AGENTS USED IN PARKINSON'S DISEASE

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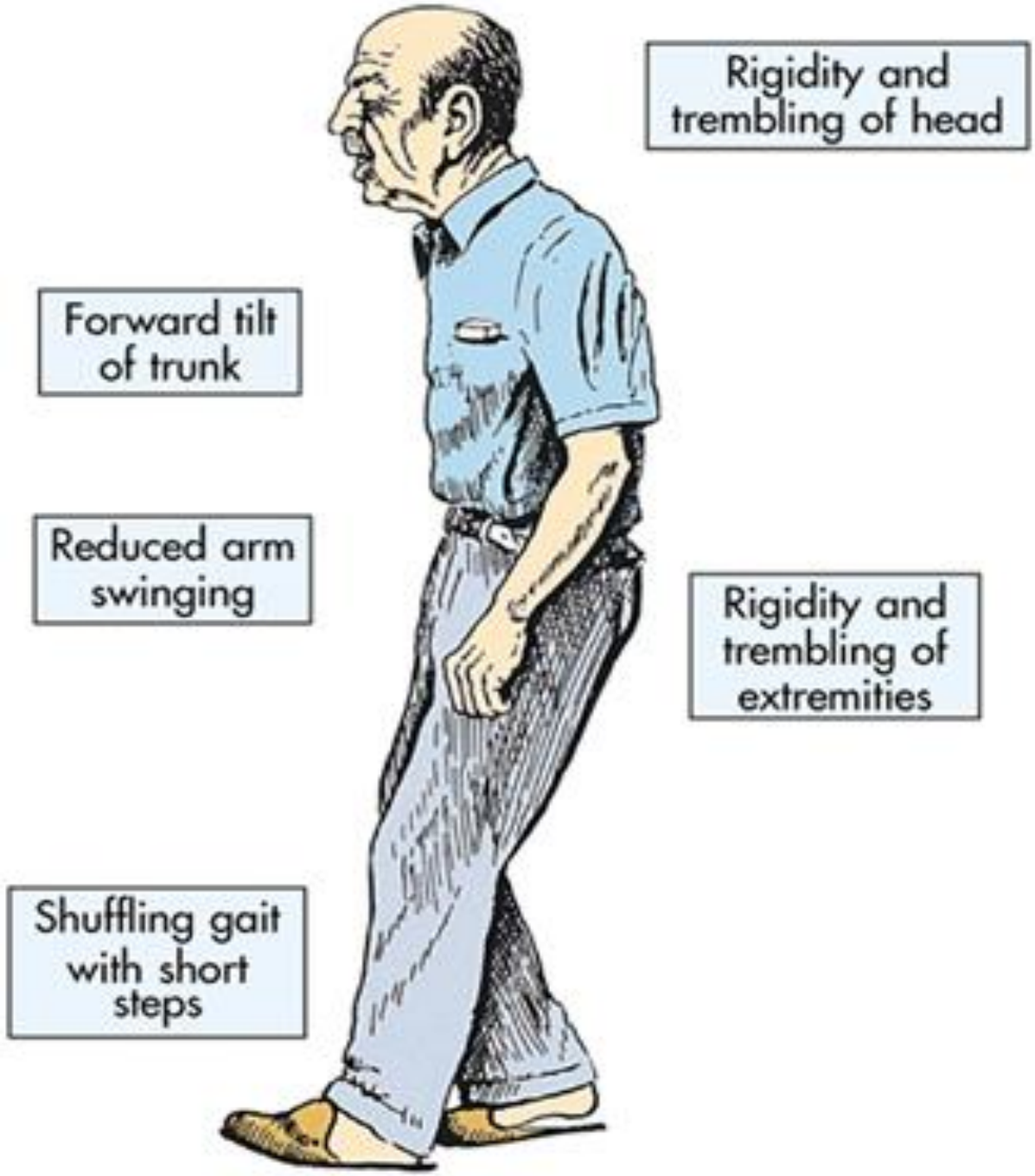
1. Overview of Parkinson's Disease

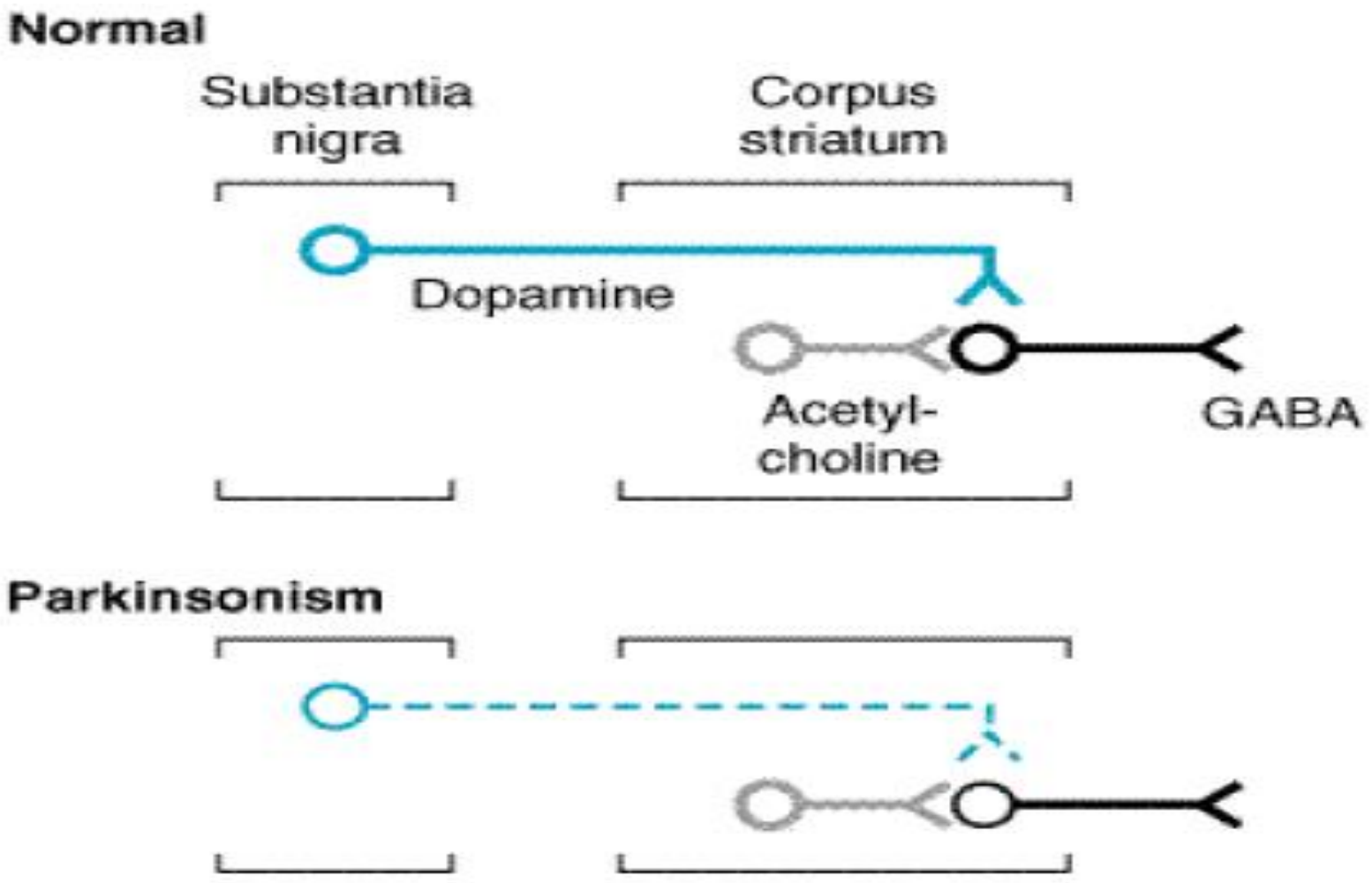
- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities.
- Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.


Rigidity and trembling of head
Forward tilt of trunk
Reduced arm swinging
Rigidity and trembling of extremities
Shuffling gait with short steps

2. ETIOLOGY

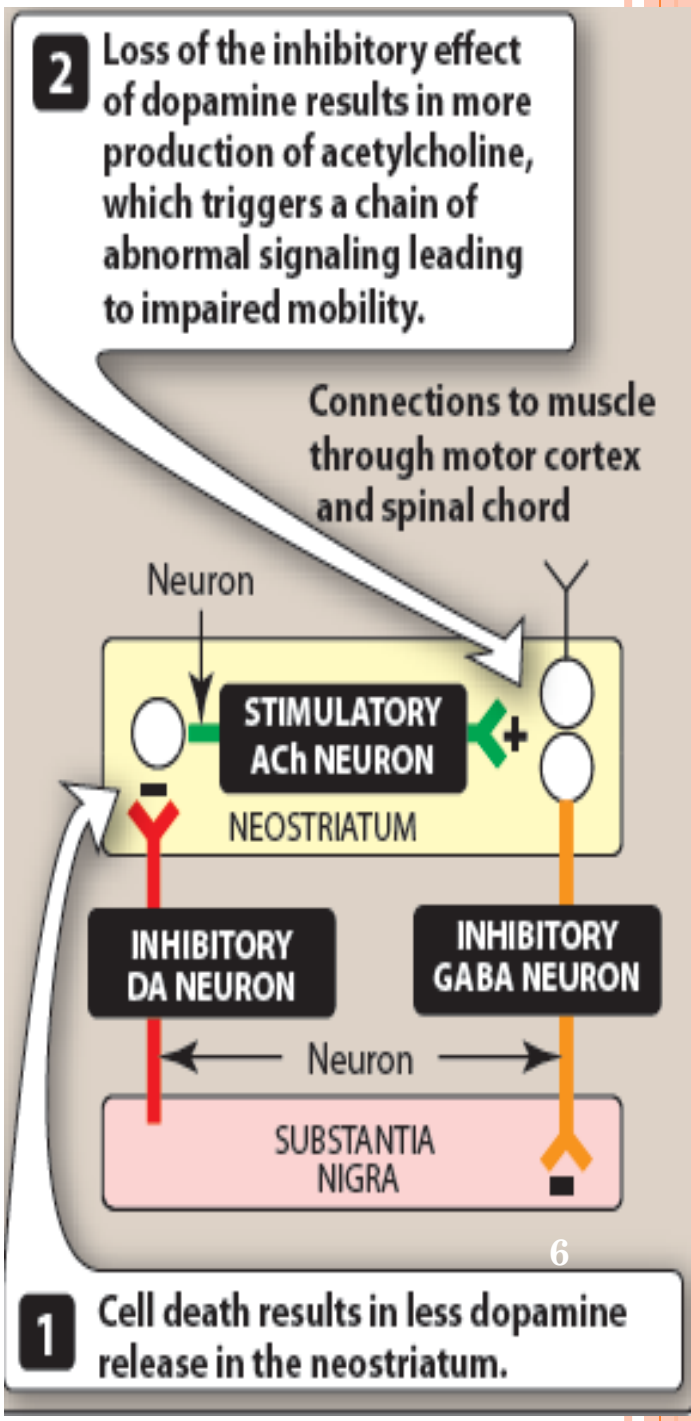
- The cause of Parkinson's disease is **unknown**

- The disease is correlated with **destruction of dopaminergic neurons in substantia nigra** with reduction of dopamine actions in **corpus striatum** (parts of brain's basal ganglia system that are involved in motor control)



Top: Dopaminergic neurons (color) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (gray) exert an excitatory effect. **Middle:** In parkinsonism, there is a selective loss of dopaminergic neurons (dashed, color)

- Normally, the neostriatum is connected to the substantia nigra by neurons (shown as orange) that secrete the inhibitory transmitter GABA at their termini in the substantia nigra.
- In turn, cells of the substantia nigra send neurons (shown red) back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini.
- This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas.



- In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals responsible for secreting dopamine in the neostriatum.

- Thus, the normal modulating 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 (shown as green).

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

Secondary Parkinsonism

It can be caused by:

1. Following **viral encephalitis**

2. Multiple small vascular lesions

3. Drugs such as phenothiazines & haloperidol, whose major pharmacologic action is **blockade of dopamine receptors in brain**, may also produce parkinsonian symptoms. These drugs should not be used in parkinsonian patients

Strategy of treatment

- Many of symptoms of parkinsonism reflect an **imbalance between excitatory cholinergic neurons & diminished number of inhibitory dopaminergic neurons**
- **Therapy is aimed at:**
  - **Restoring dopamine in basal ganglia**
  - **Antagonizing excitatory effect of cholinergic neurons**

- Currently available **drugs offer temporary relief from symptoms** of disorder
- But they **do not arrest or reverse neuronal degeneration** caused by disease

A. Levodopa and carbidopa

B. Monoamine-oxidase-B inhibitors (Selegiline & rasagiline)

C. Catechol-O-methyltransferase inhibitors (Entacapone & tolcapone)

D. Dopamine-receptor agonists (Bromocriptine, ropinirole, pramipexole & rotigotine, apomorphine)

E. Amantadine

F. Antimuscarinic agents

ANTI-PARKINSON DRUGS

Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL, CYCLOSET
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/Carbidopa) SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NOT AVAILABLE IN U.S
Selegiline (Deprenyl) ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl ARTANE

A. Levodopa and Carbidopa

- **Levodopa** is a metabolic **precursor of dopamine**

- It restores dopaminergic by **enhancing synthesis of dopamine in surviving neurons of substantia nigra**

- **In patients with early disease**, number of dopaminergic neurons in substantia nigra (about 20% of normal) is adequate for conversion of levodopa to dopamine

- Thus, **in new patients**, **therapeutic response to levodopa is consistent**

- Unfortunately, **with time, number of neurons decreases** & fewer cells are capable of taking up exogenously administered levodopa & converting it to dopamine

- Consequently, **motor control fluctuation develops**

- Relief provided by levodopa is only symptomatic & it lasts only while drug is present in body

1. Mechanism of action:

A. Levodopa:

- Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, levodopa, is actively transported into the CNS and is converted to dopamine in the brain
- Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery
- This results in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

2. Carbidopa:

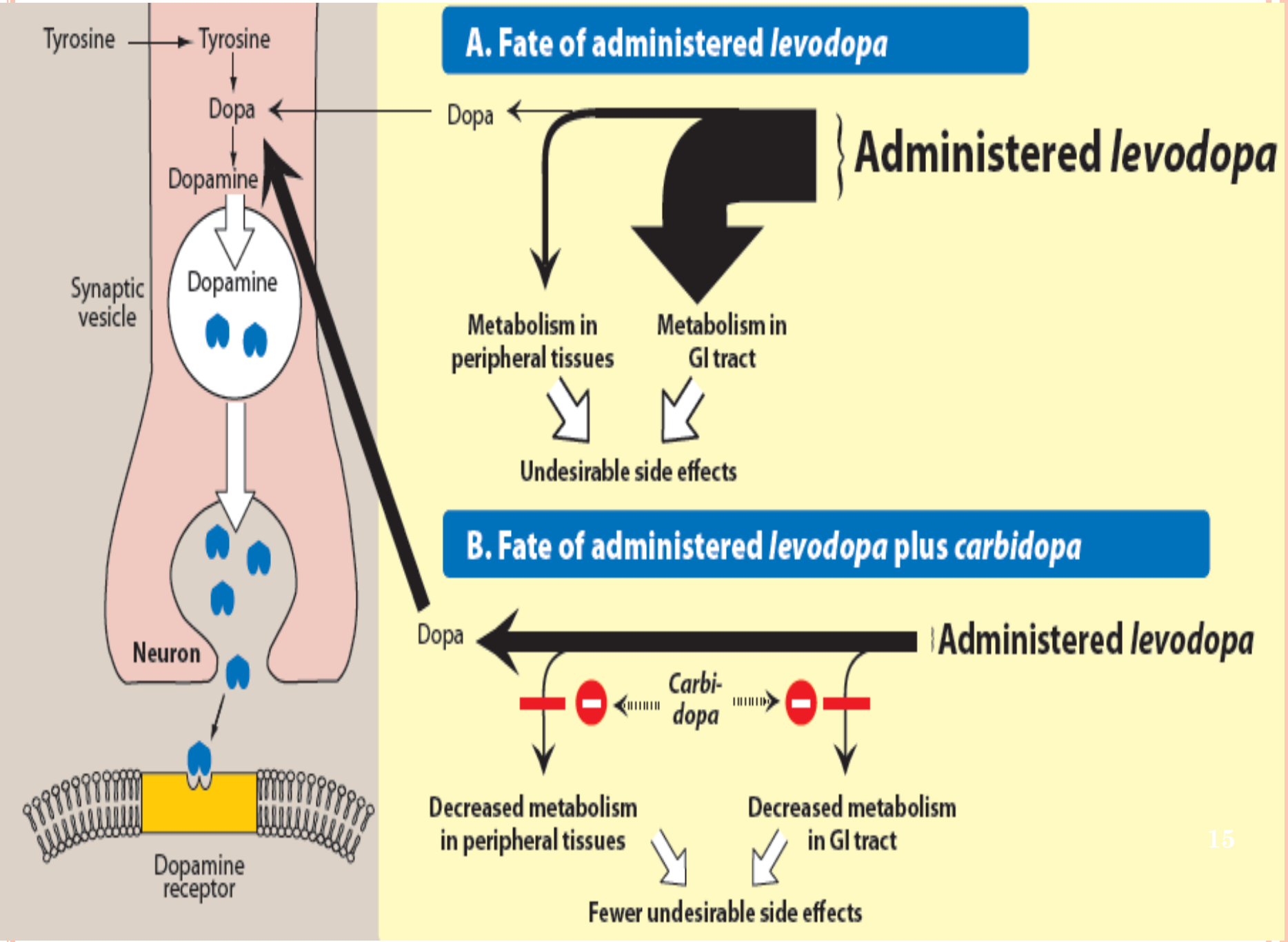
- The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa,

- It is a dopa decarboxylase inhibitor that does not cross the blood-brain barrier.

- Carbidopa diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues;

- Thus, it increases the availability of levodopa to the CNS.
- The addition of carbidopa lowers the dose of levodopa needed by four- to five-fold and,

- Therefore, it decreases the severity of the side effects arising from peripherally formed dopamine.


Tyrosine
Tyrosine
Dopa
Dopamine
Synaptic vesicle
Dopamine
Neuron
Dopamine receptor
A. Fate of administered levodopa
Dopa
Administered levodopa
Metabolism in peripheral tissues
Metabolism in GI tract
Undesirable side effects
B. Fate of administered levodopa plus carbidopa
Dopa
Administered levodopa
Carbi-dopa
Decreased metabolism in peripheral tissues
Decreased metabolism in GI tract
Fewer undesirable side effects

2. Therapeutic uses:

- Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism.

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

- Patients then typically experience a decline in response during the third to fifth year of therapy.

3. Absorption & Metabolism

- The drug is absorbed rapidly from small intestine (when empty of food)
- Levodopa should be taken on empty stomach, typically **45 minutes before a meal**
- Levodopa has **short half-life (1-2 hours), which causes fluctuations in plasma concentration.** This may produce **fluctuations in motor response**

4. Adverse Effects

a. Peripheral effects:

- Anorexia, nausea, & vomiting occur because of stimulation of chemoreceptor trigger zone of medulla
- Tachycardia & ventricular extra systoles result from dopaminergic action on heart
- Hypotension
- Adrenergic action on iris causes mydriasis
- Saliva & urine are a brownish color because of melanin pigment produced from catecholamine oxidation

b. CNS:

- Visual and auditory hallucinations & abnormal involuntary movements (dyskinesias).
- These CNS effects are opposite of parkinsonian symptoms & reflect overactivity of dopamine at receptors in basal ganglia

- Mood changes, depression, psychosis & anxiety

5. Drug interactions and contraindications:

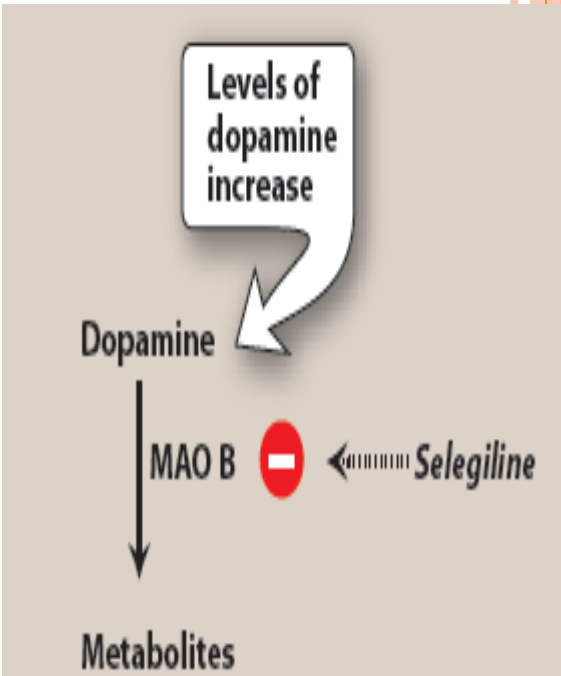
A. The vitamin pyridoxine (B_6) increases the peripheral breakdown of levodopa and diminishes its effectiveness
B. Concomitant administration of levodopa and monoamine oxidase (MAO) inhibitors, such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production
C. In many psychotic patients, levodopa exacerbates symptoms, possibly through the buildup of central catecholamines.
D. In patients with glaucoma, the drug can cause an increase in intraocular pressure.
E. Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias.
F. Antipsychotic drugs are generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves..

B. Monoamine-oxidase-B inhibitors

- **Selegiline and rasagiline**

- **Selegiline** (also called **deprenyl**) selectively inhibits MAO Type B (which metabolizes dopamine)

- Thus **decreasing metabolism of dopamine, increases dopamine levels in brain**



- Enhances actions of levodopa when these drugs are administered together

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

- **Rasagiline** an irreversible and selective inhibitor of brain (MAO) Type B, has five times the potency of selegiline.

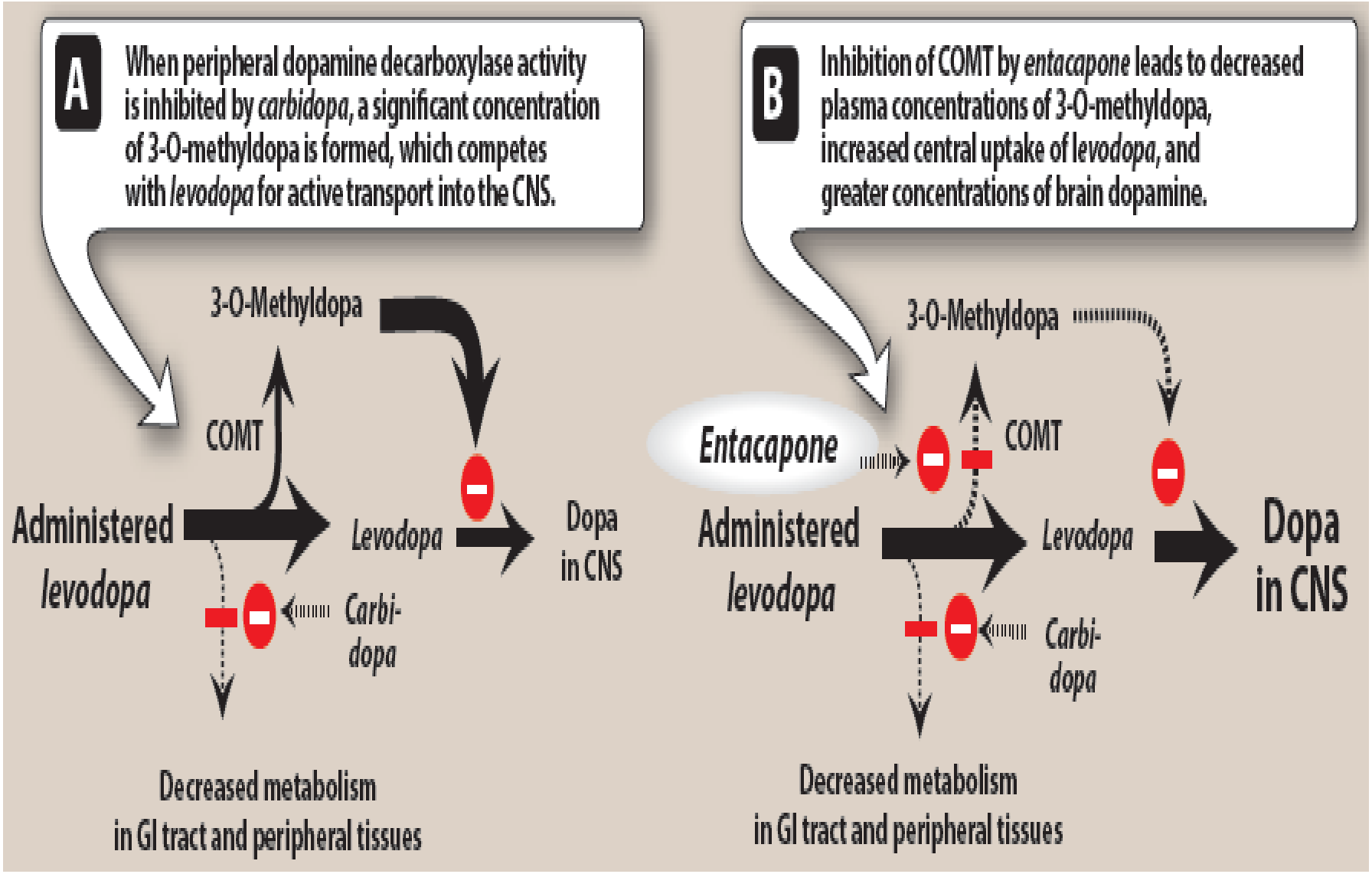
- Unlike selegiline, it is not metabolized to an amphetamine-like substance.

C. Catechol-O-methyltransferase inhibitors

- **Entacapone and tolcapone**

- Normally, methylation of levodopa by **catechol-O-methyltransferase (COMT)** to **3-O-methyldopa** is pathway for levodopa metabolism

- However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, **a significant concentration of 3-O-methyldopa is formed** that **competes with levodopa** for active transport into CNS


A
When peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed, which competes with *levodopa* for active transport into the CNS.
3-O-Methyldopa
COMT
Administered *levodopa*
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues
B
Inhibition of COMT by *entacapone* leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine.
3-O-Methyldopa
Entacapone
COMT
Administered *levodopa*
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues

➢**Inhibition of COMT** by entacapone or tol-capone leads to **decreased plasma concentrations of 3-O-methyldopa**, **increased central uptake of levodopa** & greater concentrations of brain dopamine

➢Both of these agents have been demonstrated to **reduce symptoms of "wearing-of"** phenomena seen in patients on levodopa–carbidopa

Levodopa + carbidopa + Entacapone= Stalevo

Adverse effects:

- Diarrhea, postural hypotension, nausea, anorexia, dyskinesia, hallucinations

- Most seriously, **fulminating hepatic necrosis is associated with tolcapone use**. Therefore, it should be used with appropriate hepatic function monitoring only in patients in whom other modalities have failed
- **Entacapone** does not exhibit this toxicity & has largely replaced tolcapone

D. Dopamine-receptor agonists

- **Bromocriptine and new drugs ropinirole, pramipexole and rotigotine**
- These agents **have durations of action longer than that of levodopa** and, thus, have been effective in patients exhibiting fluctuations in their response to levodopa
- **Initial therapy with newer drugs** is associated with **less risk of developing dyskinesia and motor fluctuations** when compared to patients started with levodopa therapy
- Effective **in patients with advanced Parkinson's disease complicated by motor fluctuations and dyskinesia**

- **Bromocriptine Side effects severely limit utility of dopamine agonists**

- The **actions of bromocriptine are similar to those of levodopa**, except hallucinations, confusion, delirium, nausea & orthostatic hypotension are more common, whereas dyskinesia is less prominent

➢**Apomorphine, pramipexole, ropinirole, & rotigotine**

➢**Apomorphine & rotigotine** are newer dopamine agonists available in **injectable & transdermal delivery systems**, respectively

Side effects:
Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension

E. AMANTADINE

- **PK-MERZ**
- **Antiviral drug effective in treatment of influenza**
- Has an antiparkinsonism action

- Amantadine has several effects on a number of neurotransmitters implicated in causing parkinsonism, including:
  - **Increasing release of dopamine**
  - **Blockading cholinergic receptors**
  - **Inhibiting N-methyl-D-aspartate (NMDA) type of glutamate receptors**

F. Antimuscarinic agents

- The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy.
- **benztropine, trihexyphenidyl, procyclidine and biperiden**
- All of these drugs can induce mood changes and produce xerostomia and visual problems, as do all muscarinic blockers.
- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.
- Adverse effects are similar to those caused by high doses of atropine for example, pupillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

Thank you