DRUGS THAT ACT IN THE CNS

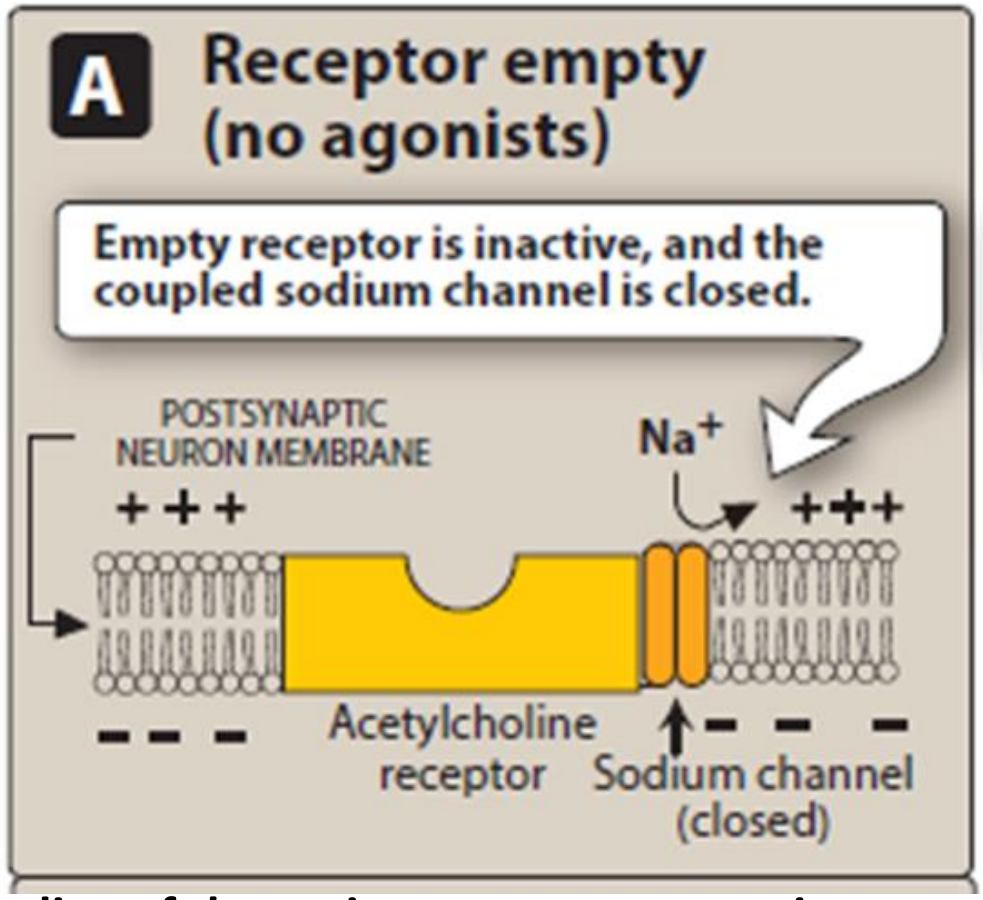
Drugs for Neurodegenerative Diseases 1

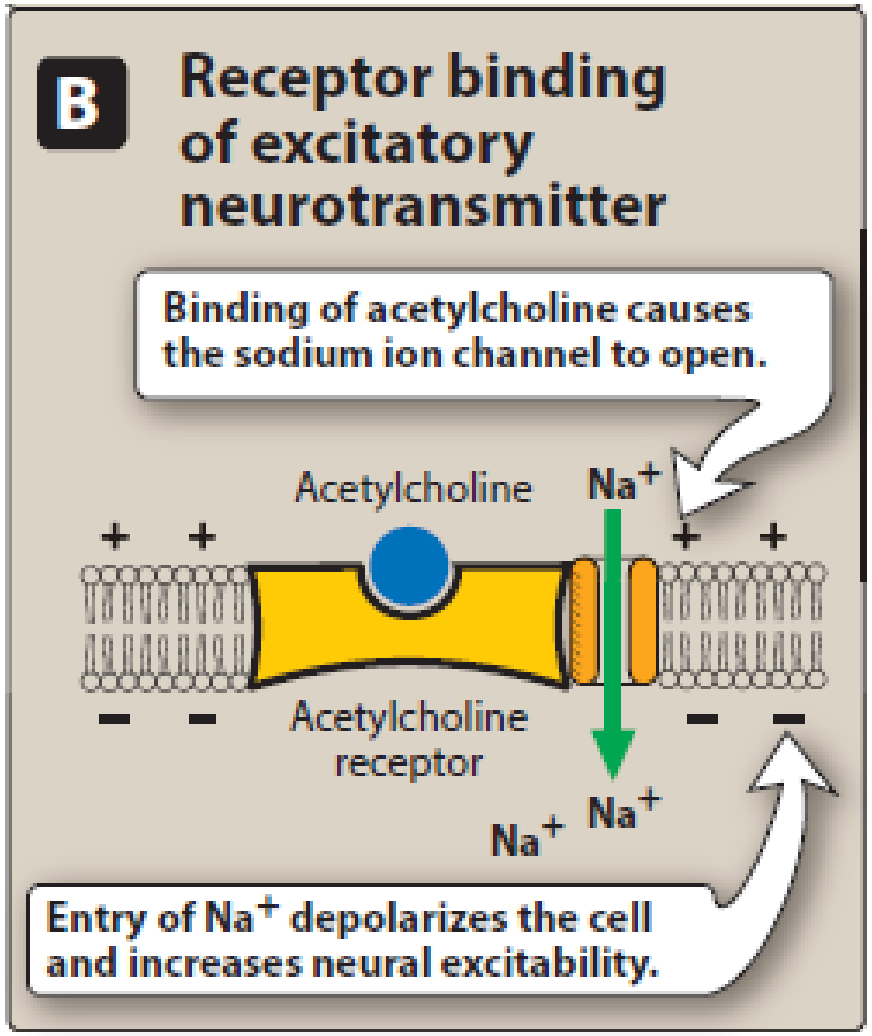
Dr Karamallah S. Mahmood

PhD Clinical Pharmacology

SYNAPTIC POTENTIALS/

A. Excitatory pathways

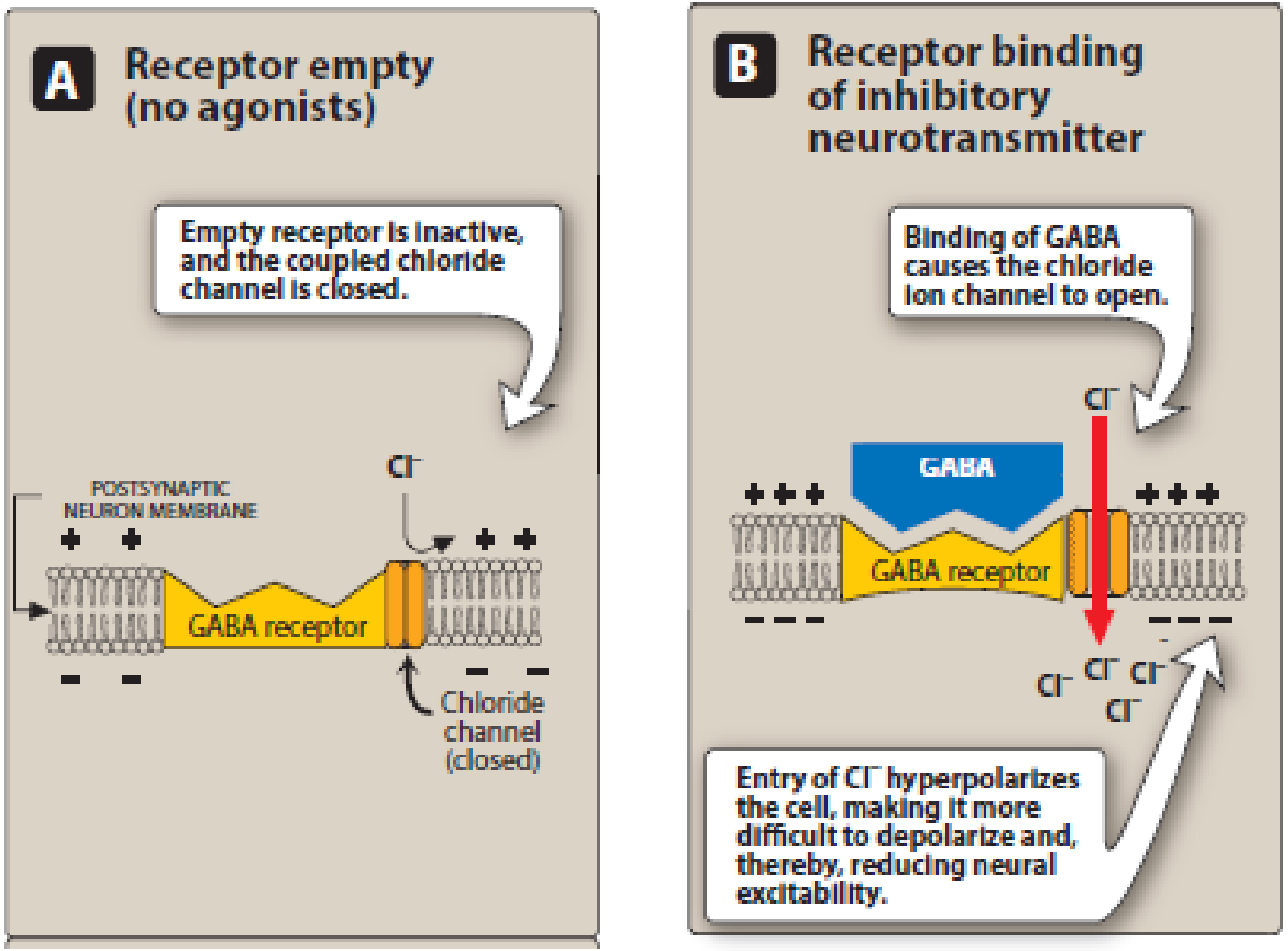




Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

SYNAPTIC POTENTIALS/ B. Inhibitory pathways

Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron.



NEURODEGENERATIVE DISEASES

Neurodegenerative diseases of the CNS include **Parkinson's disease, Alzheimer's disease, MS, and ALS.**

These devastating illnesses are characterized by the progressive **loss of selected neurons** in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE

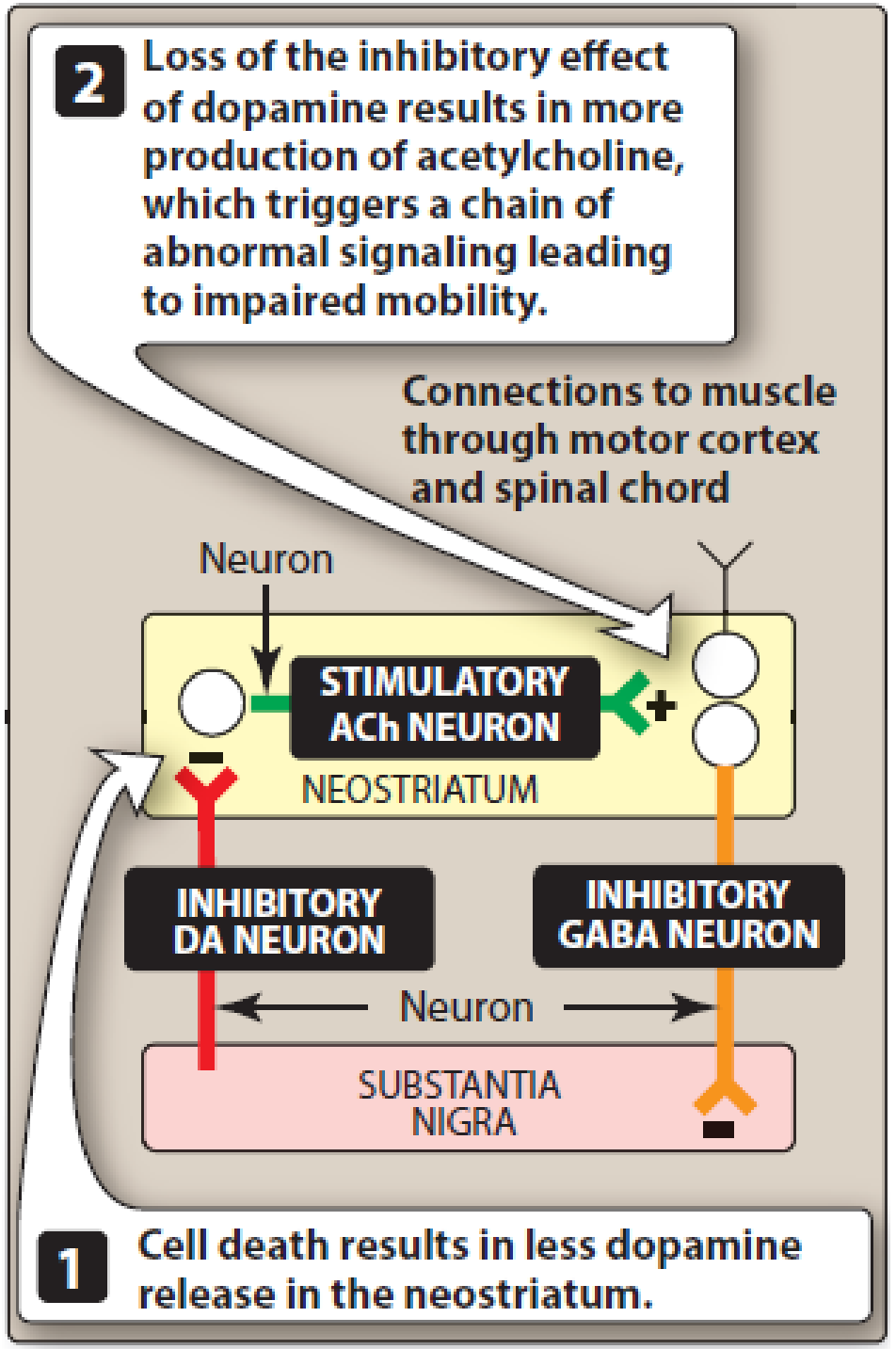
Parkinsonism is a progressive **neurological disorder of muscle movement**, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural abnormalities.

Most cases involve people **over the age of 65**, among whom the incidence is about 1 in 100 individuals.

NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE/ A. Etiology

The cause of Parkinson's disease is unknown for most patients.

The disease is correlated with **destruction of dopaminergic neurons in the substantia nigra** with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.



NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE/ A.Etiology

1. Substantia nigra: The substantia nigra, **part of the extrapyramidal system,** is the source of **dopaminergic neurons** that terminate in the neostriatum.

Each dopaminergic neuron makes **thousands of synaptic contacts** within the neostriatum and, therefore, modulates the activity of a large number of cells.

These dopaminergic projections from the substantia nigra fire **tonically** rather than in response to specific muscular movements or sensory input.

Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE/ A.Etiology

2. Neostriatum: Normally, the neostriatum is **connected to the substantia nigra** by neurons that secrete the inhibitory transmitter **GABA** at their termini.

In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter **dopamine** at their termini.

This mutual inhibitory pathway normally maintains a degree of inhibition of both areas.

In Parkinson's disease, **destruction of cells in the substantia nigra** results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum.

NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE/ A.Etiology

2. Neostriatum:

Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons.

This triggers a chain of **abnormal signaling**, resulting in loss of the control of muscle movements.

3. Secondary parkinsonism: Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is **blockade of dopamine** receptors in the brain, may produce parkinsonian symptoms (also called **pseudoparkinsonism**).

These drugs should be used with caution in patients with Parkinson's disease.

NEURODEGENERATIVE DISEASES/ PARKINSON'S DISEASE/ 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 .

Many of the symptoms of parkinsonism reflect an imbalance between the **excitatory cholinergic** neurons and the greatly diminished number of **inhibitory dopaminergic** neurons.

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 USED IN PARKINSON'S DISEASE

A. Levodopa and carbidopa : Levodopa is a metabolic **precursor of dopamine** .

It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.

In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of levodopa to dopamine.

Thus, **in new patients**, the therapeutic response to levodopa is consistent, and the patient rarely complains that the drug effects "wear off."

Unfortunately, **with time**, the number of neurons decreases, and fewer cells are capable of converting exogenously administered levodopa to dopamine.

DRUGS USED IN PARKINSON'S DISEASE

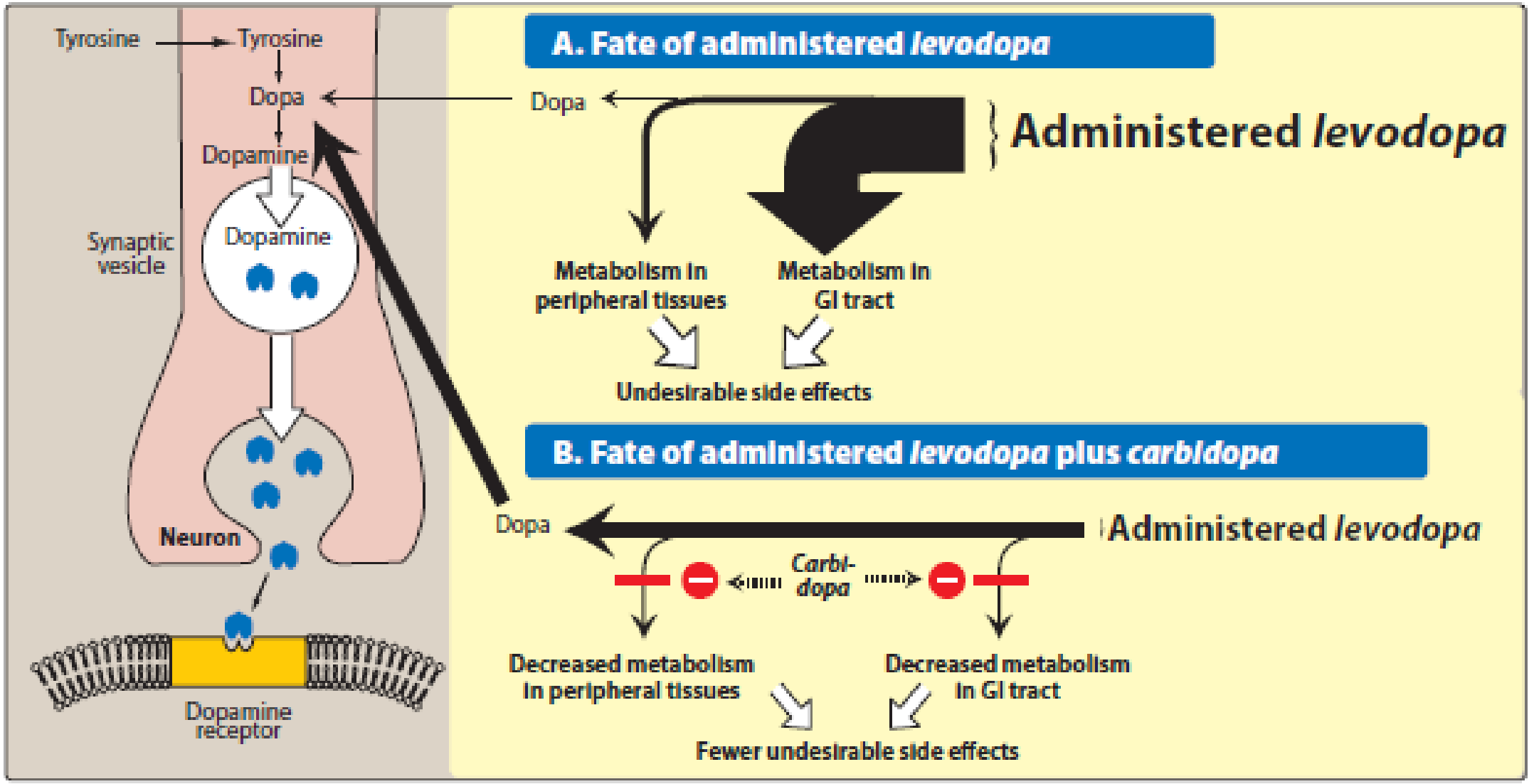
Consequently, motor control fluctuation develops.

Relief provided by levodopa is **only symptomatic**, and it lasts only while the drug is present in the body.

The effects of levodopa on the CNS can be greatly enhanced by **coadministering carbidopa** , a **dopamine decarboxylase inhibitor** that **does not** cross the blood–brain barrier.

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/

Mechanism of action:



DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Mechanism of action:

a. Levodopa: Dopamine does not cross the blood–brain barrier, but its immediate precursor, levodopa, is actively **transported into the CNS** and converted to dopamine .

Levodopa **must** be administered with carbidopa.

Without carbidopa, much of the drug is decarboxylated to dopamine **in the periphery**, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension.

b. Carbidopa: Carbidopa, a **dopamine decarboxylase inhibitor**, diminishes the metabolism of levodopa in the periphery, thereby increasing the availability of levodopa to the CNS.

The addition of carbidopa **lowers the dose** of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Therapeutic uses:

Levodopa in combination with carbidopa is an efficacious drug regimen for the treatment of Parkinson's disease.

It decreases rigidity, tremors, and other symptoms of parkinsonism.

In approximately **two-thirds of patients** with Parkinson's disease, levodopa–carbidopa substantially reduces the severity of symptoms for the first few years of treatment.

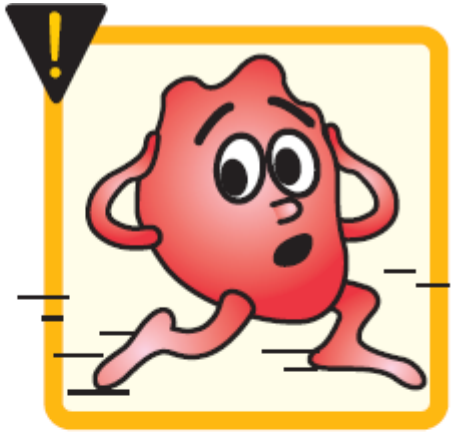
Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/

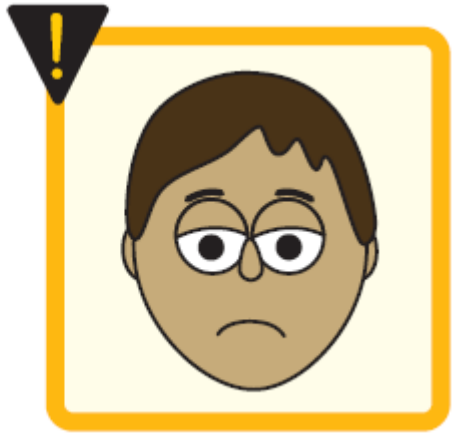
Adverse effects:

Anorexia

Tachycardia



Psychiatric problems



Nausea

Hypotension

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Adverse effects:

a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the **chemoreceptor trigger zone** .

Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart.

Hypotension may also develop. **Adrenergic action** on the iris causes **mydriasis**.

In some individuals, **blood dyscrasias** and a positive reaction to the Coombs test are seen.

Saliva and urine are a **brownish color** because of the melanin pigment produced from catecholamine oxidation.

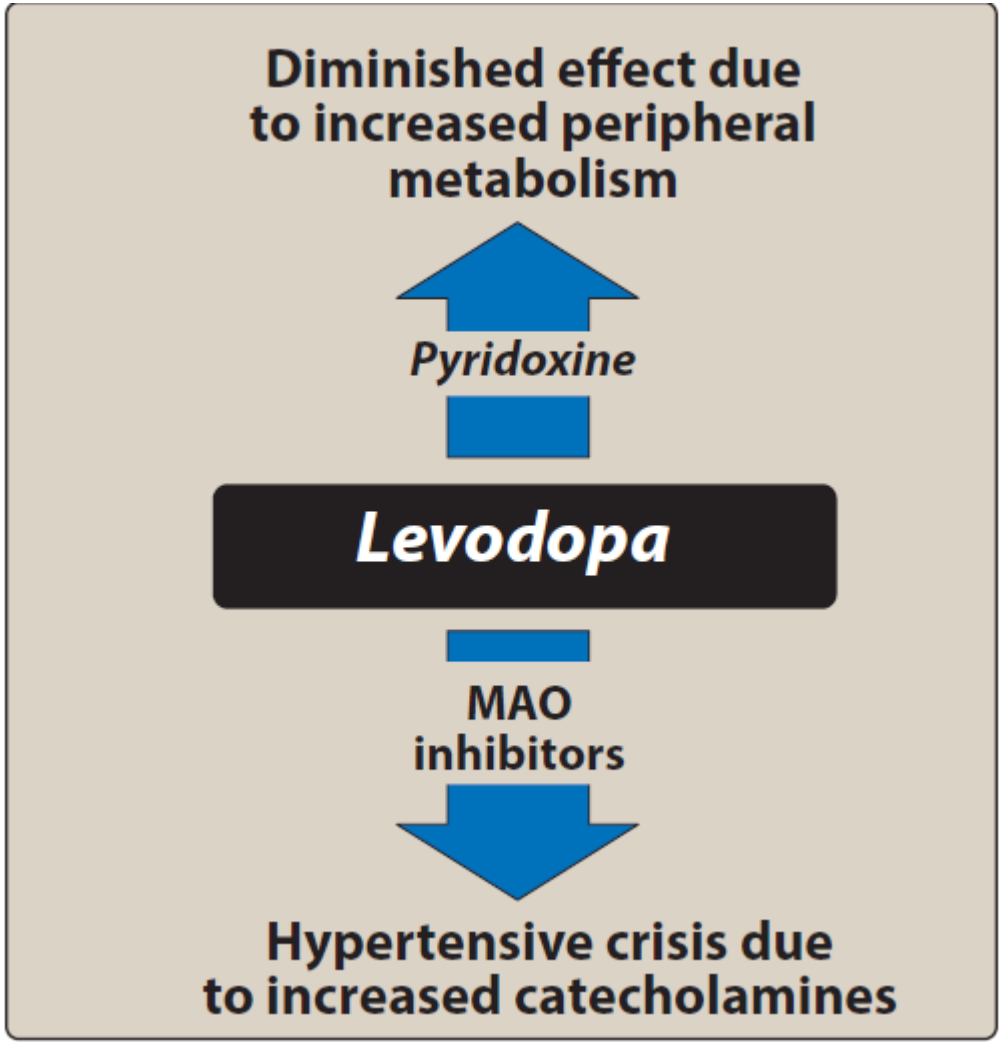
DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Adverse effects:

b. CNS effects: Visual and auditory **hallucinations** and abnormal involuntary **movements** (dyskinesias) may occur.

These effects are the **opposite of parkinsonian symptoms** and reflect overactivity of dopamine in the basal ganglia.

Levodopa can also cause mood changes, depression, psychosis, and anxiety.

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Interactions:



DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Interactions:

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

Concomitant administration of levodopa and non-selective monoamine oxidase inhibitors (MAOIs), such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production.

DRUGS USED IN PARKINSON'S DISEASE/ A. Levodopa and carbidopa/ Interactions:

Cardiac patients should be carefully monitored for the possible development of arrhythmias.

Antipsychotic drugs are generally **contraindicated in Parkinson's disease**, because they potently block dopamine receptors and may augment parkinsonian symptoms.