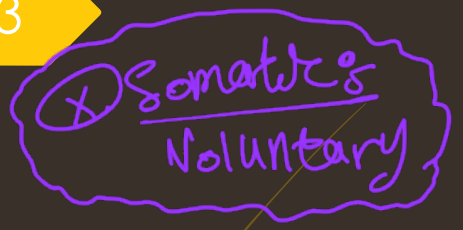
Autonomic Nervous System

- Parasympathomimetic drugs
- Parasympatholytics
- Sympathomimetics
- Sympatholytics

	Sympathetic	Parasympathetic
Anatomy: 1- Origin	From 1st thoracic to 3rd lumber segments	-Cranial: (III,VII,IX&X) -Sacral: (S2,3,4)
2- Ganglia	Close to spinal cord	Near or embedded in organs
3- Preganglionic	Short	Long
4- Postganglionic	Long	Short
5- Innervation: • Most organs receive dual nerve supply **except**:	*Sympathetic only* • Dilator pupillae muscle [DPM]. • Erector pili M. • Sweat glands • Adrenal medulla. • Ventricles •Blood vessels	*Parasympathetic only* • Constrictor pupillae muscle [CPM]
Physiology: • Tone	Blood vessels & sweat glands.	All organs except blood vessels& sweat gland.



Autonomic Nervous System

Involuntary

The autonomic nervous system(ANS) is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life.

The autonomic nervous system has two divisions:

sympathetic & parasympathetic.

	Sympathetic	Parasympathetic
• Actions	They are antagonistic except for atrial conduction and salivation [both ↑] متعاونين مع بعض	
• Cardiovascular: - Heart	↑ all cardiac properties.	↓ all cardiac properties.
- Blood vessels	Vasoconstriction -VC of skin &mucous membrane blood vessels. vasodilatation -VD of coronary & skeletal blood vessels (Heart الأول)	Not innervated
-Blood pressure	Increased	Decreased
• Eye	Active mydriasis [++DPM] ↓ widning of Papils	1-Miosis[+++CPM] constriction of Pupils 2- Accommodation for near vision 45↑ → Happenes 3-↓↓ IOP → Intra Ocular Pressure
• Bronchi	Bronchodilation	Bronchoconstriction

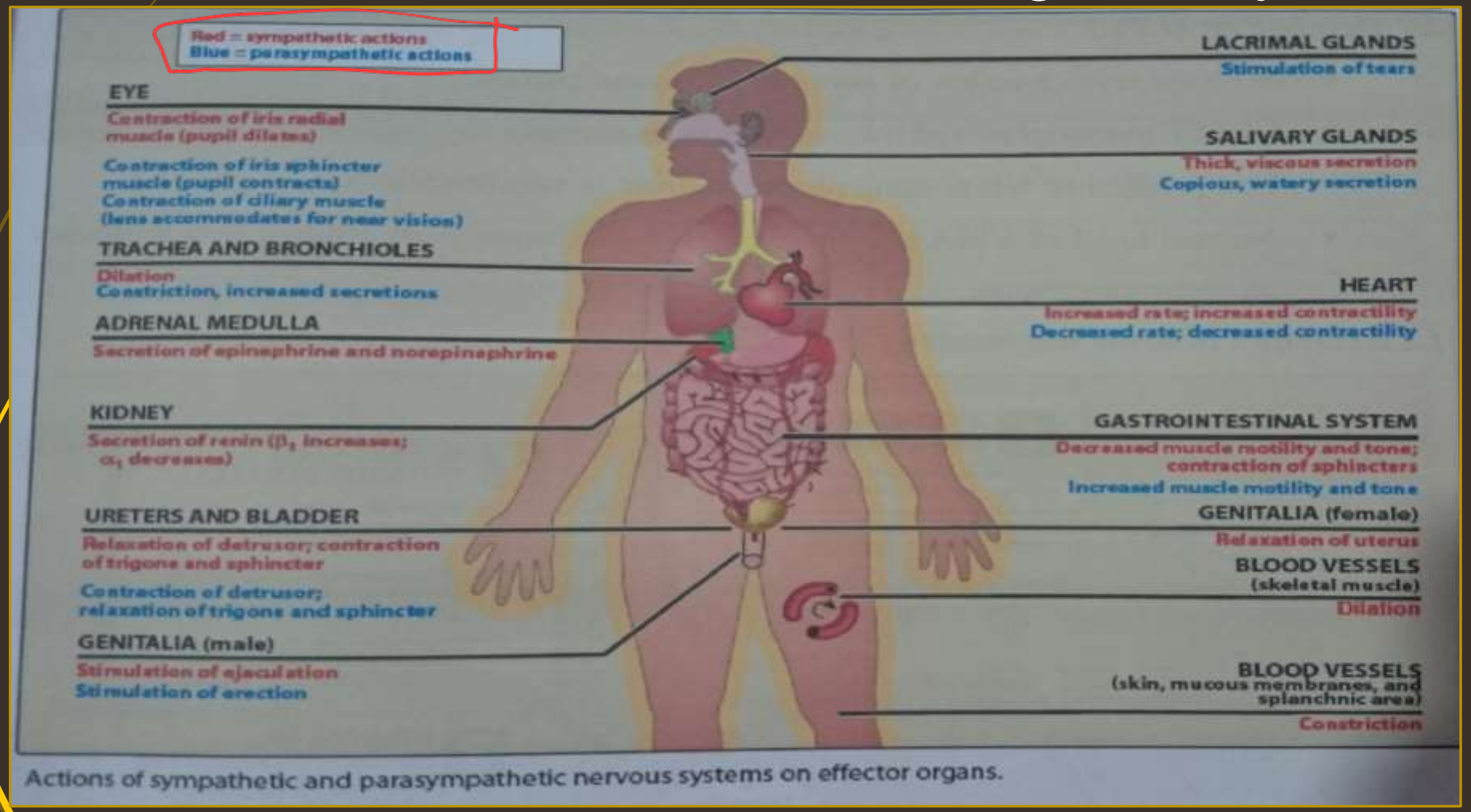
	Sympathetic	Parasympathetic
• GIT & Urinary tract	Relax wall& contract sphincters	Contract wall& contract sphincters
• Genital	Ejaculation in male Relaxation of uterus in female	Erection in male
• Exocrine glands: - Salivary - Sweat	Thick & viscid Increase	Watery No effect
Neurotransmitters • Ganglia	Ach	Ach
• Postganglionic	Norepinephrine(NE) ***except*** in sweat glands Ach is released	Ach

	Sympathetic	Parasympathetic
• Synthesis	1. Phenylalanine → tyrosine (by hydroxylase) 2. Tyrosine → DOPA (by tyrosine hydroxylase) 3. DOPA → dopamine (by dopa decarboxylase) 4. Dopamine is actively transported into synaptic vesicles by carrier system 5. Finally, NE is formed by hydroxylation of dopamine (via dopamine B-hydroxylase) * In the adrenal medulla & some CNS tracts, epinephrine(adrenaline) is formed via methylation of NE by phenyl ethanolamine N-methyl-transferase [PENMT]	- Choline is transported into cholinergic neurons by carrier system - Choline is acetylated to Ach by choline acetyl-transferase in presence of acetyl CoA

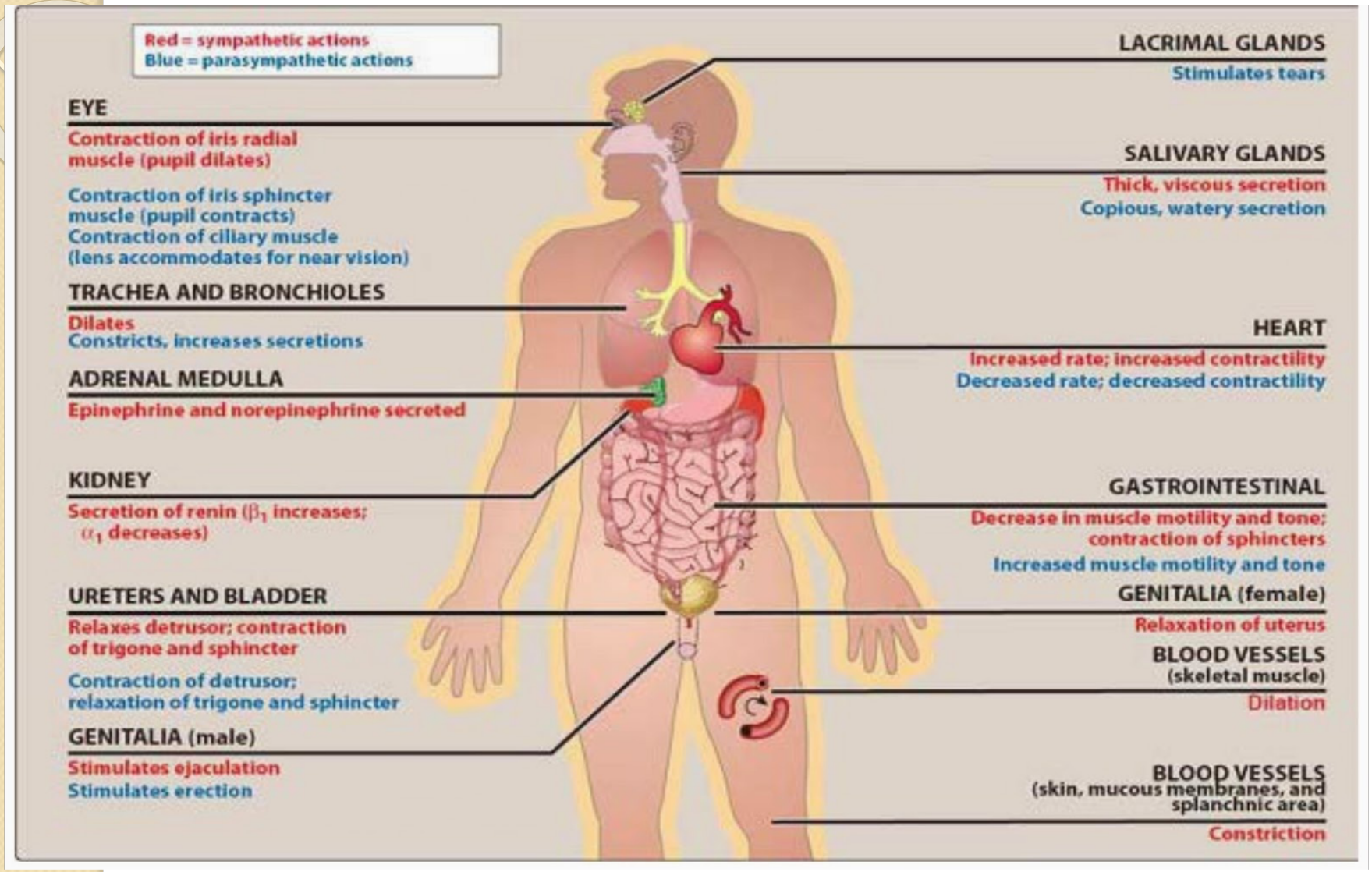
Q) What are the 2 places that produce EPi? or Adrenaline?

Release of transmitters:

- Arrival of impulse to the nerve ending.
- Opening of voltage-activated Ca^{2+} channel → calcium influx into nerve ending.
- Fusion of vesicles with membrane of the nerve ending and exocytosis of the transmitter.

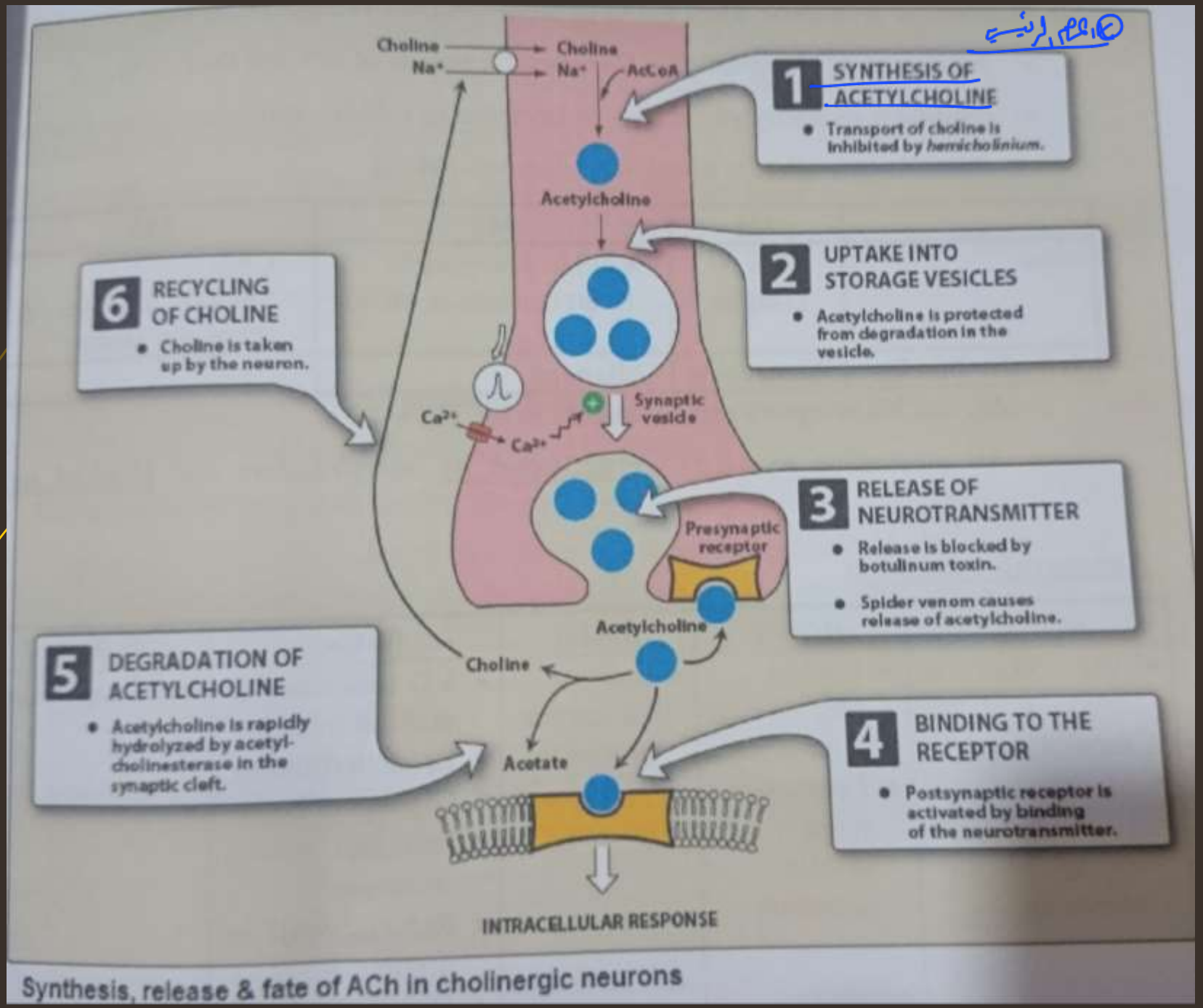


Actions of sympathetic and parasympathetic nervous systems on effector organs.


Red = sympathetic actions
Blue = parasympathetic actions
EYE
Contraction of iris radial muscle (pupil dilates)
Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)
TRACHEA AND BRONCHIOLES
Dilates
Constricts, increases secretions
ADRENAL MEDULLA
Epinephrine and norepinephrine secreted
KIDNEY
Secretion of renin (β_1 increases; α_1 decreases)
URETERS AND BLADDER
Relaxes detrusor; contraction of trigone and sphincter
Contraction of detrusor; relaxation of trigone and sphincter
GENITALIA (male)
Stimulates ejaculation
Stimulates erection
LACRIMAL GLANDS
Stimulates tears
SALIVARY GLANDS
Thick, viscous secretion
Copious, watery secretion
HEART
Increased rate; increased contractility
Decreased rate; decreased contractility
GASTROINTESTINAL
Decrease in muscle motility and tone; contraction of sphincters
Increased muscle motility and tone
GENITALIA (female)
Relaxation of uterus
BLOOD VESSELS (skeletal muscle)
Dilation
BLOOD VESSELS (skin, mucous membranes, and splanchnic area)
Constriction

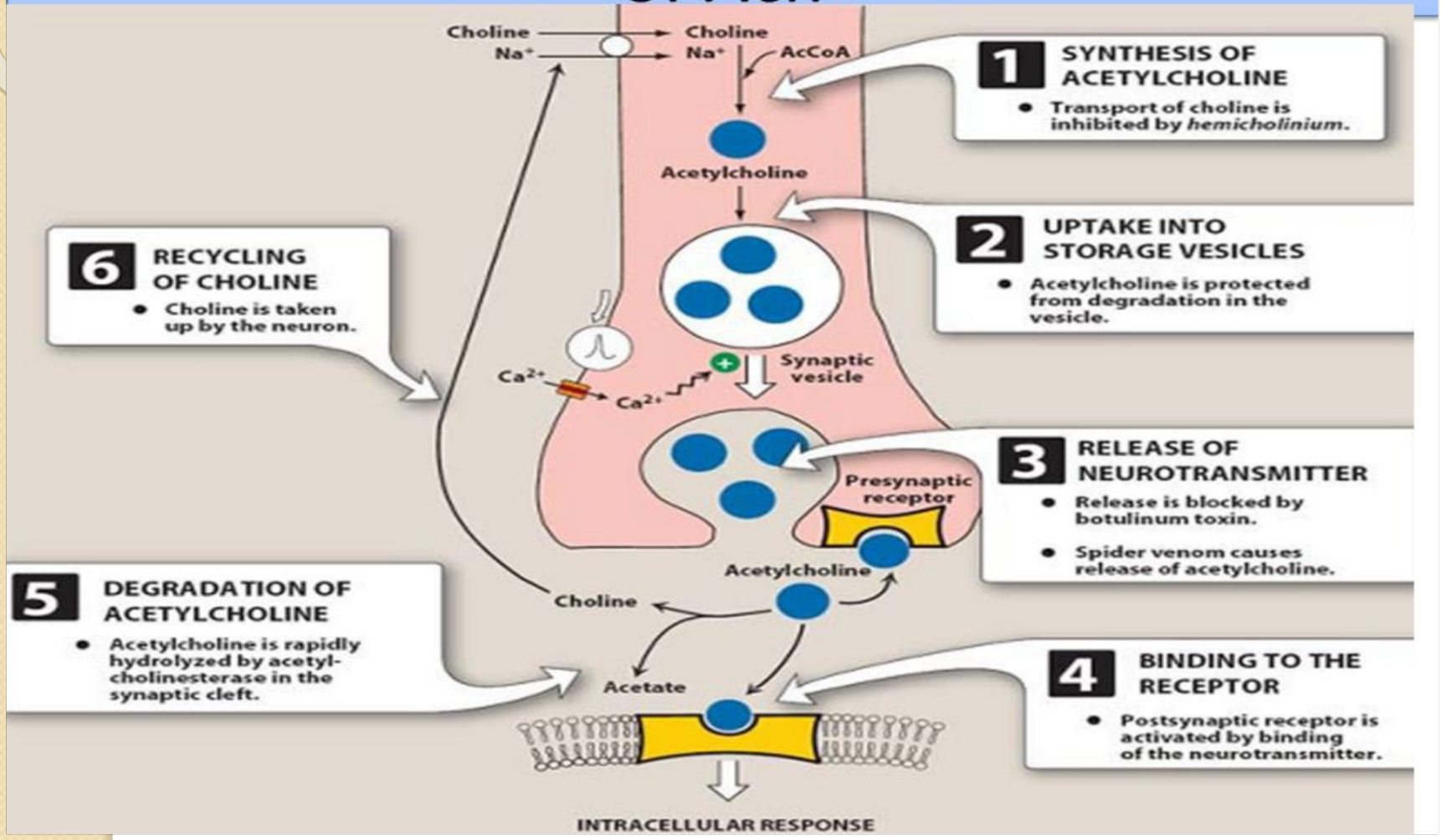
Fate of ACh: Metabolism by cholinesterase [2types]

	True cholinesterase الأقوى	Pseudo-cholinesterase
Sites	Cholinergic structures, RBSs and CNS.	Contract wall& contract sphincters
Specificity	ACh , Methacholine	Non specific- destroys Ach, procaine and succinylcholine.
Regeneration	In 3 month ⊗الأقوى يحتاج وقت أطول	In 3 weeks



Synthesis, release & fate of ACh in cholinergic neurons

Synthesis, Storage, release & degradation of Ach



Autonomic Receptors

Cholinergic receptors: Cholinergic receptors are classified into:

A. ***Nicotinic receptors:*** They are directly **coupled to Na^+ channels** and mediate fast excitatory synaptic transmission at:

1. The neuromuscular junction.
2. Autonomic ganglia.
3. Adrenal medulla.
4. Various sites in CNS

B. ***Muscarinic receptors:*** They are **G-protein-coupled receptors** causing :

- Activation of phospholipase C (hence formation of IP3 and DAG) **[$M_{1,3,5}$].**
- Inhibition of adenylyl cyclase ⟶ decrease in cAMP, activation of potassium channels or inhibition of calcium channels **[$M_{2,4}$].**

	M1	M2	M3
Sites	- CNS - Ganglia	- CNS & presynaptic - Heart (mainly of atria)	- CNS - Smooth muscles & secretory glands
Selective blocker	Pirenzepine	Gallamine	

- M_4 and M_5 receptors present mainly in the CNS.
- All muscarinic receptors are **<u>activated by</u>** ***acetylcholine*** and **<u>blocked by atropine.</u>**

Autonomic drugs

1. Parasympathomimetics.
2. Parasympatholytics.
3. Sympathimetics.
4. Sympatholytic.
5. Ganglion stimulants & ganglion blockers.

Parasympathomimetics [Cholinomimetic drugs]

Acetylcholine (ACh) receptor stimulants and cholinesterase inhibitors together comprise a large group of drugs that **mimic** Ach (cholinomimetics or parasympathomimetics).

Cholinoceptor stimulants: they are either:

1-Direct-acting cholinomimetic agents bind to and activate muscarinic and/or nicotinic receptors: **1- Choline esters:**

***Ach** *** Methacholine** *** Carbachol** *** Bethanechol**

2- Cholinomimetic alkaloids: * Pilocarpine

Q/ What is pilocarpine?

II-*Indirect-acting agents* inhibit cholinesterases → increase the endogenous Ach in synaptic clefts and neuroeffector junction → stimulate cholinoceptors. The are classified into:

Reversible	Irreversible
▪ Physostigmine & neostigmine. ▪ Neostigmine substitutes: (edrophonium, pyridostigmine, ambenonium, benzpyrinium and demecarium)	▪ Organophosphorus compounds: - Echothiophate -Isoflurophate - Ware gases e.g. sarin &soman. - Thiophosphate insecticides e.g. parathion &malathion.

نحفظ اسامي؟ ماندري

I-Direct Cholinomimetics

(1) Choline esters

They are poorly absorbed and poorly distributed into CNS (they are hydrophilic).

Choline Ester	Susceptibility to cholinesterase	Muscarinic action	Nicotinic action	Selectivity
Acetylcholine	True and pseudo	+++ 3 positive	+++	No selectivity
Methacholine	True only	++++	None	Heart
Carbachol	Non	++	+++	Eye,GIT,urinary
Bethanechol	Non	++	None	GIT,urinary

Pharmacological actions:

Eye:

Muscarinic (M_3)

1) Contraction of constrictor pupillae muscle → resulting in miosis.
2) Contraction of the ciliary muscle. Responsible for Accodomation for Near vision, 45↑ → No!

- As a result of 1&2 → the iris is pulled away from the angel of the anterior chamber, and the trabecular meshwork at the base of the ciliary muscle is opened. Both effects facilitate aqueous humor outflow into the canal of Schlemm, and ↓ **I.O.P** .

Aqueous humor بتطلع

3) Accommodation for near vision.

@ Glucoma = increas in the Intra ocular pressure
watery blue eye

Nicotinic: Lid twitches due to activation of nicotinic receptors in the eye lid muscles.

إنتباظات بالجفن

Q) Why carbacol causes miosis and lid twitching? 2 Rs. (N + M)

When applied to eye, carbachol → miosis& lid twitches (muscarinic and nicotinic).

Cardiovascular System

Vasodilatator ↑ effect on BT

1) Vasodilation: Stimulation of M_3 ⟶ production of NO (endothelium – derived relaxing factor), which diffuses to smooth muscles cells of blood vessels ⟶ ↑ cGMP ⟶ VD.
2) Bradycardia & delay AV conduction are due to stimulation of M_2

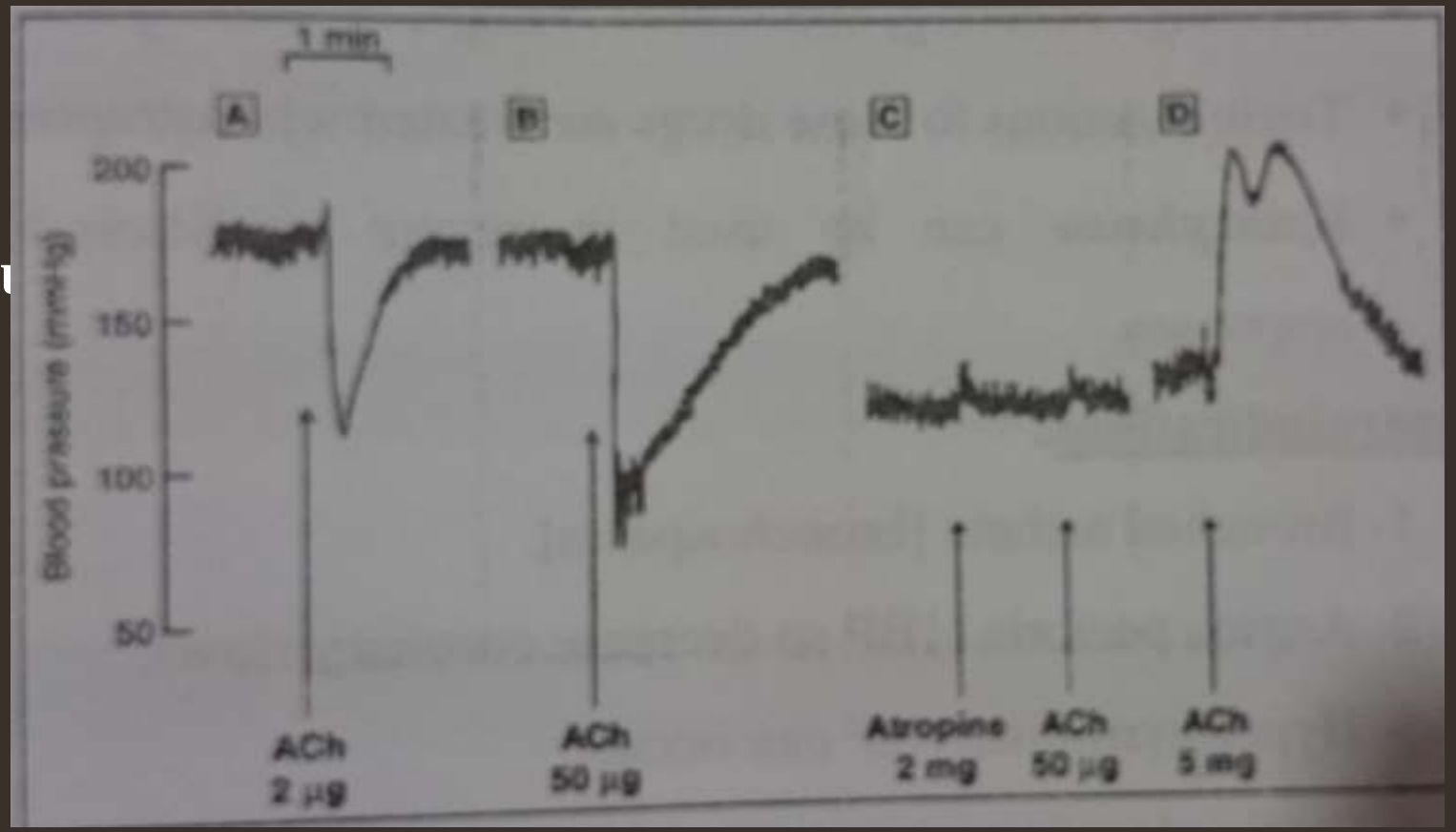
- Experimental IV injection of a small dose of Ach ⟶ hypotension.
- If large doses of Ach are injected after atropine [muscarinic blocker] ⟶ hypertension, due to stimulation of adrenal medulla and autonomic gaglia [nicotinic action of Ach] ⟶ release catecholamines into the circulation and at postganglionic sympathetic nerve ending ⟶ reversal of action of Ach on blood pressure.

Para is blocked due to blockage of M_2Rs

why ?

*Atropine can **reverse** the hypotensive action of parasympathomimetics having both nicotinic and muscarinic actions [Ach, carbachol& anticholinesterase], but only abolish the hypotensive effect of drugs having only muscarinic actions [Methacholine & Pilocarpine]*

The effect of intravenou injection of Ach on the pressure



Gastrointestinal and Urinary Tracts ($M_{2,3}$) : Stimulation of the wall (M_3) and relaxation the sphincters (M_2).

Respiratory System:

- Bronchospasm
- Increase bronchial secretion

This combination of effects can cause symptoms, especially in individuals with asthma.

Exocrine Glands (M_3) :

- Stimulate secretion of all glands [sweat, lacrimal, salivary, nasopharyngeal glands, gastric, pancreatic and intestinal].

Neuromuscular Junction (N_m) :

- Activation of N_m receptors results in Na influx and depolarization of skeletal muscle with muscle contraction. High concentration of Ach results in persistent depolarization → muscle weakness and paralysis.

Clinical uses:

Bethanechol is very occasionally used in post operative urinary retention and paralytic ileus. paralysis in the GIT.

- It acts mainly on M_3 receptors and has little effect on the heart.

Ach, Carbachol & methacholine are used as experimental tools.

Side effects:

- Flushing , sweating, abdominal cramps, bronchospasm, headache, and salivation .
- Toxic reactions to these drugs are treated with ***atropine***.
- ***Epinephrine*** can be used in severe cardiovascular or bronchoconstrictor responses.

Contraindications:

Q) When should I NOT give it? All the following, except?

1- Bronchial asthma [bronchospasm].

2- Angina pectoris [↓ BP so decrease coronary flow].

3- Hyperthyroidism [AF can occur].

4- Peptic ulcer [++ gastric secretion].

5- Hypotension [cause vasodilation].

2) Cholinomimetic alkaloids (Pilocarpine)

- Alkaloid from leaves of Pilocarpus Jaborandi
- Tertiary amine so:
  - well absorbed from most sites of administration.
  - Excreted in urine.
- Crosses BBB (avoided in Parkinsonism) Not metabolized by Ch.E → long duration.
- Has muscarinic action, but no nicotinic actions(***its hypotensive effect is abolished by atropine)***