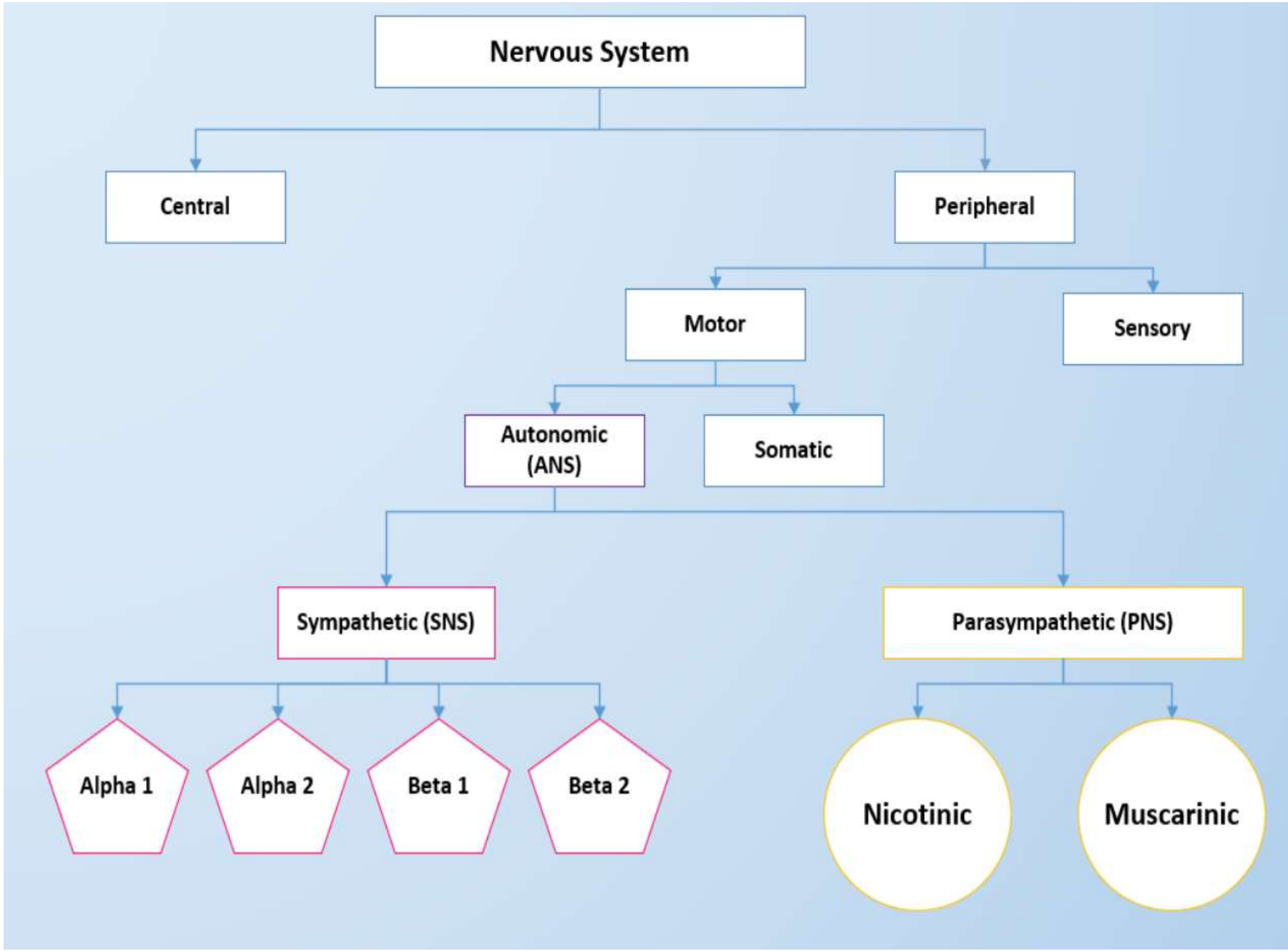
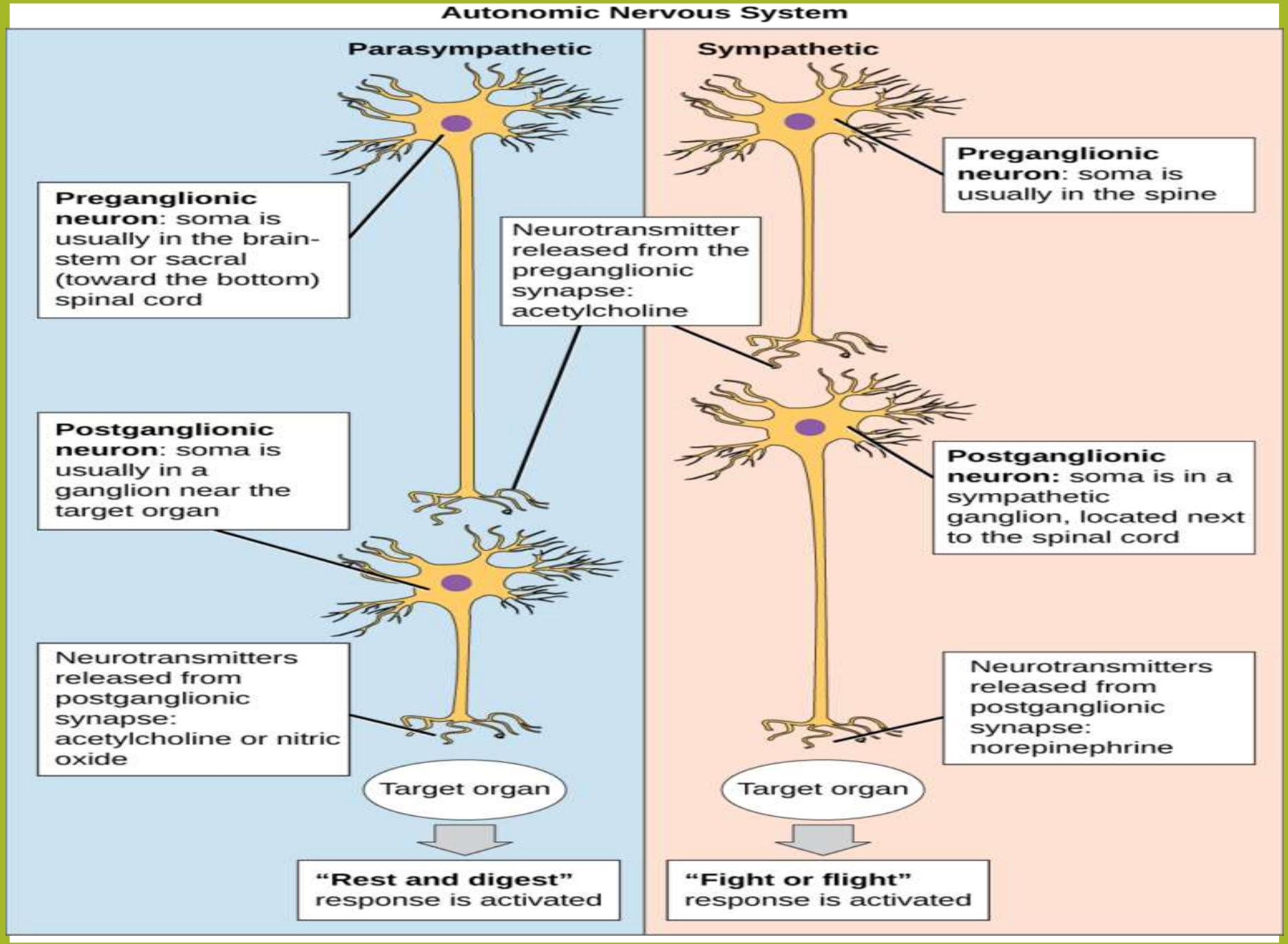
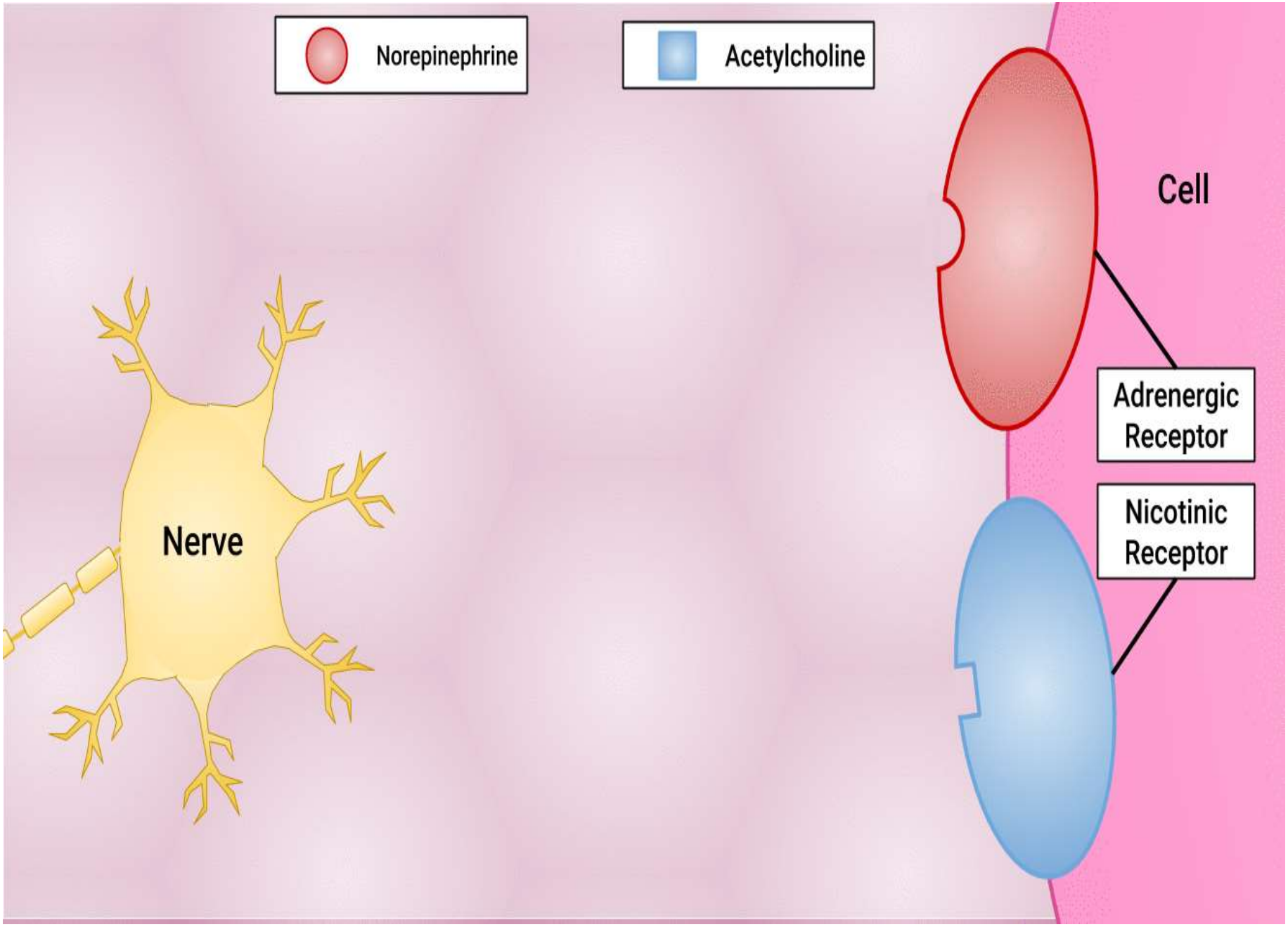
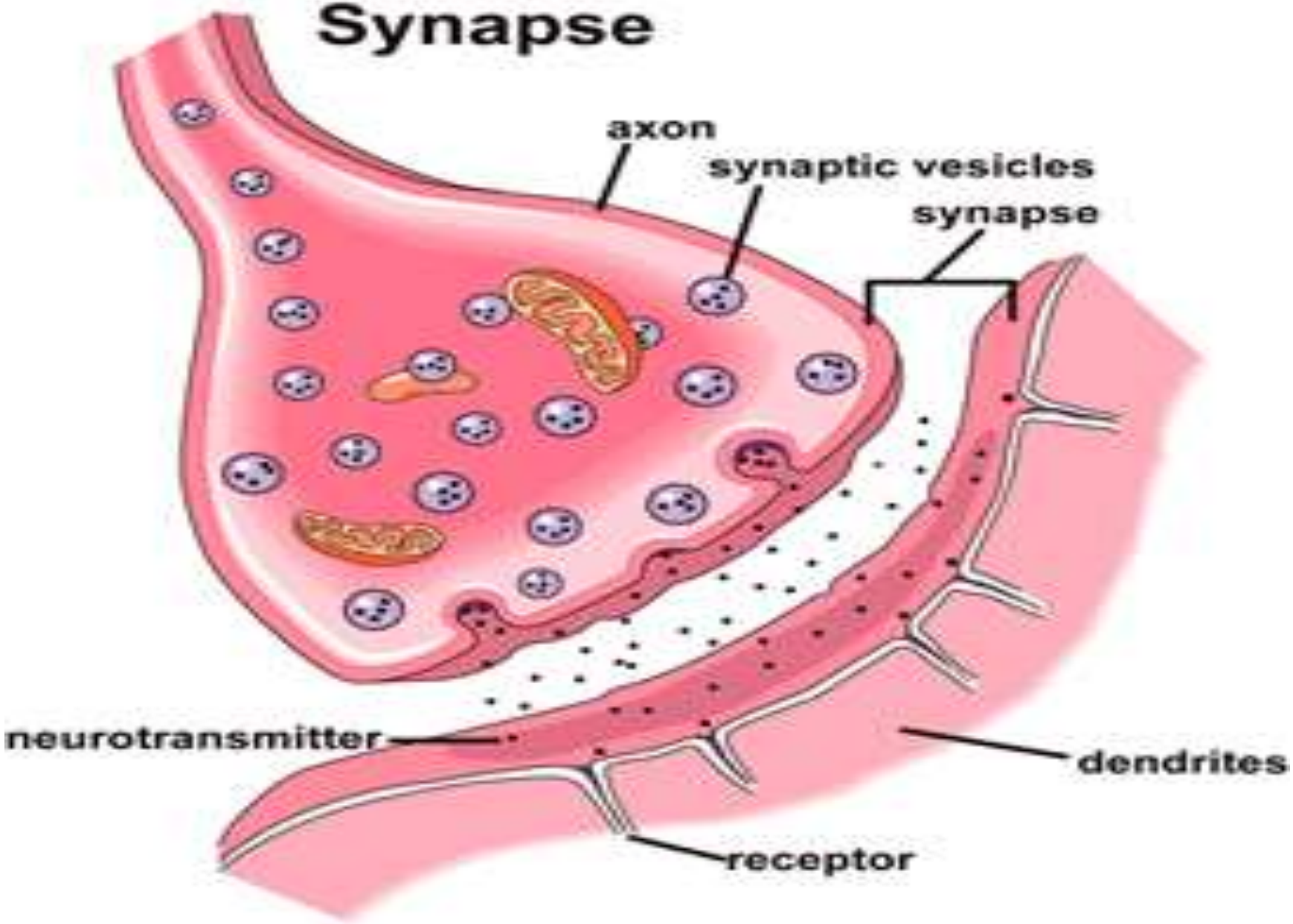
Introduction to Autonomic drugs

Prepared by: Heba Ahmed Hassan
Assistant Professor of Clinical Pharmacology
Faculty of Medicine, MUTAH University, JORDEN


Nervous System
Central
Peripheral
Motor
Sensory
Autonomic (ANS)
Somatic
Sympathetic (SNS)
Parasympathetic (PNS)
Alpha 1
Alpha 2
Beta 1
Beta 2
Nicotinic
Muscarinic


Autonomic Nervous System
Parasympathetic
Sympathetic
Preganglionic neuron: soma is usually in the brain-stem or sacral (toward the bottom) spinal cord
Neurotransmitter released from the preganglionic synapse: acetylcholine
Preganglionic neuron: soma is usually in the spine
Postganglionic neuron: soma is usually in a ganglion near the target organ
Postganglionic neuron: soma is in a sympathetic ganglion, located next to the spinal cord
Neurotransmitters released from postganglionic synapse: acetylcholine or nitric oxide
Neurotransmitters released from postganglionic synapse: norepinephrine
Target organ
Target organ
"Rest and digest" response is activated
"Fight or flight" response is activated


Norepinephrine
Acetylcholine
Cell
Adrenergic Receptor
Nicotinic Receptor
Nerve


Synapse
axon
synaptic vesicles
synapse
neurotransmitter
dendrites
receptor

Types of synapses in ANS

1) **Neuron-neuron synapse**, between the pre- and postganglionic fiber (Ganglia).

2) **Neuron-effector organ synapse**, nerve end of postganglionic fiber and the organ.

Types of the autonomic nerve fibers:-

According to the type of chemical mediator, the ANF are classified into:

1- Cholinergic nerve fibers where ACh acts as chemical mediator.

2- Adrenergic nerve fibers where NE acts as chemical mediator.

PARASYMPATHETIC

I- SYNTHESIS, STORAGE, RELEASE AND METABOLISM OF ACETYLCHOLINE:

(1) Synthesis:

ACh is synthesized in nerve terminal by the combination of choline and acetyl COA (active acetate) using **acetyl choline transferase** enzyme.

(2) Storage:

ACh is transported for storage inside vesicles.

(3) Release:

Nerve impulse causes influx of Ca^{++} ions and release of ACh from the storage vesicles by exocytosis.

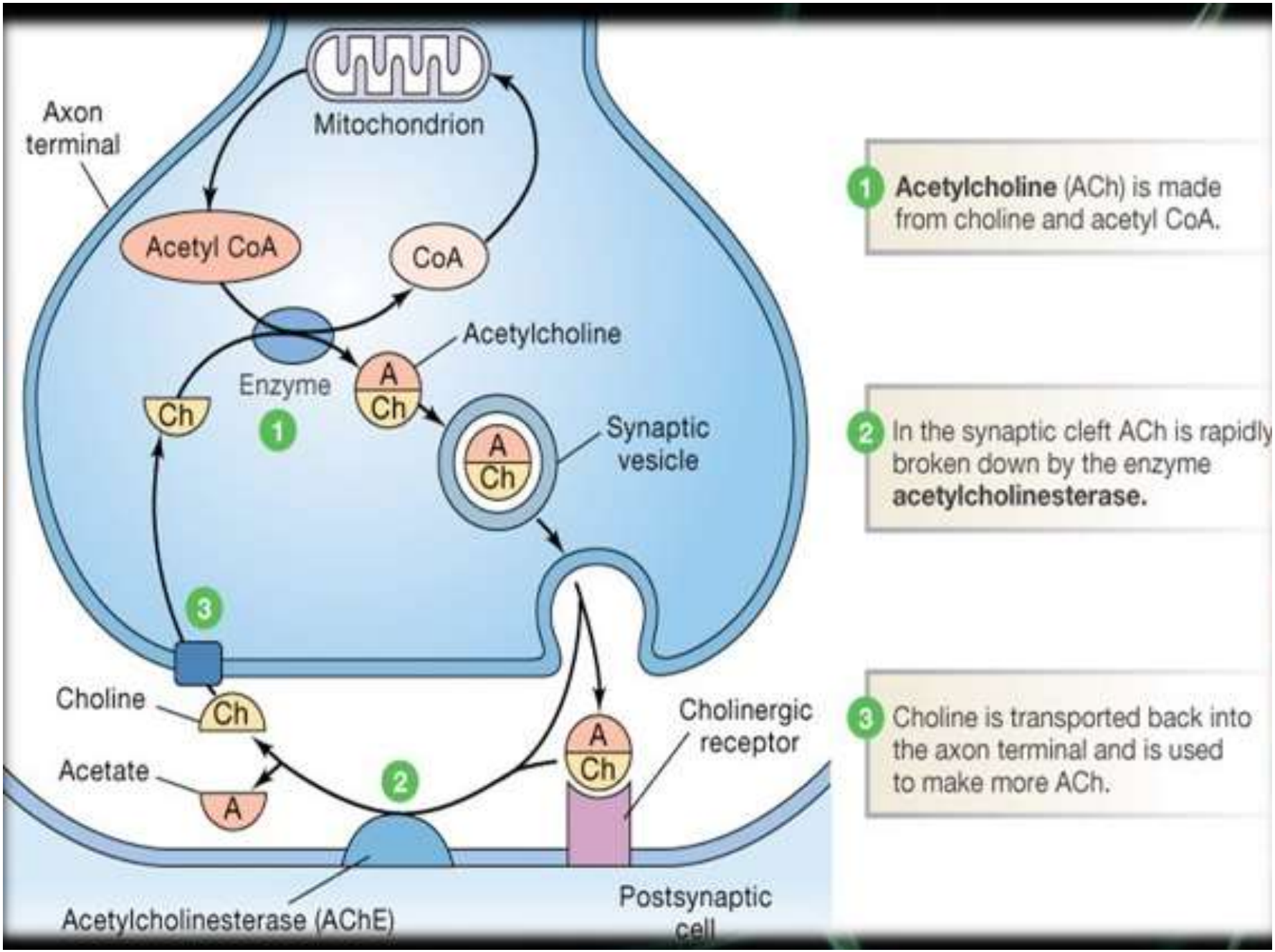
(4) Metabolism:

Mainly enzymatically by

a) **Acetyl cholinesterase (true cholinesterase),** which is found in the neurons and neuromuscular junction and responsible for hydrolysis of ACh that is released in the process of cholinergic transmission.

b) **Butyryl cholinesterase (pseudocholinesterase),** which is found mainly in the plasma and liver.

- This metabolism can be inhibited by anticholinesterases as neostigmine.


Axon terminal
Mitochondrion
Acetyl CoA
CoA
Acetylcholine
Enzyme
1
Ch
A
Ch
Synaptic vesicle
3
Choline
Ch
Acetate
A
2
Cholinergic receptor
Acetylcholinesterase (AChE)
Postsynaptic cell
1 Acetylcholine (ACh) is made from choline and acetyl CoA.
2 In the synaptic cleft ACh is rapidly broken down by the enzyme acetylcholinesterase.
3 Choline is transported back into the axon terminal and is used to make more ACh.

II- Types of cholinergic receptors:

(a) Muscarinic receptors

M_1 in the autonomic ganglia.

M_2 in the heart.

M_3 in smooth muscles and secretory glands.

M_4 and M_5 are recently discovered, found mainly in CNS.

(b) Nicotinic receptors

N_M in the neuromuscular junction

N_N in autonomic ganglia, adrenal medulla and CNS

(Nm = nicotinic muscle, Nn = nicotinic neuronal).

III-Molecular mechanisms and signal transduction of cholinergic receptors:

(a) Nicotinic receptors:

Ligand - gated ion channels.

Their stimulation increases the permeability to Na^+

(b) Muscarinic receptors:

They are G-protein-coupled receptors.

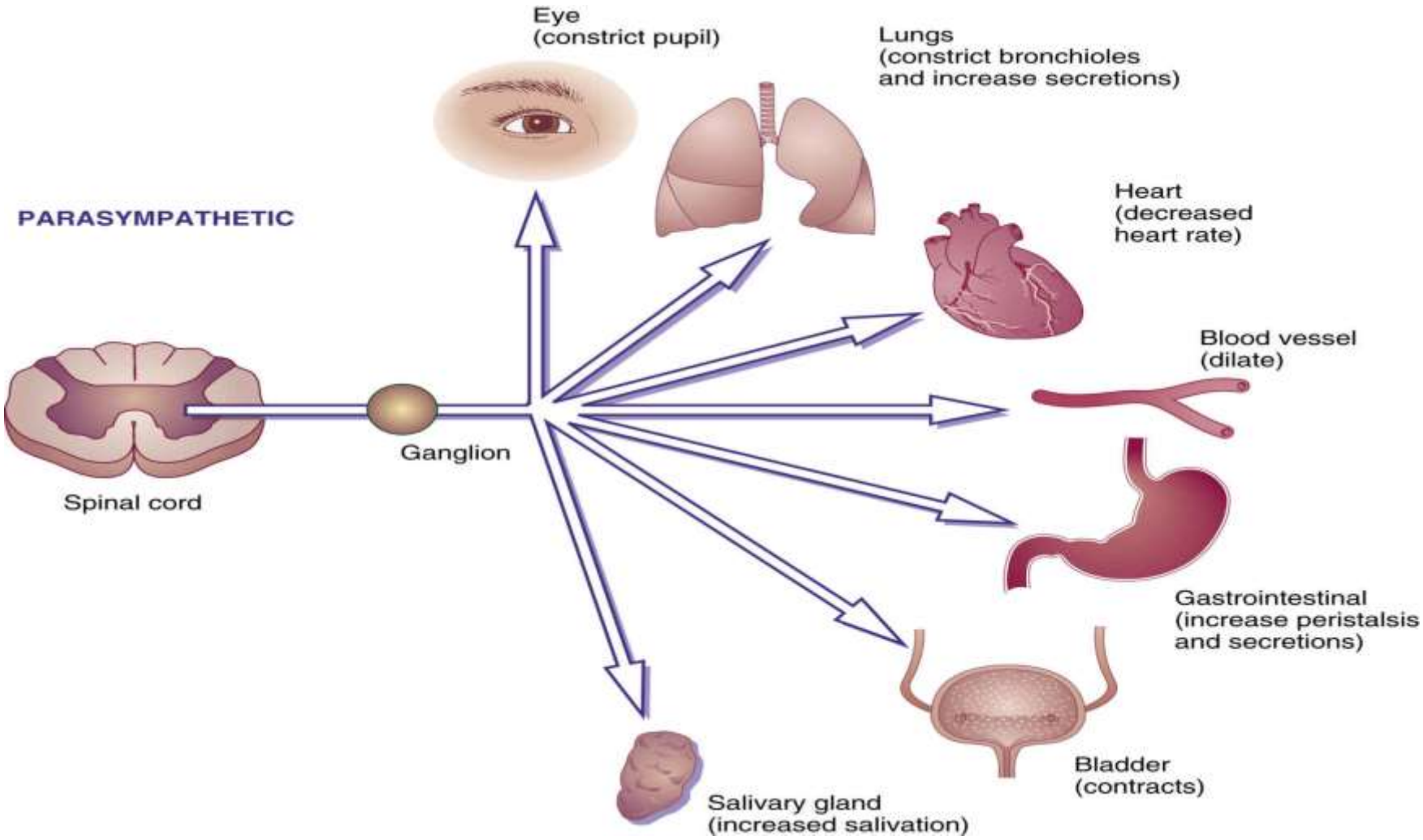
M_1: Gq, causes stimulation of phospholipase C causing increase in the second messenger [Ca^{++}, inositol triphosphate ($I P_3$) and diacylglycerol (DAG)]

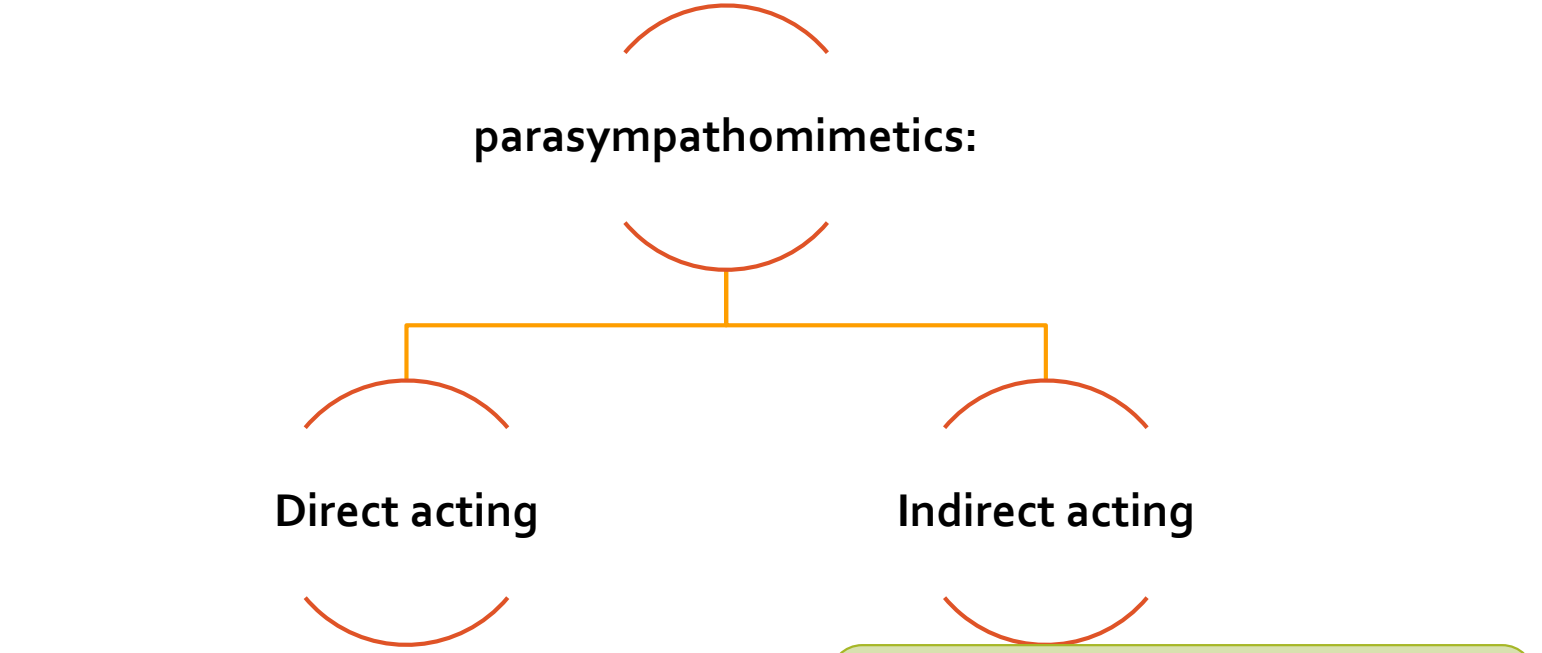
M_2: Gi (B and γ subunits) causes opening of K^+ channels.

Gi that causes inhibition of adenyl cyclase which decreases cAMP.

M_3: Similar to M_1.

PHARMACOLOGICAL ACTIONS





Drugs which act by direct binding to the receptors

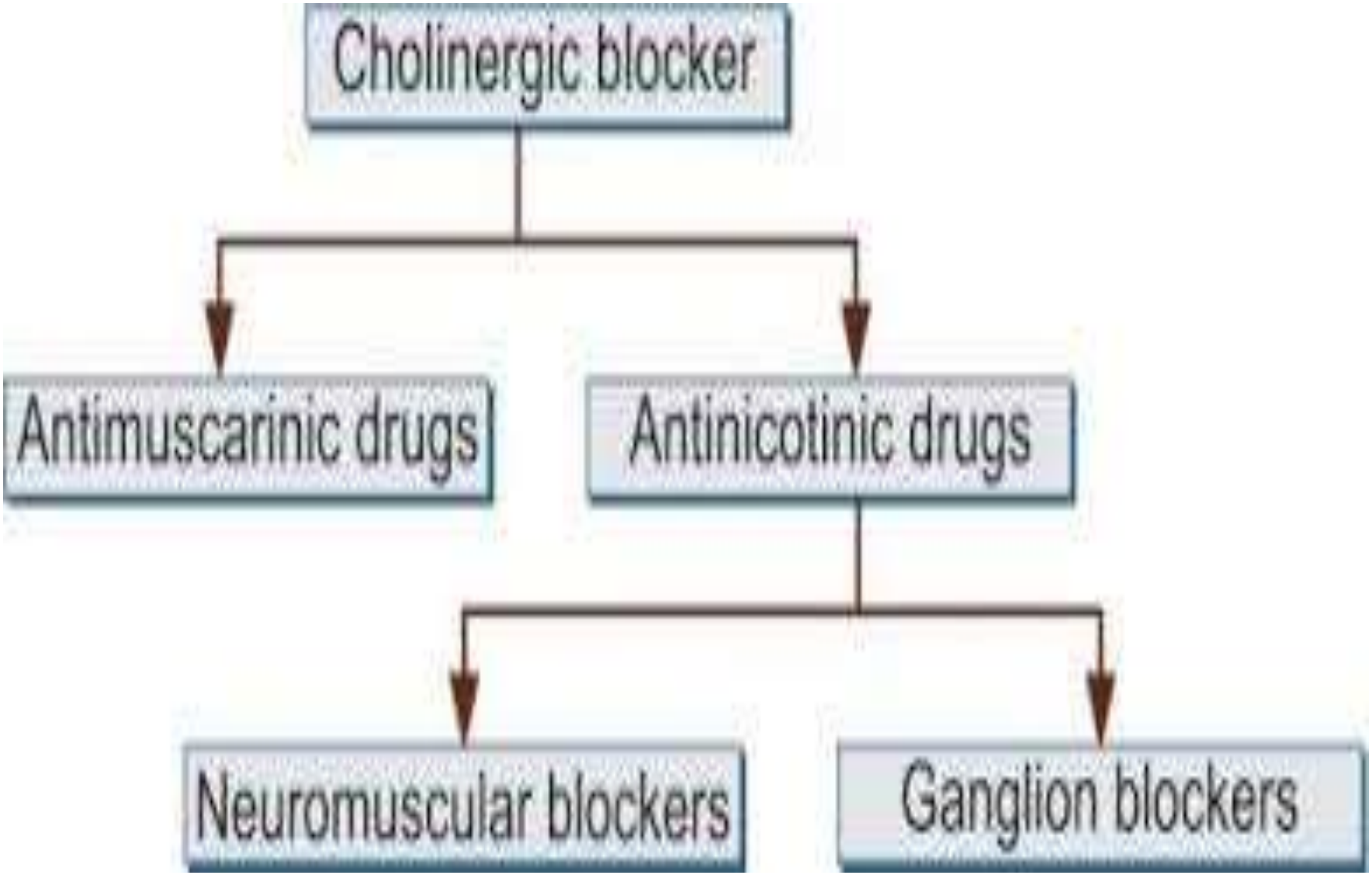
1-Choline esters:
acetylcholine, methacholine, carbachol and bethanechol.

2-Naturally occurring alkaloids: pilocarpine, muscarine and arecoline

inhibition of cholinesterase enzyme

1- Reversible cholinesterase inhibitors: physostigmine, neostigmine, edrophonium.

2) Irreversible cholinesterase inhibitors: organophosphorus compounds.


Cholinergic blocker
Antimuscarinic drugs
Antinicotinic drugs
Neuromuscular blockers
Ganglion blockers

SYMPATHETIC

I-Synthesis, storage, release and termination of the action of catecholamines

(I) Synthesis:

1- It occurs in the sympathetic nerve endings.

2-**Tyrosine** is actively transported from extracellular fluid to sympathetic endings by Na^+ dependent carrier.

3- In the cytoplasm:

• Tyrosine is hydroxylated to **DOPA** by tyrosine hydroxylase and this is the ***rate limiting step*** in the synthesis of catecholamines

• DOPA is decarboxylated to **dopamine** by dopa decarboxylase; dopa decarboxylase is non-specific enzyme as it can also convert α-methyldopa to α-methyldopamine.

4- **Dopamine** is transported into the vesicle by a carrier. The same carrier can transport NE and several other amines into these vesicles.

5- Inside the vesicles dopamine is hydroxylated to **NE**.

6- In the **adrenal medulla** and certain areas of the brain NE is methylated to **EP** by N-methytransferase.

(II) Storage:

-NE is stored in specific granules at the nerve endings.

III) Release:

1- Release of the transmitter occurs when the action potential opens voltage-sensitive Ca^{++} channels leading to increase in the intracellular Ca^{++} which cause fusion of the vesicles with the surface membrane (exocytosis) resulting in expulsion of NE, cotransmitters (as ATP and certain peptides) and dopamine hydroxylase

-The released **NE** acts on the adrenoceptors on the post-synaptic membrane causing change in ionic conductance.

(IV) Termination of the action of the released catecholamines:

-It occurs by 2 mechanisms:

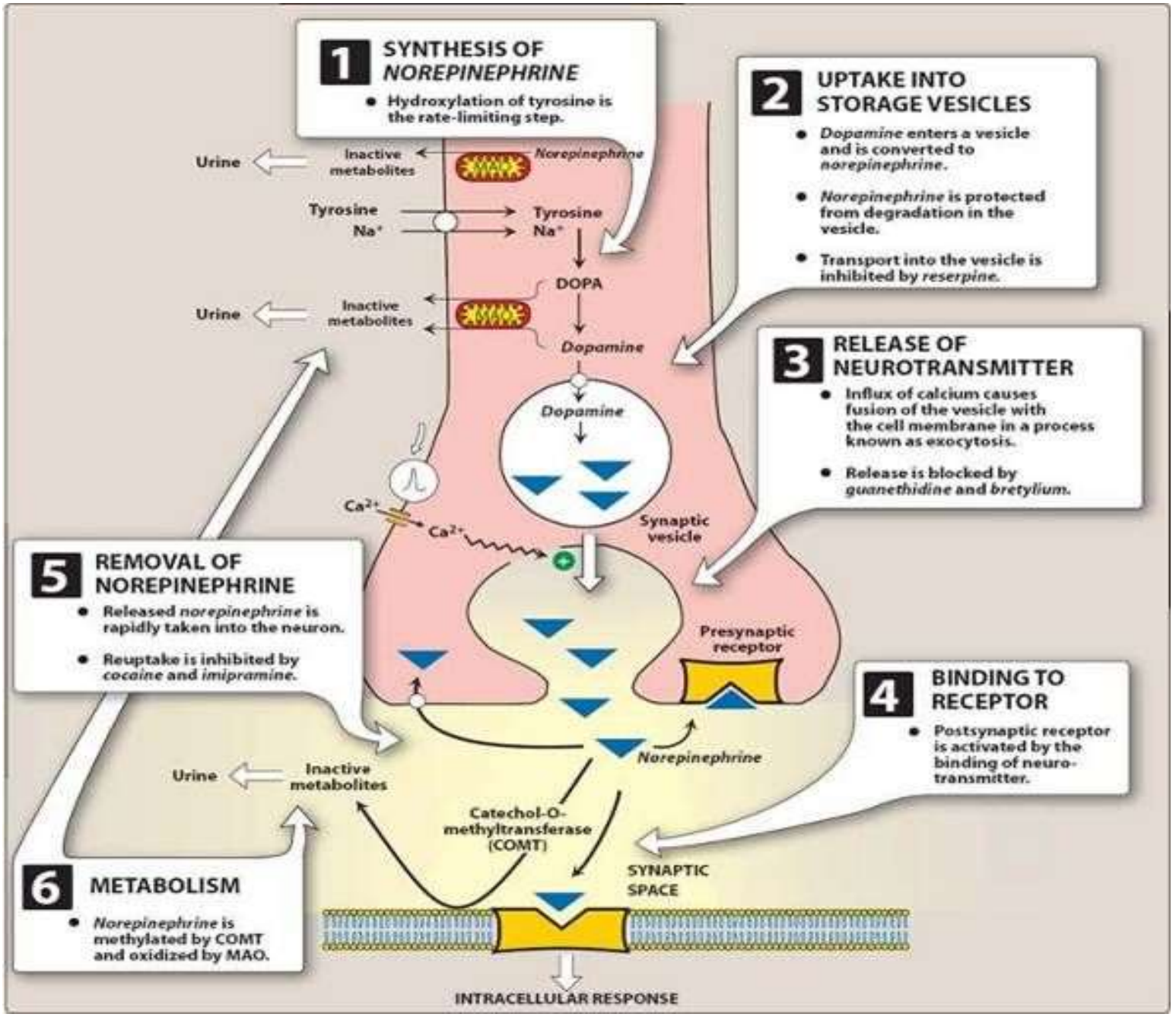
a) **Active reuptake** which is ***the most important*** mechanism and includes:

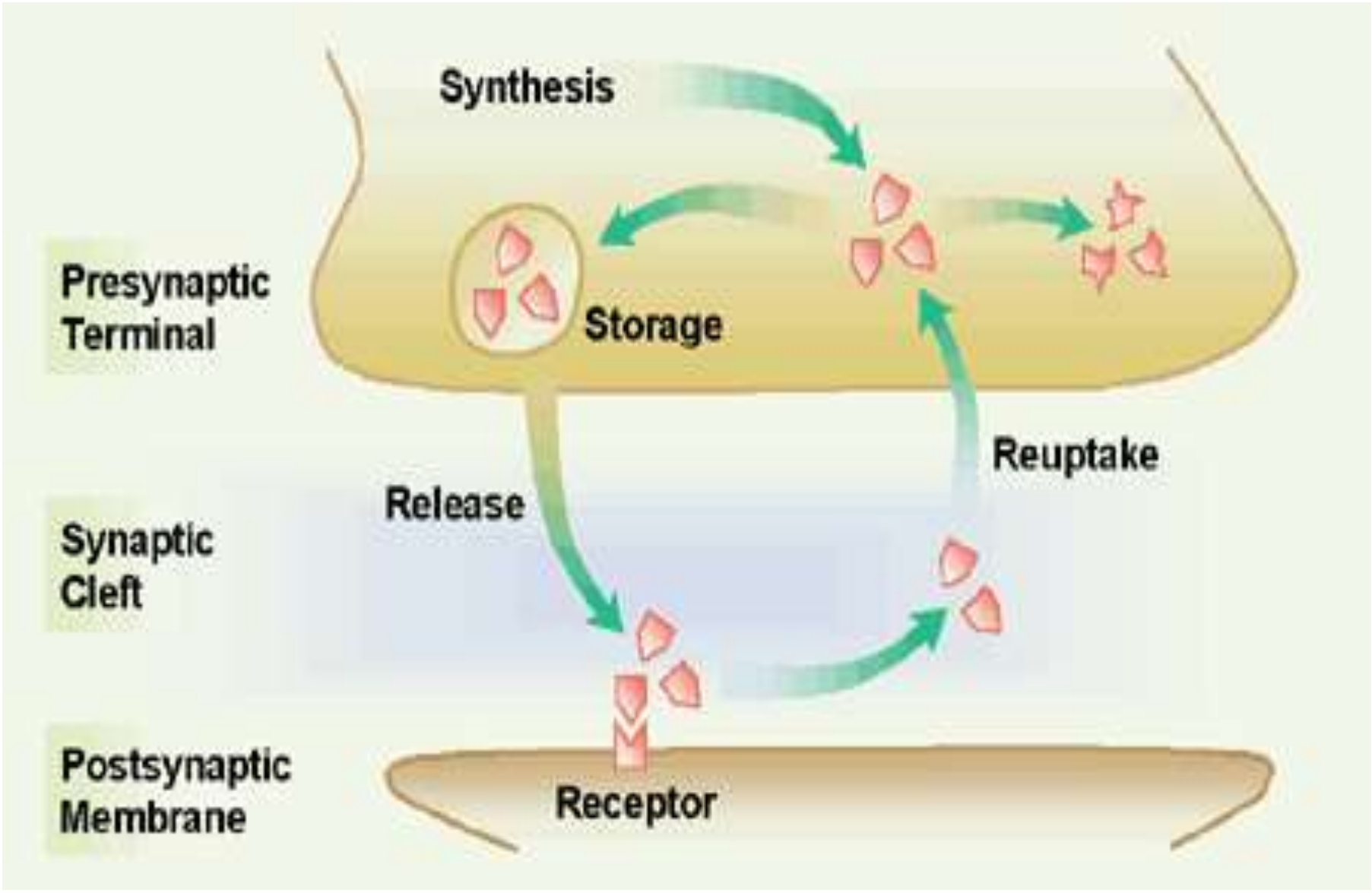
-Uptake 1 into the sympathetic nerve terminal which is ***the most important***

-Uptake 2 into post-junctional cells (***less important***) to be metabolism by **COMT**.

b) **Enzymatic metabolism** by **MAO** and **COMT**:

-Both MAO and COMT are widely distributed throughout the body including the brain with highest concentration in ***liver and kidney.*** However, **little or no COMT is found in adrenergic neurons.**


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
Ca2+
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
INTRACELLULAR RESPONSE


Synthesis
Presynaptic Terminal
Storage
Reuptake
Release
Synaptic Cleft
Postsynaptic Membrane
Receptor

Adrenergic receptors

- **Alpha (1 and 2)**
- **Beta (1, 2 and 3)**
- **Dopamine (D1,2,3,4,5)**

Molecular mechanism and signal transduction of adrenergic receptors:

(a) Beta receptors (β_1, β_2 and β_3)

- They are G-protein-coupled receptors.
- Their stimulation causes activation of Gs that stimulates adenyl cyclase which increases cAMP.

(b) Alpha-1 receptors (α_1) (similar to M_1)

- Their stimulation causes activation of Gq which stimulates phospholipase A_2, C and D that increase the second messengers (I P_3, DAG and Ca^{++}).

(c) Alpha-2 receptors (α_2) (similar to M_2)

- Their stimulation causes:

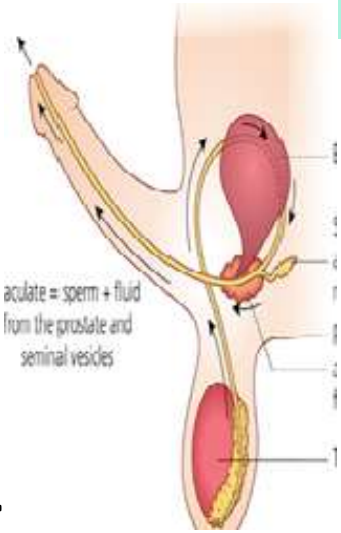
- Activation of Gi which inhibits adenyl cyclase that decreases cAMP.
- Activation of Gi (B and γ subunits) which opens K^+ channels.

α 1 stimulation

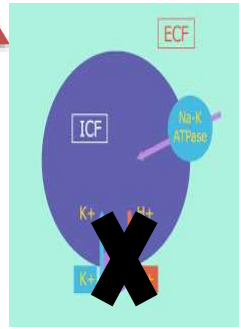
V.C

Mydriasis

Contraction of sphincter

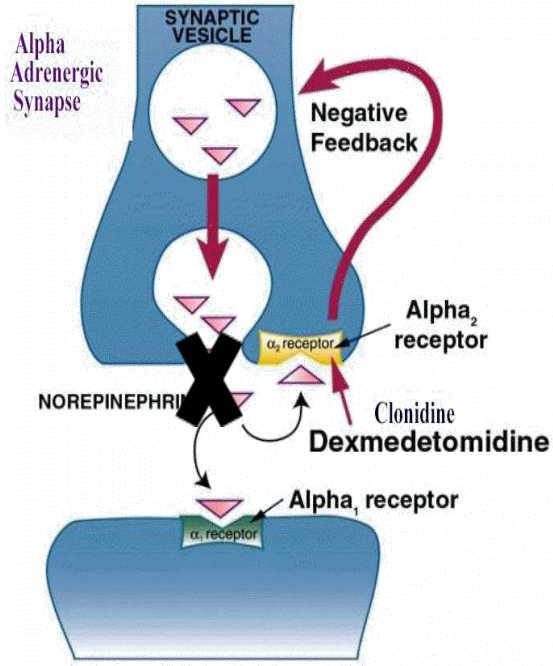


ejaculation

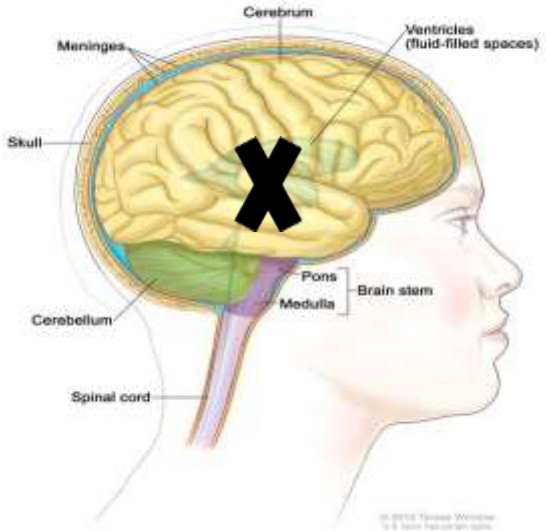


hyperkalemia

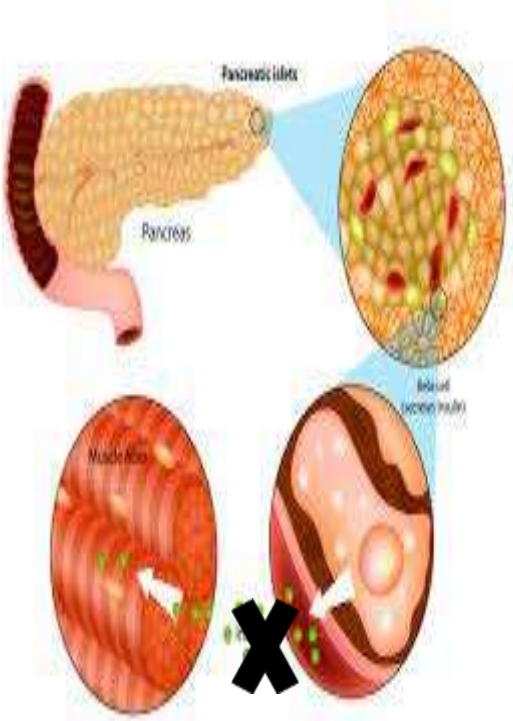
α 2 stimulation(inhibitory)



Inhibit NE, epinephrine and Ach

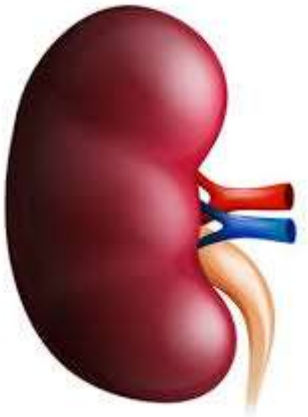


- Sympathetic flow



Inhibit insulin release

β 1 stimulation



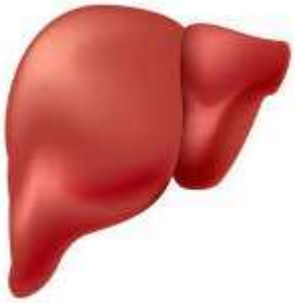
↑ renin release

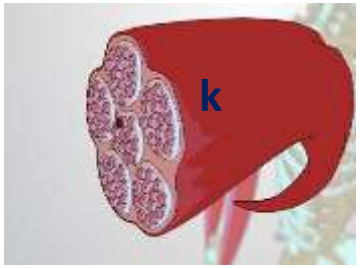
↑ all cardiac properties

β 2 stimulation

(coronary and skeletal)

V.D





Relaxation

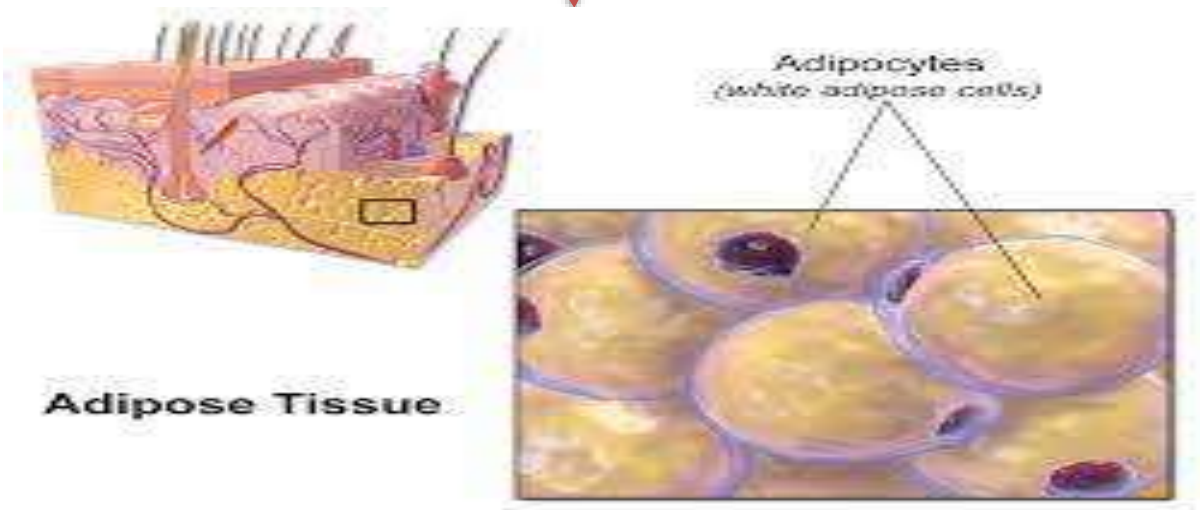
Bronchodilatation

Glycogenolysis: ↑ glucose blood level

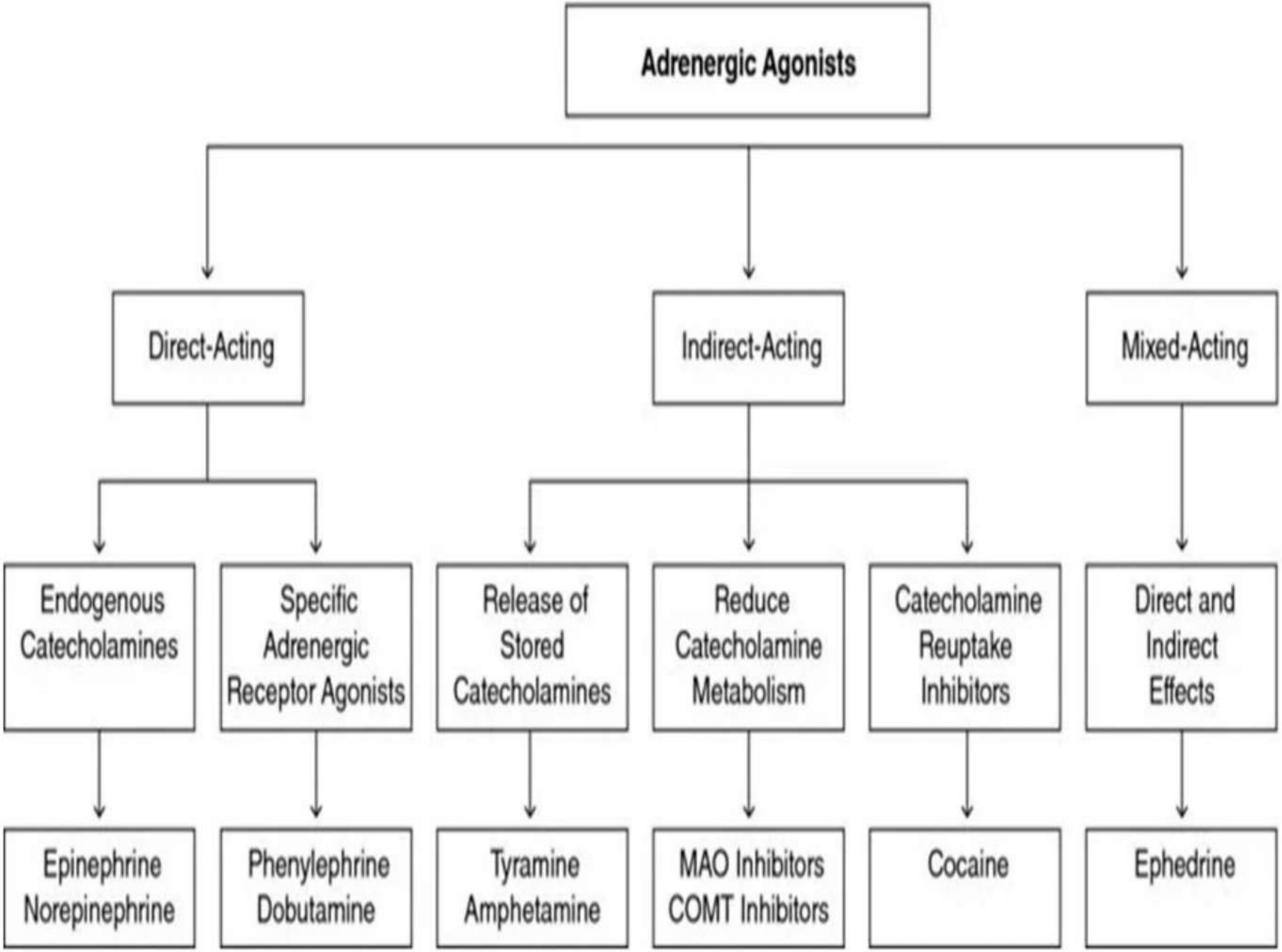
Gluconeogenesis: ↑ glucose blood level

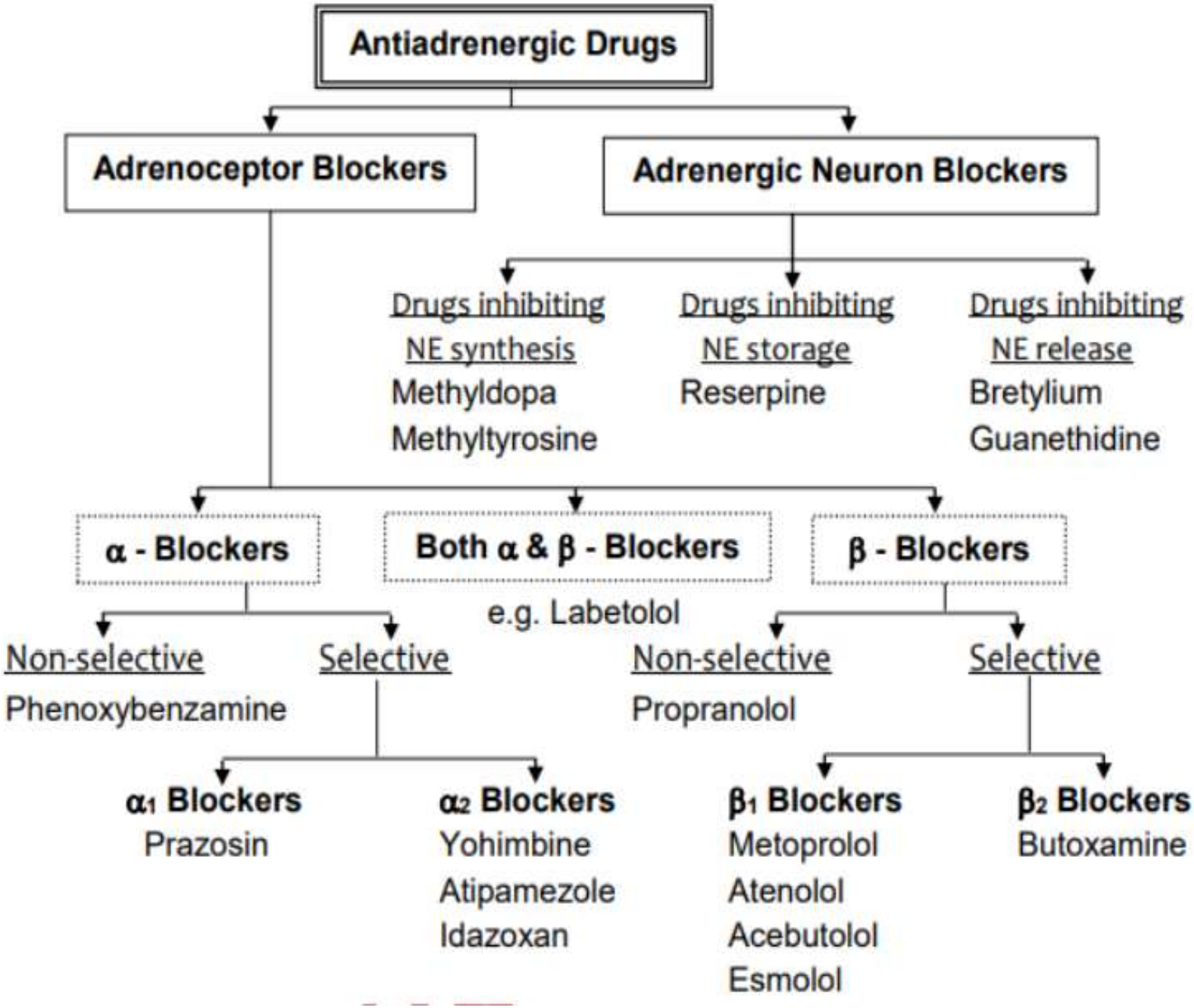
↑K uptake by muscles : hypokalemia

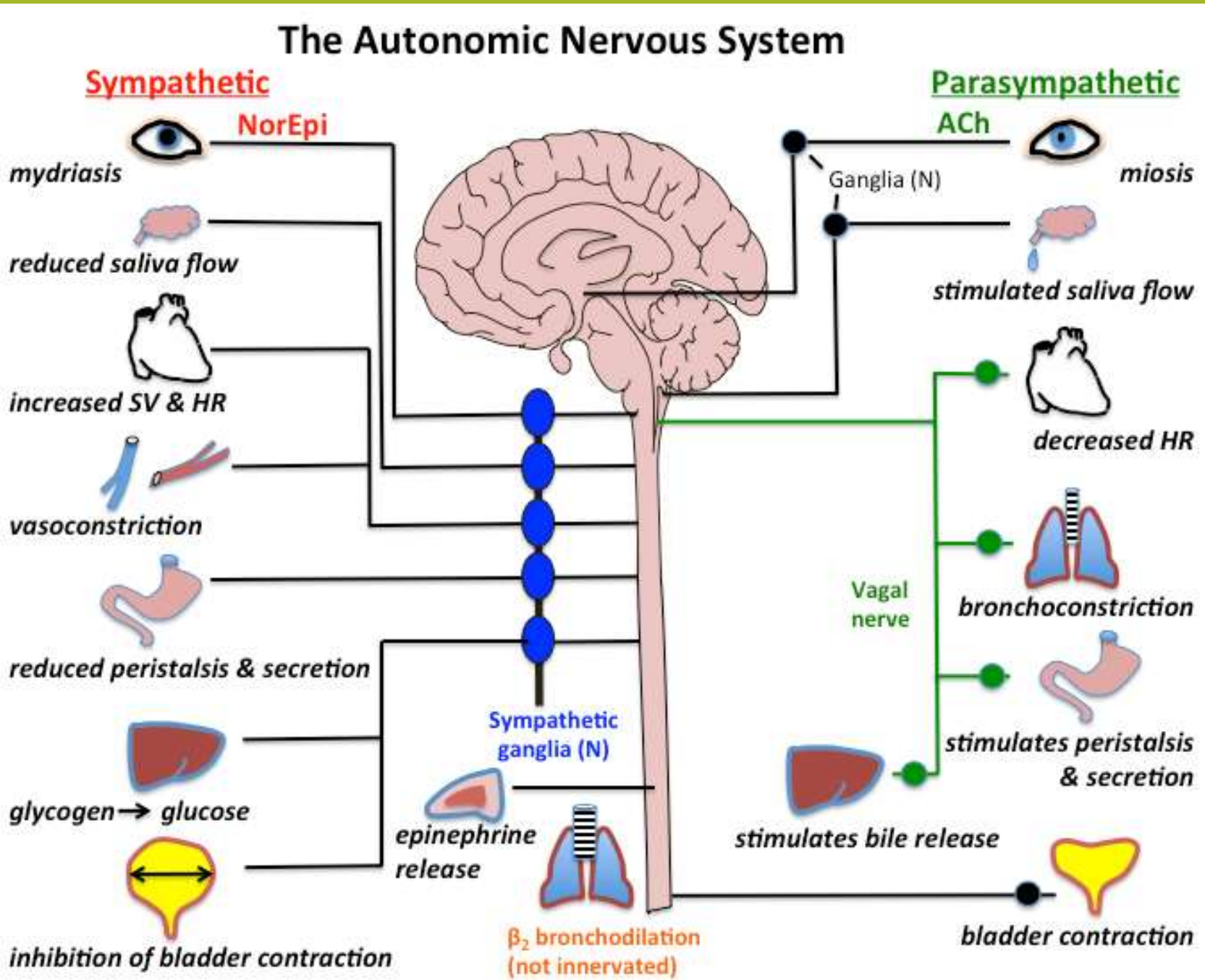
β 3 stimulation



+ lipolysis


Adrenergic Agonists
Direct-Acting
Indirect-Acting
Mixed-Acting
Endogenous Catecholamines
Specific Adrenergic Receptor Agonists
Release of Stored Catecholamines
Reduce Catecholamine Metabolism
Catecholamine Reuptake Inhibitors
Direct and Indirect Effects
Epinephrine Norepinephrine
Phenylephrine Dobutamine
Tyramine Amphetamine
MAO Inhibitors COMT Inhibitors
Cocaine
Ephedrine


Antiadrenergic Drugs
Adrenoceptor Blockers
Adrenergic Neuron Blockers
Drugs inhibiting NE synthesis
Methyldopa
Methyltyrosine
Drugs inhibiting NE storage
Reserpine
Drugs inhibiting NE release
Bretylium
Guanethidine
α - Blockers
Both α & β - Blockers
e.g. Labetolol
β - Blockers
Non-selective
Phenoxybenzamine
Selective
Non-selective
Propranolol
Selective
α1 Blockers
Prazosin
α2 Blockers
Yohimbine
Atipamezole
Idazoxan
β1 Blockers
Metoprolol
Atenolol
Acebutolol
Esmolol
β2 Blockers
Butoxamine


The Autonomic Nervous System
Sympathetic
NorEpi
mydriasis
reduced saliva flow
increased SV & HR
vasoconstriction
reduced peristalsis & secretion
glycogen → glucose
inhibition of bladder contraction
Sympathetic ganglia (N)
epinephrine release
β2 bronchodilation (not innervated)
Parasympathetic
ACh
Ganglia (N)
miosis
stimulated saliva flow
decreased HR
Vagal nerve
bronchoconstriction
stimulates peristalsis & secretion
stimulates bile release
bladder contraction


Thank
you!!