السلام عليكم ورحمة الله وبركاته

Al-Mustaqbal University College

Department of Pharmacy

Pharmacology II 4th stage

Treatment of Neurodegenerative Diseases

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General Learning Objectives

Upon completion of the lecture, attendances will be able to:

- Understand the term Parkinsonism.
- Differentiate between idiopathic parkinson's disease and other causes of parkinsonism.
- Understand the pathophysiology of parkinsonism and how this influences the choice of pharmacology treatment.
- Classify drug classes that are commonly used.

Neurodegenerative diseases

- Parkinson's Disease
- Alzheimer's Disease

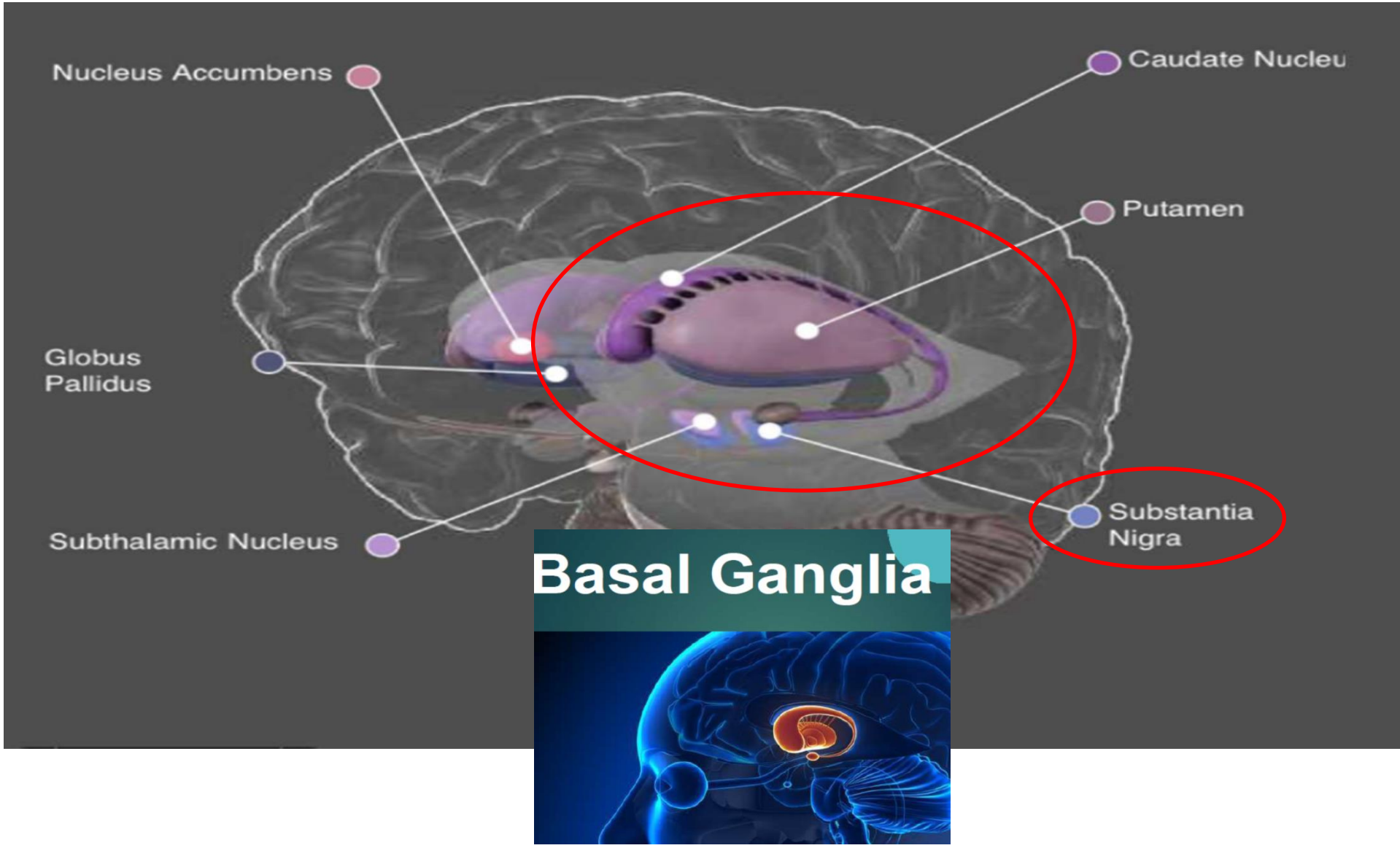
Neurodegenerative diseases are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

For example, Alzheimer disease is characterized by the loss of cholinergic neurons in the nucleus basalis

whereas Parkinson disease is associated with a loss of dopaminergic neurons in the substantia nigra.

Parkinson's disease: **is chronic progressive neurodegenerative disease**

- **Loss of dopaminergic neurons in substantia nigra**

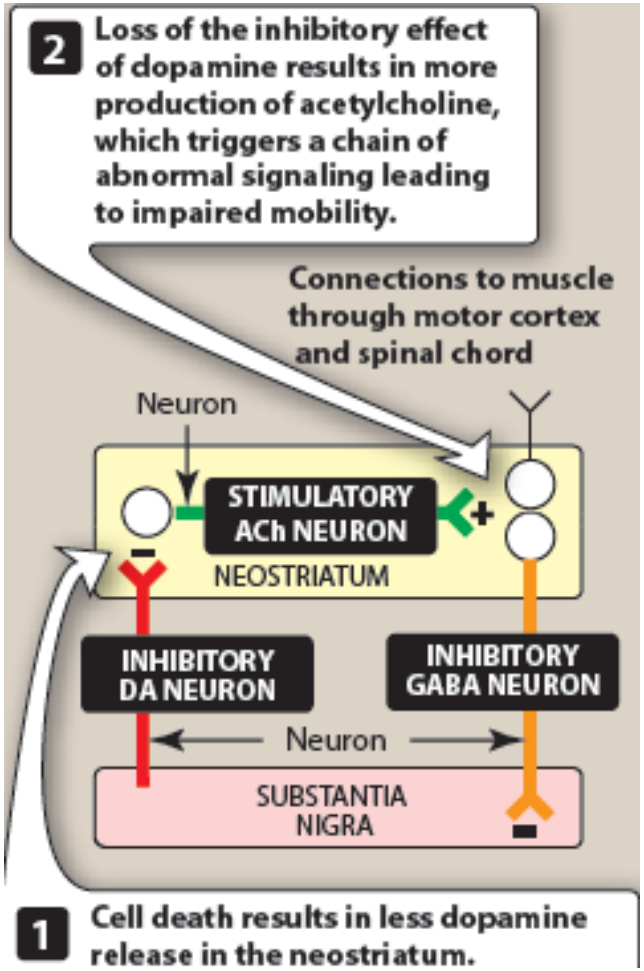


Secondary parkinsonism:

- Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions.

- Drugs such as the phenothiazines and haloperidol, induce parkinsonism like symptoms

❖**Balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed**

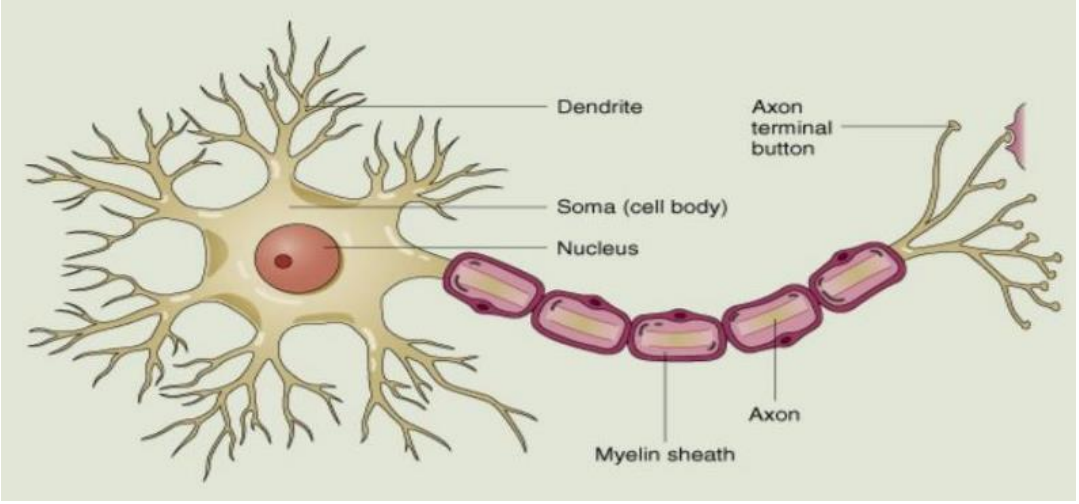


Very Important Five
Refreshment Slides

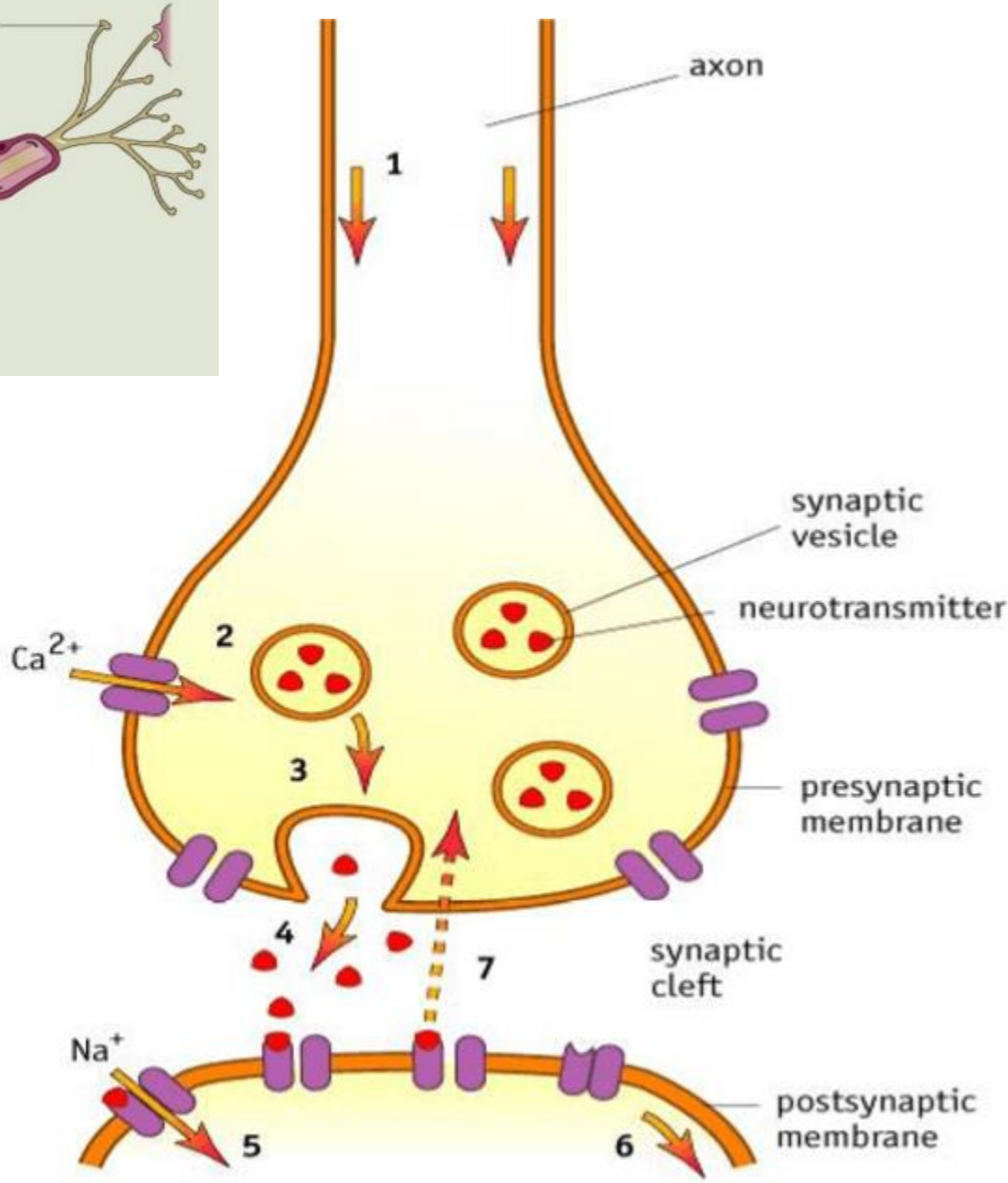
Synaptic Cleft and Action Potential

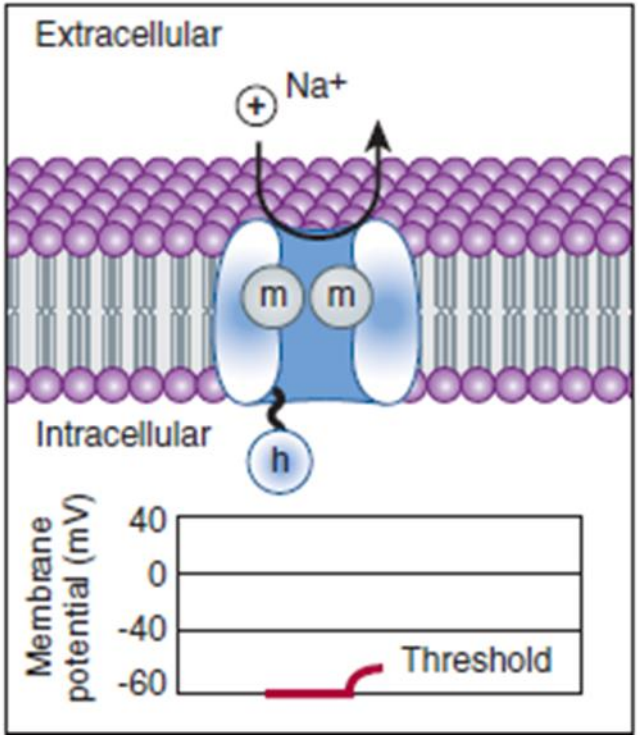
Action potential: Sudden, fast, transitory and propagating change of the resting membrane potential

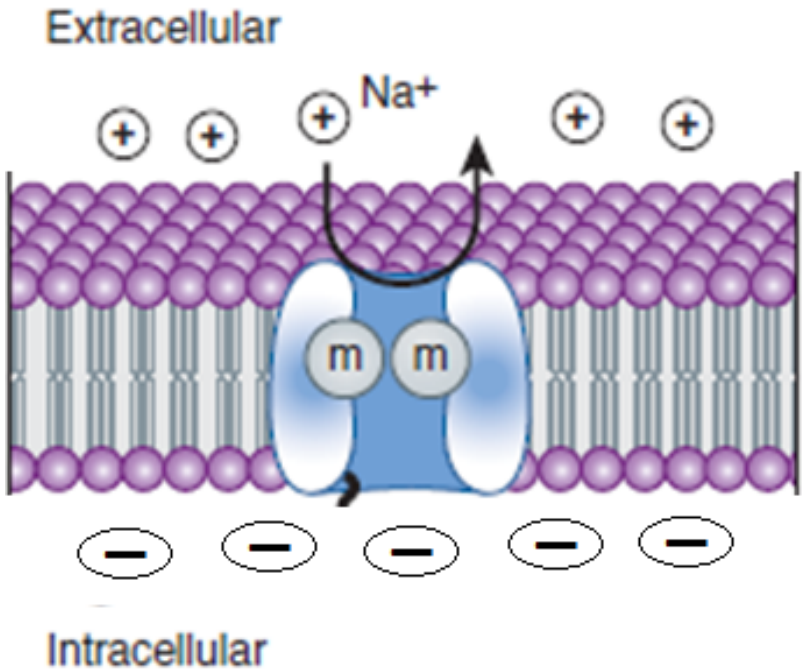
Action potentials are nerve signals. Neurons generate and conduct these signals along their processes in order to transmit them to the target tissues.



SYNAPTIC CLEFT AND ACTION POTENTIAL



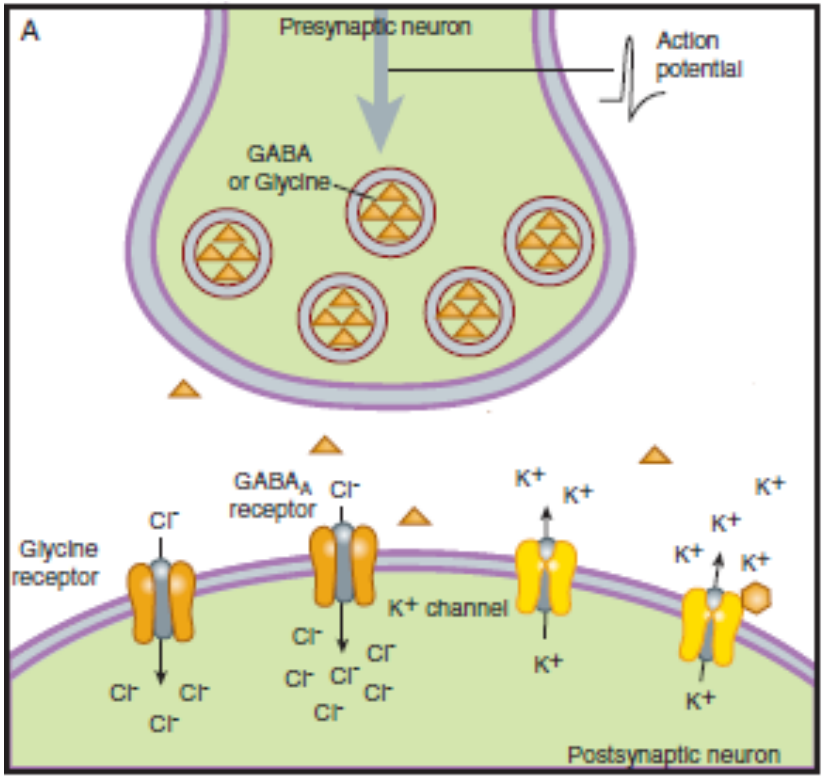




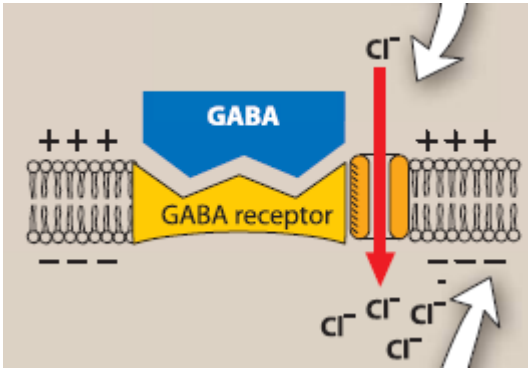
polarized cell membrane

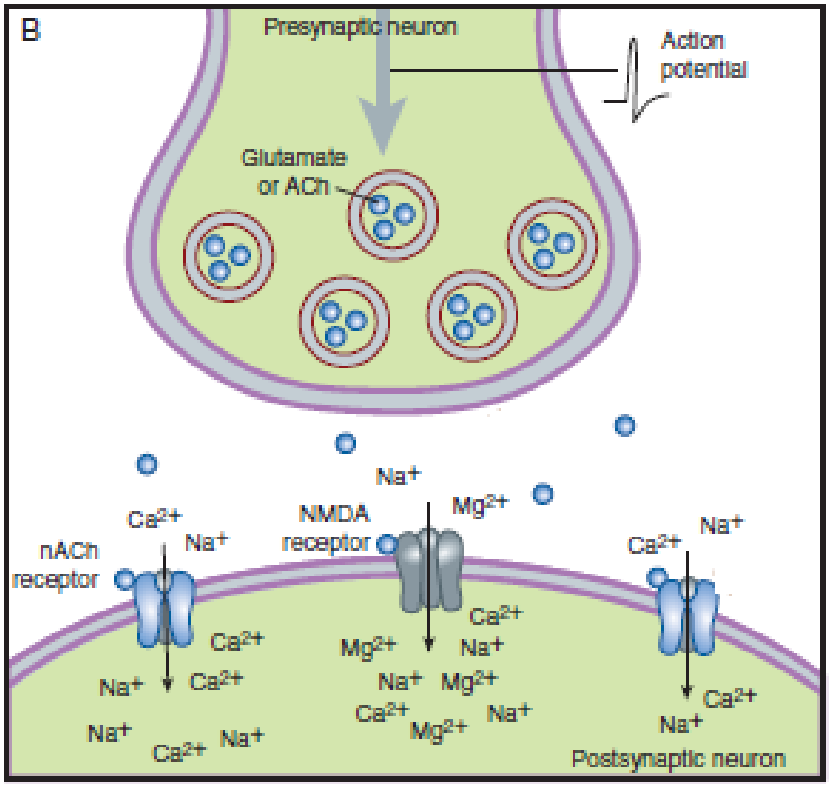
Resting membrane potential

Inhibitory postsynaptic potentials (IPSP)



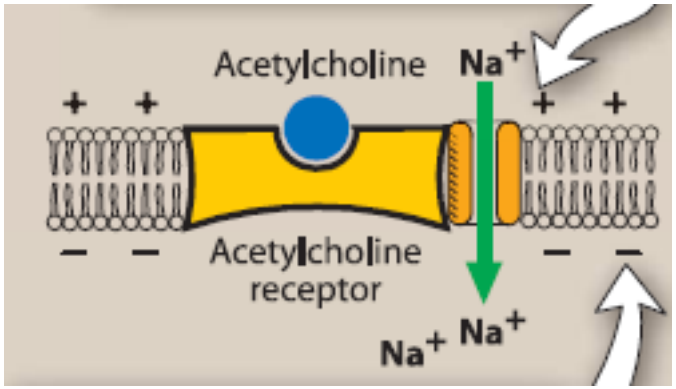
hyperpolarized cell membran





excitatory postsynaptic potentials (EPSP)

depolarized cell membrane



Parkinsonism Characterized by 4 cardinal features –

1- Bradykinesia

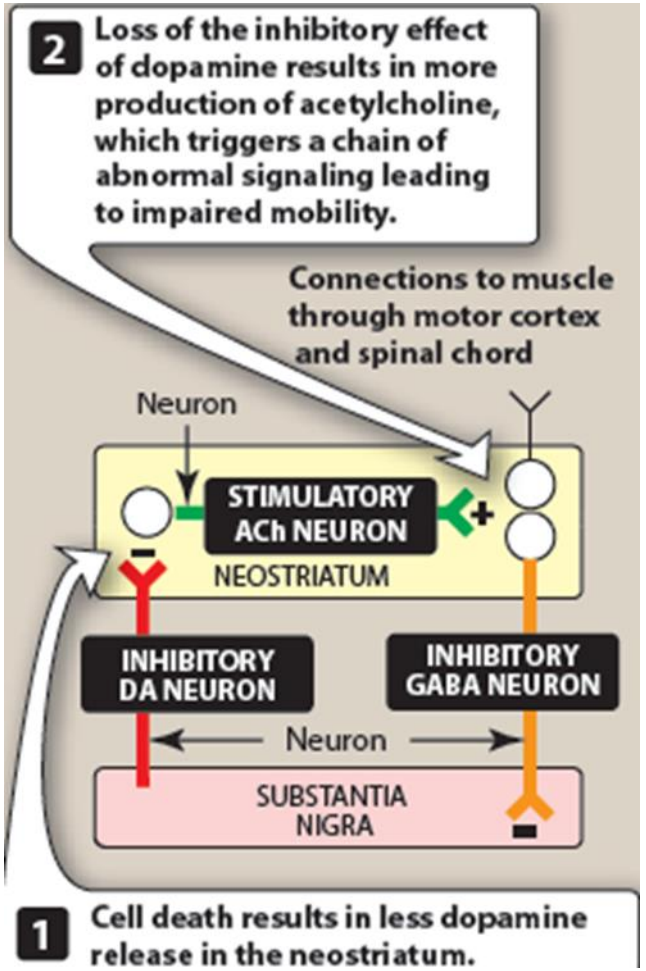
2- Muscular rigidity

3- Resting tremors

4- Loss of postural reflexes

Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine.



Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

Drugs treatment dose not prevent disease progression but improves quality of life.

Antiparkinsonism drugs either increase dopaminergic activity. or decrease cholinergic activity.

I- Drugs increase dopaminergic activity:

1- Dopamine precursor (levodopa)

Levodopa is a metabolic precursor of dopamine.

• It restores dopamine levels in the extrapyramidal centers (substantia nigra) that atrophy in parkinsonism.

• In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra is adequate for conversion of levodopa to dopamine. Thus, the patient rarely complains that the drug effects "wear off."

• With time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered levodopa and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops.

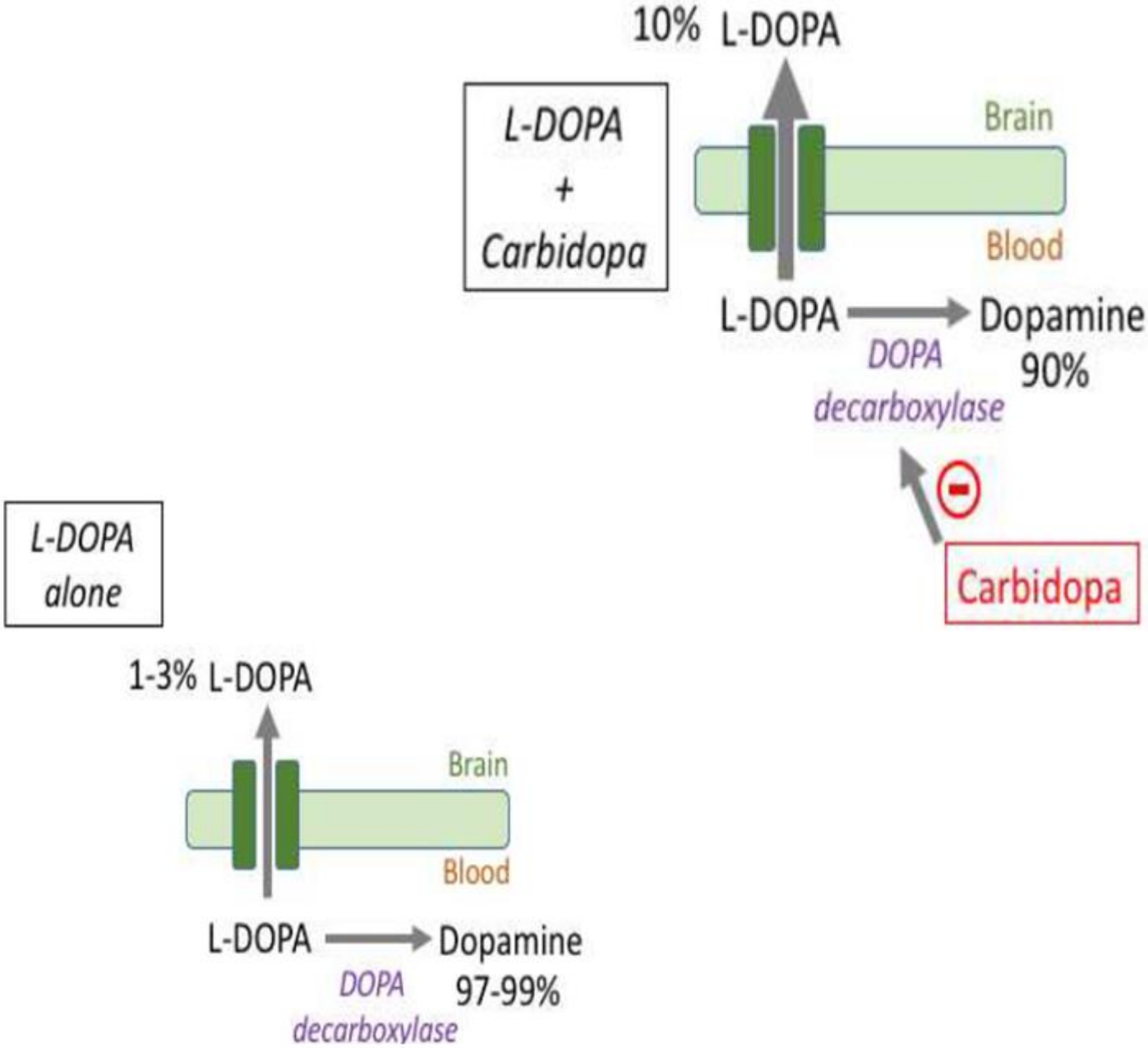
Mechanism of action

Levodopa: Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, levodopa, is readily transported into the CNS and is converted to dopamine by dopa decarboxylase enzyme in the brain.

Unfortunately dopa decarboxylase present out of CNS also and converted a lot of levodopa to dopamine before pass into brain, which decrease effect of levodopa on CNS and increases peripheral dopamine side effects (nausea, vomiting, cardiac arrhythmias, and hypotension).

Carbidopa is **Dopa decarboxylase inhibitor** and does not cross the blood-brain barrier, it is combined with levodopa to decrease decarboxylation of levodopa in peripheral tissue.

The addition of carbidopa
1.lowers the dose of levodopa needed by four- to five-fold
2.decreases the severity of the side effects of peripherally formed dopamine


10% L-DOPA
L-DOPA + Carbidopa
Brain
Blood
L-DOPA
Dopamine
90%
DOPA decarboxylase
Carbidopa
L-DOPA alone
1-3% L-DOPA
Brain
Blood
L-DOPA
Dopamine
97-99%
DOPA decarboxylase

2. Actions: Levodopa effectively decreases the rigidity, tremors symptoms of parkinsonism.

3. Therapeutic uses: levodopa-carbidopa treatment reduces the severity of the disease for the first few years of treatment.

4. Absorption and metabolism:
The drug is absorbed rapidly from the small intestine (when empty of food) so it taken 30 minute prior meal.

- The short half-life (1 to 2 hours) of levodopa causes fluctuations in plasma concentration. which may produce fluctuations in motor response ("on- off" phenomenon).

- A high protein meals and large neutral amino acids meals, interfere with the transport of levodopa into CNS.

Adverse effects: Peripheral effects:

GIT: Anorexia, nausea, and vomiting occur because of stimulation of the emetic center.
CVS: Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop.
Eye: Adrenergic action on the iris causes mydriasis,

CNS effects:
Flactuation in response (on-off phenomenon)
hallucinations.
abnormal involuntary movements (dyskinesia).
These CNS effects are the opposite of parkinsonian symptoms and reflect the over activity of dopamine at receptors in the basal ganglia.
Levodopa can also cause mood changes, depression, and anxiety.

Interactions:

• The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness.

• Concomitant administration of levodopa and monoamine oxidase (MAO) inhibitors, such as **phenelzine**, can produce a hypertensive crisis.

• In many psychotic patients, levodopa exacerbates symptoms, possibly through the buildup of central amines.

• In patients with glaucoma, the drug can cause an increase in intraocular pressure.

• Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias.

• Antipsychotic drugs are contraindicated in parkinsonian patients, because these block dopamine receptors and produce a parkinsonian syndrome themselves.

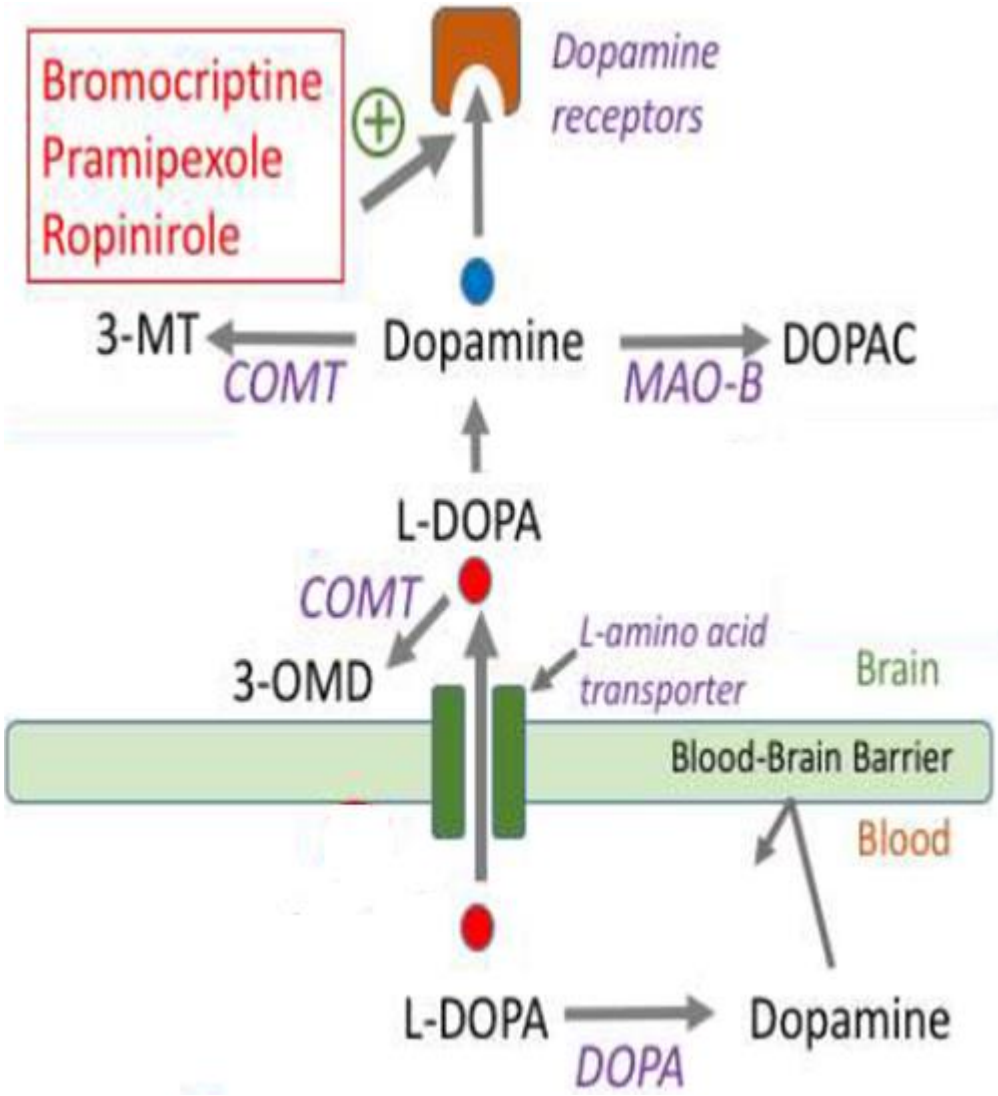
2- Dopamine receptor agonists

a- Ergot derivatives,
bromocriptine and pergolide,

b- Non-ergot drugs, Apomorphine, pramipexole, ropinirole, and rotigotine

Advantages:

- Have durations of action longer than that of levodopa
- less risk of dyskinesias and motor fluctuations when compared to patients started with levodopa therapy.



Dopamine receptor agonists

Bromocriptine and pergolide

They are Ergot derivatives and pergolide is potent of the two.

• The dose is increased gradually during a period of two to three months.

Side effects: Hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common than levodopa, whereas dyskinesia is less prominent.

• In psychiatric illness, they may cause the mental condition to worsen.

• In patients with a history of myocardial infarction, cardiac problems may develop.

• In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and

• In patients with peptic ulcer, there is a worsening of the ulcer.

• have the potential to cause **pulmonary and retroperitoneal fibrosis.**

Apomorphine, pramipexole, ropinirole, and rotigotine

• They are non-ergot dopamine receptors agonists.

Pramipexole and ropinirole are orally active agents.

Apomorphine is injection.

Rotigotine is administered as a once-daily transdermal patch that provides even drug levels over 24 hours.

• They alleviate the motor deficits in both patients never taken levodopa and patients with advanced Parkinson disease taking levodopa.

• They delay the need to use levodopa therapy in early Parkinson, and may decrease the dose of levodopa in advanced Parkinson.

1- these drugs do not exacerbate peripheral vasospasm, or cause fibrosis.

2- Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are common side-effects of these drugs;

3- dyskinesias are less frequent than with levodopa.

4- Pramipexole is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction.

5- The fluoroquinolone antibiotics shown to inhibit the metabolism of ropinirole.

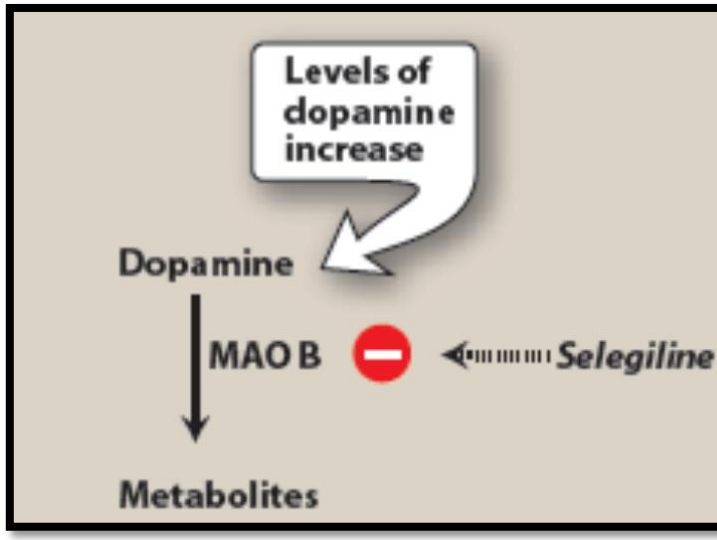
3- Dopamine metabolism inhibition

A- MAO B ibhibitors

- Selegiline

selectively inhibits MAO B (which metabolizes dopamine), but does not inhibit MAO A (which metabolizes norepinephrine and serotonin).
Thus decreasing the metabolism of dopamine and increases dopamine levels in the brain.

- It enhances the actions of levodopa, when administered together, it reduces the required dose of levodopa.



- If selegiline is administered at high doses, the selectivity of the drug is lost, and the patient is at risk for severe hypertension.

- Has a neuroprotective effect by suppressing the formation of oxidative metabolites of dopamine (antioxidant).

- Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.

- Rasagiline, an irreversible and selective inhibitor of brain MAO type B, has five times the potency of selegiline.

Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.

- Safinamide is also a selective inhibitor of MAO type B indicated for use as an adjunct to levodopa–carbidopa.

B- Catechol-O-methyltransferase inhibitors

- Entacapone or Tolcapone

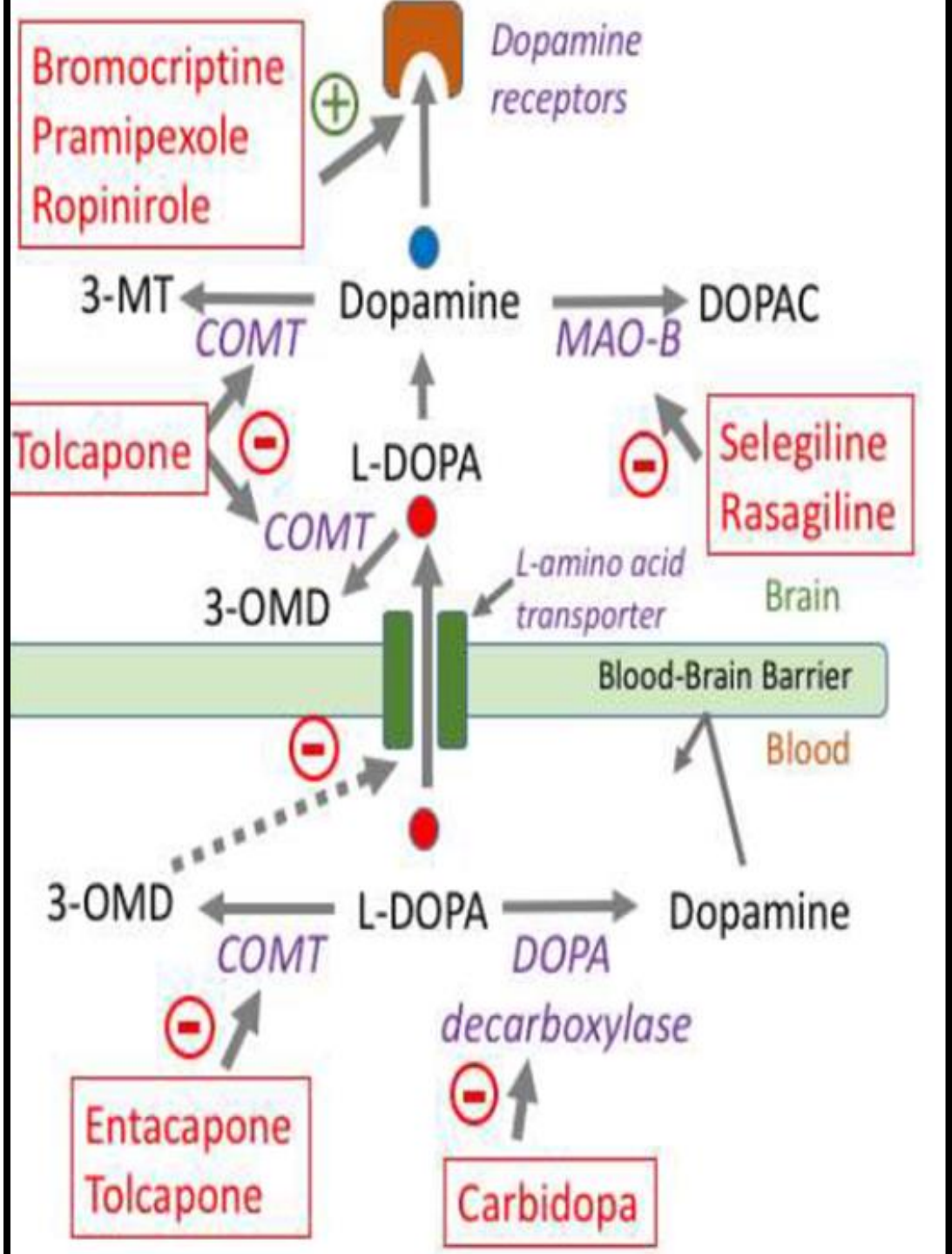
• the methylation of levodopa by catechol-0-methyltransferase (COMT) to 3-0-methyldopa is a minor pathway for levodopa metabolism.

•when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-0-methyldopa is formed that competes with levodopa for active transport into the CNS.

•inhibition of COMT by **entacapone or tolcapone** leads to decreased plasma concentrations of 3-0-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.

•Both reduce the symptoms of "wearing-off" phenomena seen in patients on levodopa-carbidopa.

Catechol-O-methyltransferase inhibitors



Absorption: Oral absorption of both drugs occurs readily and is not influenced by food.

Distribution: They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution.

• Tolcapone **penetrates the blood-brain barrier** and inhibits COMT in the CNS.

Metabolism: Both drugs are extensively metabolized

• Dosage may need to be adjusted in patients with moderate or severe cirrhosis.

• Tolcapone has a long duration of action.

Adverse effects

• diarrhea, nausea, anorexia, **postural hypotension,** dyskinesias, hallucinations, and sleep disorders.

• fulminating hepatic necrosis is associated with tolcapone use. Entacapone does not exhibit this toxicity and has largely replaced tolcapone in clinical practice.

II- Antimuscarinic agents

• The antimuscarinic agents are much less efficacious than levodopa and may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.

benztropine, trihexyphenidyl, biperiden, orphenadrine and procyclidine.

• they are contraindicated in patients with glaucoma, prostatic hypertrophy or pyloric stenosis.

• Blockage of cholinergic transmission produced effects similar to augmentation of dopaminergic transmission.

• Adverse effects are similar to those caused by high doses of atropine—for example, pupillary dilation, confusion, hallucination, urinary retention, constipation and dry mouth.

Amantadine

• It is antiviral drug amantadine, used in the treatment of influenza.

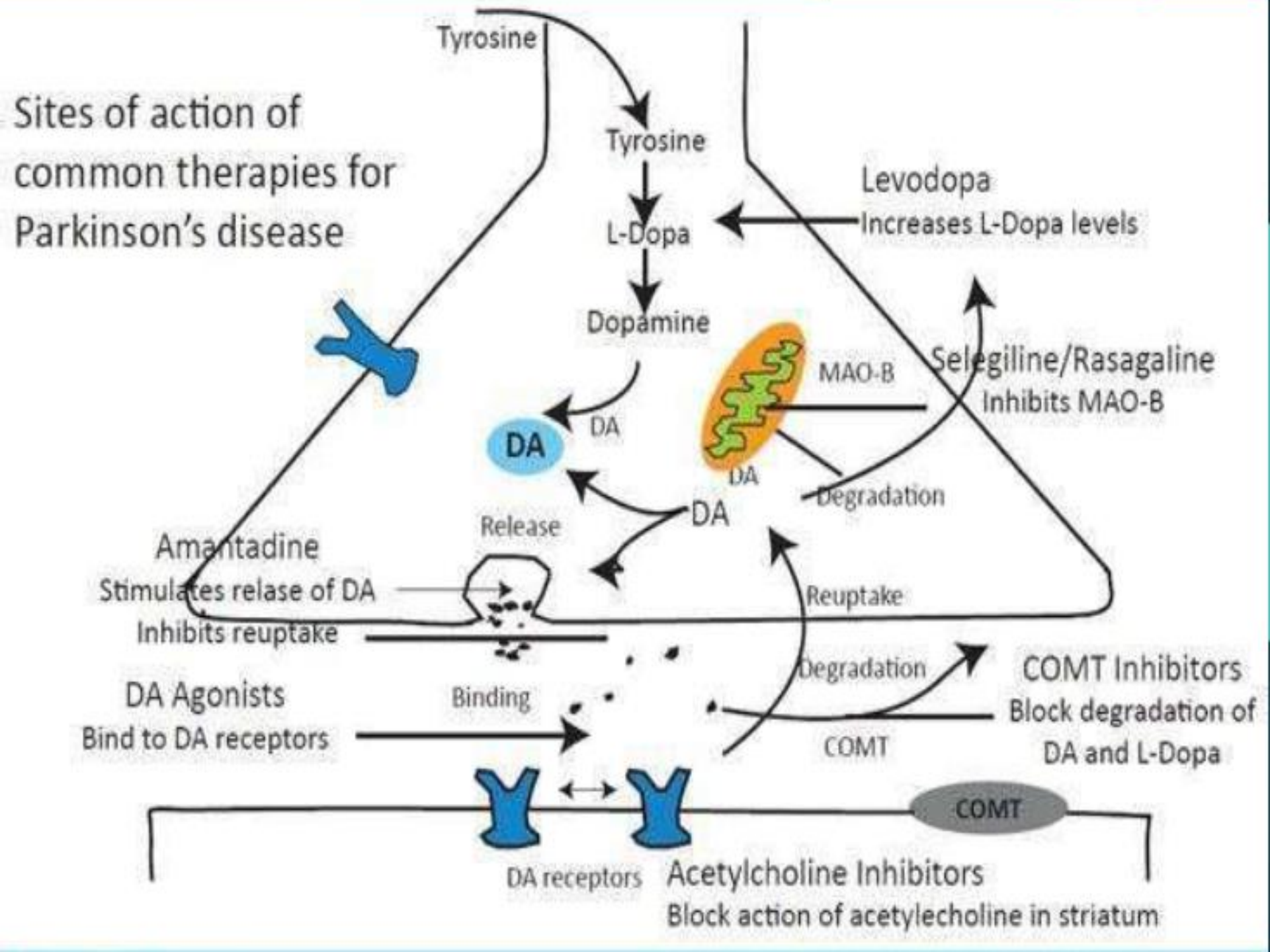
• Amantadine increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type glutamate receptors.

• The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis.

• Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.

• Amantadine is less efficacious than levodopa, and Tolerance develops more readily.

• The drug has little effect on tremor, but is more effective than the anticholinergics against rigidity and bradykinesia.


Sites of action of common therapies for Parkinson's disease
Tyrosine
Tyrosine
L-Dopa
Dopamine
Levodopa
Increases L-Dopa levels
MAO-B
Selegiline/Rasagaline
Inhibits MAO-B
DA
DA
DA
Degradation
Release
Amantadine
Stimulates relase of DA
Inhibits reuptake
Reuptake
Degradation
COMT Inhibitors
Block degradation of DA and L-Dopa
DA Agonists
Bind to DA receptors
Binding
COMT
COMT
DA receptors
Acetylcholine Inhibitors
Block action of acetylecholine in striatum

Drugs Used in Alzheimer Disease

Dementia of the Alzheimer type has distinguishing features:

1) accumulation of prone proteins.

2) loss of cortical neurons, particularly cholinergic neurons.

Current therapies aim to either

1- improve cholinergic transmission within the CNS or

2- prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.

Pharmacologic intervention for Alzheimer disease is only palliative and provides modest short-term benefit.

A. Acetylcholinesterase inhibitors

It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning.

The reversible AChE inhibitors approved for the treatment of Alzheimer disease include:
donepezil,
galantamine,
and rivastigmine

Rivastigmine is the only agent approved for the management of dementia associated with Parkinson disease and also the only AChE inhibitor available as a **transdermal formulation**.

Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps

B. NMDA receptor antagonist

overstimulation of glutamate receptors, particularly of the NMDA type may damage neurons and lead to neurodegenerative or Apoptosis (programmed cell death).

Memantine is an NMDA receptor antagonist indicated for moderate to severe Alzheimer disease.

Memantine is well tolerated, with few dose-dependent adverse events.

Given its different mechanism of action and possible neuroprotective effects, memantine is often given in combination with an AChE inhibitor.

8.1 A 75-year-old man with moderate Parkinson disease is no longer responding to anticholinergic treatment for his tremors and bradykinesia. Which combination 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, carbidopa, and selegiline

References

Rey J. (2015) Drugs for Neurodegenerative Diseases. Karen W. *et al. Lippincott Illustrated Reviews: Pharmacology*. 7TH ed, Wolters Kluwer.

- Aminoff M., (2015) Pharmacologic Management of Parkinsonism & Other Movement Disorders. Katzung, B., G. and Trevor, A., J. *Basic and clinical pharmacology*. (13thed.). McGraw-Hill.

Thank you