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Parkinson's Disease: Neurobiology and Therapeutic Strategies

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Parkinson's Disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease. Diagnosis is primarily clinical and is based on the presence of asymmetric or unilateral resting tremor, bradykinesia and rigidity. These motor features are predominantly the result of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and loss of striatal innervation. Accumulation of α-synuclein in intraneuronal Lewy bodies and neurites is a pathological hallmark of PD. 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 clinical diagnosis of PD may be preceded for several years by prodromal features that include hyposmia, rapid eye movement sleep behaviour disorder, depression and constipation. The known causes of PD include several different gene mutations of proteins including α-synuclein, LRRK2, parkin and PINK1 and glucocerebrosidase (GBA1).

Environmental and Genetic Factors

There is increasing evidence that complex genetics plays a major role in the etiology of PD. Several individual gene mutations are associated with autosomal dominant or recessive PD, together now accounting for about 15% of PD cases, and about 20% of those with young onset. GBA1 variants are found in 10-15% of PD; LRRK2 mutations are 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 (<30 years) PD. Both GBA1 and LRRK2 have variable penetrance. Genome-wide association studies have identified a number of association loci, including α-synuclein, tau and GBA1, as well as genes in inflammatory, mitochondrial and lysosomal pathways. Several of the mutations result in mitochondrial and lysosomal dysfunction with effects on cell bioenergetics and protein homeostasis; these are important factors in PD pathogenesis.

No environmental cause of PD has been identified. However, epidemiological studies suggest that rural living, pesticide exposure, and certain toxins may have a small effect on PD risk, although the results are inconsistent. Smoking tobacco and drinking coffee reduce risk. It is hypothesized that there may be genetic-environmental interactions that can influence PD penetrance, although no such examples are yet confirmed.

The Genes and Proteins Involved in Parkinson's Disease

Gene	Locus Name	Protein Name	Inheritance	Clinical	Frequency in PD	Protein Function
SNCA	PARK1/4	α-synuclein	AD	EOPD	<1%	Synaptic
PRKN	PARK2	Parkin	AR	EOPD, slow progression + dystonia	1-5% (up to 44% in EOPD)	Ubiquitin-ligase
UCHL1	PARK5	UCHL-1	AD	EOPD, LOPD	<1%	Uncertain
PINK1	PARK6	PTEN-induced putative kinase I	AR	EOPD, slow progression	2-5%	Mitochondrial kinase
DJ-1	PARK7	Protein DJ-1	AR	EOPD, slow progression	1%	Cellular sensor of oxidative stress
LRRK2	PARK8	Leucine-rich repeat serine/threonine-protein kinase 2	AD	LOPD, slow progression	1-5% (up to 40% in North African Berber Arab patients)	Multiple functions domain dependent
AT-P13A2	PARK9	ATPase type 13A2	AR	Atypical parkinsonism, Kufor-Rakeb syndrome	<1%	Lysosomal protein
PLA2G6	PARK14	A_2 phospholipase	AR	EOPD, dystonia-parkinsonism	<1%	Unknown
FOXB7	PARK15	F-box protein 7	AR	EOPD, atypical parkinsonism	<1%	Unknown
VPS35	PARK17	Vacuolar protein sorting-associated protein 35	AD or risk	LOPD	<1%	Unknown
GBA		Glucocerebrosidase	Risk factor	Earlier onset + dementia	5-25% (10-30% in Ashkenazi Jewish patients)	Lysosomal protein

AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset PD; LOPD, late onset PD

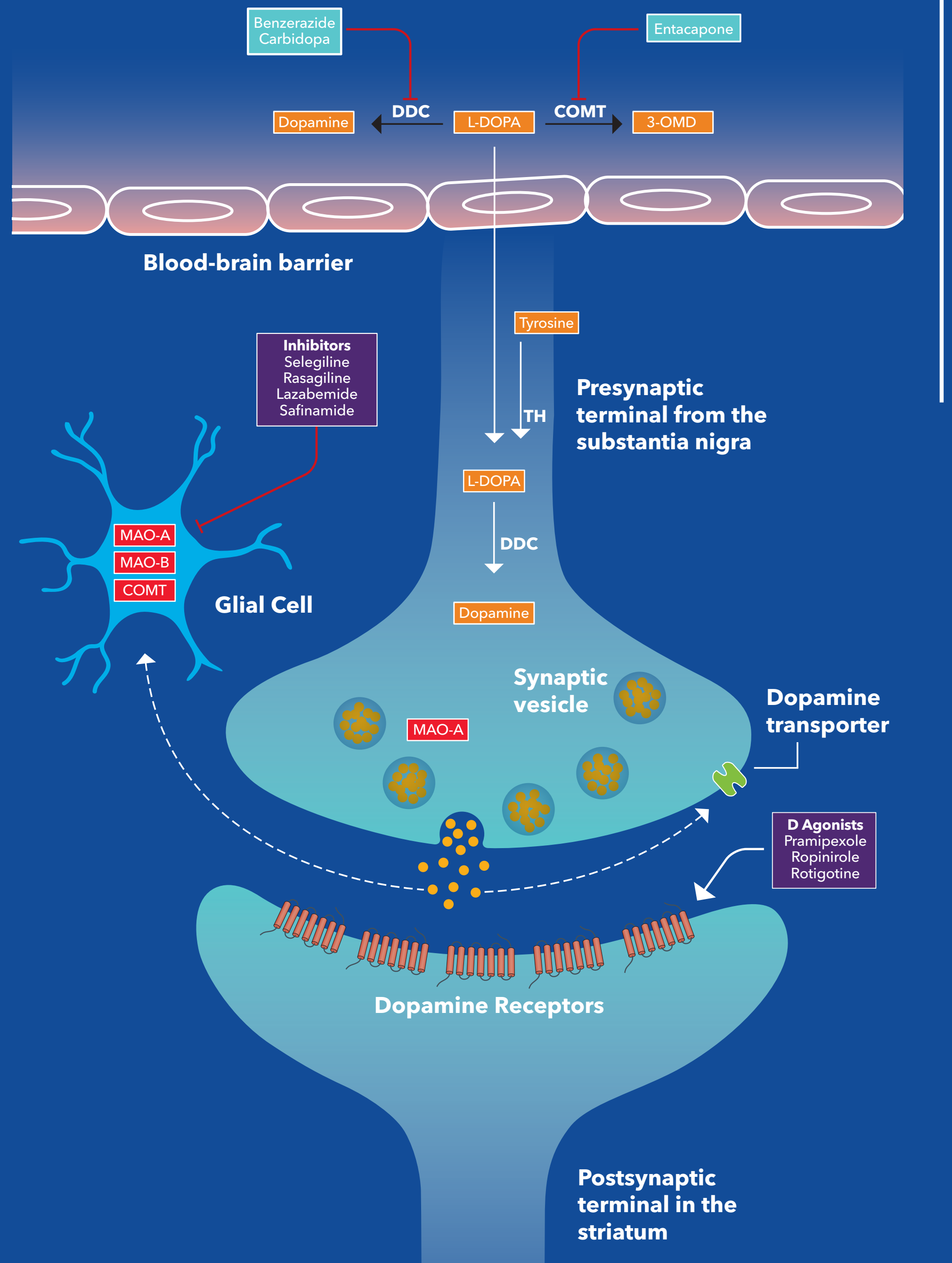
Current and Emerging Treatments for PD

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 provide 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 postsynaptic dopamine D_1, D_2 and D_3 receptors, depending upon their particular profile. They can be given orally, by inhalation, skin patch or subcutaneously, 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 presynaptic terminal. COMT inhibitors are active orally, but function in the intestines to reduce peripheral metabolism of levodopa and enhance its central nervous system penetration and duration of action.

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 dopamine agonist depending on their clinical profile. Inevitably, all PD patients will need levodopa, and this is always used in combination with a peripheral dopa-decarboxylase inhibitor and often 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 disease-modifying treatments. Therapeutic strategies already exist for relieving the symptoms of PD, including surgical interventions such as deep brain stimulation, but with new genetic insights it may be possible to use preventative neuroprotective treatments for those at risk of developing PD, delaying the onset and progression of disease.

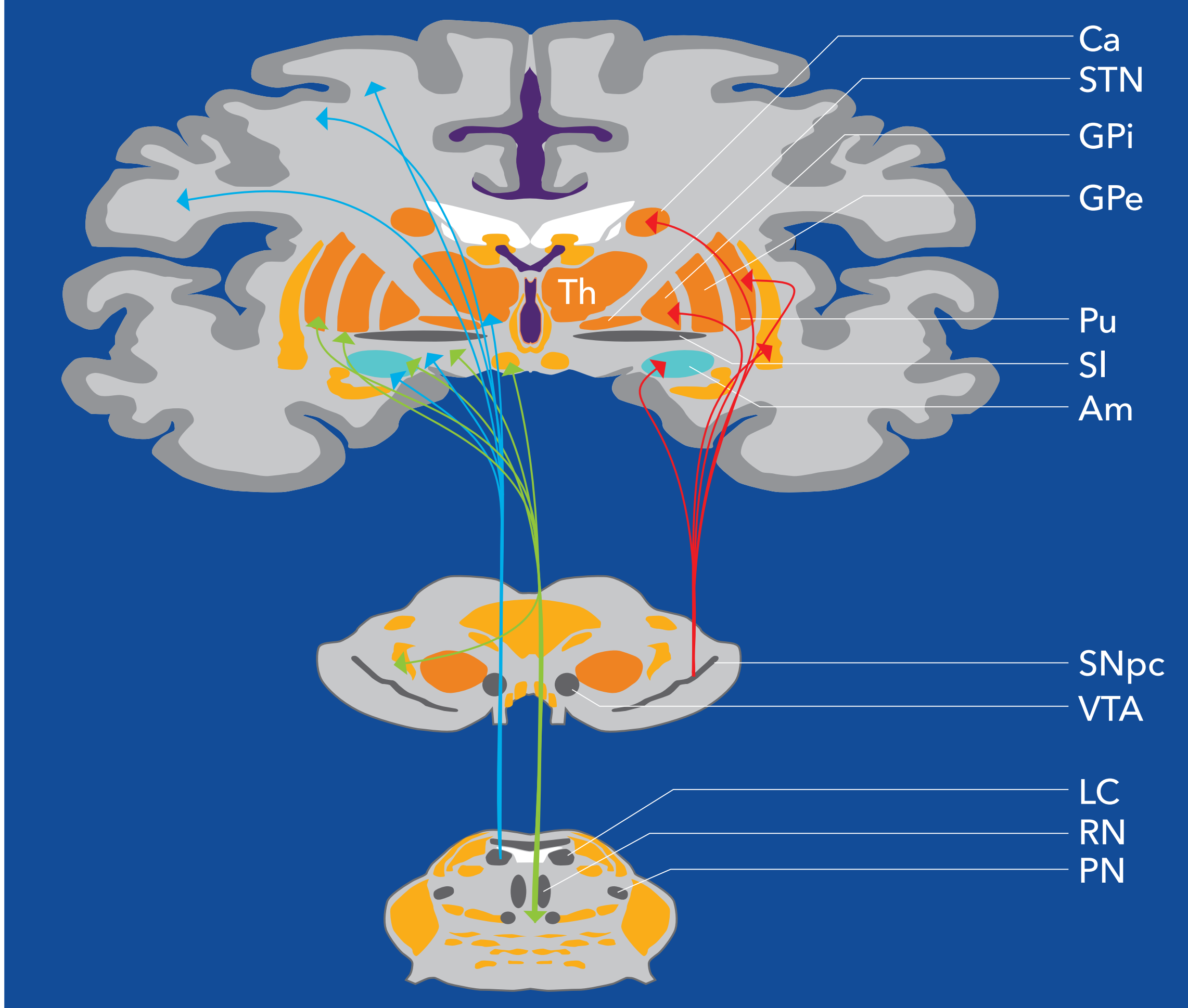


DDC	Dopa decarboxylase
TH	Tyrosine hydroxylase
L-DOPA	Levodopa
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
COMT	Catechol-*O*-methyltransferase
3-OMD	3-*O*-methyldopa

Disease Stages and Potential Therapeutic Strategies

Molecular prodrome	**Primary Prevention**: LRRK2 inhibitors and GBA modulators
Damaged but fully compensated	**Promotion of compensation:** Increase mitochondrial function, reduce oxidative stress, administer anti-inflammatory drugs, normalize protein metabolism
Dysfunction	**Multifunctional Multitarget**: Protein dysaggregation promoters, mitochondrial enhancers
Degeneration	**Cell Replacement**: Stem cell therapy

Disruption of Neuronal Pathways



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STN	Subthalamic nucleus	**VTA**	Ventral tegmental area
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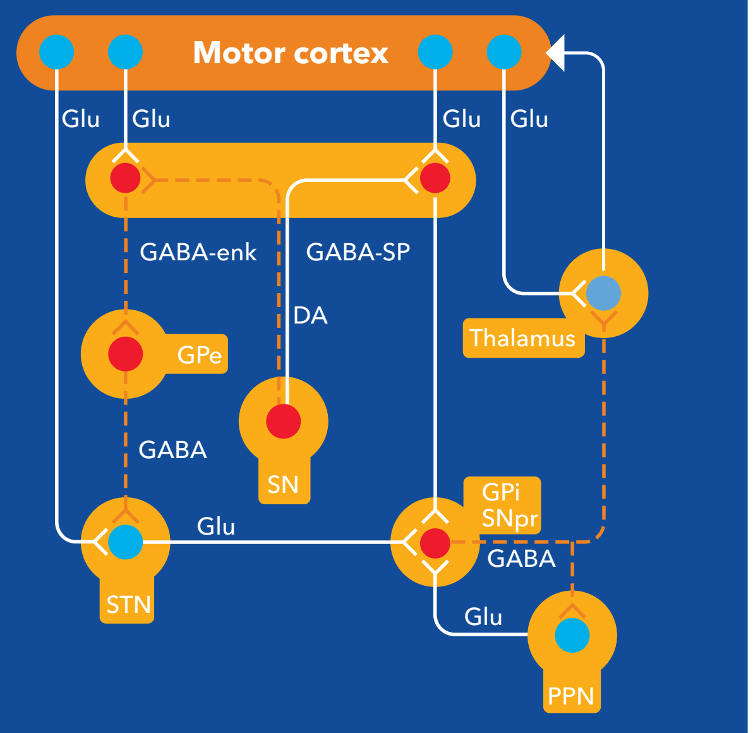
Not all PD symptoms are caused by degeneration of the dopaminergic systems alone; serotonin, noradrenaline, acetylcholine (not shown) and GABA (not shown) pathways are also severely affected in PD. Lewy bodies appear early in the olfactory bulb and lower brainstem, but without neuronal cell loss. As 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. 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.



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PPN	Pedunculopontine nucleus
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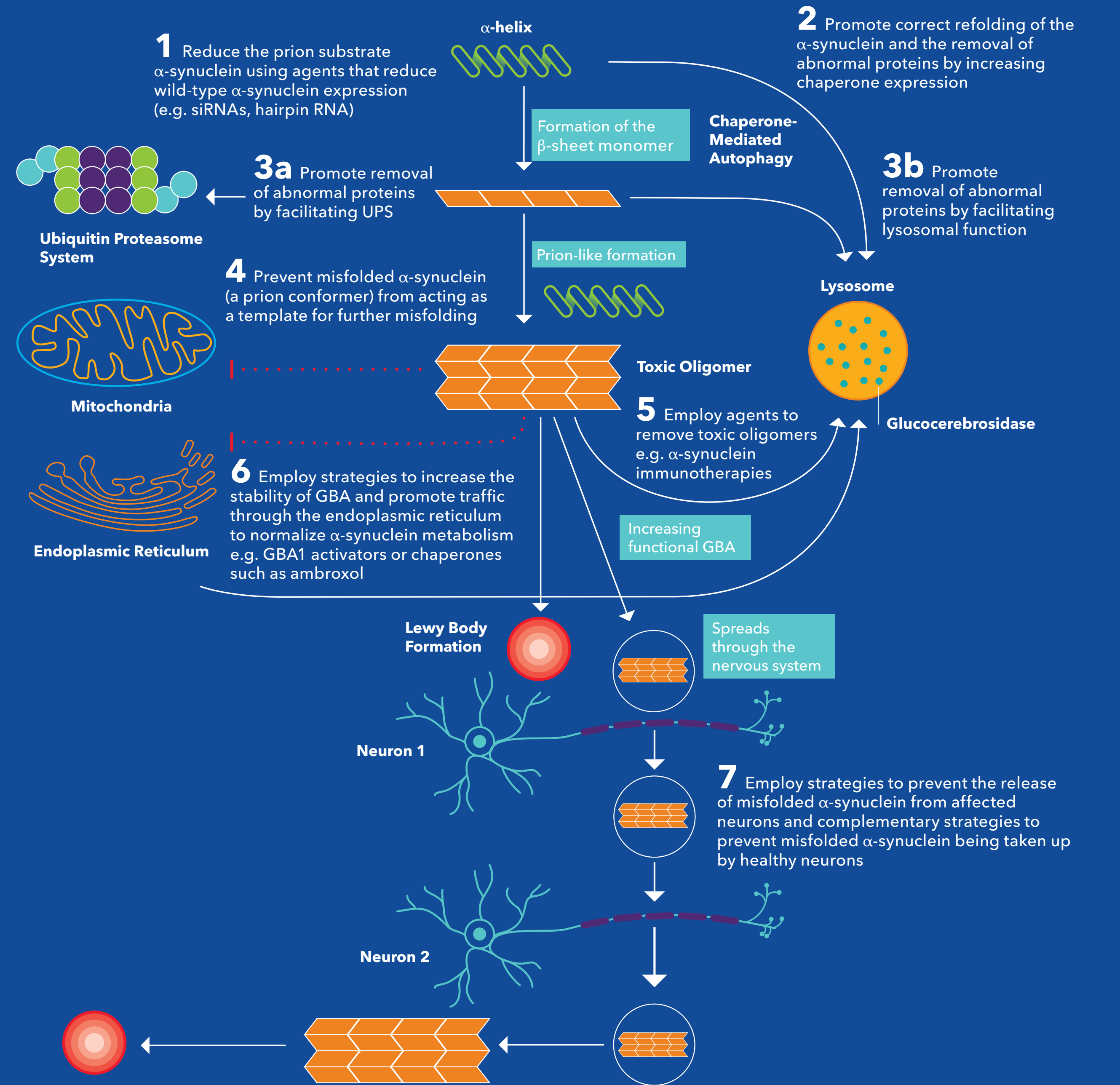
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulata
STN	Subthalamic nucleus

Potential Neuroprotective Interventions

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 GBA1 mutations, and the involvement of LRRK2 in autophagy add 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 (see figure to the right). Additional strategies for disease modification in PD include the use of GLP-1 agonists e.g. exenatide, LRRK2 kinase inhibitors and ursodeoxycholic acid.

The contribution of the gut microbiota to PD pathogenesis has attracted increasing interest. The formation of intestinal α-synuclein in response to gut inflammation and its passage along the vagus nerve to the dorsal motor nucleus would explain the observations of Lewy bodies in the brain stem early in the disease process. Support for a role of the microbiome in PD is provided by the exacerbation of α-synuclein pathology in mice by fecal microbial transfer from PD patients but not controls.


α-helix
Formation of the β-sheet monomer
Chaperone-Mediated Autophagy
Ubiquitin Proteasome System
Prion-like formation
Lysosome
Mitochondria
Toxic Oligomer
Glucocerebrosidase
Endoplasmic Reticulum
Increasing functional GBA
Lewy Body Formation
Spreads through the nervous system
Neuron 1
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1 Reduce the prion substrate α-synuclein using agents that reduce wild-type α-synuclein expression (e.g. siRNAs, hairpin RNA)

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6 Employ strategies to increase the stability of GBA and promote traffic through the endoplasmic reticulum to normalize α-synuclein metabolism e.g. GBA1 activators or chaperones such as ambroxol

7 Employ strategies to prevent the release of misfolded α-synuclein from affected neurons and complementary strategies to prevent misfolded α-synuclein being taken up by healthy neurons

Tocris Products

Dopamine

D_1 and D_5 Receptors
A 68930
Dihydrexidine
SCH 23390
SCH 39166
SKF 81297
SKF 83959

D_2 Receptors
L-741,626
(-)-Quinpirole
Raclopride
Ropinirole
Sumanirole

D_3 Receptors
Eticlopride
(+)-PD 128907
Pramipexole
SB 277011A

D_4 Receptors
L-745,870
PD 168077

Dopamine Transporters
GBR 12909
Indatraline

Non-selective Dopamine
(R)-(-)-Apomorphine
L-DOPA

Monoamine Oxidase

Moclobemide
Rasagiline

Catechol *O*-Methyltransferase

Entacapone
OR-486
Tolcapone

Adenosine A_{2A} Receptors

CGS 21680
Istradefylline
PSB 0777
SCH 442416
SCH 58261
ZM 241385

LRRK2

GSK2578215A
LRRK2-IN-1
MLi-2
CZC 25146

Decarboxylases

(S)-(-)-Carbidopa

Caspases

Cisplatin
Z-DEVD-FMK
Z-VAD-FMK

$GABA_A$ Receptors

(-)-Bicuculline methochloride
CGP 54626
CGP 55845
Muscimol
SCH 50911
SR 95531

Glutamate Receptors

NMDA Receptors
D-AP5
(RS)-CPP
Ifenprodil
(+)-MK 801
Ro 25-6981

AMPA Receptors
(S)-AMPA
Cyclothiazide
Naspm
NBQX
Talampanel

Kainate Receptors
ACET
GYKI 53655
UBP 302

mGlu Group I Receptors
(S)-3,5-DHPG
MTEP

mGlu Group II Receptors
BINA
LY 341495
LY 379268

mGlu Group III Receptors
L-AP4
MPEP
(S)-3,4-DCPG
AMN 082

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
EMD 281014
Ketanserin
MDL 100907
Risperidone
TCB-2

5-HT_{2C} Receptors
RS 102221
SB 242084
WAY 161503

Na_v channel blocker

Ambroxol

Glucagon-like peptide 1 receptor

Exenatide (Exendin-4)

References

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2. Schapira *et al* (2017) *Nat. Rev. Neurosci.* **18** 435
3. Menozzi *et al* (2017) *Ann. Med.* **53** 611

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The details of this information are understood to be subject to interpretation.

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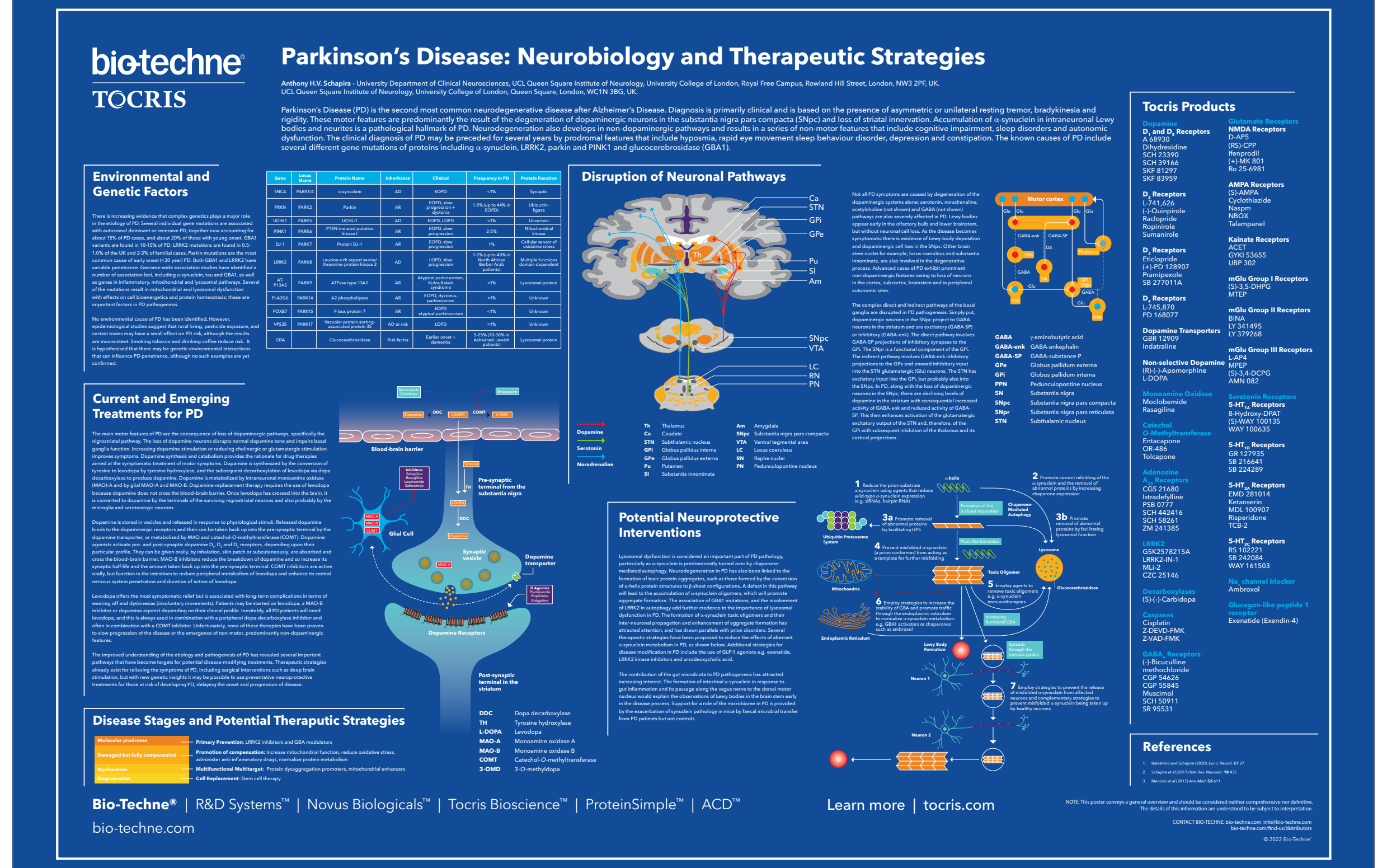
Wall Poster



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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 dopamine agonist depending on their clinical profile. Inevitably, all PD patients will need levodopa, and this is always used in combination with a peripheral dopa-decarboxylase inhibitor and often 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.

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SKF 81297
SKF 83959

D_2 Receptors
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Adenosine A_{2A} Receptors
CGS 21680
Istradefylline
PSB 0777
SCH 442416
SCH 58261
ZM 241385

LRRK2
GSK2578215A
LRRK2-IN-1
MLi-2
CZC 25146

Decarboxylases
(S)-(-)-Carbidopa

Caspases
Cisplatin
Z-DEVD-FMK
Z-VAD-FMK

$GABA_A$ Receptors
(-)-Bicuculline methochloride
CGP 54626
CGP 55845
Muscimol
SCH 50911
SR 95531

Glutamate Receptors

NMDA Receptors
D-AP5
(RS)-CPP
Ifenprodil
(+)-MK 801
Ro 25-6981

AMPA Receptors
(S)-AMPA
Cyclothiazide
Naspm
NBQX
Talampanel

Kainate Receptors
ACET
GYKI 53655
UBP 302

mGlu Group I Receptors
(S)-3,5-DHPG
MTEP

mGlu Group II Receptors
BINA
LY 341495
LY 379268

mGlu Group III Receptors
L-AP4
MPEP
(S)-3,4-DCPG
AMN 082

Serotonin Receptors

$5\text{-}HT_{1A}$ Receptors
8-Hydroxy-DPAT
(S)-WAY 100135
WAY 100635

$5\text{-}HT_{1B}$ Receptors
GR 127935
SB 216641
SB 224289

$5\text{-}HT_{2A}$ Receptors
EMD 281014
Ketanserin
MDL 100907
Risperidone
TCB-2

$5\text{-}HT_{2C}$ Receptors
RS 102221
SB 242084
WAY 161503

Na_v channel blocker
Ambroxol

Glucagon-like peptide 1 receptor
Exenatide (Exendin-4)

References

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NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

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