ANTIPARKINSONIAN DRUGS

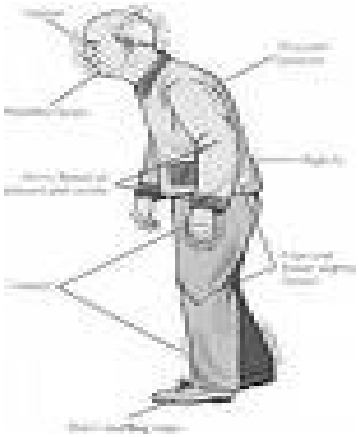
DRUGs ACT ON CNS

(Pharmacology)

Unit-5(8)

Parkinsonism (PD)

- Extrapyramidal motor function disorder characterized by
  - Rigidity
  - Tremor
  - Hypokinesia/Bradykinesia



  - Impairment of postural balance - falling

Parkinsonism (PD) – contd.

- Rigidity
  - Increased resistance to passive motion when limbs are moved through their range of motion – normal motions
    - **"Cogwheel rigidity"** -- Jerky quality – intermittent catches of movement
    - Caused by sustained involuntary contraction of one or more muscles
      - Muscle soreness; feeling tired & achy
      - Slowness of movement due to inhibition of alternating muscle group contraction & relaxation in opposing muscle groups

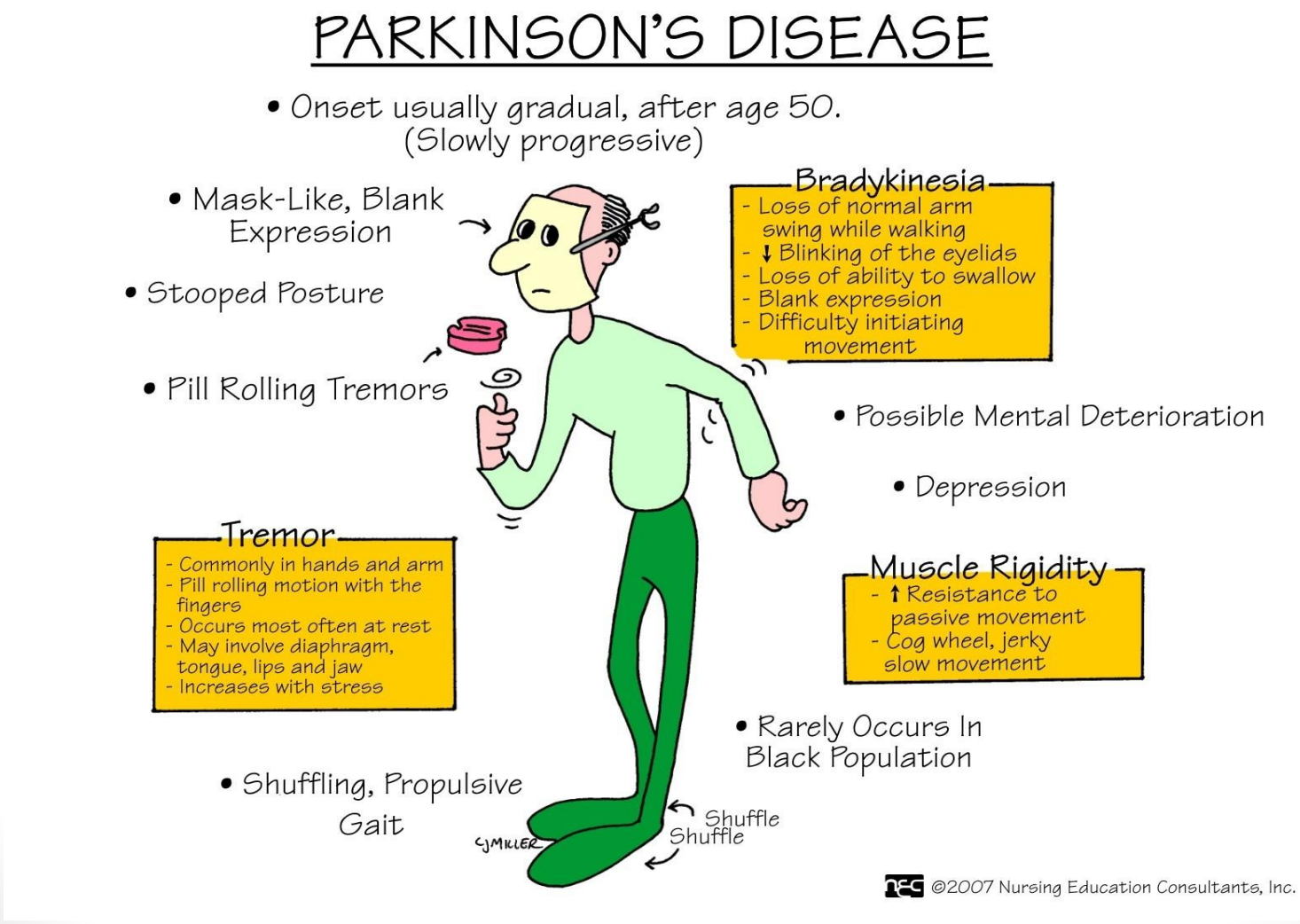
Parkinsonism (PD) – contd.

- Tremor
  - First sign
  - Affects handwriting – trailing off at ends of words
  - More prominent at rest
  - Aggravated by emotional stress or increased concentration
  - “Pill rolling” – rotary motion of thumb and forefinger
  - NOT essential tremor – intentional

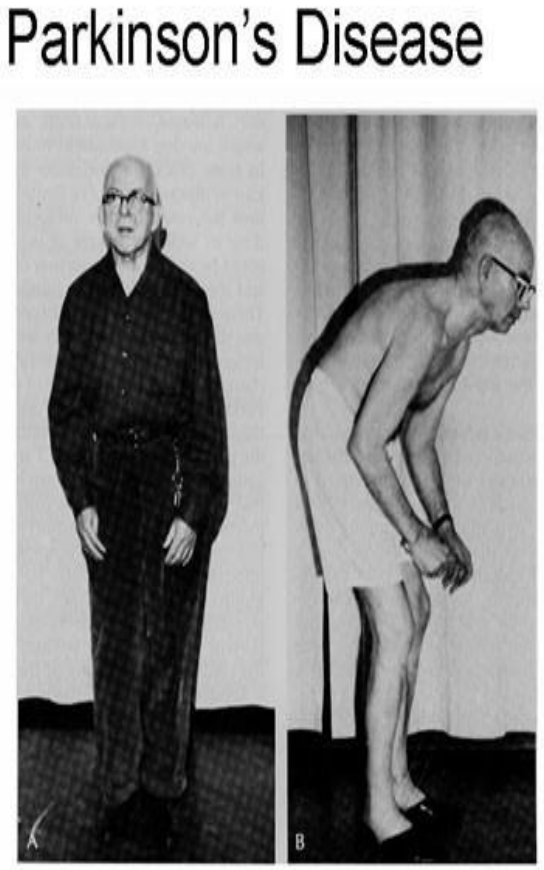
Parkinsonism (PD) – contd.

- Bradykinesia
  - Loss of automatic movements:
    - Blinking of eyes, swinging of arms while walking, swallowing of saliva, self-expression with facial and hand movements, lack of spontaneous activity, lack of postural adjustment
    - Results in: stooped posture, masked face, drooling of saliva, shuffling gait (festinating); difficulty initiating movement

Parkinsonism (PD) - signs



Parkinsonism (PD) - signs

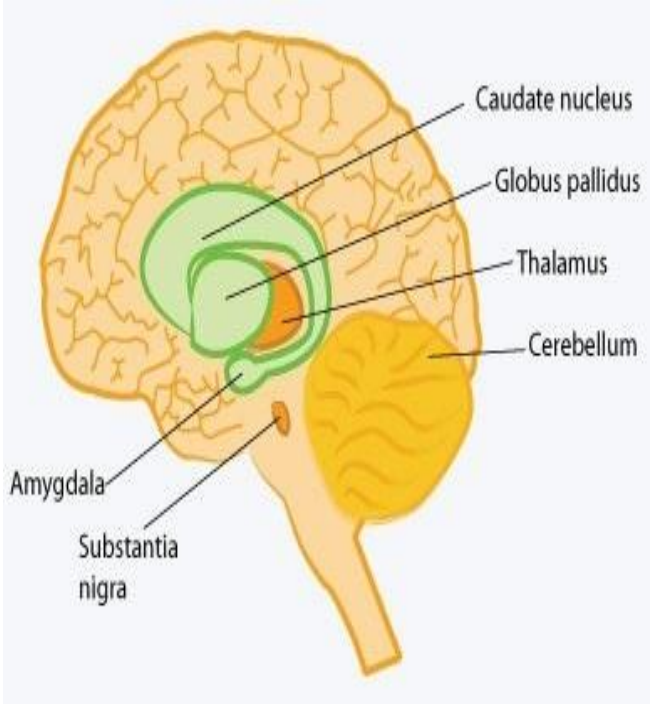


History – Parkinson`s disease

- Parkinson's disease was first formally described in "An Essay on the Shaking Palsy," published in 1817 by a London physician named James Parkinson, but it has probably existed for many thousands of years. Its symptoms and potential therapies were mentioned in the Ayurveda, the system of medicine practiced in India as early as 5000 BC, and in the first Chinese medical text, Nei Jing, which appeared 2500 years ago

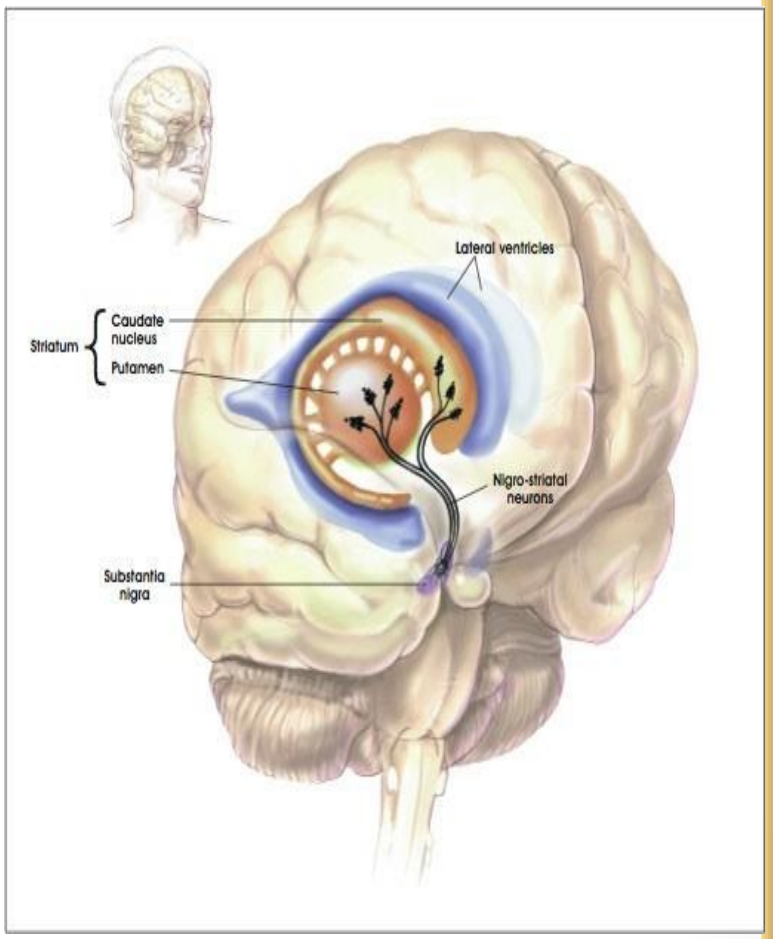
Parkinson`s disease - Pathophysiology

- The Basal Ganglia Consists of Five Large Subcortical Nuclei that Participate in Control of Movement:
  - Caudate Nucleus
  - Putamen
  - Globus Pallidus
  - Subthalamic Nucleus
  - Substantia Nigra



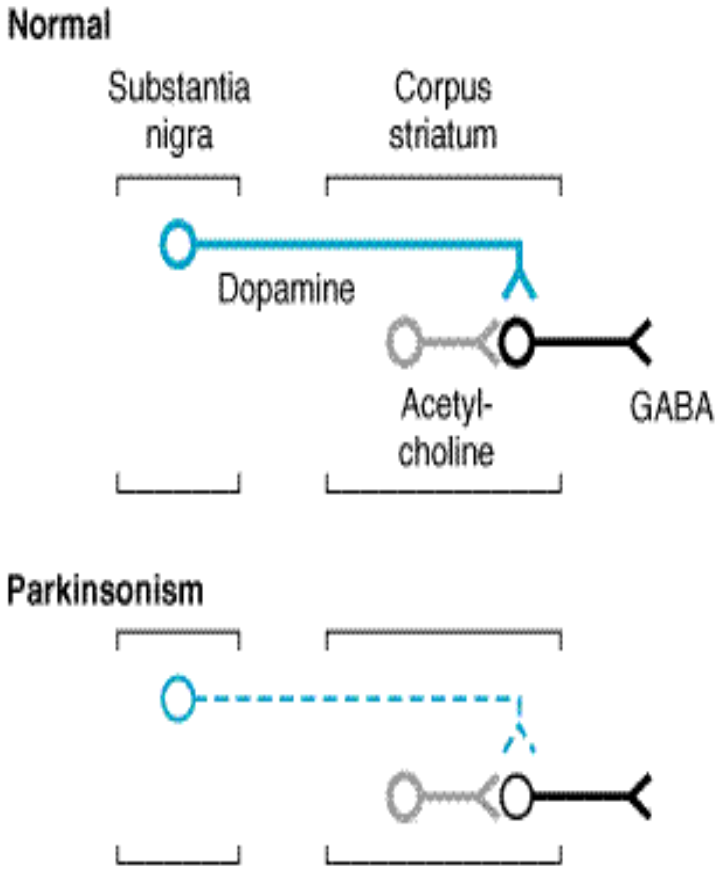
PD, Pathophysiology – contd.

- Striatum – Caudate Nucleus and Putamen
- Substancia nigra pars compacta provide DA innervation to striatum



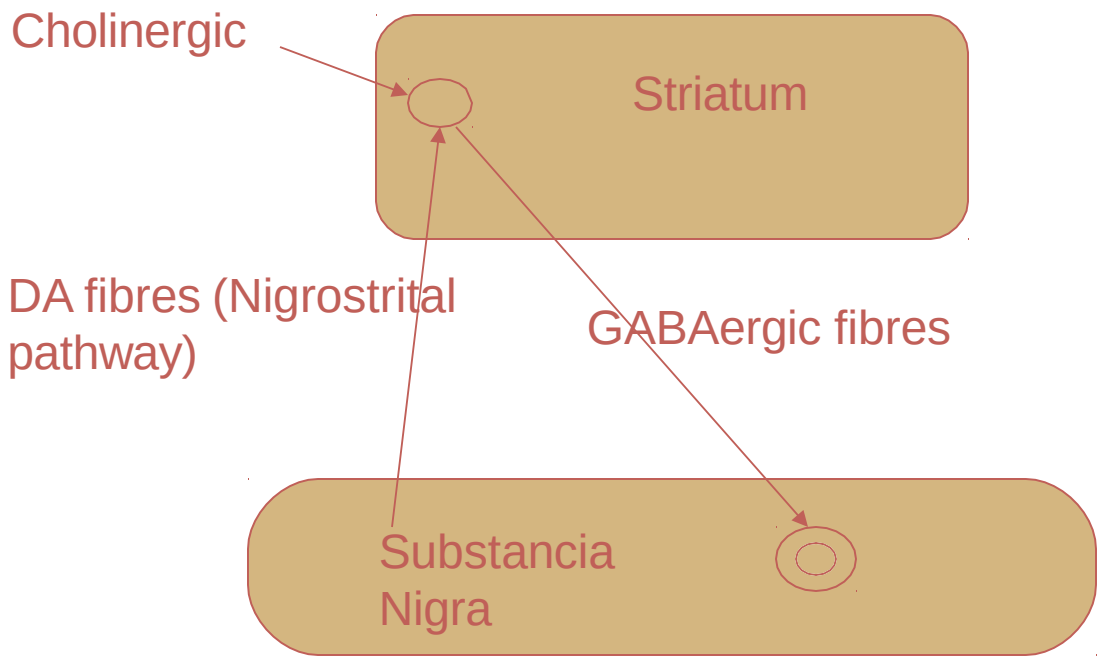
PD, Pathophysiology – contd.

- Degeneration of neurones in the substantia nigra pars compacta
- Degeneration of nigrostriatal (dopaminergic) tract
- Results in deficiency of Dopamine in Striatum - >80%



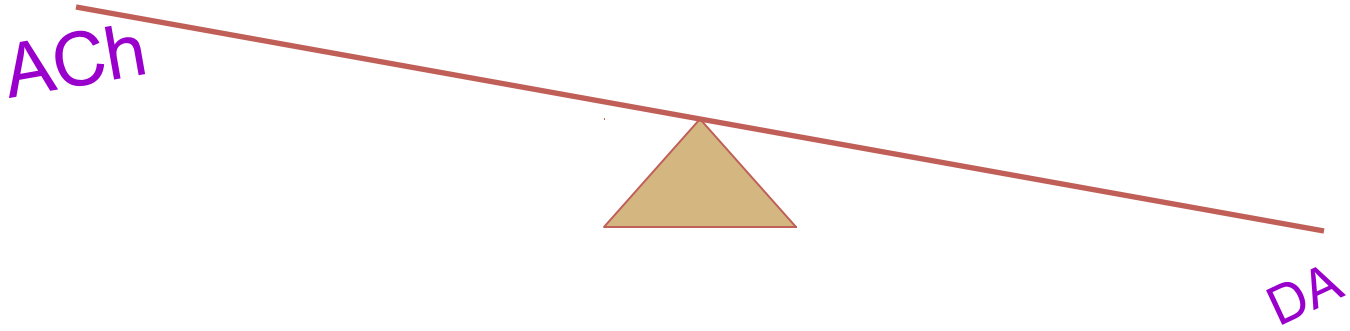
PD, Pathophysiology – contd.

- Disruption of balance between Acetylcholine and Dopamine:



PD, Pathophysiology – contd.

- Imbalance primarily between the excitatory neurotransmitter Acetylcholine and inhibitory neurotransmitter Dopamine in the Basal Ganglia



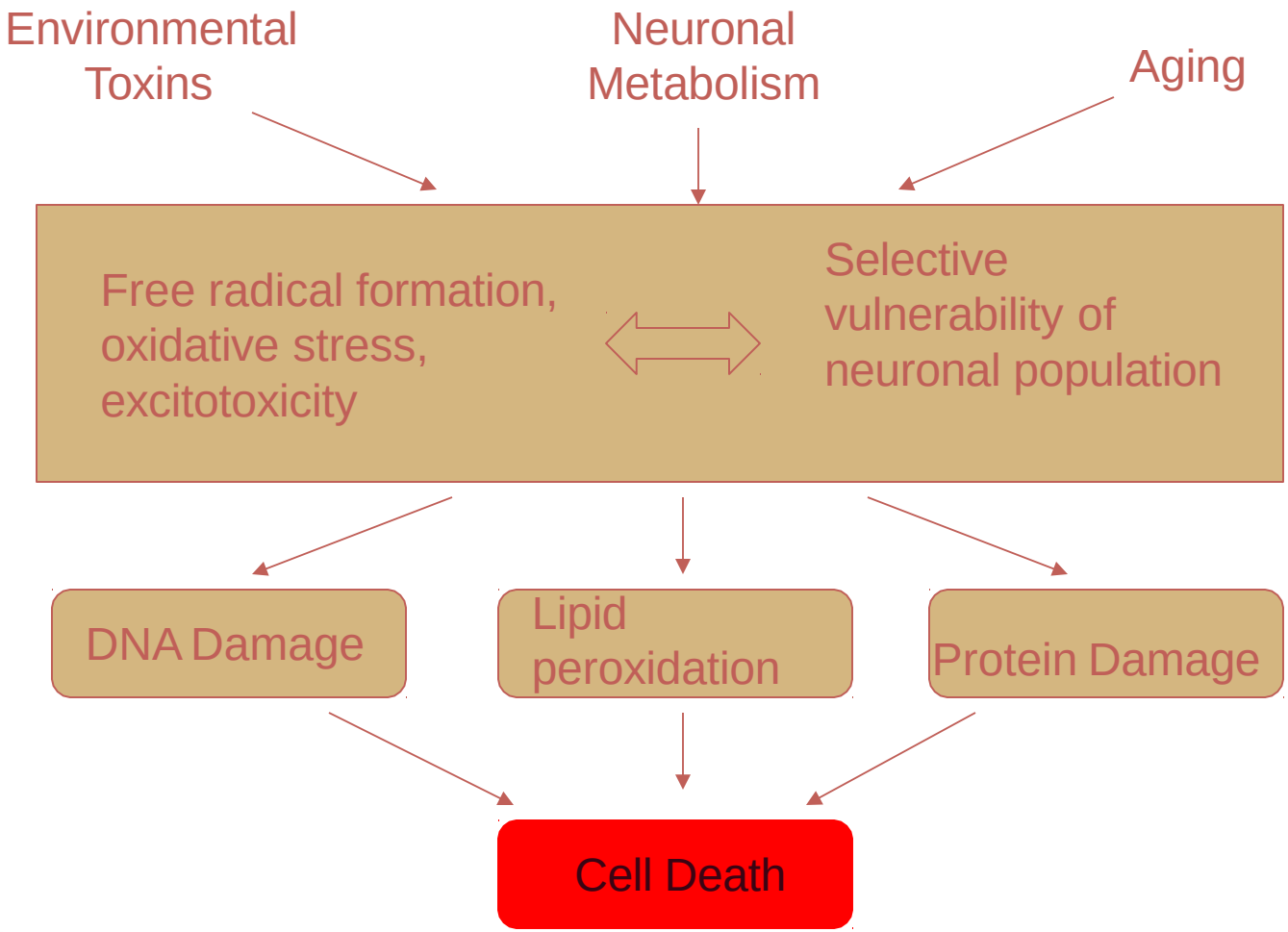
PD - Etiology

- Oxidation of DA by MAO B and aldehyde dehydrogenase – free radical (OH) in presence of Iron
  - Normally quenched by glutathione
  - Age related changes/or acquired defects – damages DNA and lipid membranes
- Common factors:
  - Cerebral atherosclerosis
  - Viral encephalitis
  - Side effects of several antipsychotic drugs (i.e., phenothiazides, butyrophenones, reserpine)
  - Pesticides, herbicides, industrial chemicals - contain substances that inhibit complex I in the mitochondria

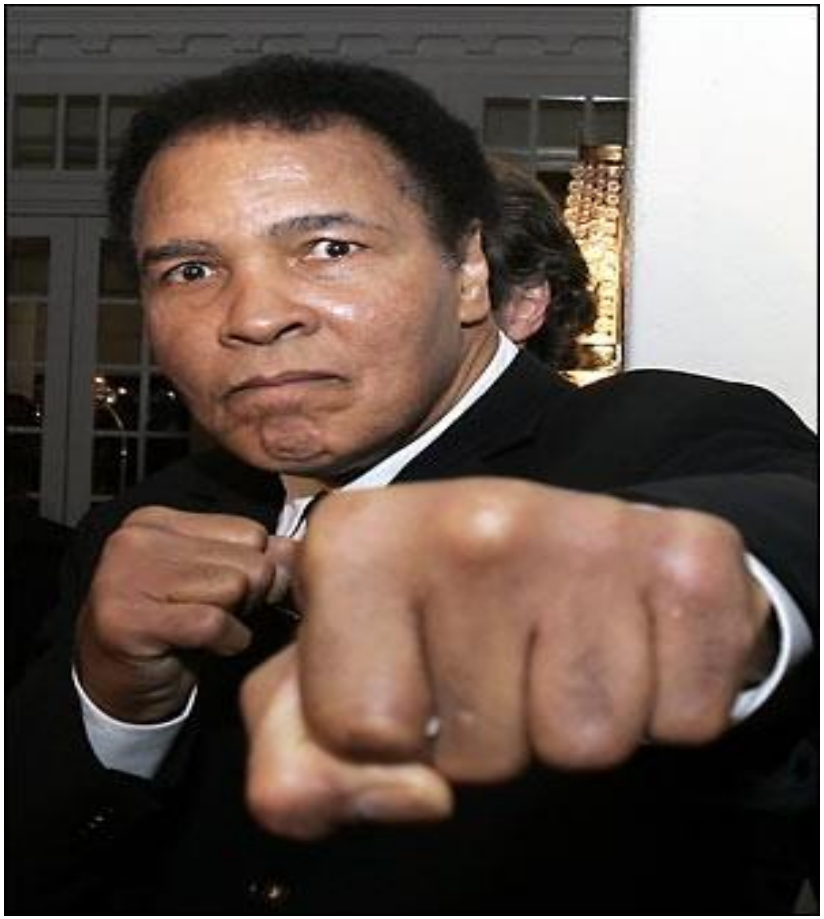
Etiology of PD – contd.

- Genetic:
  - α-sinuclein (synaptic protein)
  - Parkin (a ubiquitin protein ligase)
  - UCHL1
  - DJ-1 protein
- Environmental triggers:
  - Infectious agents – Encephalitis lethargica (epidemc)
  - Environmental toxins - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
  - Acquired Brain Injury
- Excitotoxicity
  - Glutamate, the normal excitatory transmitter in neurones in excess
  - Mediated by activated NMDA receptor
  - Ca++ overload – destructive processes
- Energy metabolism and aging:
  - Reduction in function of complex 1 of mitochondrial-electron transport chain
  - MPTP
- Oxidative stress: Free radicals (`OH) – hydrogen peroxide and oxyradicals

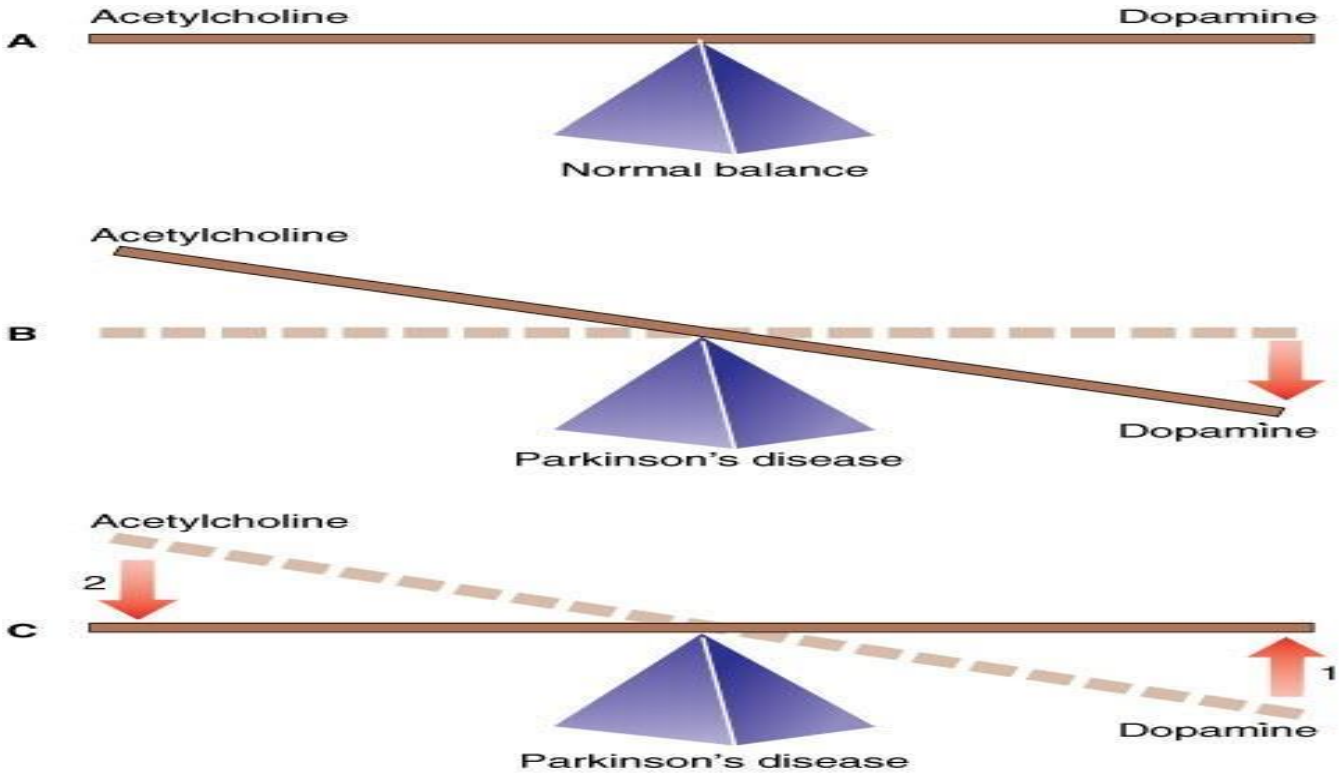
PD - Mechanism



The Fighting agents (Drugs)



Treatment of PD



A, Normal balance of acetylcholine and dopamine in the CNS.
B, In Parkinson's disease, a decrease in dopamine results in an imbalance.
C, Drug therapy in Parkinson's disease is aimed at correcting the imbalance between acetylcholine and dopamine. This can be accomplished by either
1. increasing the supply of dopamine or
2. blocking or lowering acetylcholine levels.

Fig. 14-1. The neurotransmitter abnormality of Parkinson's disease.

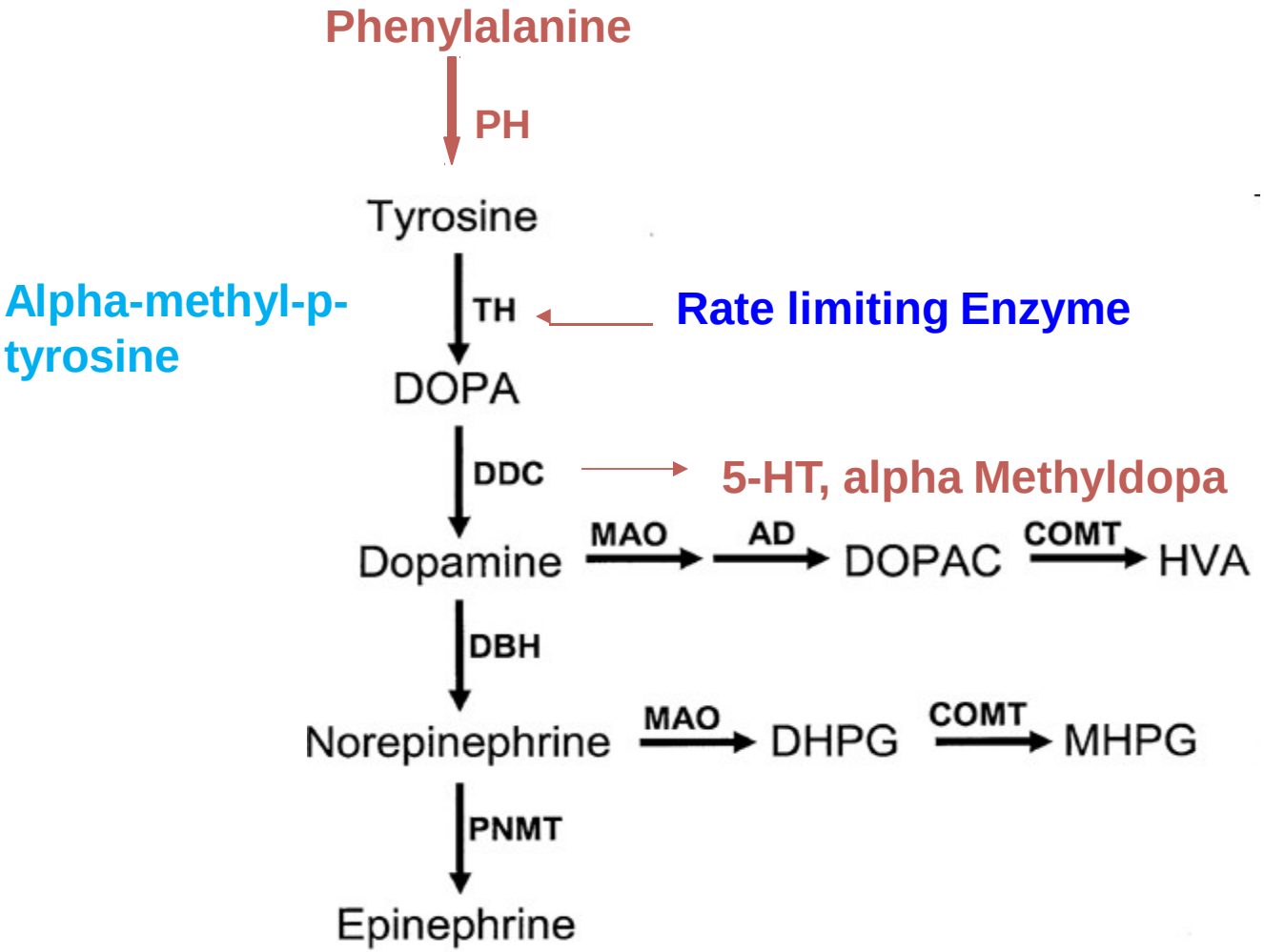
Classification of antiparkinsonian Drugs:

- Drugs acting on dopaminergic system:
  - Dopamine precursors – *Levodopa (l-dopa)*
  - Peripheral decarboxylase inhibitors – *carbidopa and benserazide*
  - Dopaminergic agonists: *Bromocriptyne, Ropinirole and Pramipexole*
  - MAO-B inhibitors – *Selegiline, Rasagiline*
  - COMT inhibitors – *Entacapone, Tolcapone*
  - Dopamine facilitator - *Amantadine*
- Drugs acting on cholinergic system
  - Central anticholinergics – *Teihexyphenidyl (Benzhexol), Procyclidine, Biperiden*
  - Antihistaminics – *Orphenadrine, Promethazine*

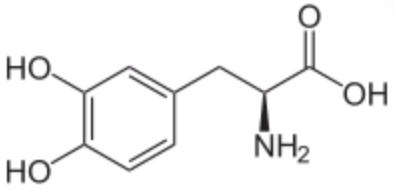
Antiparkinsonian Drugs – contd.

- Dopamine and Tyrosine Are Not Used for Parkinson Disease Therapy, Why?
  - Dopamine Doesn't Cross the Blood Brain Barrier
  - Huge amount of tyrosine decreases activity of rate limiting enzyme Tyrosine Hydroxylase

Biosynthesis of Catecholamines



Individual Drugs

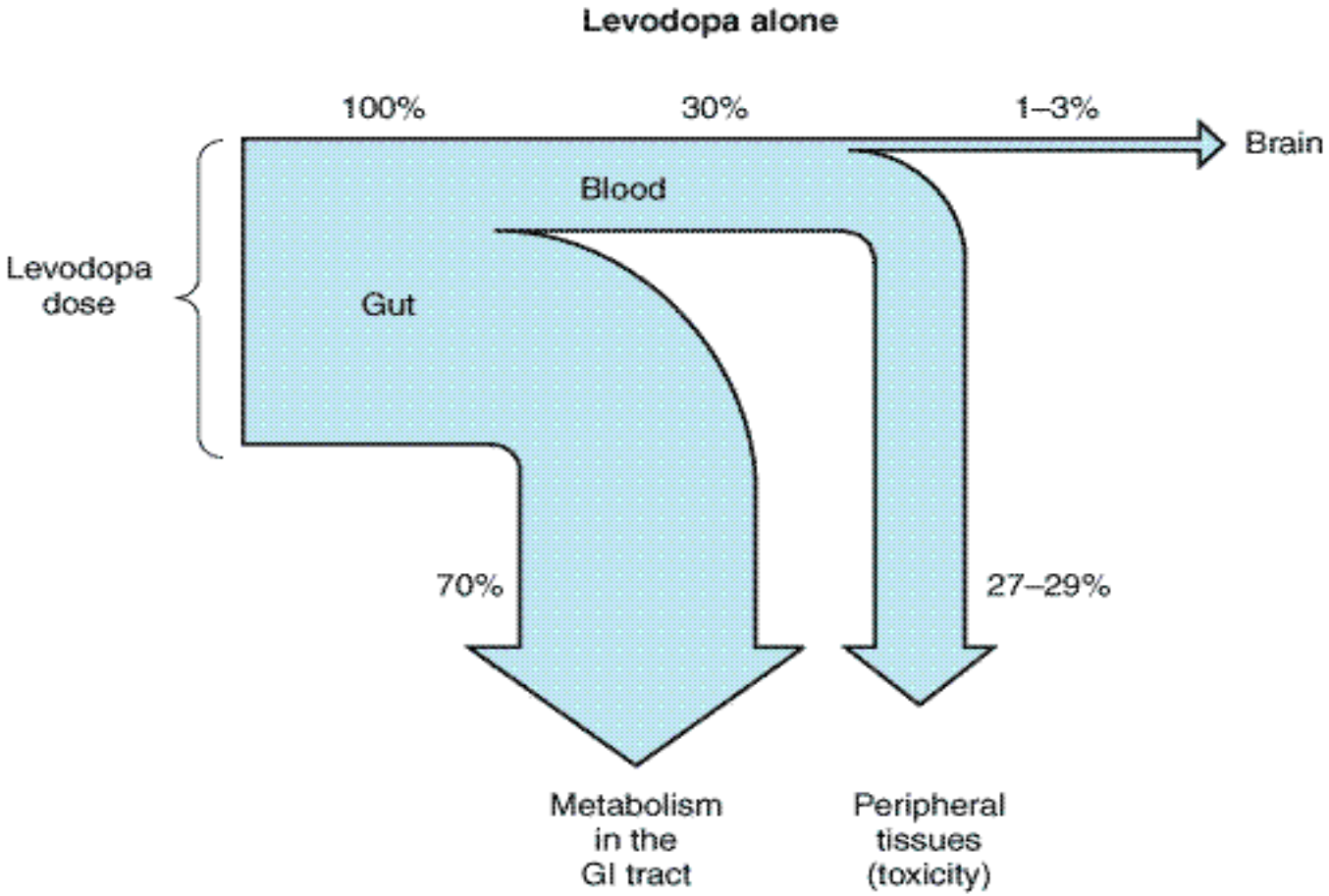


- Levodopa:
  - Single most effective agent in PD
  - Inert substance – decarboxylation to dopamine
  - 95% is decarboxylated to dopamine in gut and liver
  - 1 - 2% crosses BBB, taken up by neurones and DA is formed

Levodopa - Pharmacokinetics

- Absorbed rapidly from small intestine – aromatic amino acid transport system
- High First Pass Effect – large doses
- Peak plasma conc. 1-2 hrs and half life - 1 to 3 Hrs
- Depends on gastric emptying and pH
- Competition for amino acids present in food competes for the carrier
- Metabolized in liver and peripherally - secreted in urine unchanged or conjugated with glucoronyl sulfate
- Central entry into CNS (1%) - mediated by membrane transporter for aromatic amino acids – competition with dietary protein
- In CNS – Decarboxylated and DA is formed – therapeutic effectiveness
- Transport back by presynaptic uptake or metabolized by MAO and COMT

Levodopa (Pharmacokinetics) – contd.



Levodopa (Pharmacological actions)

- CNS:
  - Effective in Eliminating Most of the Symptoms of Parkinson Disease
  - Bradykinesia and Rigidity Respond Quickly
  - Reduction in Tremor Effect with Continued therapy
  - Handwritting , speech, facial expression and interest in life improves gradually
  - L Dopa less Effective in Eliminating Postural Instability and Shuffling Gait Meaning Other Neurotransmitters Are Involved in Parkinson Disease

Levodopa (Pharmacological actions) - contd

- CVS:
  - Cardiac Stimulation Due to Beta adrenergic effect on Heart - Propranolol produces
  - Though stimulates peripheral adrenergic receptor – no rise in BP
  - Orthostatic Hypotension - some individuals – central DA and NA action
  - In elderly cardiovascular problems - transient tachycardia, cardiac arrhythmias and hypertension
  - Tolerance to CVS action develops within few weeks
- CTZ: DA receptors cause stimulation – nausea and vomiting – tolerance
- Endocrine: Decrease in Prolactin level and increase in GH release

Levodopa (adverse effects) -Initial Therapy:

- Nausea and vomiting - 80% of patients (CTZ outside BBB)
- Postural hypotension – 30 % of patients tolerance develops (Central alpha-2 action)
- Cardiac arrhythmias - due to beta adrenergic action
- Exacerbation of angina

Levodopa (adverse effects) - Initial Therapy:

- Abnormal movements: Facial tics, grimacing, tongue thrusting, choreoathetoid movements
- Behavioural effects:
  - 20 to 25% of Population
  - Trouble in Thinking (Cognitive Effects)
  - L Dopa can induce: Anxiety, psychosis, confusion, hallucination, delusion
  - Hypomania - Inappropriate Sexual Behavior; "Dirty Old Man", "Flashers“

    - *Drug Holiday*

Levodopa (Pharmacological actions) - contd.

- Behavioural Effects:
  - Partially Changes Mood by elevating mood, and increases Patient sense of well being
  - General alerting response
  - Disproportionate increase in sexual activity
  - No improvement in dementia

Levodopa (adverse effects) - Prolonged therapy – contd.

- Fluctuation in Motor Performance:
  - Initial therapy – each dose - good duration of action
  - Prolonged therapy – "*buffering"* capacity is lost – each dose causes fluctuation of motor state - each dose has short duration of action– short therapeutic effect (1 – 2 Hrs) – bradykinesia and rigidity comes back quickly
  - Increase in dose and frequency – DYSKINESIA – excessive abnormal involuntary movements
  - Dyskinesia often with high plasma conc. of levodopa
  - Dyskinesia = Bradykinesia and Rigidity in terms of patient comfortness
  - "On/off" Phenomenon
  - Like a Light Switch: Without Warning

Levodopa (adverse effects) - Prolonged therapy – contd.

- Denervation Supersensitivity:
  - In Basal Ganglia – destruction of Dopaminergic Neurons –increase in Dopamine Receptors postsynaptically
  - L Dopa Therapy - increase Dopamine at synaptic Cleft - but too many Receptors - *Denervation Supersensitivity*
  - Effect - Increased Postsynaptic Transmission
  - Initial disappearance of Parkinson Syndrome
  - Onset of Dyskinesia

Levodopa – Drug Interactions

- *Pyridoxine* – abolishes therapeutic effect of levodopa
- *Antipsychotic Drugs* – Phenothiazines, butyrophenones block the action of levodopa by blocking DA receptors.
- Antidopeminergic – domperidone abolishes nausea and vomiting
- *Reserpine* – blocks levodopa action by blocking vesicular uptake
- *Anticholinergics* – synergistic action but delayed gastric emptying – reduced effect of levodopa
- *Nonspecific MAO Inhibitors* – Prevents degradation of peripherally synthesized DA – hypertensive crisis by the tyramine-cheese effect (tyramine is found in cheese, coffee, beer, pickles and chocolate), when given to a person taking a MAO Inhibitor - tyramine is not broken down - tremendous release of Norepinephrine)

Classification of antiparkinsonian Drugs:

- Drugs acting on dopaminergic system:
  - Dopamine precursors – *Levodopa (l-dopa)*
  - Peripheral decarboxylase inhibitors – *carbidopa and benserazide*
  - Dopaminergic agonists: *Bromocriptyne, Ropinirole and Pramipexole*
  - MAO-B inhibitors – *Selegiline, Rasagiline*
  - COMT inhibitors – *Entacapone, Tolcapone*
  - Dopamine facilitator - *Amantadine*
- Drugs acting on cholinergic system
  - Central anticholinergics – *Teihexyphenidyl (Benzhexol), Procyclidine, Biperiden*
  - Antihistaminics – *Orphenadrine, Promethazine*

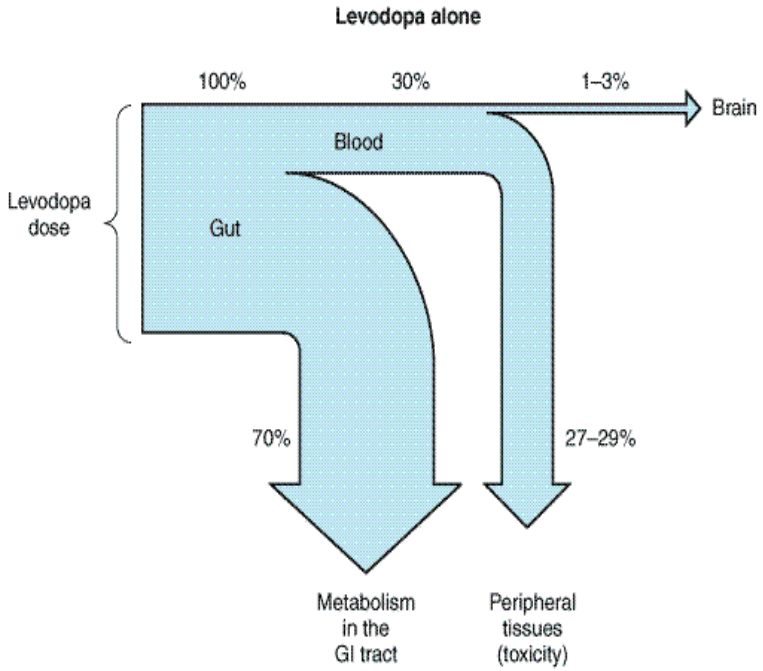
Levodopa and Peripheral decarboxylase inhibitors combined – Why ??

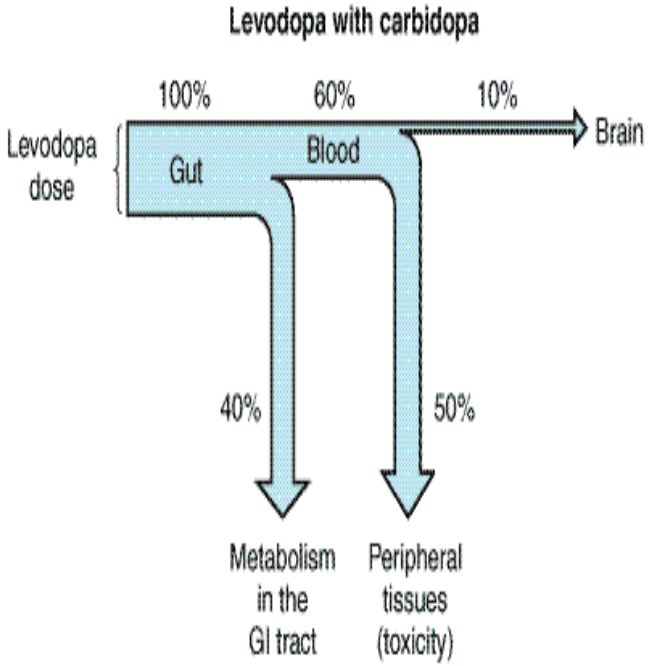
- Carbidopa and Benserazide:
  - In practice, almost always administered
  - Do not penetrate BBB
  - Do not inhibit conversion of l-dopa to DA in brain
  - Co-administration of Carbidopa - will decrease metabolism of l-dopa in GI Tract and peripheral tissues - increase l-dopa conc in CNS - meaning decrease l-dopa dose and also control of dose of l-dopa

Levodopa and Peripheral decarboxylase inhibitors – contd.

- Benefits:
  - Plasma $t_{1/2}$ – prolonged
  - Dose of levodopa – 30% reduction
  - Reduction in systemic complications
    - Nausea and Vomiting – less
  - Cardiac – minimum complications
  - Pyridoxine reversal of levodopa – do not occur
  - On/Off effect – minimum
  - Better overall improvement of patient – even in non responding patients to levodopa

Levodopa Vs Peripheral decarboxylase inhibitors – contd.





Dopamine receptors agonists

- **D1 and D2 receptors express differentially – different areas of brain**
  - D1 is excitatory (cAMP and PIP3)
  - D2 is inhibitory (Adenylyl cyclase and K+ and Ca++ Channels)
  - Both present in striatum – involved in therapeutic response of levodopa
  - **Stimulation of Both – smoothening movement and reduced muscle tone**
- **Bromocriptine, pergolide, Ropinirole and Pramipexole:**
  - Bromocryptine – potent D2 agonist and D1 partial agonist and antagonist
  - Pergolide – Both D1 and D2 agonist
  - Newer (Pramipexole and Ropinirole) – D2 and D3 effect with low D1 effect

Bromocriptine – Synthetic ergot derivative

- Basically used in hyperprolactinemia and acromegally
- Levodopa like action in CNS
- Quick improvement of PD symptoms and longer lasting (1 hr and 6-10 Hrs)
- Monotherapy:
  - High doses and expensive
  - Intolerable side effects – vomiting, hallucinations, hypotension (1st dose) and nasal stuffiness
- Uses: late cases as supplement to levodopa – 1.25 mg OD at night and increasing upto 5-10 mg tds
- Benefits:
  - End of Dose phenomenon smoothening and less “on-off” phenomenon
  - Also less DYSKINESIA

Ropinirole and Pramipexole

- Newer agents with selective D2/D3 agonist property with low D1 activity
- Like Bromocriptine, both are well absorbed orally
- Similar therapeutic action and used in advance cases as supplementary drugs
- Advantages over Bromocriptine
  - less GIT symptoms (vomiting)
  - Dose titration for maximum improvement in 1-2 weeks
- Started using as monotherapy – comparable efficacy with levodopa
  - Supplementary levodopa is not required (but with Bromocriptine)
  - Meta analysis – slower degeneration

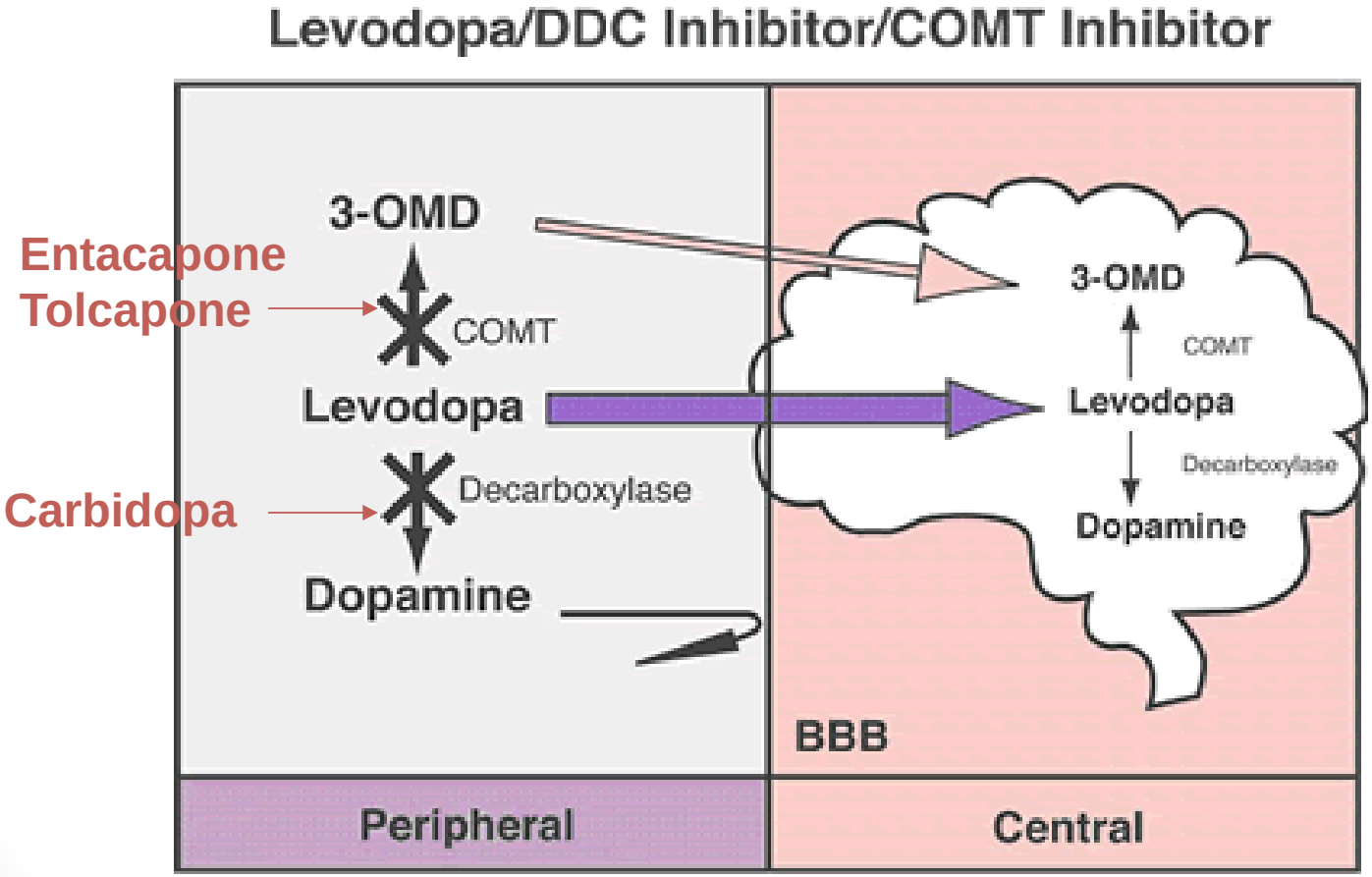
Ropinirole and Pramipexole – contd.

- Adverse effects
  - Nausea, dizziness, postural hypotension and hallucination
  - Episodes of day time sleep
- Restless leg syndrome

Dopamine receptors agonists – contd.

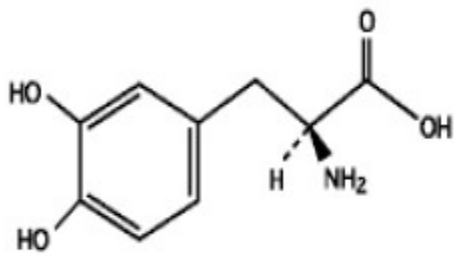
- Newer Vs Older DA receptor agonists
  - More tolerable – Nausea, vomiting and fatigue
  - Dose titration - Slow upward adjustment of dose
  - Newer ones – Somnolence (Irresistible Sleepiness)
- Initial treatment of PD: Newer drugs are used now:
  - Longer duration of action than L-dopa – less chance of on/off effect and dyskinesia
  - No oxidative stress and thereby loss of dopaminergic neurons
  - Reduced rate of motor fluctuation
  - Restless leg syndrome/Wittmaack-Ekbom's syndrome/the jimmylegs - Ropinirole

COMT inhibitors: Entacapone and Tolcapone



Entacapone and Tolcapone – contd.

- Reduce wearing off phenomenon in patients with levodopa and carbidopa
- Common adverse effects similar to levodopa
- Entacapone:
  - Peripheral action on COMT
  - Duration of action short (2 hrs)
  - No hepatoxicity

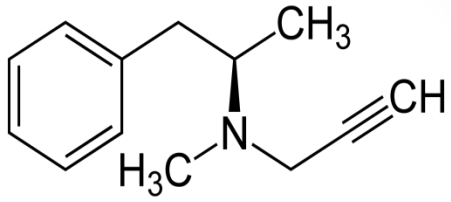


- Tolcapone:
  - Central and peripheral inhibition of COMT
  - Long duration of action – 2 to 3 times daily
  - Hepatoxicity (2%)
- Both are available in fixed dose combinations with levodopa/carbidopa

MAO-B inhibitors: Selegiline

- Selective and irreversible MAO-B inhibitor
- MAO-A and MAO-B are present in periphery and intestinal mucosa – inactivate monoamines
- MAO-B is also present in Brain and platelets
- Low dose of Selegiline (10 mg) – irreversible inhibition of the enzyme
  - Does not inhibit peripheral metabolism of dietary amines, so safely levodopa can be taken
  - No lethal potentiation of CA action – no cheese reaction, unlike non-specific inhibitors
  - Dose more than 10 mg – inhibition of MAO-A should be avoided.

Selegiline – contd.



- Selegiline can be used alone in mild early PD
- Adjunct to levodopa in early cases - benefits
  - Prolong levodopa action
  - Reduction in dose of levodopa
  - Reduces motor fluctuations
  - Decreases *wearing off* phenomenon
  - Advance cases of *on/off – not improved*
  - Levodopa side effects (hallucinations) etc, worsens
- Neuroprotective properties – protect dopamine from free radical and oxidative stress
- Protects from MPTP induce parkinsonism

Central Anticholinergics: Teihexyphenidyl (Benzhexol), Procyclidine, Biperiden

- These are the Drugs with higher *central : peripheral* anticholinergic action than Atropine
- Reduce unbalanced cholinergic activity in striatum
- Duration af action is 4-8 Hrs
- Tremor is benefited more than rigidity – least to hypokinesia
- Overall activity is lower than levodopa
- Used alone in mild cases and when levodopa is contraindicated
- Combination with levodopa to reduce its dose
- Also used in Drug Induced Parkinsonism
- Antihistaminic like Orphenadrine, Promethazine are used in PD for their anticholinergic action

Dopamine facilitators: Amantadine

- Antiviral agent
- Several pharmacological action
- Alter the dopamine release in striatum and has anticholinergic properties
- Blocks NMDA glutamate receptors
- Used as initial therapy of mild PD
- Also helpful in dose related fluctuations and dyskinesia
- Dose is 100 mg twice daily
- Dizziness, lethargy and anticholinergic effects – mild side effects

Drug Induced Parkinsonism:

- Antipsychotics: Chlorpromazine, Fluphenzine and Haloperidol
- Antihypertensive like Reserpine
- Antiemetics: Metochlopramide (Reglan) and Prochlorperazine (Compazine),
- Not associated with loss of nerve cells in the substantia nigra
- Differ from the permanent PD associated with the nerve toxin MPTP - loss of nerve cells in the substantia nigra.

Points to remember:

- None of the present drugs alter basic pathology of PD
- Initiation of levodopa therapy should be delayed as far as possible
- Monotherapy with Selegiline or anticholinergics or amantadine - in mild cases. Newer Drugs like Ropirinole etc. can also be used
- In deterioration phase – levodopa and carbidopa combination, not levodopa alone. Slow and careful initiation
- Benefit from drug therapy *wears off* – *dyskinesia* develops. Later on/off phenomenon develops – patient problem becomes same as with drugs or without drugs
- Peripheral decarboxylase inhibitors decreases early, but not late complications
- DA agonists like Ropinirole are used to supplement levodopa to prevent on/off phenomenon and reduce levodopa dose
- COMT inhibitors like entacapone are added to levodopa carbidopa to prolong their action and to reduce on/off

Newer Fields:

- Neurotrophic proteins--These appear to protect nerve cells from the premature death that prompts Parkinson's. One hurdle is getting the proteins past the blood-brain barrier.
- Neuroprotective agents--Researchers are examining naturally occurring enzymes that appear to deactivate "free radicals,"
- Neural tissue transplants
- Genetic engineering--Scientists are modifying the genetic code of individual cells to create dopamine-producing cells from other cells, such as those from the skin

Thanking you