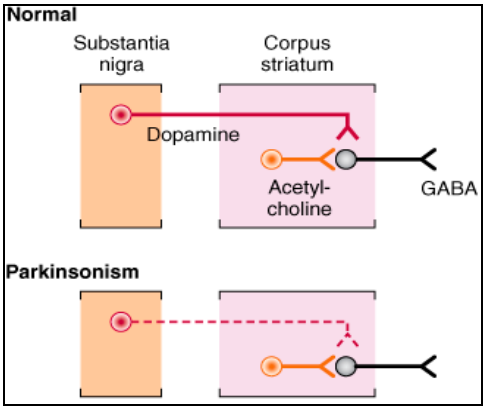
Unit VIII – Problem 5 – Pharmacology: Treatment of Parkinson's disease

- **Landmarks in understanding Parkinson's disease:**
  - **The 1st anti-hypertensive drug was reserpine** → which is depleting dopamine → leading to manifestations of extrapyramidal tract lesion.
  - **Chlorpromazine is a drug used in treating patients with schizophrenia** → is a dopamine receptor blocker → also producing manifestations of extrapyramidal tract lesion.
  - **A history of some patients in US who used heroin contaminated with MPTP** → which is destroying dopaminergic neurons → inducing Parkinson's disease.
    Note: from these 3 conditions, you can notice that Parkinson's disease is mainly related to deficiency of dopamine.
- **The deficiency in dopamine render cholinergic neurons unchecked** → therefore, there will be increased release of Ach → leading to imbalance of circuits (formation of reverberating circuits) → extrapyramidal system problem (hypokinesia, lead-pipe rigidity and tremor at rest).



- **Therapeutic strategies in Parkinson's disease:**
  - **Administrating the precursor (L-DOPA) → levodopa is given orally to the patient.**
    - ✓ Levodopa is the cornerstone treatment for Parkinson's disease.
    - ✓ Levodopa is given in combination with carbidopa in 2 forms:
      - ❖ *Either sinemet.*
      - ❖ *Or sinemet-CR*: in which there is sustained release of the drug.
        Note: levodopa is converted to dopamine outside the central nervous system → this dopamine will cause cardiac side effects and it cannot cross the blood-brain barrier and thus not reaching the brain → therefore a decarboxylase inhibitor which will inhibit peripheral decarboxylation but does not cross the blood-brain barrier (allowing decarboxylation in CNS) is administered in conjugation with levodopa.
    - ✓ Adverse effects:
      - ❖ *CNS*: nausea, vomiting and hallucinations.
      - ❖ *CVS (cardiovascular system):* orthostatic hypotension
      - ❖ *Motor complications*: on-off phenomenon at trough (controlled with CR preparations) and dyskinesia (occurring when levodopa is reaching its peak concentration).
    - ✓ Drug interactions:
      - ❖ Vitamine B6 is increasing peripheral decarboxylation of levodopa to dopamine → resulting in failure of the therapy.
      - ❖ Tricyclic antidepressents and anticholinergics prolong gastric emptying time and increase decarboxylation in the gut.

- Food which is rich in neutral amino acids interferes with the transport of L-DOPA across the blood-brain barrier.
- Anti-psychotic drugs (neuroleptics) and metoclopramide (used for vomiting) block dopaminergic receptors.

- **After years of treating Parkinson's disease using the precursor replacement strategy → there will be failure of DOPA-therapy → so you have to administer dopamine agonists:**
  - ✓ Which are classified to:
    - *Ergolines*:
      - Bromocriptine (D2 receptor). It is also used for the treatment of hyperprolactenemia.
      - Pergolide (D1 + D2 receptors).
    - *Non-ergolines (these are mainly used nowadays):*
      - Pramipexole (D3 receptor).
      - Ropinirole (D2 receptor). It has less side effects than pramipexole.
  - ✓ Adverse effects:
    - Nausea and vomiting.
    - Orthostatic hypotension.
    - Hallucinations and psychosis.
- **Administrating monoamine oxidase-B (MAO-B) or catechol-o-methyl-transferase (COMT) inhibitors to prevent degredation of dopamine (this strategy is not effective as DOPA-therapy).**
  - ✓ MAO-B inhibitor (selegiline):
    - *Adverse effects:*
      - Serotonin syndrome: due to interaction with pethidine and SSRI antidepressants.
      - Dyskinesia: due to interaction with levodopa.
      - Insomnia and vivid dreams: due to metabolites such as amphetamines.
  - ✓ COMT inhibitors: (entacapone and tolcapone):
    - *Adverse effects:*
      - Increasing levodopa-induced dyskinesia.
      - Dry mouth, urine discoloration and iron chelation in gut.

- **Anticholinergics (blocking muscarinic receptors):**
  - **Examples include:**
    - ✓ Orphenadrine (important)
    - ✓ Benztropine.
    - ✓ Trihexyphenidyl.
    - ✓ Procyclidine.
  - **Mainly used in treating tremors and extrapyramidal problems occurring in patients treated with antipsychotics.**
  - **Adverse effects:**
    - ✓ CNS: memory impairment and confusion.
    - ✓ Autonomic: glaucoma and urinary retention.
- **Antihistamines (diphenhydramine which is belonging to the 1st generation):**
  - **Mechanism of action**: central anticholinergic effect.
  - **Adverse effects**: sedation.
- **NMDA receptor antagonists (amantadine: it is an antivural drug):**
  - **Useful for controlling bradykinesia.**
  - **Adverse effects:**
    - ✓ CNS: confusion, hallucination, insomnia, nightmares, dizziness and nausea.
    - ✓ CVS: orthostatic hypotension.

  - Note that memantine is an approved drug nowadays for the treatment of slow dementia (which is occurring in severe forms of Parkinson's disease).
- **β-blockers (nadolol and propranolol) are used mainly for controlling intention tremor and tremor associated with anxiety.**
- **Atypical antipsychotics (clozapine and quetiapine) are used to treat hallucination.**
- **Iatrogenic parkinsonism is caused by:**
  - **Neuroleptics (typical antipsychotics).**
  - **Methyldopa: which is used to treat hypertension in pregnancy.**
  - **Metoclopramide.**
  - **Reserpine.**
- **Fava beans are a good natural source to extract levodopa from.**