Parkinson's Disease: Neurobiology and Therapeutic Strategies

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Parkinson or Parkinson's Disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease. Diagnosis is based on the presence of asymmetric or unilateral resting tremor, bradykinesia and rigidity. These motor features are the result of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Neurodegeneration also develops in non-dopaminergic pathways and results in a series of non-motor features that include cognitive impairment, sleep disorders and autonomic dysfunction. The causes of PD include several different gene mutations of proteins including α-synuclein, LRRK2, Parkin and PINK1, with glucocerebrosidase (GBA) mutations conferring the greatest risk for the development of PD.

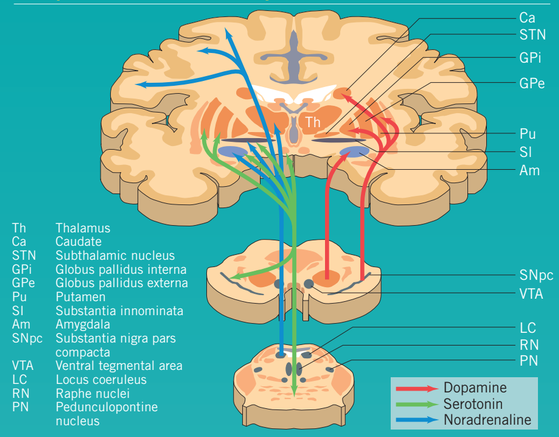
Environmental and Genetic Factors

There is increasing evidence that genetics plays a major role in the etiology of PD. Several individual gene mutations are associated with autosomal dominant or recessive PD, and together account for 10-15% of PD cases. *LRRK2* mutations are the most common cause of PD, found in 0.5-1.0% of the UK and 2-3% of familial cases. *Parkin* mutations are the most common cause of early onset (<30y) PD. Genome-wide association studies have identified a number of association loci, including *tau* and *GBA*, as well as genes in inflammatory, mitochondrial and lysosomal pathways; for example, mutations in *PINK1* and *Parkin* genes cause mitochondrial dysfunction, which is an important feature of PD pathogenesis. Numerically, *GBA* mutations represent the most important risk factor for PD. In the UK it is estimated that 7-10% of PD patients have a *GBA* mutation. In contrast, no environmental factor has been shown to cause PD, however rural living, pesticide exposure, and certain toxins have been found to increase PD risk by 2-3 fold, while cigarette smoking and coffee intake reduce risk.

Mutation	Inheritance	Locus	Onset/Age	Lewy Bodies	Gene
Park 1	AD	4q21	40s	Yes	α-synuclein
Park 2	AR	6q25	20s	No	Parkin
Park 3	AD	2p13	60s	Yes	?
Park 4	AD	4q21	30s	Yes	α-synuclein
Park 5	AD	4p13	50s	Yes	UCH-L1
Park 6	AR	1p35	30s	Yes	PINK1
Park 7	AR	1q36	30s	?	DJ1
Park 8	AD	12q12	-	Yes/no	LRRK2
Park 9	AR	1P36	-	?	ATP13A2
Park 10	AR	1p32	-	?	?
Park 11	AD	2q36-37		?	?

AD, autosomal dominant; AR, autosomal recessive

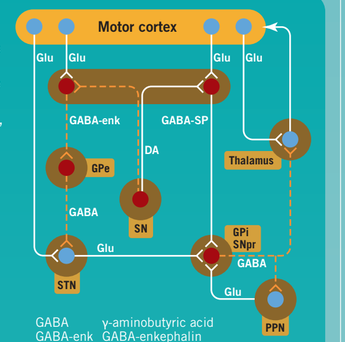
Disruption of Neuronal Pathways



Th	Thalamus
Ca	Caudate
STN	Subthalamic nucleus
GPi	Globus pallidus interna
GPe	Globus pallidus externa
Pu	Putamen
SI	Substantia innominata
Am	Amygdala
SNpc	Substantia nigra pars compacta
VTA	Ventral tegmental area
LC	Locus coeruleus
RN	Raphe nuclei
PN	Pedunculopontine nucleus

Not all PD symptoms are caused by degeneration of the dopaminergic systems alone; serotonin, noradrenaline, acetylcholine (not shown) and GABA (not shown) pathways are also severely affected in PD. Lewy bodies appear early in the olfactory bulb and lower brain stem, but without neuronal cell loss. As the disease becomes symptomatic there is evidence of Lewy-body deposition and dopaminergic cell loss in the SNpc. Other brain stem nuclei for example, locus coeruleus and substantia innominata, are also involved in the degenerative process. Very advanced cases of PD exhibit prominent non-dopaminergic features owing to loss of neurons in the cortex, subcortex, brainstem and in peripheral autonomic sites.

The complex direct and indirect pathways of the basal ganglia are disrupted in PD pathogenesis. Simply put, dopaminergic neurons in the SNpc project to GABA neurons in the striatum and are excitatory (GABA-SP) or inhibitory (GABA-enk). The direct pathway involves GABA-SP projections of inhibitory synapses to the GPi. The SNpr is a functional component of the GPi. The indirect pathway involves GABA-enk inhibitory projections to the GPe and onward inhibitory input into the STN glutamatergic (Glu) neurons. The STN has excitatory input into the GPi, but probably also into the SNpc. In PD, along with the loss of dopaminergic neurons in the SNpc, there are declining levels of dopamine in the striatum with consequential increased activity of GABA-enk and reduced activity of GABA-SP. This then enhances activation of the glutamatergic excitatory output of the STN and, therefore, of the GPi with subsequent inhibition of the thalamus and its cortical projections.



GABA	γ-aminobutyric acid
GABA-enk	GABA-enkephalin
GABA-SP	GABA-substance P
GPe	Globus pallidum externa
GPi	Globus pallidum interna
PPN	Pedunculopontine nucleus
SN	Substantia nigra
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulata
STN	Subthalamic nucleus

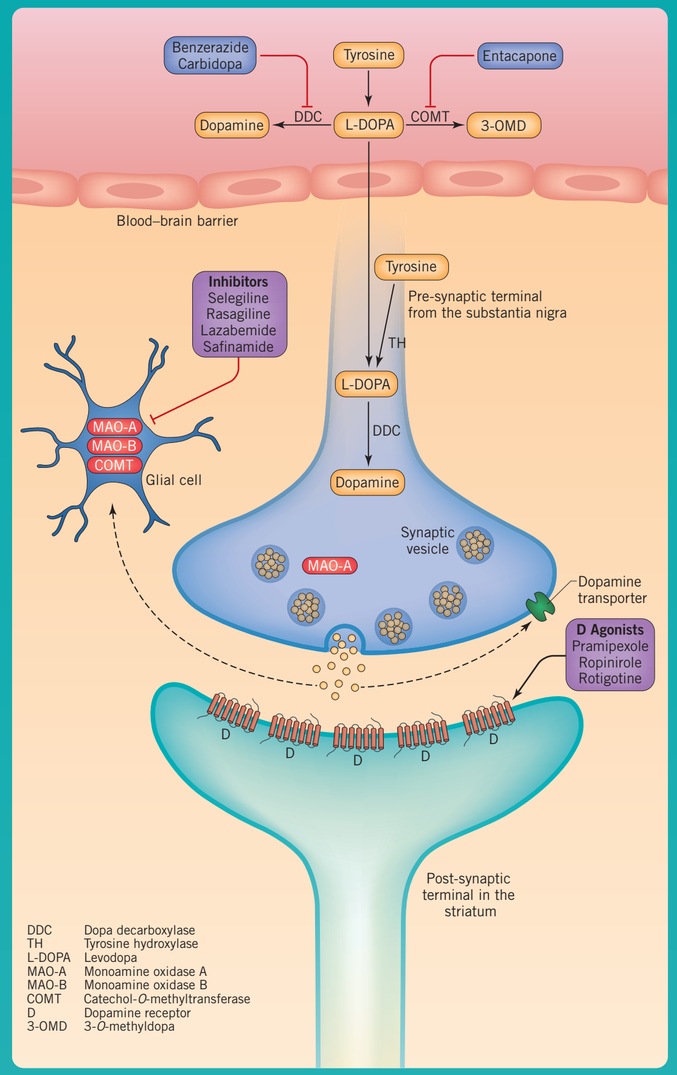
Current and Emerging Treatments for PD

The main motor features of PD are the consequence of loss of dopaminergic pathways, specifically the nigrostriatal pathway. The loss of dopamine neurons disrupts normal dopamine tone and impairs basal ganglia function. Increasing dopamine stimulation or reducing cholinergic or glutamatergic stimulation improves symptoms. Dopamine synthesis and catabolism provides the rationale for drug therapies aimed at the symptomatic treatment of motor symptoms. Dopamine is synthesized by the conversion of tyrosine to levodopa by tyrosine hydroxylase, and the subsequent decarboxylation of levodopa via dopa decarboxylase to produce dopamine. Dopamine is metabolized by intraneuronal monoamine oxidase (MAO)-A and by glial MAO-A and MAO-B. Dopamine-replacement therapy requires the use of levodopa because dopamine does not cross the blood–brain barrier. Once levodopa has crossed into the brain, it is converted to dopamine by the terminals of the surviving nigrostriatal neurons and also probably by the microglia and serotonergic neurons.

Dopamine is stored in vesicles and released in response to physiological stimuli. Released dopamine binds to the dopaminergic receptors and then can be taken back up into the pre-synaptic terminal by the dopamine transporter, or metabolized by MAO and catechol-*O*-methyltransferase (COMT). Dopamine agonists activate pre- and post-synaptic dopamine D_1, D_2 and D_3 receptors, depending upon their particular profile. They can be given orally, are absorbed and cross the blood–brain barrier. MAO-B inhibitors reduce the breakdown of dopamine and so increase its synaptic half-life and the amount taken back up into the pre-synaptic terminal. COMT inhibitors are active orally, but function in the intestines to reduce peripheral metabolism of levodopa and enhance its central nervous system penetration.

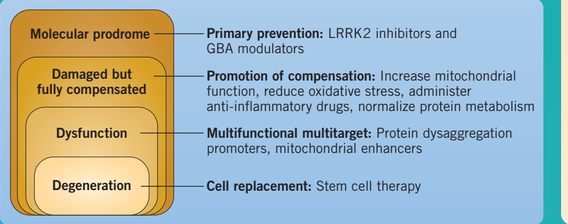
Levodopa offers the most symptomatic relief but is associated with long-term complications in terms of wearing off and dyskinesias (involuntary movements). Patients may be started on levodopa, a MAO-B inhibitor or agonist depending on their clinical profile. Inevitably, all PD patients will need levodopa, and this is often now used in combination with a COMT inhibitor. Unfortunately, none of these therapies have been proven to slow progression of the disease or the emergence of non-motor, predominantly non-dopaminergic features.

The improved understanding of the etiology and pathogenesis of PD has revealed several important pathways that have become targets for potential treatments. Therapeutic strategies already exist for relieving the symptomatic stages of PD, but with new genetic insight it may be possible to use preventative neuroprotective treatments for those at risk of developing PD, delaying the onset and progression of disease. In parallel to the efforts of prevention and control of symptomatic PD, researchers are also looking to stem cells to replace the diseased neurons.



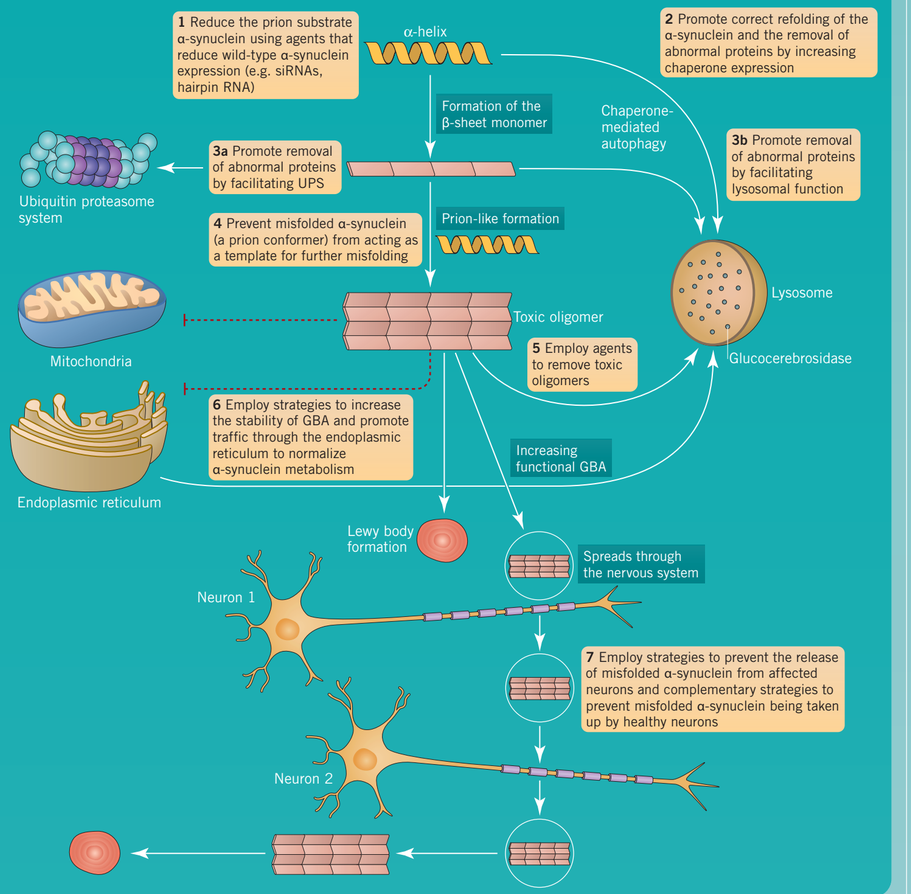
DDC	Dopa decarboxylase
TH	Tyrosine hydroxylase
L-DOPA	Levodopa
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
COMT	Catechol-*O*-methyltransferase
D	Dopamine receptor
3-OMD	3-*O*-methyldopa

Disease Stages and Potential Therapeutic Strategies



Pathways for Potential Intervention in Aberrant α-synuclein Metabolism

Lysosomal dysfunction is considered an important part of PD pathology, particularly as α-synuclein is predominantly turned over by chaperone-mediated autophagy. Neurodegeneration in PD has also been linked to the formation of toxic protein aggregates, such as those formed by the conversion of α-helix protein structures to β-sheet configurations. A defect in this pathway will lead to the accumulation of α-synuclein oligomers, which will promote aggregate formation. The association of *GBA* mutations, and the involvement of LRRK2 in autophagy adds further credence to the importance of lysosomal dysfunction in PD. The formation of α-synuclein toxic oligomers and their inter-neuronal propagation and enhancement of aggregate formation has attracted attention, and has drawn parallels with prion disorders. Several therapeutic strategies have been proposed to reduce the effects of aberrant α-synuclein metabolism in PD, as shown below.



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GABA Receptors	
$GABA_A$ Receptors	(-)-Bicuculline methochloride, CGP 54626, CGP 55845, Muscimol, SCH 50911, SR 95531
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mGlu Group I Receptors	(*S*)-3,5-DHPG, MTEP
mGlu Group II Receptors	BINA, LY 341495, LY 379268
mGlu Group III Receptors	L-AP4, MMPIP, VU 0364439
Serotonin Receptors	
5-HT_{1A} Receptors	8-Hydroxy-DPAT, (*S*)-WAY 100135, WAY 100635
5-HT_{1B} Receptors	GR 127935, SB 216641, SB 224289
5-HT_{2A} Receptors	AT 1015, EMD 281014, Ketanserin, MDL 100907, Risperidone, TCB-2
5-HT_{2C} Receptors	CP 809101, *N*-Desmethylclozapine, MK 212, Ro 60-0175, RS 102221, SB 242084, WAY 161503

References
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