quizlet: https://quizlet.com/216756008/pharmacology-2-flash-cards/

Parkinson's Disease

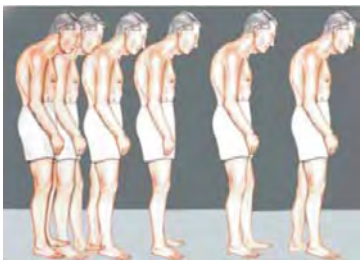
- **Detail the cardinal features and pathophysiology of PD**

The are 6 cardinal features of PD.

Early Signs:

1. **Tremor at rest**: To-and-fro movement (**'pill – rolling'**), sequence of contraction of agonistic and atagonistic muscles + resting temor, 5 Hz, Micrographia (Small, illegible handwriting)
2. **Akinesia/bradykinesia/hypokinesia:** Slow initiation/sluggishness/diminished spontaneous movement, Often on one side of body (early, hypokinesia), Craniofacial effects: masklike facies (hypomimia), defective mouth closure, reduced blinking, dysphagia, drooling
3. **Rigidity:** Elevated muscle tone - muscle tension, stiffness or spasm, Sometimes with cogwheel/ratchet resistance - muscle moves freely, then meets resistance or remains fixed in new position.

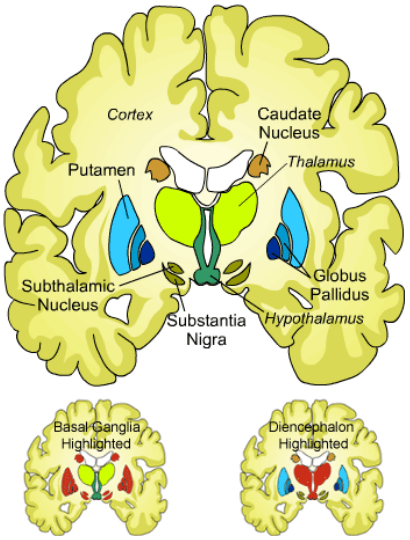
Later signs:



4. **Flexed posture of neck, trunk and limbs:** 'Simian-like' stooped posture
5. **Loss of postural reflexes:** Loss of balance leads to falls, Acceleration of the gait (festination) to avoid falling
6. **Freezing phenomenon:** Feet 'stuck' to the ground, start, turning and destination freezing, Difficulty beginning / maintaining body motion

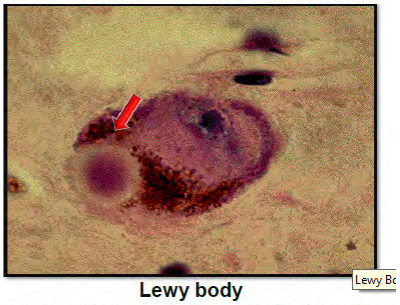
Gait impairment: postural instability, propulsion, festination

Pathophysiology of PD



- First described in 6 patients by Parkinson in 1817
- Movement disorder - dysfunction in basal ganglia
- Depigmentation in substantia - nigra (loss of neuromelanin - oxidised DA)
- Lewy bodies (intracytoplasmic eosinophilic inclusion bodies deposits of alpha-synuclein

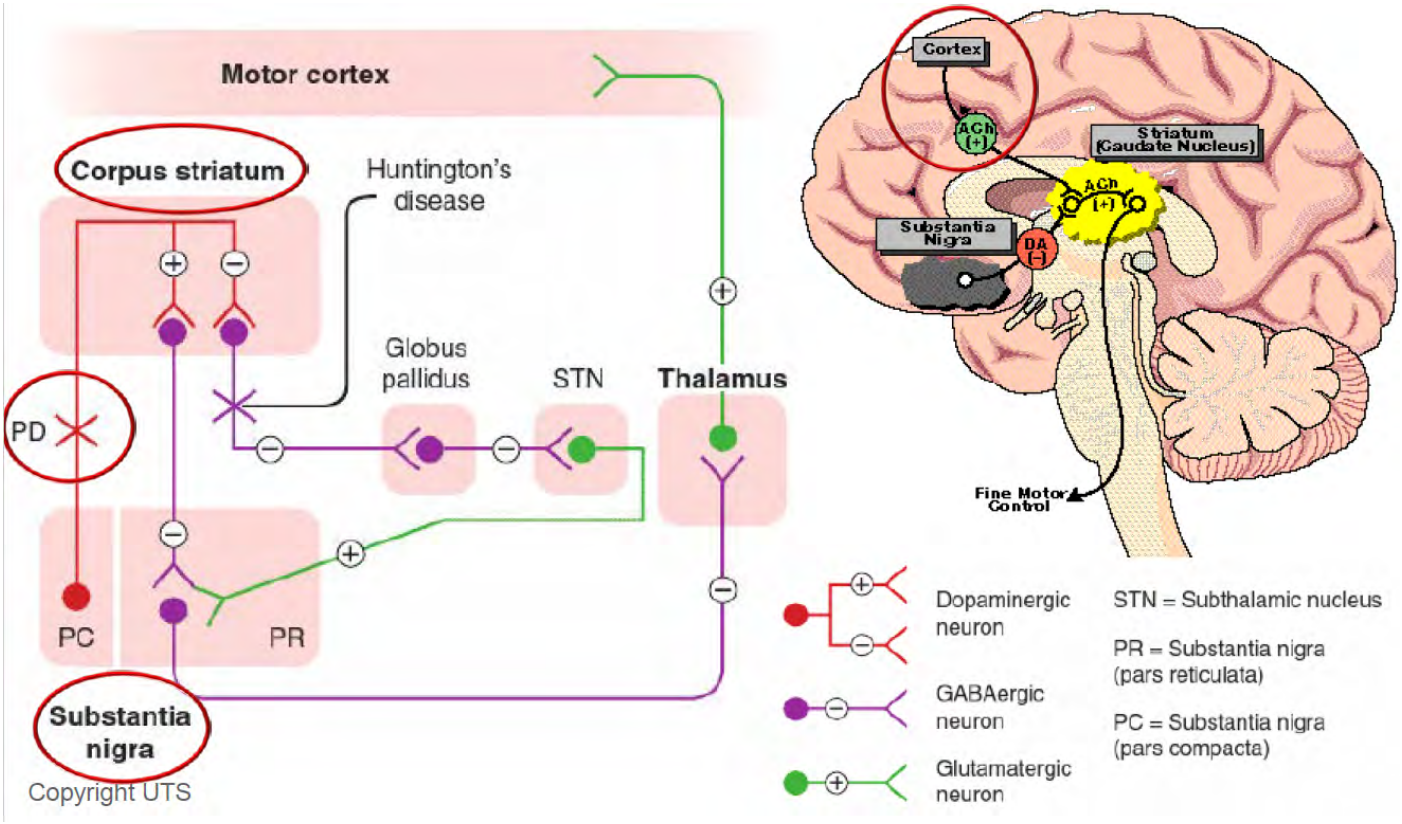
Transverse sections through the midbrain



Lewy body

http://members.fortunecity.com/danilhammoudim

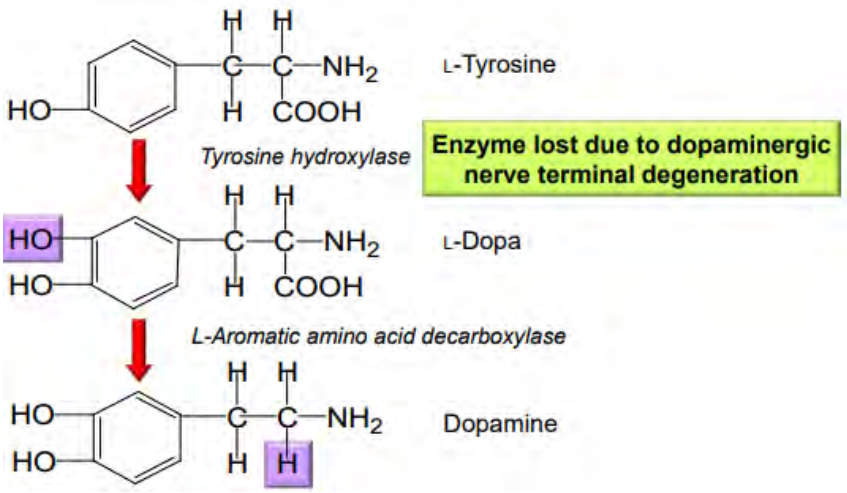
- Parkinsonism due to progressive degeneration of neurons in the substantia nigra and nigrostriatal pathway resulting in a decreased dopaminergic(DA) influence on striatal neurons
- Output from striatum regulates fine skeletal motor activity and depends upon balance of AChand DA activity.
    - Striatum receives:
        - Dopaminergic inhibitory innervation from substantia nigra
        - Cholinergic excitatory innervation from cortex and other brain areas
- Decrease in DA transmission is accompanied by reciprocal increase in cholinergic transmission



Regional Differences in Dopamine (DA) and Acetylcholine (ACh) Levels in Parkinsonism and Psychosis

Striatum	Limbic System	Parkinsonism	Side-effects
DA ACh	DA	Normal	Normal
DA ACh	DA	Dopamine Degeneration	(Similar to Parkinsonian Side-effects from Antipsychotic Drugs)
DA ACh	DA	L-Dopa or DA Agonist Therapy	Risk of Psychotic Side-effects
DA ACh	DA	OR Anticholinergic Drug Therapy	Dry mouth, urinary retention, constipation, blurred vision, postural hypotension

- **Outline the pharmacology and clinical uses of drugs in PD**
  - **Dopamine (DA) precursors**



Mechanism of action of levodopa:

- DA does not cross the BBB thus its amino acid precursor, levodopa (L-DOPA) is used
- Levodopa readily absorbed in GIT via active transport
- Levodopa crosses BBB by an amino acid carrier
  - But Levodopa metabolised by MAO_A in intestinal wall - low bioavailability
  - Peripheral conversion of levodopa to DA by peripheral Laromatic amino acid decarboxylase (dopa decarboxylase)
- Levodopa usually given with carbidopa (or benserazide)
  - Dopa decarboxylase inhibitors don't cross BBB, but will reduce peripheral conversion of levodopa
  - Permits about 75% reduction in dose (ca. 90% of levodopa now reaches CNS)

- Thus only 1-5% of dose actually reaches CNS and bind to D1 and D2 receptors

Therapeutic effectiveness

- Increases life expectancy due to improved motor function
- Does not cure PD, and responsiveness decreases with time (disease progression? receptor downregulation?)
- Deterioration in response to levodopa therapy occurs in 30- 50% of patients after 3-5 years

Unwanted Effects

- Dyskinesia – involuntary writhing movements; within 2 yrs of treatment; probably due to its short duration of action resulting in fluctuations in plasma concentration
- Rapid fluctuations in clinical state (sudden worsening of hypokinesia and rigidity followed by improvement of symptoms) - 'on-off' phenomena
  - Not seen in untreated PD patients or with other anti-PD drugs
  - Due to fluctuating plasma concentrations and to the inability of neurons to store dopamine as PD advances
  - Sustained-release preparations, or in combination with COMT inhibitors (entacapone) to inhibit dopamine inactivation in periphery
- Experienced initially but disappears after a few weeks
- Less common when levodopa is used with carbidopa since less L-dopa is used
- Anorexia, nausea and vomiting
  - Incidence of GI side effects without carbidopa are very high (80%)
  - With carbidopa they are less severe and less common (20%)
  - Treated with domperidone, a DA antagonist that does not target the basal ganglia

- Postural hypotension
- Psychological effects - anxiety, agitation, confusion, delusions, hallucination, depression, disorientation, insomnia, nightmares

Levodopa + dopa decarboxylase (DDC) inhibitor and drug interactions

Other drugs	Likely effect
Anticonvulsants	Decreased levodopa effect due to increased metabolism
Antipsychotics	Decreased levodopa effect due to blocking dopamine receptors
Antihypertensives	Increased risk of postural hypotension
Monoamine oxidase (MAO) inhibitors type A	Result in hypertensive crisis
MAO inhibitors type B	Increased nausea and CNS effects
Ferrous sulfate	Decrease absorption of levodopa + DDC inhibitor

- **DA agonists**

Non-ergot-derived dopamine agonists

- Pramipexole and ropinirole
  - D_2 and D_3 selective
  - Better tolerated
  - Do not show fluctuations efficacy
- Effective as first-line drugs
- Once daily preparation
- Same efficacy as levodopa/dopa-decarboxylase inhibitor
- Associated with less dyskinesia
- Can be given in combination with levodopa

Ergot-derived dopamine agonists: Bromocriptine, pergolide, cabergoline

- Orally active ergot derivatives acting on D1 and D2 receptors
- Mimic effects of DA on the pyramidal pathway
- Generally less effective than levodopa but useful in conjunction with levodopa to suppress incidence of ‘ on-off’ phenomenon
- Due to their unwanted side effects, they are replaced by non-ergot compounds

Unwanted effects

- Inhibition of lactation
- Vasoconstriction, ischemia, hypertension due to α agonism
- Flushing, hypotension due to α antagonism
- Uterine contraction
- Bromocriptine: nausea, vomiting, somnolence
- Cabergoline and pergolide: cardiac valvular and pulmonary fibrosis
  - maybe irreversible
  - Suspected in patients taking the drug for ≥ 6 months or at high doses
- Pramipexole and ropinirole: somnolence, hallucinations, compulsive behaviours (gambling, eating, sex)

- **Drugs that inhibit DA breakdown**