CHAPTER

49

Neurotransmitters and Disorders of the Basal Ganglia

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OUTLINE

ANATOMY AND PHYSIOLOGY OF THE BASAL GANGLIA

The basal ganglia are components of larger circuits

The basal ganglia are a group of anatomically related subcortical nuclei that include the neostriatum (the caudate nucleus and putamen), the ventral striatum, the external and internal segments of the globus pallidus (GPe and GPi, respectively), the subthalamic nucleus (STN) and the substantia nigra pars reticulata and compacta (SNr and SNc, respectively) (DeLong & Wichmann, 2007). These structures are topographically organized, and are linked to functionally similarly specific cortical and thalamic areas in the form of re-entrant circuits (Figure 49-1). Based on the presumed function of their cortical sites of origin, these circuits are designated as skeletomotor, oculomotor, associative and limbic. These cortico-basal ganglia–thalamocortical circuits appear to operate in parallel and remain largely segregated (Alexander et al., 1986).

Of the circuits that involve the basal ganglia, the skeletomotor circuit has received the most attention, because it is strongly implicated in the pathophysiology of movement disorders. We will describe the anatomy and some of the proposed functions of this circuit in some detail here. The anatomy, and likely also the processing functions, of the other circuits are thought to be analogous to those of the skeletomotor circuit.

The skeletomotor circuit is centered on somatosensory, motor and pre-motor cortices, which send overlapping projections to the movement-related portions of the striatum, i.e., the putamen, as well as to the STN. Information from these input stations of the basal ganglia is then transmitted to the output nuclei, GPi and SNr. The connections between the striatum and GPi/SNr are organized into direct and indirect pathways (Alexander & Crutcher, 1990). The *direct* pathway is a monosynaptic projection between striatum and GPi/SNr, while the *indirect* pathway is a polysynaptic connection that traverses GPe and STN before reaching GPi/SNr. While most of the striatofugal projections belong either to the direct

or the indirect pathway, some striatofugal neurons collateralize to reach GPe, GPi/SNr and STN, thus contributing to both direct and indirect pathways. Other inputs to the putamen and the motor portion of the STN arise from the centromedian nucleus of the thalamus (CM).

Basal ganglia output from GPi/SNr is directed to the thalamus. Movement-related basal ganglia output from GPi is directed largely to the ventrolateral nucleus, which, in turn, projects towards the primary motor cortex, the supplementary motor area, and other pre-central motor cortical areas. GPi and SNr also project to the brainstem pedunculopontine nucleus (PPN) and to the thalamic nucleus CM.

Involvement of the basal ganglia in movement control

A basic understanding of basal ganglia function in the control of movement can be gleaned from considering the effects of cortical activation on striatal and subthalamic neurons (Figure 49-1). Voluntary movements appear to be initiated at the cortical level of the motor circuit. Activation of GABAergic direct pathway neurons in the putamen by cortical inputs will act to inhibit the GABAergic basal ganglia output neurons in GPi, which, in turn, will disinhibit related thalamocortical neurons, and ultimately facilitate movement. In contrast, activation of indirect pathway neurons in the putamen by cortical inputs will lead to increased basal ganglia output and, presumably, to suppression of movement. In primate studies most GPi neurons increase their firing rate with movement so that the primary role of the basal ganglia motor circuit may be to inhibit the activity of thalamocortical neurons, resulting in the inhibition of movement.

The functions of the motor circuit of the basal ganglia are not known. However, based on findings in diseases with basal ganglia pathology, and on animal experimentation, the basal ganglia have been implicated in a large number of behaviors, including self-initiated (internally generated) movements, procedural learning, scaling of movement parameters and movement sequencing [e.g., Schultz (1998)]. Learning and motor sequencing in the basal ganglia may involve modifications of the strength of glutamatergic synapses onto medium spiny neurons in the striatum. Interactions between the glutamatergic, dopaminergic and cholinergic systems, timed to salient external events, may play a role in this process. It is thought that phasic changes in acetylcholine release signal the salience of environmental events, while phasic dopamine release in the striatum provides a reinforcing signal. The dopamine signals may directly influence LTP and LTD at corticostriatal synapses through processes that also involve cannabinoid receptors and perhaps other systems. Other functions of the basal ganglia motor circuit may be related to the interplay between direct and indirect pathways in GPi. These interactions may be important for a basal ganglia control of the amplitude and velocity of movement (the so-called "scaling"-hypothesis) or for a role of these structures in the focusing of movements, allowing intended movements and suppressing conflicting movements (discussed in Wichmann & DeLong, 2007).

Multiple neurotransmitter systems are found in the basal ganglia

The basal ganglia contain several of the classical neurotransmitters and a number of neuropeptides that may participate in the modulation of information transfer. Some of the more important systems will be discussed in the following paragraphs.

GABA

The inhibitory transmitter GABA is the major intrinsic transmitter of the basal ganglia, and, consequently, inhibition and disinhibition are considered to be the most important modes of information transfer in these nuclei (Galvan & Wichmann, 2007) (see Chapter 18). With the exception of efferents from the STN, all of the intrinsic projections of the basal ganglia are GABAergic. More than 90% of all neurons in the striatum are GABAergic medium spiny neurons. These neurons have very low levels of spontaneous activity, but are driven by glutamatergic cortical and thalamic inputs. Modification of synaptic transmission at the medium spiny neurons by the action of dopamine and acetylcholine is strongly implicated in the proposed "learning" and reinforcement functions of the basal ganglia. Striatal medium spiny neurons give rise to the direct and indirect striatal output pathways (see above). Direct pathway neurons also contain substance P and dynorphin, while indirect pathway neurons contain enkephalin as a co-transmitter. The functions of these co-transmitters are not known. In addition to the output neurons, the striatum also contains several types of GABAergic interneurons. GABAergic neurons are the major cell type in GPi, GPe and SNr.

Both GABA-A and GABA-B receptor subtypes (see Chap. 18) are found in the basal ganglia. GABA-A receptors, which are mostly found postsynaptically, are inhibitory ionotropic receptors (forming a chloride channel whose conductance is rapidly modulated by ligand binding), whereas GABA-B receptors are pre- or postsynaptic G-protein coupled receptors which may serve to modulate GABA release, or result in postsynaptic inhibitory effects on a slower time scale than achieved by GABA-A receptor activation.

GABAergic transmission is also influenced via plasma membrane–bound GABA transporters (GATs). Of the four identified GAT genes, i.e., GAT-1, GAT-2, GAT-3 and B-GAT, only GAT-1 and GAT-3 have been found in the basal ganglia. Both are expressed in glia, and to a lesser extent in pre-terminal axons. Similar to those of GABA receptors, GAT functions appear to be regulated in response to changes in extracellular GABA concentrations, most likely as a compensatory phenomenon.

As mentioned above, the modulation of the GABAergic direct and indirect pathway neurons in the striatum has a central role in most models of basal ganglia function. In addition, changes in GABAergic transmission have taken center stage in models of Parkinson's disease (PD) and other disorders. It is important that, rather than being simply inhibitory, phasic changes in GABA release in the basal ganglia may trigger rebound bursts (that is, burst firing that follows an episode of inhibition), and may be involved in the generation of abnormal oscillatory firing patterns that are common in PD and other diseases (see Chs. 41 and 47 for more about PD).

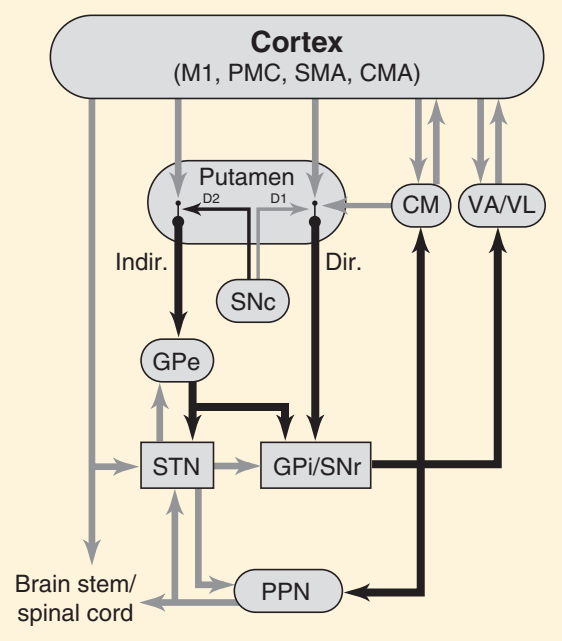

FIGURE 49-1 Simplified diagram demonstrating the anatomical connections within the basal ganglia circuitry. Abbreviations: GPe, external pallidal segment; STN, subthalamic nucleus; GPi, internal pallidal segment; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; PPN, pedunculopontine nucleus; CM, centromedian nucleus of the thalamus; VA, ventral anterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus. Grey arrows denote excitatory connections, black arrows identify inhibitory (GABAergic) connections. Figure from Galvan et al., *Clin Neurophysiol* 119:1459–1474 (2008), with permission.

Glutamate

Glutamate is another classic neurotransmitter playing an important role in basal ganglia functions (Johnson et al., 2009) (Chapter 17). Glutamatergic transmission is found in cortical efferents to the basal ganglia, efferents from the PPN and thalamus, and from the STN to other basal ganglia nuclei (Figure 49-1).

Ionotropic glutamate receptors, i.e., NMDA-, kainate- and AMPA-receptors are present throughout the basal ganglia, and are mostly located postsynaptically. In the striatum, these receptors may be involved in the information transfer between cortical and thalamic inputs and medium spiny neurons. Medium spiny neurons have specialized synaptic regions (dendritic spines) at which corticostriatal inputs end. In recent years, pathologic processes at the glutamatergic synapses have been shown to occur in a variety of conditions, including Parkinson's disease (where glutamatergic synapses may be lost), Huntington's disease (where glutamatergic transmission may contribute to the neuronal degeneration in the striatum), and fragile X syndrome (where alterations of the morphology of such synapses have been found). As mentioned above, modulation of ionotropic glutamatergic transmission is also known to be involved in fundamental learning function of the basal ganglia, through long-term potentiation (LTP) and long-term depression (LTD). Another source of ionotropic glutamatergic excitatory transmission in the basal ganglia is the STN. STN output reaches GPi, GPe and SNr, and may act as a major driving force of neurons in these nuclei.

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 regulate neuronal excitability and synaptic transmission throughout the basal ganglia (Conn et al., 2005). In general, group I mGluRs (mGluRs 1, 5) are postsynaptic, while mGluRs belonging to groups II (mGluRs 2,3) or III (mGluRs 4, 6, 7, 8) are expressed presynaptically, where they may act to regulate glutamatergic and GABAergic transmission (see also Ch. 17).

Acetylcholine

Cholinergic neurons synthesize acetylcholine from acetylcoenzyme A and choline by the enzyme choline acetyltransferase. Once released, acetylcholine interacts with acetylcholine receptors and is then rapidly metabolized by the action of acetylcholinesterase into choline and acetate (Chapter 13).

Most of the acetylcholine in the basal ganglia is found in the striatum, as the neurotransmitter of the large spiny interneurons (Pisani et al., 2007). These interneurons account for about 3% of all striatal neurons. Cholinergic interneurons are spontaneously active, and provide a cholinergic tone in the striatum. The other basal ganglia nuclei, including the STN, the pallidum, and both portions of the substantia nigra, receive cholinergic (and glutamatergic) projections from the PPN. The pallidum may also receive a small projection from forebrain cholinergic neurons.

There are two classes of acetylcholine receptors, i.e., nicotinic and muscarinic receptors. Nicotinic receptors are pentameric structures, containing several of 12 different subunits. These rapidly desensitizing ionotropic receptors are permeable to sodium, potassium, and chloride ions. Muscarinic receptors are more slowly acting metabotropic receptors. Five subtypes of muscarinic receptor have been cloned (M1, M2, M3, M4 and M5). M1, M3 and M5 receptors are Gq/11 coupled, and mobilize intracellular calcium via phospholipase-C activation. M2 and M4 receptors are Gi/o coupled and inhibit adenylate cyclase. Most muscarinic receptors are postsynaptic M1 receptors. In addition, M2 receptors function as presynaptic inhibitory autoreceptors on cholinergic terminals. M4 receptors may play a role in the regulation of acetylcholine and dopamine release, and are primarily found on direct pathway neurons. Low concentrations of M5 receptors have been identified in the substantia nigra (Ch. 13).

The physiological functions of acetylcholine in the basal ganglia appear to intersect with some of the functions of dopamine (see below). Both transmitters appear to be involved in the proposed function of the basal ganglia in learning, by mediating and modulating plastic changes at glutamatergic corticostriatal synapses. Activation of muscarinic receptors on the glutamatergic corticostriatal terminals and postsynaptically, on medium spiny neurons, may promote the induction of LTP, while low acetylcholine levels may promote the induction of LTD.

Dopamine

The synthesis and metabolism of dopamine is shown in Figure 49-2 (Chapter 14). Dopamine synthesis in dopaminergic terminals requires tyrosine hydroxylase, which, in the presence of tetrahydropteridine, oxidizes tyrosine to 3,4-dihydroxyphenylalanine (levodopa, l-DOPA). Levodopa is decarboxylated to dopamine by aromatic amino acid decarboxylase, an enzyme that requires pyridoxyl phosphate as a coenzyme. Dopamine acts on dopamine receptors (see below) that regulate transmitter release or impulse conduction at synapses or at extrasynaptic sites which are reached by spillover from synaptic release sites (so-called 'volume' transmission).

The actions of released dopamine are terminated through diffusion and presynaptic uptake into dopamine terminals via the dopamine transporter (DAT), a molecule that is exclusively expressed in dopaminergic neurons. Some of the dopamine that has been taken up is then reincorporated into vesicles, while the rest is metabolized. 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 predominately 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).

Modeling studies (Rice & Cragg, 2008) have shown that the role of the uptake process is not as important for dopamine as it is for glutamate or other 'fast' neurotransmitters. These studies demonstrated that the dopamine transporter has, in fact, little effect on synaptic dopamine concentrations, and only modest (and region-specific) effects on extrasynaptic dopamine concentrations, which appear to be more strongly affected by diffusion-related reductions of dopamine concentrations. The sphere of effect surrounding a given release site is also highly dependent on the affinity of the receptors reached (see below).

Dopamine is present in the highest concentration in the striatum, and in much lower concentrations in the other basal ganglia nuclei (Smith & Villalba, 2008). Dopamine found in the caudate nucleus and putamen originates in the SNc. Neurons in the ventral tegmental area (VTA) contribute to the dopamine supply to the ventral striatum. The most important site of extrastriatal dopamine release is the SN, where it is released from dendrites of SNc neurons. Other basal ganglia neurons, specifically those in GPi, GPe and STN, also receive dopaminergic inputs via axonal release of dopamine.

Dopamine acts on G-protein–coupled receptors belonging to the D1 family of receptors (so-called 'D1-like receptors', or D1LRs, composed of D1- and D5-receptors), and the D2 family of receptors ('D2-like receptors', or D2LRs composed of D2-, D3- and D4-receptors). D1LRs stimulate adenylate cyclase activity and, possibly, also phosphoinositide hydrolysis, while activation of D2LRs reduces adenylate cyclase activity. Both, D1LRs and D2LRs can have high- or low-affinity states (with EC_{50} values of 1 µM vs. 10 nM). Under physiologic conditions,

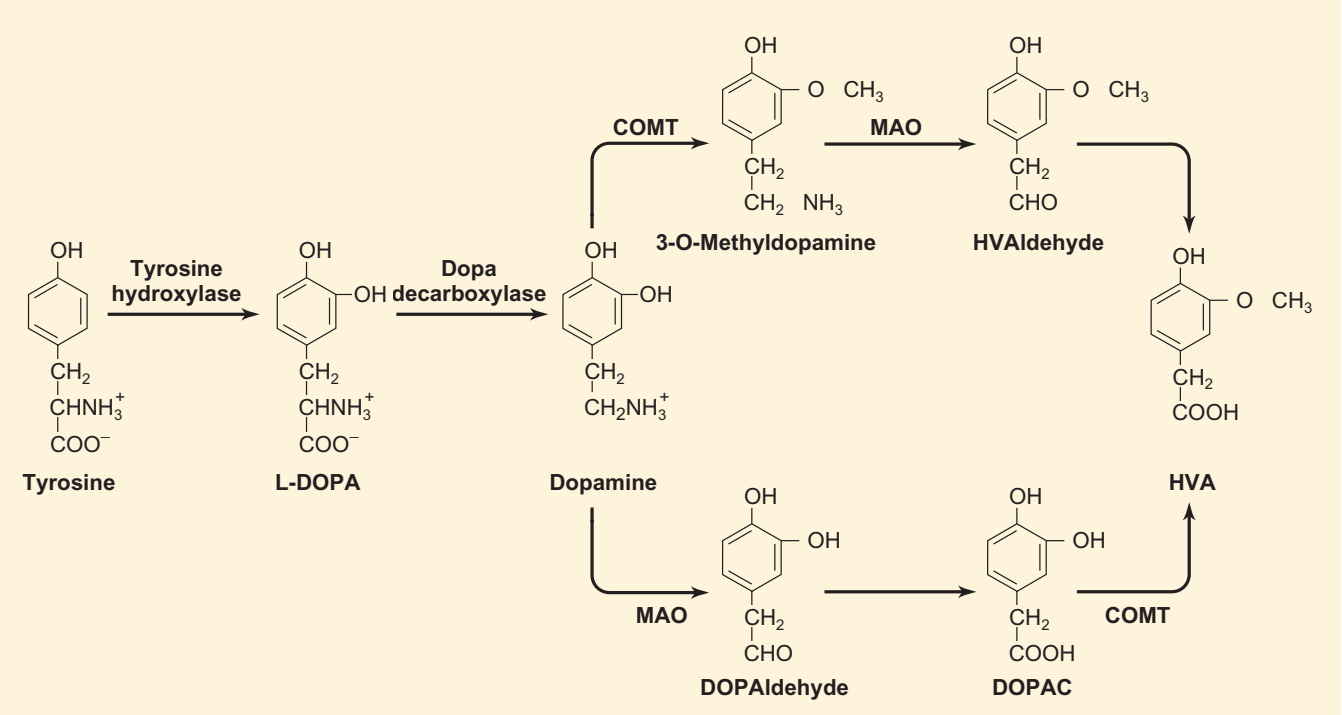

FIGURE 49-2 **Synthesis and metabolism of dopamine**. MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; HVA, homovanillic acid; DOPAC, 3,4–dihydroxyphenylacetic acid.

most D1LRs are likely in the low-affinity state, while the majority of D2LRs may be in the high-affinity state. The aforementioned modeling studies (Rice & Cragg, 2008) have shown that, together with other factors, this translates into a small region of influence of dopamine for activation of D1LRs (~2 μm radius from the release site), and into a larger region of influence for D2LRs (~8 μm). Related to this, the effects of dopamine at D1LRs may be terminated more quickly than those at D2LRs after release of a quantum of dopamine.

In the striatum, D1LRs are predominately associated with medium spiny neurons of the direct pathway. These receptors are thought to increase transmission at corticostriatal inputs terminating on the direct pathway neurons. D2LRs have been found as autoreceptors on dopaminergic terminals, as heteroreceptors on cholinergic interneurons, and on indirect pathway neurons. The latter are thought to inhibit corticostriatal transmission onto indirect pathway neurons. In the SN and GPi, D1LRs are located on terminals of the direct pathway projection while D2LRs appear to function as (inhibitory) autoreceptors. In GPe, D2LRs are located on indirect pathway axons. In these extrastriatal regions, dopamine receptors may also be located on other tissue elements (such as glutamatergic terminals), but these are less well defined. Extrastriatal regions of the basal ganglia receive dopaminergic inputs, probably in part as collaterals of the nigrostriatal projection, although exclusive nigro-pallidal dopaminergic projections have also been described.

Dopamine–acetylcholine balance

The idea that a balance of dopamine and acetylcholine concentrations in the basal ganglia is needed to achieve normal motor function was initially advanced based on the clinical experience that both dopamine replacement therapy and anticholinergic drugs help in patients with basal ganglia disorders, such as Parkinson's disease. However, while a convincing case can be made that dopaminergic drugs work mostly through actions in the basal ganglia, cholinergic fibers and acetylcholine receptors are widely distributed throughout the forebrain, so that medications targeting these systems are likely to act not only in the basal ganglia, but also outside of them, independent of dopamine.

Nevertheless, research has demonstrated some interactions between the two transmitter systems within the basal ganglia under physiologic conditions. For instance, D1LR activation enhances striatal acetylcholine release *in vivo*, while D2LR activation reduces its release. Furthermore, dopamine receptor activation may reduce GABAergic input onto cholinergic neurons, thereby producing an (indirect) inhibition of acetylcholine release. Loss of dopamine (as occurs in Parkinson's disease, see below) is associated with an increase in striatal acetylcholine levels. Studies have recently suggested that this may not only result from the loss of D2 receptor stimulation on cholinergic neurons, but may also involve the effects of dopamine depletion on the efficacy of the cholinergic M4 autoreceptors.

Depending on the state of the dopaminergic neuron, activation of nicotinic receptors may enhance or inhibit dopamine release within the striatum. Dopamine release in the striatum is also modulated by muscarinic receptors. However, muscarinic receptors are probably not present on dopaminergic terminals, so that indirect mechanism (involving GABAergic and nicotinic neurons in the striatum) may mediate these effects.

Dopamine and acetylcholine also act together to shape the excitability and plasticity of striatal output neurons. Acetylcholine release appears to be involved in mediating signals related to the salience of external events, while dopamine release conveys reward-related information to striatal neurons. Similar interactions may also exist in the other basal ganglia structures, although these structures receive much smaller cholinergic and dopaminergic innervations.

Adenosine, cannabinoid and neuropeptides function in the basal ganglia

Adenosine transmission in the basal ganglia has been intensely studied in recent years, because of the possibility that treatments targeting the A2A adenosine receptor (A2AR) may be useful in treating parkinsonian patients (Schwarzschild et al., 2006; Schiffmann et al., 2007) (Ch. 19). 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 are found on dendrites of medium spiny neurons that give rise to the indirect pathway, and may promote GABAergic signaling in these neurons, in functional opposition to 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 striatopallidal neurons. The physiologic source of adenosine in these brain areas has not been identified.

Cannabinoids and cannabinoid receptors are also are present in significant quantities in the basal ganglia, as well as in the limbic system, the hippocampus, and the cerebellum (Ferre et al., 2010). Brain cannabinoid receptors fall into two groups, i.e., CB1 receptors, found on neurons, and CB2 receptors, found mostly on immune system cells such as microglia. The receptors bind several endogenous cannabinoids (endocannabinoids), including anandamide, 2-arachidonoyl glycerol and others. Endocannabinoids serve as signaling molecules between cells, but differ from traditional neurotransmitters in that they signal retrogradely, i.e., they are released from the postsynaptic membrane to influence presynaptic functions. For instance, endocannabinoids, released from medium spiny neurons in the striatum upon receiving corticostriatal input, may inhibit the subsequent release of glutamate from the same corticostriatal terminals. Due to their hydrophobicity, the tissue diffusion of endocannabinoids is low, resulting in highly local effects. Cannabinoid transmission appears to be involved in plasticity at corticostriatal synapses.

Neuropeptides may also play important modulatory roles in basal ganglia function, especially in the striatum (Ch. 20). Neuropeptides are often co-expressed with the classic neurotransmitters. Thus, GABAergic direct striatal pathway neurons contain substance P, while indirect pathway neurons contain enkephalin. Subtypes of GABAergic striatal interneurons contain parvalbumin or nitric oxide synthetase. The functional role of these compounds has not been clarified.

DISORDERS THAT INVOLVE BASAL GANGLIA DYSFUNCTION

Parkinson's disease is a hypokinetic movement disorder

PD manifests itself with prominent movement abnormalities, including slowness of movement (bradykinesia), impaired movement initiation (akinesia), a 4–6 Hz tremor at rest, muscular rigidity and flexed posture (see Chs. 41 and 47). These motor problems are summarily called "parkinsonism." The disease is often unilateral at onset, but most patients show bilateral signs at later stages of the condition. Non-motor signs and symptoms, such as depression, apathy, autonomic dysfunction, cognitive decline and sleep disturbances, occur in a large proportion of patients, and are a major source of disability. While parkinsonism responds to known treatments, this is not the case for many of the other problems mentioned above.

Well over a million cases of PD are found in North America, with an annual incidence of 300 cases per 100,000. These numbers are expected to increase substantially with the increasing average age of the population. The median age of onset is 62 years. Males are more frequently affected than females.

Pathology

PD is a progressive neurodegenerative disease, i.e., a member of a group of conditions in which selected populations of neurons become dysfunctional and progressively die. Degenerating neurons can be identified by the presence of eosinophilic intracytoplasmic inclusions, called Lewy bodies (when such inclusions are found within the soma) or Lewy neuritis (when found in axons and terminals). PD is traditionally classified as a basal ganglia disease, characterized pathologically by Lewy bodies in degenerating dopaminergic neurons in the SNc. However, autopsy series have shown that Lewy bodies and neurites occur also in structures outside of the basal ganglia, such as the olfactory bulb, brainstem structures, and the nervous system of the gastrointestinal tract (Braak et al., 2003). These pathologic changes may represent early non-motor stages of PD, which may help to explain the finding that the motor symptoms of the disease are often preceded by non-motor symptoms, such as the inability to smell (anosmia), depression or sleep disturbances.

The cardinal motor abnormalities of PD arise in large part from degeneration of the dopaminergic neurons in the SNc, accompanied by low-level inflammatory responses that may contribute to cell death. Animal studies and neuroimaging studies in humans have suggested that the loss of SNc neurons lead to a steep decline of striatal dopamine concentrations, which becomes clinically detectable as parkinsonism when more than 70% of striatal dopamine is lost (corresponding to a 50% neuron loss in the SNc). In early phases of PD, dopamine loss affects primarily the posterior putamen (the striatal motor area). In later stages of the disease, dopamine loss becomes more widespread.

It is now clear that the loss of dopaminergic neurons has consequences that go beyond the mere absence of dopamine. Thus, experiments in animals and humans have demonstrated that dopamine loss leads to prominent secondary morphological changes in the brain areas that receive dopaminergic innervation, specifically the striatum, where the lack of dopamine is accompanied by loss of dendritic spines of striatal projection neurons. More widespread (and dopamine-independent) neuronal degeneration may account for some of the late-stage non-motor aspects of PD.

Etiology

Most cases of 'sporadic' PD are thought to arise from a combination of genetic predisposition and exposure to environmental factors. Purely (mono-) genetic forms of the disease probably account for less than 10% of cases, but the risk of family members of an affected patient developing PD is significantly increased, even in 'sporadic' PD (Ch. 41).

Epidemiologic studies have identified several environmental factors that affect the occurrence of the disease. In particular, living in rural areas, drinking well water, pesticide exposure and having suffered head trauma are associated with an increased risk of developing PD, while caffeine consumption, the use of nonsteroidal anti-inflammatory medications, and smoking tobacco are associated with a decreased risk.

Forms of parkinsonism that are exclusively due to environmental insults are uncommon. A historically important entity in this regard was post-encephalitic parkinsonism. Most cases of this disorder were caused by a viral epidemic in the early 20th century that caused an encephalitis of brainstem and midbrain structures, which (among other symptoms) resulted in parkinsonism. Other, similarly rare, forms of environmentally caused parkinsonism are due to exposures to toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP exposure was linked to parkinsonism in the early 1980s when a group of drug users were exposed to this agent as an accidental byproduct of the synthesis of an analogue of the narcotic meperidine. MPTP is a lipophilic pro-toxin which gains access to the brain. It is then converted in glia into the active toxin, 1-methyl-4-phenylpyridine (MPP^+), which is a substrate for DAT on dopaminergic neurons. The presence of DAT in terminals of dopaminergic neurons in the SNc leads to the relatively selective vulnerability of these cells. The entry of MPP^+ into these cells results in death of the dopaminergic cells via several mechanisms, most importantly via inhibition of the mitochondrial complex I. In susceptible humans and nonhuman primates, MPTP exposure results in the subacute development of parkinsonism, mimicking many of the typical characteristics of PD. Autopsy studies in patients with MPTP-induced parkinsonism have confirmed near-complete loss of dopaminergic neurons in the SNc, but no Lewy body pathology. Other forms of toxin- or medication-induced parkinsonism are mentioned below.

Although neuronal damage has been described to occur in PD in many brain regions, we know the most about damage occurring in SNc neurons. Even in healthy individuals, cells in the SNc are subject to an unfavorable balance between neuroprotective factors, such as the antioxidant glutathione, and oxidative stress because of the presence of dopaminergic metabolism, iron accumulation and other factors, rendering them vulnerable to metabolic insults. Neuronal damage to SNc neurons in PD has been attributed to either mitochondrial

dysfunction, a reduction of the cell's ability to eliminate damaged or mutated proteins through the ubiquitin proteasome system (McNaught et al., 2001), or calcium overload, perhaps caused by the reliance of adult SNc neurons on calcium channels to maintain their autonomous pacemaking activities (Chan et al., 2007).

Monogenetic forms of PD are rare. The first description of such a disease, in 1997 (Polymeropoulos et al., 1997), concerned mutations of the gene coding for α-synuclein, a brain protein that is found in synaptic vesicles and membranes along axons and terminals in many neurons, were found to result in degeneration of dopaminergic neurons. The same protein was also described to be a major component of Lewy bodies and Lewy neurites (see above). After this discovery, many researchers have focused on the role of α-synuclein in the pathogenesis of PD. The protein tends to aggregate as the result of a conformational change of the molecule from its unfolded, soluble form into an insoluble, β-pleated sheath. It is not clear whether aggregated α-synuclein is toxic, or whether it is simply a byproduct of the disease process. However, parallels have been drawn between α-synuclein aggregation in PD, and the self-aggregating properties of prion proteins, a group of proteins that cause progressive brain diseases such as Creutzfeld-Jakob disease (see Ch. 50) (Olanow & Prusiner, 2009). The recent finding that, once initiated, α-synuclein aggregation may spread to formerly healthy cells within the nervous system (Desplats et al., 2009) may provide an explanation for the apparent ascending progression of PD from brainstem to other brain areas, as described by Braak and others. The interesting finding that α-synuclein aggregates can also be found outside of the central nervous system (for instance, in the gastrointestinal tract) in individuals who do not (yet) exhibit signs of PD has given rise to the hypothesis that the pathologic process that is responsible for the degeneration of brain neurons in PD may start in the periphery, in intestine, and then enter the nervous system retrogradely via the vagus nerve. Early, almost universal involvement of the olfactory bulb also suggests exposure to an environmental toxin. At this time, however, this pathogenetic scheme remains speculative.

In addition to mutations in the α-synuclein gene, other genetic forms of PD have been described (designated as PARK diseases). Most of these are rare; however, PARK8, a form of autosomal dominant PD that is caused by a mutation in the gene encoding leucine-rich repeat kinase 2 (LRRK2, or dardarin), is relatively common. PARK8 has not only been found in families with obvious genetic forms of PD, but has also been identified in some individuals with seemingly sporadic PD, particularly in Jewish patients, with fewer cases found among Asians. It is not clear how LRRK2 mutations damage cells. Pathological studies have identified degeneration of nigral and locus coeruleus neurons, but Lewy bodies are not always present.

Animal models

Animal models for PD generally fall into two categories. One of these consists of models that mimic the loss of dopaminergic transmission in the brain. This can be accomplished with acutely administered (principally reversible) medications, such as the dopamine-depleting agent reserpine and dopamine receptor blockers, or through the use of toxins such as 6-hydroxy-dopamine or MPTP that destroy dopaminergic neurons. Such toxins have been used in rodents and primates. Of this group of animal models, the MPTP-treated primate most closely replicates the cardinal motor features of PD, but suffers, as do the other toxin models, from being relatively acute in onset (as opposed to the chronic progressive nature of PD). Furthermore, the MPTP-model replicates only dopamine (and, to a lesser degree, norepinephrine) depletion, but does not show the typical progressive and widespread pathology and symptomatology of sporadic PD in humans. Despite these shortcomings, the dopamine-depletion models of the disease are very useful for understanding the changes in brain function that are caused by dopamine loss, and for the development of symptomatic treatments for the dopamine-dependent signs and symptoms of the disease.

A second group of models utilizes genetically altered animals, some of which replicate abnormalities in α-synuclein function. While these genetic models replicate elements of the pathologic changes in PD, they are phenotypically less convincing than the toxin-induced models. These models may be particularly useful for exploring the mechanisms of cell loss and developing neuroprotective therapies. An interesting new rodent model is the VMAT2LO mouse model in which a defect in the vesicular monoamine transporter, a molecule needed for packaging dopamine into releasable synaptic vesicles, results in progressive parkinsonian signs, and even in the appearance of some of the non-motor signs of PD.

Pathophysiology

Initial studies of metabolic and neuronal activity in the MPTP primate model of parkinsonism demonstrated that the neuronal discharge in STN, GPi and SNr is increased, as compared to normal controls, while tonic neuronal discharge in GPe is decreased (Figure 49-3). These results indicated that striatal dopamine loss results in reduced activity in the direct pathway and increased activity in the indirect pathway, which together were thought to result in excessive activity in the basal ganglia output nuclei and greater inhibition of thalamocortical and brainstem neurons, thus leading to the hypokinetic features of parkinsonism (Albin et al., 1989).

Because this so-called 'rate hypothesis' is difficult to reconcile with the results of some of the later studies investigating the neuronal (and clinical) effects of basal ganglia lesioning [see discussions in Ch. 21], the focus has now shifted away from rate-based models of basal ganglia dysfunction towards models in which alterations in discharge patterns take center stage. One of the obvious abnormalities is the emergence of abnormal oscillatory activity of groups of cells in the motor circuit including, the basal ganglia, thalamus and cortex in parkinsonism which may act to disrupt normal processing. Based on the recording of local field potentials (LFPs) from the STN, a hypothesis was developed in which pathologic coherent low-frequency beta oscillations (<30 Hz) dominate the cortico-basal ganglionic interaction in parkinsonism, interfering with the initiation and control of movement. In addition to oscillatory activities, the appearance of abnormal burst patterns of discharge and increased synchrony between neurons may be highly important as well.

Our knowledge of the pathophysiology of non-dopaminergic signs and symptoms of Parkinson's disease lags behind that

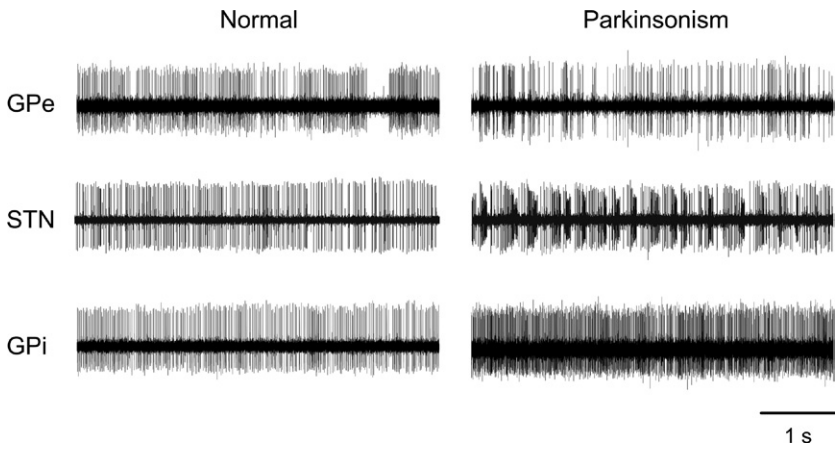

FIGURE 49-3 **Changes in the activity of single cells in GPe, STN or GPi of MPTP-treated monkeys**. Shown are examples of separate neurons, recorded with standard methods for extracellular electrophysiologic recording in normal and parkinsonian animals. Each data segment is 5 seconds in duration. Figure from Galvan et al., *Clin Neurophysiol* 119:1459–1474 (2008), with permission.

of the consequences of dopamine loss. Findings in pathologic studies may provide initial inroads to a better appreciation of the abnormalities that are responsible for some of these findings. For instance, pathologic changes in brainstem, amygdala, thalamus and cortex may contribute to dopamine-unresponsive motor signs (e.g., loss of balance), depression, anxiety, sleep disturbances and cognitive impairment. Loss of neurons in the intermediolateral cell column of the spinal cord may be responsible, at least in part, for orthostatic hypotension, i.e., abnormal decrease in blood pressure when changing from a prone to an upright position. Likewise, it has been hypothesized that local changes in the wall of the intestinal tract may underlie reduced intestinal motility and constipation in Parkinson's disease, and loss of cortical neurons (as well as dopamine loss in non-motor areas of the basal ganglia) may contribute to the cognitive changes seen in the disorder.

Symptomatic drug treatment of PD

Most of the currently available treatments for PD are symptomatic. These treatments address the motor signs of the disease, but do not alter the course or prognosis. The oldest antiparkinsonian treatments, which are still in limited use today, are anticholinergic medications such as trihexiphenidyl and benztropine. These drugs act as antagonists at muscarinic acetylcholine receptors. The mechanism of action of these drugs is frequently described as a resetting of the disturbed balance between dopaminergic and cholinergic transmission in the striatum (see above). These medications are primarily useful in the treatment of parkinsonian tremor. However, side effects, such as memory disturbances, blurred vision, sedation, dry mouth, and urinary retention often limit their use, particularly in older patients.

Dopamine replacement therapies are the mainstay of treatment of the disorder. The first agent to be introduced was the dopamine precursor levodopa, an amino acid that is metabolized into dopamine both peripherally and centrally. Levodopa is given in conjunction with peripherally acting blockers of the converting enzyme amino acid decarboxylase, such as carbidopa or benserazide. These reduce the gastrointestinal and autonomic side effects of levodopa and increase the availability of levodopa in the brain. More recently, entacapone or tolcapone, i.e., blockers of COMT (see above), have also been added to levodopa treatment. Monoamine oxidase B (MAO-B) inhibitors such as selegiline and rasagiline have also been used. Selegiline has been used for decades, whereas the more selective rasagiline was more recently introduced. Both drugs boost the levels of dopamine by inhibiting the breakdown of dopamine. These agents prolong the half-life of levodopa treatment and are used as adjunctive therapy for patients who suffer from fluctuations in their response to levodopa. Like other dopaminergic medications, levodopa therapy may induce nausea, autonomic disturbances or hallucinations. Levodopa exposure also has troublesome long-term side effects in some patients, such as the induction of involuntary movements (dyskinesias), wearing off of medication effects, or motor fluctuations and 'freezing', i.e., the sudden unpredictable loss of effect of the drug.

An important alternative to levodopa therapy is the use of dopamine receptor agonists such as ropinirole, pramipexole, apomorphine and rotigotine. These drugs are effective in treating parkinsonian signs, but generally do not reach the level of effect that can be achieved with levodopa treatment. Dopamine receptor agonists are frequently used as monotherapy in patients with mild PD. Because pramipexole and ropinirole (both used in tablet form) have a longer half-life than levodopa/carbidopa, they are also useful in later stages of the disease as add-on therapy to levodopa treatment in patients whose response to levodopa/carbidopa fluctuates. Other dopamine receptor agonists (such as apomorphine) have a shorter time to onset of effect and a shorter half-life, and can be used as an injectable "rescue" treatment for patients who suffer from episodes of sudden freezing. The side effects of the dopamine receptor agonists are similar to those of levodopa, including nausea and hallucinations. These drugs, when used alone, are not likely to induce dyskinesias, although their use may exacerbate levodopa-induced dyskinesias. Other common side effect of dopamine receptor agonists (and to a lesser degree other dopaminergic drugs) are daytime sedation and the development of impulse control disorders, characterized by excessive

and compulsive behaviors such as gambling, shopping and hypersexuality.

Drugs acting at other transmitter systems in the basal ganglia are also under development. There is substantial interest in developing medications that may act at A2ARs, since these drugs may reduce activity in the (overactive) indirect pathway in PD. Experiments in rodents and primates, and preliminary studies in humans, have shown that an A2AR antagonist (KW-6002) may potentiate and prolong the antiparkinsonian response to low-dose L-dopa, and may attenuate the induction and expression of drug-induced dyskinesias and other motor response fluctuations. There is also interest in drugs that target the glutamatergic system. Initial attempts have focused on antagonists that block ionotropic glutamate receptors. Studies with these medications (e.g., MK-801, 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 (Greenamyre et al., 1994). More recently, metabotropic glutamate receptors have emerged as potential targets for therapeutic interventions. Compounds acting at these receptors have the advantage of being relatively selectively located in specific basal ganglia loci, so that side effects are less likely to occur than with the ionotropic glutamate receptor ligands. Finally, the use of highly selective muscarinic receptor ligands (rather than the nonselective ones that are currently in clinical use) has shown promise in studies in dopamine-depleted animals.

Surgical therapy

Following promising results from animal experimentations which demonstrated reversal of parkinsonian motor signs through lesioning of the STN in MPTP-treated monkeys (Bergman et al., 1990), there has been renewed interest in surgical treatments of parkinsonism, particularly for patients whose motor signs are no longer adequately controlled with existing drugs because of the development of motor fluctuations or dyskinesias. This was first employed in the form of GPi lesions (pallidotomy). Subsequently, electrical high-frequency deep brain stimulation (DBS) of the STN or GPi was found to reverse parkinsonism in a manner similar to ablation. This treatment modality is currently preferred over lesions because DBS is reversible and adjustable. The precise mechanism of action of DBS remains controversial. Follow-up studies in patients who have been treated with the neurosurgical procedures have demonstrated that the disease continues to progress, but that the patients get highly significant symptomatic benefit, which may last in excess of five years. The neurosurgical treatments are only effective in patients who have a demonstrated benefit of levodopa treatment but are experiencing significant medication side effects, as they reduce both the severity of dyskinesias and wearing off.

Other surgical procedures have also been tested. For instance, transplantation of dopaminergic cells has been extensively evaluated in parkinsonian patients. Initial transplantation studies focused on the use of dopaminergic adrenal or fetal mesencephalic donor tissues. Owing to the mixed results of studies investigating the use of such grafts in parkinsonian patients, these procedures have largely been abandoned. A particular problem is the appearance of transplantation-induced dyskinesias, which may be the result of unregulated dopamine release from the transplanted tissue (Freed et al., 2001). Because of ethical and efficacy concerns, it is likely that graft procedures will increasingly rely upon somatic stem cells or encapsulated genetically modified cells, which may offer the opportunity to use to regulate the graft's dopamine production.

Clinical tests have examined the possible benefits of nerve growth factors to maintain or restore dopaminergic function in the brain. Initial clinical experiments involving the infusion of glia-derived nerve growth factor (GDNF), or viral delivery of a related compound, Neurturin, into the brain failed to demonstrate significant benefit, but further experiments with Neurturin are still being conducted.

Other surgical trials are examining the viral delivery of a combination of the genes for tyrosine hydroxylase, GTP-cyclohydrolase and dopa decarboxylase into the striatum, with the hypothesis that expression of such enzymes in striatal cells may result in production of dopamine at the striatal level even after the degeneration of the (native) nigrostriatal tract. Finally, there is also a trial of the effects of transfecting subthalamic nucleus cells to express the GABA-synthesizing enzyme glutamic acid dehydrogenase (GAD). These experiments do not directly address the loss of dopamine in the striatum, but attempt to remedy one of the network effects of dopamine loss, i.e., overactivity of the subthalamopallidal projections.

Neuroprotective treatment of PD

Many attempts have been made to develop neuroprotective treatments for PD. A principal problem with the evaluation of such treatments is that there is no universally agreed-upon method to measure the neuroprotective properties of a medication. A second issue is that many of the drugs that have been tested were developed with the belief that PD is largely the result of degeneration of the dopaminergic system. We now know that many other systems may contribute to the clinical presentation of PD. The overall impact of a treatment that solely protects dopaminergic neurons is, therefore, limited to the treatment of parkinsonism and does not address the numerous non-motor and dopamine-resistant motor symptoms of PD, including speech, gait and balance difficulties in patients with advanced disease.

The first controlled clinical trial for neuroprotection in PD evaluated the MAO inhibitor selegiline and the antioxidant vitamin E. 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 (Anonymous, 1989). The initial studies with this medication were complicated by the fact that selegiline also has modest symptomatic effects, which were not sufficiently considered in these experiments. Rasagiline, a more selective MAO-B inhibitor, has recently been suggested as neuroprotective treatment, but the clinical benefits are uncertain. This agent may act through anti-apoptotic effects, independent of the MAO-B inhibition. Coenzyme Q-10, an agent that may help to augment mitochondrial complex-I function, has also been shown in small preliminary trials to slow the loss of activities of daily living in parkinsonian patients, and is currently undergoing more extensive testing in patients with recent onset of PD.

A large number of additional compounds have been suggested for neuroprotection in this disease, including drugs

such as antioxidants, anti-inflammatory drugs, and glutamate receptor antagonists and agents that reduce α-synuclein aggregation or inhibit apoptosis. In addition, growth factors and agents to protect mitochondrial function have also been proposed as neuroprotective agents. Conceivably, combinations of such drugs may be used to provide effects beyond those achievable with single-drug approaches. Finally, animal studies suggest 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 stimulation of nerve growth factors, which help to support the dopaminergic system.

Huntington's disease is a hyperkinetic movement disorder

In 1872, George Huntington described a family in which several members showed involuntary arrhythmic jerky movements of the limbs (chorea) (Chapter 48). This disease, later named 'Huntington's disease,' usually manifests itself after the third decade of life, although juvenile cases have been reported (Novak & Tabrizi, 2010). Early in the disease process, the chorea is often focal and may present only as increased blinking, grimacing, or fidgetiness. It then progresses to involve multiple body parts, reaching its maximum within about 10 years, after which time it is gradually replaced by bradykinesia and rigidity, i.e., symptoms reminiscent of PD. Prominent non-motor signs such as depression, behavioral disturbances, and cognitive impairment are also seen, and often represent the most significant source of disability. Many patients have additional symptoms such as weight loss and autonomic dysfunction. Most patients die as the result of medical complications of the disease, usually 15–20 years after symptom onset. Men and women are equally affected, with a prevalence of 5–10 patients per 100,000 individuals.

In support of the notion that Huntington's disease is a basal ganglia disease, output neurons in the striatum appear to be particularly prominently affected early in the disease (Reiner et al., 1988), but autopsy studies have shown more widespread neuronal degeneration in cortex, basal ganglia, thalamus and brainstem as the disease progresses.

Genetic and molecular aspects

Huntington's disease is an autosomal dominant disease, resulting from a mutation of a highly conserved gene on the short arm of chromosome 4 [e.g., Reddy et al. (1999)]. The gene codes for the cytosolic and nuclear protein huntingtin, which is associated with microtubules and synaptic vesicles and is widely expressed throughout the nervous system and non-neuronal tissues. The function of the protein remains unclear. Huntingtin has been proposed to function in development, may have a role in axonal transport, and may be involved in processes counterbalancing apoptosis (see Chs. 6–8, 28).

The genetic defect in the huntingtin gene (H. s. D. C. R. Group, 1993) involves the expansion of a DNA section that consists of repeated segments of the trinucleotide sequence CAG, resulting in the expansion of a polyglutamine sequence in the related gene product. The age of onset is correlated with the number of CAG repeats. Within a given family, the age of onset tends to decrease from one generation to the next (anticipation), due, at least in part, to further expansion of the CAG repeat sequence.

The expansion of polyglutamine sections within huntingtin may represent 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 (Figure 49-4). Mutant huntingtin also increases the expression of pro-apoptotic factors, such as caspase-1 and activated caspase-3. Huntingtin may also act to impair proteasomal function and lead to transcriptional dysregulation. This may be associated with changes in activation of various associated proteins, such as huntingtin-associated protein 1 (HAP1), and huntingtin-interacting proteins, which, in turn, may affect intracellular transport pathways, the cellular Ca^{2+}-homeostasis and other phenomena. Disturbances of mitochondrial energy metabolism have also been identified in Huntington's disease.

Animal models

Early animal models of the disease (Ramaswamy et al., 2007) were directed at mimicking the loss of striatal neurons in Huntington's disease, by injections of neurotoxins into the striatum (Brouillet et al., 1999). Striatal injection of excitatory neurotoxins, such as kainic acid or ibotenic acid, causes destruction of intrinsic GABA-containing and cholinergic neurons but spares glia and afferent axons. 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. None of these models reproduces faithfully the involuntary movements seen in the human disease. Injections into the primate striatum of the neurotoxin 3-nitropropionic acid, an irreversible inhibitor of complex II of the mitochondria respiratory chain, induces selective striatal degeneration similar to that observed in Huntington's disease, as well as involuntary movements (Schwarcz et al., 2010).

Genetically modified animals that express either full-length mutant human huntingtin gene or sections of the 5-prime end of this gene, which contains the CAG expansion, are useful subjects in which to study the degenerative process. These models mimic many of the pathologic and some of the behavioral features of the disease. While this approach has traditionally been used in rodents, a transgenic primate model in which some of the behavioral signs of the disease are present has also been produced.

Treatment

There is no proven therapy to prevent or delay the disease, but several partially effective symptomatic therapies are in existence. The chorea of Huntington's disease responds often to treatment with dopamine receptor blockers (neuroleptics), which may help to increase basal ganglia output to more normal levels, essentially utilizing the pro-parkinsonian features of these dopamine-blocking agents. Dopamine depletors such as reserpine and tetrabenazine have also been used. These agents are moderately effective, and they should only be used if the chorea strongly interferes with activities of daily living or produces social embarrassment. Neuroleptics and dopamine-depleting agents need to be discontinued in the late

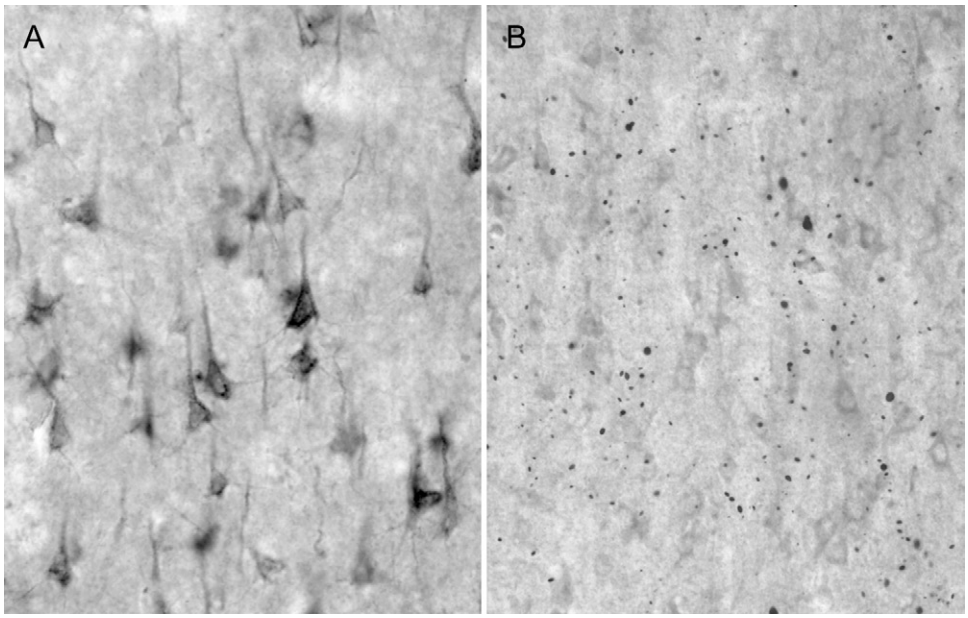

FIGURE 49-4 **A. Huntingtin distribution in a normal control in cortex (visualized using an antibody recognizing the internal epitope of the huntingtin molecule). B.** Huntingtin aggregates in cortex a patient with Huntington's disease (visualized with an antibody recognizing the N-terminal epitope of huntingtin). Both images were taken at same magnification. Courtesy of Dr. Claire-Anne Gutekunst (Emory University).

akinetic-rigid stage of the disease. The non-motor signs of the disorder are also partially treatable with symptomatic medications, such as antidepressants, anxiolytics or neuroleptic medications.

Because Huntington's disease has a known and testable gene defect, and often has a long preclinical phase, this disorder is considered to be an almost ideal candidate for the development of neuroprotective treatments. It is known that a continuous influx of the mutant protein is required to maintain inclusions and symptoms, raising the possibility that blockade of polymer formation, which depends on the action of transglutaminases, may be an effective treatment. In transgenic mice, use of the transglutaminase inhibitor cystamine indeed 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.

Dystonia is a disorder with involuntary movements

In patients with dystonia, normal movements are disrupted by co-contraction 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 (Fernandez-Alvarez, 2010; Pont–Sunyer et al., 2010; Schmidt & Klein, 2010). Many of these conditions involve the basal ganglia, although dystonia may also arise from pathology in other areas of the brain (for instance, the cerebellum). Clinically, dystonia can be classified as either a generalized or focal disorder. The most common forms of dystonia are focal (torticollis, blepharospasm, writer's cramp, etc.) and occur in adults, while many of the childhood dystonias are generalized. Another classification scheme groups these disorders into 'primary' (i.e., clinically pure) and 'secondary' dystonias. Secondary dystonias are associated with structural lesions, toxin or drug exposure, or other neurodegenerative disorders.

While genetic forms of dystonia are only clearly present in the minority of patients with dystonia, scientific investigations in genetic forms of dystonia are highly interesting, because detailed studies of these cases may help us to better understand the biological and biochemical changes in dystonia. More than 20 genetically determined forms of dystonia have been described. They differ in their mode of inheritance and the genes involved. The most common primary form of dystonia, idiopathic torsion dystonia (DYT1), is an autosomal dominant disorder with a penetrance of only 30%. The disease often begins in childhood or adolescence with involuntary posturing of the limbs, and tends to generalize within a few years. It is caused by a 3–base pair deletion in the torsin A gene on the short arm of chromosome 9, which codes for the ATP-binding protein torsin A. Torsin A belongs to a family of proteins that is involved in many cellular functions such as membrane trafficking, protein chaperone functions and others. The specific functions of torsinA are unknown, although it may play a role in development: DYT1 dystonia starts during a discrete period of time in human patients, and it has been observed that homozygous mice that express the gene defect die shortly after birth. Mutant torsin A is enriched in the nuclear envelope in neurons in the basal ganglia and other

brain regions. The presence of mutant torsin A does not result in gross degeneration of neurons, and it is therefore assumed that the mutation results in a defect of function rather than a structural deficit. However, the link between the mutation and the development of the movement disorder remains unclear. DYT1 dystonia is often responsive to high-dose anticholinergic treatment; this is potentially explained by the finding of changes in striatal cholinergic transmission in mouse models of the disease.

In some cases of dystonia, an obvious link to dopaminergic transmission can be established, thus implicating an involvement of the basal ganglia, which have the highest dopamine content in the brain (Wichmann, 2008). Thus, an interesting inherited form of dystonia results in a combination of dystonia and parkinsonian features at a young age, which responds to treatment with low-dose levodopa ('dopamine-responsive dystonia', DYT5) as well as with anticholinergics. Most of 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. Dystonia may also develop in the setting of PD, either as an early parkinsonian sign, or in response to dopaminergic drugs. Furthermore, there is some evidence that DYT1 dystonia is also associated with subtle changes in dopamine release in the striatum, and that rapid-onset dystonia/parkinsonism (DYT11) may be associated with dopaminergic deficits. Finally, chronic exposure to dopamine receptor antagonists may result in so-called "tardive" dystonia (see below).

Pathophysiology

The pathophysiology of dystonia is poorly defined (Breakefield et al., 2008). It is known that this disorder is, in some instances, associated with (or even due to) abnormalities in dopaminergic transmission, and that it is often associated with widespread loss of inhibition and excessive neuroplasticity in cortical and subcortical levels of the brain. Other mechanisms, such as abnormal cerebellar processing, may also contribute to the development of dystonia.

As mentioned above, some forms of dystonia can be linked to dopaminergic dysfunction. In other cases the disorder results from lesions affecting the striatum. 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, resulting in abnormalities in the activities of the indirect and direct pathways. In support of this concept, D2LR antagonists are known to induce or exacerbate dystonia, presumably by increasing striatal outflow to GPe via the indirect pathway. Recent positron emission tomography (PET) studies and single-cell recordings of basal ganglia structures in human patients with dystonia have suggested that some forms of dystonia may indeed feature increases in activity along both the direct and indirect pathways.

Plasticity has been examined specifically in forms of dystonia that are generated or exacerbated through overuse of the dystonic extremities, such as writer's cramp or musician's dystonia, and a loss of specificity in sensorimotor maps at the cortical level has been found. The aberrant plasticity is not likely to be isolated to the specific dystonic movement, but may reflect a generalized disorder. For instance, patients who try to shift their activities away from a specific dystonic movement to another set of movements frequently find that the new movements may become dystonic as well. The brain location at which the aberrant plasticity occurs is not identified, but it is tempting to speculate that some of these changes may involve plastic changes at corticostriatal synapses that are dopamine dependent and are known to be involved in motor learning. Recent studies in a transgenic mouse model of DYT1 have suggested that LTD is reduced and LTP is increased at these synapses. Interestingly, these changes could be reversed by treatment with muscarinic receptor antagonists (Martella et al., 2009). The possibility that dystonia involves aberrant plasticity is also supported by the observation that the beneficial effects of neurosurgical interventions for dystonia, such as pallidotomy or DBS, are typically delayed for several weeks or months, and recent studies indicate a reduction in plasticity following DBS.

Treatment

Except in rare instances where known mechanisms are present and specific therapies are available (such as levodopa-responsive dystonia, DYT5), treatment for dystonia is symptomatic. The available treatments are empiric, and include supportive and rehabilitation efforts, pharmacotherapy, and, in some cases, functional neurosurgery.

Treatment with high-dose anticholinergic drugs, such as trihexyphenidyl, is the most effective form of pharmacological treatments for generalized dystonia. The use of these medications is often limited by side effects such as constipation, dry mouth, blurred vision, urinary retention and impaired short-term memory. Benzodiazepines, including clonazepam or diazepam, also have some benefit for dystonia, either given alone or in combination with anticholinergics. The doses are raised slowly until benefits are obtained or side effects occur, including sedation, ataxia and confusion. Baclofen, a drug similar to the naturally occurring neurotransmitter GABA, is also somewhat effective for treating dystonia. As with the other medications, side effects are often limiting. Delivery of baclofen via intrathecal infusion may be helpful in cases of dystonia involving trunk or legs. Dopaminergic drugs are only occasionally beneficial in dystonia, although dramatic benefits are seen in individuals with dopamine-responsive dystonia (DYT5, see above). In general, the response of focal dystonias to systemic drug treatments is unsatisfactory. However, focal dystonias (or generalized dystonias with prominent focal symptoms) respond favorably to botulinum toxin injections into the affected muscle groups.

Surgical interventions, such as pallidotomy or DBS of the GPi, are now frequently being used in patients with generalized dystonia who fail to respond adequately to systemic treatments, particularly in individuals with generalized primary dystonia. Bilateral surgery is usually necessary to obtain control of axial dystonia. As mentioned above, the clinical effects of DBS and pallidotomy procedures often require several weeks or months to fully materialize.

Neuropsychiatric disorders

While basal ganglia pathology is strongly involved with movement disorders, structural or biochemical abnormalities in these structures may also contribute to non-motor

symptoms and signs. Far less is known about this topic than about the involvement of the basal ganglia in movement disorders. However, it is very likely that disorders such as PD or Huntington's disease affect the non-motor circuitry of the basal ganglia in much the same way as they affect the motor portions of the basal ganglia, and that some of the non-motor symptoms of these conditions may be explained by primary abnormalities in the non-motor portions of the basal ganglia, including the caudate nucleus, portions of the putamen anterior to the anterior commissure, and the ventral striatum (nucleus accumbens). This may be particularly true for the frequent psychiatric and mood disturbances in these diseases, but may also apply to some of the cognitive abnormalities.

Psychiatric disorders, such as depression, obsessive–compulsive disorder and Tourette's syndrome, have also been linked to disturbances in the limbic circuit of the basal ganglia. In addition, abnormally enhanced dopaminergic transmission in the reward circuitry in the ventral striatum is seen as a central component in psychostimulant addiction (e.g., addiction to cocaine or amphetamine; see Ch. 61).

Drugs affecting the basal ganglia

In addition to MPTP (see above), other drugs that alter dopaminergic transmission may induce movement disorders. Only a few examples will be presented here.

Dopamine depleting agents

Exposure to agents that interfere with dopamine metabolism may result in parkinsonism. Thus, dopamine depleting agents such as tetrabenazine and reserpine, which block the vesicular transport of monoamines, may lead to the depletion of stores of endogenous dopamine, resulting in reversible parkinsonism. While this effect is a side effect when these agents are used to treat conditions other than movement disorders (for instance hypertension), both reserpine and tetrabenazine have been used with some success to reduce hyperkinetic movement disorders. Tetrabenazine is currently approved by the FDA only for the treatment of chorea in Huntington's disease, but may also be effective in the treatment of other hyperkinetic movement disorders, such as tardive dyskinesias.

Dopamine receptor blocking agents

Neuroleptics, a group of dopamine receptor blocking drugs that are used in the treatment of schizophrenia and other psychiatric disorders, frequently produce parkinsonian symptoms, as well as other movement disorders. However, antipsychotic and pro-parkinsonian actions of these drugs do not necessarily coincide: Some 'atypical' neuroleptics, including clozapine and quetiapine, predominantly affect D3 receptors and limbic functions, having comparatively little effect on movement.

Tardive syndromes

In addition to the classic pro-parkinsonian effects of 'typical' neuroleptics and dopamine-depleting drugs (see above), these agents can induce involuntary movements with a more protracted course, named 'tardive' syndromes. Although this is not proven, it is assumed that these syndromes develop because of changes in neuronal activity patterns in the basal ganglia, primarily because these drugs affect the dopamine system.

By definition, tardive syndromes present with involuntary movements (other than tremor) that result from treatment with a neuroleptic drug for at least three months in younger individuals, or one month in those older than 60 years. Tardive movements may appear even after discontinuation of the offending agent. A long list of agents has been linked to tardive movements, including 'typical' neuroleptics, i.e., phenothiazines (such as thorazine); thioxanthines (such as navane); butyrophenones (such as haloperidol); dibenzoxazepines (such as loxapine); other drugs, including metoclopramide, frequently prescribed to treat gastrointestinal symptoms; and flunarizine, a calcium channel blocker. The more recently developed 'atypical' neuroleptics also block dopamine receptors, but are believed to be less commonly associated with tardive syndromes. However, recent studies have shown that the risk of developing 'extrapyramidal' side effects (i.e., parkinsonism or tardive symptoms) is nearly as high with the use of 'atypical' neuroleptics as with the earlier 'typical' neuroleptics.

Fifty percent of all tardive dyskinesias are stereotypic movements, often in the form of oro-bucco-lingual dyskinesias, facial movements (such as eye blinking or nose wrinkling), head and neck movements, or choreoid movements of other body parts. Tardive dystonia is seen in 25% of cases, and other tardive movements, such as restlessness (akathisia), tics or muscle jerking (myoclonus), in the remaining cases.

Tardive dyskinesias occur with an annual incidence of about 5% in young patients, and 20% in the elderly, resulting in prevalence rates of 10–15% in young patients and 50–75% in older individuals who are treated with typical neuroleptics. Risk factors for the development of this iatrogenic movement disorder include a history of epilepsy; head injury; dementia; diabetes mellitus; and the use of alcohol, tobacco or other drugs. The risk of developing tardive symptoms is twice as high in African Americans as in Caucasians.

The prognosis of tardive symptoms is to some extent dependent on the specific type of syndrome. Overall, 50% of patients see a remission of their symptoms over time, usually within the first five years after discontinuation of the offending drug. However, tardive dystonia remits in only 10% of cases. Tardive symptoms result in permanent disability in more than 20% of cases.

The disease mechanisms underlying the development of abnormal movements are poorly understood, but may involve D2 receptor supersensitivity. Furthermore, genetic polymorphisms affecting D2 receptor binding appear to influence the risk for developing tardive symptoms.

The treatment of tardive symptoms remains empirical. It is recommended that the inciting antipsychotic agents be discontinued (if possible). A variety of symptomatic medications can be used, including dopamine-depleting drugs (for instance, tetrabenazine). In severe cases, surgical lesioning or DBS of the internal pallidal segment can be performed.

CONCLUSION

Research into anatomical, neurochemical and functional aspects of the basal ganglia has resulted in a wealth of

CLINICAL SYMPTOMS IN PARKINSON'S AND HUNTINGTON'S DISEASES REFLECT LOSS OF CONNECTIVITY RATHER THAN LOSS OF NEURONS

Scott T. Brady

Descriptions of neurodegenerative diseases like Parkinson's (PD) and Huntington's (HD) typically focus on the loss of specific neuronal populations, and therapeutic strategies are often based on neuroprotection (Nakamura & Lipton, 2009). Unfortunately, successful reductions in the amount of neuronal cell death have not translated to effective treatments for any neurodegenerative disease (Chiesa et al., 2005; Gould et al., 2006; Waldmeier et al., 2006). Neuronal cell death and activation of apoptotic pathways associated with loss of neurons is a late event in the pathogenesis of these and other late-onset neurodegenerative diseases (Brady & Morfini, 2010). Although neuronal apoptosis is an inevitable component of neurodegeneration, the clinical symptoms associated with these diseases are the result of synaptic dysfunction and loss of critical connections.

Clinically, the resting tremor, bradykinesia, rigidity and postural changes that are associated with parkinsonism can be produced through a variety of mechanisms including synucleinopathies and Lewy pathology (see Ch. 47), mutations in multiple genes (main text and see Ch. 41), exposure to environmental neurotoxins like MPTP and rotenone, or treatment with toxic chemicals like 6-hydroxy-dopamine. In each case, symptoms present when loss of synaptic connections between dopaminergic neurons in the substantia nigra and the striatum exceeds a threshold (loss of >80% connections and >70% of dopamine). Treatments that ameliorate parkinsonism typically increase availability of dopamine directly or indirectly to compensate for loss of functional synapses in the striatum, losing efficacy when losses become too great.

A similar early loss of neuronal connections is seen in HD, where connections made by a population of medium spiny GABAergic projection neurons are particularly vulnerable (Han et al., 2010). As in PD, clinical symptoms precede significant loss of these neurons, suggesting that synaptic dysfunction and loss of connections is the proximate cause of functional losses. In both PD and HD, affected neurons exhibit a pattern of dying back neuropathy or distal axonopathy (Brady & Morfini, 2010; Coleman, 2005; Morfini et al., 2009). This mode of neuronal cell death exhibits an initial loss of presynaptic function and subsequent degeneration of distal axons that may be prolonged for years after the first reductions in synaptic function can be detected. Neuronal cell death only becomes a prominent feature of the disease when loss of functional synaptic connections exceeds a critical threshold.

Curiously, the sequence of events leading to neuronal apoptosis in PD and HD as well as a number of other adult-onset neurodegenerative diseases (Burns et al., 2009) exhibits striking parallels with programmed cell death during development of the nervous system (Brady & Morfini, 2010). In both cases, a failure to couple synaptic activity to uptake and return of neurotrophins to the cell body (see Chs. 8 and 29) may trigger neuronal apoptosis. Consistent with this idea, BDNF levels are reduced in affected brain regions for both PD and HD (Zuccato & Cattaneo, 2009). Similarly, evidence exists for disruption of trophic relationships due to misregulation of axonal transport of neurotrophins or neurotrophin receptors in both PD (Ittner et al., 2008; Morfini et al., 2007) and HD (Morfini et al., 2009; Zala et al., 2008). Loss of connectivity thus leads to critical loss of trophic relationships between vulnerable neurons and their targets. As a result, preservation of neuronal cell bodies through neuroprotective strategies is ineffective treatment of neurodegeneration unless appropriate functional connections are preserved or restored.

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information about the functional organization and neurobiology of the basal ganglia and the pathophysiology of a wide variety of neurologic and psychiatric disorders, but many unanswered questions remain. The development of detailed and testable circuit and pathophysiologic models has been particularly fruitful for neurologic disorders. In addition, the first models of neuropsychiatric diseases are currently being developed. The growing understanding of the neurochemical abnormalities in many of these diseases has helped to develop better pharmacological treatments for many of these disorders.

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