



# 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 brainstem 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

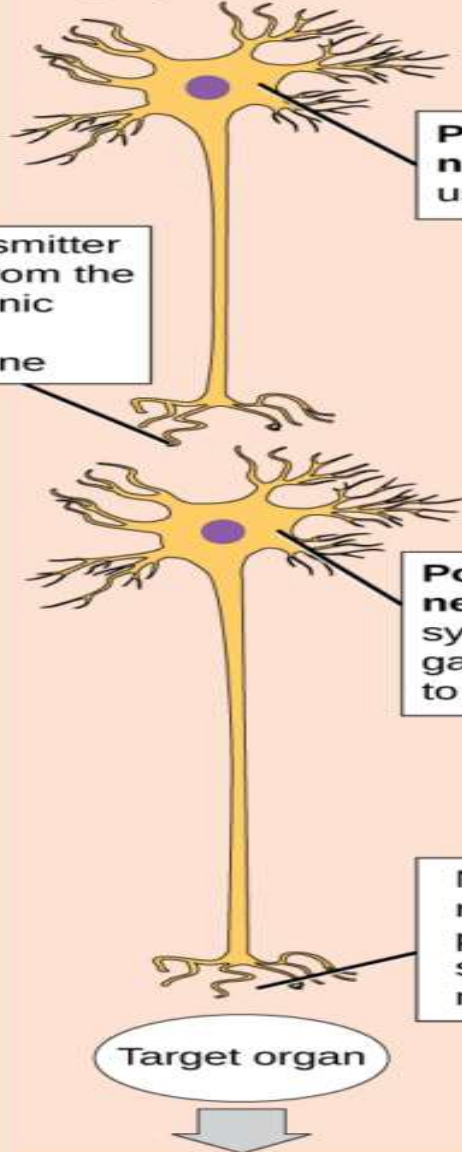
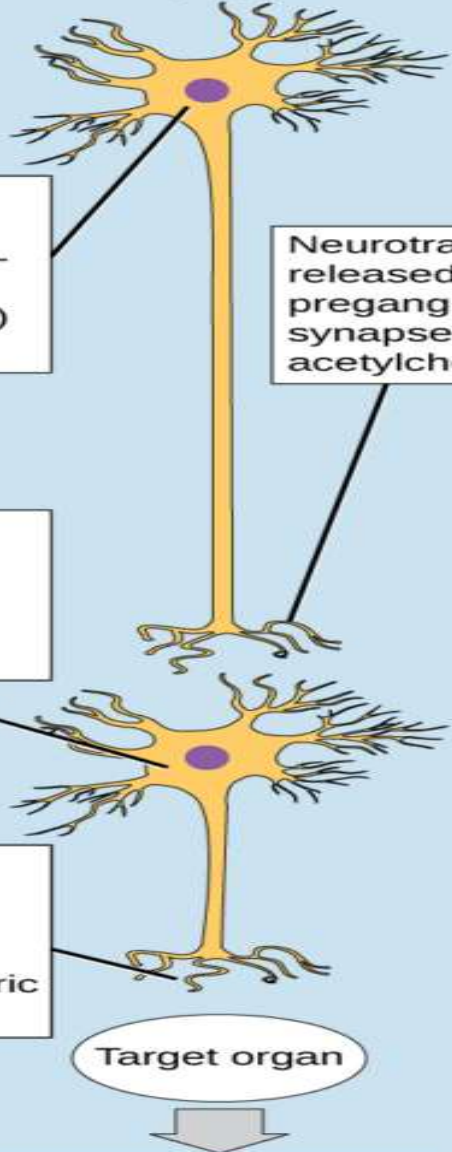
Neurotransmitters released from postganglionic synapse: norepinephrine

Target organ


Target organ

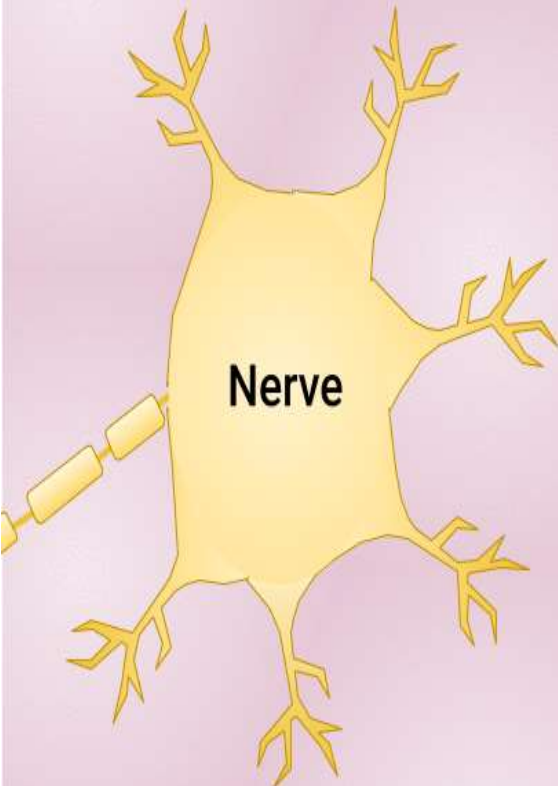
**"Rest and digest"** response is activated

**"Fight or flight"** response is activated



 Norepinephrine

 Acetylcholine



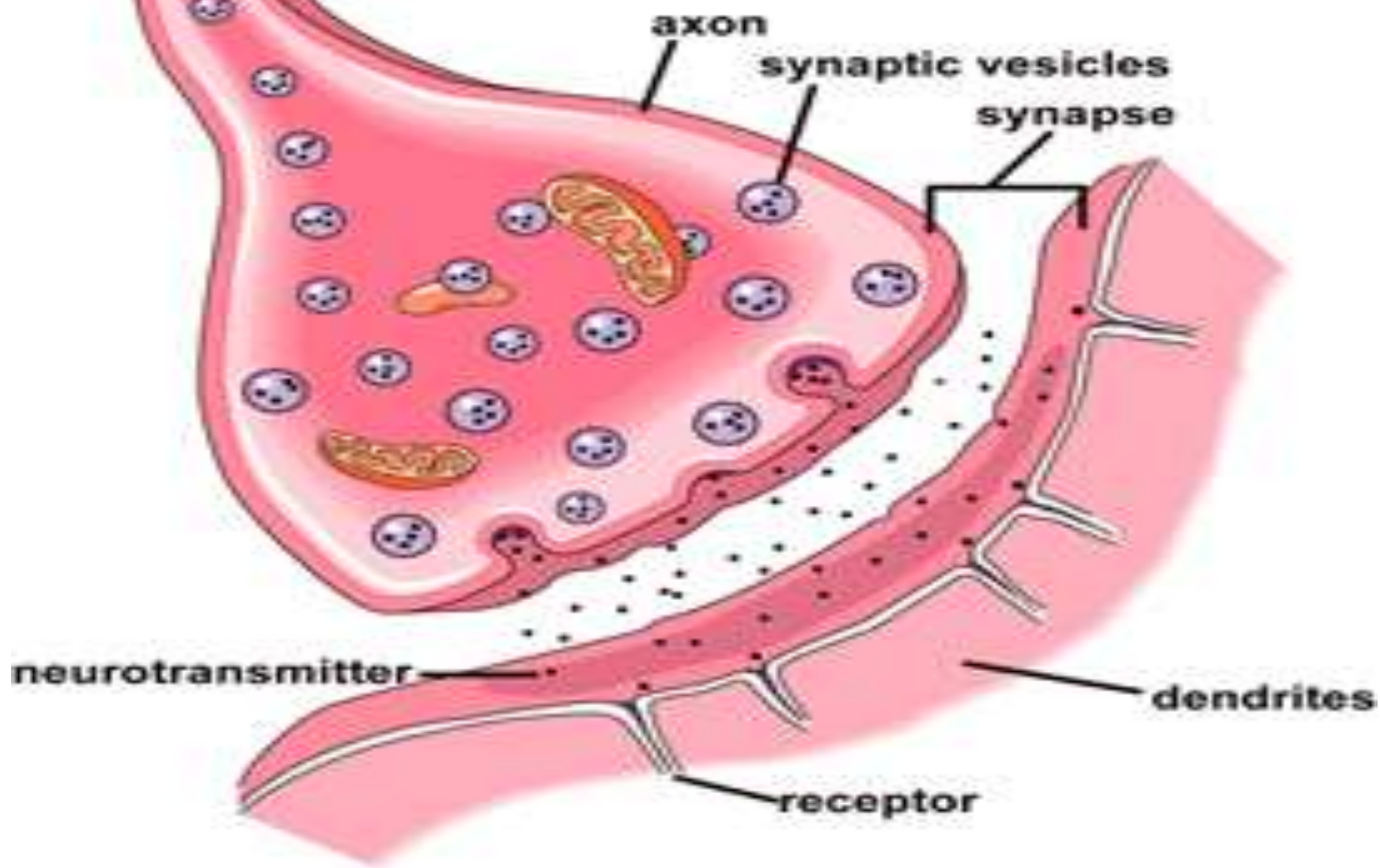
Cell

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  $\text{Ca}^{++}$  ions and release of ACh from the storage vesicles by exocytosis.



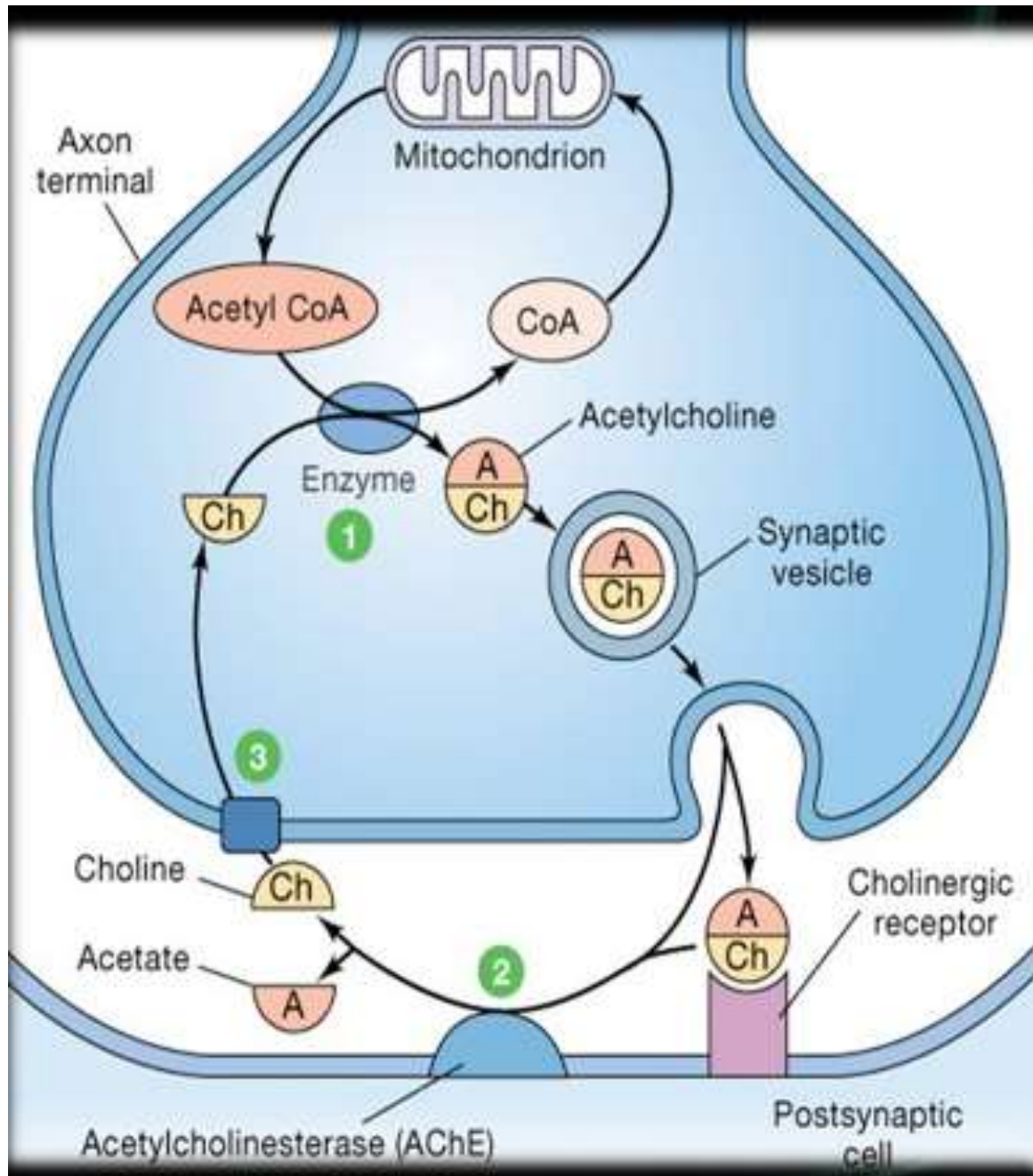
## **(4) Metabolism:**

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  $\text{Na}^+$

### **(b) Muscarinic receptors:**

They are G-protein-coupled receptors.

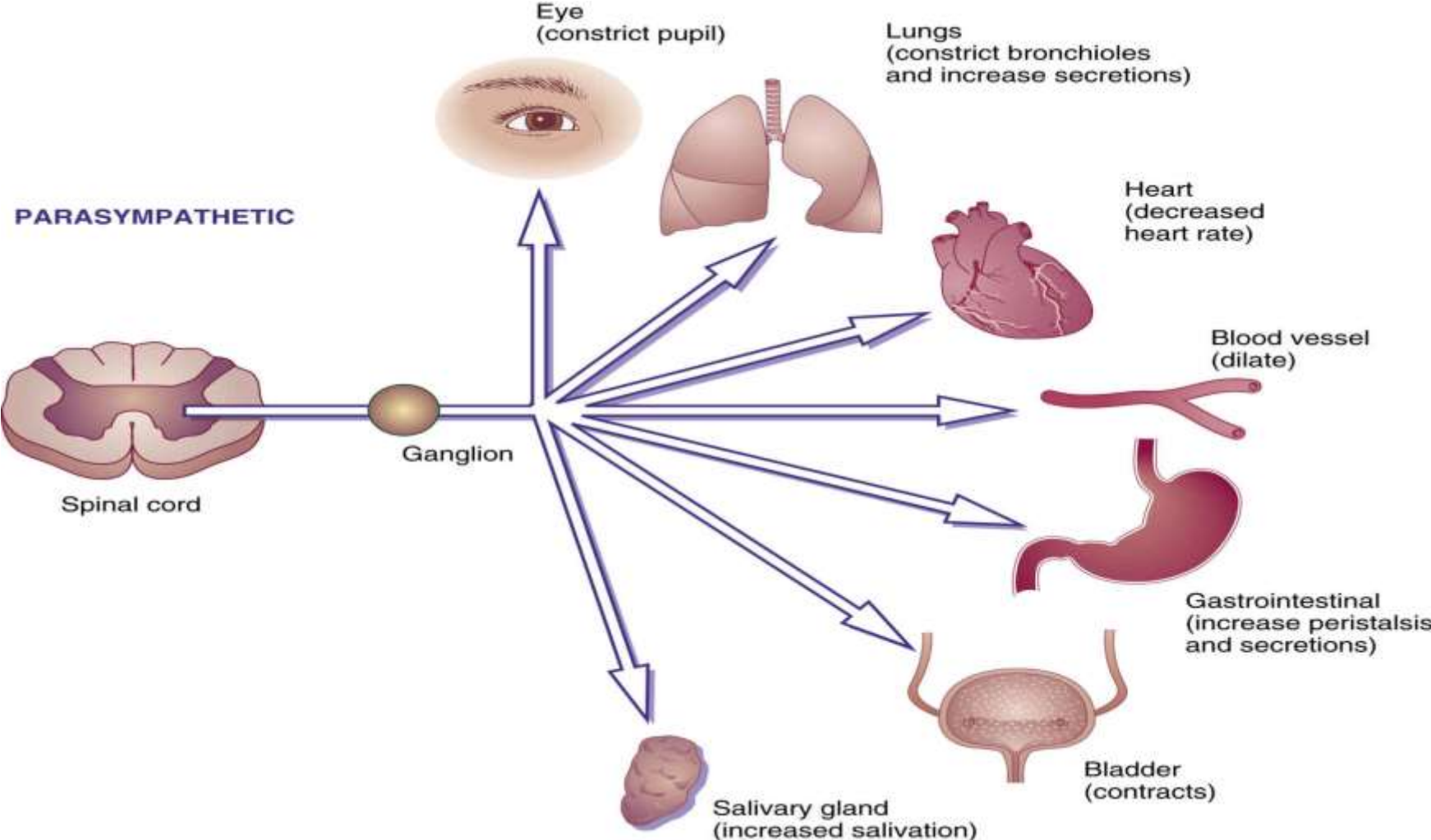
$\text{M}_1$ :  $\text{G}_q$ , causes stimulation of phospholipase C causing increase in the second messenger [ $\text{Ca}^{++}$ , inositol triphosphate ( $\text{I P}_3$ ) and diacylglycerol (DAG)]

$\text{M}_2$ :  $\text{G}_i$  (B and  $\gamma$  subunits) causes opening of  $\text{K}^+$  channels.

$\text{G}_i$  that causes inhibition of adenylyl cyclase which decreases cAMP.

$\text{M}_3$ : Similar to  $\text{M}_1$ .

# PHARMACOLOGICAL ACTIONS



## parasympathomimetics:

Direct acting

Indirect acting

Drugs which act by direct binding to the receptors

### 1-Choline esters:

acetylcholine, methacholine, carbachol and bethanechol.

### 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

**FIGHT**



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

**OR**

***Flight***



Give way, retreat, discard, remove yourself, give up, make do.

# 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<sup>+</sup> 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  $\alpha$ -methyldopa to  $\alpha$ -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<sup>++</sup> channels** leading to increase in the intracellular Ca<sup>++</sup> 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

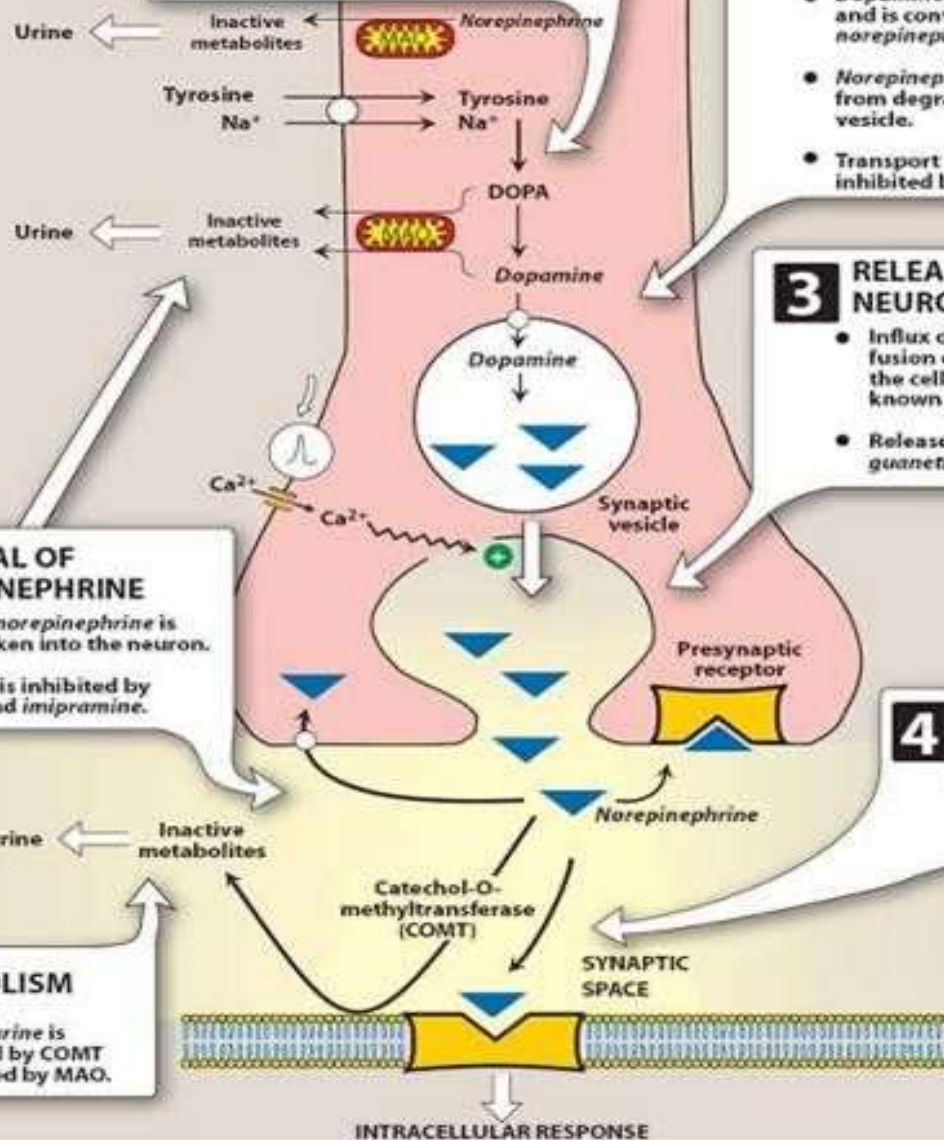
- Postsynaptic receptor is activated by the binding of neurotransmitter.

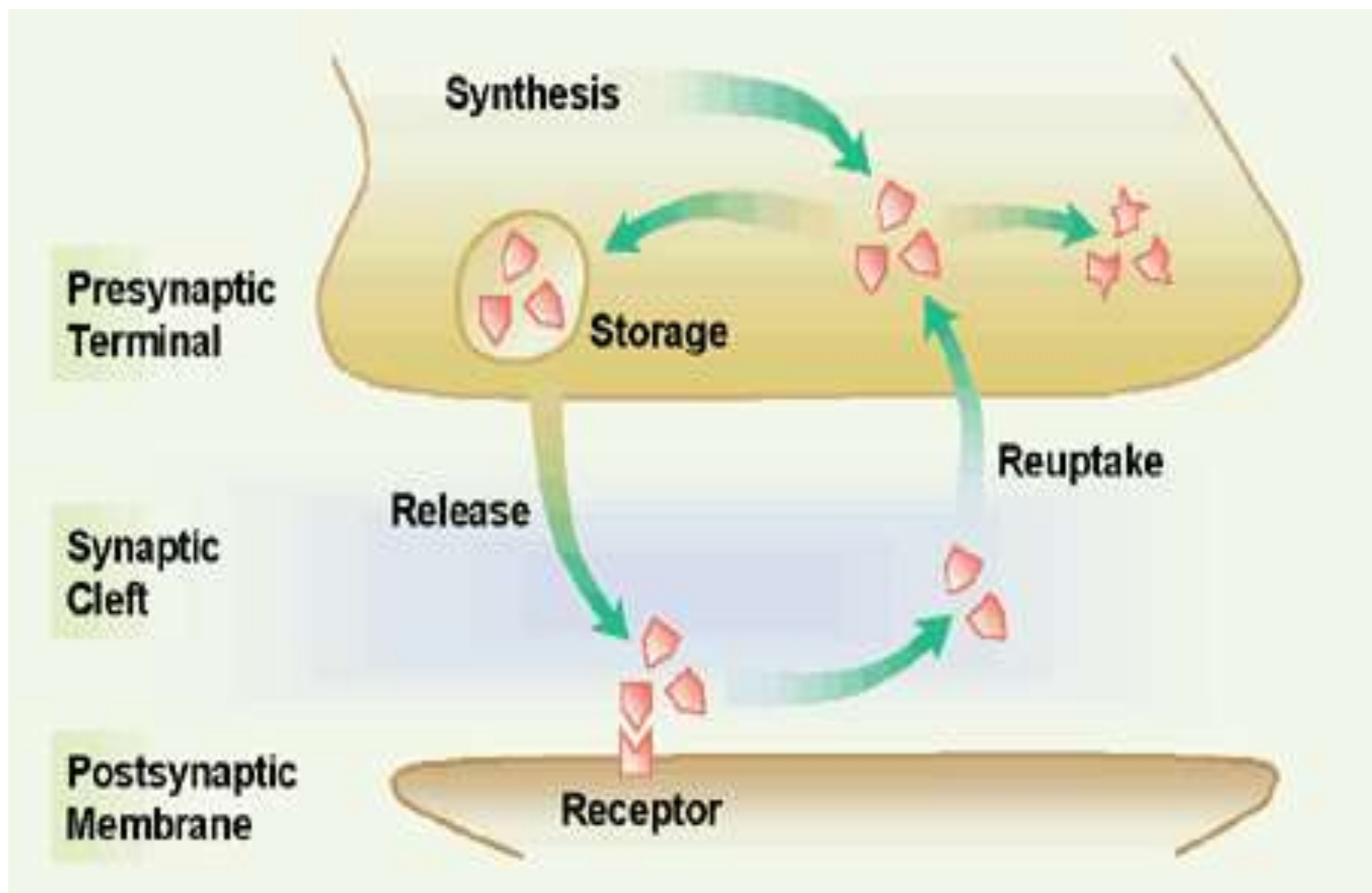
# 5 REMOVAL OF NOREPINEPHRINE

- 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.





# 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 ( $\beta_1$ , $\beta_2$ and $\beta_3$ )

- They are G-protein-coupled receptors.
- Their stimulation causes activation of  $G_s$  that stimulates adenylyl cyclase which increases cAMP.

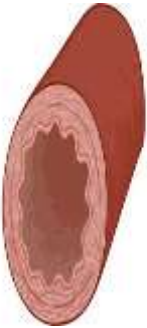
## (b) Alpha-1 receptors ( $\alpha_1$ ) (similar to $M_1$ )

- Their stimulation causes activation of  $G_q$  which stimulates phospholipase  $A_2$ , C and D that increase the second messengers (IP<sub>3</sub>, DAG and Ca<sup>++</sup>).

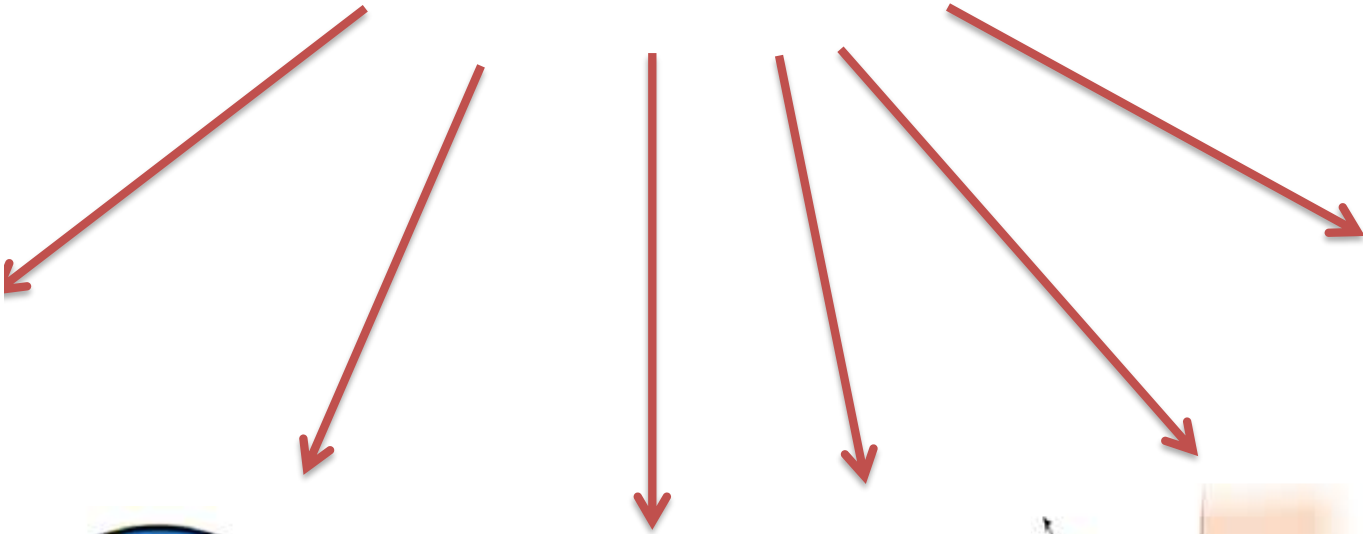
## (c) Alpha-2 receptors ( $\alpha_2$ ) (similar to $M_2$ )

- Their stimulation causes:
  - Activation of  $G_i$  which inhibits adenylyl cyclase that decreases cAMP.
  - Activation of  $G_i$  ( $\beta$  and  $\gamma$  subunits) which opens K<sup>+</sup> channels.

# $\alpha 1$ stimulation



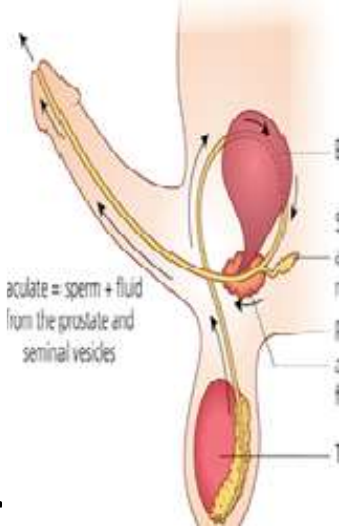
V.C



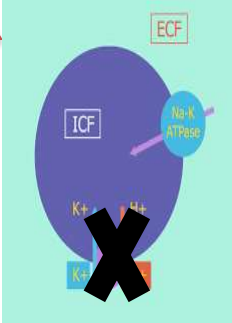
Mydriasis



Contraction of sphincter

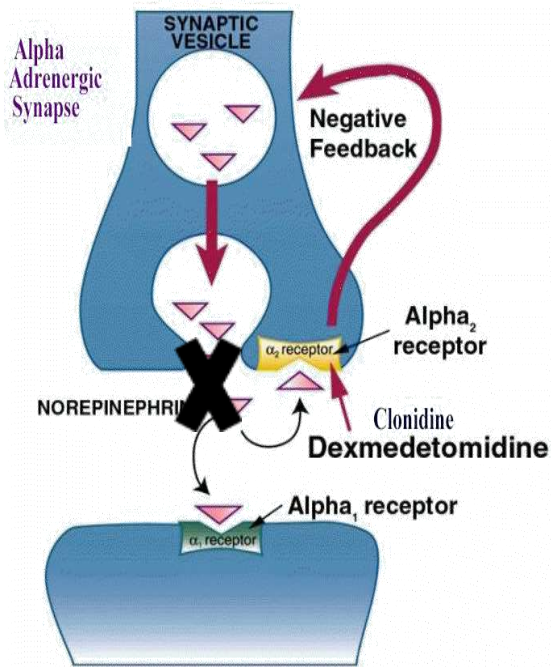
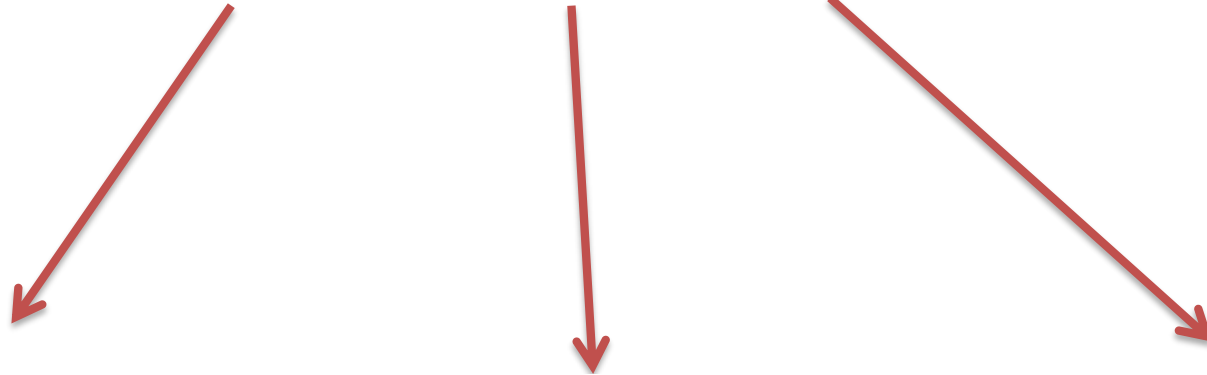


ejaculation

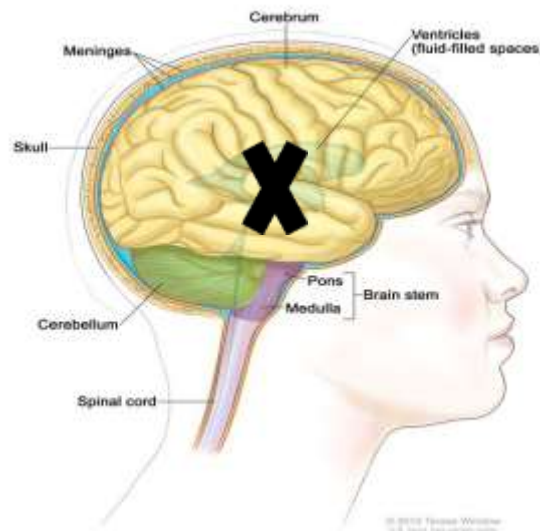


hyperkalemia

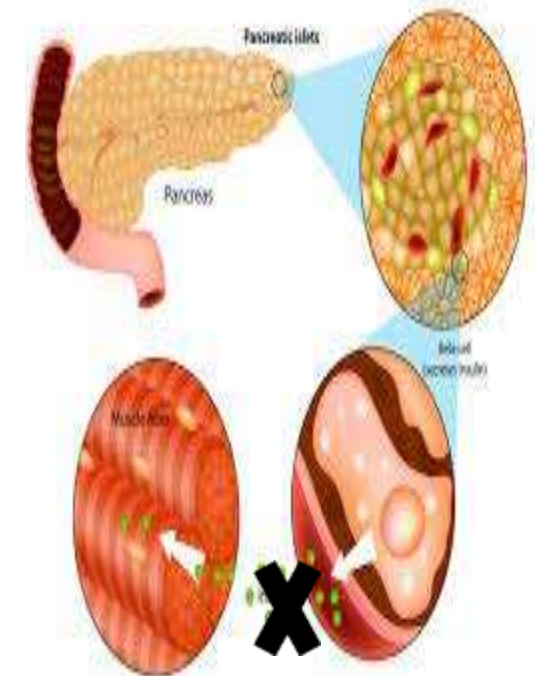
# $\alpha_2$ stimulation (inhibitory)



Inhibit NE, epinephrine  
and Ach

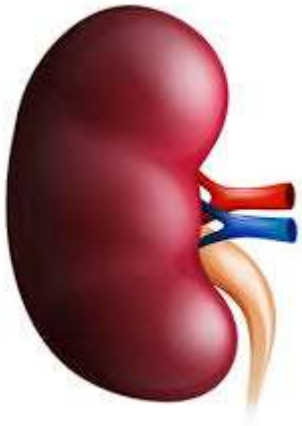
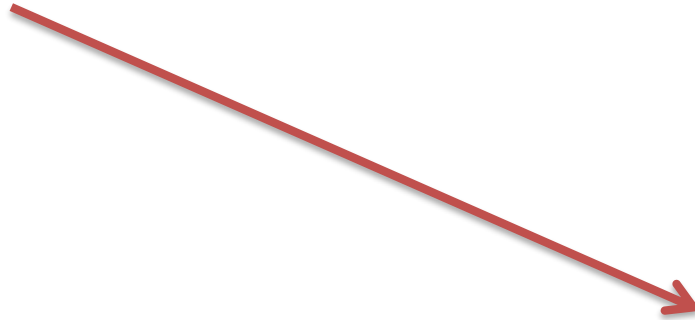
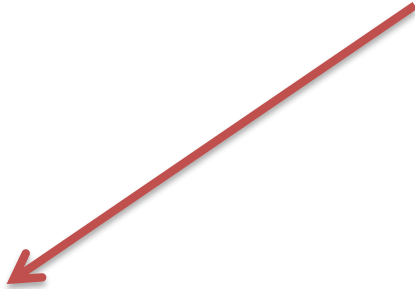


- Sympathetic  
flow



Inhibit insulin release

# $\beta$ 1 stimulation



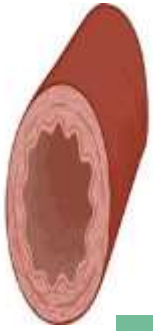
**↑ renin release**



**↑ all cardiac properties**

# $\beta$ 2 stimulation

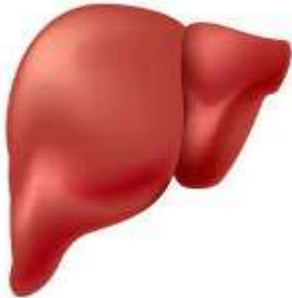
(coronary and skeletal)



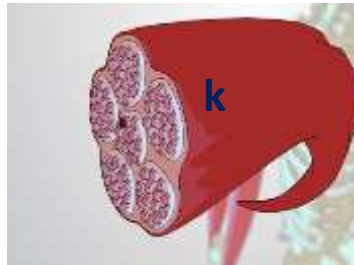
V.D



**Bronchodilatation**



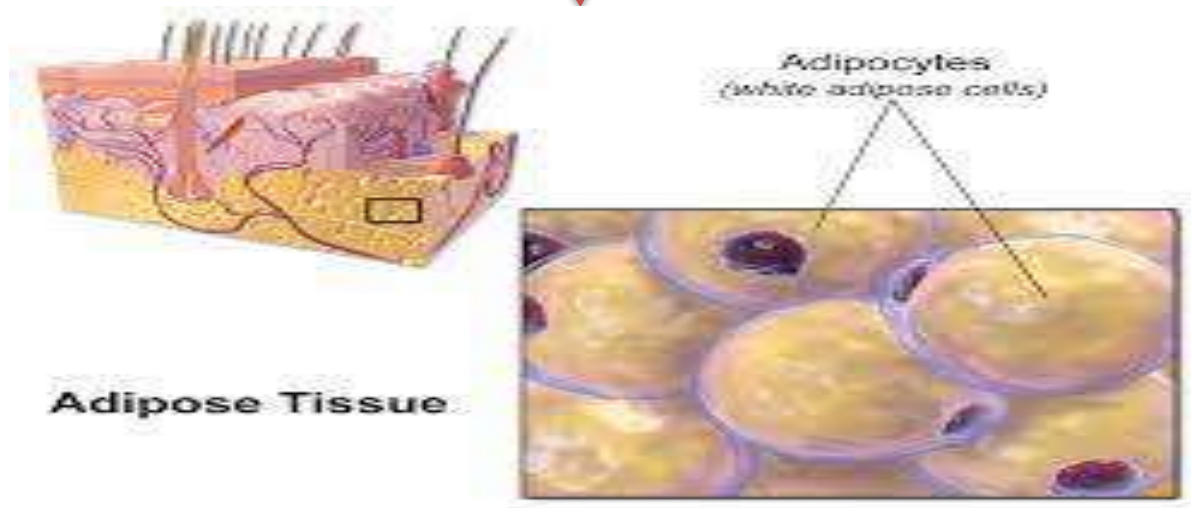
**Glycogenolysis:  $\uparrow$  glucose blood level**  
**Gluconeogenesis:  $\uparrow$  glucose blood level**  
 **$\uparrow$  K uptake by muscles : hypokalemia**



**Relaxation**



# $\beta$ 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

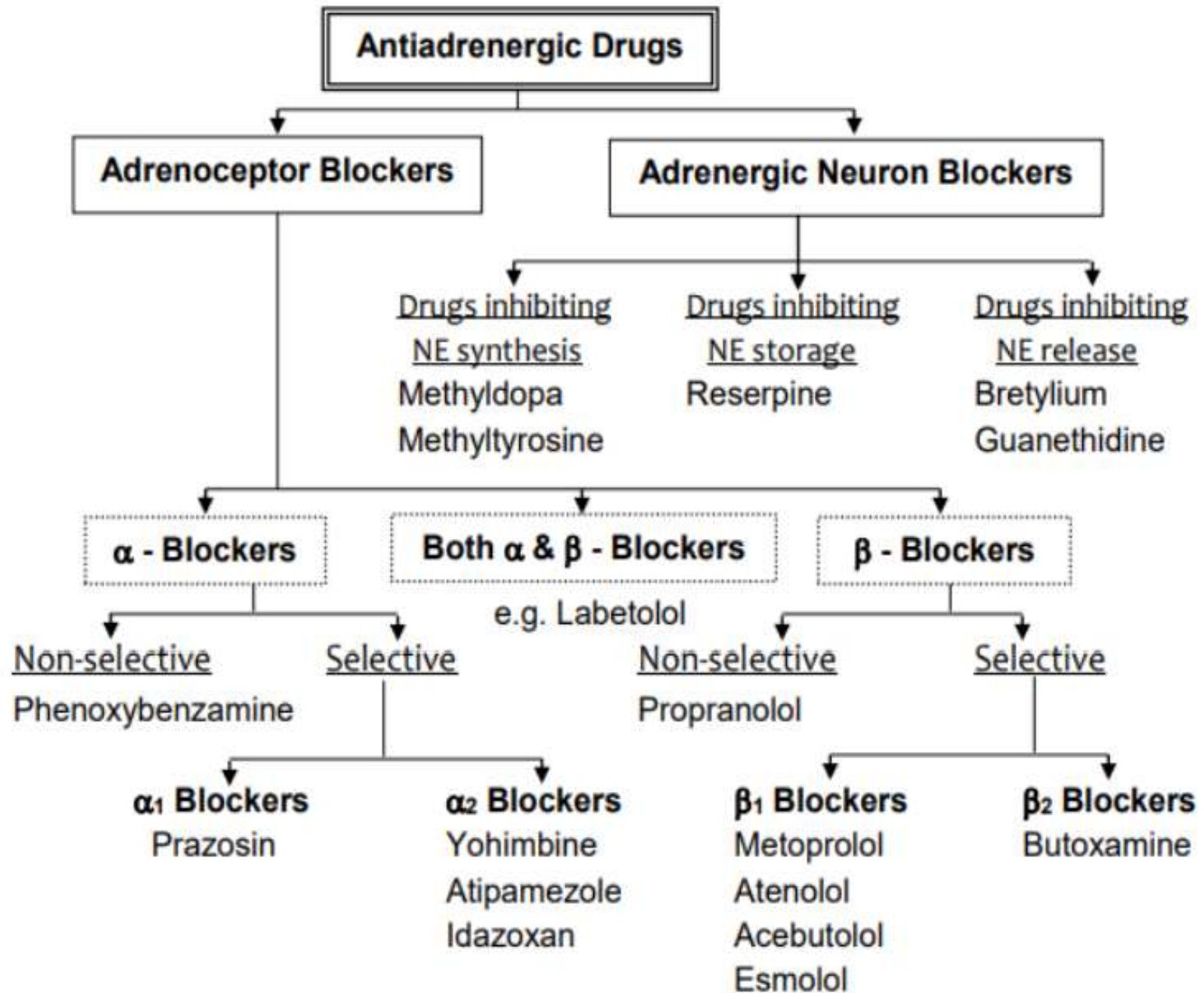
Cocaine

Mixed-Acting

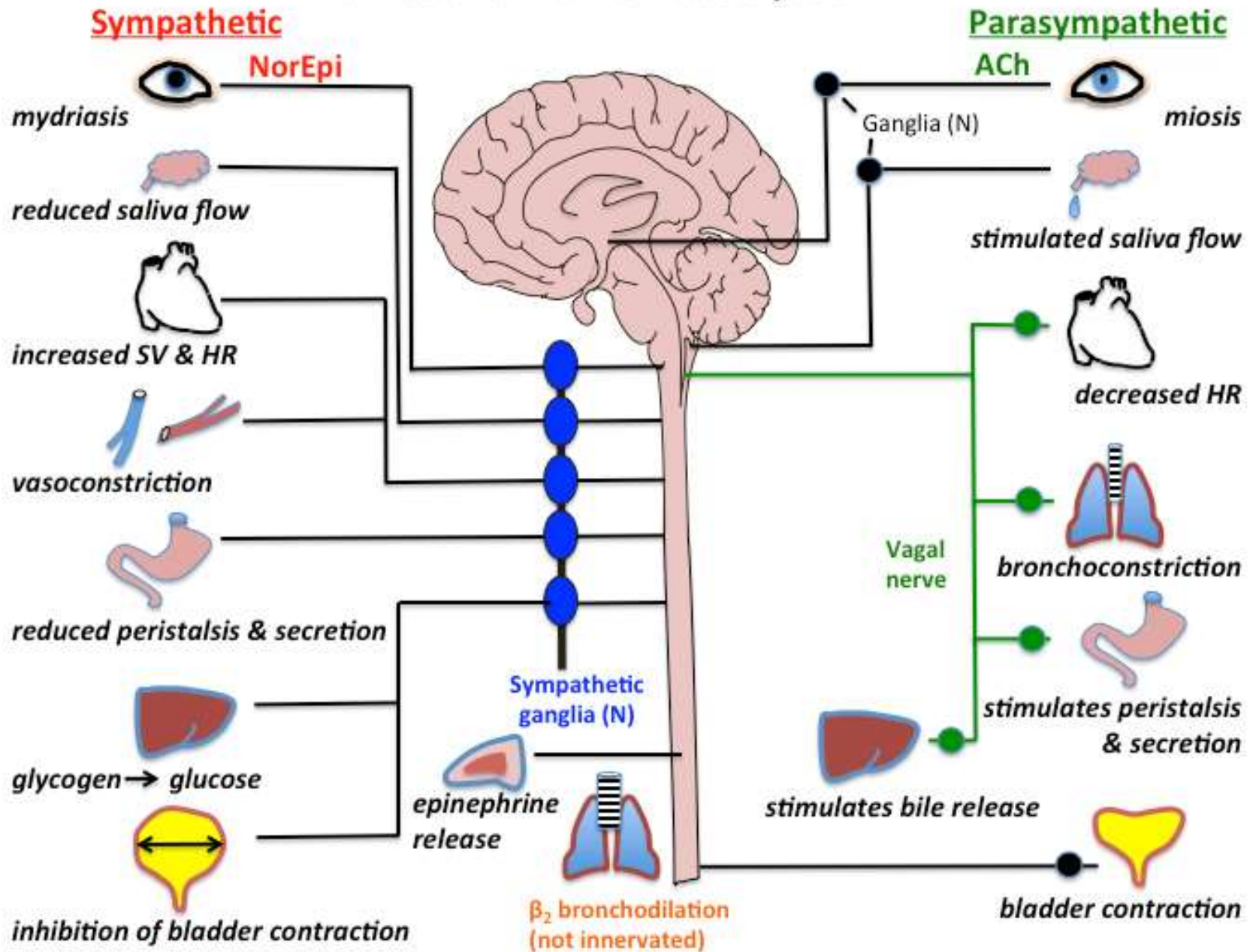
Direct and  
Indirect  
Effects

Ephedrine





# The Autonomic Nervous System





Thank  
you!!