Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder

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Parkinson's disease (PD) is the second most common movement disorder. The characteristic motor impairments—bradykinesia, rigidity, and resting tremor—result from degenerative loss of midbrain dopamine (DA) neurons in the substantia nigra, and are responsive to symptomatic treatment with dopaminergic medications and functional neurosurgery. PD is also the second most common neurodegenerative disorder. Viewed from this perspective, PD is a disorder of multiple functional systems, not simply the motor system, and of multiple neurotransmitter systems, not merely that of DA. The characteristic pathology—intraneuronal Lewy body inclusions and reduced numbers of surviving neurons—is similar in each of the targeted neuron groups, suggesting a common neurodegenerative process. Pathological and experimental studies indicate that oxidative stress, proteolytic stress, and inflammation figure prominently in the pathogenesis of PD. Yet, whether any of these mechanisms plays a causal role in human PD is unknown, because to date we have no proven neuroprotective therapies that slow or reverse disease progression in patients with PD. We are beginning to understand the pathophysiology of motor dysfunction in PD, but its etiopathogenesis as a neurodegenerative disorder remains poorly understood.

Parkinson's disease (PD), which afflicts nearly 1% of the population above the age of 60, is a multisystem neurodegenerative disorder in which progressive loss of midbrain dopamine (DA) neurons, with resulting dopaminergic deafferentation of the basal ganglia, gives rise to characteristic motor disturbances that include slowing of movement, muscular rigidity, and resting tremor. These signs of motor dysfunction, if lateralized, can be clinically diagnostic of PD.[1] They are, however, only a subset of the assorted motor, cognitive, affective, autonomic, and even sensory impairments that result from selective degeneration of different neuron types at multiple levels of the central and peripheral nervous systems. A definitive diagnosis of PD requires pathological confirmation of two invariant features: distinctive intraneuronal inclusions known as Lewy bodies (LBs) in regions of predilection, and reduced numbers of DA neurons in the substantia nigra pars compacta (SNc).

PD is, for the most part, a sporadic disorder. Loose familial clustering, in which the pattern of inheritance is not apparent, occurs in up to 15% of cases. Forms of familial PD in which inheritance follows a mendelian pattern are exceedingly rare, accounting for less than 1% of all PD patients. Among all PD patients, the average age at symptom onset is 60. Except for the rare forms of familial PD with mendelian inheritance, the disease is rare in those under 40 years of age. Thereafter, the prevalence rises rapidly, so that by the end of the seventh decade an

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State of the art

estimated 1 person in 200 has the disease, and by the end of the eighth decade the proportion is 1 in 40.[2] At this point, the annual rate of newly diagnosed cases has risen to about 1 for every 1000 persons of comparable age.[3] In spite of tremendous improvements in the quality of life of PD patients since the introduction of levodopa, mortality rates continue to be increased in those with the disease, ranging from 1.5 to 2.3 times higher than rates for those without PD.[4-6] In most series, the frequency of PD is the same for both sexes.[2]

For nearly 150 years after the first clinical description of the disease in 1817—*An Essay on the Shaking Palsy* by James Parkinson—little was known about the biology of PD. The landmark observation in 1960 that striatal DA levels were sharply reduced in PD patients led directly to a series of remarkable advances that greatly enriched our understanding of the pathophysiology of this disorder.[7] Already known to be a precursor of DA and suitable for oral administration, levodopa was promptly tested and found effective in treating the symptoms of PD. Chronic oral administration of levodopa became a mainstay of PD pharmacotherapy and remains so today[8]—notwithstanding the current availability of effective direct-acting DA agonists, and mounting concerns about levodopa's possible long-term toxic effects on DA neurons.[9]

A second breakthrough in PD research came in the early 1980s, with the serendipitous and insightful discovery of a toxin-induced model of PD in humans. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was the unintended byproduct of an illicitly manufactured opiate whose users rapidly developed progressive, levodopa-responsive parkinsonism resembling that seen in sporadic PD.[10] This human model of MPTP-induced parkinsonism was characterized by profound losses of brain-stem monoaminergic neurons and corresponding depletion of striatal DA, mirroring many of the clinical and pathological features of sporadic PD.[10] The principal exception was the paucity of LB pathology in the MPTP model of PD. Further study revealed that the active metabolite of MPTP was MPP+ (1-methyl-4-phenylpyridium ion),[11] a potent mitochondrial toxin that is readily concentrated within SNc neurons due to its affinity for the dopamine transporter (DAT).[12,13] By inhibiting mitochondrial complex I of the respiratory chain, MPP+ markedly enhances oxidative stress in SNc neurons.[14]

Neuropathology: multisystem neurodegeneration

Although PD is known primarily as a movement disorder originating in the basal ganglia, the neurodegenerative process targets select neuron groups distributed throughout the neuraxis, including specific parts of cortex, thalamus, brain stem, and spinal cord, as well as sympathetic and parasympathetic ganglia *(Table I)*. Among the neurotransmitters and neuromodulators represented in these extranigral neuron losses are acetylcholine (ACh), serotonin (5-hydroxytryptamine [5-HT]), noradrenaline (NA), and glutamate. Despite the obvious complexities, the neuropathology appears the same in each of the regions affected, suggesting a common underlying pathogenic process.

Midbrain DA neurons

The defining motor deficits in PD are linked to the selective vulnerability of a particular subgroup of nigral DA neurons.[15,16] Cell loss is most profound in the lateral half of the ventral tier of neurons in the SNc, corresponding to the subset of nigrostriatal neurons that give rise to most of the dopaminergic innervation of the lateral neostriatum, which includes the sensorimotor region of the putamen.[17] Preferential loss of these neurons accounts for the characteristic topography of DA depletion in PD, with the steepest reductions in striatal DA levels being measured in the target zones of their projections.[18] Progression of motor dysfunction in PD is correlated with reductions in various markers of nigrostriatal DA terminals within the same striatal territories.[19-21]

Involvement of midbrain DA neurons in PD is remarkably selective. While neuron loss is severe within ventrolateral SNc, the remainder of the nucleus is relatively spared.[22,23] Moreover, the nearby A8 group of DA neurons (SNc corresponds to the group designated A9 in early histochemical studies) is spared entirely, as are all but two of the seven nuclei constituting the A10 group.[24] The A10 group constitutes the principal source of dopaminergic projections to frontal and limbic cortex (the so-called "mesocortical" pathway).[25] Restricted cell loss in A10 may explain the notably circumscribed character of the cortical DA reductions observed in PD.[24] Depletion of mesocortical DA is limited to cortical layer I in PD, while the remaining and far more substantial dopaminergic input to deeper layers of cortex is well preserved.[26]

Retinal DA neurons

Certain visual impairments occur commonly in PD, in conjunction with loss of DA-producing retinal amacrine cells in the inner nuclear and ganglion cell layers and sec-

ondary depletion of the dopaminergic fiber plexus of the inner plexiform layer.[27] Resulting loss of dopaminergic modulation of the early stages of visual processing[28] is associated with impaired color perception and reduced spatial and temporal contrast sensitivity,[29,30] as well as electroretinographic abnormalities and altered pattern-evoked potentials.[31,32] These visual disturbances are correlated with disease severity[33] and can be partially reversed with levodopa therapy.[34,35]

Olfactory DA neurons

Olfactory dysfunction occurs early and often in PD, in association with early neuron loss and LB formation in the anterior olfactory nucleus and extensive LB pathology in the olfactory bulb.[36,37] Hyposmia is demonstrable in up to 90% of PD patients in whom olfaction is formally tested,[38] but this deficit is unrelated to disease duration or severity and is typically asymptomatic.[39] In contrast to the characteristic depletion of DA neurons in SNc, the population of DA neurons in the olfactory bulb

Region	Cell group	Neuromodulator	Clinical manifestations
• **Central nervous system**			
Retina	Amacrine cells of inner nuclear layer	DA	Dyschromatopsia, reduced contrast sensitivity
Pons	Locus ceruleus	NA	Hypokinesia? Depression? RBD?
Pons	Dorsal raphe nucleus	5-HT	Depression? RBD?
Pons	Nucleus pedunculopontinus pars compacta	ACh	Akinesia, RBD?
Midbrain	Substantia nigra pars compacta	DA	Bradykinesia, rigidity, tremor
Hypothalamus	Supraoptic nucleus, paraventricular nucleus	Oxytocin, VP	Hypotension?
Thalamus	Centromedian nucleus, parafascicular nucleus	Glu	Bradykinesia, rigidity, tremor
Basal forebrain	Nucleus basalis	ACh	Cognitive impairment
Basal forebrain	Anterior olfactory nucleus	ACh, CRF	Hyposmia
Amygdala	Cortical nucleus	CCK, glu	Hyposmia
Amygdala	Basolateral nucleus	Glu	Visual hallucinations
Cerebral cortex	Parahippocampal gyrus	Glu	Minimal cognitive impairment
Cerebral cortex	Insular cortex	Glu	Postural instability?
Cerebral cortex	Presupplementary motor area	Glu	Bradykinesia, hypokinesia
• **Sympathetic autonomic nervous system**			
Preganglionic	Intermediolateral nucleus of spinal cord	ACh	Orthostatic hypotension
Postganglionic	Sympathetic chain	NA	Cardiac sympathetic denervation
• **Parasympathetic autonomic nervous system**			
Preganglionic	Dorsal glossopharyngeus-vagus complex	ACh	Dysphagia, esophageal and gastric dysmotility
Postganglionic	Myenteric plexus	ACh	Esophageal, gastric, and colonic dysmotility

Table I. Clinical correlates of neuron loss in Parkinson's disease. DA, dopamine; NA, noradrenaline; 5-HT, 5-hydroxytryptamine (serotonin); VP, vasopressin; Glu, glutamate; ACh, acetylcholine; CRF, corticotrophin-releasing factor; CCK, cholecystokinin; RBD, rapid eye movement (REM) sleep behavior disorder.

actually *increases* in PD (in fact it more than doubles), mainly within the glomerular layer.[40] While this increase may appear paradoxical, its association with hyposmia is consistent with—and may be explained by[40]—separate evidence that olfactory transmission within the glomerular level is inhibited by DA[41] due to a local predominance of d_2 receptor types.[42]

A similar increase in the population of intrinsic DA neurons of the striatum occurs in the MPTP model of PD.[43] The normally small population of these tyrosine hydroxylase (TH)–positive interneurons[44] increased more than threefold in the putamen of monkeys rendered parkinsonian by destruction of the nigrostriatal DA neurons.[43]

Pontine noradrenergic neurons

By the time of SNc involvement in PD, extranigral pathology has generally extended to other vulnerable cell groups within the brain stem.[45] Notable among these are the noradrenergic neurons of the locus ceruleus (LC)[46,47] and the serotonergic nuclei of the median raphe (nMR).[37,48] The wide-ranging and profuse axonal projections of LC neurons provide noradrenergic innervation to virtually the entire central nervous system (CNS)—*except* for the basal ganglia.[49] Apart from a restricted portion of the ventral striatum (the shell region of the nucleus accumbens), neither the striatum nor the globus pallidus receives significant input from LC[49]; noradrenergic innervation of the subthalamic nucleus appears to be minimal in primates.[50] Loss of LC neurons in PD results in marked reductions in NA levels in cerebellum[51] and frontal cortex.[26] It is not known whether this accounts for the reported association between the severity of neuron loss in LC and clinical signs of akinesia and rigidity in PD.[15]

Pontine serotonergic neurons

Loss of 5-HT–producing nMR neurons leads to corresponding serotonergic denervation throughout the neuraxis, including cerebral cortex, basal ganglia, brain stem, and spinal cord.[48] Severity of neuron loss in nMR has been linked to the occurrence of clinical depression in PD.[15] Depletion of these neurons may also contribute, along with characteristic losses of LC and SNc neurons, to the remarkably strong association between PD and REM (rapid eye movement) sleep behavior disorder (RBD).[52-54] In some PD patients, development of RBD symptomatology may precede the onset parkinsonism by several years.[55]

Pontine cholinergic neurons

Selective loss of cholinergic neurons in the pedunculopontine nucleus (PPN) is another characteristic of PD pathology.[56,57] PPN contains two populations of neurons, cholinergic neurons in pars compacta (PPNc) and glutamatergic neurons in pars dissipatus (PPNd).[58,59] PPNd neurons send glutamatergic projections to globus pallidus pars interna (GPi)/substantia nigra pars reticulata (SNr), SNc, and subthalamic nucleus (STN). The cholinergic neurons project to thalamus and to GPi/SNr. PPN is somatotopically organized in primates, receiving corticotegmental inputs from motor cortex and from multiple nonprimary cortical motor fields that converge in topographic fashion to represent each body part.[60] Despite this somatotopical segregation, there is compelling anatomical evidence that functionally segregated GPi outflow from motor, associative, and limbic territories overlaps within PPN to provide functionally integrated input to the target neurons, which are limited to the noncholinergic projection neurons of PPN.[61]

The cholinergic neurons of PPN and laterodorsal tegmental nuclei promote REM sleep with muscular atonia through excitatory modulation of the REM sleep induction region within the medial pontine reticular formation.[62] Both PPN and the laterodorsal tegmental nuclei receive converging monoaminergic inputs from nMR (5-HT), LC (NA), and SNc (DA) neurons, and all of these neuromodulatory inputs are effectively inhibitory due to the particular types of slow postsynaptic receptor they engage (5-HT$_{1A}$, β, and d_2 receptor types, respectively).[62] Loss of these combined sources of inhibitory modulation of REM sleep induction might explain the increased frequency of RBD in patients with PD if RBD resulted simply from overactivity of the REM sleep induction center. However, RBD involves not only the inappropriate induction of REM sleep activity, but the loss of REM-associated muscular atonia as well.[63] Recent experimental studies suggest that basal ganglia sources of GABAergic (GABA, γ-aminobutyric acid) input to PPN may also be important to the normal control of REM sleep with atonia.

PPN also receives substantial GABAergic projections from the basal ganglia output nuclei, GPi and SNr, which are tonically overactive and show variable amounts of abnormal oscillatory activity in PD and experimental parkinsonism (see below). Electrical microstimulation of SNr has been shown recently to disrupt REM sleep with

atonia induced by activation of PPN.[64] Moreover, activation of different foci within SNr produced variable dissociation of REM sleep and muscular atonia components. Intermingled throughout lateral SNr were microstimulation sites that attenuated REM sleep but not atonia, atonia but not REM sleep, or both components.[64] In PD, degenerative loss of some PPN neurons combined with excessive and oscillatory $GABA_A$-mediated inhibition of the others via the SNr afferents seems a plausible mechanism that may account for the frequent occurrence of RBD is this disease.

Studies of experimental parkinsonism have also implicated in PPN in the pathophysiology of akinesia. Fiber-sparing lesions, pharmacological inactivation, and high-frequency stimulation of PPN in normal monkeys result in akinesia.[65-67] The akinesia in PD might result from excessive GABAergic inhibitory outflow from GPi/SNr to PPN. This is suggested by the observation that akinesia in MPTP-induced parkinsonism can be reversed by microinjection of the $GABA_A$ antagonist bicuculline into PPN.[68]

Basal forebrain cholinergic neurons

Loss of cholinergic neurons of the basal nucleus of Meynert (nBM) is common in PD, and can be associated with dementia.[49,69,70] Of course, depletion of nBM neurons is also seen—characteristically so—in Alzheimer's disease (AD), which is by far the most common neurodegenerative disorder. The prevalence of AD exceeds that of PD by more than an order of magnitude.[71] Reports linking dementia with ostensibly PD-induced cell loss in nBM have been appropriately careful to include only those cases in which the neurodegenerative changes in nBM were characteristic of PD rather than AD, ie, where LBs were demonstrable in surviving neurons and signs of AD—senile plaques and neurofibrillary tangles—were minimal or absent.[72]

Amygdala: basolateral and cortical nuclei

Pathological involvement of the basolateral nucleus of the amygdala is also frequent in PD, although cell loss here is typically minimal despite extensive LB pathology.[73,74] The glutamatergic neurons of this nucleus have linkages with both ventromedial prefrontal cortex and ventral striatum, and are believed to play significant roles in memory and learning.[75,76] In PD patients with visual hallucinations, the proportion of basolateral neurons containing LBs was reported to be roughly twice that of patients who were free of hallucinations.[73]

An additional factor that may contribute to hyposmia in PD is the neuron loss and associated LB pathology that typically affects the cortical nucleus of the amygdala.[73,74] The nucleus has powerful reciprocal connections with olfactory structures.

Cortical, thalamic, and hypothalamic neurons

Neuron loss and LB pathology is also seen commonly in select regions of cerebral cortex, thalamus, and hypothalamus in PD brains, including presupplementary motor area,[77] insular and anterior temporal cortex, centromedian and parafascicular thalamic nuclei,[78] and supraoptic and paraventricular hypothalamic nuclei.[79,80] Yet, as we have seen, while neuron loss and LB formation are widespread in PD, they are also highly select in targeting only particular cell groups and generally sparing all but a few circumscribed regions of cortex.[74,81] This serves to distinguish idiopathic PD from Lewy body dementia (LBD), a much rarer condition in which the neurodegenerative changes are qualitatively indistinguishable from those of PD yet differ sharply in quantitative terms.[82-84] In LBD, unlike PD, there is diffuse and severe cortical involvement, which appears to explain the prominent cognitive decline that appears early in LBD, but is seldom a feature of PD.

Autonomic nervous system

Autonomic disturbances in PD are frequent and varied, due to cell loss and LB pathology involving both preganglionic and postganglionic components of both the sympathetic and parasympathetic nervous systems.[85-87] The earliest pathological changes in PD are in fact extranigral, beginning with formation of LBs and loss of cholinergic neurons within the dorsal glossopharyngeus-vagus complex.[37,45] Progressive loss of these preganglionic parasympathetic neurons is one of the factors contributing to the dysphagia and esophageal dysmotility that occur frequently in PD patients.[88,89] Postganglionic parasympathetic cell loss and LB pathology within upper portions of the myenteric plexus account for the esophageal and gastric dysmotility syndromes that are common accompaniments of PD[87]; esophageal involvement, when severe, can be indistinguishable from achalasia.[90] Involvement of the

colonic myenteric plexus in PD is associated with constipation and more severe forms of colonic inertia, depending on the magnitude of cell loss.[86]

One of the most common disturbances in PD is orthostatic hypotension, presumably resulting from the characteristic loss of preganglionic sympathetic neurons in the intermediolateral nucleus of the thoracic spinal cord.[91] Destruction of postganglionic neurons within the sympathetic chain results in sympathetic denervation of the heart, as indicated by diminished cardiac uptake of a tracer that uses the same neuronal transport mechanism as NA.[92] While the clinical effects of cardiac sympathetic denervation are unknown, the diagnostic significance may be considerable.[93] Evidence of cardiac sympathetic denervation occurs early and often in PD, but not in other forms of parkinsonism, such as multiple system atrophy.[94]

Etiopathogenesis

Although the etiology and pathogenesis of sporadic PD have yet to be established, several predisposing factors and pathogenic pathways have been implicated. Among the latter are *oxidative stress* associated with mitochondrial dysfunction,[95-98] *proteolytic stress* due to dysfunction of the ubiquitin-proteasome system (UPS),[99,100] and local *inflammation*.[101-103] These are not exclusive mechanisms; in fact, they can be mutually reinforcing.[104] Moreover, each of the three pathways may lead to activation of the intracellular machinery of programmed cell death (PCD), suspected of being a final common mechanism of the neuron loss in PD.[104]

The suspected causal factors in PD include *environmental* toxins, particularly enhancers of oxidative stress,[105-107] and nuclear *genetic* defects. Evidence of mitochondrial dysfunction in PD ensured that defective mitochondrial genes linked to PD would be sought assiduously in PD patients, yet to date there is still no compelling evidence for such a link.[108,109] On the other hand, studies of families in which the inheritance of PD follows mendelian patterns have already identified five genes in which mutations are associated with typical PD phenotypes *(Table II)*.[110,111]

Genetic factors

Three of the PD-related genes—*PARK1*, *PARK2*, and *PARK5*—code for proteins found in LBs.[110,112] Two of these—parkin (the product of *PARK2*) and UCH-L1 (the product of *PARK5*)—are enzymatic components of the UPS for intracellular protein clearance.[99] The third is α-synuclein, the product of *PARK1* and a presynaptic protein that, in the fibrillar form, constitutes roughly 40% of a typical LB.[113] A fourth gene, *PARK7*, codes for DJ-1, a protein linked to oxidative stress defenses and possible chaperone functions that could help to limit misfolding of other proteins and thereby reduce proteolytic stress.[114] The fifth PD gene, *NR4A2* (also known by its product's name, NURR1),[115-117] encodes a protein that regulates transcription of the TH gene and whose postmitotic expression is critical to the specification and development of midbrain DA neurons.[118-121] Defects in this gene could lead to striatal DA depletion and the characteristic motor impairments of PD, but of course such mutations by themselves would not account for the neurodegenerative process in PD, which invariably extends well beyond the midbrain and affects numerous types of nondopaminergic cell groups *(Table I)*.

Gene	Locus	Inheritance	Onset	LB pathology	Product	Properties	Functional role	Found in LBs
PARK1	4q21	AD	Late	Yes	α-Synuclein	Presynaptic protein	Vesicle maintenance? Plasticity?	Yes
PARK2	6q25-27	AR	Early	No	Parkin	E3 ubiquitin ligase	Preproteolytic ubiquitination	Yes
PARK5	4p14	AD	Late	Unknown	UCH-L1	Ubiquitin C-terminal hydroxylase L1	Ubiquitin removal for recycling	Yes
PARK7	1p36	AR	Early	Unknown	DJ-1	Antioxidant? Molecular chaperone?	Oxidative stress response?	No
NR4A2	2q22-23	AD	Late	No	NURR1	Transcription factor for DAT and TH	Dopaminergic neurogenesis	No

Table II. Genes implicated in familial Parkinson's disease. AD, autosomal dominant; AR, autosomal recessive; LB, Lewy body; DAT, dopamine transporter; TH, tyrosine hydroxylase.

The burgeoning linkage data related to these and other loci have reignited interest in the possibility of identifying potential susceptibility genes[122-124] that might interact with environmental factors in polygenic fashion to produce the range phenotypes observed in nonfamilial PD. Recent evidence suggests that some *PARK5* mutations may increase susceptibility to development of late-onset PD,[125] while others may actually decrease susceptibility.[126] Thus far, however, it does not appear that single gene mutations figure prominently in sporadic PD.[127-130] Moreover, twin studies have repeatedly indicated that heritability factors among patients with late-onset PD are minimal to nonexistent.[131,132]

Environmental factors

The search for environmental factors that might initiate or enhance the neurodegenerative process in PD intensified following the discovery of MPTP-induced parkinsonism. As oxidative stress had been clearly implicated in the pathogenesis of MPTP-induced parkinsonism,[14,133] it was natural to focus to some extent on environmental oxidants and inhibitors of mitochondrial respiration. Tetrahydroisoquinoline (TIQ) and β-carboline (β-C) derivatives, which are structurally related to MPTP and occur naturally in many foods, produce nigrostriatal damage in experimental animals and have been detected in brain and cerebrospinal fluid (CSF) in PD patients.[106,134] As with MPTP's conversion to MPP$^+$, there is metabolic activation of TIQ and β-C derivatives by conversion to quinolinium and β-carbolinium species, respectively, which are DAT substrates and appear to be toxic to mitochondria.[106,134]

Pesticides have also been suggested as possible causal or contributing factors in some cases of sporadic PD.[105] Both paraquat and rotenone are potent inhibitors of mitochondrial complex I, and both are potentially neurotoxic.[135,136] While neuronal toxicity of paraquat is generally lacking in specificity, rotenone has been shown to produce an excellent model of PD in rodents when administered chronically in low doses.[137] Chronic infusions of rotenone produce selective degeneration of nigrostriatal DA neurons and formation of α-synuclein–positive LB-like structures, accompanied by signs of parkinsonism.[138,139] Although epidemiological studies have often suggested a linkage between exposure to pesticides and development of PD,[140,141] the interpretability of such findings has generally been limited by uncertainties concerning the chemical identity, route, intensity, and duration of exposures.[106,134]

Oxidative stress

Signs of oxidative stress are abundant in the substantia nigra of patients with PD.[95] Mitochondrial complex I activity is depressed.[142] Levels of intrinsic antioxidants, such as glutathione, are reduced,[143] while oxidized products of proteins, lipids, and DNA increase significantly.[144-147] Increasing levels of oxidative stress can eventually lead to apoptosis through the intrinsic (or "mitochondrial") PCD pathway due to cytoplasmic release of cytochrome c, which is proapoptotic, from dysfunctional mitochondria.[104]

Pathogenic factors peculiar to DA neurons

Factors peculiar to midbrain DA neurons may enhance the risk of oxidative damage in SNc, though they clearly are not essential to the neurodegenerative process, as it affects most other vulnerable cell groups. Cytosolic DA can increase oxidative stress within nigral neurons by several routes. Spontaneous autooxidation of DA produces reactive DA-quinone species and the superoxide anion ($O_2^{\bullet-}$), as well as hydrogen peroxide (H_2O_2).[148] When not sequestered in synaptic vesicles, DA can form complexes with cysteine that inhibit mitochondrial complex I.[149] Glutamatergic activation of *N*-methyl-D-aspartate (NMDA) receptors on SNc neurons results in Ca^{2+} influx that may activate nitric oxide (NO) synthase (NOS),[149] thereby increasing the availability of NO that could in turn combine with the superoxide anion to produce peroxynitrite ($ONOO^{\bullet-}$), which can cause nitrative damage to proteins, lipids, and DNA.[96,150,151]

In PD, there is progressive accumulation of intracellular iron in SNc neurons and microglia.[152-154] Why this occurs is uncertain,[153,155] but the excess nigral iron is likely to enhance local oxidative stress. Ordinarily, accumulation of tissue iron is accompanied by concomitant increases in local ferritin levels, which serve to moderate the risk of local redox toxicity that would otherwise be associated with the increased iron. However, in PD, the expected increase in local ferritin does not occur.[155,156] Iron is chemically inactive when bound to ferritin as Fe^{3+}, whereas unbound iron in the ferrous state (Fe^{2+}) can combine with H_2O_2 in the Fenton reaction to produce the reactive hydroxyl radical ($OH^{\bullet}$).[152] This and other reactive oxygen species (ROS) are also generated in the course of DA metabolism and turnover.[148] Activities of TH and monoamine oxidase generate H_2O_2. In the presence of ferrous iron, the superoxide anion and H_2O_2—two

weakly reactive free radical species—can combine in the Haber-Weiss reaction to produce the more reactive OH• radical; this is believed to be the dominant pathway for biological production of the OH• radical.[155]

Neuromelanin (NM) may play a role in nigral, and possibly LC, degeneration, but whether that role is toxic or protective remains uncertain. In humans and nonhuman primates, both the DA-producing neurons of SNc and the NA-producing neurons of LC are darkly pigmented due to perikaryal accumulation of NM within double-membraned organelles known as NM granules.[152,157] NM is produced by spontaneous autooxidation of cytosolic DA and NA in SNc and LC neurons, respectively.[152] The selective vulnerability of SNc and LC neurons in both PD and MPTP-induced parkinsonism prompted early suggestions that NM might contribute to the neurodegenerative process. Recent studies suggest NM may have the opposite effect, at least early in the disease. For example, it was noted that the nigral DA neurons most susceptible to early loss in PD—those in the ventral tier of the SNc—typically contain *lower* amounts of NM than do their less vulnerable counterparts in the dorsal tier.[16] Biochemical studies have shown that as NM is synthesized and accumulates intracellularly during the life of an SNc neuron, it appears to be capable of binding and inactivating redox-active metal ions (in particular Fe^{2+}), intrinsically generated quinones and ROS,[152,158] and environmental toxins such as paraquat.[157]

While SNc iron levels are still relatively low early in the course of PD, NM contains a preponderance of high-affinity iron-binding sites that could oxidize redox-active Fe^{2+} and chelate the inactive Fe^{3+} that results, thereby reducing the potential for oxidative stress.[157] Later, as PD progresses and cytosolic Fe^{2+} concentrations rise due to continued accumulation of intracellular iron, NM's high affinity iron-binding sites could become saturated, leaving only the low-affinity sites to bind redox-active Fe^{2+}, which they do without oxidizing it to the inactive ferric form.[152] NM-bound Fe^{2+} would then remain free to catalyze production of OH• radicals via the Fenton reaction.[134,152,157]

Proteolytic stress

A second mechanism implicated in PD pathogenesis is proteolytic stress resulting from dysfunction of the UPS of nonlysosomal protein degradation.[99] The UPS is an essential pathway for degradation and clearance of mis-folded or otherwise damaged intracellular proteins. Several converging lines of evidence suggest that protein aggregation related to proteolytic stress could be an important aggravating or contributing factor in the neurodegeneration of PD.

LBs, the *sine qua nons* of PD, are proteinaceous inclusions, of which the principal component is fibrillar α-synuclein.[159,160] The normal role of α-synuclein as a presynaptic protein is unknown, but it may be involved in synaptic maintenance or plasticity.[161,162] Approximately half of the α-synuclein within a presynaptic terminal remains unfolded, as a cytosolic protein capable of binding to synaptic vesicles; the remainder is concentrated near synaptic vesicles where it binds to plasma membranes in a predominantly α-helical form.[148] These and other properties have led to suggestions that α-synuclein plays a role in the maintenance and recycling of synaptic vesicles.[162] As concentrations of cytosolic α-synuclein rise, it may itself begin to have adverse effects. It may increase demands on the UPS for protein degradation and clearance, thus enhancing proteolytic stress.[163] In its native form, α-synuclein may bind to and thus sequester an important antiapoptotic protein, 14-3-3, thereby compromising a potential safeguard against activation of the machinery of PCD.[148] In high concentrations, unfolded α-synuclein forms β-pleated sheets known as protofibrils, which may be cytotoxic.[164] Protofibrils may increase the permeability of synaptic vesicles, causing leakage of DA into the cytoplasm which increases oxidative stress.[164,165] By a seeding process, protofibrils can form nontoxic fibrils of α-synuclein, which are the main constituents of LBs.[166]

LBs also contain lesser amounts of several UPS-related proteins. These include the following: (i) ubiquitin, the peptide with which damaged proteins are tagged in preparation for degradation by the 26S proteasome; (ii) fragments of the 26S proteasome; (iii) the E3 ubiquitin ligase parkin, which assists in preproteolytic ubiquination; and (iv) ubiquitin C-terminal hydroxylase L1 (UCH-L1), which removes ubiquitin for recycling following proteasomal degradation.[111,148] This evidence for a role of proteolytic stress in the pathogenesis of sporadic PD is reinforced by the fact that mutations in the genes coding for α-synuclein, parkin, and UCH-L1 are associated with some forms of familial PD.[111,167]

Oxidative stress can exacerbate proteolytic stress by increasing the amounts of oxidized and nitrated proteins that must be cleared by the UPS. DA-quinones produced

by spontaneous autooxidation of DA can form covalent bonds with α-synuclein, also contributing to proteolytic stress.[148,168] DA-quinone bonding might also interfere with α-synuclein's putative role in maintenance and recycling of synaptic vesicles,[148,149] which could in turn result in increased levels of unsequestered cytosolic DA thereby enhancing oxidative stress.

Inflammation

Local inflammation is readily apparent at sites of neuron loss in both PD and MPTP-induced parkinsonism.[103,169,170] Most of the inflammatory cells at these sites are activated microglia, although lesser numbers of reactive astrocytes are seen as well.[103,170,171] While the astrocytes are suspected of playing an overall protective role in PD by such mechanisms as sequestration and metabolization of DA, glutathione-mediated scavenging of ROS and production of glial-derived neurotrophic factor (GDNF), the microglia are believed instead to facilitate the neurodegenerative process in PD.[149,155,172] Microglial accumulation and activation occurs in sites where neurons eventually die and are lost, such as SNc. NM is known to be proinflammatory when released to the extracellular environment, as occurs of course when NM-laden nigral neurons eventually succumb to the neurodegenerative process.[149,155,172] Microglial infiltration in regions of neuron loss could therefore represent merely a secondary response to the presence of dead and dying neurons.[149,155] Yet experimental studies in toxin-induced animal models suggest that such inflammation also plays a causal role in the neurodegenerative process inasmuch as they show that death of SNc neurons can be averted by treatment with anti-inflammatory agents.[103]
Activated microglia appear to be the main source of increased levels of inducible NOS (iNOS) in parkinsonian nigra.[104] Induction of iNOS is associated with sustained increases in local NO production.[173] NO can diffuse readily across cell membranes to enter nearby SNc neurons, where it could combine with locally produced superoxide anion to produce peroxynitrite, exacerbating nitration-induced damage to intracellular lipids, proteins, and DNA in nigral neurons.[151,174]
Activated microglia also produce cytokines capable of amplifying the local inflammatory response by activating still more microglia in the vicinity.[175] Several of these, including tumor necrosis factor α (TNF-α), have been identified in nigral tissue of PD patients.[175,176] By binding

to TNF receptor 1 on the surface of nearby SNc neurons,[176] microglial-derived TNF-α could activate the TNF receptor family "death domain" and thereby trigger the extrinsic (or "death receptor") PCD pathway leading from initiator caspase 8 to the executioner caspases and cell death.[104] Postmortem nigral tissue in PD patients is characterized by elevated caspase activities[177] and other indicators of PCD.[178-181]

Implications of pathogenesis for neuroprotective therapy

Current understanding of the pathogenesis of PD implies that appropriate neuroprotective therapies aimed at reducing oxidative or proteolytic stress, blocking the putative toxic effects of microglial activation, or promoting neuronal growth and repair, should be effective in preventing, slowing, or reversing both the underlying neurodegenerative process and the natural progression of the disease. Such therapies could include antioxidants, anti-inflammatory agents, neuronal growth factor infusions, and neural "transplant" procedures, as well as potential gene therapies and pharmacological interventions targeting enhancement of intracellular protein clearance or suppression of PCD pathways. To date, these approaches have had little success in achieving the intended outcomes. We still have no proven neuroprotective or restorative therapies that prevent, slow, or reverse the neurodegeneration or progression of PD, despite concerted efforts to develop such measures over the past two decades.[182,183] It remains uncertain, therefore, whether any of the pathogenic mechanisms proposed to date has a primary role in disease initiation, although it does seem likely that all, when present, could contribute to disease progression. This suggests that current models of the pathogenesis of PD remain incomplete. Such is the case especially for those predisposing factors that may be selective for nigral DA neurons. The roles of iron and NM, and the toxic effects of DA metabolism in SNc neurons, do not explain the similar pathology in other cell groups such as dorsal glossopharyngeus-vagus complex or the intermediolateral column of spinal cord.
Various experimental strategies—including pharmacological and gene-based therapies aimed at reducing oxidative or proteolytic stress or inflammation or reversing defective neurogenesis—do protect against genetic or toxin-induced parkinsonism in certain animal models.[184] Such protection, however, often requires that the

therapy has been in place at or before the time of toxic exposure or expression of toxic alleles. This may account in part for the lack of effective neuroprotective strategies in human PD, as these can only be tested in subjects if they already have the disease.[182,185] Nonetheless, until we are able to intervene directly in the neurodegenerative process by blocking one or more of the implicated pathogenic pathways, the causative role of these mechanisms in human disease will remain uncertain.

Pathophysiology of motor dysfunction

While the neurodegenerative process in PD affects multiple neuromodulator systems and diverse groups of neurons at many levels of the neuraxis *(Table I)*, the characteristic motor impairments in this disorder appear to result primarily, if not exclusively, from depletion of striatal DA caused by selective degeneration of nigrostriatal neurons. There is compelling evidence for this view, including the striking effectiveness of DA agonists and antagonists in respectively ameliorating and exacerbating the motor deficits of PD, and the corresponding lack of effect on such deficits of agonists and antagonists of NA or 5-HT, the other two monoamines that are depleted in this disease. Depletion of striatal DA in human PD and in the nonhuman primate model of MPTP-induced parkinsonism is associated with specific changes in neuronal activity patterns in the motor circuitry of the basal ganglia, including increased rates of neuronal discharge within the main output nucleus of the basal ganglia, Gpi, and in the STN, and minimally decreased discharge in the globus pallidus pars externa (GPe).[186-188] Administration of dopaminergic agents results in normalization of neuronal activity and reversal of motor impairment.[188,189] Fiber-sparing ablation[190] or muscimol-induced inactivation of STN[191] reverses the motor deficits of monkeys made parkinsonian with MPTP. Radiofrequency lesioning[192,193] or high-frequency electrical stimulation—deep brain stimulation (DBS)—of the motor territory of GPi[194,195] provides effective treatment for all of the primary motor impairments of patients with PD. DBS applied to STN[194,196,197] is also effective in restoring normal movement control to PD patients. Some patients have been treated successfully with subtotal STN lesions[198-200]—however, the added risk of persistent hemiballismus[201,202] with this approach serves to lessen its appeal.

It would be difficult to exaggerate the complexity of the interconnected cortical, basal ganglia, and thalamic neuronal networks affected by the depletion of striatal DA in PD. These networks comprise multiple layers and side loops, vast numbers of neuronal elements, and a wide range of neurotransmitters, neuromodulators, axonal and dendritic branching patterns, and layer-to-layer connectivity. Nonetheless, from a large-scale perspective, these same networks can be viewed more simply as an array of contiguous but functionally specialized pathways linking basal ganglia, thalamus, and cerebral cortex in circular fashion to form a corresponding family of parallel, partially closed and largely segregated basal ganglia-thalamocortical circuits or loops.[203-207]

According to this schema, each loop takes its origin from a particular set of anatomically and functionally related cortical fields (sensorimotor, oculomotor, dorsolateral prefrontal, ventromedial prefrontal, limbic), passing through the corresponding portions of the basal ganglia, and returning to parts of those same cortical fields by way of specific basal ganglia–recipient zones in the dorsal thalamus. To the extent that information processing remains functionally segregated throughout the course of each loop, each subserves a different set of behavioral functions. Thus, the sensorimotor and oculomotor circuits participate in the control of skeletal and ocular movements, respectively; dorsolateral prefrontal and ventromedial prefrontal circuits subserve executive/visuospatial and behavioral set-switching functions, respectively; and the limbic circuit contributes to emotional processing. Evidence supporting this schema comes from both humans and nonhuman primates.[203,208-210]

Due to maintained segregation along each of these corticobasal ganglia–thalamocortical circuits, there is limited direct communication among the separate functional domains, except by way of corticocortical interactions. While essentially the entire cortical mantle is mapped topographically onto the striatum[210]—which is often considered the "input" portion of the basal ganglia—the cortically directed signals from the basal ganglia output nuclei (internal pallidum and SNr) are returned exclusively to foci within the frontal lobe (after first passing through the corresponding portions of the thalamus.) Because of the parallel organization of these circuits, the operations performed at corresponding stations (eg, striatum, pallidum, thalamus) are predicted to be similar. Accordingly, clarification of how the motor circuit operates may be relevant to our understanding of how the other circuits might function. On the basis of what is already known or suspected about the functions subserved by each circuit in the normal state, multiple studies have begun to address predic-

tions that some of those functions may be lost in PD due to impaired information processing caused by depletion of striatal DA *(Table III)*.[193,209,211-223]

The pathophysiology of motor dysfunction in PD has been clarified recently by advances on several fronts, including physiological studies in animal models of parkinsonism, neuronal recordings and DBS in humans with PD, functional brain imaging in PD patients, and computational modeling of neuronal circuitry. To understand these developments, it is useful to consider the functional organization of basal ganglia motor circuitry in some detail.

Role of DA in basal ganglia circuitry

DA has a pivotal and extremely complex role in controlling the flow of information through the basal ganglia. SNc provides dopaminergic innervation to the entire neostriatum, including the motor territory within the putamen. Through an intricate web of presynaptic and postsynaptic connections, nigrostriatal neurons modulate the responsiveness of striatal projection neurons—medium spiny neurons (MSNs)—to converging glutamatergic inputs from cortex and thalamus and local GABAergic feedback from neighboring MSNs. The nigrostriatal pathway provides an extraordinarily dense dopaminergic input to each MSN, comparable in magnitude to the 5000 or so corticostriatal synapses that individual MSNs receive.[224-226] Dopaminergic terminals from SNc form postsynaptic axospinous and axodendritic synapses with MSNs, and presynaptic axoaxonic synapses with the terminal boutons of corticostriatal fibers, which synapse mainly on the spines of MSNs.[44,226,227]

Unlike the fast-acting neurotransmitters glutamate and GABA, DA does not itself cause depolarization or hyperpolarization of the postsynaptic membrane.[228] As a slow-acting neurotransmitter, or neuromodulator, DA's synaptic effects unfold over hundreds of milliseconds and may last a minute or more. In contrast, glutamate and GABA, when acting through ionotropic receptors, produce their corresponding depolarizing and hyperpolarizing postsynaptic effects within a millisecond of binding to their individual receptors, and these effects last only from about a millisecond to a few tens of milliseconds, respectively.

DA receptors belong to the A family of seven-transmembrane receptors and are grouped into two subclasses, d_1 and d_2, based on their coupling to G-proteins that either increase (d_1-like) or decrease (d_2-like) cytoplasmic cyclic adenosine monophosphate (cAMP).[229] The d_1 subclass includes the d_1 and d_5 receptors, and the d_2 subclass comprises d_2, d_3, and d_4 receptors.[229] DA's synaptic actions are mediated through intracellular signaling pathways that regulate the phosphorylation of DARPP-32 (DA and cAMP-regulated phosphoprotein, molecular weight = 32 kda), which in turn controls the sensitivity of glutamate and GABA receptors.[230] By controlling the particular sites and level of DARPP-32 phosphorylation, DA exerts an indirect but powerful influence over the efficacy of converging synaptic actions of the fast-acting neurotransmitters glutamate and GABA.[231] This control is imposed through DARPP-32's regulation of the phosphorylation of synaptic receptors for these and other neurotransmitters. Activation of d_1-like receptors leads to increased phosphorylation—and hence increased sensitivity—of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) and NMDA glutamate receptors as well as $GABA_A$ receptors.[231] Activation of d_2-like receptors leads to the opposite effect: decreased phosphorylation and sensitivity of AMPA, NMDA, and $GABA_A$ receptors to their respective agonists. DARPP-32 is heavily concentrated within the spines of MSNs.[232,233] While nigrostriatal DA neurons send topographical projections to restricted foci within the striatum, the stria-

Basal ganglia–thalamocortical loop	Striatal component	Clinical manifestations
Sensorimotor	Postcommissural putamen	• Bradykinesia, rigidity, tremor • Impaired motor sequencing
Oculomotor	Postcommissural caudate	Gaze shift fragmentation
Dorsolateral prefrontal	Rostrodorsal caudate, precommissural putamen	• Impaired cognitive sequencing • Visuospatial deficits
Ventromedial prefrontal	Rostroventral caudate	• Perseveration • Abulia
Limbic	Ventral striatum	Anhedonia

Table III. Clinical correlates of striatal dopamine deficiency in Parkinson's disease.

tonigral input they receive in turn is convergent, arising from much broader segments of the striatum than the circumscribed territories they themselves innervate.[234] For example, ventrolateral SNc DA neurons that project selectively to the sensorimotor territory within the putamen receive striatonigral input not only from putamen but from associative (caudate nucleus) and limbic striatum as well.[234] This multimodal striatal input may account for the remarkable fact that the activity of midbrain DA neurons appears to encode a secondary reinforcement signal distilled in real time from complex contingencies implicit in a subject's ongoing behavior. In nonhuman primates performing tasks with variable probability of reward, transient deviations in the otherwise monotonous discharge patterns of midbrain DA neurons reflect the subject's realized error in predicting the future probability of behavioral reinforcement.[235] Discharge rates of midbrain DA neurons briefly increase when the subject receives positive reinforcement that had not been expected, and decrease when positive reinforcement that had been expected is not received.[236] When the primary reinforcement (eg, food or liquid reward) has become associated with a conditioned stimulus, the change in discharge rate will be linked to the unexpected presence or absence of the conditioned stimulus rather than that of the primary reward. This type of signal has been used successfully in certain types of adaptive neural networks that incorporate an "adaptive critic" to support autonomous learning.[237] In an analogous manner, by encoding such a signal, nigrostriatal DA neurons could play an important role in learning by broadcasting the optimal times at which striatal synapses should be strengthened or weakened. In fact, the signal itself might initiate the process required for changing synaptic strength. This would be consistent with the demonstration that DARPP-32 phosphorylation triggered by activation of d_1-like receptors is critical for the induction of both long-term potentiation (LTP) and long-term depression (LTD) in striatal neurons.[238]

Direct and indirect basal ganglia pathways

The striatum is often designated as the input (or afferent) division of the basal ganglia because it receives nonreciprocated corticostriatal projections from essentially all areas of cerebral cortex.[208,239-251] Approximately half of the striatal MSNs project directly to the basal ganglia output nuclei, GPi, and SNr,[252-260] which in turn send non-

reciprocated projections to the thalamus.[261-268] The remaining MSNs do not directly innervate the output nuclei, but project instead to an intervening nucleus, GPe.[253] While all MSNs are GABAergic, they form two distinct (though intermingled) populations that are differentiated by their connectivity and by the particular neuromodulators they produce.[253,256,269,270] The MSNs that give rise to the "*direct* pathway" contain substance P and dynorphin and project directly to the output nuclei (GPi/SNr). Those that give rise to the "*indirect* pathway" contain enkephalin and project to the GPe.

The indirect pathway has two arms. The GABAergic neurons of GPe project to STN,[271] whose excitatory, glutamatergic neurons send feedforward connections to GPi/SNr to complete one arm of the indirect pathway, and feedback connections to GPe.[272,273] A second arm of the indirect pathway is formed by GPe projections that pass directly to GPi/SNr.[269,270] A remarkable consequence of this arrangement is that activation of MSNs associated with *either* of the two arms will tend to increase neuronal activity at the level of GPi/SNr, in one case by disinhibiting the STN along with its excitatory projections to GPi/SNr, and in the other by disinhibiting GPi/SNr directly. In contrast, activation of MSNs associated with the *direct pathway* should *decrease* basal ganglia output by directly suppressing activity at the level of GPi/SNr. Given the reentrant nature of basal ganglia–thalamocortical connections, cortically initiated activation of the direct pathway should therefore result in positive feedback at cortical levels, due to thalamic disinhibition. Conversely, cortically initiated activation of the indirect pathway should have the opposite effect, due to the polarity-reversing effects of an intercalated stage of processing within GABAergic GPe.

The direct and indirect pathways differ sharply in their connections with the intralaminar thalamus. The basal ganglia output nuclei, GPi and SNr, send GABAergic pallidothalamic and nigrothalamic projections to the centromedian (CM) and parafascicular (Pf) nuclei, respectively, as well as to the corresponding pallidal and nigral target zones in the ventrolateral or "motor" thalamus.[264,274] Thalamostriatal projections from CM innervate the postcommissural (sensorimotor) putamen, while those from Pf are directed to the precommissural (associative) putamen, caudate nucleus, and ventral striatum.[261] The projections from CM to putamen show considerable selectivity in their terminal ramifications. They maintain strict topographical mappings that link corresponding thalamo-

striatal, striatopallidal, and pallidothalamic projection zones in CM, putamen, and GPi, respectively.[261] Moreover, thalamostriatal axons of CM neurons terminate almost exclusively on the spines and dendrites of putaminal MSNs that project to GPi, while avoiding those that project to GPe.[253]

The neuromodulatory effects of DA on the integrative activity of striatal MSNs differ considerably for the direct and indirect pathways, due to the dissimilar distributions of d_1-like and d_2-like receptors on the two types of MSNs.[227,270] Multiple studies have shown that substance P–containing, GPi/SNr–projecting striatal neurons of the direct pathway express a preponderance of d_1-like receptors, while enkephalin-containing, GPe-projecting neurons of the indirect pathway express a higher proportion of d_2-like receptors[227,275-277] despite variable degrees of colocalization of the two receptor types among a subset of each of the two categories of striatal projection neurons.[278]

The direct- and indirect-projecting MSNs also differ with respect to their responses to ACh, due to differences in the muscarinic receptors they express. Both types of MSNs express m_1 receptors to comparable degrees.[224] However, m_4 receptors are expressed predominantly by the substance P–containing neurons of the direct pathway.[279] Like the DA receptors, muscarinic receptors belong to the A family of seven-transmembrane receptors, and the G-protein to which the m_4 receptor is coupled acts to decrease cAMP levels, making its neuromodulatory effect analogous to that of d_2-like receptors. Although the striatum does receive limited extrinsic input from the cholinergic PPN,[58,280] by far the largest source of striatal ACh is the intrinsic population of large, aspiny interneurons.[281,282] Unlike putaminal MSNs, these large interneurons are spontaneously active and they do not discharge in relation to specific parameters of movement preparation or execution, such as direction or force, although they do show selectivity for the mode of movement guidance (eg, self-initiated versus visually guided versus memory-guided).[283] Rather, they discharge briefly and synchronously following the presentation of a conditioned sensory stimulus that signifies the imminent delivery of a reward.[284,285] In this respect, their behavior is similar to that of nigrostriatal DA neurons. And yet, there is a crucial difference: cholinergic interneurons signal the subject's prediction that a reward is imminent, while DA neurons signal reward prediction errors.[286,287] The cholinergic large aspiny neurons are the only striatal cells that express significant levels of the m_2 receptor,[224] which—

like the m_4 receptor—is coupled to a G-protein that decreases intracellular cAMP. The m_2 receptors are concentrated on cholinergic axons of aspiny interneurons that form symmetric synapses on the proximal dendrites and cell bodies of MSNs.[224]

Pathophysiology of nigrostriatal DA depletion in the motor circuit

The data recounted above are consistent with the relatively simple functional models of basal ganglia circuitry developed throughout the 1990s to provide a framework for approaching the pathophysiology of motor dysfunction in PD.[188,204,288] These models typically emphasized the opposing actions of the direct and indirect pathways in determining the level of thalamic inhibition exerted by the basal ganglia output nuclei. Studies of MPTP-induced parkinsonism had revealed increased tonic discharge rates in GPi and SNr neurons as well as in STN, and decreased rates of discharge in GPe.[186,187,190] This suggested that excessive inhibition of the thalamic targets to which GPi and SNr projected might be the basis for the hypokinesia and rigidity of parkinsonism.[188] Reduced dopaminergic activation of d_1-like receptors on striatal-GPi/SNr spiny neurons would reduce the effectiveness of their glutamatergic inputs from cortex and CM/Pf, leading to disinhibition of GPi/SNr. Reduced dopaminergic activation of d_2-like receptors on striatal-GPe neurons would increase the effectiveness of their glutamatergic inputs, leading to increase inhibition of GPe, which would in turn disinhibit STN. The resulting increase in glutamatergic drive from STN would further increase the activity of GPi/SNr neurons, further depressing thalamocortical activity. Perhaps the opposite effect, excessively low levels of tonic basal ganglia outflow, was the basis for certain hyperkinetic disorders, including levodopa-induced dyskinesia.

The effectiveness of GPi and STN lesions or functional inactivation in relieving parkinsonism in MPTP-treated monkeys,[190,191,289-291] and motor dysfunction in patients with PD,[192,193,195-198,292,293] was consistent with predictions of thalamic disinhibition models based on mean firing rates of basal ganglia neurons. Still, the models were unable to account for a number of observations that had emerged from experimental and clinical studies.[294,295] To begin with, the fact that GPi lesions relieved hypokinesia without inducing dyskinesia had never been satisfactorily accounted for by simple firing rate models; yet one of the

most reliable benefits of the medial pallidotomy procedure was reduction or elimination of levodopa-induced dyskinesia.[192,296] Models based on firing rates predicted that lesions of GPe would produce parkinsonism by disinhibiting both STN and GPi, but this was not confirmed.[297,298] According to these same models, lesions of the pallidothalamic projection zone in ventrolateral (motor) thalamus should result in hypokinesia or akinesia; but such was not the case.[299,300] Finally, simple models based on firing rates could not explain why tremor was such a prominent feature of PD. Tremor-like bursting of basal ganglia and thalamic neurons had been observed throughout the 1990s in nonhuman primates with MPTP-induced parkinsonism[186,301-303] and in PD patients undergoing microelectrode-guided neurosurgical procedures, but it was not known whether the bursting contributed to—or was caused by—the parkinsonian state. Recent electrophysiological and computational modeling studies have helped to clarify the situation.

These newer approaches have focused on *dynamic* features of neuronal activity changes in PD—such as oscillatory bursting and synchronization of discharge among neighboring neurons—rather than *static* features such as mean firing rates. Recordings in PD patients and primates with experimental parkinsonism reveal low-frequency (4-30 Hz) oscillatory field potentials and rhythmic neuronal bursting in both STN and GPe.[298,301,304,305] Neurons in both structures show correlated discharge in the parkinsonian state.[306] Effective symptomatic treatment with dopaminergic medication reduces or abolishes the low-frequency oscillatory activity as well as the correlations among neurons.[307]

STN and GPe have strong reciprocal connections that are functionally antagonistic, the glutamatergic output of STN being excitatory, while the GABAergic output of GPe is inhibitory. Recent anatomical studies have demonstrated remarkably tight functional and topographic mapping of homologous territories in the reciprocal connections of STN and GPe (as well as in the respective projections that each of these nuclei sends to GPi).[269] Brain slice and in vivo studies have shown that phasic activation of GPe neurons results in powerful $GABA_A$-mediated inhibition of their STN targets followed by postinhibitory rebound excitation of STN neurons whose glutamatergic return projections then reactivate their targets in GPe.[308,309] This endows the GPe-STN-GPe circuitry with a propensity to sustain synchronized, oscillatory discharges between and within the two nuclei.[308-310] Neurons in both nuclei have inherent rhythmic potential due in part to low-threshold T-type Ca^{2+} currents that predispose the cells to rebound excitation; such conductances are known to underlie many forms of pacemaker activity.[311-314] The predilection for oscillatory interactions between GPe and STN is normally restrained by powerful local GABAergic feedback that desynchronizes the output of neighboring neurons in GPe.[315,316]

These and other connectional and biophysical properties of the GPe-STN network have been incorporated into dynamic computational models that successfully reproduce and illuminate much of the pathophysiology of oscillatory activity observed in PD and MPTP-induced parkinsonism.[317] Such models show, for example, that increased striatal activity along the indirect pathway can lead to oscillatory activity in the GPe-STN network by two concurrent mechanisms. Increased GABAergic striatal input to GPe will reduce the latter's tonic GABAergic suppression of STN activity, allowing the oscillatory potential of the reciprocal antagonism between GPe and STN to be expressed.[317] Accompanying the increased release of GABA at striatoGPe synapses will be a corresponding increase in the release of colocalized enkephalin.[256,318] Local diffusion of enkephalin within GPe will lead to presynaptic suppression of GABA release not only at the striatoGPe terminals themselves, but also at the sites of local GABAergic feedback from neighboring GPe neurons[318]; the net effect of this reduced lateral inhibition will be enhanced synchronization among the GPe-STN projection cells.[317]

The recent incorporation of dynamic features of neuronal interactions into the ever more complex functional models of basal ganglia circuitry[317] permits us now to account for most if not all of the observed motor dysfunction in PD. With the demonstrable linkage between motor deficits and abnormal oscillatory activity, and growing understanding of how the oscillatory activity arises naturally under conditions of striatal DA depletion, it seems we are approaching the point of having a reasonably comprehensive and testable theory of the pathophysiology of PD. Much of the testing can and should be carried out in experimental studies of basal ganglia-thalamocortical circuitry in MPTP-induced parkinsonism. Some will likely be incidental to attempts to refine and improve current symptomatic therapies, both pharmacological and neurosurgical, in patients with PD. ❏

Biología de la enfermedad de Parkinson: patogénesis y fisiopatología de un trastorno neurodegenerativo multisistémico

La enfermedad de Parkinson (EP) es el segundo trastorno del movimiento más frecuente. Los característicos deterioros motores –bradiquinesia, rigidez y temblor de reposo– se deben a la pérdida degenerativa de neuronas dopaminérgicas mesencefálicas en la sustancia nigra, y responden a tratamiento sintomático con fármacos dopaminérgicos y neurocirugía funcional. La EP es también el segundo trastorno neurodegenerativo más común. Desde esta perspectiva, la EP es un trastorno de múltiples sistemas funcionales, no simplemente del sistema motor, y de múltiples sistemas de neurotransmisión, y no sólo de dopamina. La patología característica –inclusiones intraneuronales de cuerpos de Lewy y un número reducido de neuronas sobrevivientes– es similar en cada uno de los grupos de neuronas, lo que sugiere un proceso neurodegenerativo común. Estudios experimentales y de patología indican que el estrés oxidativo, el estrés proteolítico y la inflamación destacan notablemente en la patogénesis de la EP. Todavía no se conoce si alguno de estos mecanismos juega un papel causal en la EP del ser humano, porque a la fecha no se han probado terapias neuroprotectoras que retrasen o reviertan la progresión de la enfermedad en pacientes con EP. Estamos comenzando a comprender la fisiopatología de la disfunción motora en la EP, pero su etiopatogénesis como un trastorno neurodegenerativo continúa poco comprendido.

Biologie de la maladie de Parkinson : pathogenèse et physiopathologie d'un trouble neurodégénératif multisystémique

La maladie de Parkinson (MP) est le deuxième trouble moteur le plus fréquent. Les dysfonctionnements moteurs caractéristiques – bradykinésie, rigidité, et tremblement de repos – sont la conséquence d'une perte dégénérative de neurones dopaminergiques du locus niger dans le mésencéphale et sont sensibles au traitement symptomatique par des médicaments dopaminergiques et à la neurochirurgie fonctionnelle. La MP est aussi le deuxième trouble neurodégénératif le plus fréquent. Vue sous cet angle, la MP est un trouble de plusieurs systèmes fonctionnels, pas seulement le système moteur, et de multiples systèmes de neuromédiateurs, et pas simplement le système dopaminergique. La pathologie caractéristique – inclusions intraneuronales à corps de Lewy et nombre réduit de neurones survivants – est semblable dans chacun des groupes de neurones ciblés, suggérant un processus neurodégénératif commun. Les études expérimentales et de pathologie montrent que le stress oxydatif, le stress protéolytique et l'inflammation occupent une place importante dans la pathogenèse de la MP. Jusqu'à présent on ignore si l'un de ces mécanismes joue un rôle causal dans la MP chez l'homme, car à ce jour, nous n'avons aucun traitement neuroprotecteur ayant prouvé son efficacité qui ralentisse ou s'oppose à la progression de la maladie chez les parkinsoniens. Nous commençons à comprendre la physiopathologie du dysfonctionnement moteur dans la MP, mais son étiopathogenèse en tant que trouble neurodégénératif reste mal comprise.

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