Antiparkinsonian drugs

Semester IV

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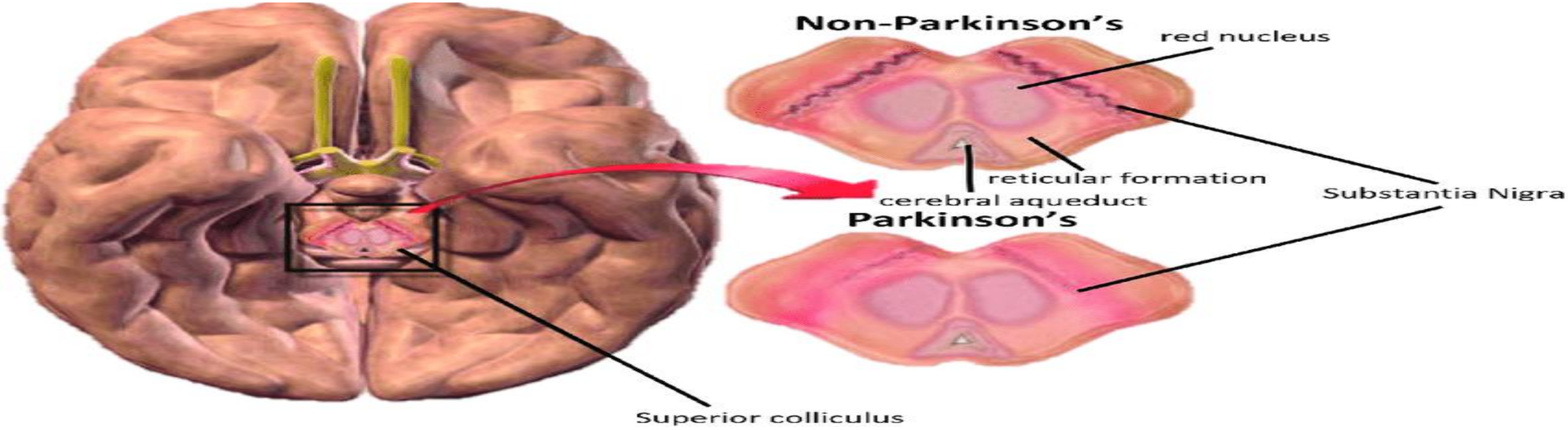
Learning Outcomes

By the end of the lecture, the students will be able to:

1. **Identify classification of antiparkinsonian drugs**
2. **Identify Levodopa mechanism of action and adverse effects.**
3. **Identify COMT inhibitors mechanism and adverse effects.**
4. **Identify MAO inhibitors used in parkinsonism mechanism and adverse effects.**
5. **Identify dopamine agonists used in parkinsonism mechanism & adverse effects .**
6. **Identify amantadine as antiparkinsonian drug.**
7. **Recognize anticholinergics used in parkinsonism mech and adverse effects.**

Parkinsonism

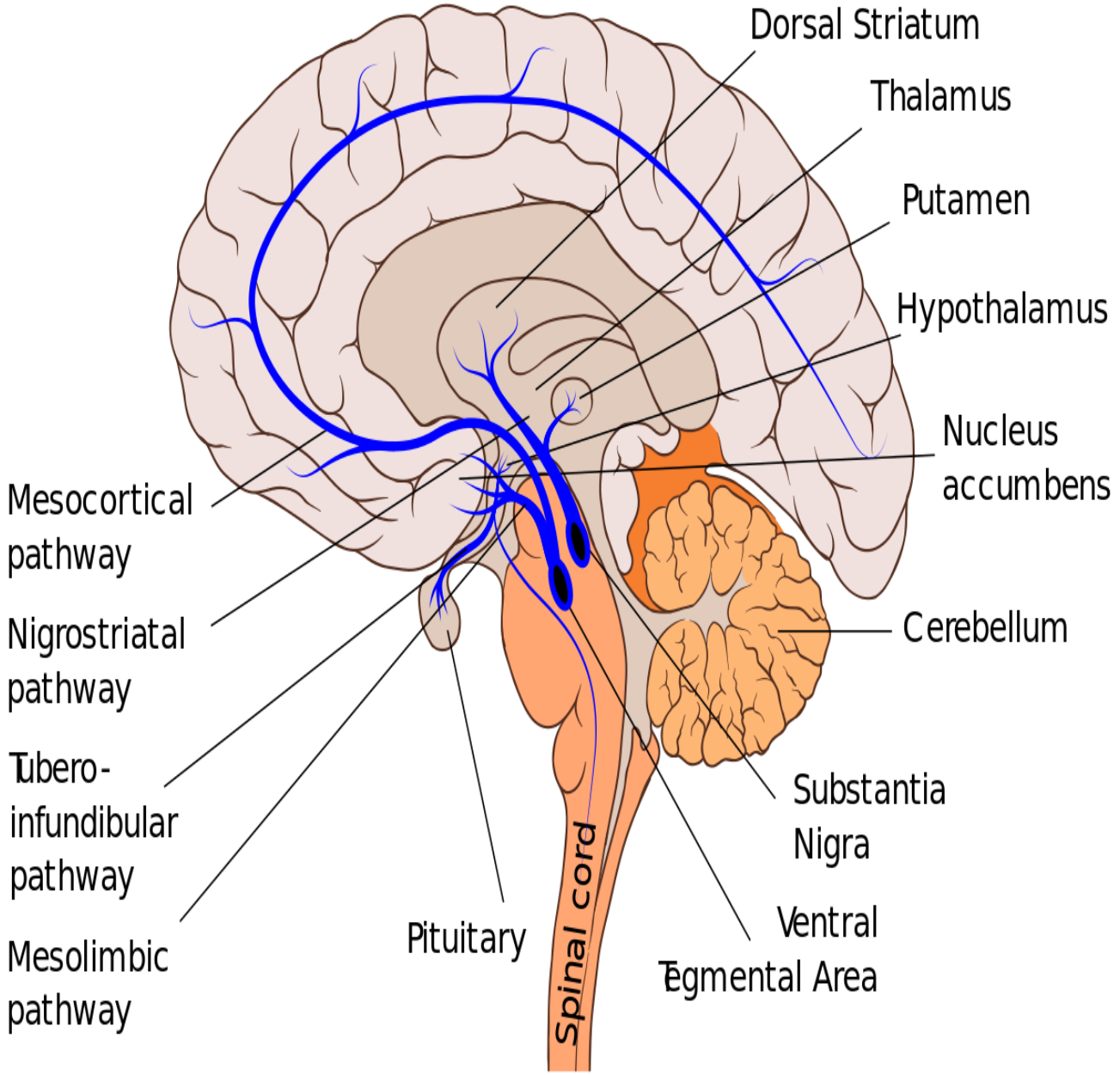
A progressive neurological disorder of muscle movement characterized by muscle rigidity, tremors, bradykinesia and postural instability due to loss of dopaminergic neurons in substantia nigra resulting in imbalance of dopaminergic (inhibitory) and cholinergic (excitatory) influences on the extrapyramidal system.



Sites of dopamine in the brain

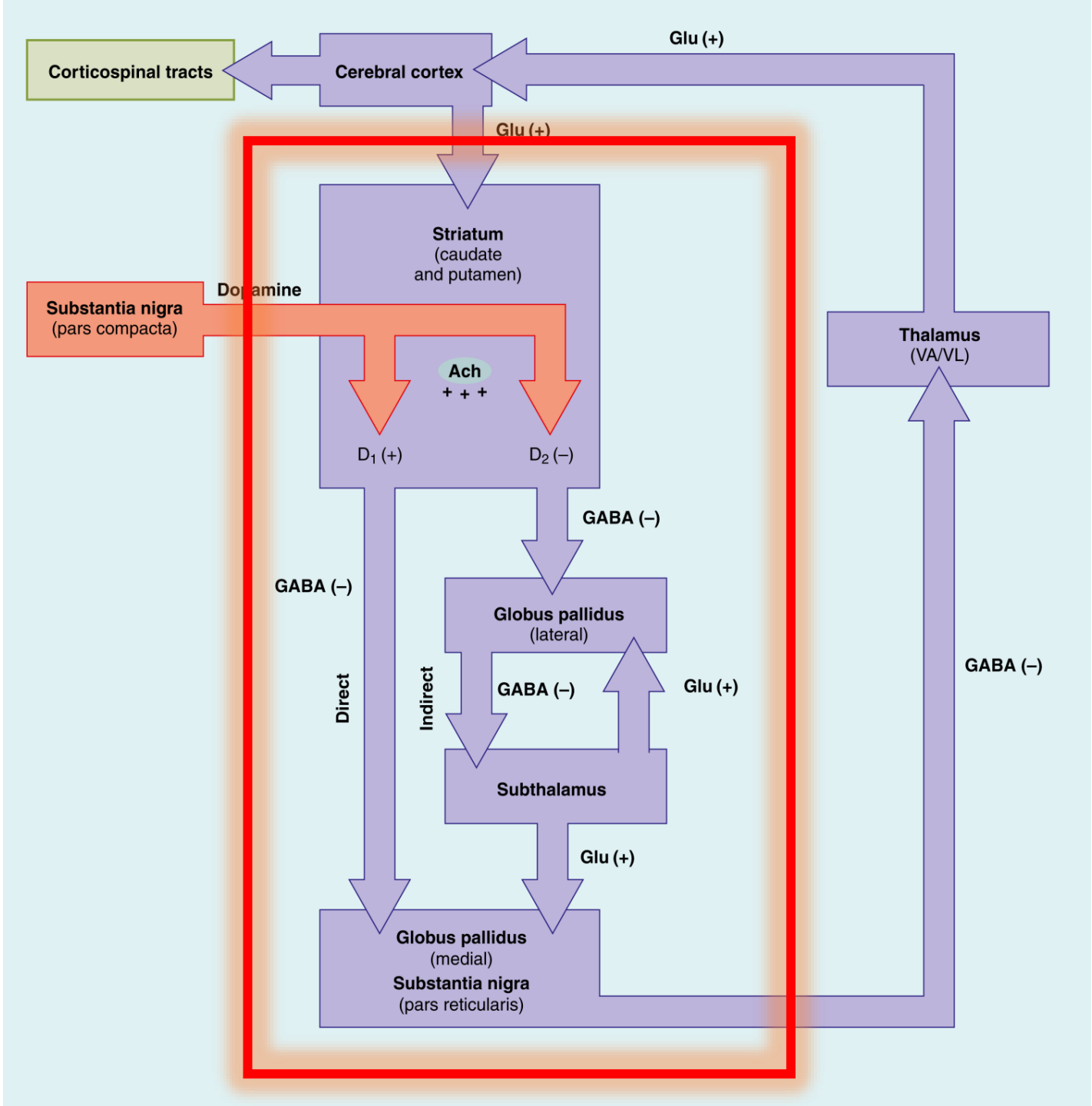
Dopamine is an important neurotransmitter regulating:

- **Voluntary movement**
- Reward and **addictive behavior**, **mood**, **cognition, memory**, learning, sleep and food intake.
- I**nhibits the synthesis and secretion of prolactin** from the pituitary gland



Pathogenesis of PD

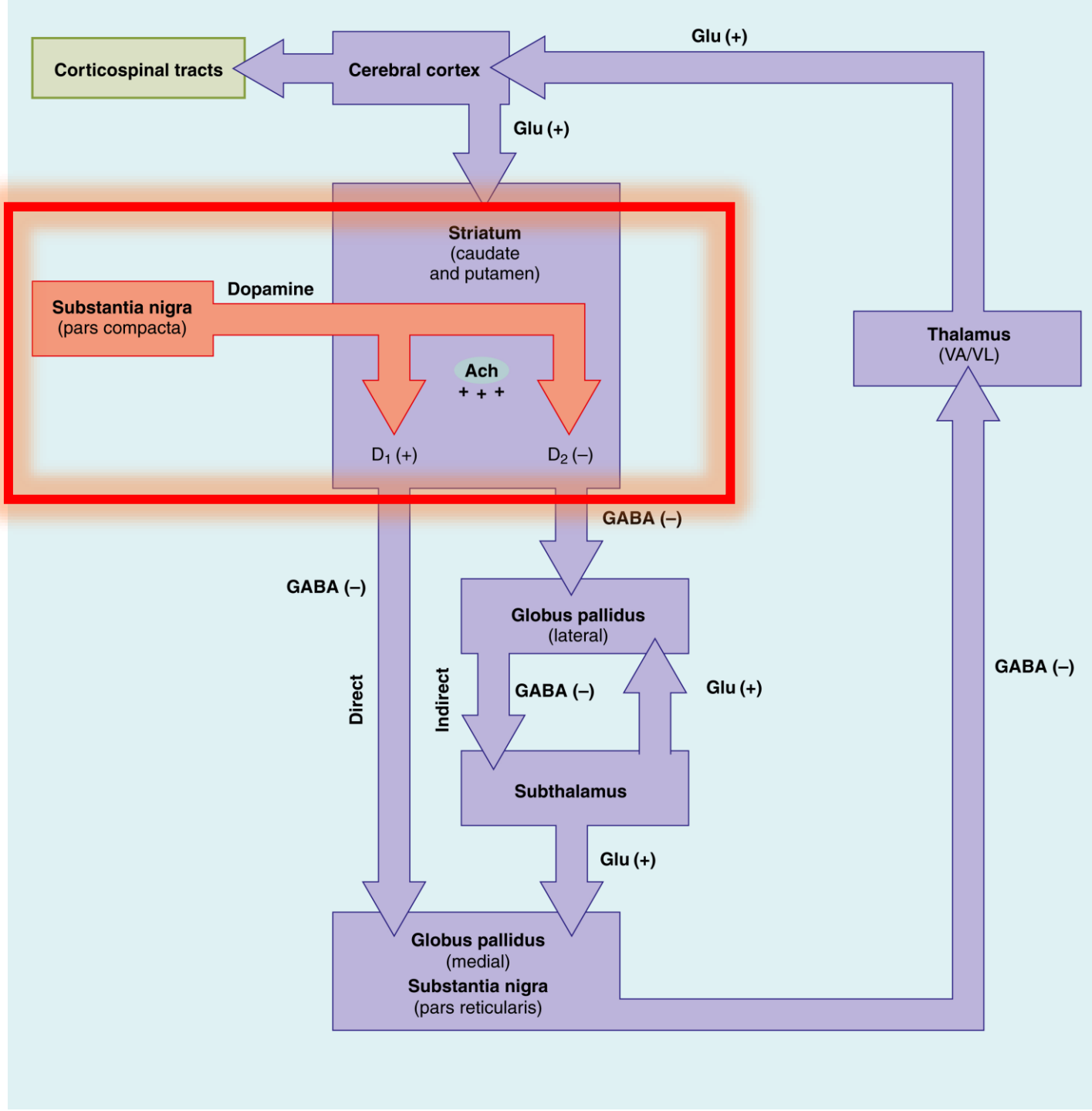
- ***The basal ganglia*** ➔ group of interconnected subcortical nuclei ➔ the **striatum**, **substantia nigra**, globus pallidus, and subthalamus
- In healthy individuals, the basal ganglia receive input from the cerebral cortex ➔ process this information ➔ send feedback to the motor cortex ➔ leads to **smooth coordination of body movement.**



Pathogenesis of PD

During movement initiation ➔

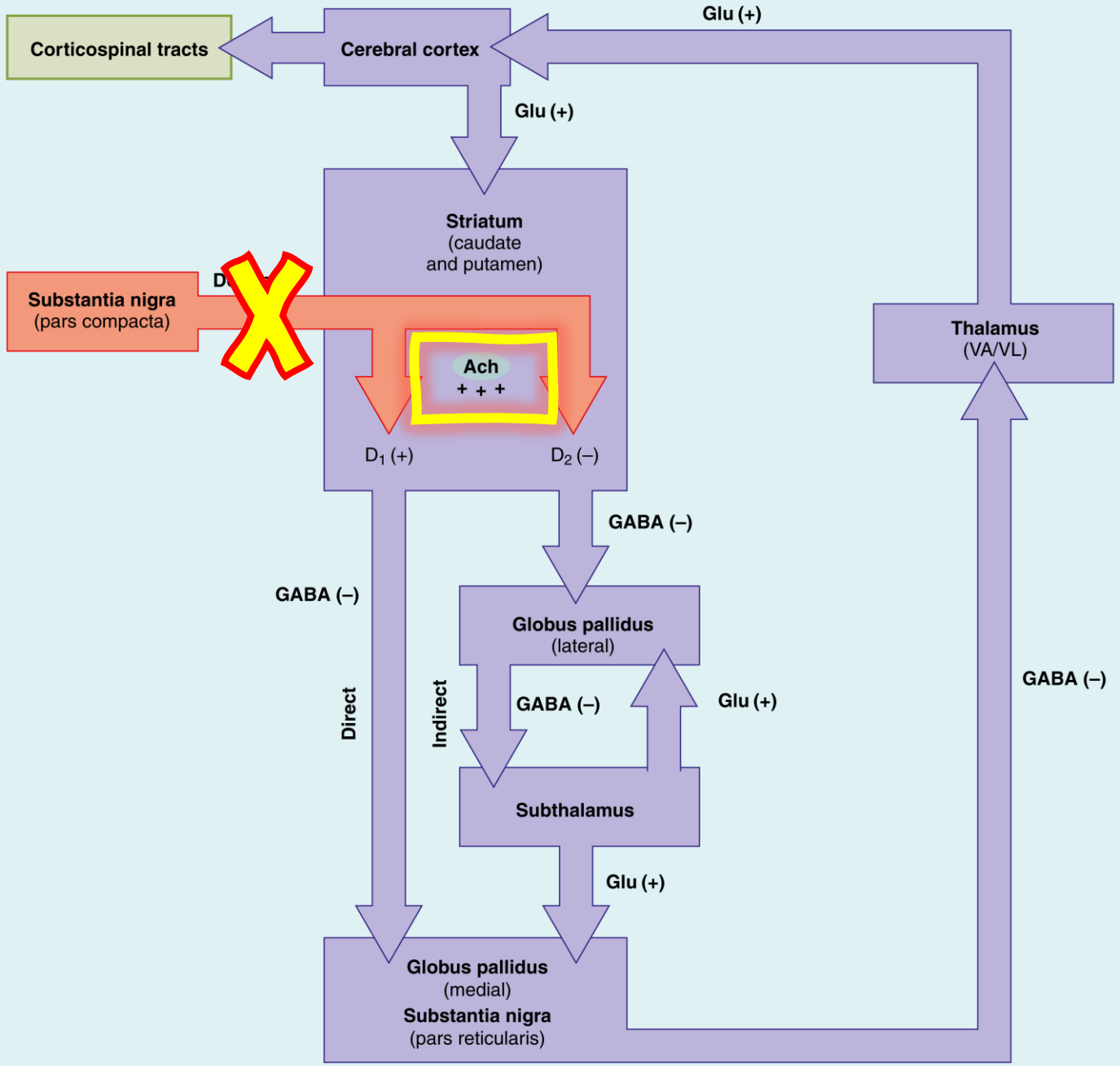
1. The cerebral cortex sends information to the basal ganglia ➔
2. **Substantia nigra** sends **inhibitory DA projections** to the **striatum** via the nigrostriatal pathway ➔
3. **Inhibition of the inhibitory** striatal **direct/indirect** projections to the thalamus frees the thalamus ➔
4. The thalamus then feeds information back to the motor area of the cortex ➔ smooth coordination of motor functions.



Pathogenesis of PD

In PD ➔ degeneration of inhibitory DA neurons of the nigrostriatal pathway ➔ increased striatal inhibition of the thalamus ➔ reduced thalamic input to the motor cortex ➔ the patient exhibits rigidity and bradykinesia.

- The reduction in the inhibitory DA activity of the nigrostriatal pathway results in unopposed cholinergic neuron hyperactivity in the striatum, which contributes to the pathological features of parkinsonism.



Parkinsonism

Parkinson's disease and other akinetic rigid syndromes I
Fuller, Geraint, MA MD FRCP, Neurology, 88-89

Posture in Parkinson's disease. Note the slight stoop and the position of the right arm.

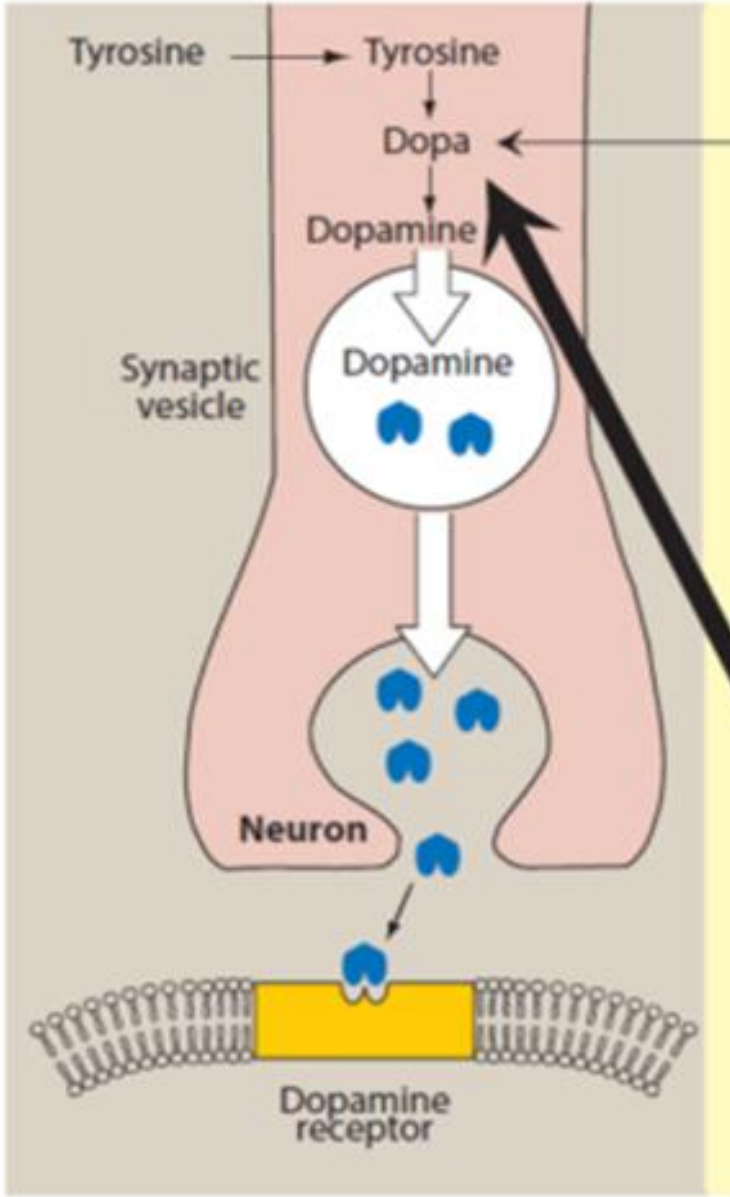
Classification of antiparkinsonian drugs

Dopaminergic drugs:

- **Dopamine précurseurs: Levodopa (L-dopa).**
- **COMT inhibitors: Tolcapone – Entacapone**
- **Selective MAO-B inhibitors: Selegiline**
- **Dopamine agonists: Bromocriptine**
- **Releaser of dopamine : Amantadine**

Anticholinergic drugs:

- **Synthetic atropine substitutes(M1):**
  Benztropine –Trihexyphenidyl



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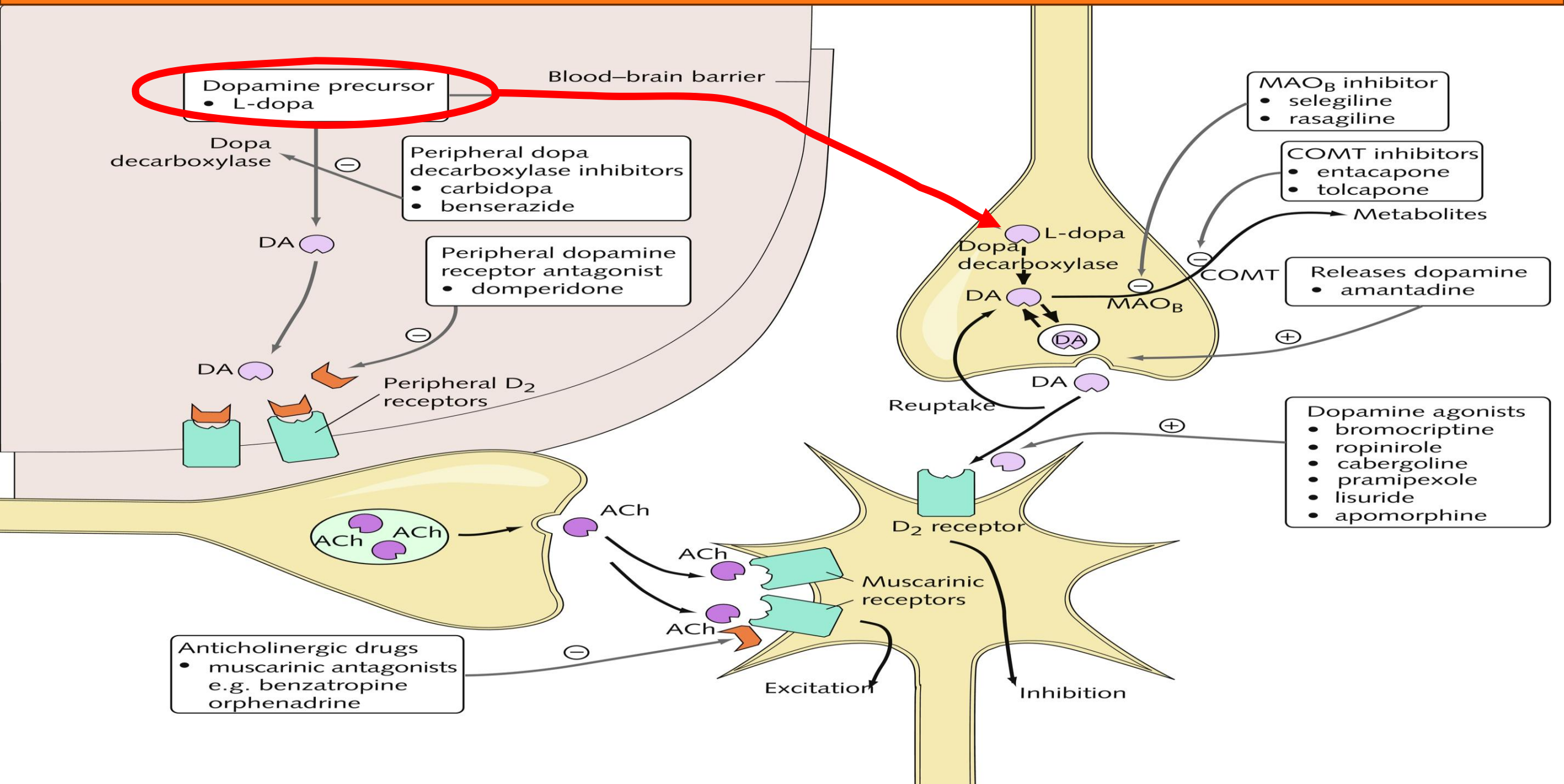
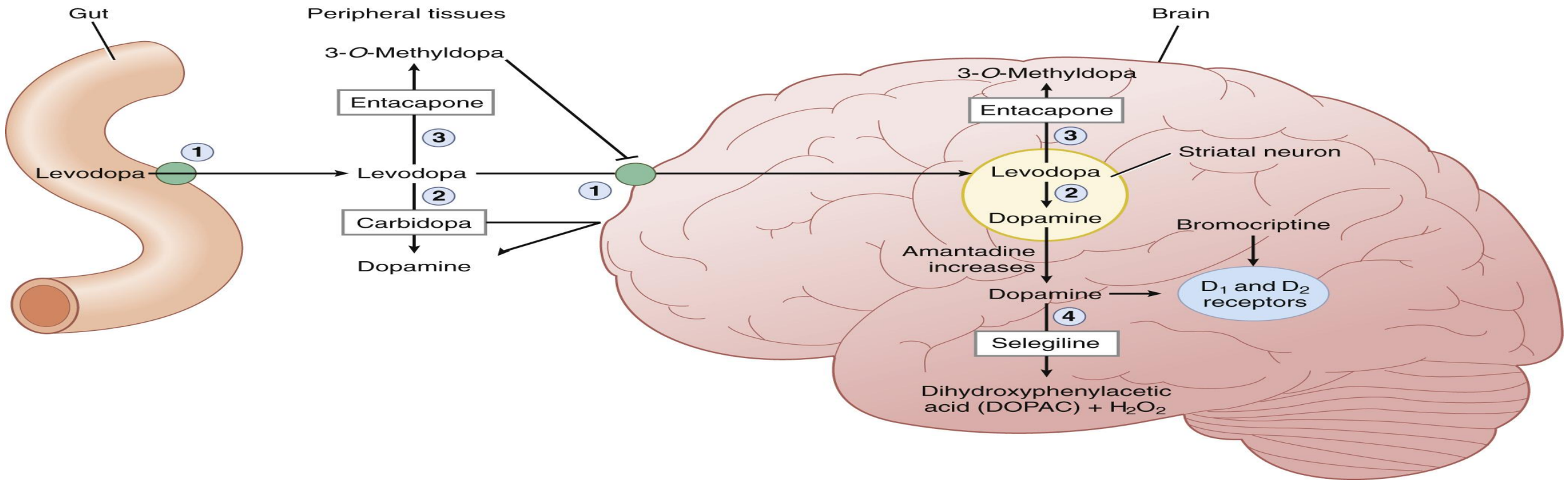


Classification of antiparkinsonian drugs



Drugs for Neurodegenerative Diseases
Brenner, George M., PhD, Brenner and Stevens' Pharmacology, Chapter 24, 273-284

Mechanisms of dopaminergic drugs used in the treatment of Parkinson disease . Levodopa is transported across the gut wall and the blood-brain barrier and is converted to dopamine in striatal neurons. Carbidopa inhibits the peripheral decarboxylati...

ELSEVIER

ClinicalKey®

1. Levodopa (L-dopa)

Pharmacokinetics

- **Absorbed rapidly from the small intestine.**
- **Short $t_{1/2}$ (1-2 h).**
- **This short $t_{1/2}$ may produce *"on-off phenomenon"***

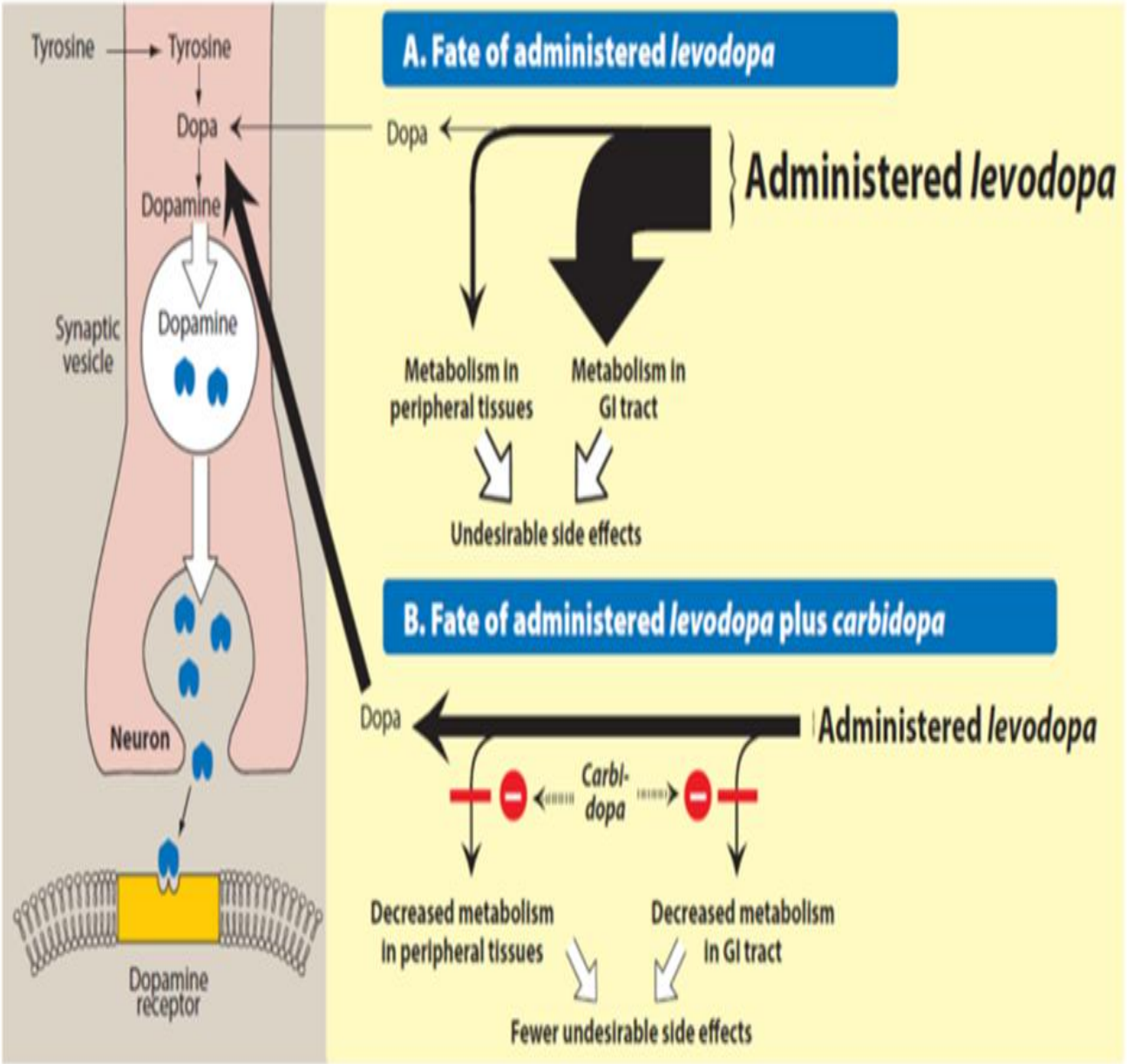
i.e. rapid fluctuation of the clinical state in the form of sudden tremors & immobility after short period of recovery (how to avoid).

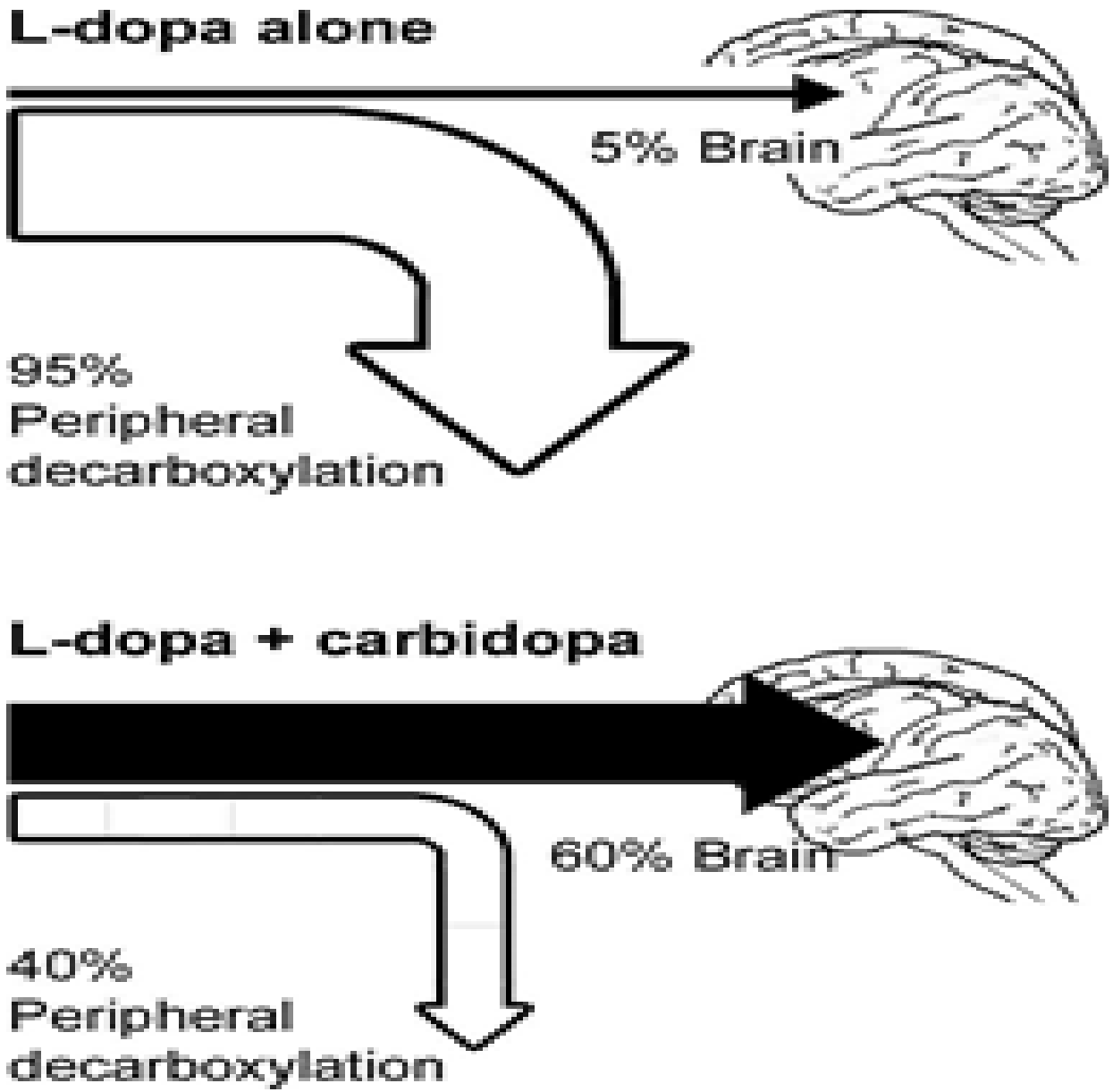
- **Amino acids (e.g. leucine& isoleucine) compete with L-dopa absorption from the gut so it should be taken on an <u>empty stomach.</u>**

Mechanism of action of Levodopa

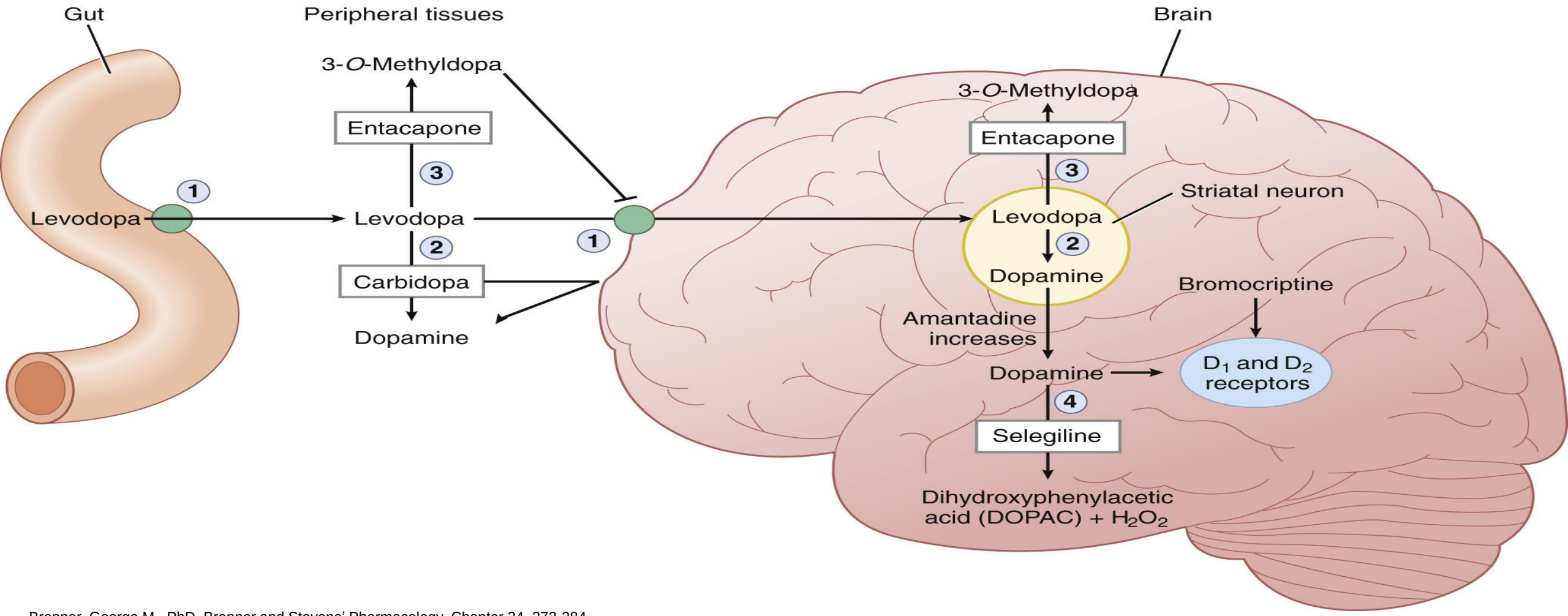
- **Dopamine can’t cross BBB but L-dopa can.**
- **It is considered the 1st line treatment of parkinsonism.**
- **More than 95% of the administered dose is rapidly decarboxylated into dopamine in the peripheral tissues. Only a small fraction escapes and crosses BBB.**
- **Peripheral decarboxylation can be minimized by administration of a decarboxylase inhibitor which can't cross BBB e.g. carbidopa, Such a combination helps to reduce the dose of L-dopa and hence the adverse effects**

Mechanism of action of Levodopa





1. Levodopa (L-dopa)



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Mechanisms of dopaminergic drugs used in the treatment of Parkinson disease . Levodopa is transported across the gut wall and the blood-brain barrier and is converted to dopamine in striatal neurons. Carbidopa inhibits the peripheral decarboxylati...

Adverse effects of levodopa

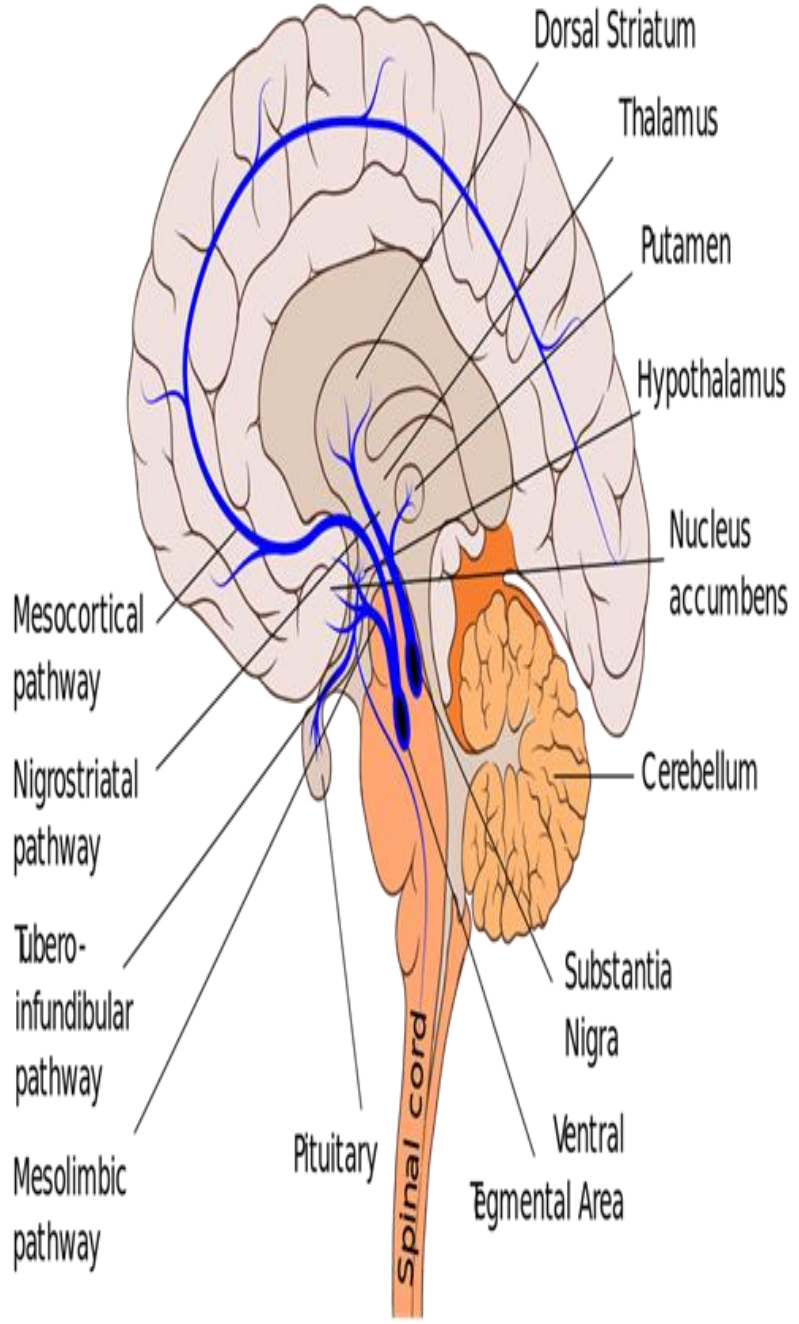
GIT: nausea & vomiting

CNS: Mood changes, hallucinations and nightmares.

On-off phenomenon: rapid fluctuation of the clinical state in the form of sudden tremors and immobility after a short period of recovery due to the short $t_{1/2}$.

Dyskinesia: involuntary movements of the head, lips, and tongue.

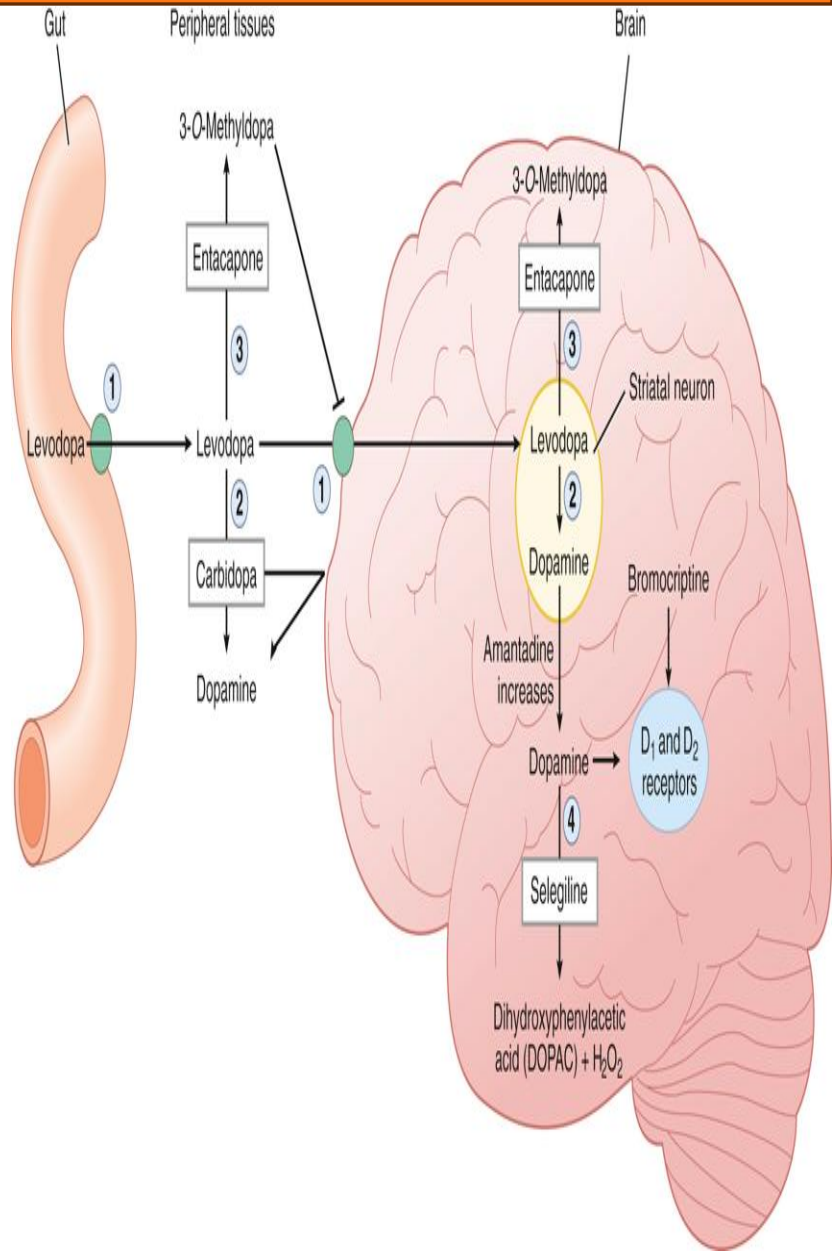
Autonomic: postural hypotension, arrhythmias(B1), mydriasis (peripheral effect)



2. COMT inhibitors (Tolcapone-Entacapone)

Mechanism of action

- **Reversibly inhibit COMT enzyme that converts L-dopa to 3-O-methyldopa (3OMD) in the gut and liver.**
- **Increases the efficacy of L-dopa and stabilizes dopamine levels in the striatum and improves motor function.**



Adverse effects

Hepatic necrosis and same side effects of L-dopa ??

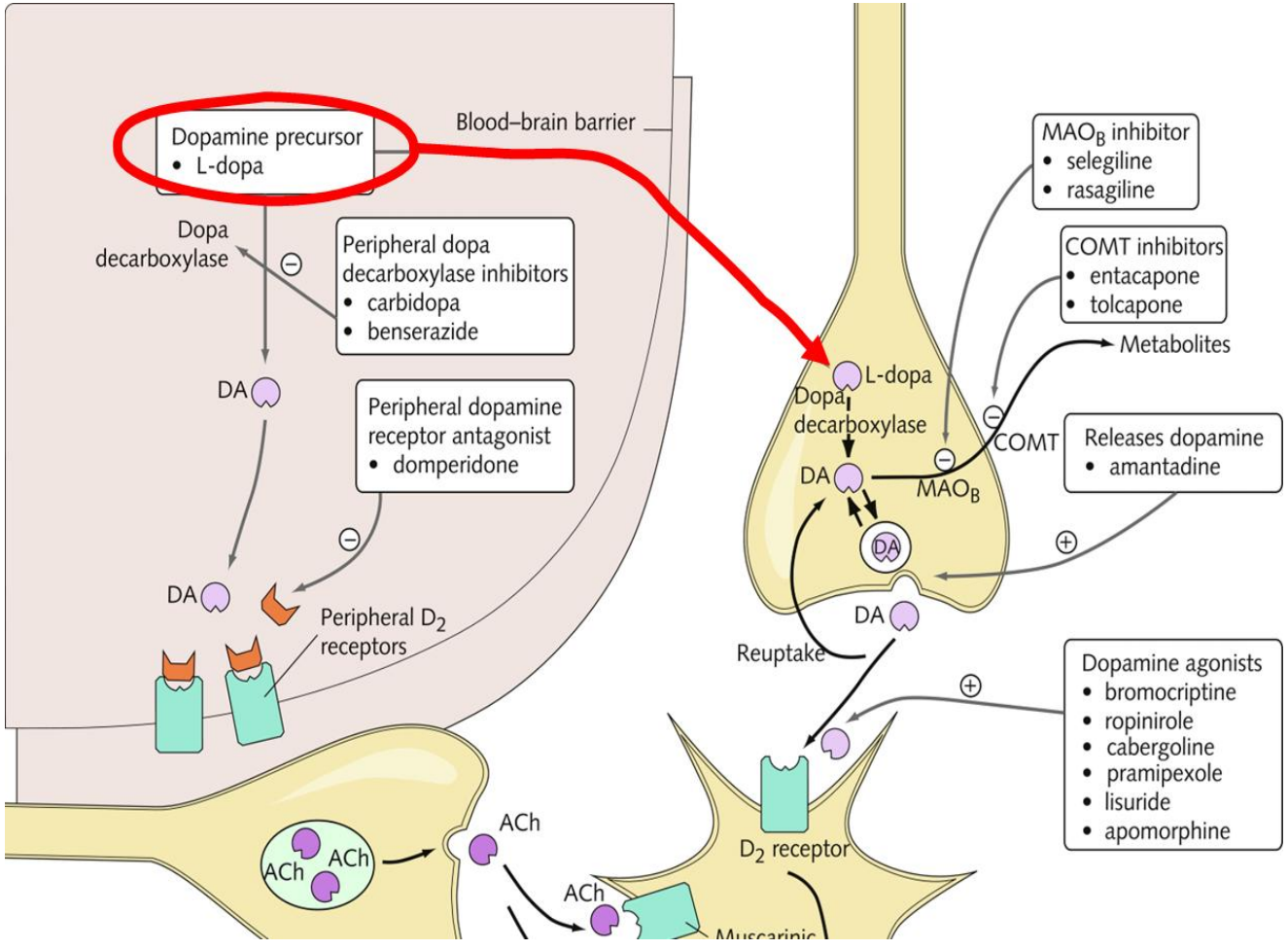
3. MAO inhibitors (Selegiline)

Mechanism of action

Selective MAO-B inhibitor decreasing breakdown of dopamine in the brain.

Adverse effects

- **GIT upset (nausea and vomiting).**
- **Hallucinations& mood changes**
- **Insomnia.**



Quiz 1

Which one of the following combinations of antiparkinsonian drugs is an appropriate treatment plan?

A. Amantadine, carbidopa, and entacapone.

B. Levodopa, carbidopa and entacapone.

C. Pramipexole, carbidopa, and entacapone.

D. Ropinirole, selegiline, and entacapone.

E. Ropinirole, carbidopa, and selegiline.

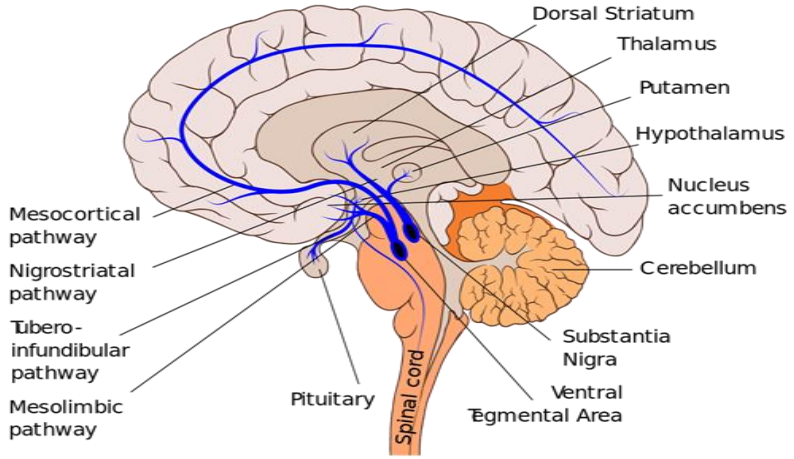
4. Dopamine agonists

Bromocriptine

- Dopamine (D_2) agonist derived from ergot alkaloids.
- It differs from L-dopa in: Faster onset, longer duration, No on-off effect (don't require a functional dopaminergic neuron to produce their effects).

Adverse effects

- GIT upset.
- Hallucinations & mood changes in large doses.
- Postural hypotension.



Pulmonary fibrosis& vasospasm(ergot)

4. Dopamine agonists

Pramipexole and Ropinirole

- Not ergot alkaloids.
- Both act as selective D_2 -receptor agonists.
- Pramipexole or ropinirole can delay the need for levodopa when used in early stages of PD(younger patient). In advanced stages, these agents can reduce the "off" period and decrease the levodopa dosage requirement.

Apomorphine

- Chemically related to morphine, does not bind to opioid receptors but rather is a dopamine receptor agonist.
- Approved for the treatment of acute intermittent hypomobility *(freezing)* episodes associated with advanced PD (SC injection).

Quiz 2

Which one of the following antiparkinsonian drugs may cause vasospasm?

A. Amantadine.

B. Bromocriptine.

C. Carbidopa.

D. Entacapone.

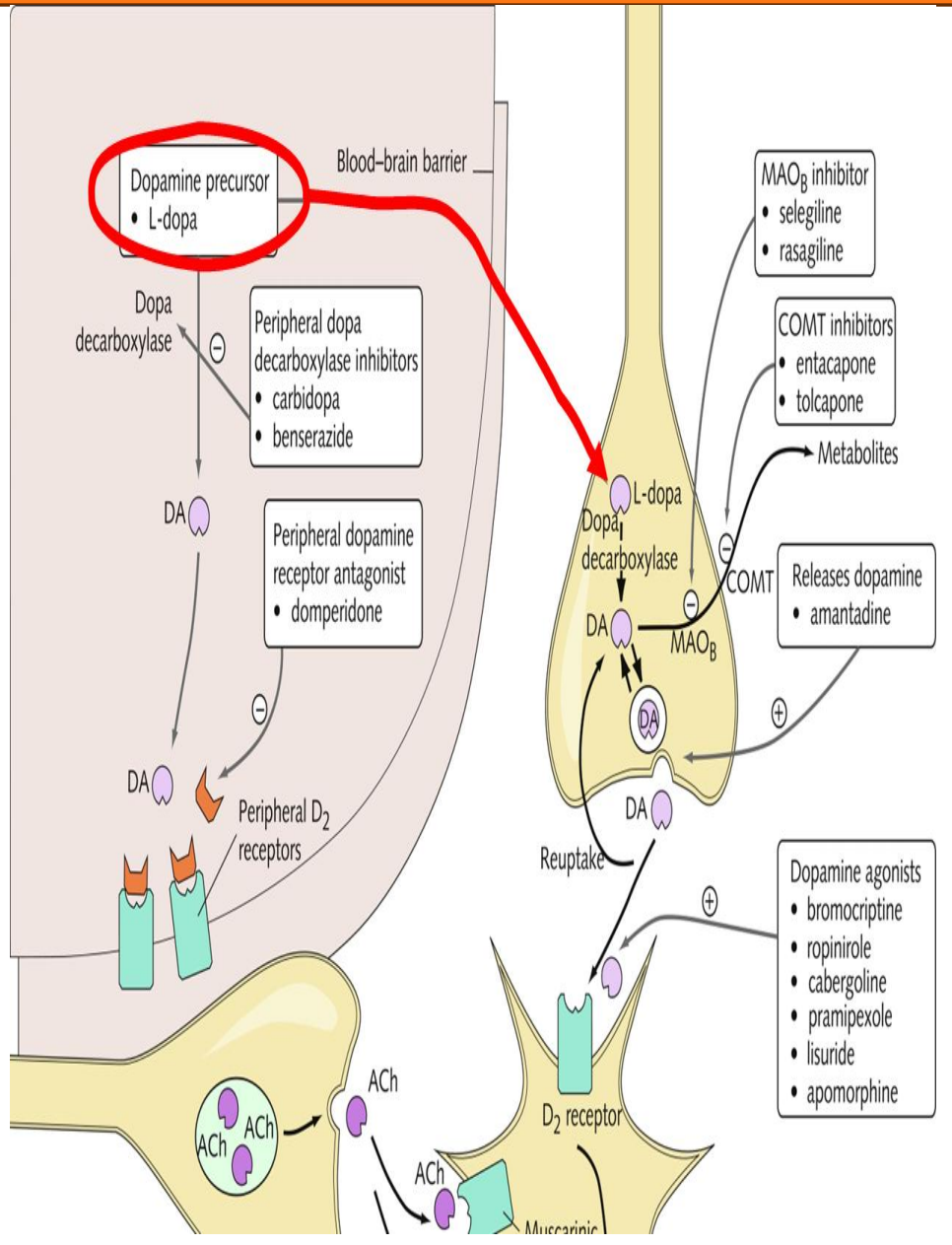
E. Ropinirole.

5. Amantadine

An antiviral drug for influenza A2 virus.

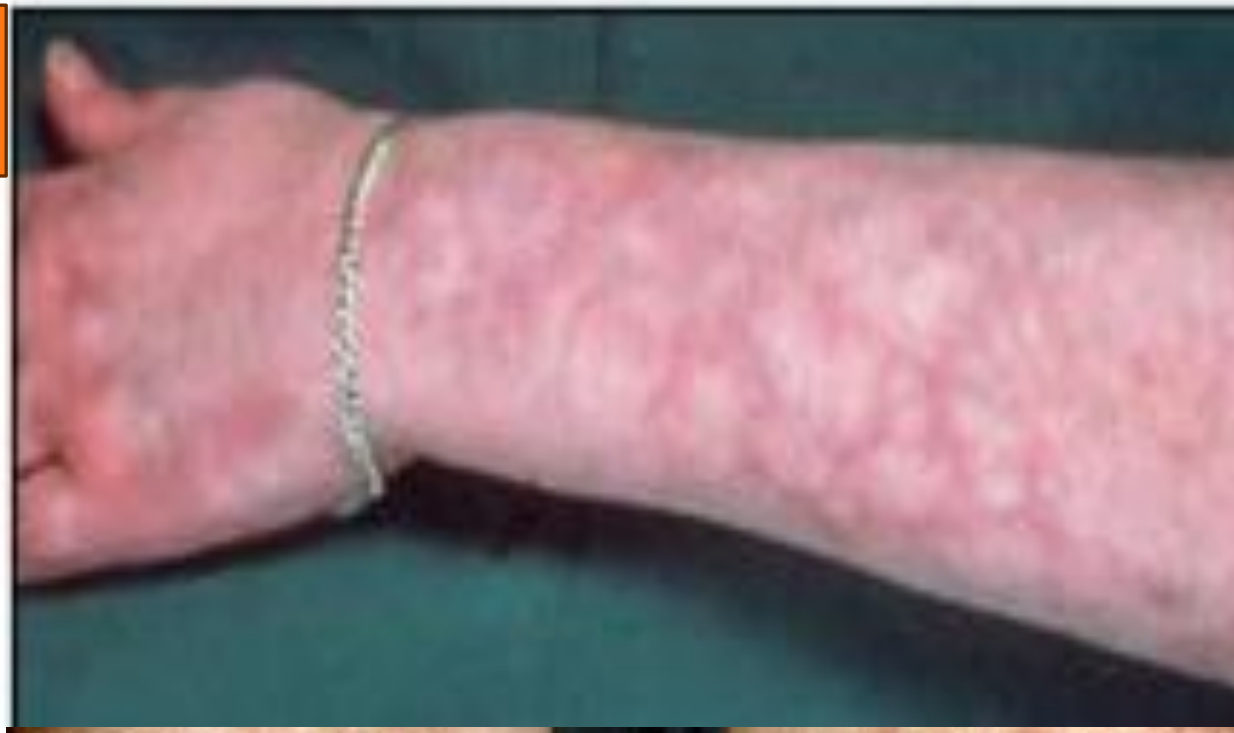
Mechanism:

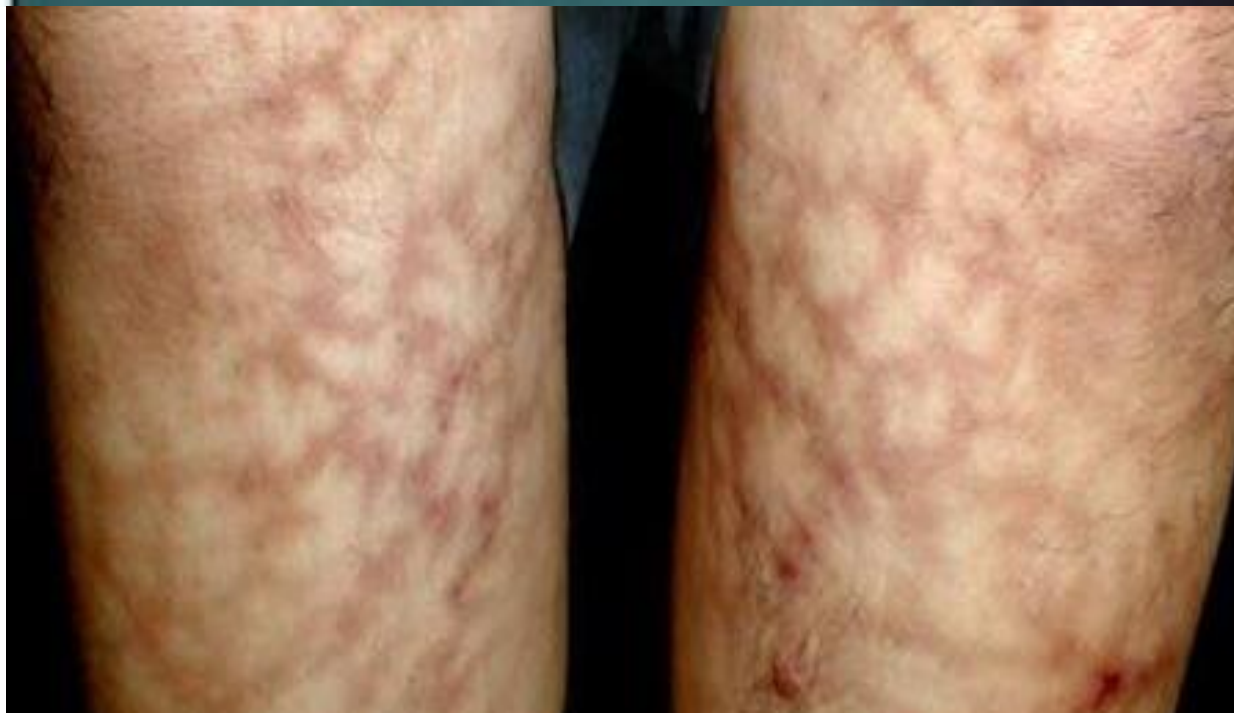
- **It stimulates release of dopamine stored in nerve terminals.**
- **Reduces reuptake of released dopamine by the presynaptic neuron.**
- **Weak glutamate N -methyl- d -aspartate (NMDA) receptor antagonist, reducing glutamatergic overactivity .**



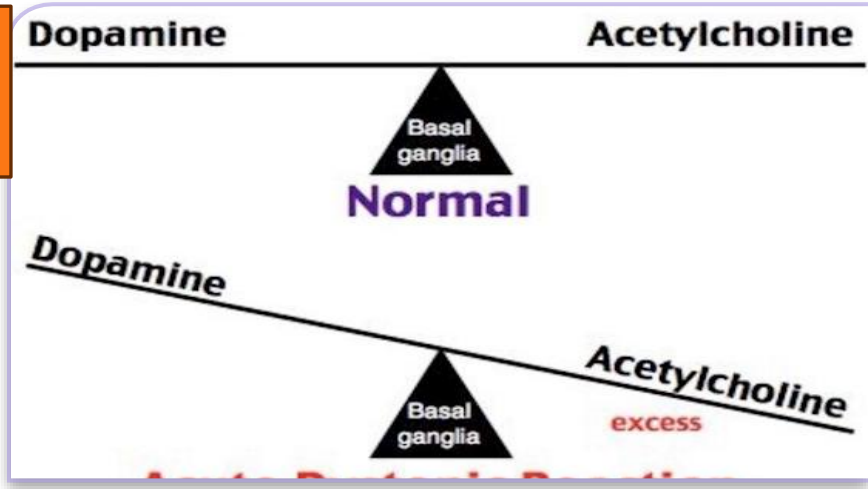
Adverse effects of amantadine

- **GIT upset.**
- **Hallucinations& mood changes.**
- **Postural hypotension.**
- **Skin pigmentation (moteld skin) dilatation of capillaries (Livedoreticularis).**



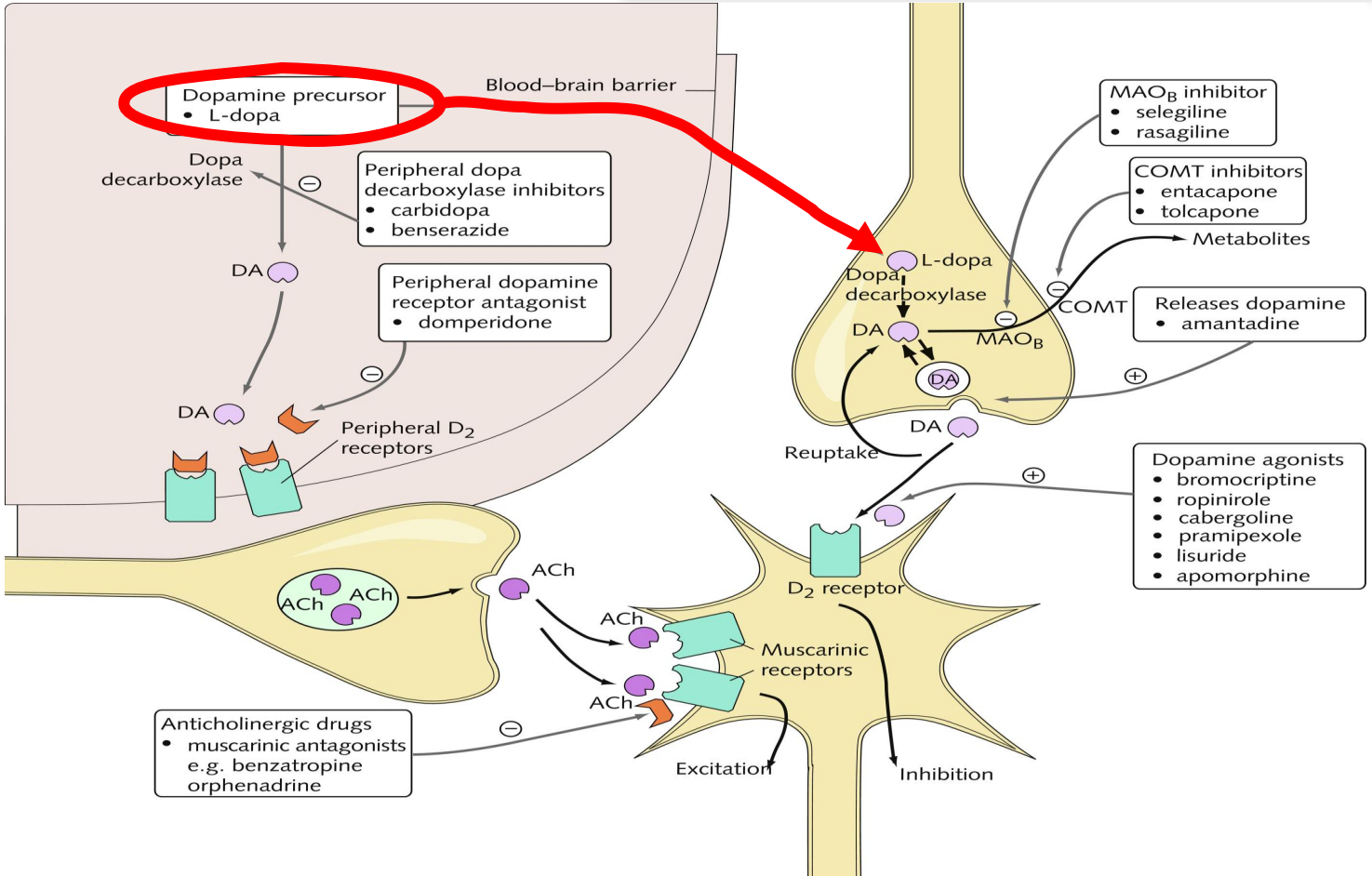


6. Anticholinergic drugs:
Benztropine –Trihexyphenidyl



Mechanism of action:

- **Selectivity block central than peripheral muscarinic receptors (M1).**
- **Improve tremors**
- **Little effect on muscle rigidity.**



6. Anticholinergic drugs:

Uses

- **Parkinsonism (less effective than L-dopa)**
- **Drug-induced extrapyramidal side effects.**

Adverse effects

- **In patients suffering from Parkinsonism, there is some degree of dementia associated with atrophy of cortical neurons. Anticholinergic drugs may aggravate dementia and memory loss.**
- **Urine retention ,glaucoma**

Quiz 3

Early-stage female experienced a minor fall (3 months ago) after tripping over her dog and landed on an outstretched right hand, leading to wrist pain, also complained of some recent trouble with balance and a small hand tremor. She was referred to a neurologist and diagnosed with early-stage idiopathic Parkinson's disease

What is the proper treatment of this patient?

Answer

- **Sustained-release carbidopa-levodopa is considered first-line treatment for these patients.**
- **Inadequate response can be handled by a trial of immediate-release carbidopa-levodopa and then addition of a dopamine agonist when maximum levodopa doses are reached.**

Summary and wrap up

- **Dopamine precursors: Levodopa (L-dopa) is the first line treatment increasing dopamine in basal ganglia improving symptoms but also in vomiting centre and meso-cortical pathway leading to adverse effects .**
- **COMT inhibitors: Tolcapone – Entacapone increases the efficacy of L-dopa and stabilizes dopamine levels in the striatum**
- **Selective MAO-B inhibitors: Selegiline decreasing breakdown of dopamine in the brain.**
- **Dopamine agonists: Bromocriptine (ergot alkaloid), the newer non ergot drugs are Pramipexole and Ropinirole**
- **The antiviral drug Amantadine improve the symptoms may has a neuroprotective effect**
- **Anticholinergic drugs: Benztropine –Trihexyphenidyl selectivity block central than peripheral muscarinic receptors (M1) restoring the balance between dopamine and ACh.**

References & recommended readings

1- Brenner, C.S. G. Brenner and Stevens' Pharmacology. [ClinicalKey Student]. Retrieved from: https://clinicalkeymeded.elsevier.com/#/books/9780323391665/

2- Wecker, L. Brody's Human Pharmacology. [ClinicalKey Student]. Retrieved from https://clinicalkeymeded.elsevier.com/#/books/9780323476522/

3- Waller D. G., & Sampson A. (2017). Medical Pharmacology and Therapeutics Elsevier eBook on Vitalsource. [ClinicalKey Student]. Retrieved from https://clinicalkeymeded.elsevier.com/#/books/9780702071935/

thanks

For Watching