Parkinson’s Disease: Neurobiological and Therapeutic Strategies

Anthony H.V. Schapira
University of Clinical Neuroscience Institute, University of London, Royal Free Campus, Rowland Hill Street, London, NW3 2PF, UK.
Institute of Neurology, University of London, Queen Square, London, WC1N 3BG, UK.

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 loss of a neuron in the substantia nigra pars compacta (SNC). Necrodegeneration also develops in non-dopaminergic pathways and results in the emergence of non-motor symptoms, including 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 PD, and in some cases, with at-risk of developing PD. 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.

Disruption of Neuronal Pathways
Lysosomal dysfunction is considered an important part of PD pathology, particularly as α-synuclein is predominantly turned over by chaperone-mediated autophagy. Disruption of normal lysosomal function 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 configuration. A defect in this pathway will lead to the accumulation of GBA mutations, and the formation of Lewy bodies, as well as the formation of Lewy bodies in the brain. The main motor features of PD are the consequence of loss of dopaminergic neurons, specifically the nigrostriatal pathway. The loss of dopaminergic neurons disrupts normal dopamine tone and impairs basal ganglia function. Increasing dopaminergic inhibition or reducing cholinergic or glutamatergic input improve symptoms. Dopaminergic reinnervation and cationic neurotransmission is thought to be an important feature of PD pathogenesis. Dopaminergic neurons are able to reinnervate areas of the nervous system, and may be modified by the administration of L-DOPA, which is metabolized by MAO and catechol-O-methyltransferase (COMT). Released dopamine binds to the dopaminergic receptors and then can be taken up by 2-3 fold, while

Pathways for Potential Intervention in Abnormal 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. Disruption of normal lysosomal function 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 configuration. A defect in this pathway will lead to the accumulation of GABA-A and -B receptors, as well as the formation of Lewy bodies in the brain. The main motor features of PD are the consequence of loss of dopaminergic neurons, specifically the nigrostriatal pathway. The loss of dopaminergic neurons disrupts normal dopamine tone and impairs basal ganglia function. Increasing dopaminergic inhibition or reducing cholinergic or glutamatergic input improve symptoms. Dopaminergic reinnervation and cationic neurotransmission is thought to be an important feature of PD pathogenesis. Dopaminergic neurons are able to reinnervate areas of the nervous system, and may be modified by the administration of L-DOPA, which is metabolized by MAO and catechol-O-methyltransferase (COMT). Released dopamine binds to the dopaminergic receptors and then can be taken up by 2-3 fold, while

Current and Emerging Treatments for PD
The main motor features of PD are the consequence of loss of dopaminergic neurons, specifically the nigrostriatal pathway. The loss of dopaminergic neurons disrupts normal dopamine tone and impairs basal ganglia function. Increasing dopaminergic inhibition or reducing cholinergic or glutamatergic input improve symptoms. Dopaminergic reinnervation and cationic neurotransmission is thought to be an important feature of PD pathogenesis. Dopaminergic neurons are able to reinnervate areas of the nervous system, and may be modified by the administration of L-DOPA, which is metabolized by MAO and catechol-O-methyltransferase (COMT). Released dopamine binds to the dopaminergic receptors and then can be taken up by 2-3 fold, while

Disease Stages and Potential Therapeutic Strategies

References
Schapira AHV et al. (2014) The Lancet 384:549

Tocris products

- GABA, GAD-67, RVP-119
- DA, DA-DOPA, Rotenone
- Dopamine Transporter (DAT) inhibitors
- L-DOPA, Carbidopa
- Dopamine Agonists
- Anticholinergics
- MAO-B inhibitors
- Glucocerebrosidase

Tocris products

- GABA, GAD-67, RVP-119
- DA, DA-DOPA, Rotenone
- Dopamine Transporter (DAT) inhibitors
- L-DOPA, Carbidopa
- Dopamine Agonists
- Anticholinergics
- MAO-B inhibitors
- Glucocerebrosidase

Tocris products

- GABA, GAD-67, RVP-119
- DA, DA-DOPA, Rotenone
- Dopamine Transporter (DAT) inhibitors
- L-DOPA, Carbidopa
- Dopamine Agonists
- Anticholinergics
- MAO-B inhibitors
- Glucocerebrosidase

Tocris products

- GABA, GAD-67, RVP-119
- DA, DA-DOPA, Rotenone
- Dopamine Transporter (DAT) inhibitors
- L-DOPA, Carbidopa
- Dopamine Agonists
- Anticholinergics
- MAO-B inhibitors
- Glucocerebrosidase