia who fail botulinum toxin injections. Stereotactic surgery is used primarily for severe generalized dystonia unresponsive to other treatments. In recent years, follow-
ing the success with PD, pallidotomy and DBS of the pallidum are being used with promising results. The best candidates for surgery appear to be individuals with pri-
mary dystonia. Patients with secondary forms of dystonia are less likely to benefit. Bilateral surgery is usually neces-
sary to obtain control of axial dystonia.

Many drugs and toxins induce movement disorders. In addition to MPTP, other drugs that alter the availability of dopamine or that affect its actions at receptors may induce movement disorders with parkinsonian features. Some drugs have an opposite effect, producing hyperactive states with involuntary, abnormal movements. Indeed, an important and distressing adverse effect of levodopa therapy is the development of dyskinesias. Furthermore, the neurons of the basal ganglia and associated structures are uniquely vulnerable to the effects of a variety of toxins, and this sensitivity is a critical factor in the neurological complications that accompany these substances. Generally, toxins produce more extensive neurological damage and a greater variety of clinical deficits than are found in PD. Damage to the nigrostriatal dopaminergic neurons appears to be responsible for the parkinsonian features that occur after exposure to these toxins, whereas involvement of other basal ganglia or associated systems may be responsible for the development of involuntary dyskinesias.

Dopamine depleting agents. Reserpine, a natural alkaloid that blocks vesicular transport of monoamines, depletes stored monoamines, including DA. DA depletion is asso-
ciated with the emergence of parkinsonism. This effect of reserpine was among the first clues that PD is the result of DA deficiency (see above). Generally, the parkinsonism resulting from reserpine is reversible.

As indicated earlier, α-methyl-
dopa treatment of hypertension sometimes results in the appearance of parkinsonian symptoms. This is presumed to be a consequence of DA depletion by replacement of DA with the relatively inactive false transmitter α-methyl-
dopamine, as well as by inhibition of AADC (Ch. 12).
Dopamine receptor blocking agents. Many of the neuroleptics used in the treatment of schizophrenia frequently produce parkinsonian symptoms as unwanted effects. Neuroleptics block dopamine receptors and their thera
tpeutic effect seems to be related to this action. Although these drugs act on DA systems without distinction, some are more selective. Thioridazine, clozapine and melperon, for example, have electrophysiological effects in the limbic region of the brain but little action in the nigro-striatal area. This selectivity may be related to receptor subtype specificity (see Chs 12 and 54).

Patients who have received neuroleptics for long periods of time may develop a hyperkinetic disorder of the extrapyramidal system characterized by involuntary, purposeless movements affecting many parts of the body. This is known as tardive dyskinesia. Most commonly, these are manifested in a syndrome involving abnormal movements of the tongue, mouth and masticatory muscles. There are also choreoathetoid movements of the extremities. The mechanism by which these symptoms develop remains unknown.

Effects similar to those of the neuroleptics have also been described for other dopamine-blocking agents. Thus, parkinsonism and tardive symptoms may result from use of metoclopramide, a drug which is commonly used to enhance gastric motility, or certain antiemetics, such as perphenazine.

Manganese. A small proportion of miners exposed to manganese dust develop manganism. Manganese is absorbed from the intestine as well as through the pulmonary epithelium, and once in the systemic circulation, it readily enters the brain. After a relatively short interval (months) of exposure to high doses of the dust, the disease is ushered in by psychiatric problems. ‘Manganese madness’ is characterized by emotional lability, hallucinations, irritability and aggressiveness. When the exposure is to low amounts of manganese, the behavioral changes may be mild and reversible. After more prolonged exposure, behavioral symptoms are replaced by signs of neurological damage. In contrast to PD, the globus pallidus and SNr are the sites of greatest damage; but the striatum, STN, frontal and parietal cortex, cerebellum and hypothalamus may also be involved. Epidemiological studies have shown no risk for the development of PD from drinking of well water rich in manganese. This discrepancy demonstrates the need for further research into the mechanism(s) of manganese-induced movement disorders.

Iron. Iron plays a vital role during development and growth and is an important factor in many metabolic reactions, including protein synthesis as a cofactor of both heme and nonheme enzymes, and in the development of neuronal processes. However, free iron, particularly Fe⁺⁺, is highly toxic by virtue of its ability to trigger cellular dele
terious effects, including the Fenton reaction, which generates free radical species and lipid peroxidation (Ch. 32).

Fe⁺⁺ (the oxidized form of Fe⁺⁺) and total iron are both found in increased concentration in the substantia nigra of patients with PD. It is now clear that exposure to iron does not pose an increased risk for the occurrence of parkinsonism, so that the increase of this metal may be related to some alteration in iron homeostasis.

Carbon disulfide. Carbon disulfide is a volatile, lipidsoluble industrial solvent that enters the body by inhalation or absorption through the skin. The early symptoms of carbon disulfide poisoning resemble those of manganese poisoning; subsequently, neurological deficits are widespread and include peripheral neuropathy as well as encephalopathy with memory loss, incoordination and parkinsonism. Relatively little is known about the pathological changes in humans, but in monkeys exposed to carbon disulfide, damage to the globus pallidus and substantia nigra suggest that similar pathological changes may account for the parkinsonian features of toxicity in humans. Other sulfur compounds, such as sulfuric acid and sulfur hydride, have also been implicated in inducing parkinsonian-like clinical features.

Carbon monoxide. Inhalation of carbon monoxide, which binds avidly to hemoglobin and to cytochromes, is one of the most fatal forms of poisoning. Survivors of acute carbon monoxide poisoning may develop, over several days or weeks, a delayed encephalopathy with memory loss, personality changes and some parkinsonian movement deficits, usually associated with damage to the globus pallidus, which has been reported among the pathological features of this syndrome at autopsy. In spite of all of these detrimental effects, CO is also a putative neurotransmitter (see Ch. 10).

REFERENCES


### BOX 46-1

**Summary of Polyglutamine Repeat Disorders**

*Sangram Sisodia*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reference</th>
<th>Gene</th>
<th>Locus</th>
<th>Parent-of-origin</th>
<th>Normal</th>
<th>Disease</th>
<th>Repeat location</th>
<th>Regions effected</th>
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<tr>
<td>Huntington's disease</td>
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<td>HD</td>
<td>4p16.3</td>
<td>paternal</td>
<td>10–34</td>
<td>40–121</td>
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<td>Dentatorubro-pallidolysian atrophy (Haw River syndrome)</td>
<td>[3, 4, 5]</td>
<td>DRPLA</td>
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<td>7–25</td>
<td>49–75</td>
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<td>38–62</td>
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<td>SCA1</td>
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*The mutated gene products in all these cases exhibit toxic gain of function. See Triplet Repeat Disorders in Ch. 39 and Huntington's Disease in Chs 39 and 46 for discussions of genetic pathology.*