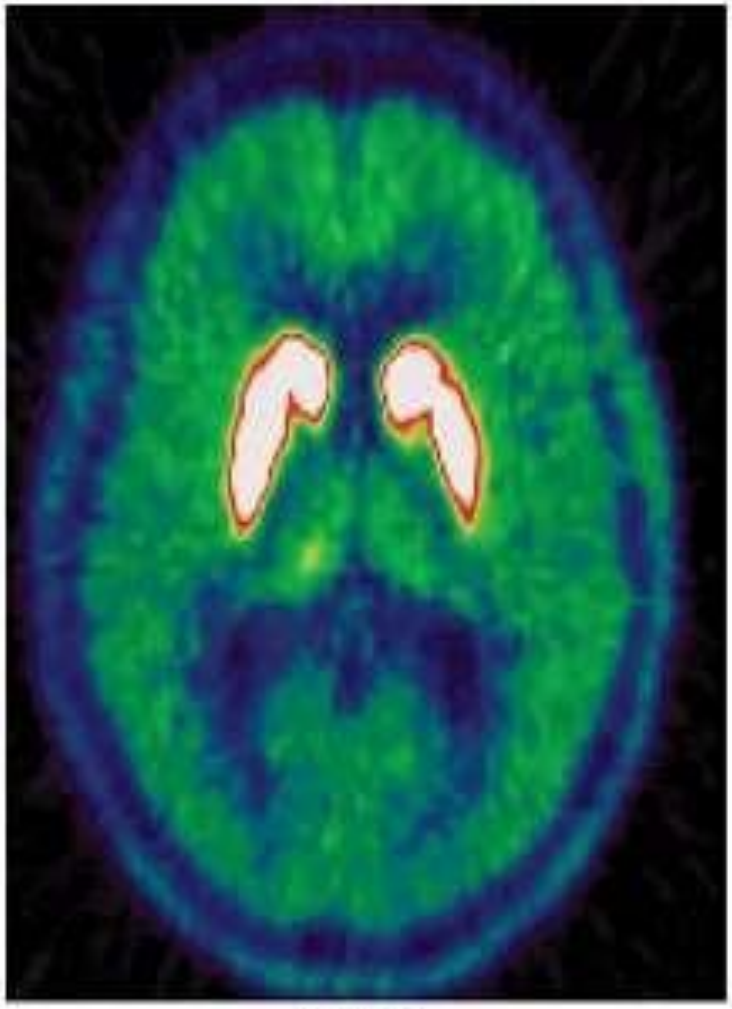
PARKINSON'S DISEASE

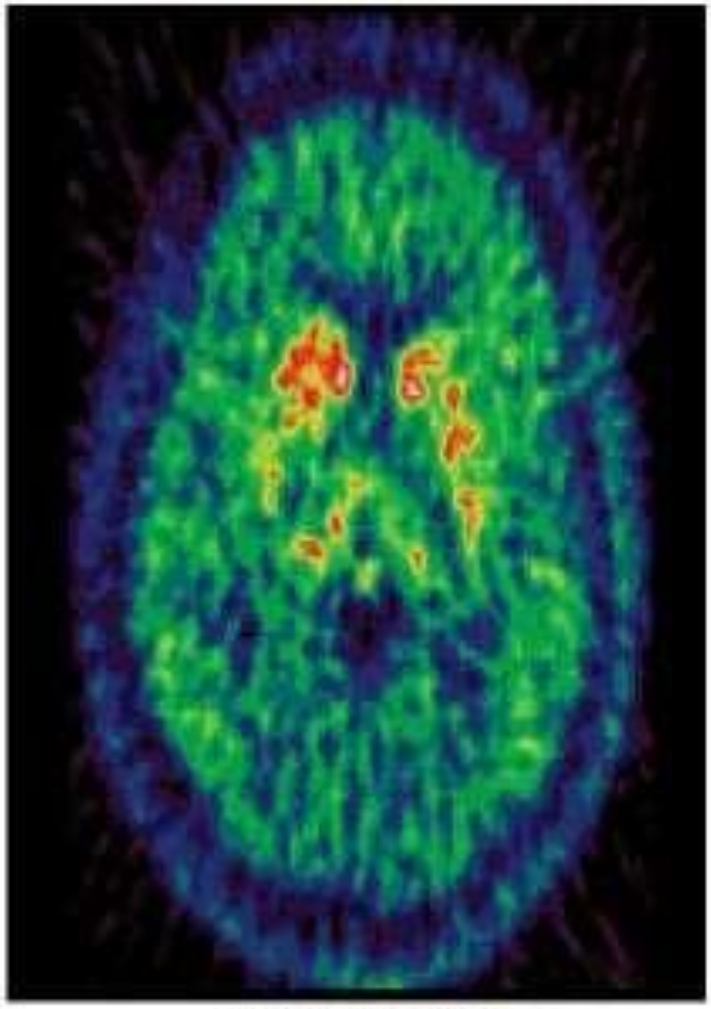
	stimulatory	Inhibitory
Acetyl choline	m1, m3, m5	m2, m4
Dopamine	D1, D5	D2, D3, D4

PARKINSON'S DISEASE

- Parkinson's disease (PD) is the second commonest neurodegenerative disease.
- It is estimated 1 million persons in the US
- 5 million persons in the world.
- English doctor James Parkinson, who published the first detailed description in *An Essay on the Shaking Palsy* in 1817



Normal



Parkinson's Disease

Fluorodopa-PET in a normal individual (*A*) and a PD patient (*B*).

Striatal FD-PET provides a measure of the integrity of the nigrostriatal system. Note reduced striatal uptake in PD compared to a control, which tends to be more pronounced in the caudate than in the putamen. *(Courtesy of Dr. Jon Stoessl.)*

Risk factors of PD

- *Age* -The most important risk factor
- Positive family history
- Male gender
- Environmental exposure: Herbicide and pesticide exposure, metals (manganese, iron), well water, farming, rural residence, wood pulp mills; and steel alloy industries
- Life experiences (trauma, emotional stress, personality traits such as shyness and depressiveness)

PD – classification.

Parkinson's Disease

- Genetic
- Sporadic

Dementia with Lewy bodies

Atypical Parkinsonisms

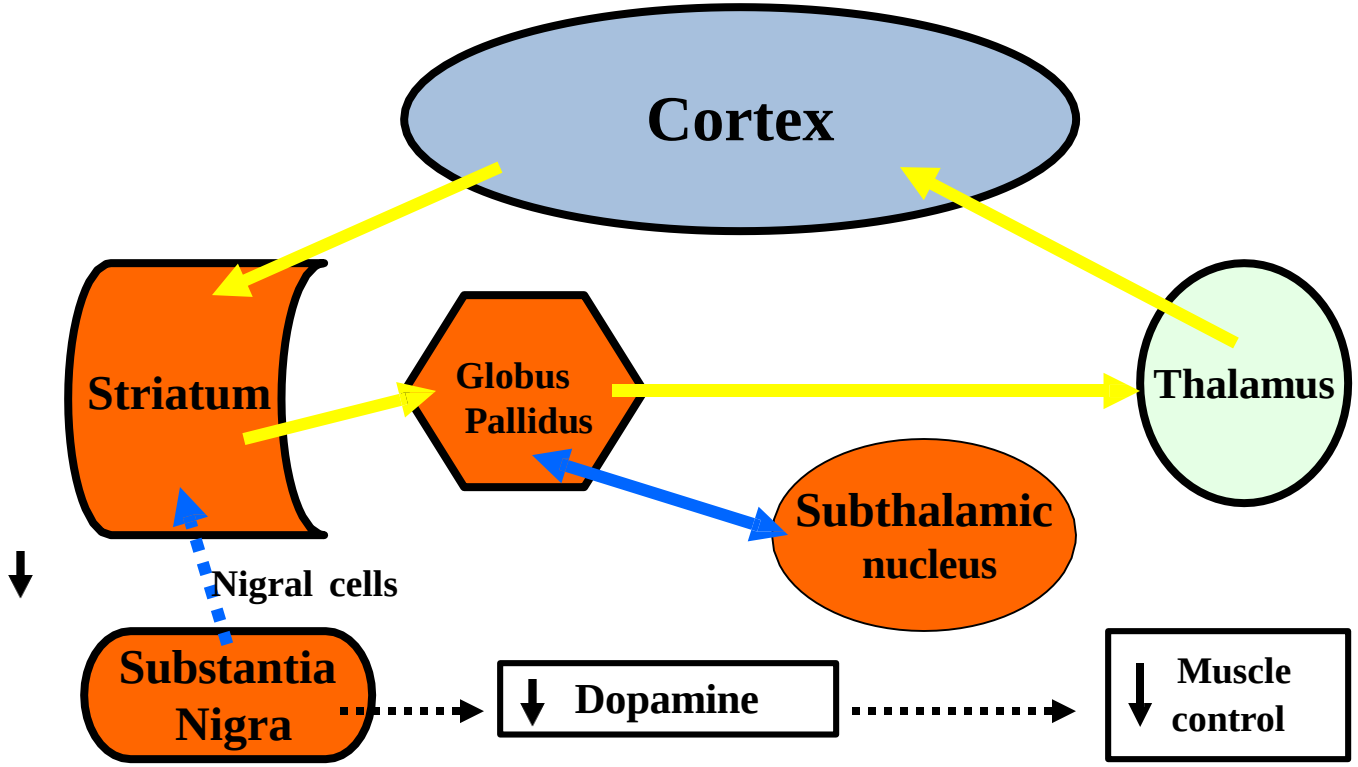
- Multiple-system atrophy
  - Cerebellar type (MSA-c)
  - Parkinson type (MSA-p)
- Progressive supranuclear palsy
- Corticobasal ganglionic degeneration
- Frontotemporal dementia

Secondary Parkinsonism

- Drug-induced
- Tumor
- Infection
- Vascular
- Normal-pressure hydrocephalus
- Trauma
- Liver failure
- Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)

Parkinson's Disease - Pathophysiology

The Basal Ganglia



- In PD the striatum portion of the basal ganglia receives an inadequate amount of nigral cells, which impairs a person's ability to control movement.
- The basal ganglion's connection to the cortex and the thalamus also affects movement.

Porth, 2012

Why are SNc cells especially vulnerable?

•Dopamine metabolism is considered to be critical for the preferential susceptibility of ventrolateral SNc cells to damage in Parkinson's disease.

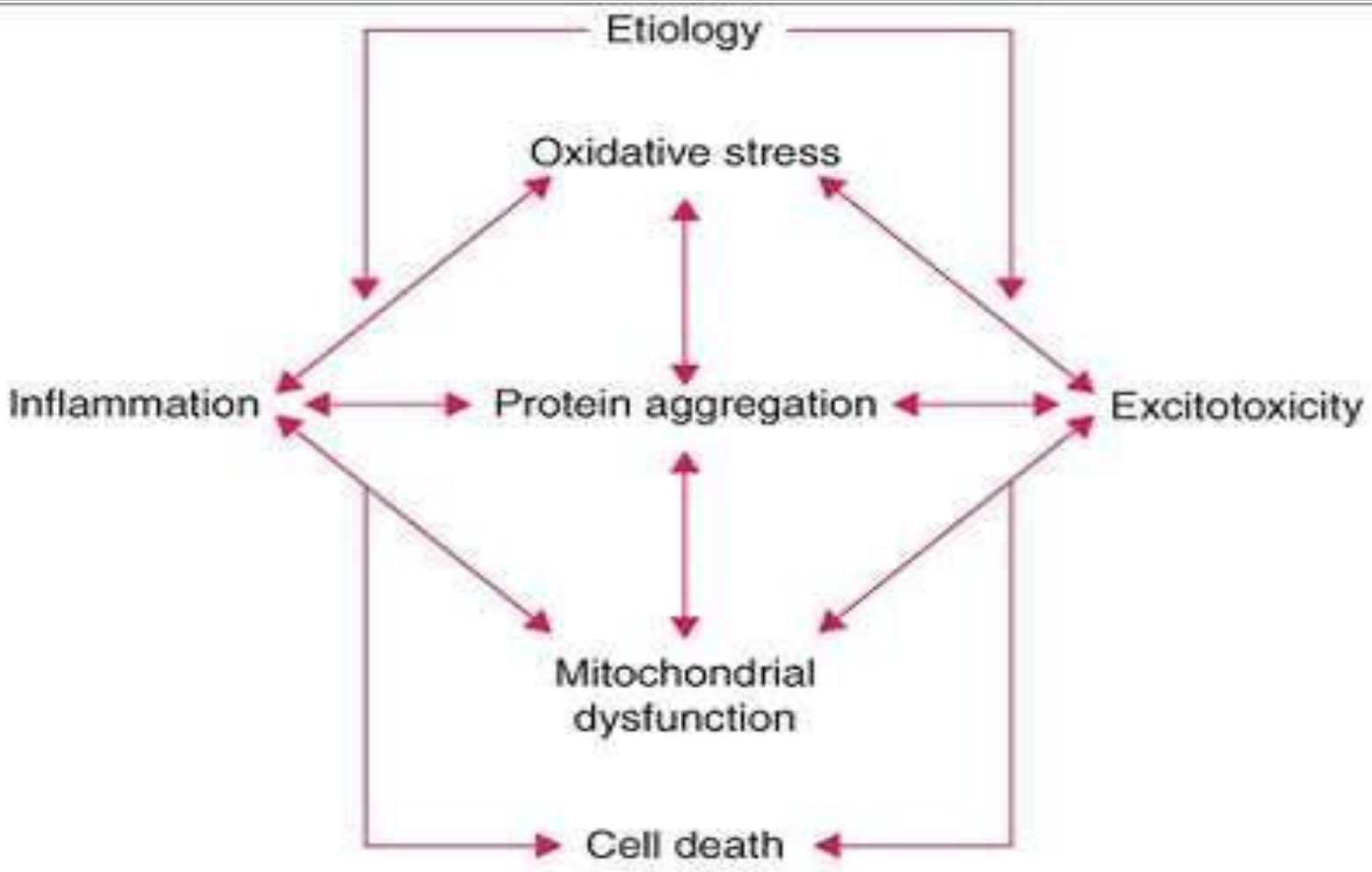
•Dopamine metabolism produces highly reactive species that oxidize lipids and other compounds, increase oxidative stress and impair mitochondrial function.

•**L-tyrosine + THFA + O2 + Fe^{2+} → L-dopa + DHFA + H_2O + Fe^{2+}**

•**L-tyrosine + Fe^{2+} + O2→ L-tyrosine + Fe^{3+} + O^-_2 (superoxide anion).**

•Emphasis has recently been placed on calciummediated toxicity in SNc neurons through Cav1.3 channels, as compared to neurons of the ventral tegmental area, which use sodium channels for

PD – Etiology and Pathogenesis.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

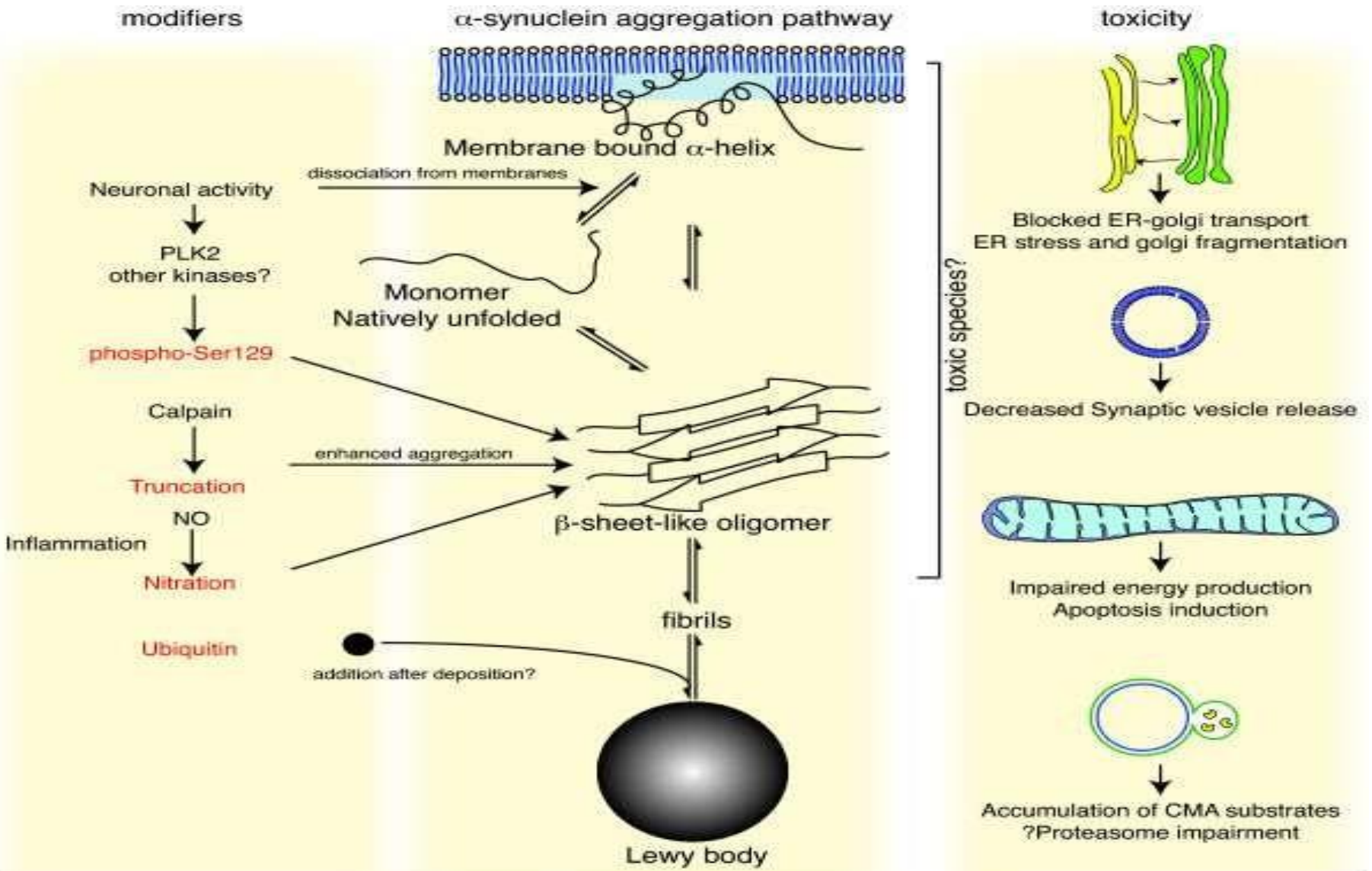
PD – Etiology and Pathogenesis.

- It has been proposed that most cases of PD are due to a "double hit" involving an interaction between a gene mutation that induces susceptibility coupled with exposure to a toxic environmental factor.

- The most significant of these mechanisms appear to be protein misfolding and accumulation and mitochondrial dysfunction.
- Lewy bodies and Lewy neurites, which are composed of misfolded and aggregated proteins.
- Protein accumulation could result from either increased formation or impaired clearance of proteins.

PD – Etiology and Pathogenesis.

- Mutations in alpha-synuclein promote misfolding of the protein and formation of oligomers and aggregates thought to be involved in the cell death process.
- wild-type alpha-synuclein gene can itself cause PD, indicating that increased production of even the normal protein can cause PD.
- Increased levels of unwanted proteins could also result from impaired clearance.
- Proteins are normally cleared by the ubiquitin proteasome system or the autophagy/lysosome pathway.
- These pathways are defective in patients with sporadic PD

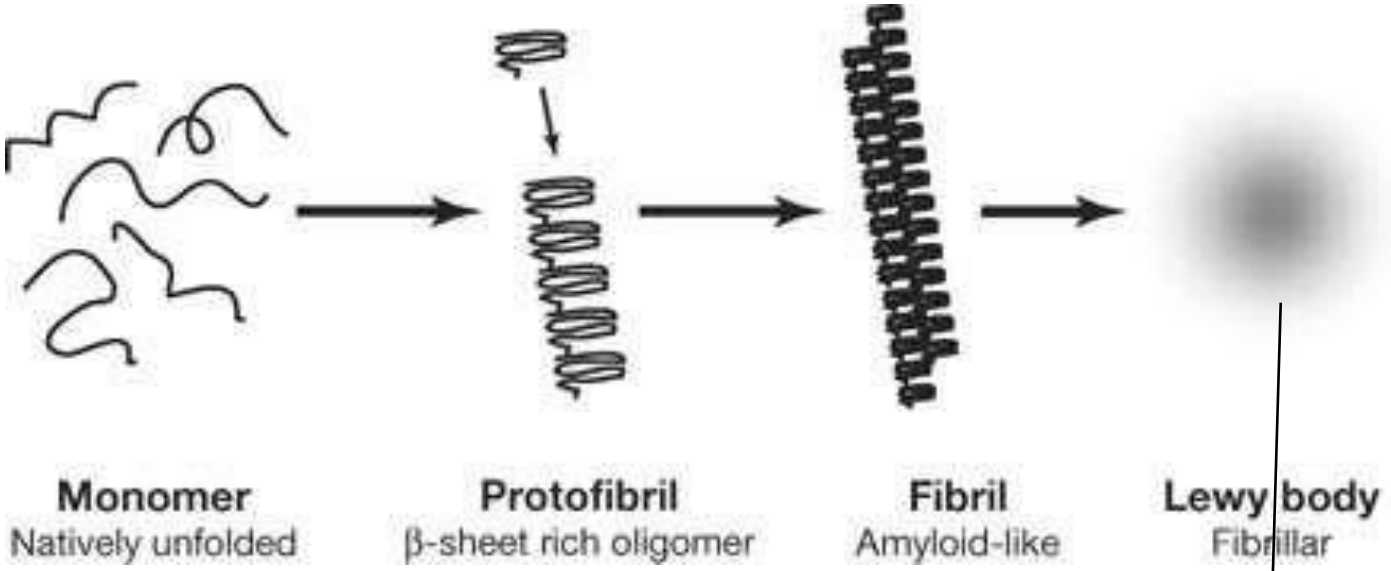


Potential therapeutic opportunities

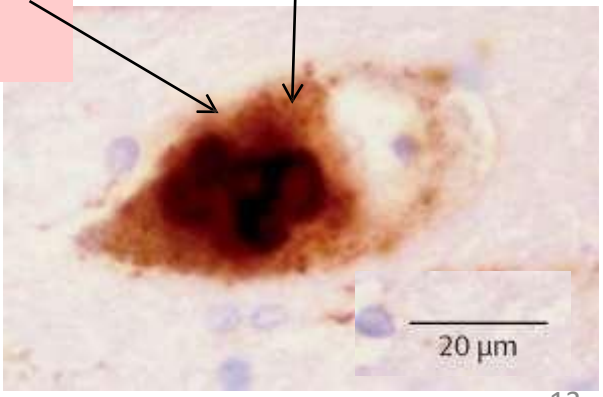
Kinase inhibitors Protease inhibitors Anti-inflammatory?	Knockdown total α–synuclein Limit formation or remove oligomers or other aggregates	Improve organelle function Limit cell death

α-synuclein has an unknown function; it's an "intrinsically disordered protein".

Mutant α-synuclein forms fibrils.



The hallmark of PD pathology:
Intracellular "Lewy bodies", especially in dopamine neurons



Improper mitochondrial fission / fusion
may be one of the early events
(Prof. D. Chan, Caltech)

PD – Etiology and Pathogenesis.

- Mutations in parkin (a ubiquitin ligase that attaches ubiquitin to misfolded proteins to promote their transport to the proteasome for degradation)
- UCH-L1 (which cleaves ubiquitin from misfolded proteins to permit their entry into the proteasome) -- Familial PD.
- Mitochondrial dysfunction has also been implicated in familial PD. Several causative genes (parkin, PINK1, and DJ1) either localize to mitochondria and/or cause mitochondrial dysfunction in transgenic animals. Postmortem studies have also shown a defect in complex I ofthe respiratory chain in the SNc of patients with sporadic PD.

PD – Etiology and Pathogenesis.

- Six different LRRK2 mutations have been linked to PD, with the Gly2019Ser being the commonest. The mechanism responsible for cell death with this mutation is not known but is thought to involve altered kinase activity.
- Mutations in the glucocerebrosidase (GBA) gene associated with Gaucher's disease are also associated with an increased risk of idiopathic PD.

PD – Etiology and Pathogenesis.

Name	Chromosome	Locus	Gene	Inheritance
Park 1	Chr 4	q21-23	α-Synuclein	AD
Park 2	Chr 6	q25-27	Parkin	AR
Park 3	Chr 2	p13	Unknown	AD
Park 4	Chr 4	q21-23	α-Synuclein	AD
Park 5	Chr 4	p14	UCHL-1	AD
Park 6	Chr 1	p35-36	PINK-1	AR
Park 7	Chr 1	p36	DJ-1	AR
Park 8	Chr 12	p11-q13	LRRK2	AR/Sp
Park 9	Chr 1	p36	ATP13A2	AR
Park 10	Chr 1	p32	Unknown	Sp
Park 11	Chr 2	q36-37	GIGYF2	AD
Park 12	Chr X	q21-25	Unknown	Sp
Park 13	Chr 2	p13	Omi/HtrA2	AD
Park 14	Chr 22	q13	PLA2G6	AR
Park 15	Chr 22	q12-13	FBX07	AR
Park 16	Chr 1	q32	Unknown	SP

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; SP, sporadic.

Clinical features of PD

- **Three cardinal symptoms:**

®*resting tremor*

® *bradykinesia (generalized slowness of movements)*

® *muscle rigidity*

Symptoms worsen as disease progresses.

- <u>Resting tremor:</u> Most common first symptom, most evident in one hand with the arm at rest.

♦ usually unilateral

♦ becomes bilateral

♦ worsens with stress



Tremors

Usually --

♦ first symptom

♦ occurs in the hands or arms

can occur in head, face, jaw, & leg

♦ disappears with purposeful movement

Postural manifestations –

Postural changes cause balance instability

■ postural instability

■ rigidity

■ stooped

Patients also suffer from non-motor symptoms such as:

- ♦ cognitive impairments
- ♦ olfactory impairments
- ♦ dysphagia
- ♦ GI dysfunction
- ♦ sleep disturbances
- ♦ depression

SECONDARY PARKINSONISM

- Associated with drugs, stroke, tumour, infection, or exposure to toxins such as carbon monoxide or manganese.

Drug-induced Parkinsonism

•Side effects of some drugs, especially those that affect dopamine levels in the brain, can actually cause symptoms of Parkinsonism.

•Although tremor and postural instability may be less severe, this condition may be difficult to distinguish from Parkinson's disease.

- Medications that can cause the development of Parkinsonism include:
  - Antipsychotics
  - Metaclopramide
  - Reserpine
  - Tetrabenazine
  - Some calcium channel blockers
  - Stimulants such as amphetamines and cocaine
  - Usually after stopping those medications Parkinsonism gradually disappears

Vascular Parkinsonism

- Multiple small strokes can cause Parkinsonism.
- Patients with this disorder are more likely to present with gait difficulty than tremor, and are more likely to have symptoms that are worse in the lower part of the body.
- Some will also report the abrupt onset of symptoms or give a history of step-wise deterioration (symptoms get worse, then plateau for a period).
- Dopamine is tried to improve patients' mobility although the results are often not as successful.
- Vascular Parkinsonism is static (or very slowly progressive) when compared to other

PARKINSON PLUS SYNDROME

•Atypical parkinsonism refers to a group of neurodegenerative conditions that usually are associated with more widespread neurodegeneration than is found in PD (often involvement of SNc and striatum and/or pallidum).

•As a group, they present with (rigidity and bradykinesia) but typically have a slightly different clinical picture than PD, reflecting differences in underlying pathology.

•In the early stages, they may show some modest benefit from levodopa and be difficult to distinguish from PD.

•Neuroimaging of the dopamine system is usually not helpful, as several
•atypical parkinsonisms also have degeneration of dopamine neurons.

PARKINSON PLUS SYNDROME

Metabolic imaging of the basal ganglia/thalamus network may be helpful, reflecting a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

TYPES ATYPICAL PD.

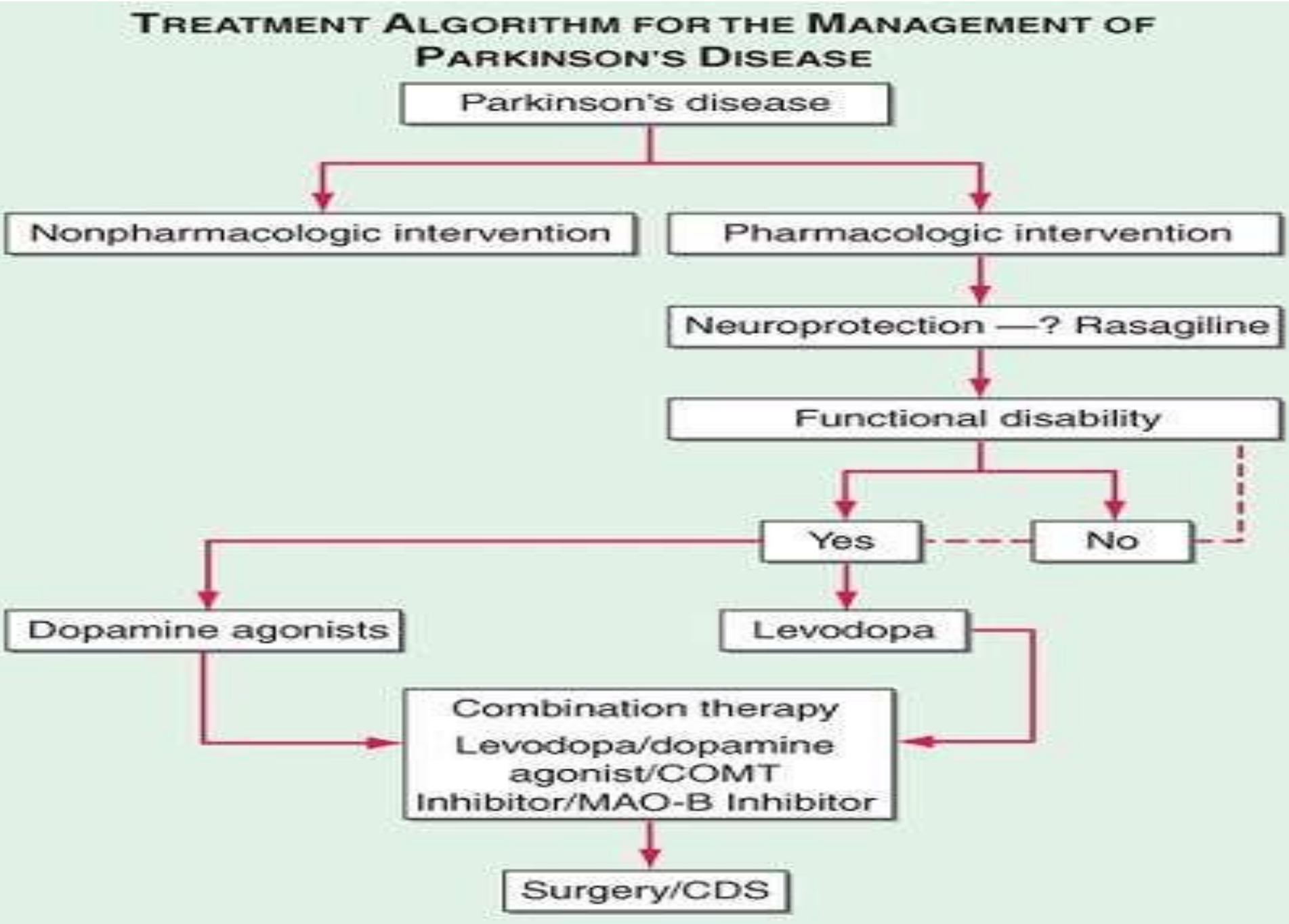
- Progressive Supranuclear Palsy (PSP)
- Corticobasal Degeneration (CBD)
- Multiple System Atrophy (MSA)

  Shy-Drager syndrome (DSD), Striatonigral degeneration (SND) and OlivoPontoCerebellar Atrophy (OPCA).

NEUROPROTECTIVE EFFECT

- Tobacco -- anabasine, anatabine and nornicotine. It also contains the monoamine oxidase inhibitors Harman and norharman.
- These beta-carboline compounds significantly decrease MAO activity in smokers.
- break down monoaminergic neurotransmitters such as.
- It is thought that the powerful interaction between the MAOIs and the nicotine is responsible for most of the addictive properties of tobacco smoking.
- The addition of five minor tobacco alkaloids increases nicotine-induced hyperactivity, sensitization and intravenous self-administration in rats.

Agent	Available Dosages	Typical Dosing
Levodopa*		
Carbidopa/levodopa	10/100, 25/100, 25/250	200–1000 mg levodopa/d 2–4 times/d
Benserazide/levodopa	25/100, 50/200	
Carbidopa/levodopa CR	25/100, 50/200	
Benserazide/levodopa MDS	25/200, 25/250	
Parcopa	10/100, 25/100, 25/250	
Carbidopa/levodopa/entacapone	12.5/50/200,18.75/75/200,25/100/200,31.25/125/200,37.5/150/200,50/200/200	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8	6–24 mg/d
Rotigotine patch	2-, 4-, 6-mg patches	4–10 mg/d
Apomorphine SC		2–8 mg
COMT Inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
MAO-B Inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	1.0 mg QAM


TREATMENT ALGORITHM FOR THE MANAGEMENT OF PARKINSON'S DISEASE
Parkinson's disease
Nonpharmacologic intervention
Pharmacologic intervention
Neuroprotection —? Rasagiline
Functional disability
Yes
No
Dopamine agonists
Levodopa
Combination therapy
Levodopa/dopamine agonist/COMT Inhibitor/MAO-B Inhibitor
Surgery/CDS

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine