Parkinson's Disease
(Pathophysiology & Therapy)

Dr. Rajesh Choudhary
M. Pharm. (Pharmacology), Ph. D.


www.youtube.com/pharmacologyconceptsbyrajeshchoudhary


www.pharmacyconcepts.com

Disclaimers: Content of the slide is taken from various books, online contents and google images for the education purpose only.

Contents of the Lecture:

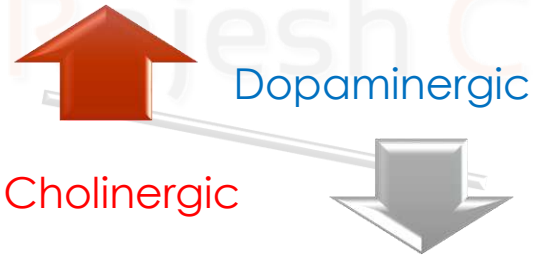
- Introduction
- Parkinson's Disease
- Neuronal Circuits
- Etiology
- Pathophysiology
- Clinical Manifestation
- Therapy
- Mode of Action of the Antiparkinson's Drugs

Introduction

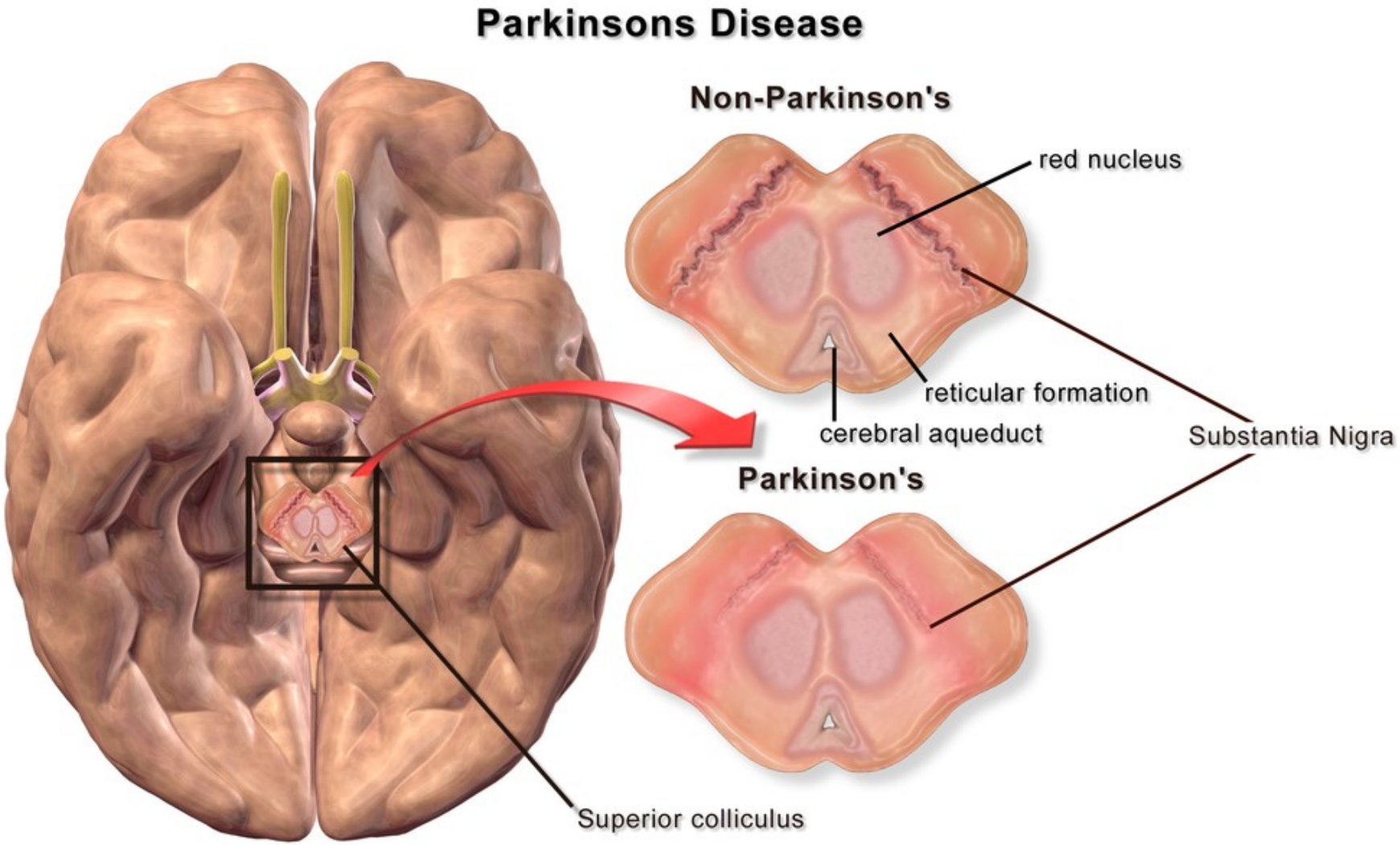
- **Parkinson's Diseases (PD)** is a chronic neuro-degenerative disorder that affects the motor function by affecting the neurons of basal ganglia of the brain.
- PD, first described as the "Shaking palsy" by James Parkinson in 1817.
- Jean-Martin Charot, proposed its current name to honoring James Parkinson.
- It generally affects the elderly and is estimated to afflict more than 1% of individuals over the age of 65.
- Mostly men are affected
- The Famous Boxer Mr. Md. Ali was suffering from this disorder.

Parkinson's Disease

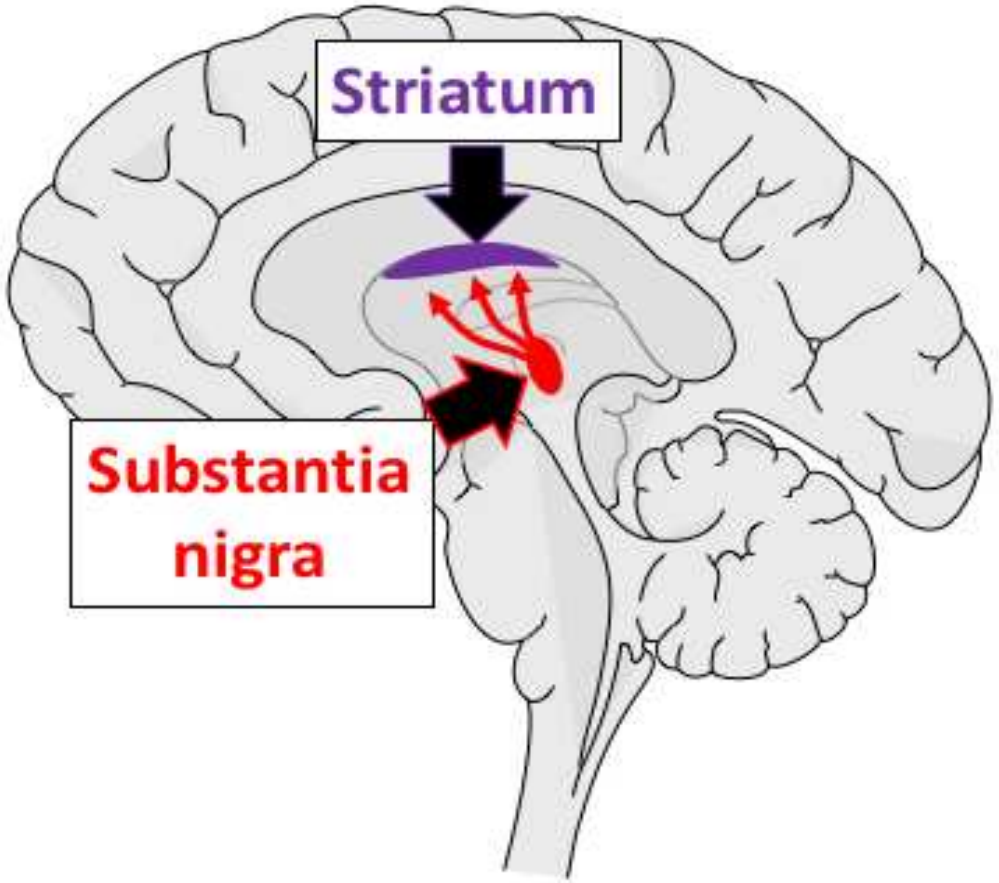
- **Parkinson's Diseases (PD)** is a chronic progressive neuro-degenerative disorder characterized by **tremors**, **muscular rigidity**, **bradykinesia** (slowness in initiating and carrying out voluntary movements).
- Parkinson's disease occurs due to reduction in the activity or loss of the inhibitory dopaminergic neurons in the substantia nigra and corpus striatum parts of the brain's basal ganglia system that are responsible for motor control. Thus known as a Motor Disorders.
- An imbalance between cholinergic (excitatory) and dopaminergic (inhibitory) neurons in straitum give rise to motor defect.

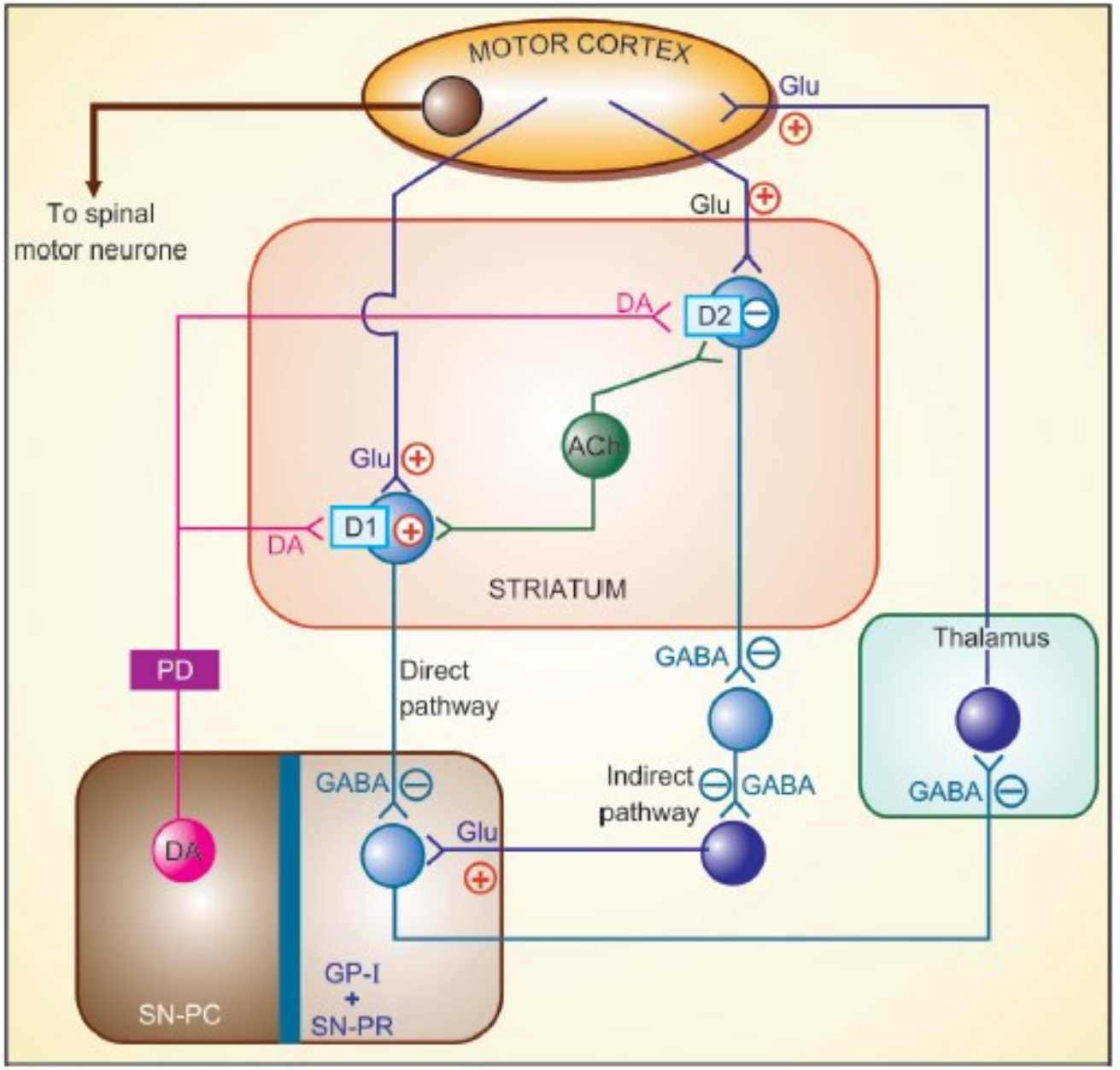


Parkinson's Disease



Neuronal Circuits





Etiology

- Heredity
- Antipsychotic drugs (or neuroleptic agents; central acting D2 blockers)
- Encephalitis infection in response to brain trauma, tumors, hydrocephalus or ischaemia
- Arteriosclerosis
- Neurotoxins such as cyanide, manganese and carbon monoxide
- Drugs like reserpine (hydropress), meyhyl dopa (aldomet), haloperidol (haldol) and phenothiazine (thorazine)

Pathophysiology

Proposed Pathways for PD

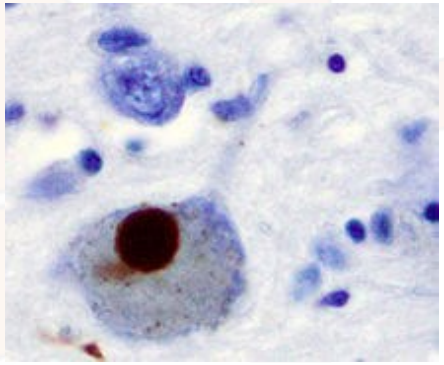
Underlying Mechanism- Loss of Dopaminergic neurons in the basal ganglia

1) Protein aggregation
2) Autophagy Distruction,
3) Changes in cell metabolism or mitochondrial function,
4) Neuroinflammation, and
5) blood-brain barrier (BBB) breakdown

Pathophysiology

1) Protein aggregation

- The first major proposed cause of neuronal death in Parkinson's disease is the bundling, or oligomerization, of proteins (**alpha-synuclein**).



Increased alpha-synuclein (insoluble) → aggregates to form Lewy bodies (pathological markers) → inhibit DNA repair system, activate ATM (ataxia-telangiectasia mutated; DNA damaging cellular kinase), increased DNA double-strand breaks and increased programmed cell death of neurons → Neuronal loss at basal ganglia → **Parkinson's Diseases**

Pathophysiology

2) Autophagy Distruction

- The second major proposed mechanism for neuronal death in Parkinson's disease, autophagy, is a mechanism by which inner components of the cell are broken down and recycled for use.

3) Changes in cell metabolism

- The third major proposed cause of cell death in Parkinson's disease involves the energy-generating mitochondrion organelle. In Parkinson's disease, mitochondrial function is disrupted, inhibiting energy production and resulting in death.
- PINK1 & Parkin complex promote the autophagy of mitochondria.

Pathophysiology

4) Neuroinflammation

- The fourth proposed major mechanism of neuronal death in Parkinson's Disease, neuroinflammation, is generally understood for neurodegenerative diseases
- One major cell type involved in neuroinflammation is the microglia. Microglia are recognized as the innate immune cells of the central nervous system

5) Blood-Brain Barrier (BBB) Breakdown

- The fifth proposed major mechanism for cell death is the breakdown of the blood-brain barrier (BBB).

Pathophysiology

5) Blood-Brain Barrier (BBB) Breakdown

- The BBB has three cell types which tightly regulate the flow of molecules in and out of the brain: endothelial cells, pericytes, and astrocytes.
- In neurodegenerative diseases, BBB breakdown has been measured and identified in specific regions of the brain, including the **substantia nigra** in Parkinson's disease and **hippocampus** in Alzheimer's disease.
- Protein aggregates or cytokines from neuroinflammation may interfere with **cell receptors** and alter their function in the BBB.
- Neuroinflammation further increase the risk of PD

Clinical Manifestation

Primary

1. Tremor
2. Rigidity (Increased resistance to passive motion)
3. Bradykinesia/Hypokinesia (Slowness of active movement)
4. Posture instability

Secondary

1. Visual disturbance
2. Speech Problem
3. Fine Motor problem
4. Autonomic Disturbance
5. Cognitive and Behavioral Imparment: Depression, Dementia, Memory deficit

Therapeutics Managements

I. 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, Rasagiline

(e) *COMT inhibitors*: Entacapone, Tolcapone

(f) *Glutamate (NMDA receptor) antagonist (Dopamine facilitator):* Amantadine.

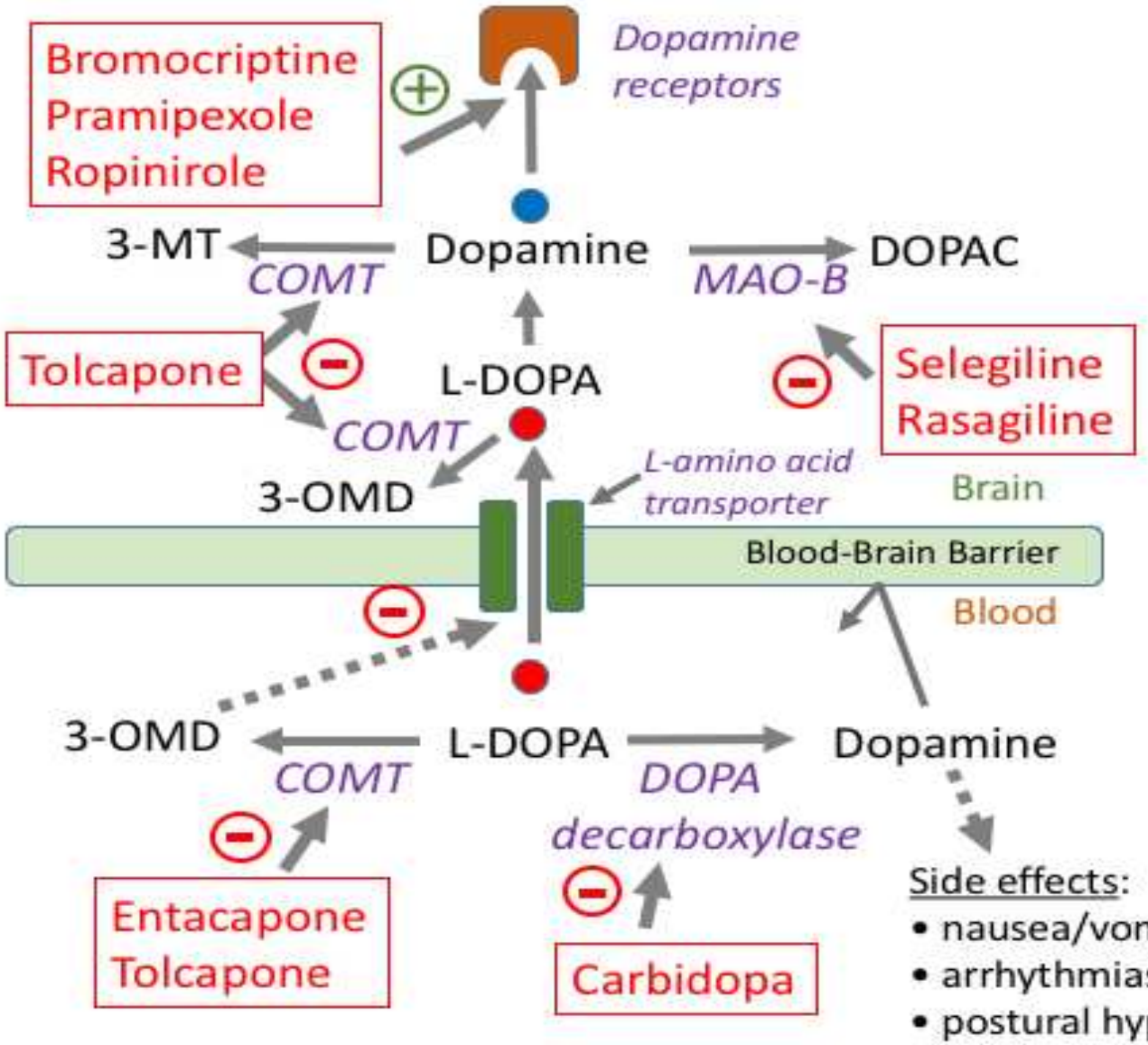
Therapeutics Managements

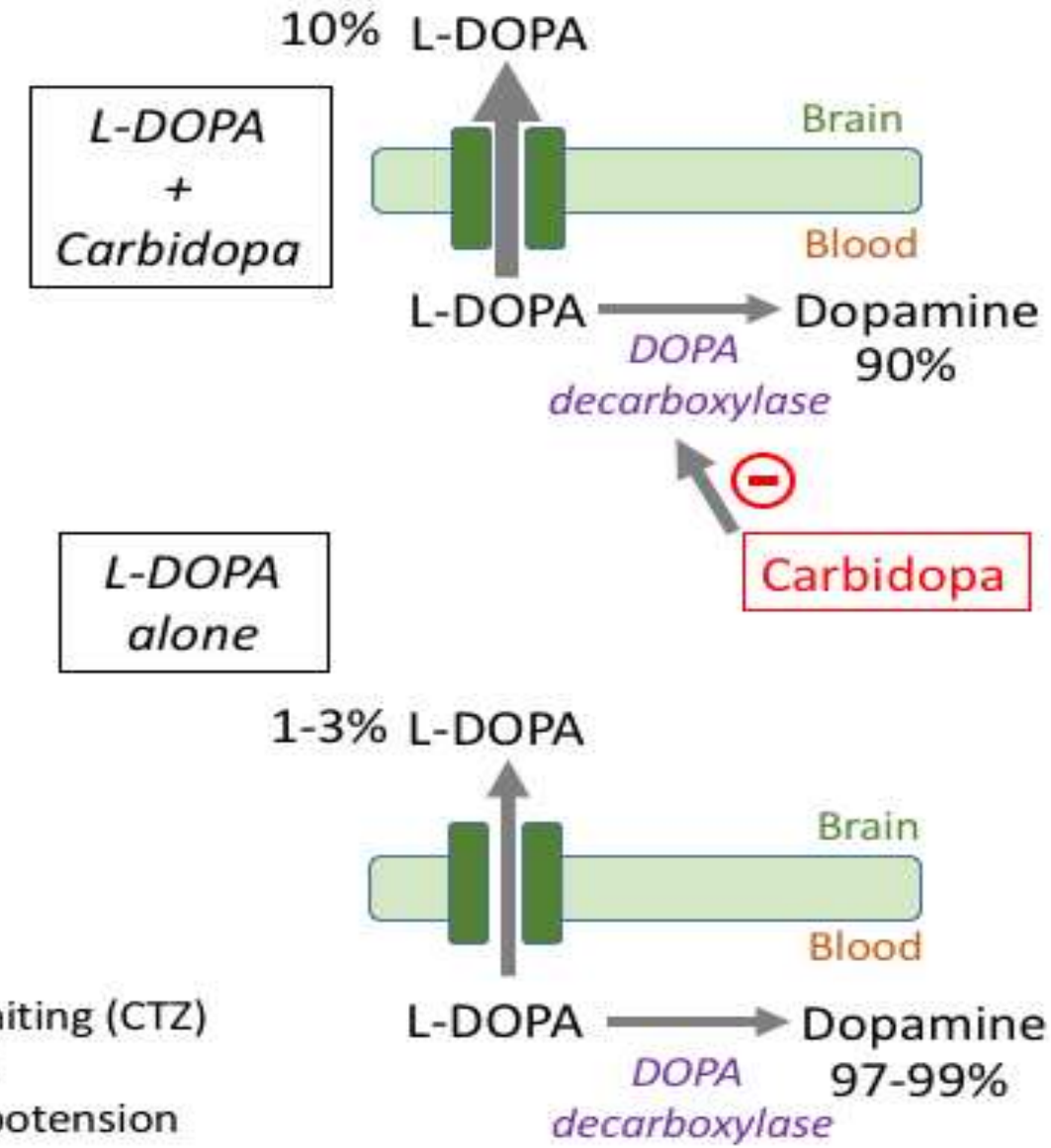
II. *Drugs affecting brain cholinergic system*

(a) *Central anticholinergics:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

(b) *Antihistaminics* : Orphenadrine, Promethazine.

Mode of Action

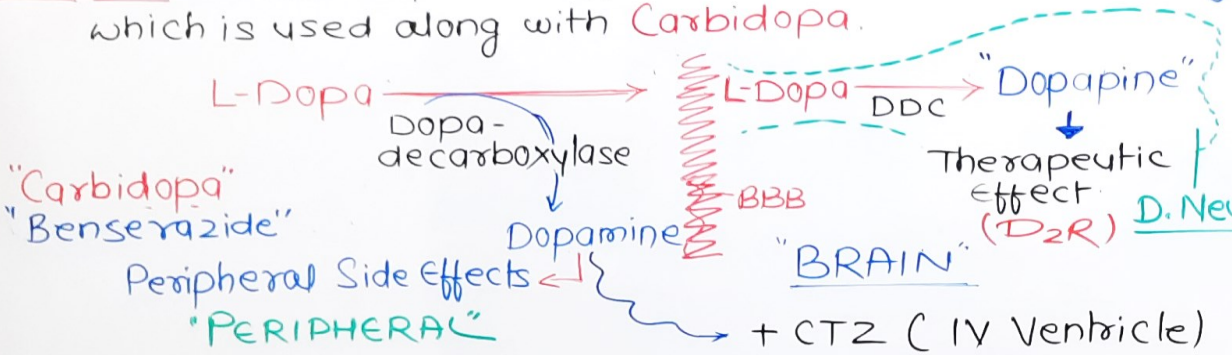




http://tmedweb.tulane.edu/pharmwiki/doku.php/pd_pathways_targets

PHARMACOLOGY OF L-DOPA & CARBIDOPA

L-DOPA – Most imp and efficacious Anti-Parkinson drug which is used along with Carbidopa.



PHARCOLOGICAL ACTION OF L-DOPA

1) CNS → # Marked Anti-PD effects, Resolve hypokinesia & rigidity first then tremmor.
   # Secondary complication like posture, gait, writting, speech, Facial Expression, etc. gradually normalize
   # Behavioural Effects ↳ "General Alerting Response" progression to excitement → Frank psychosis
   ↳ Disproportionat Sexually activity
   ↳ L-dopa has been used to produce a non specific "Awaking" effect in hepatic coma

2) CVS → May Cause Cardiac stimulation by B_1R
   ↳ ↑ HR (Tachycardia; + Chronotropic)
   ↳ ↑ Force of contract^n (+ Inotropic)
   ↳ Postural hypotension (central Action)
   ↳ Gradual Tolerance may occurs

3) CTZ → Nausea, Vomiting
4) Endocrine → ↓↓ Prolactin release, ↑ GH release

PHARMACOKINETIC → Rapidly absorb from intestine by amino ā active transport system. BA is affected by Gastric emptying time (↓BA) & amino acid diet (↓BA)
High First pass metabolism in GI mucosa & Liver
It cross the BBB by active transport system
$t_{1/2}$ - 1-2 h, excreted through urine after conjugat^n

ADR :- **During Initial Therapy** – (can ↓ by Low dose)
↳ Nausea, Vomiting, Postural hypotension, Dizziness, Arrhythmia, Angina, alter Taste.
During Prolonged → Abnormal movement (dyskinesia), Behavioural effect, affect motor function.
Contraindicat^n – Ischemic heart disease, Psychotic, hepatic & Renal disease
Interaction – # Pyridoxine – Abolish Effect by ↑ DDC
Neuroleptic → Reverse the effect of L-dopa
Non selective MAOIs – Hypertensive crises
Antihypertensive drug – Postural hypotension
Uses – Anti-Parkinson disease

PC
Pharmacology Concepts
By Rajesh Choudhary

Thanks for Watching

Subscribe my YouTube Channel