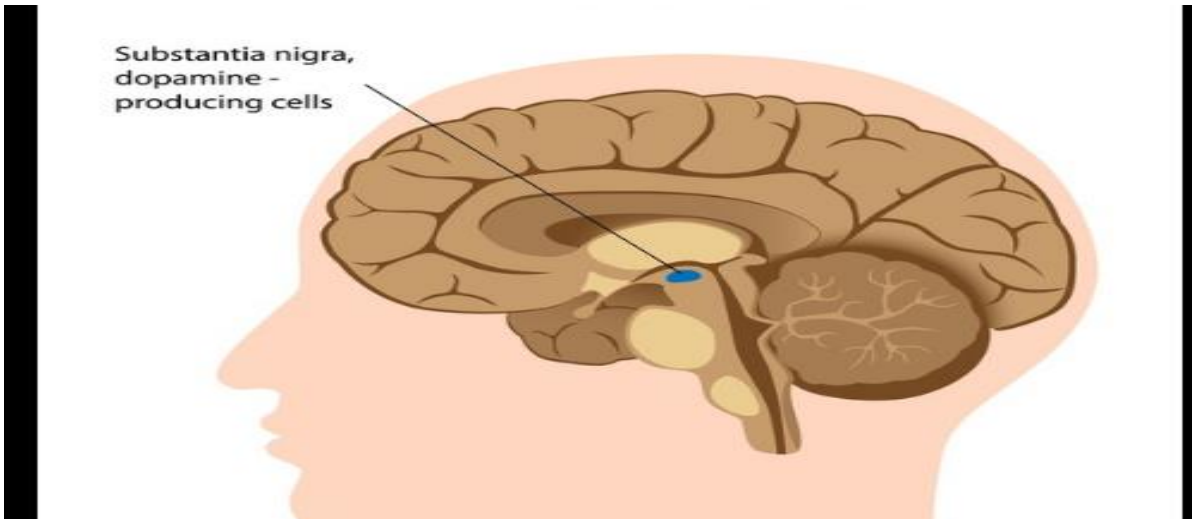
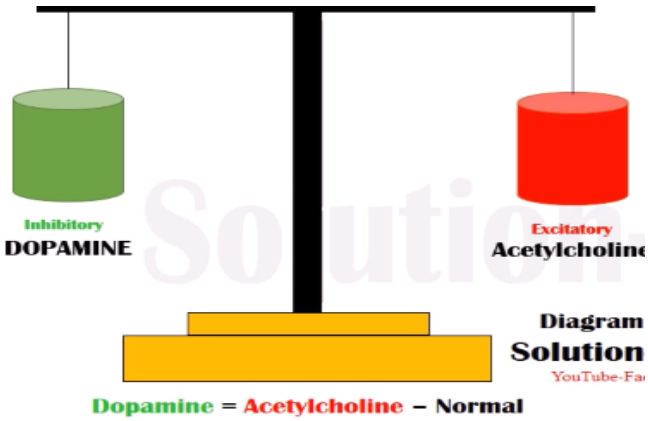
Parkinsons disease

Parkinson's disease is **a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination**. Parkinson's symptoms usually begin gradually and get worse over time. As the disease progresses, people may have difficulty walking and talking. Neurodegenerative disorder in which dopamine producing neuron of a brain structure called substantia nigra are damaged and die over time.





Drugs affecting brain dopaminergic system

(a) *Dopamine precursor* : Levodopa (l-dopa)
(b) *Peripheral decarboxylase inhibitors* : Carbidopa, Benserazide.
(c) *Dopaminergic agonists*: Bromocriptine, Ropinirole, Pramipexole
(d) *MAO-B inhibitor:* Selegiline,
(e) *COMT inhibitors:* Entacapone, Tolcapone
(f) *Dopamine facilitator:* Amantadine.

II. *Drugs affecting brain cholinergic system*

(a) *Central anticholinergics:* Trihexyphenidyl
(b) *Antihistaminics :* Orphenadrine, Promethazine.

LEVODOPA

Levodopa has a specific effect in PD:

It is inactive by itself, but is the immediate precursor of the transmitter DA. More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver). About 1–2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA which is stored and released as a transmitter.

PERIPHERAL DECARBOXYLASE INHIBITORS

Carbidopa and *benserazide* are extracerebral dopa decarboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in the brain. Administered along with levodopa, they increase its t½ in the periphery and make more of it available to cross blood-brain barrier to reach its site of action.

DOPAMINERGIC AGONISTS

The DA agonists can act on striatal DA receptors even in advanced patients who have largely lost the capacity to synthesize, store and release DA from levodopa.

MAO-B INHIBITOR

Selegiline (Deprenyl) It is a selective and irreversible MAO-B inhibitor. Two isoenzyme forms of MAO, termed MAO-A and MAO-B are recognized; both are present in peripheral adrenergic structures and intestinal mucosa,while the latter predominates in the brain.

As an adjuvant to levodopa, it is beneficial in 50–70% patients and permits 20–30% reduction in levodopa dose.

COMT INHIBITORS

Two selective, potent and reversible COMT inhibitors *Entacapone* and *Tolcapone* have been introduced as adjuvants to levodopa-carbidopa for advanced PD.

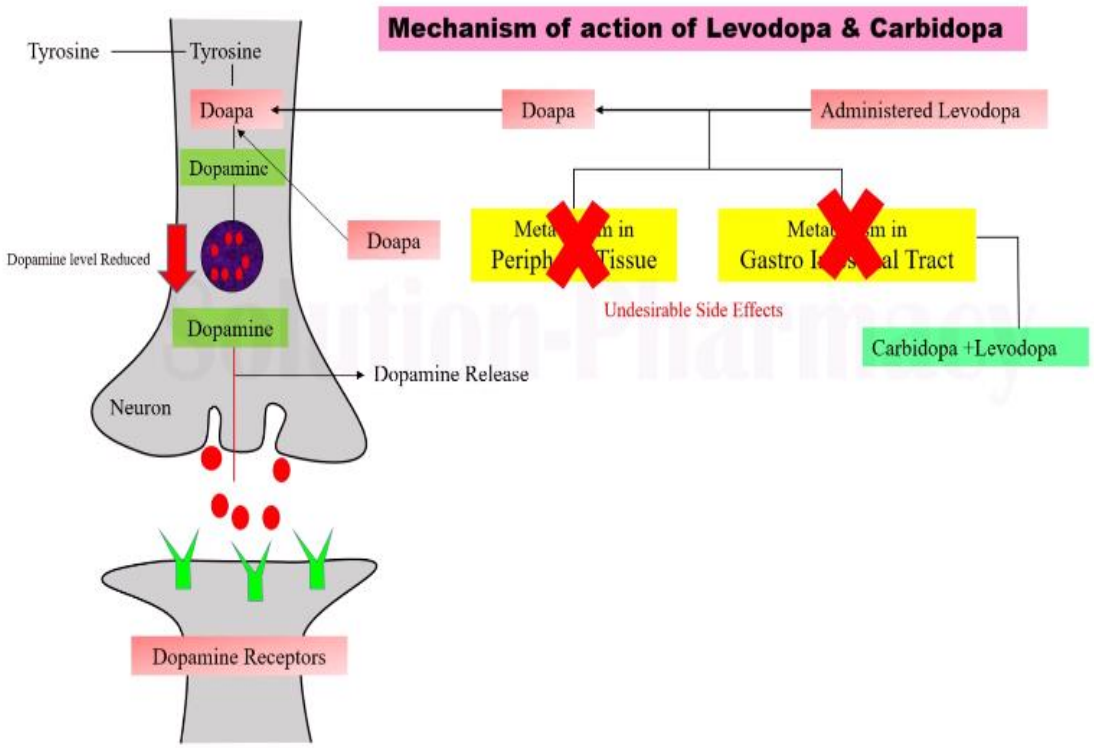
DOPAMINE FACILITATOR

Amantadine is a weak antagonist of the NMDA-type glutamate receptor, increases dopamine release, and blocks dopamine reuptake.

CENTRAL ANTICHOLINERGICS

They act by reducing the unbalanced cholinergic activity in the striatum of parkinsonian patients.

All anticholinergics produce 10–25% improvement in clinical features. Generally, tremor is benefited more than rigidity. The overall efficacy is much lower than levodopa. They may be used alone in mild cases and when levodopa is contraindicated.


Mechanism of action of Levodopa & Carbidopa
Tyrosine
Tyrosine
Doapa
Dopamine
Doapa
Doapa
Administered Levodopa
Dopamine level Reduced
Dopamine
Dopamine Release
Neuron
Dopamine Receptors
Undesirable Side Effects
Carbidopa +Levodopa