

Introduction to Autonomic drugs

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Nervous System

Central

Peripheral

Motor

Sensory

Autonomic
(ANS)

Somatic

Sympathetic (SNS)

Parasympathetic (PNS)

Alpha 1

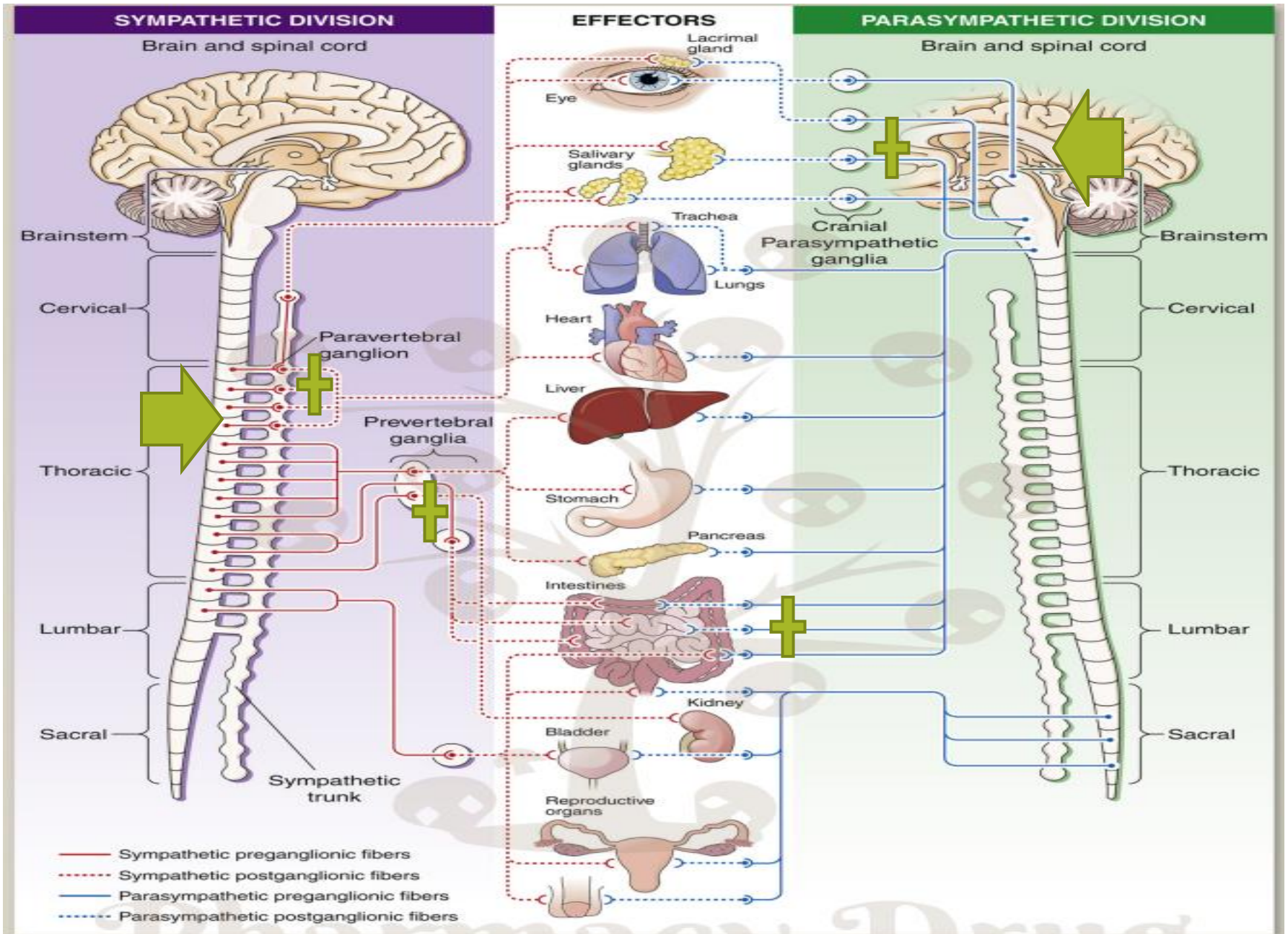
Alpha 2

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

Preganglionic neuron: soma is usually in the spine

Neurotransmitter released from the preganglionic synapse: acetylcholine

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

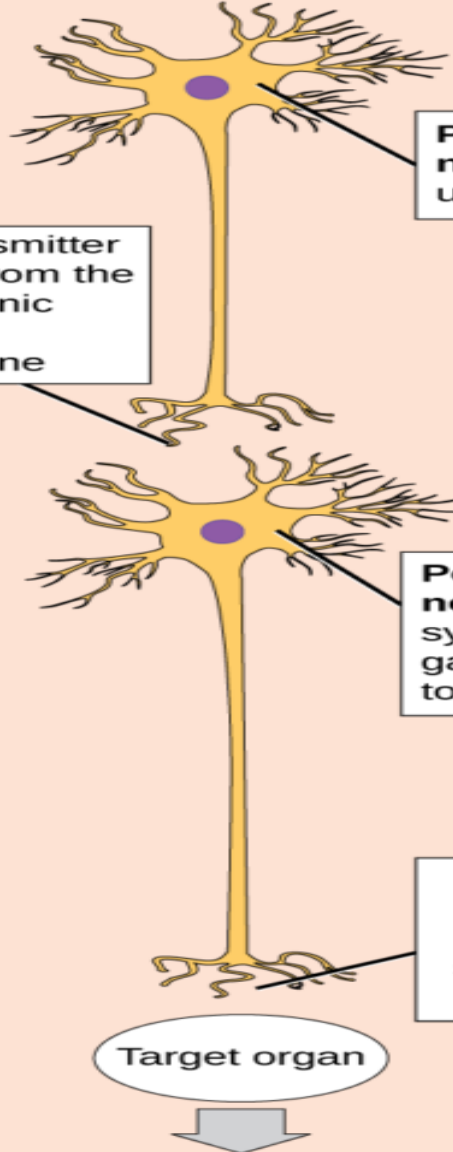
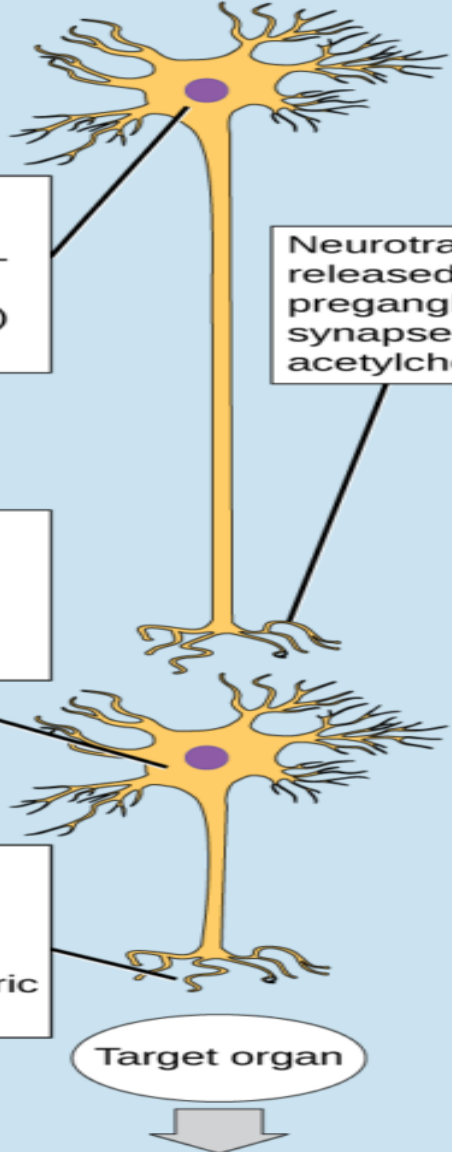
Neurotransmitters released from postganglionic synapse: norepinephrine

Target organ

Target organ

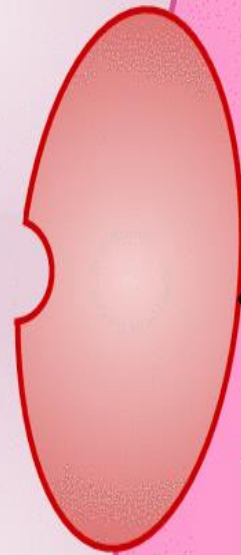
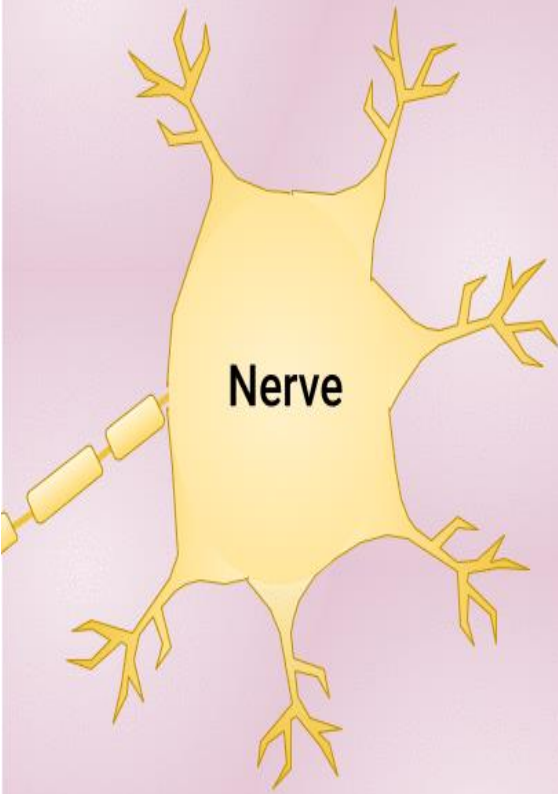
"Rest and digest" response is activated

"Fight or flight" response is activated



 Norepinephrine

 Acetylcholine



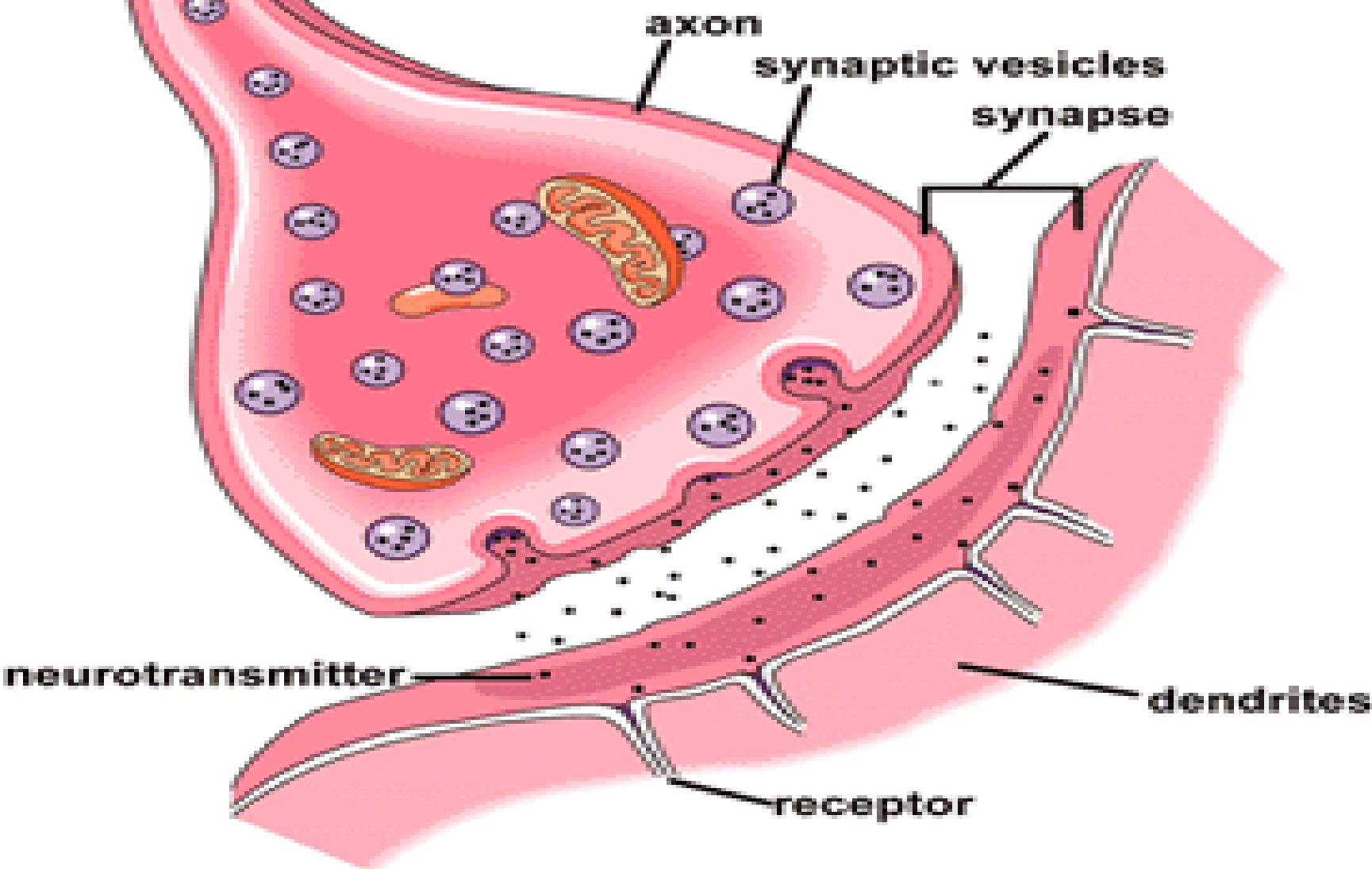
Cell

Adrenergic Receptor



Nicotinic Receptor

Synapse



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

Rest to Digest



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.

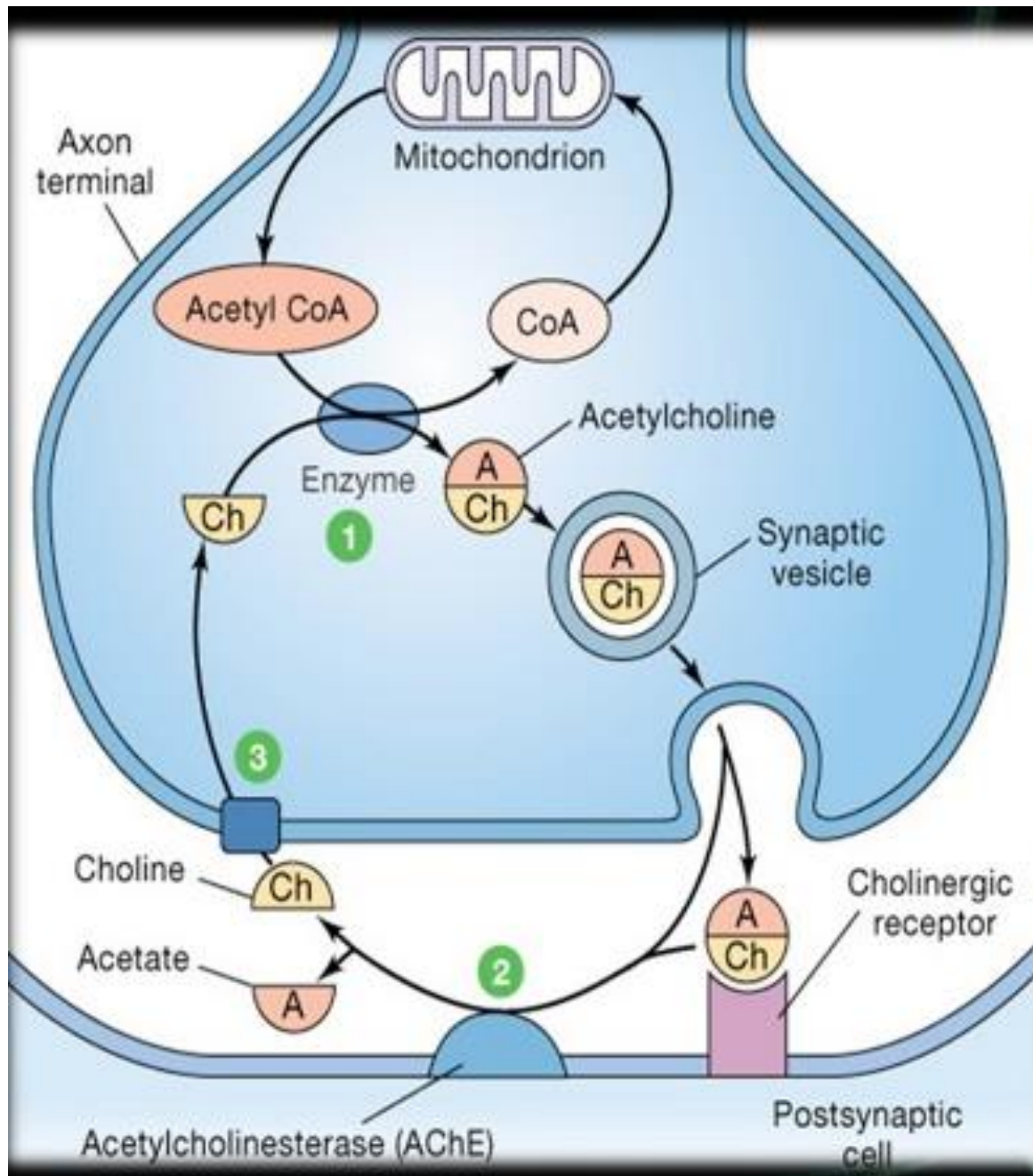
(4) Metabolism:

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.



- 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

(N_m = nicotinic muscle, N_n = 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.

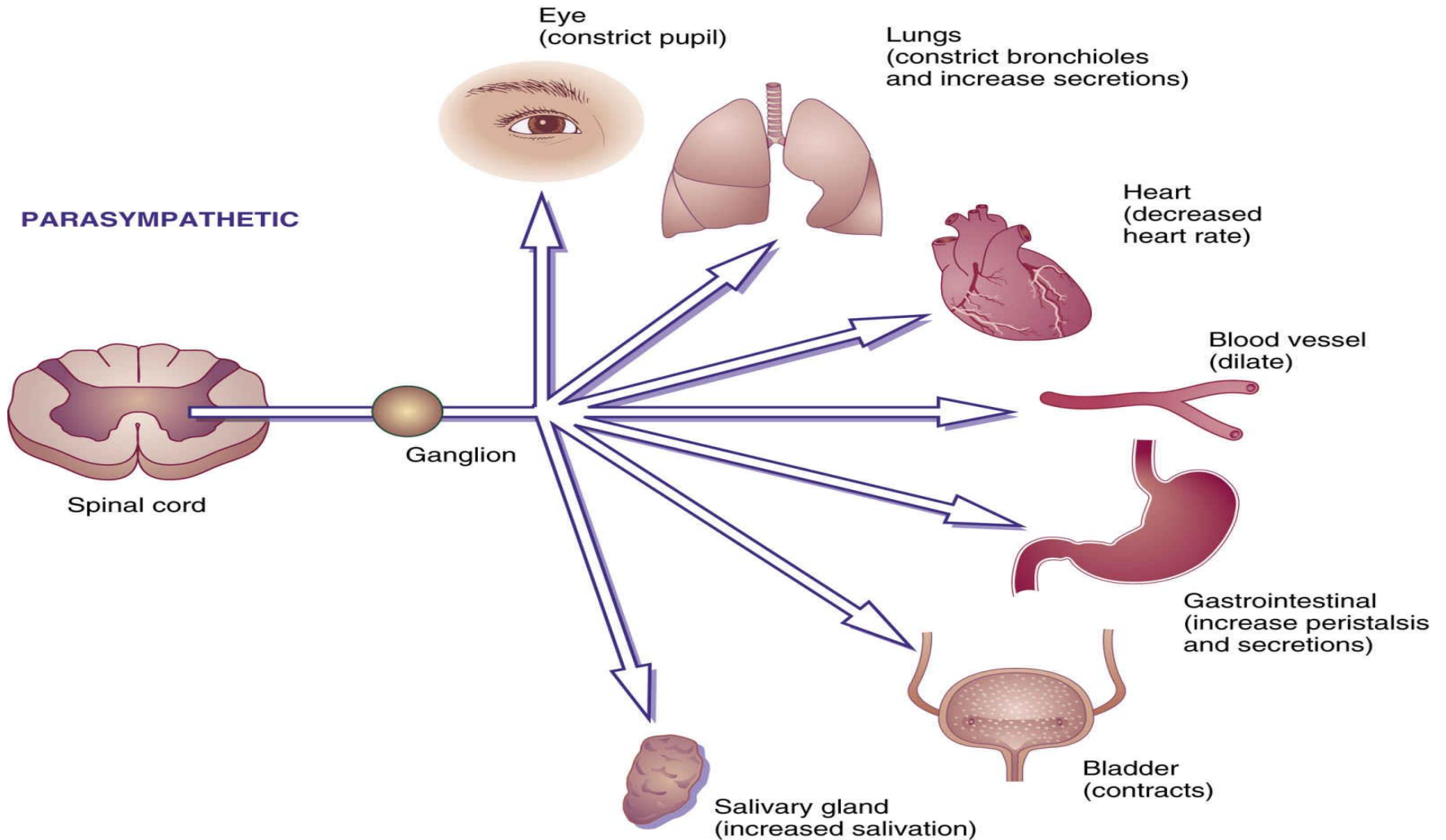
M_1 : G_q , causes stimulation of phospholipase C causing increase in the second messenger [Ca^{++} , inositol triphosphate (I P_3) and diacylglycerol (DAG)]

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

G_i that causes inhibition of adenylyl cyclase which increases cAMP.

M_3 : Similar to M_1 .

PHARMACOLOGICAL ACTIONS



parasympathomimetics:

Direct acting

Indirect acting

Drugs which act by direct binding to the receptors

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

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

FIGHT



Stand your ground, defend your position, attack, dig in, persevere!

OR

Flight



Give way, retreat, discard, remove yourself, give up, move on.

L-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-methyltransferase.

(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

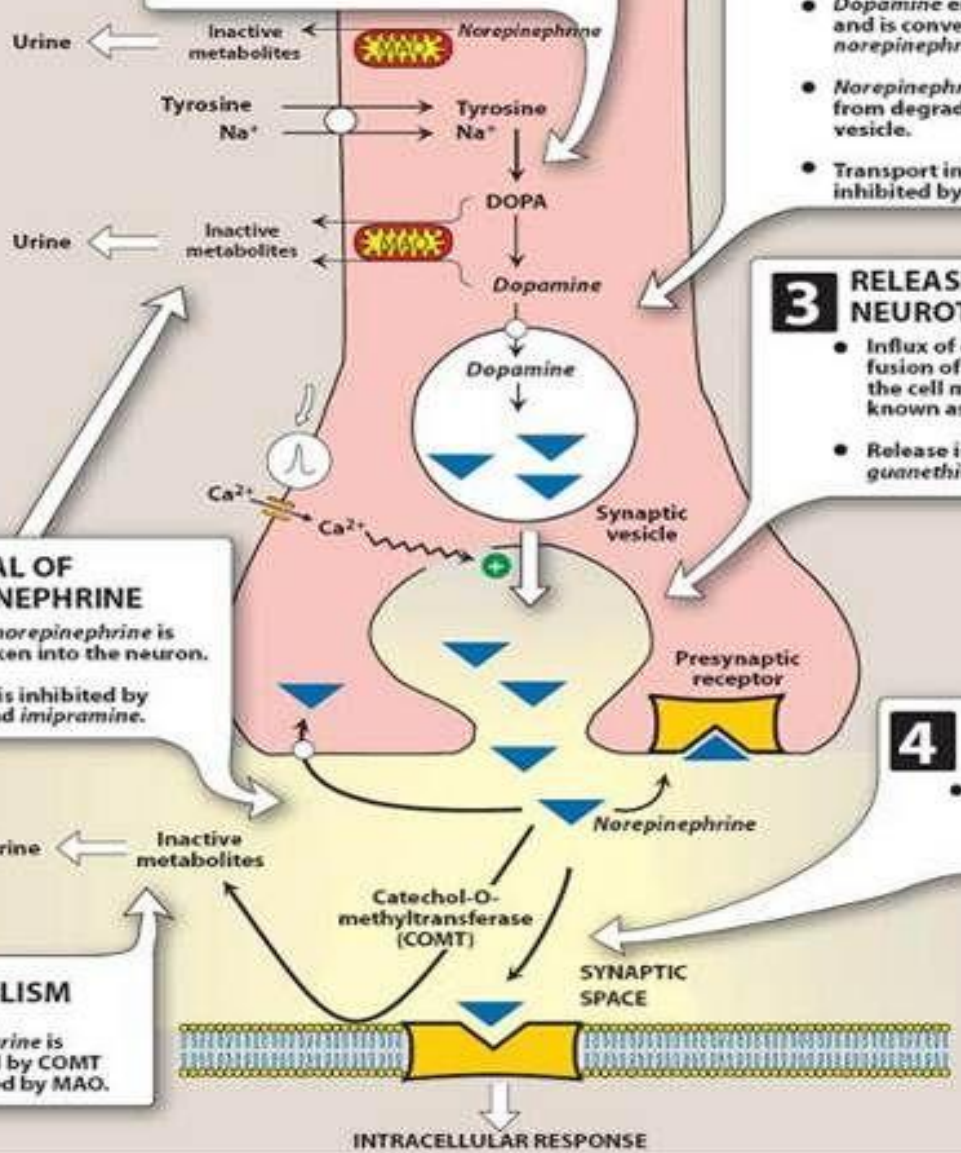
- Postsynaptic receptor is activated by the binding of neurotransmitter.

5 REMOVAL OF NOREPINEPHRINE

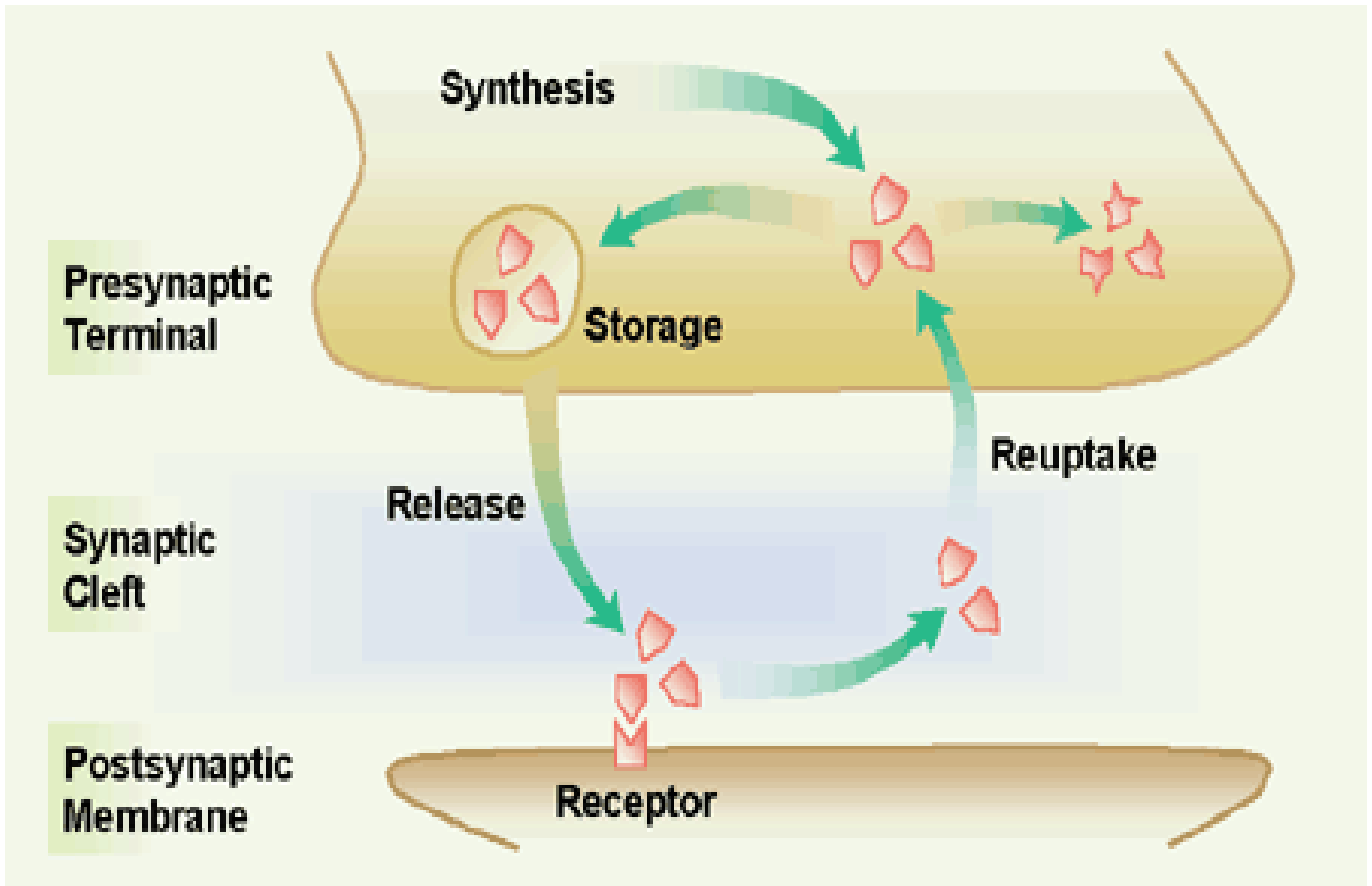
- Released norepinephrine is rapidly taken into the neuron.
- Reuptake is inhibited by cocaine and imipramine.

6 METABOLISM

- Norepinephrine is methylated by COMT and oxidized by MAO.



INTRACELLULAR RESPONSE



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 G_s that stimulates adenylyl cyclase which increases cAMP.

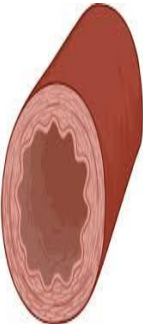
(b) Alpha-1 receptors (α_1) (similar to M_1)

- Their stimulation causes activation of G_q which stimulates phospholipase A_2 , C and D that increase the second messengers (IP₃, DAG and Ca⁺⁺).

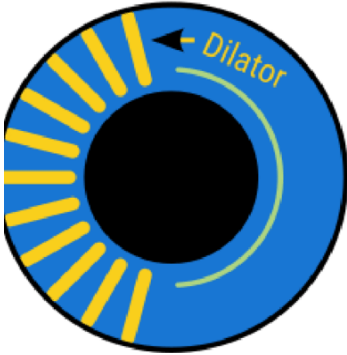
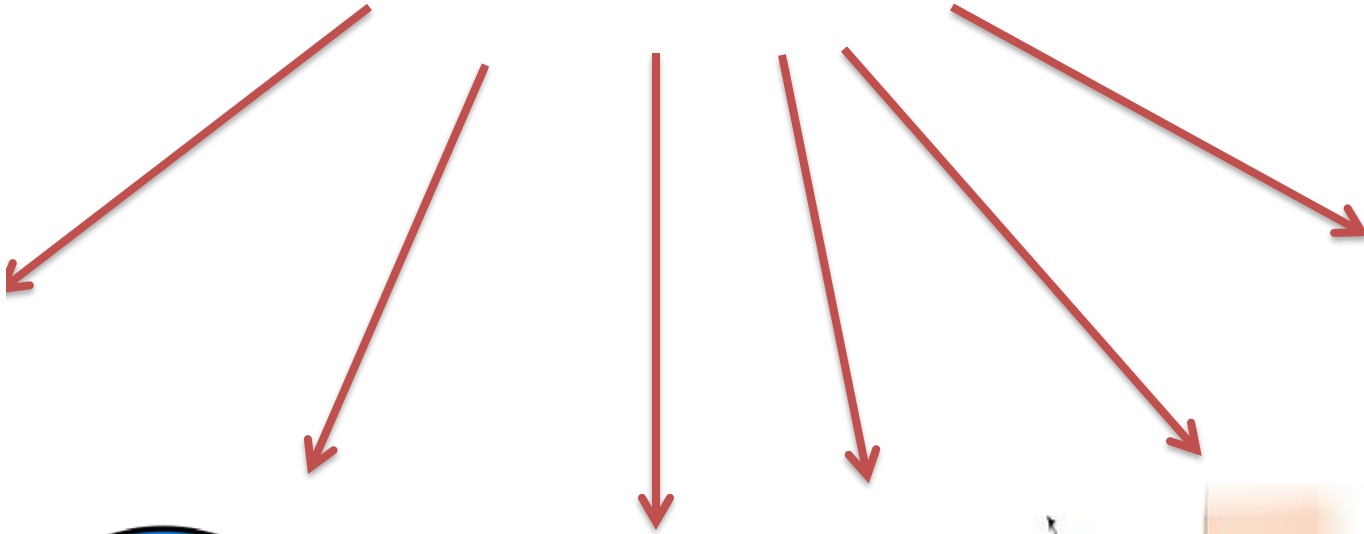
(c) Alpha-2 receptors (α_2) (similar to M_2)

- Their stimulation causes:
 - Activation of G_i which inhibits adenylyl cyclase that decreases cAMP.
 - Activation of G_i (β and γ subunits) which opens K⁺ channels.

$\alpha 1$ stimulation



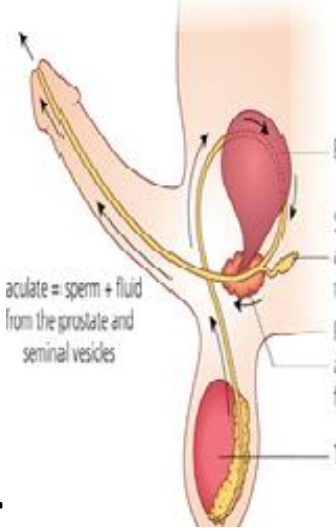
V.C



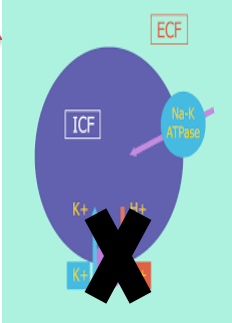
Mydriasis



Contraction of sphincter

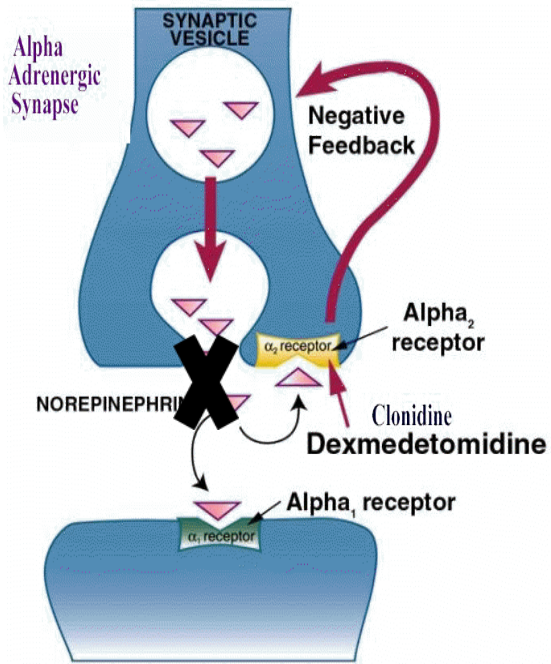
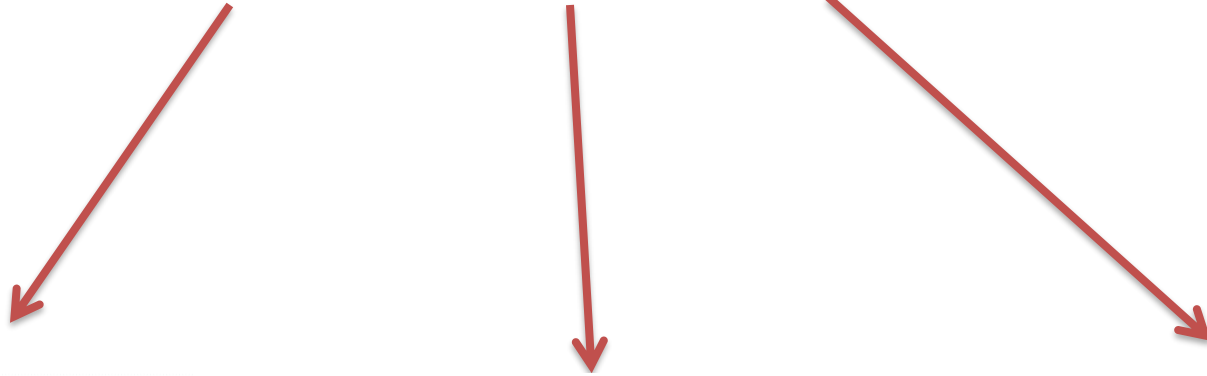


ejaculation

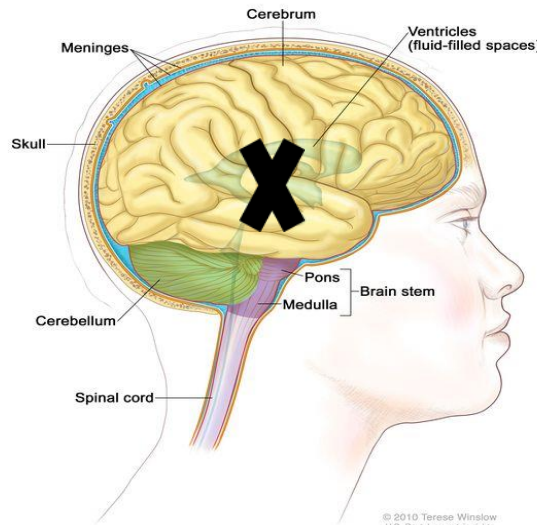


hyperkalemia

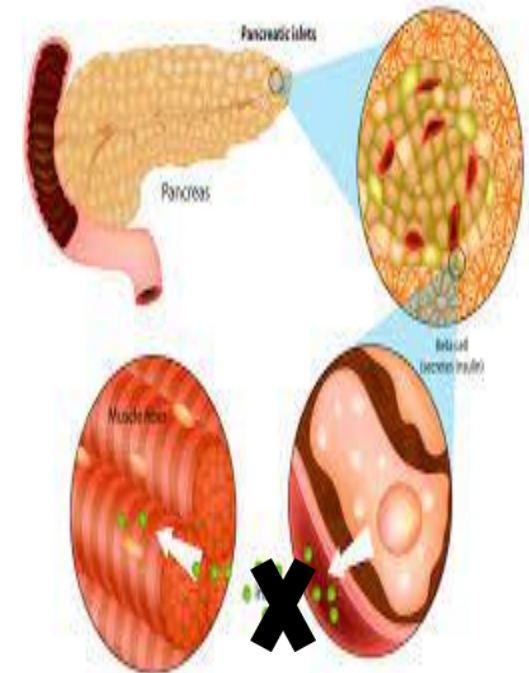
α_2 stimulation (inhibitory)



Inhibit NE, epinephrine and Ach

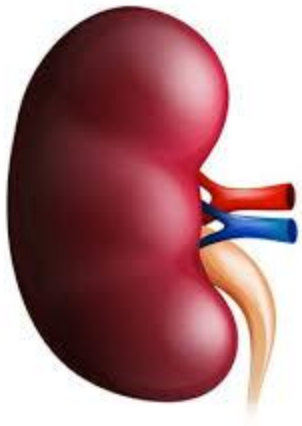
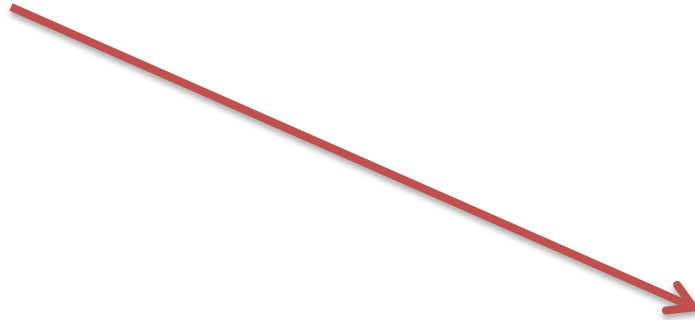
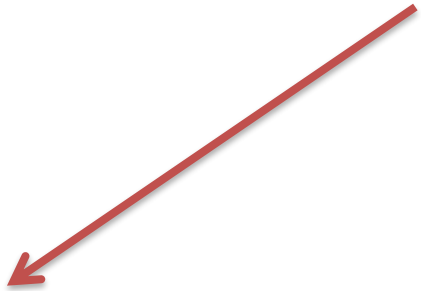


- Sympathetic flow



Inhibit insulin release

β 1 stimulation



↑ renin release

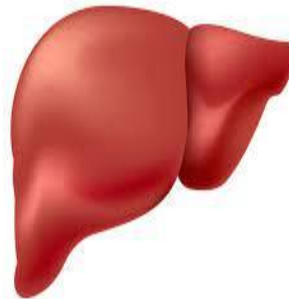
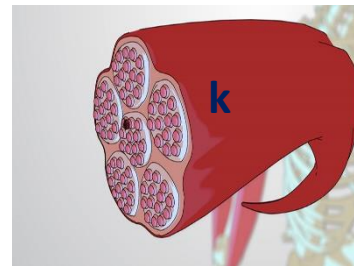


↑ all cardiac properties

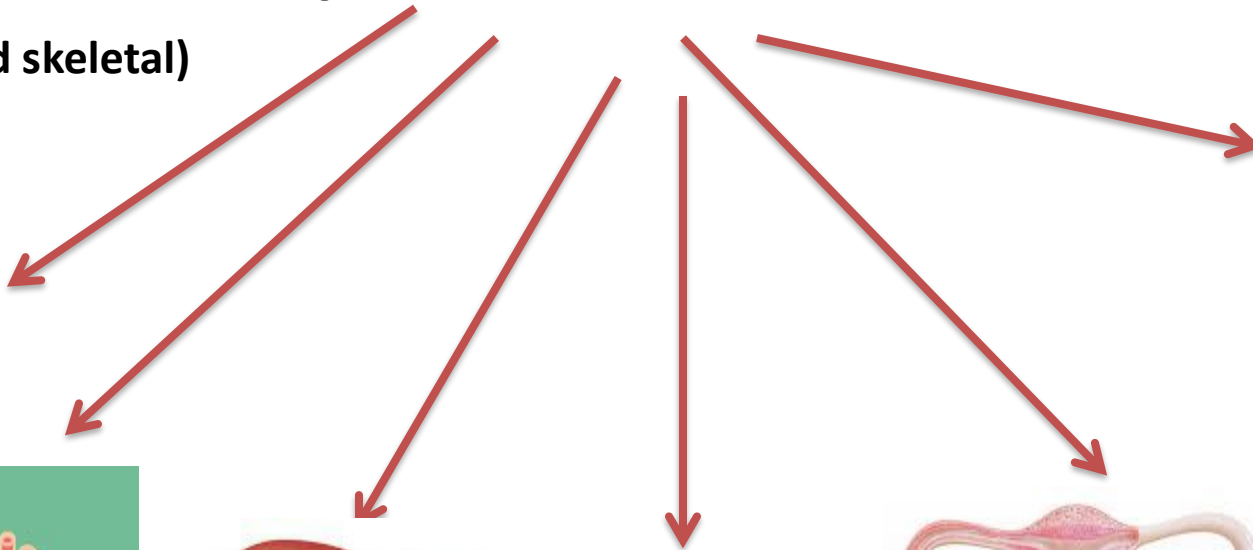
β 2 stimulation



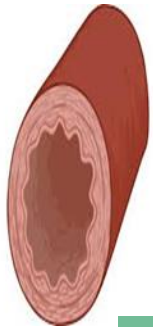
Relaxation



Glycogenolysis: \uparrow glucose blood level
Gluconeogenesis: \uparrow glucose blood level
 \uparrow K uptake by muscles : hypokalemia



(coronary and skeletal)

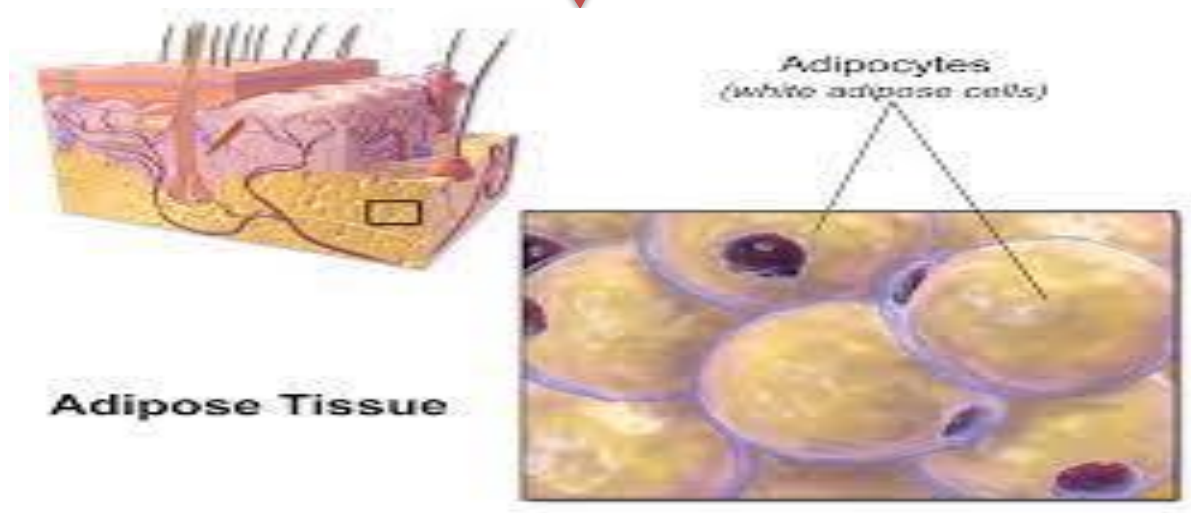


V.D



Bronchodilatation

β 3 stimulation



+ lipolysis

Adrenergic Agonists

Direct-Acting

Endogenous
Catecholamines

Epinephrine
Norepinephrine

Specific
Adrenergic
Receptor Agonists

Phenylephrine
Dobutamine

Indirect-Acting

Release of
Stored
Catecholamines

Tyramine
Amphetamine

Reduce
Catecholamine
Metabolism

MAO Inhibitors
COMT Inhibitors

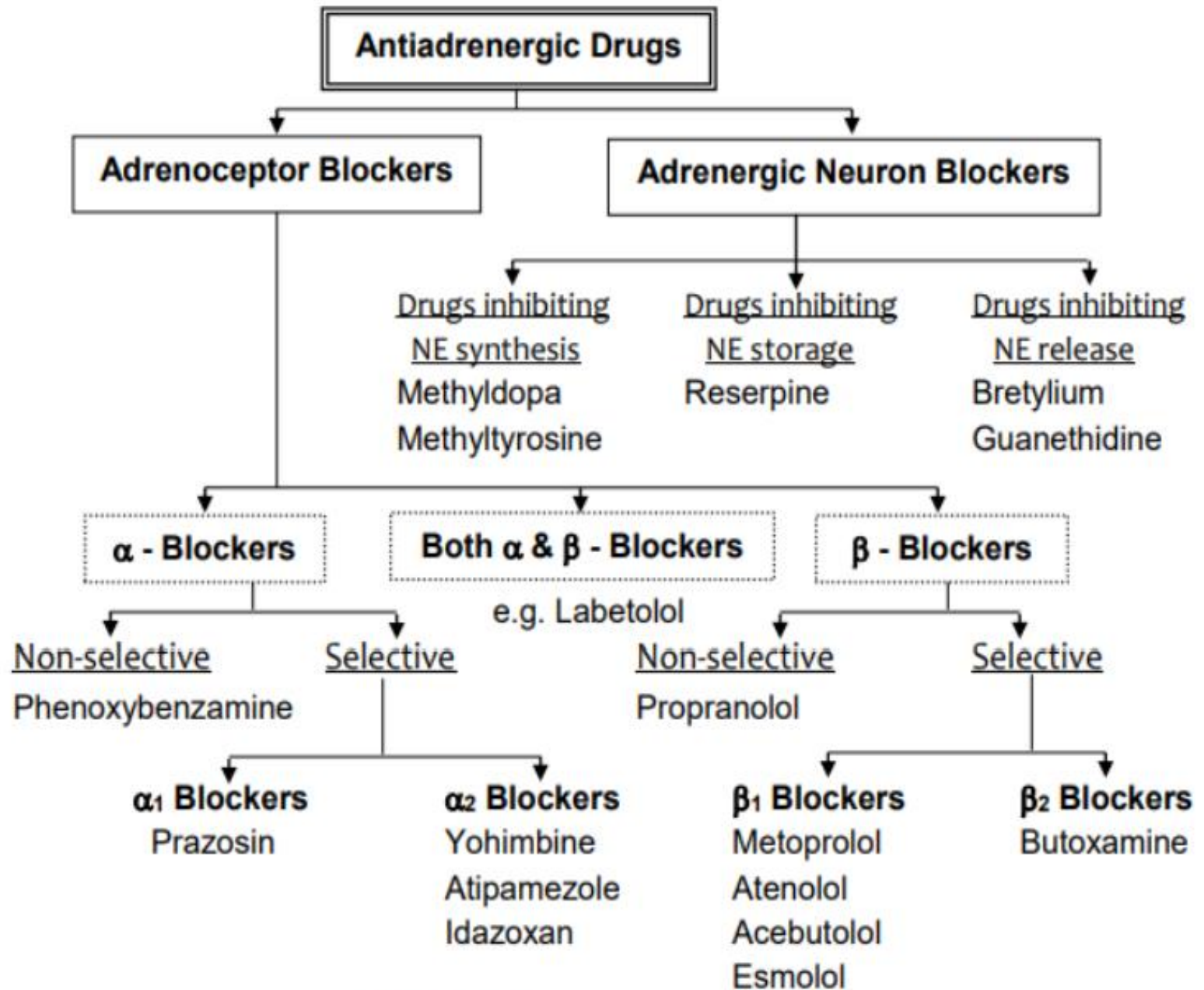
Catecholamine
Reuptake
Inhibitors

Cocaine

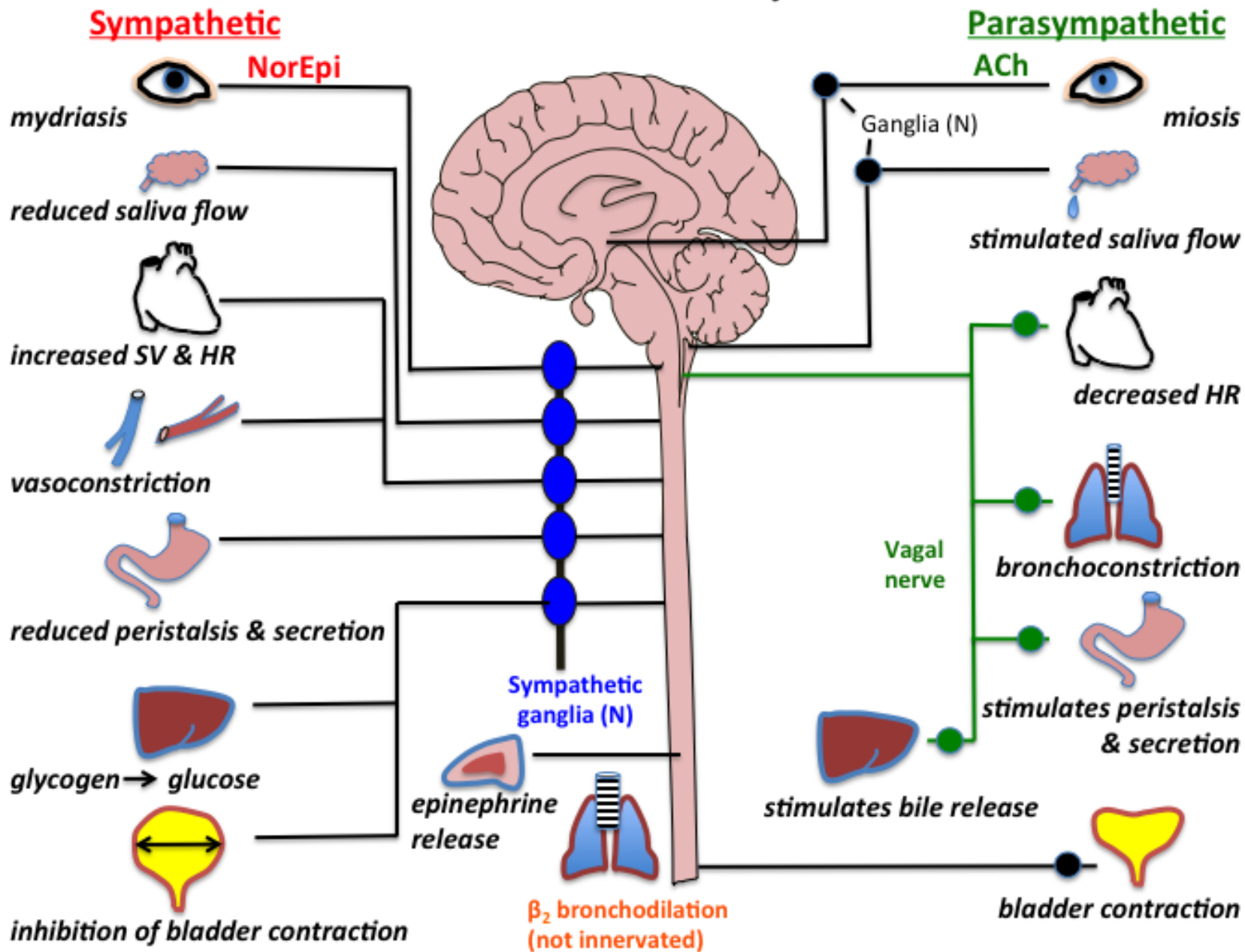
Mixed-Acting

Direct and
Indirect
Effects

Ephedrine



The Autonomic Nervous System





Thank
you!!