13/11/23

Introduction to Autonomic drugs

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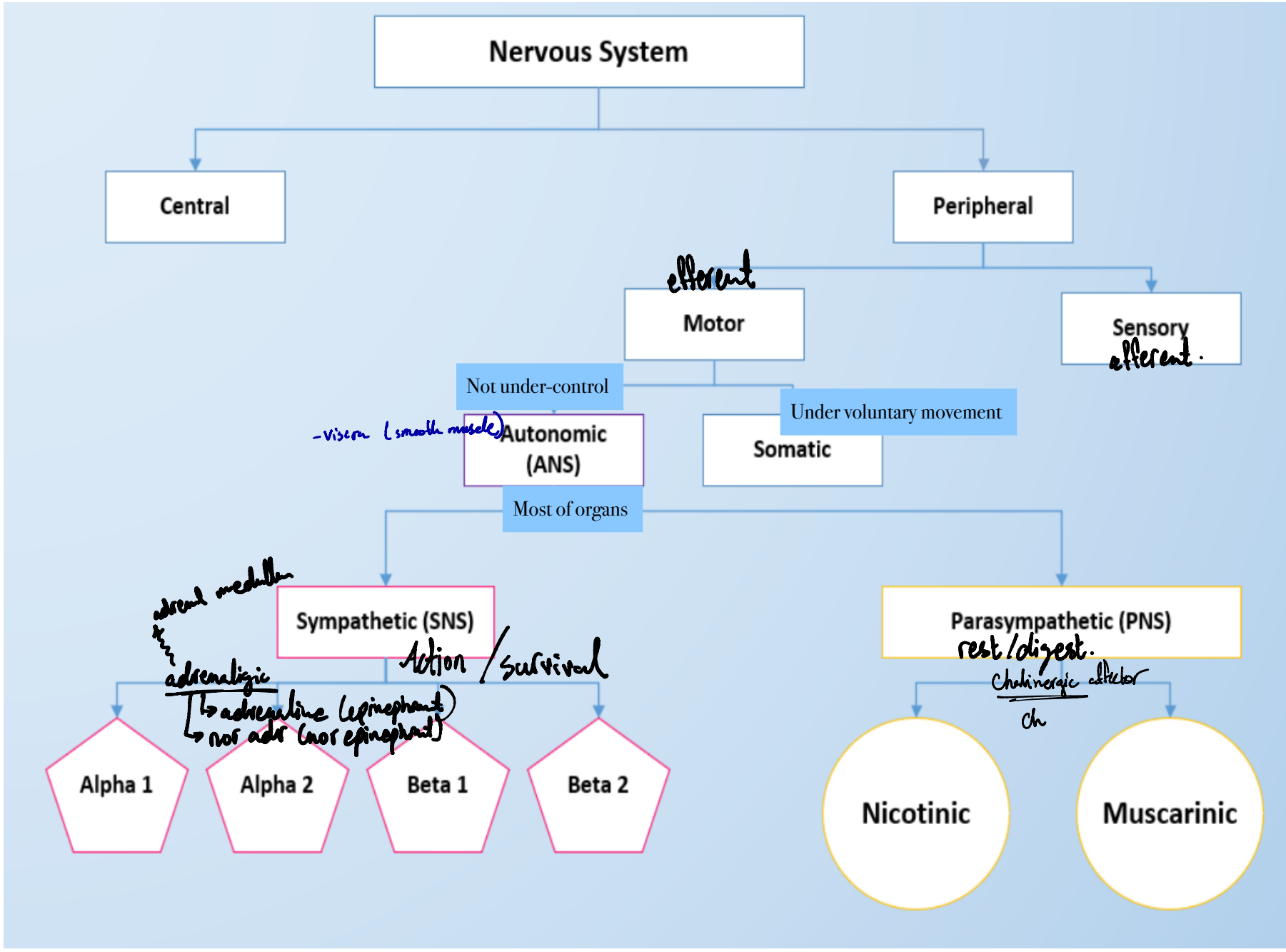
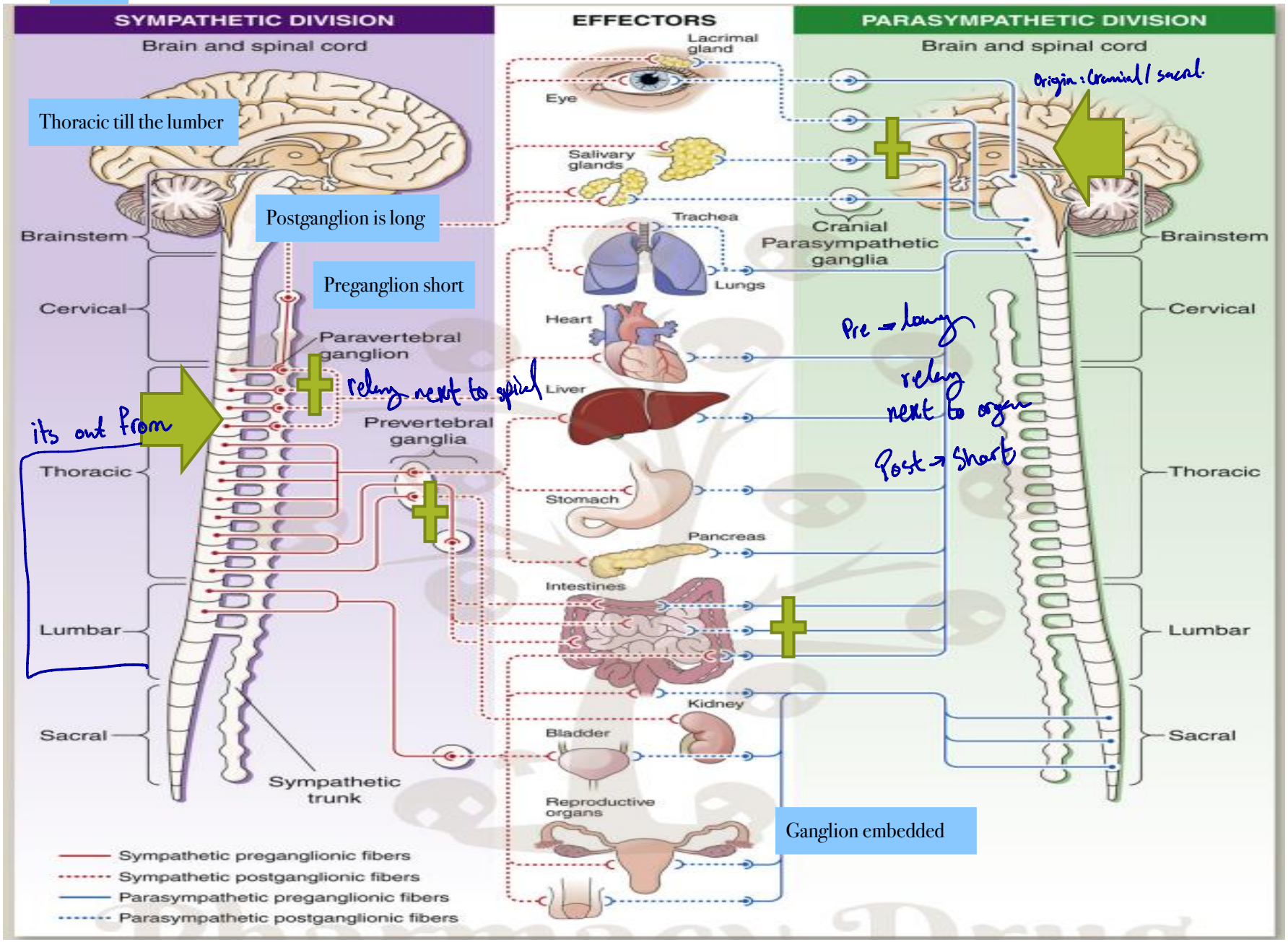

Nervous System
Central
Peripheral
efferent
Motor
Sensory
afferent.
Not under-control
Under voluntary movement
-viscera (smooth muscle)
Autonomic (ANS)
Somatic
Most of organs
adrenal medulla
Sympathetic (SNS)
Action / survival
adrenalinergic
adrenaline (epinephrine)
nor adr (nor epinephrine)
Parasympathetic (PNS)
rest / digest.
Cholinergic effector
ch
Alpha 1
Alpha 2
Beta 1
Beta 2
Nicotinic
Muscarinic

Action

Sleep



Autonomic Nervous System

Parasympathetic

Preganglionic neuron: soma is usually in the brain-stem or sacral (toward the bottom) spinal cord

Neurotransmitter released from the preganglionic synapse: acetylcholine

Postganglionic neuron: soma is usually in a ganglion near the target organ

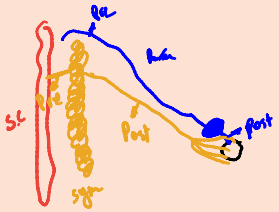
Neurotransmitters released from postganglionic synapse: acetylcholine or nitric oxide

Target organ

"Rest and digest" response is activated

Sympathetic

Preganglionic neuron: soma is usually in the spine

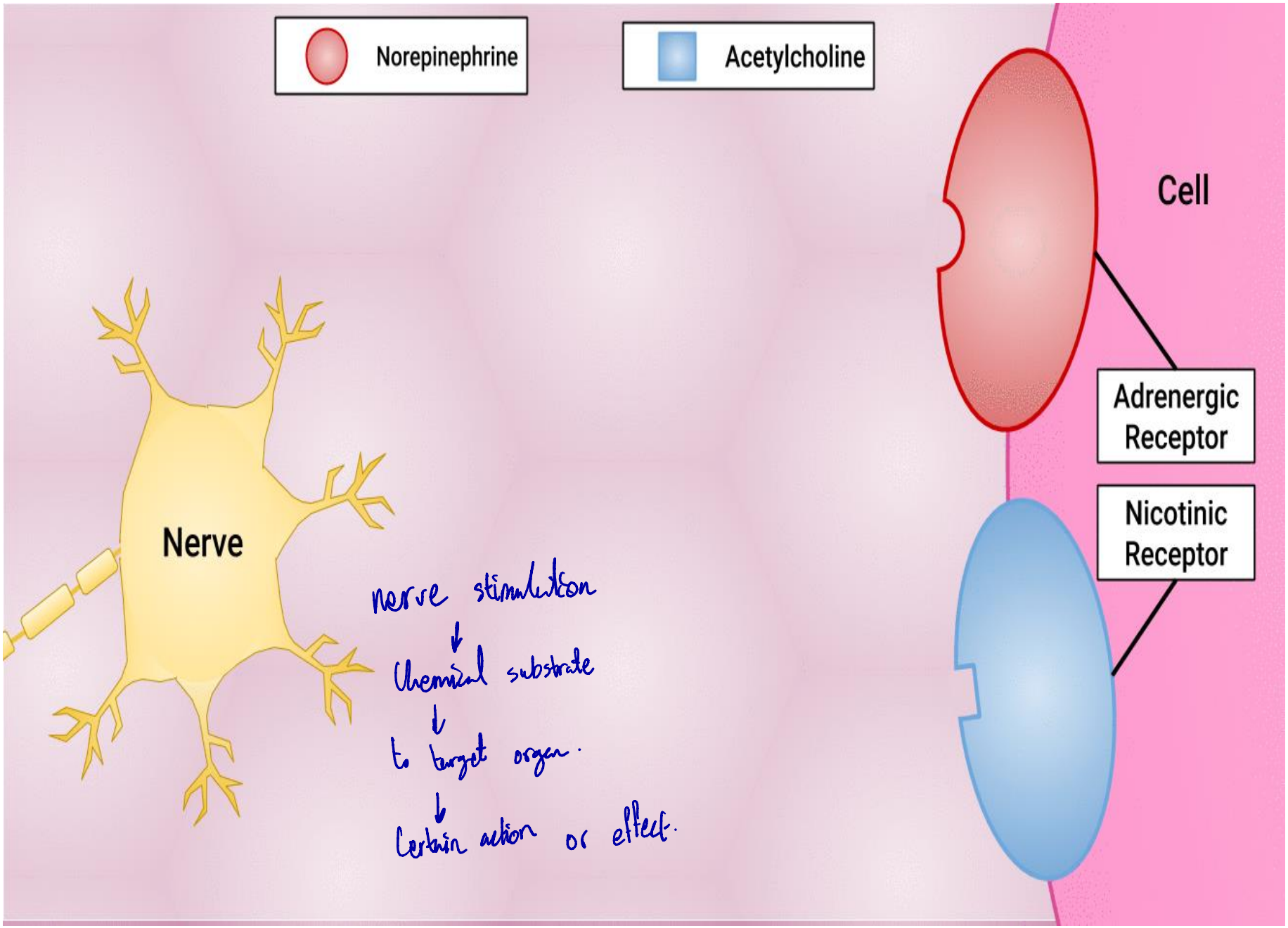


Postganglionic neuron: soma is in a sympathetic ganglion, located next to the spinal cord

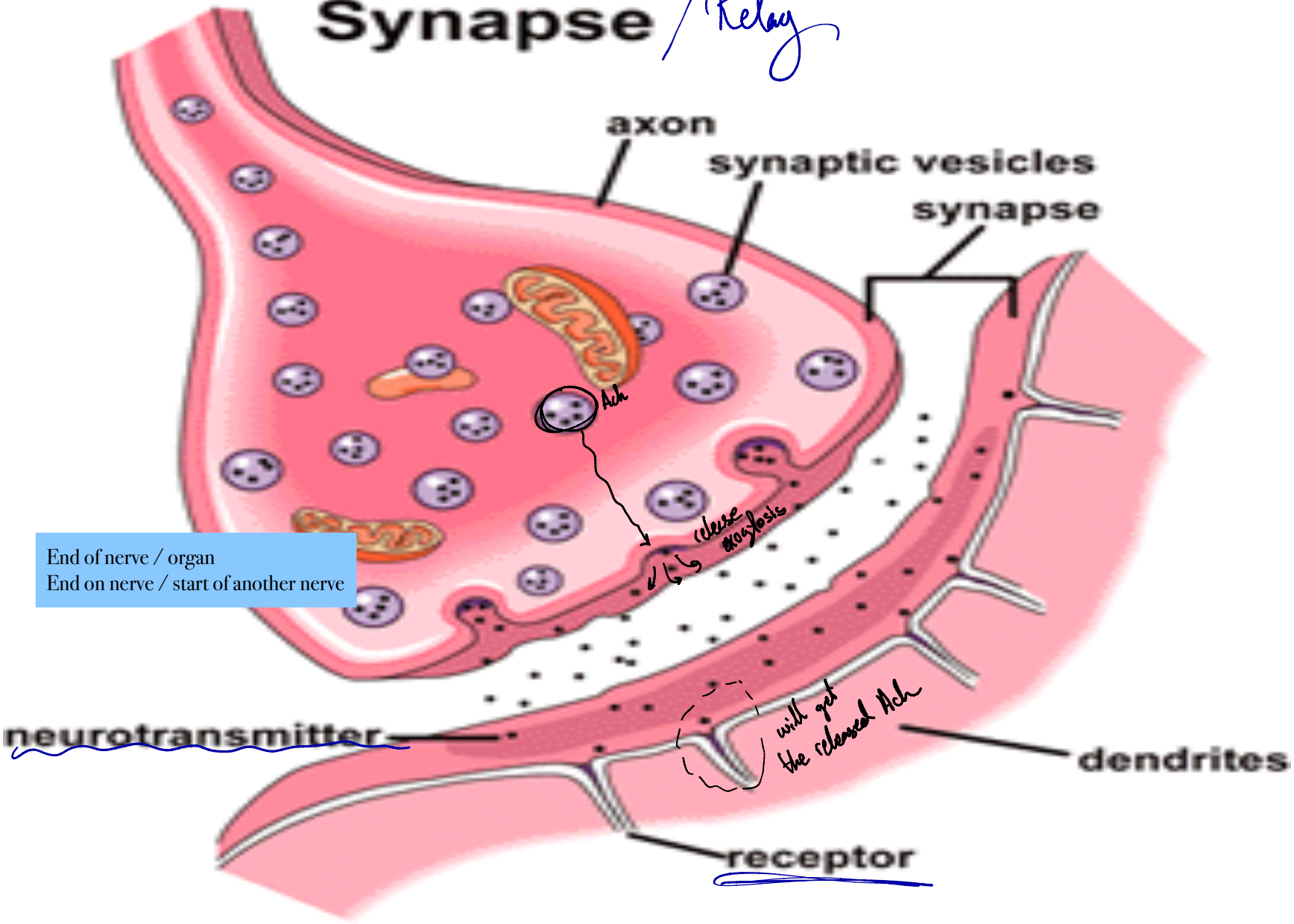
Neurotransmitters released from postganglionic synapse: norepinephrine

Target organ

"Fight or flight" response is activated


Norepinephrine
Acetylcholine
Cell
Adrenergic Receptor
Nicotinic Receptor
Nerve
nerve stimulation
Chemical substrate
to target organ.
Certain action or effect.

Synapse / Relay



End of nerve / organ
End on nerve / start of another nerve

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.

Depending on their product

nor adrenaline

PARASYMPATHETIC

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

Nerve stimulation

(1) Synthesis:

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

→Will stay inside the vesicle until its stimulated by Parasympathetic or nerve impulse.

(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.

⇝ The effect on the receptor =Will result the action.

(4) Metabolism:

Mainly enzymatically by

Mostly in neurone

original ⇒ specific for ach.

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.

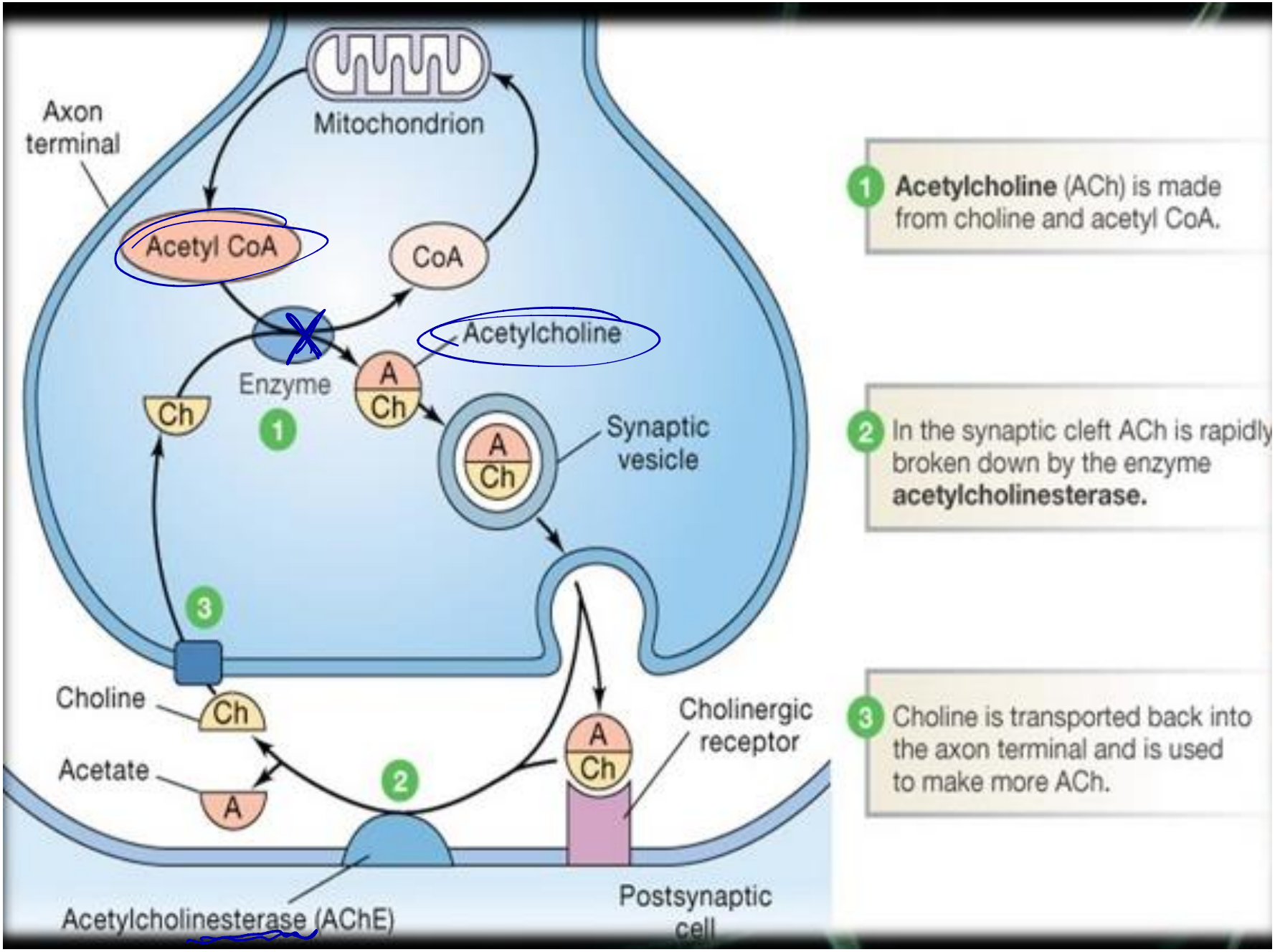
~if i took a drug to inhibit it will take 120 days to synthesize again.

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

Non specific

- This metabolism can be inhibited by anticholinesterases as neostigmine.

~it will take only 2 days to be synthesized.


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:

parasympathetic

(a) Muscarinic receptors

M_1 in the autonomic ganglia.

Depending on their location we will have the action

M_2 in the heart. will red the heart rate

M_3 in smooth muscles and secretory glands.

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

(b) Nicotinic receptors (Two types)

N_M in the neuromuscular junction: skeletal muscle relaxant? drug for paralysis to skeletal muscle

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:

Conformational changes as a result when Na^+ bind.

→ Have a specific shape to contain a receptor in its center.

Ligand - gated ion channels. → all of the nicotinic

Their stimulation increases the permeability to Na^+

(b) Muscarinic receptors:

Gs → work on acetyl cyclase
function: ATP → CAMP.

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)]

work on this enzyme

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

Gi that causes inhibition of adenyl cyclase which increases cAMP.

M_3: Similar to M_1. Gq

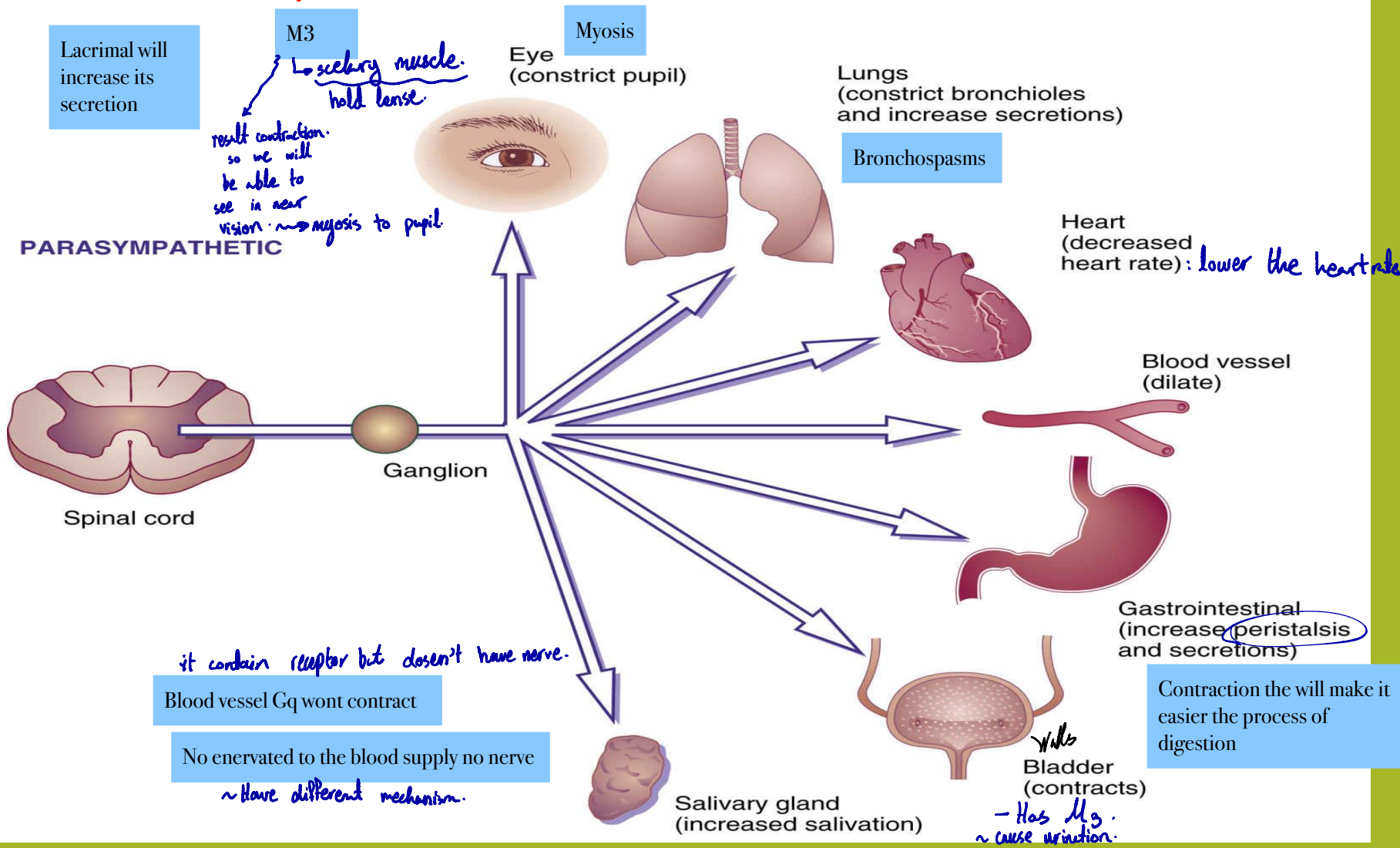
Inhibition to the heart rate

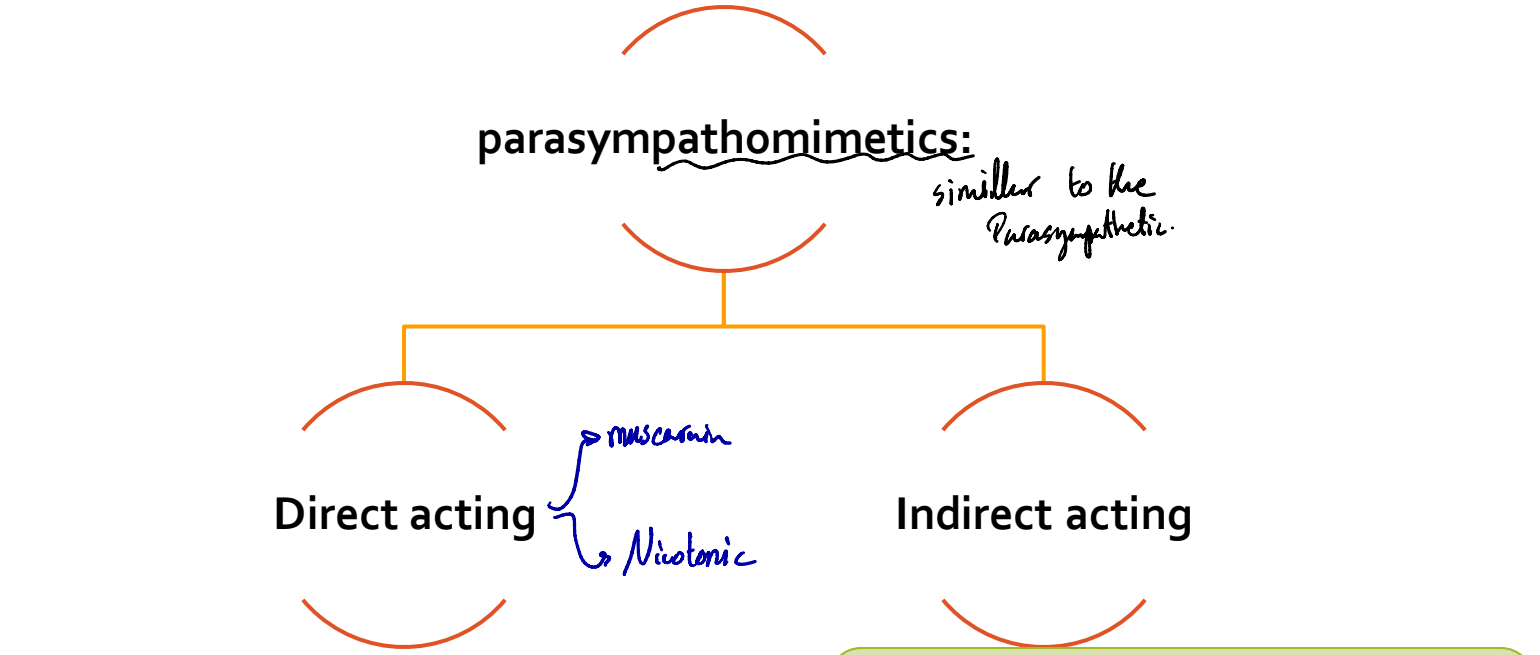
G protein pathway:

1. stimulation
2. G protein will be separated into subunits.
3. Will go into an enzyme: will release second messanger (that will cause the effect).
   - Gq: named phospholipase. release IP_3 / DAG

Gs	Stimulates adenylyl cyclase, which catalyses the conversion of ATP to cyclic AMP
Gi	Inhibits adenylyl cyclase, which catalyses the conversion of ATP to cyclic AMP
Gq	Stimulates phospholipase C, which cleaves PIP_2 in the cell membrane into IP_3 and DAG

PHARMACOLOGICAL ACTIONS





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

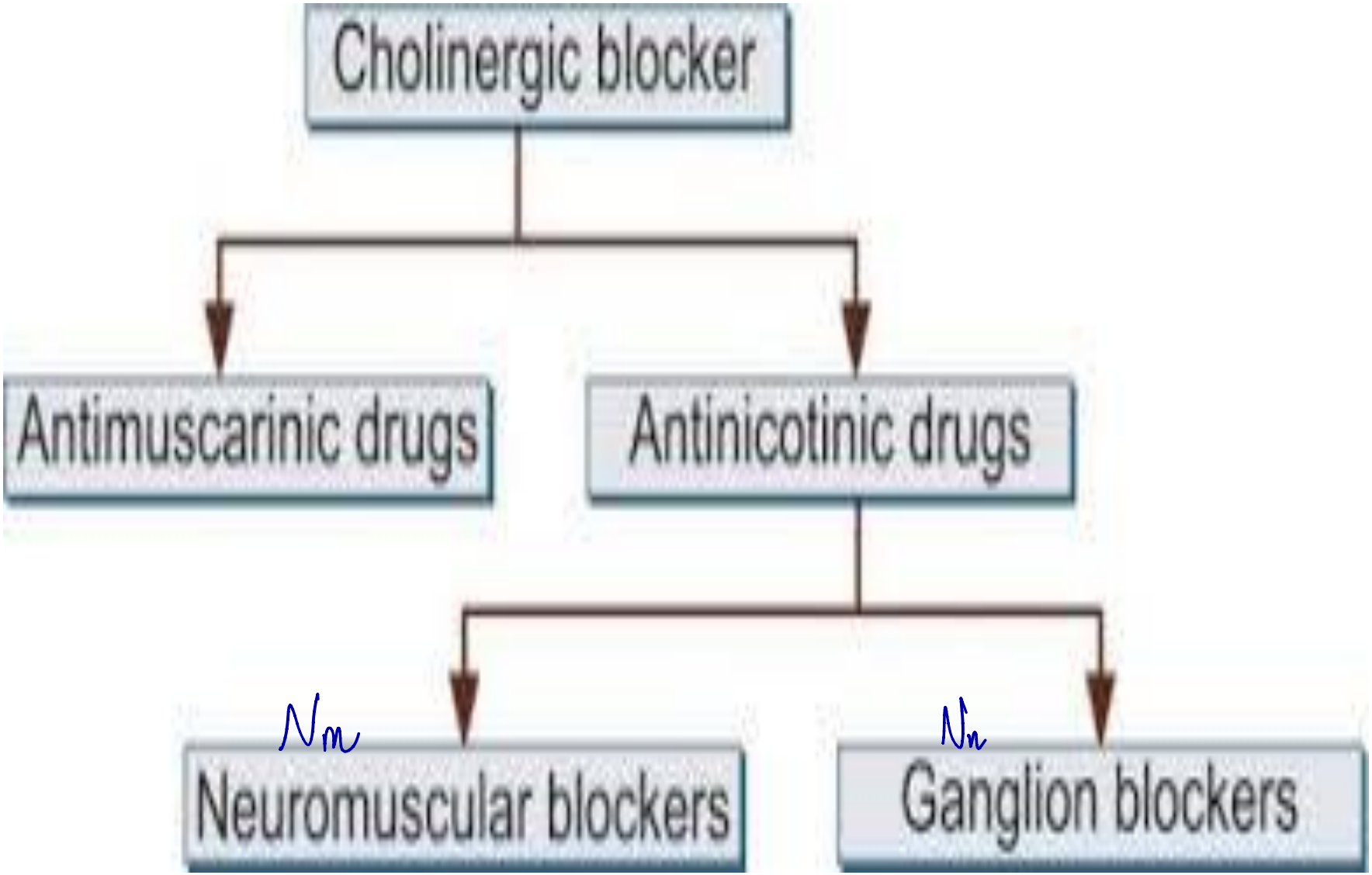
1- Reversible cholinesterase (temporary.)

inhibitors: physostigmine, neostigmine, edrophonium.

2) Irreversible cholinesterase (Permanent and will cause cell death. toxic /wors)

inhibitors:organophosphorus compounds.

end of parasympathetic



Main chemical transmitter in sympathetic is the noradrenaline

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.

There will be a process to convert noradrenaline to adrenaline that will be treated here as a hormone !!

(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:

One of them will be responsible to put it back to the neurone and the other will store it in the vesicle

-It occurs by 2 mechanisms:

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

Reuptake is the main way of termination of the action.
80 - 85% are caused by this pathway

-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**.

If the adrenaline isn't in the vesicle it will be metabolised by MAO / 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.**

For example

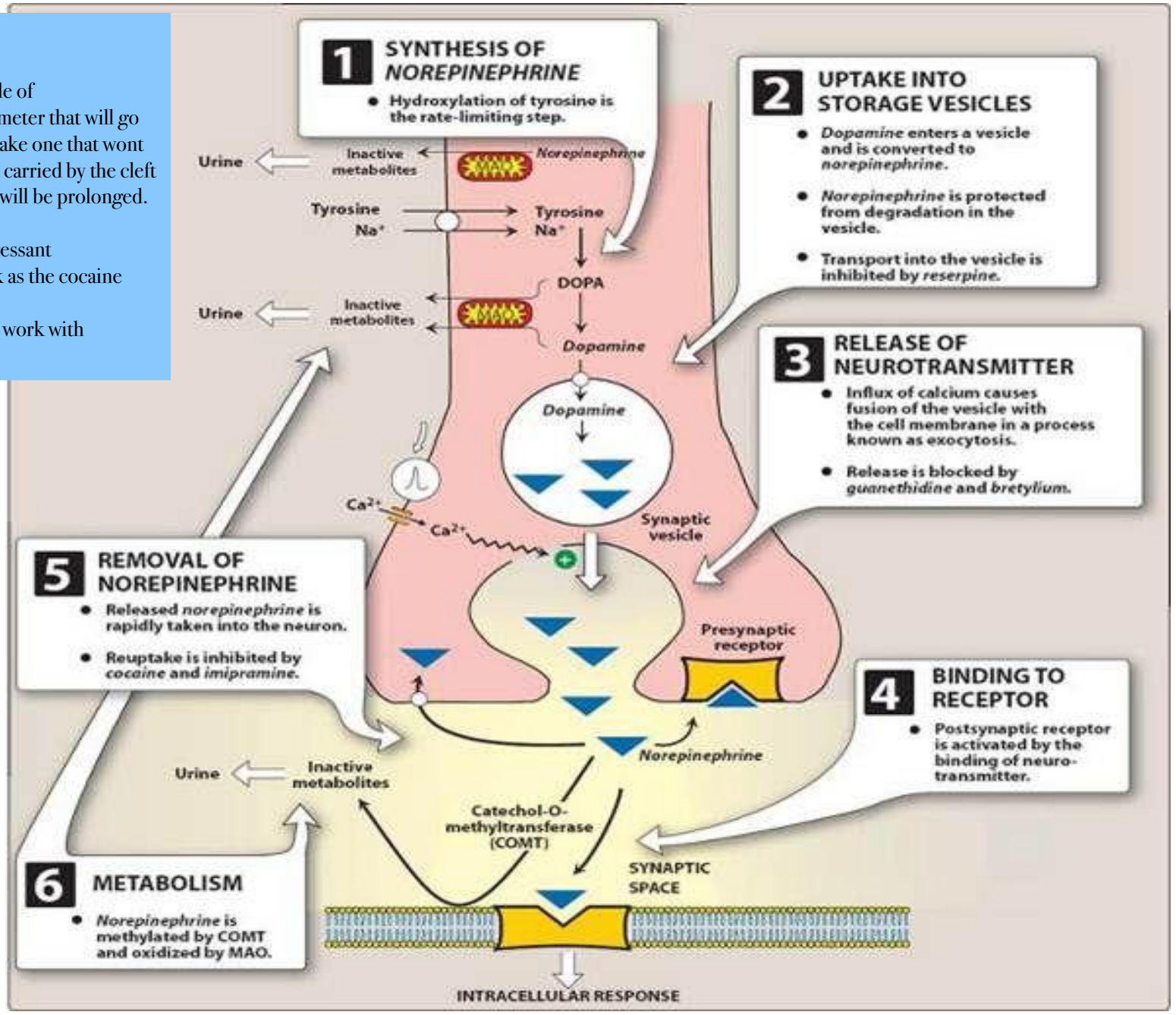
- cocaine

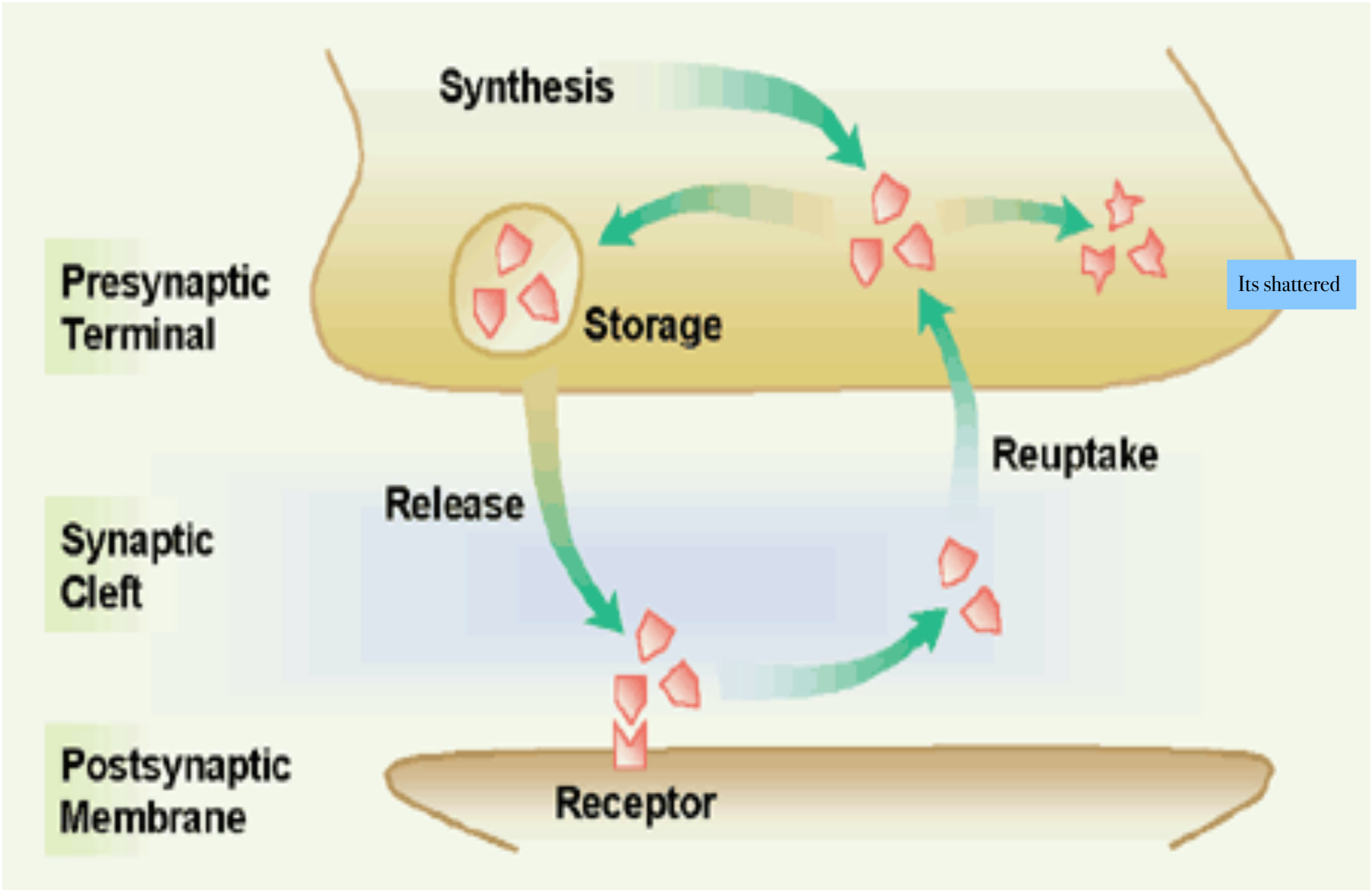
its an example of sympathomimeter that will go to the re-uptake one that wont be able to be carried by the cleft so the effect will be prolonged.

- antidepressant

doesn't work as the cocaine

-other drugs work with glandular.




Synthesis
Presynaptic Terminal
Storage
Its shattered
Reuptake
Release
Synaptic Cleft
Postsynaptic Membrane
Receptor

Adrenergic receptors

Alpha (1 and 2)

Beta (1, 2 and 3)

Dopamine (D1,2,3,4,5)

D1 D3 D5 > Gs
D2 D4 > Gi

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 (IP_3, DAG and Ca^{++}).

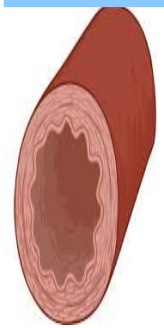
(c) Alpha-2 receptors (α_2) (similar to M_2)

- 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

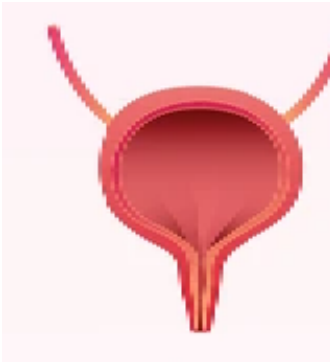
Mainly in the blood vessel responsible for the tone of blood pressure (contraction and relaxation)
= in cases of alpha one Gq in the smooth muscles of the vessel when stimulated it will be contracted so will cause high blood pressure (hypertension)



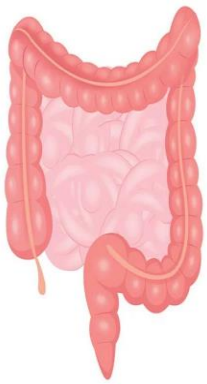
V.C

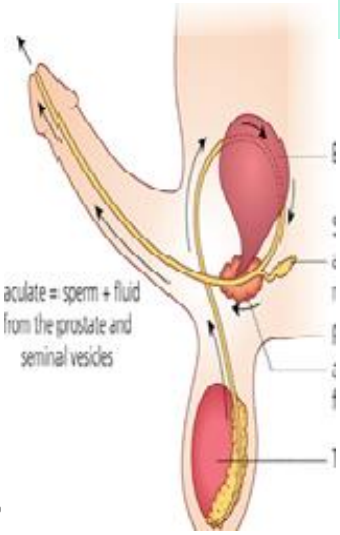
Will be shorten

Mydriasis

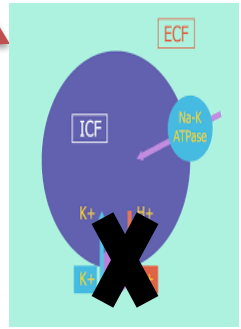


Contraction of sphincter





ejaculation

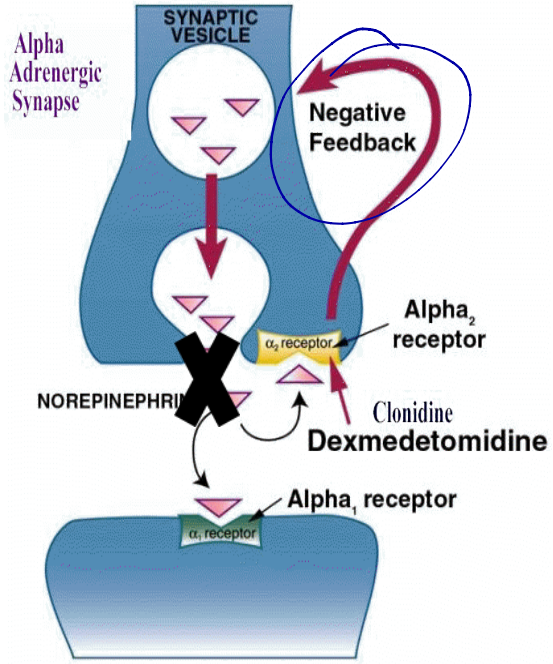


hyperkalemia

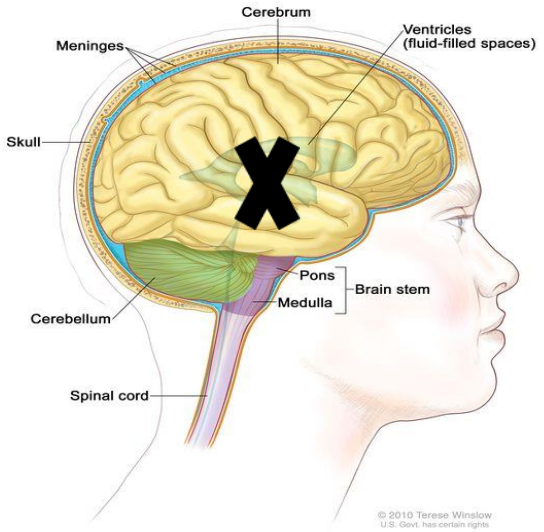
Inhibition of the sodium potassium pump so the potassium will be outside the cell

α 2 stimulation(inhibitory)

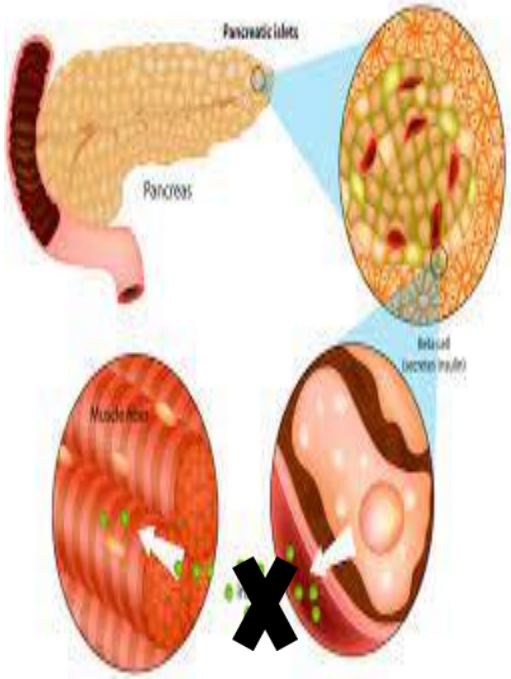
Will result inhibition of all sympathetic in the brain



Inhibit NE, epinephrine and Ach

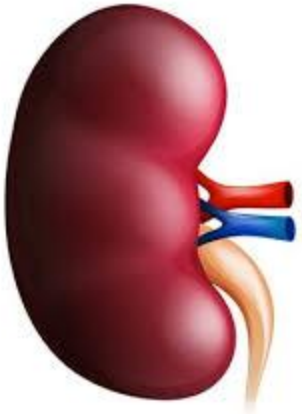


- Sympathetic flow



Inhibit insulin release

β 1 stimulation



↑ renin release

↑ all cardiac properties

Conduction / contractility / rate

β 2 stimulation

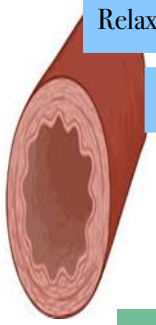
(coronary and skeletal)

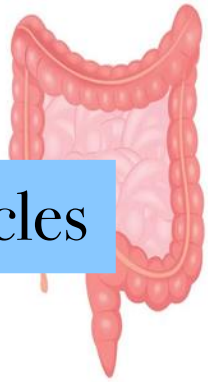
Relaxation by pro stoke

And M3

Increase tranmition in the neurotransmitters

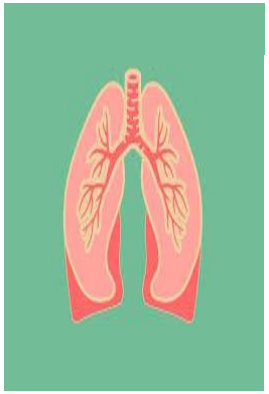
Adverse effect

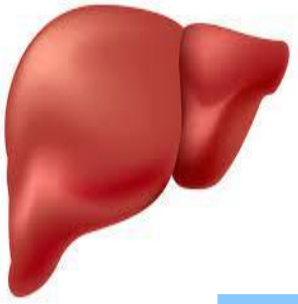




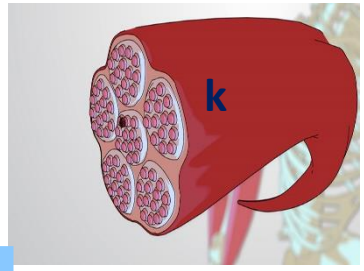
Relaxation to all smooth muscles

V.D





In liver



Relaxation

Bronchodilatation

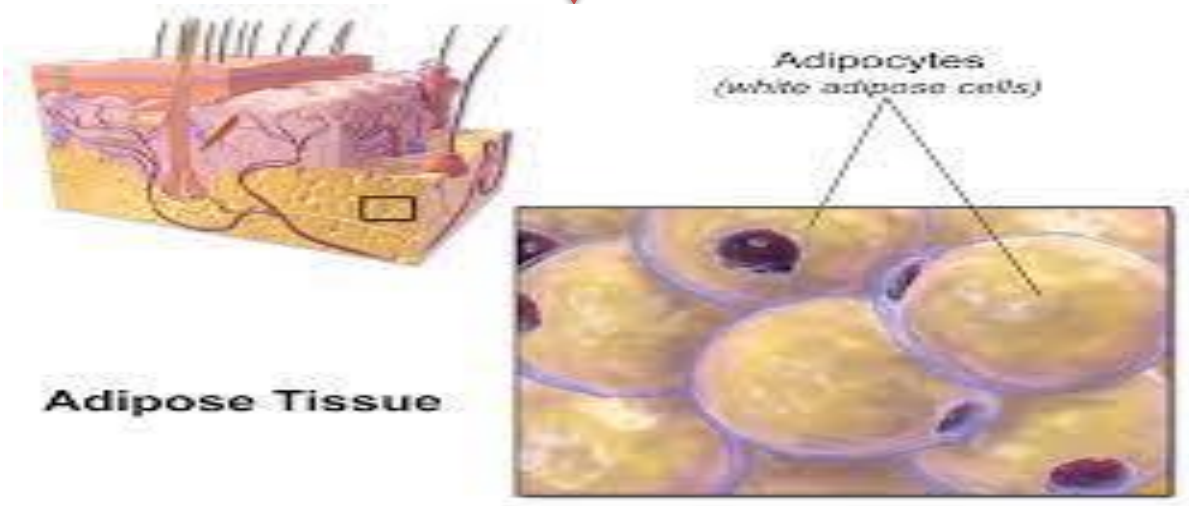
Glycogenolysis: ↑ glucose blood level

Gluconeogenesis: ↑ glucose blood level

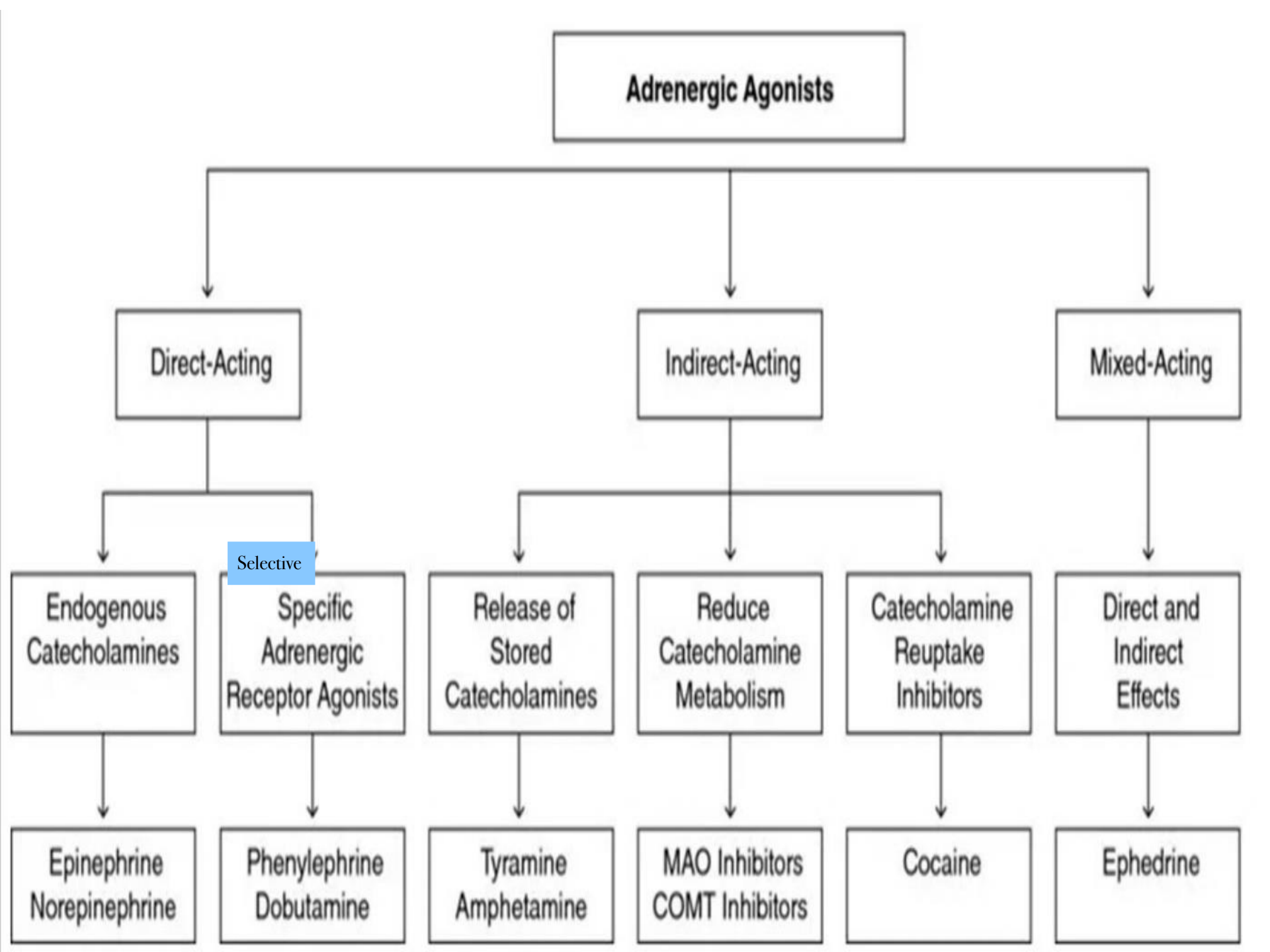
↑K uptake by muscles : hypokalemia

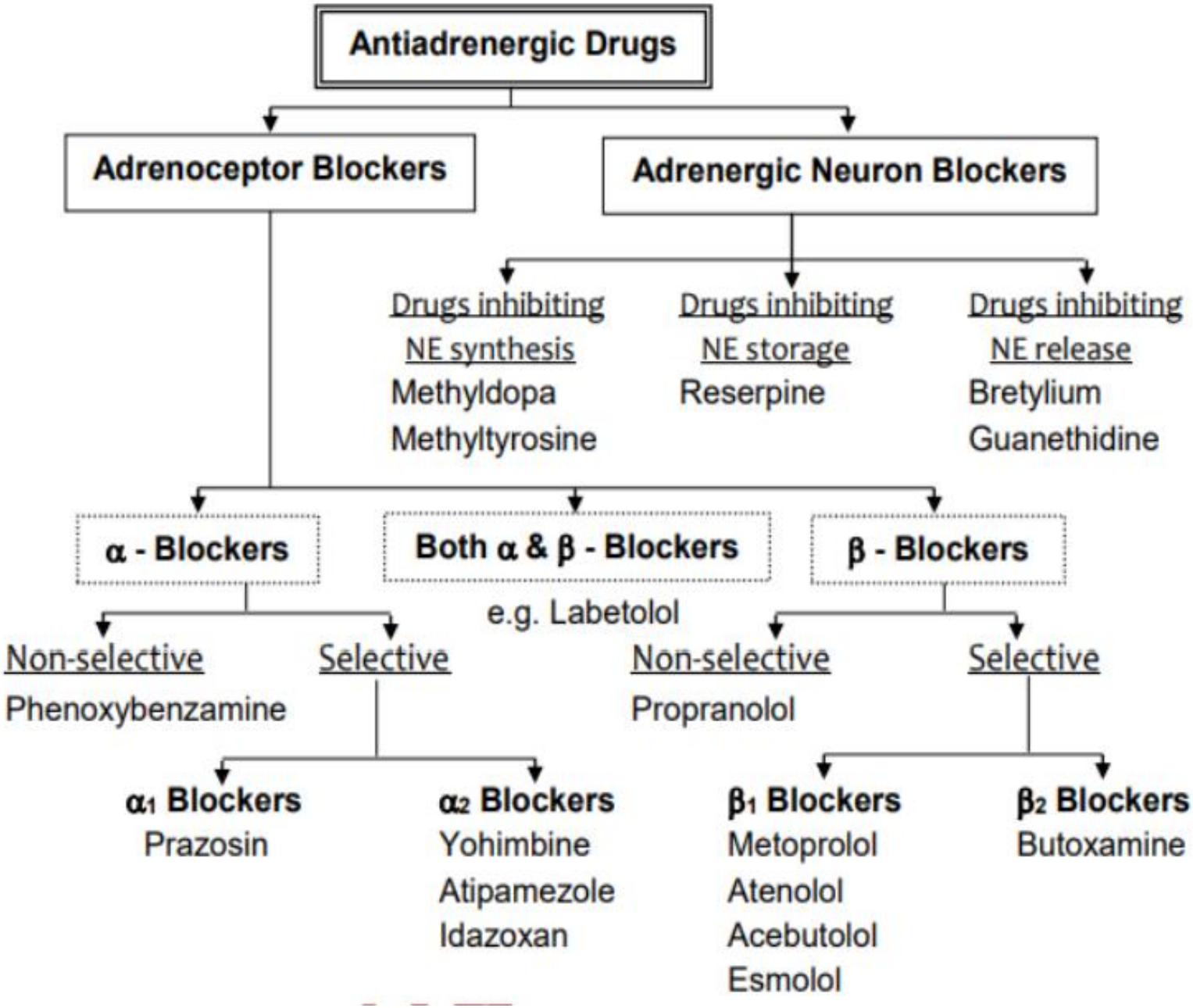
β 3 stimulation

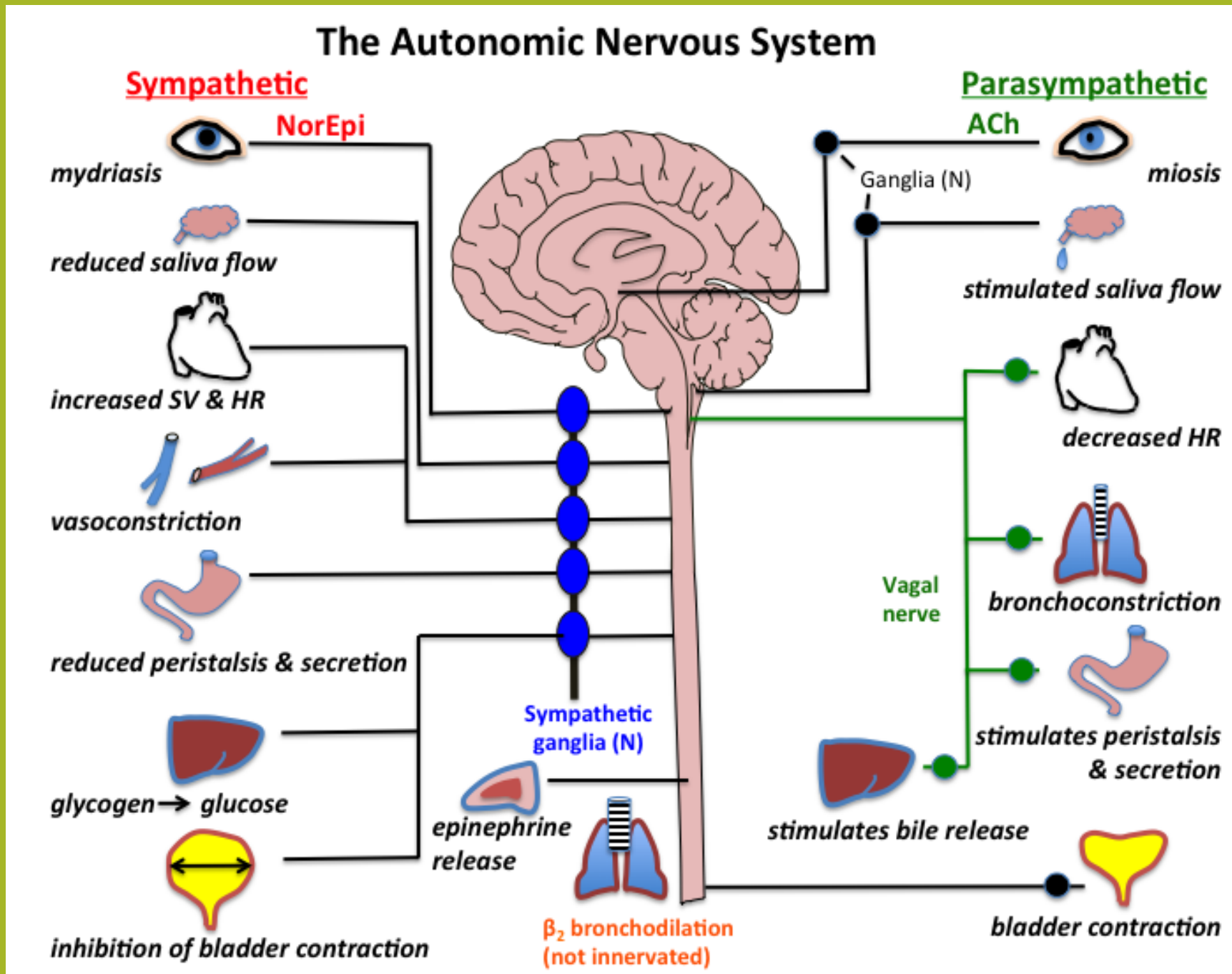
In fat



+ lipolysis


Adrenergic Agonists
Direct-Acting
Indirect-Acting
Mixed-Acting
Selective
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