Drugs used in parkinsonism

By

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Pharmacology unit

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ILOs:

At the end of this lecture you will be able to:-

- ***Recognize the symptoms and pathophysiology of parkinsonism***
- ***Understand the pharmacology of drugs used for treatment of parkinsonism.***
- ***Define pharmacokinetics, pharmacodynamics and side effects of different drugs used for the treatment of parkinsonism.***

Parkinson's Disease

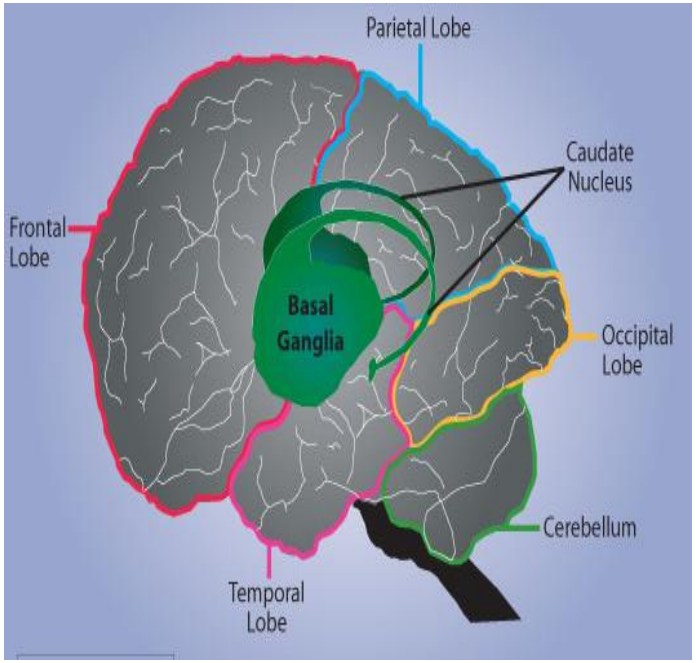
A progressive neurological disorder that occurs mainly in the elderly and can lead to disability unless effective treatment is provided.

Characters of Parkinson's disease:

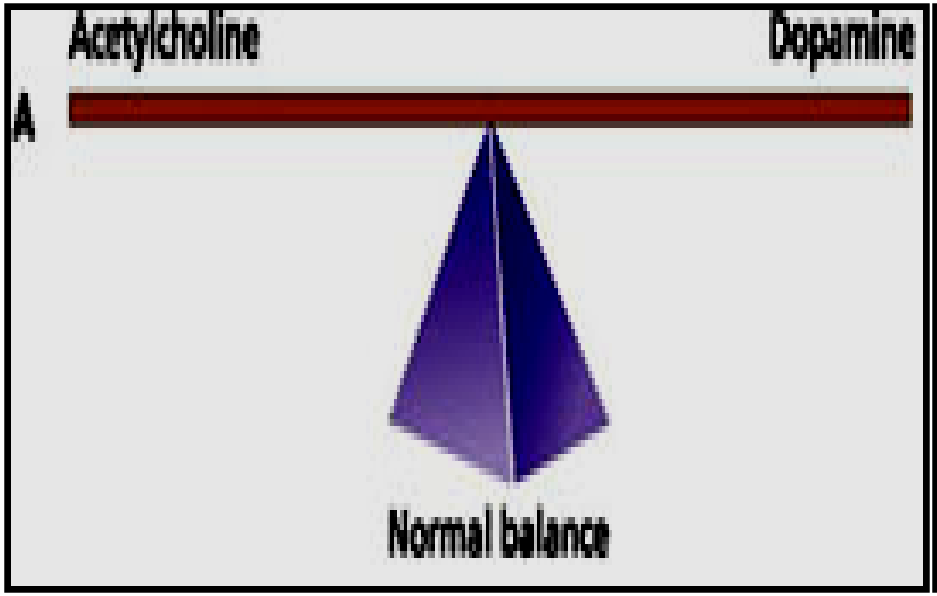
- simplified by the acronym **"TRAP"**
- **Tremors at rest**
- **Rigidity of muscles**
- **Akinesia or Bradykinesia** (slowness in initiating and carrying out voluntary movements)
- **Postural and gait abnormalities**
- **Anxiety or depression**

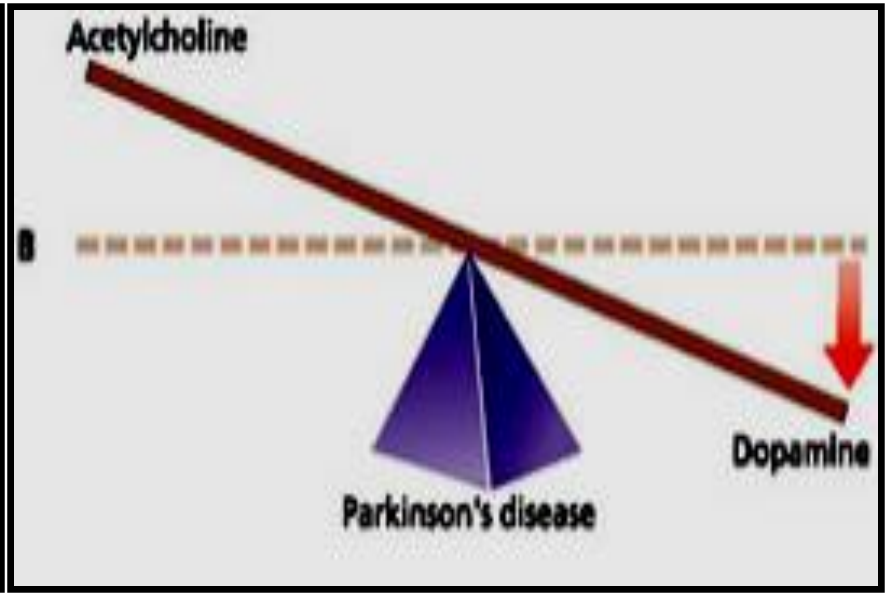
Pathphysiology of Parkinson's disease

This movement disorder occurs mainly due to dopamine/acetylcholine imbalance in basal ganglia (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control.



Parkinson’s disease





Parkinson’s disease

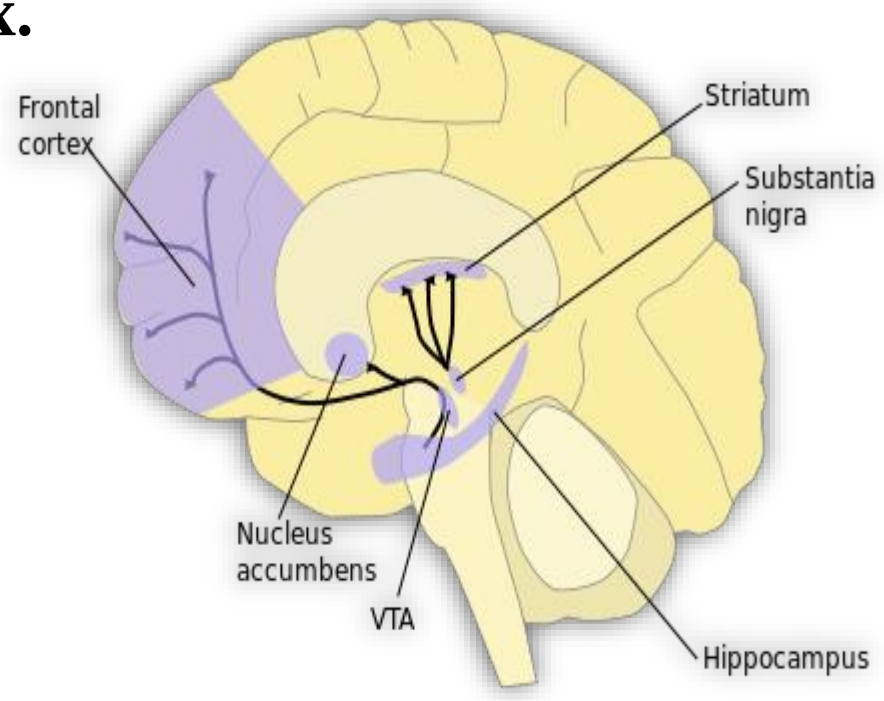
- **Deficiency of dopamine**
- **Predominance of Ach**

Dopamine Pathways

Reward pathway:

dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex.

Motor pathway: cell bodies in the substantia nigra that manufacture and release dopamine into the striatum.

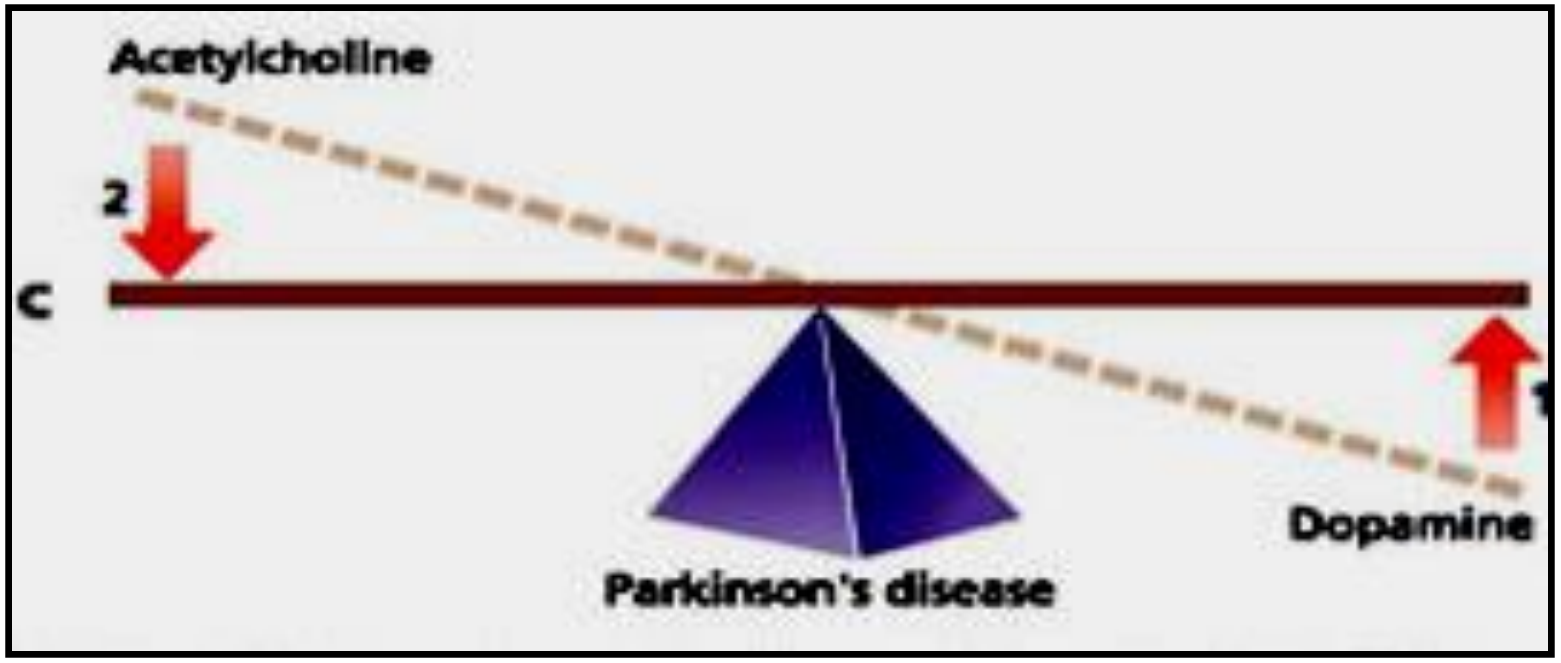


Causes

Parkinson's disease is an idiopathic disease but some causes may be:

- **Genetic.**
- **Toxins (MPTP= methyl phenyl tetrahydropyridine).**
- **Head trauma.**
- **Cerebral anoxia .**
- **Oxidative stress**
- **Drug-induced Parkinson's disease**
  - **e.g. antipsychotics like haloperidol.**
  - **Dopamine antagonists as metoclopramide (antiemetic).**

Drug Treatment



Main approach

Drugs to increase dopaminergic activity

Or

Drugs to block cholinergic activity

1) Drugs that increase dopaminergic activities:

Dopamine precursor:

L-dopa + carbidopa

Dopamine agonists

- Ergot derivatives: bromocriptine, pergolide
- Non ergot derivatives: pramipexole

Dopamine releaser: amantadine

COMT inhibitors: entacapone

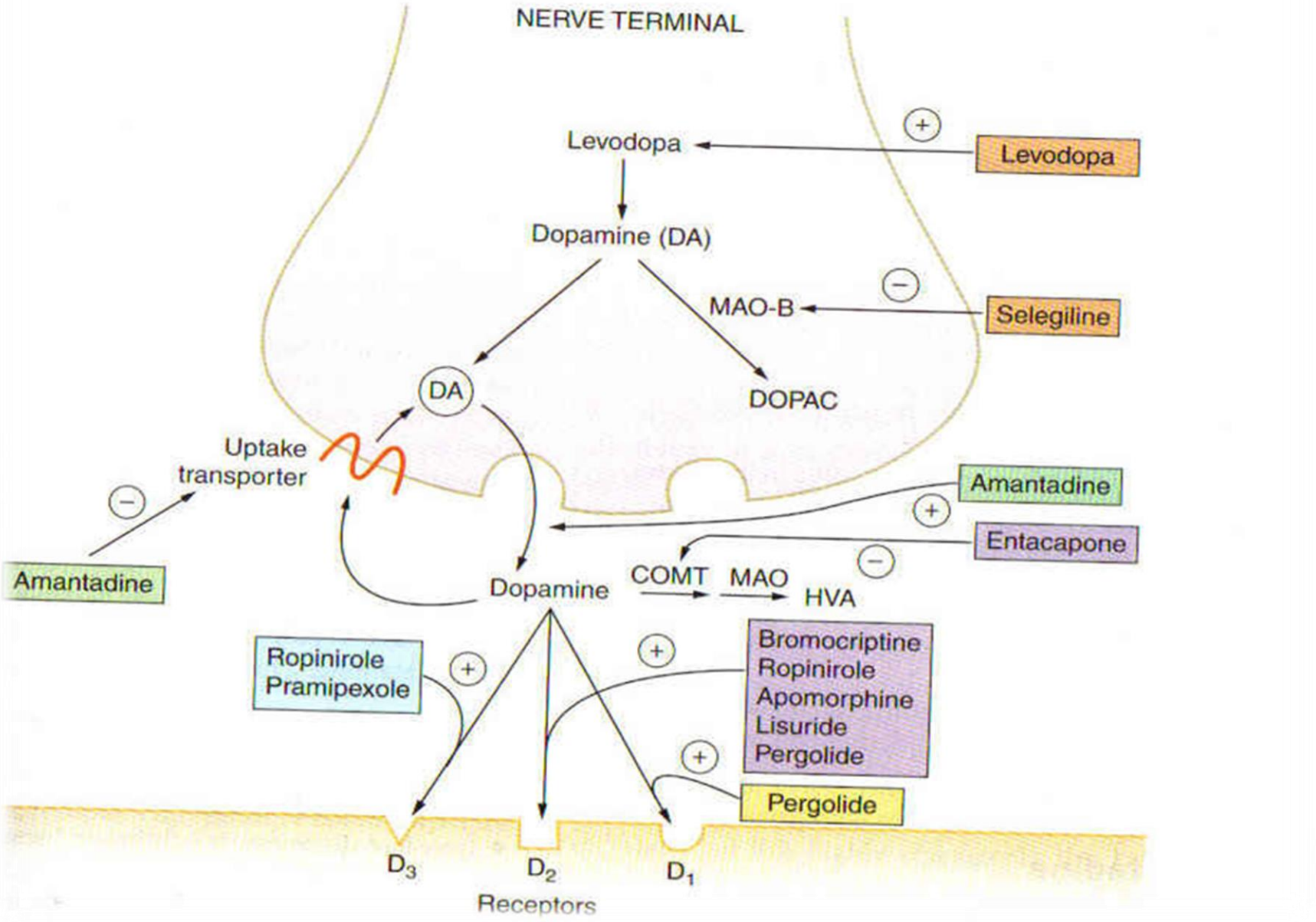
MAO-B inhibitors: selegiline

2) Drugs that decrease cholinergic activity (anticholinergic drugs):

Muscarinic antagonists

e.g. benztropine, trihexyphenidyl

Approach For treatment of Parkinson's disease



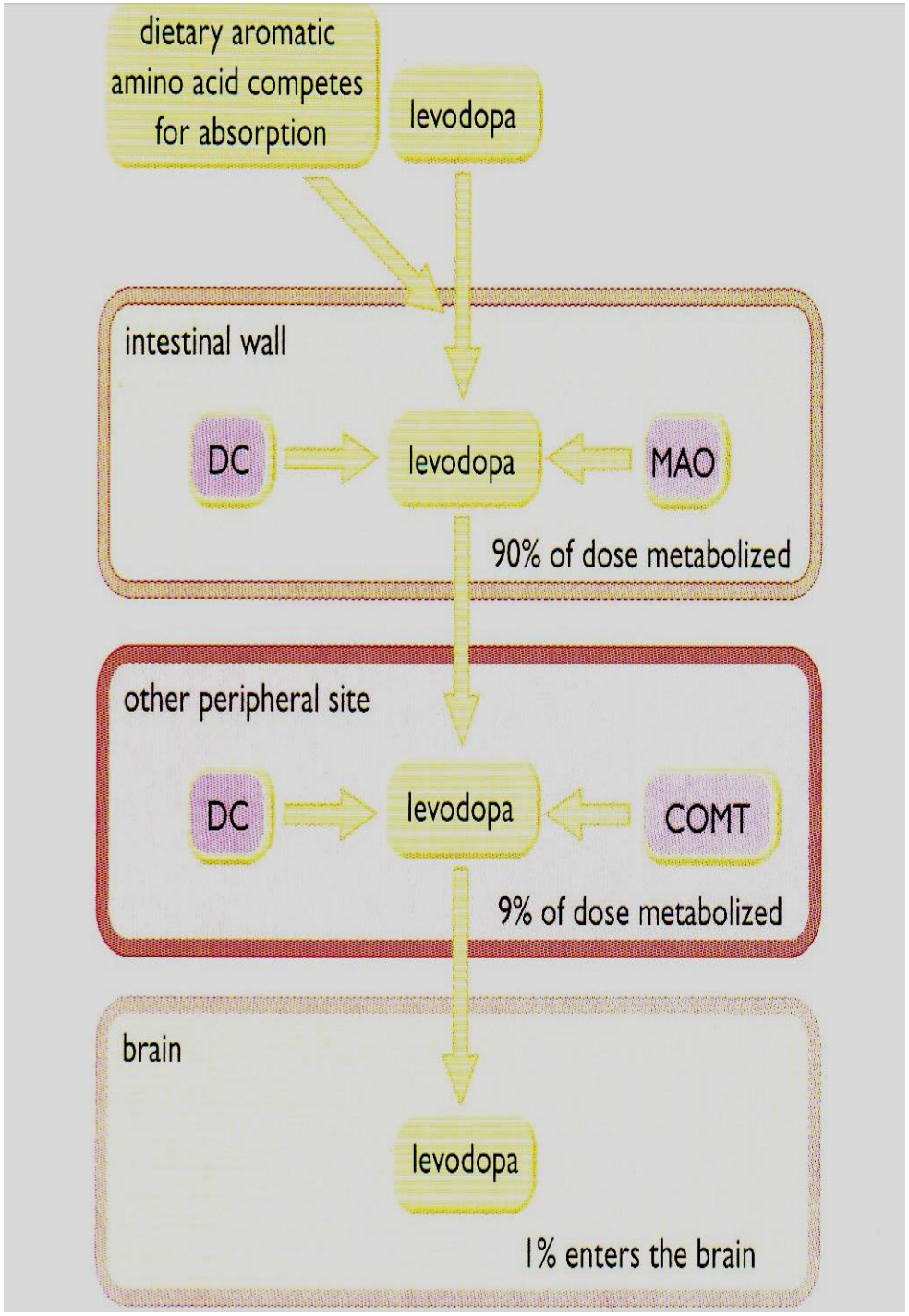
Levodopa (L-dopa)

is a precursor of dopamine (converted into dopamine **peripherally** and **centrally**) by action of An enzyme called **dopa decarboxylase *(DC)*.**

L-dopa **dopamine**

DC: Dopa decarboxylase enzyme

99% of L-dopa is decarboxylated to give dopamine in gut and liver.



DC: DOPA Decarboxylase

MAO: Monoamine Oxidase

COMT: Catechol-O-Methyl transferase

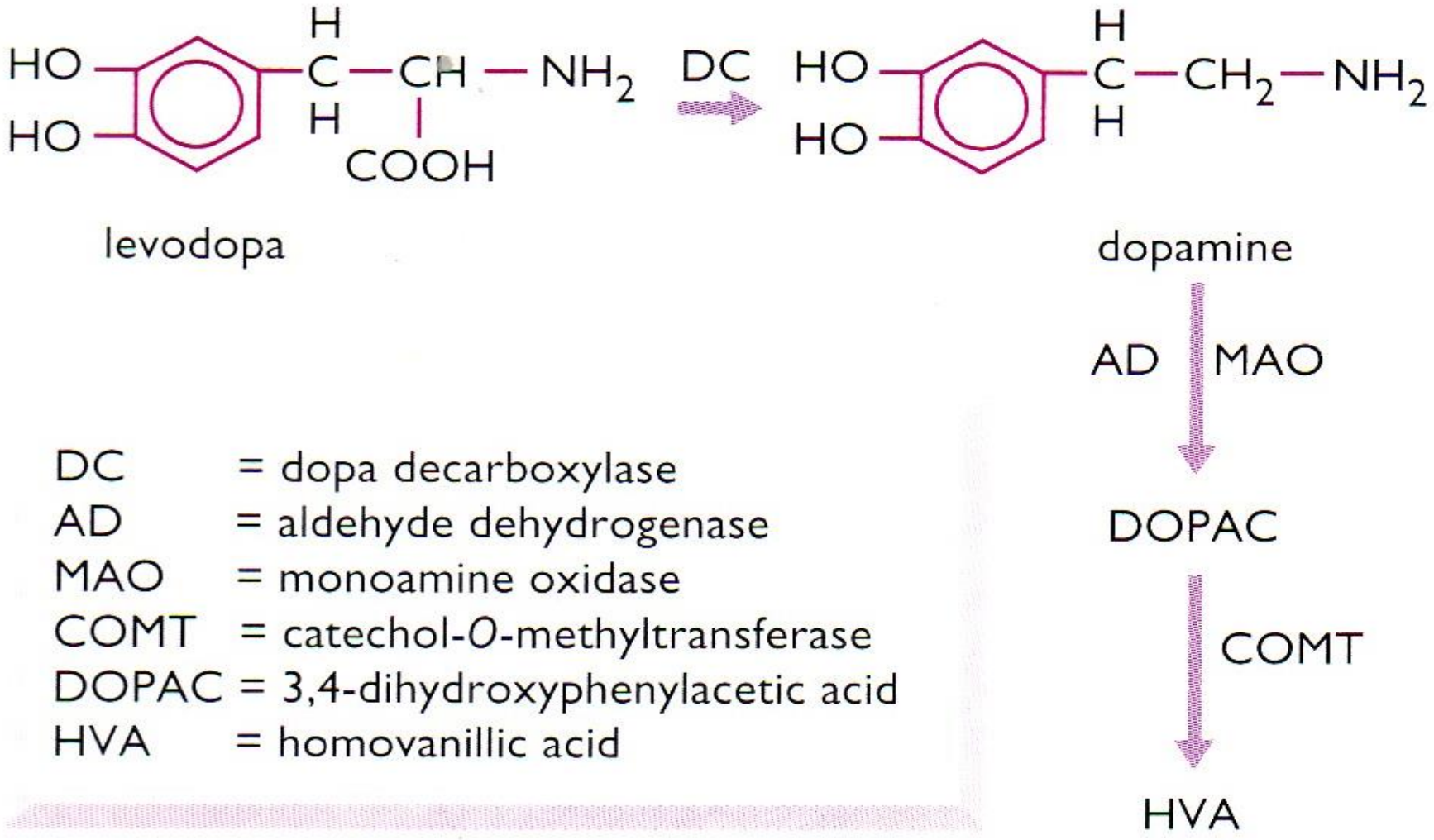
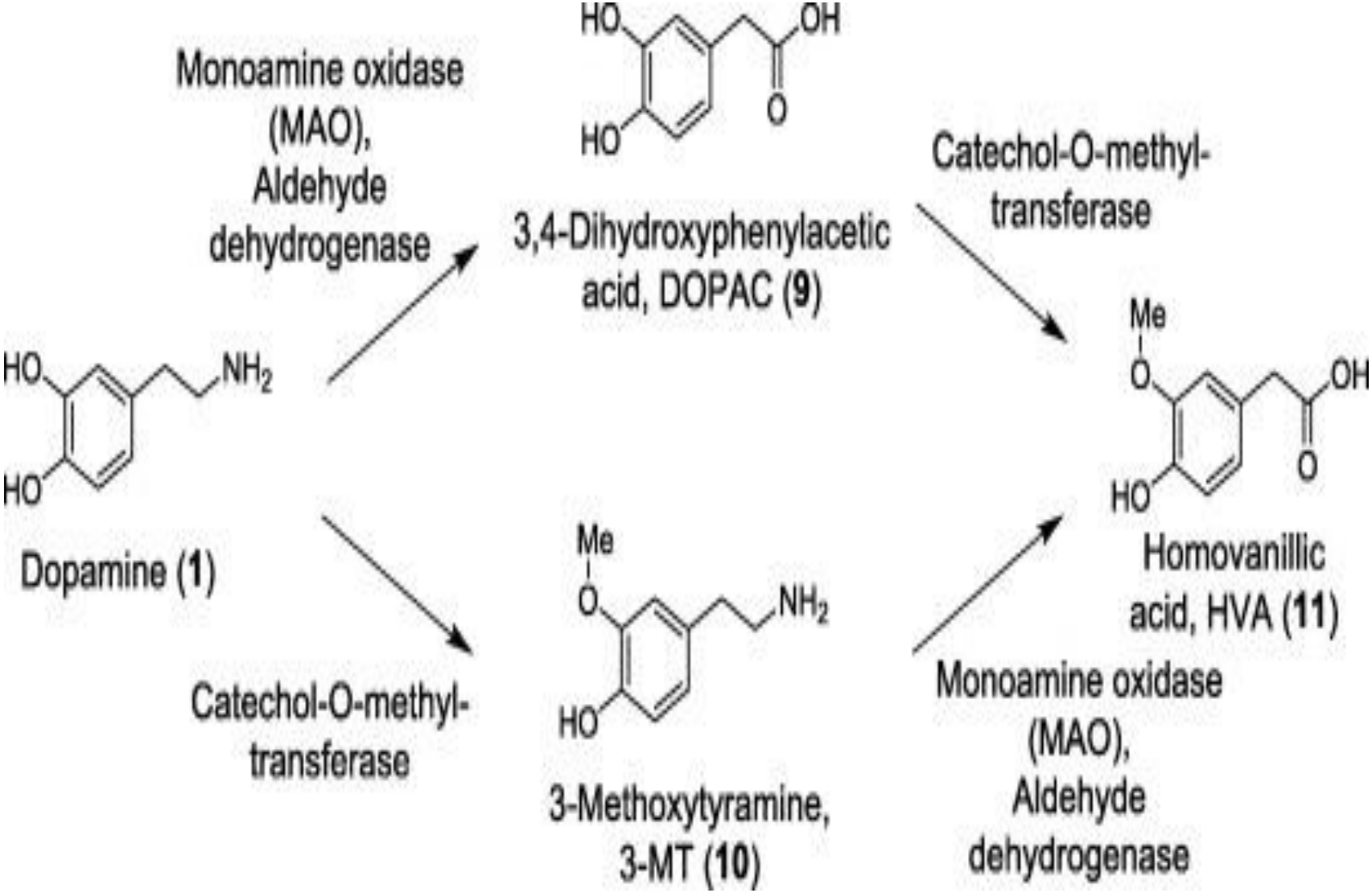


Fig. 14.51 Conversion of levadopa to dopamine and other metabolites.

Levodopa (L-dopa)

- **Dopamine formed peripherally is metabolized by MAO & COMT enzymes**
- **1% L-DOPA crosses BBB to form dopamine centrally.**
- **L-dopa is usually given combined with DC inhibitors (carbidopa or benserazide) to prevent peripheral conversion of L-dopa to dopamine.**


Monoamine oxidase (MAO), Aldehyde dehydrogenase
3,4-Dihydroxyphenylacetic acid, DOPAC (9)
Catechol-O-methyl-transferase
Dopamine (1)
Catechol-O-methyl-transferase
3-Methoxytyramine, 3-MT (10)
Monoamine oxidase (MAO), Aldehyde dehydrogenase
Homovanillic acid, HVA (11)

DC inhibitors

Carbidopa, benserazide

- **are peripheral DOPA decarboxylase inhibitors**
- **Inhibit peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues (thus increasing $t_{1/2}$).**

Why do DC inhibitors act only peripherally?

Why are DC inhibitors combined with L-dopa?

- **Lowers the effective levodopa dose**
- **Increase availability of levodopa to CNS.**
- **Reduce dose of levodopa and side effects.**

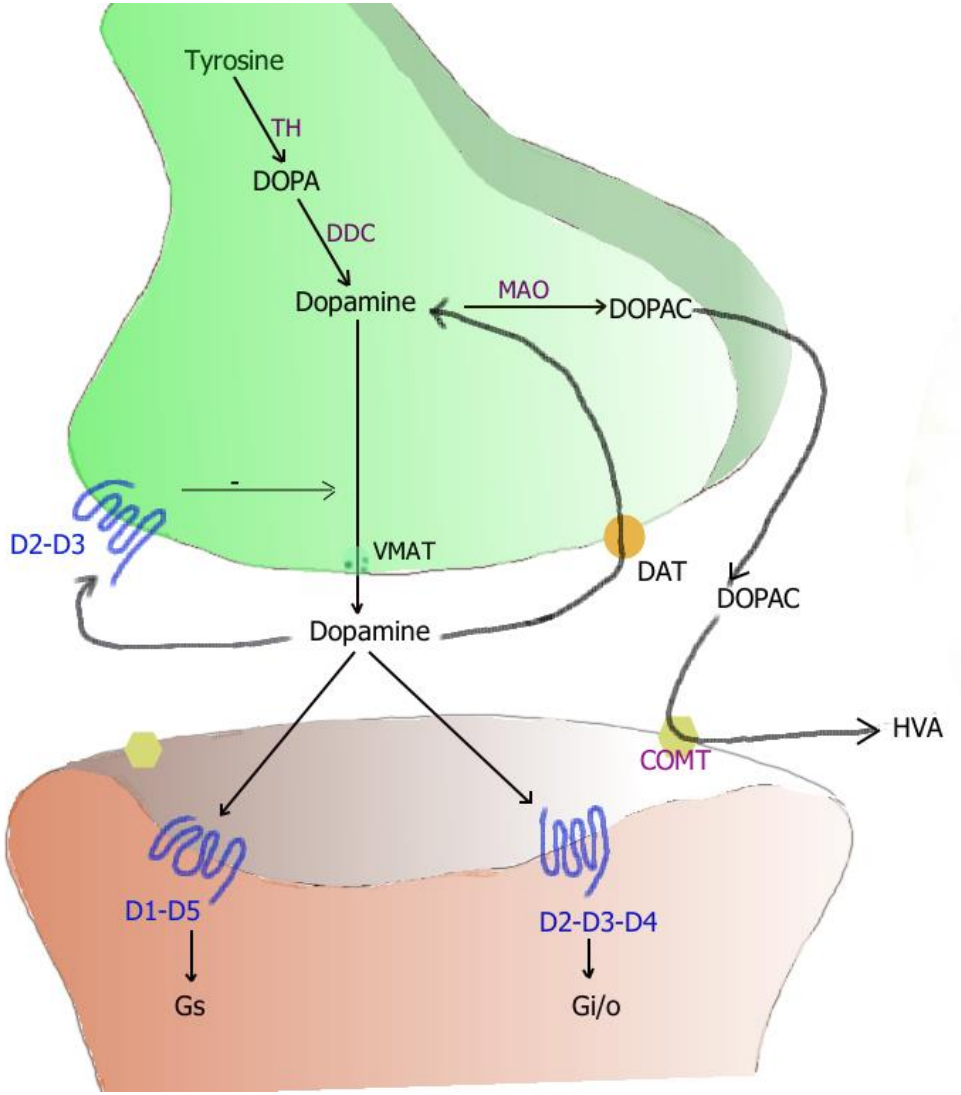
Levodopa (L-dopa)

- **Given orally (should be taken on empty stomach).**
- **absorbed from the small intestine and taken up to CNS by active transport system.**
- **High protein meal interferes with its absorption and transport into CNS**
- **Short duration of action ($t_{½}$ =2 h)**

(fluctuation of plasma concentration).

Levodopa (L-dopa)

- Dopamine acts upon dopaminergic
- (D1-D5) receptors
- G-protein linked receptors
- DI, D5: are excitatory
- D2,D3, D4 : are inhibitory.



Dopamine processing in a synapse. After release dopamine can either be taken up again by the presynaptic terminal, or broken down by enzymes. TH: tyrosine hydroxylase DOPA: L-DOPA DAT: dopamine transporter DDC: DOPA decarboxylase VMAT: vesicular monoamine transporter 2 MAO: Monoamine oxidase COMT: Catechol-O-methyl transferase HVA: Homovanillic acid

Uses

- **The most efficacious therapy**
- **The best results of levodopa are obtained in the first few years of treatment.**
- **L-dopa ameliorates all signs of parkinsonism particularly bradykinesia & rigidity but does not cure the disease.**
- Should not be used in parkinsonism associated with antipsychotic drug therapy.

Adverse drug effects

Peripheral effects:

- **Anorexia, nausea, vomiting (due to stimulation of chemoreceptor trigger zone, CTZ).**
- **Cardiac arrhythmias.**
- **Mydriasis, orthostatic hypotension**

CNS effects (Psychological disorders):

mainly depression, delusions, hallucinations, confusion, sleep disturbances (insomnia).

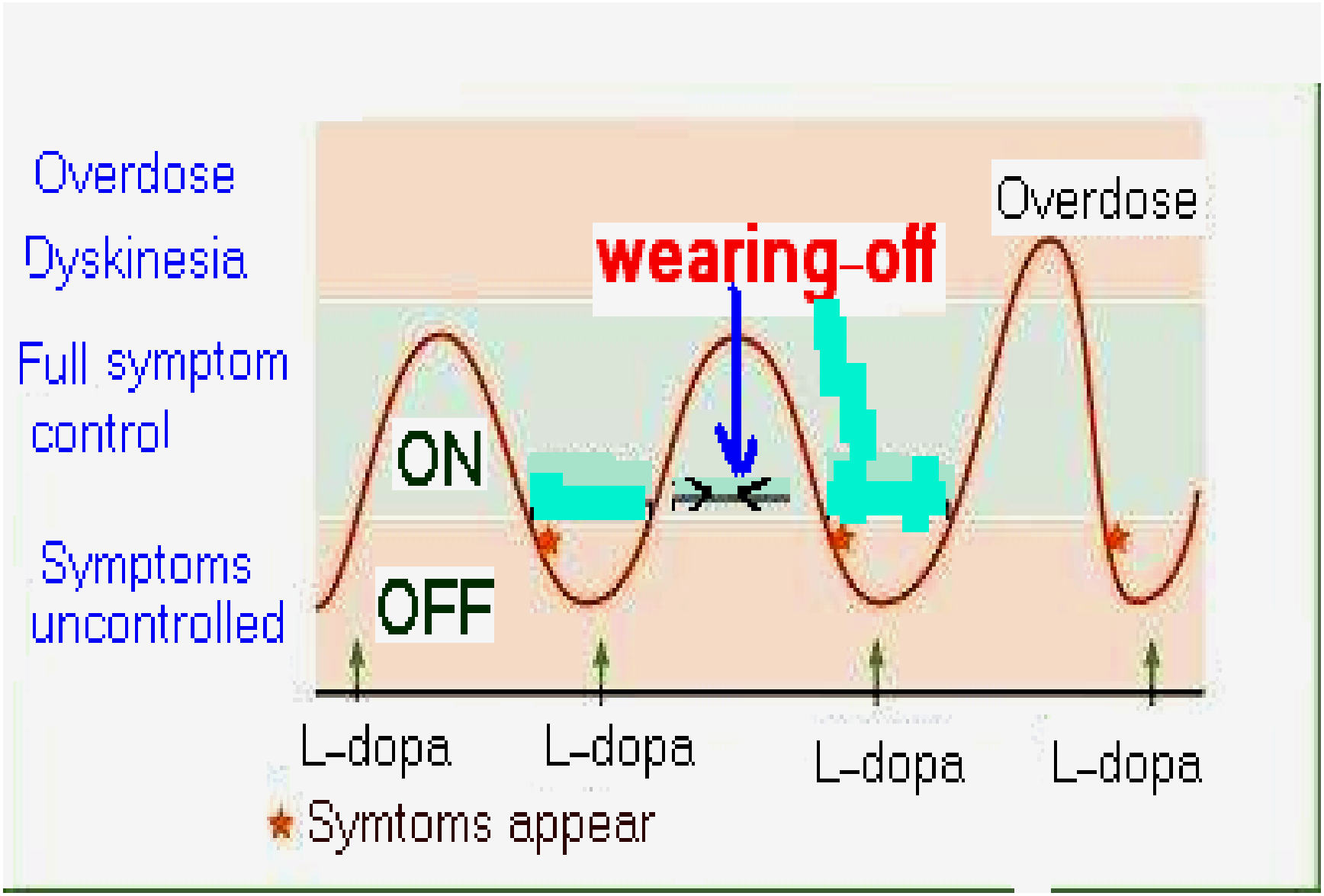
Limitation of L-DOPA treatment

- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) **due to fluctuating plasma levels of levodopa.**
- The dyskinesia can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.
- **Wearing-off effect** (duration of “on” states becomes shorter).
- **On-off phenomenon** (On= improved mobility & Off=Akinesia or hypomobility).

Limitation of L-DOPA treatment

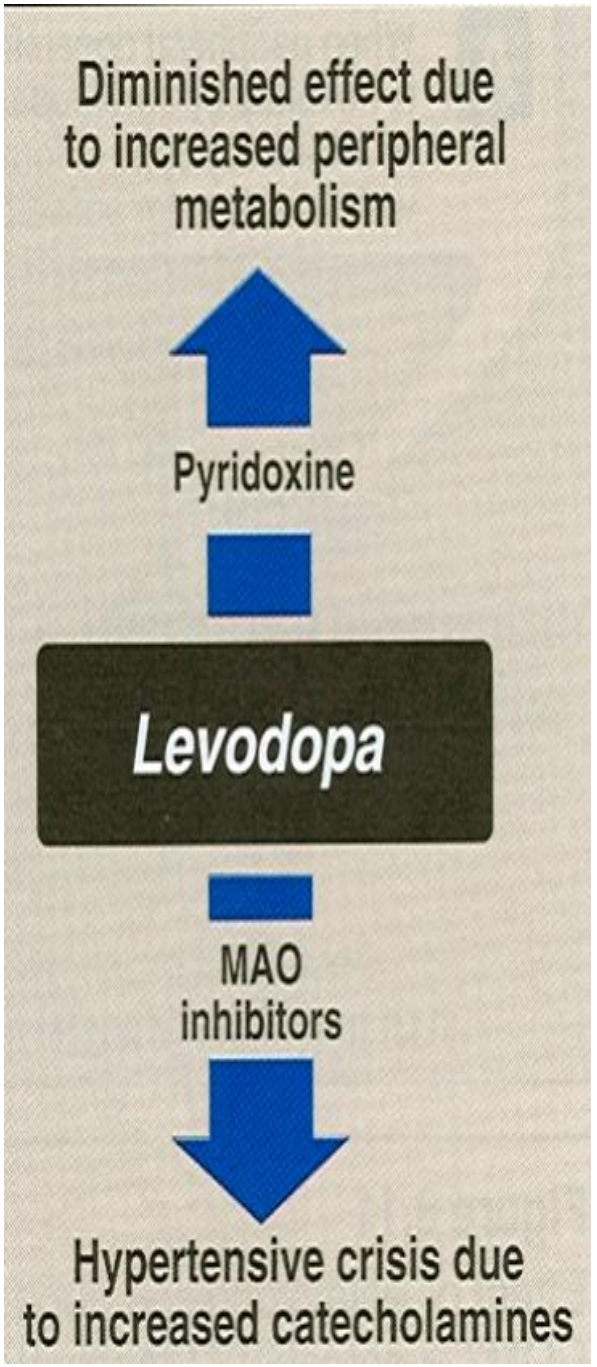
- Wearing off effect and on-off phenomena occur due to **progression of the disease and the loss of striatal dopamine nerve terminals.**

Dyskinesia and response fluctuations with L-DOPA



Drug Interactions:-

- **High proteins meals.**
- **Pyridoxine (Vitamin B6).**
- **Nonselective MAO inhibitors (phenelzine)**



Contrindications

- **Psychotic patient.**
- **Glaucoma** **(due to mydriatic effect).**
- **Patients with history of melanoma** **Why?**

Note: L-dopa is a precursor of melanin

Dopamine receptor agonists

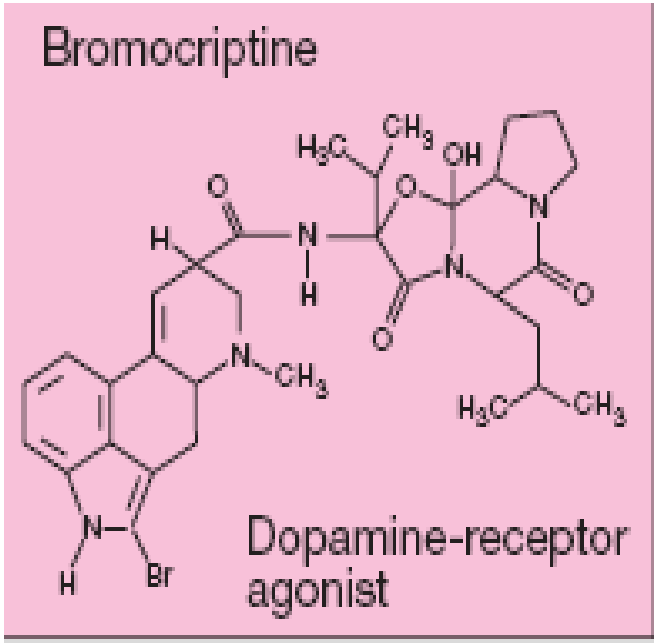
Bromocriptine, pergolide, Pramipexole

- **Ergot derivatives:** **Bromocriptine, pergolide**
- **Non ergot derivatives:** **Pramipexole**

Dopamine receptor agonists

- **Have longer duration of action than L-dopa** ***(less likely to cause dyskinesia than levodopa)***
- **As monotherapy,** the dopamine agonists are less effective than levodopa.
- **In advanced stages, dopamine agonists are used as an adjunct to levodopa,** they may contribute to clinical improvement and reduce levodopa dosage needs.

Bromocriptine



- **Is an ergot derivative**
- **D2 agonist**
- **Is given orally**
- **Half life= 6-8 h**

Used for the treatment of

- **Parkinson's disease**
- **Hyperprolactinemia *(galactorrhea).***
- **Infertility in women.**

Pramipexole

- **Non Ergot dopamine agonist**
- **D3 agonist**
  - **Is given orally**
  - **Has the advantage of being free radicals scavenger.**
- **Used alone as initial therapy or in combination with L-dopa.**
- **Side effects: similar to L-dopa, but less dyskinesia.**

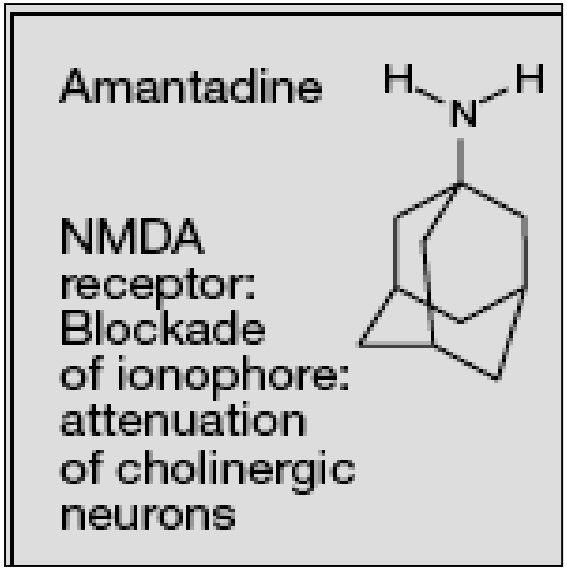
Adverse effects of dopamine agonists

- **Nausea, vomiting, cardiac arrhythmia**
- **Confusion, hallucinations, delusions**
- **Dyskinesia (*less prominent*).**

Contraindications

- **Psychosis**
- **Peripheral vascular disease (only ergot-derived agonists).**
- **Recent myocardial infarction**

Amantadine



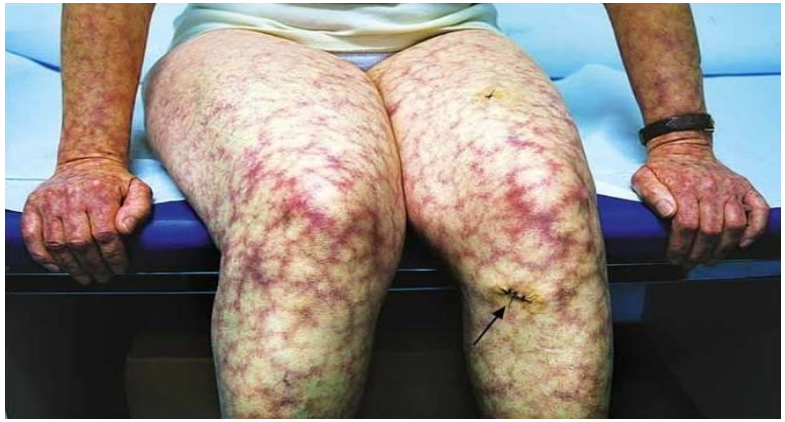
- **originally introduced as an antiviral.**
- **Amantadine inhibits dopamine reuptake thus increases dopamine release.**
- **acts as an antagonist at muscarinic and NMDA receptors *(N-methyl-D-aspartate)*.**
- **given orally with short half life**
- **most of the drug being excreted unchanged in the urine**

Amantadine

- **Less efficacious than L-dopa**
- **Tolerance develops to its therapeutic effect after 6-8 months.**
- **Its benefits last only for short period and only used for L-dopa resistance.**
- Useful in the early stages of parkinsonism or as an adjunct to levodopa therapy
- **Amantadine and the anticholinergic drugs may exert additive effects on mental functioning.**

Adverse effects of amantadine

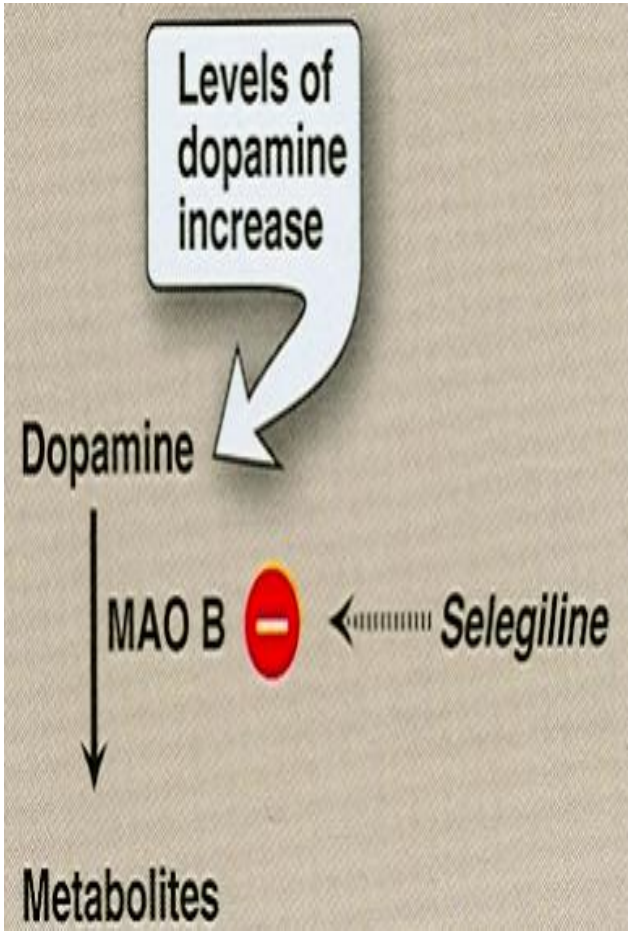
- **Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects).**
- **Dry mouth, urinary retention (anticholinergic effects).**
- **Restlessness and hallucinations.**
- **Ankle edema, and livedo reticularis**



Monoamine oxidase-B inhibitors

Selegiline

- is a selective irreversible inhibitor of MAO-B, an important enzyme for dopamine metabolism
- Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.



Selegiline

- **Selegiline may have neuroprotective effect due to:**
- **Antioxidant activity against toxic free radicals produced during dopamine metabolism.**
- **Selegiline is metabolized to desmethylselegiline, Which is antiapoptotic.**

Uses of selegiline

- **Adjunctive to levodopa / carbidopa in later-stage parkinsonism to:**
  - **reduce the required dose of levodopa**
  - **delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.**

Adverse effects of selegiline

- **At high doses, selegiline may inhibit MAO-A (hypertensive crises).**
- **May cause insomnia when taken later during the day.**

Contraindications

- co-administered with
  - Tricyclic antidepressants.
  - Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma).
  - Food restriction “low tyramine diet” is required.

COMT Inhibitors
(Catechol-O- methyl transferase) Inhibitors

Entacapone

- **Acts peripherally to inhibit COMT enzyme required for L-dopa degradation**

- **Usually given in combination with L-DOPA and carbidopa to diminishes peripheral metabolism of L-dopa.**

Side effects:

- **L-Dopa side effects.**
- **Orange discoloration of urine**

Tolcapone:

Peripheral and central COMT inhibitor

More lipid soluble than entacapone

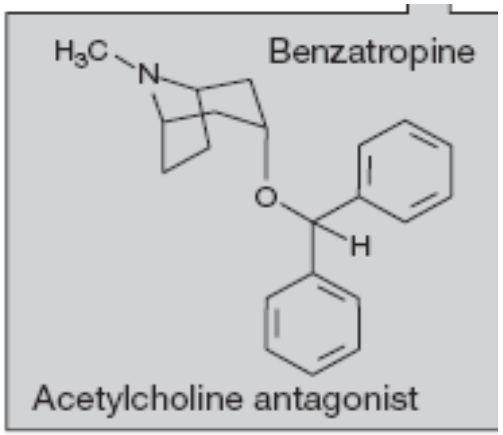
More penetration into CNS

COMT inhibitors are used as adjuvant to L-dopa+ carbidopa to:

- **Decrease fluctuations**
- **Improve response**
- **Prolonged the ON-Time**

Anticholinergic Drugs

Benztropine, Trihexphenidyl



- **Central muscarinic antagonist.**
- **Has modest anti- parkinsonian actions.**
- **They improve tremor & rigidity but have little effect on bradykinesia.**
- **Provide benefit in drug-induced parkinsonism (due to antipsychotics).**
- **used during the early stages of the disease or as an adjunct to levodopa therapy.**

Adverse effects

- **Cycloplegia, mydriasis, dry mouth, urinary retention, constipation.**
- **Confusion, delirium, and hallucinations may occur at higher doses.**

Contraindications

- **Prostatic hypertrophy**
- **Glaucoma**
- **Intestinal obstruction**

Summary

- In mild cases, selegiline, amantadine or anticholinergics can be used.
- Levodopa and carbidopa is the main treatment
- All other medications are adjuncts to levodopa therapy
- Other useful drugs include bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor), amantadine (enhances dopamine release) and benztropine (muscarinic receptor antagonist, that is used for parkinsonism caused by antipsychotic drugs.


THANK YOU