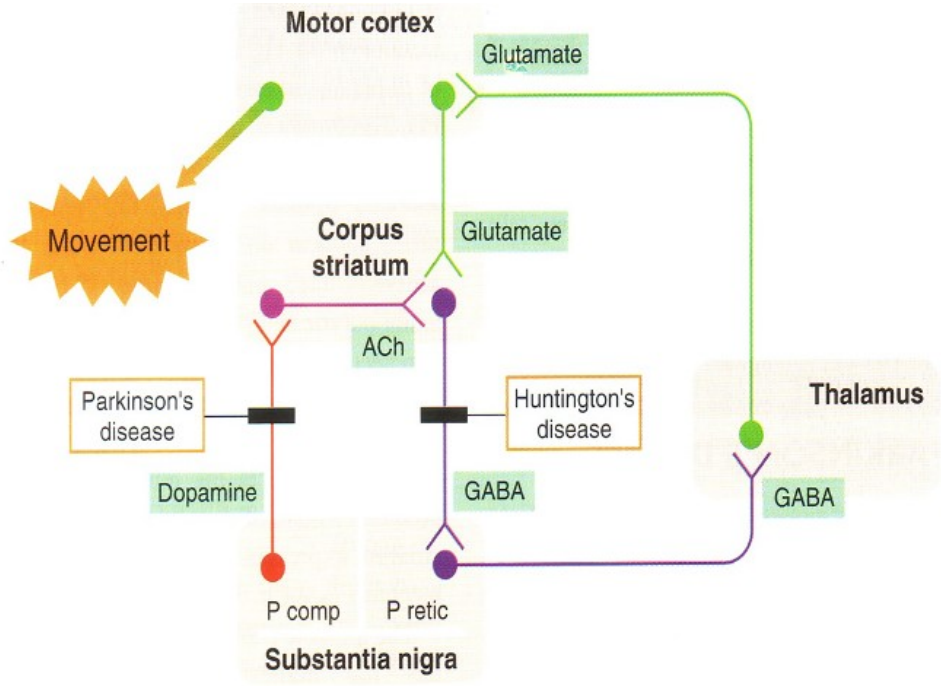
Antiparkinsons

Definition of Parkinson's disease:
A progressive disorder that occurs mainly in the elderly, characterized by:-

- Tremor at rest
- Muscle rigidity
- Hypokinesia



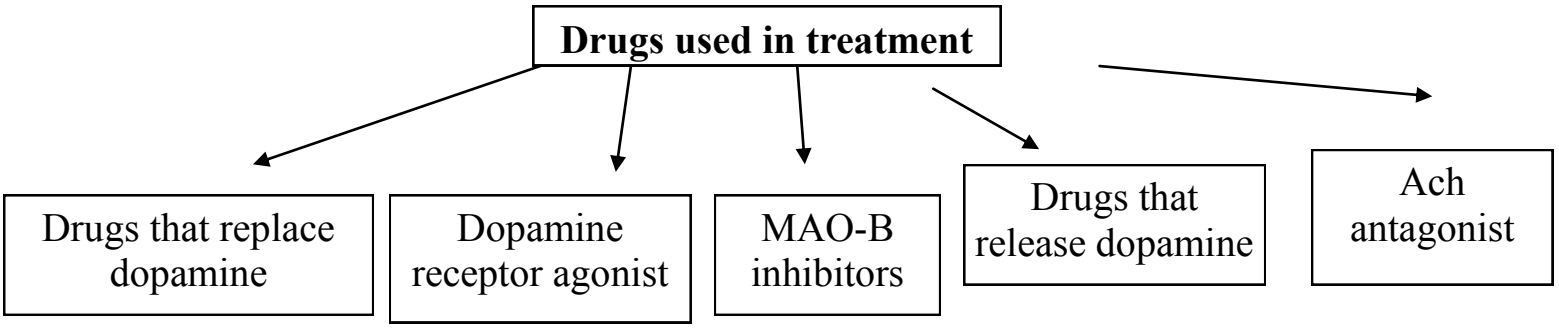
Normal physiology

Dopamine inhibits the action of acetylcholine (Ach). Thus, no interruption occurs at the level of GABA in pars reticulata. GABA will exert inhibitory action on thalamus leading to control of muscle tone.

Pathology

Decreased dopamine lets Ach exert its inhibitory effect on GABA. The thalamus in this case will not be inhibited by GABA, so the muscle tone will increase —> muscle rigidity.

Generally, what happens in Parkinson's disease is a net decrease in dopamine and increased acetylcholine.



First: drugs that replace dopamine (levodopa)

Q: why can't we use dopamine as a treatment?
Because it doesn't cross the blood brain barrier (BBB).

PK:

- Oral intake
- Dietary aromatic amino acids and Vit.C decrease its absorption. (take the drug 1/2 h before eating)
- $T_{1/2}$ = 2h
- **Metabolism:**

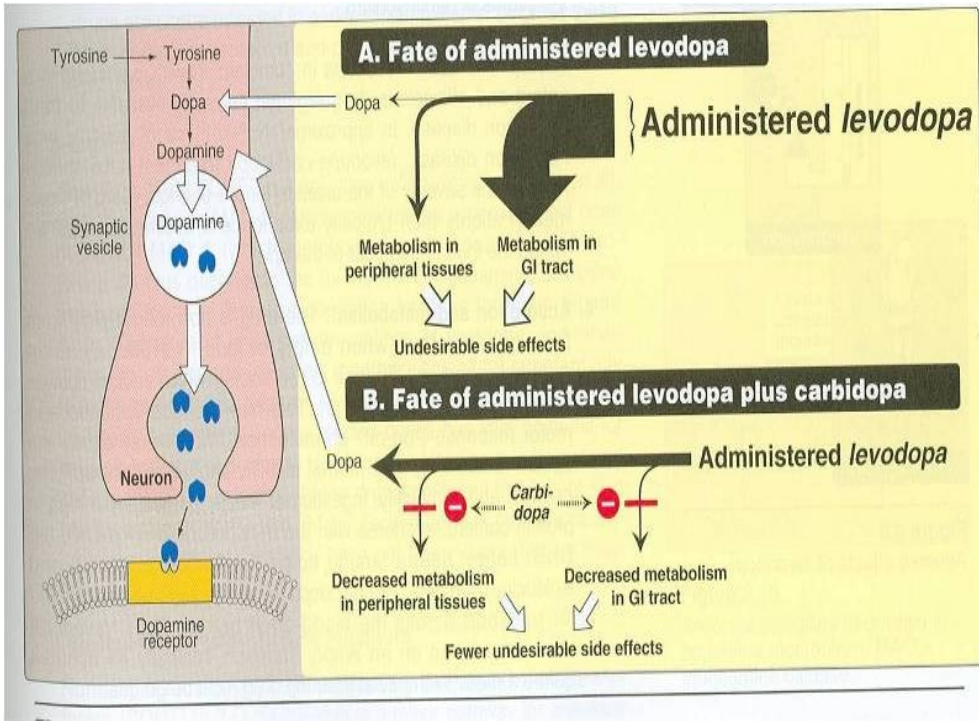
Levodopa is metabolized by the action of 2 enzymes in the blood before it enters BBB

- Aromatic L-amino acid decarboxylase (AAAD) → Metabolizes levodopa to dopamine which can not enter BBB
- Catechol-O-methyl transferase (COMT) → This metabolism will give rise to an inactive metabolite of levodopa, 3-O methyl dopa, which competes with levodopa to enter BBB

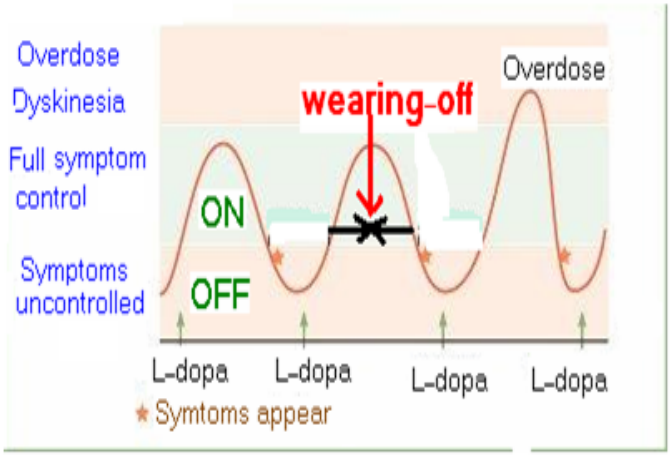
As a net result: only 1% of levodopa will ultimately enter BBB

Q: can we increase this percentage?
Yes. By the use of COMT inhibitors (**Entacapone)** and peripheral AAAD inhibitors **(carbidopa or benserazide).**

Other metabolism occurs **in the brain**:
Levodopa —> dopamine by the action of AAAD (that's why we use <u>peripheral</u> AAAD inhibitors)



* 3 strange phenomena occurs when using levodopa:
Wearing effect, on-off effect, and dyskinesea



Wearing effect
decrease duration of action of levodopa with time.

On-off effect
improvement of symptom then sudden appearance of symptoms again

these two effects are due to the progression of the disease with continuous loss of dopaminergic nigrostraital terminals or due to pathologic process directly involving striatal dopamine receptors

Dyskinesia

- Definition: diminished voluntary movements and the presence of involuntary movements
- Occurs in 40 to 90% of patients.
- fluctuating plasma levels of levodopa and the presence of hypersensitive dopamine receptors

to be continued...

- These dyskinesias can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.

Adverse effects:
- Peripheral side effects: nausea, vomiting, and anorexia.
- Orthostatic hypotension and cardiac arrhythmia in some patients due to release of epinephrine.
- Central adverse effects: vivid dreams, delusions, hallucinations, confusion, and sleep disturbances
- A positive Coomb's test with evidence of hemolysis
- Aggravation or precipitation of gout
- Abnormalities of smell or taste
- Brownish discoloration of saliva, urine, or vaginal secretions
- Priapism

Precautions:
- levodopa and adrenomimetic.
- history of cardiac arrhythmias or recent cardiac infarction.

Interactions:
- Nonselective MAO inhibitors + levodopa —> hypertensive crisis. Because levodopa —> epinephrine and MAO destroys epinephrine thus, MAO inhibitors will keep epinephrine high which lead to vasoconstriction and hypertension.
- Pharmacological doses of pyrodxine B6 + levodopa —> diminished effect due to increase peripheral metabolism.

Contraindications:
- Psychotic patients
- Angle closure glaucoma
- Active ulcer
- History of melanoma

Drug holidays:
- Discontinuance of the drug for 3-21 days
- Improve responsiveness to drug
- Carries risks of aspiration pneumonia, venous thrombosis, pulmonary embolism, depression
- Not longer recommended.

Second: dopamine receptor agonists

levodopa	Dopamine receptor agonist
More potent	Less potent
Wearing and on-off effects	No effects
Less psychotic side effects	more
Short $t_{1/2}$	Long $t_{1/2}$

- Could be used as monotherapy in mild Parkinson's disease
- Dopamine agonist + levodopa —> increase clinical improvement and reduce levodopa dosage needs

Bromocriptine

Mechanism of action

- An ergot alkaloid
- Agonist of D2 receptor and a partial antagonist of D1

PK

- Oral absorption
- Peak plasma level 1-2h
- Excreted in bile
- Used for hyperprolactinemia

Pramipexole

Mechanism of action:

- Non-ergot; a pure D3 receptor agonist

PK

- Rapid absorption
- Peak plasma level 2h
- Excreted unchanged in urine
- Adjust the dose in renal impairment

Ropinirole

Mechanism of action:
Nonergot, D2 agonist

Metabolized by CYP1A2, other drugs metabolized by this enzyme will reduce the rate of ropinirole's clearance

Adverse effects of dopamine agonists:

- Anorexia, nausea, vomiting, constipation, dyspepsia.
- Postural hypotension
- Cardiac arrhythmias (indication for stopping treatment)
- Confusion, hallucination, delusions.
- Headache, nasal congestion, increased arousal, erhythromelalgia.

Contraindications:

- Psychotic illness
- Recent MI
- Active peptic ulceration
- Peripheral vascular disease (avoid using ergot agonists)

	Pramipexole	Ropinirole
Bioavailability	>90%	55%
V_d	7 L/kg	7.5 L/kg
Half-life	8 hours[1]	6 hours
Metabolism	Negligible	Extensive
Elimination	Renal	Hepatic

Third: drugs that release dopamine (amantadine)

Mechanism of action:

- Antiviral drug
- Effects dopamine release and reuptake.
- Antagonizes muscarinic and N-methyl-D-aspartic acid (NMDA) receptors

PK

- Oral administration
- Peak plasma levels 1-4h
- $T_{1/2}$= 2-4h
- Urinary excretion

Clinical uses

- Treating symptoms of Parkinson (tremor)
- Used in early stages or adjunct to levodopa

Adverse effects

- Main side effects are ankle edema, livedo reticularis
- Nausea, dizziness, insomnia, confusion, hallucination.

Interaction

Amantadine + anticholinergic = additive effects on mental functions

Caution

With history of seizures or cardiac diseases

fourth: MAO-B inhibitors (selegiline)

Mechanism of action

- Inhibit MAO-B enzyme which destroys dopamine
- Blockade of dopamine metabolism makes dopamine more available for the receptors.
- Reduce the formation of toxic free radicals produced during the metabolism of dopamine
- Metabolized to desmethylselegiline, Which is **antiapoptotic** product

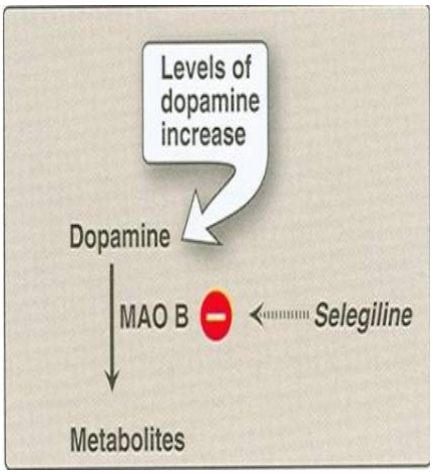
Clinical uses

- effective in the newly diagnosed patient with Parkinson's disease.
- Used with levodopa to:

1. reduce levodopa dosage requirements
2. minimize or delay the onset of dyskinesias and motor fluctuations

Adverse effects

- Insomnia when taken later during the day
- Adverse effects of levodopa may increase with the use of selegiline
- should not be coadministered with Tricyclic antidepressants, meperidine or with selective serotonin reuptake inhibitors (SSRIs), where they may cause hyperpyrexia, agitation, delirium, and coma.



fifth: Ach antagonist

Examples:
benztropine, trihexyphenidyl, procyclidine

Clinical uses
- *modest antiparkinsonian actions, used during the early stages of the disease or as an adjunct to levodopa therapy.*
- provide benefit in drug-induced Parkinsonism.

Adverse effects
- Cycloplegia, dry mouth, urinary retention, and constipation.
- Confusion, delirium, and hallucinations with higher doses
- Trihexyphenidyl may cause withdrawal symptoms

Used with caution with old people because it increases forgetfulness in this age

Contraindication
- Prostatic hyperplasia
- Obstructive gastrointestinal disease
- Angle-closure glaucoma
- Concomitant administration of drugs with anti muscarinic properties

The antihistamine diphenhydramine is used for mild Parkinsonism and in elderly who may not be able to tolerate antimuscuranics or dopamine agonists.

COMT inhibitors

Examples:
Tolcapone & entacapone

Orally absorped, $t_{1/2}$= 2h

They increase the <u>on time</u>

Adverse effects
Tolcapone therapy can cause fatal hepatotoxicity, monitoring hepatic enzymes is required