Cholinomimetic drugs:

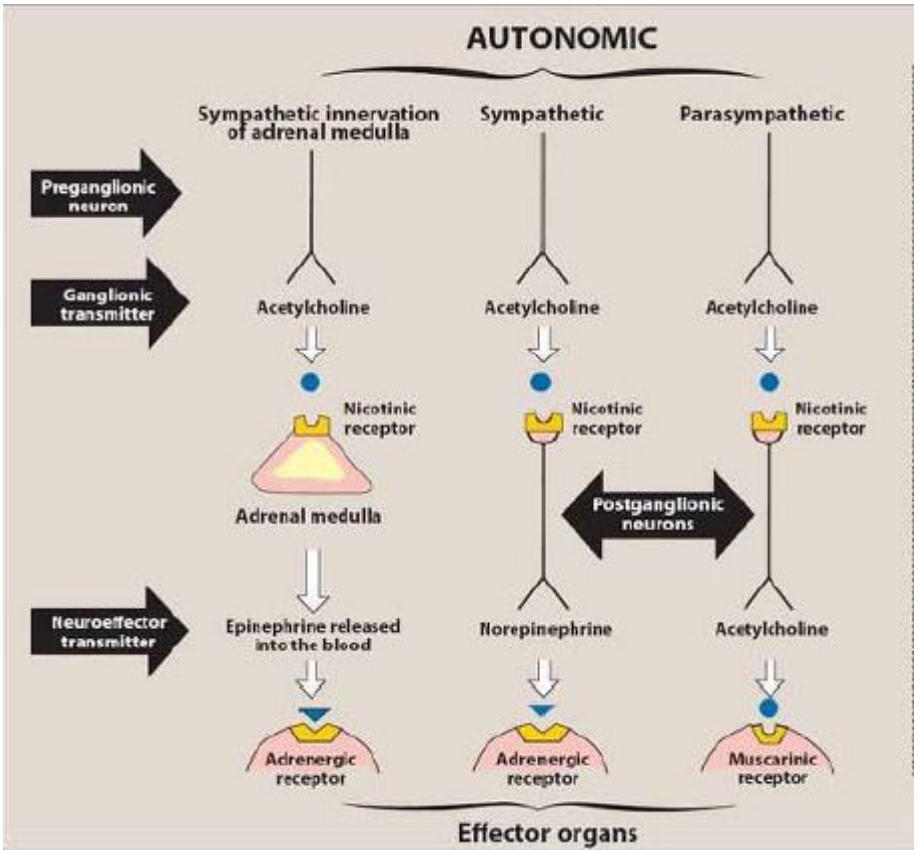
- The neuron is a communication network that allows an organism to interact with the environment in appropriate ways.
- The nervous system can be classified to the CNS&PNS.
- The CNS is composed of the brain and spinal cord.
- The PNS has both somatic nervous system and autonomic nervous system.

What are the differences between the somatic and autonomic nervous system?

Somatic	Autonomic
Controls skeletal muscles.	Control smooth muscle of viscera, blood vessels, exocrine glands and cardiac muscle.
Voluntary	Involuntary
One fiber	2 neurons

Autonomic nervous system: consist of:

1. **Sympathetic** or thoracolumbar outflow. Function: fight or flight
2. **Parasympathetic** or craniosacral outflow. Function: feed or breed
3. Enteric nervous system (mixed preganglionic PARASYMPATHETIC + postganglionic SYMPATHETIC)



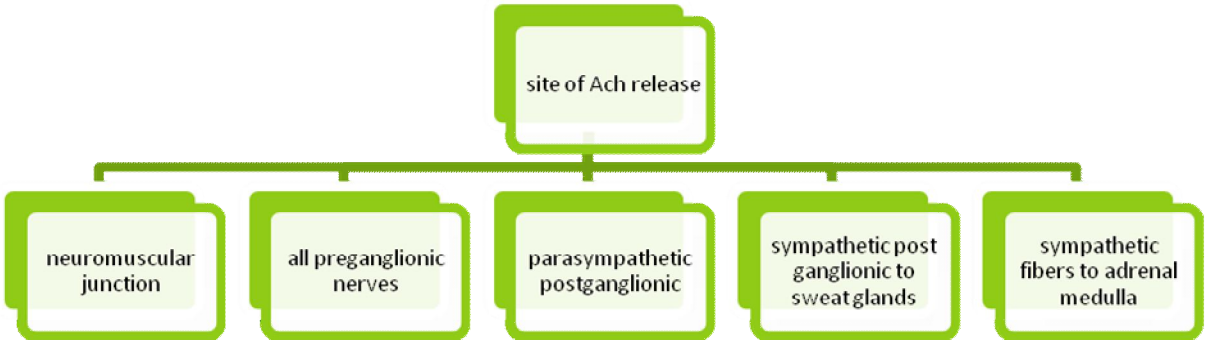
Innervations by autonomic nervous system:

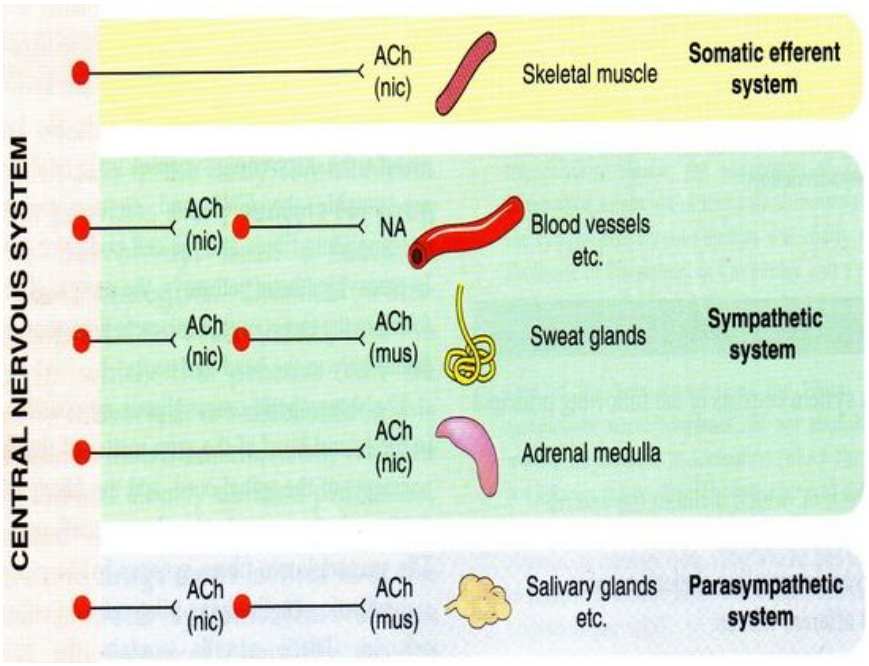
- Most of the organs are clearly innervated by both sympathetic and parasympathetic systems **but usually one predominates.**
- Some organs as adrenal medulla, kidney, blood vessels, sweat glands and pilomotor muscle (hair muscle) receive only from (sympathetic system).

Neurotransmitters:

- Chemical substances responsible for communication between nerve s with other nerves or with effector organs
- Neurotransmitter is noradrenaline in adrenergic nerves. (*e.g.sympathetic postsynaptic*)
- Neurotransmitter is acetylcholine in cholinergic nerves. (*e.g. presynaptic, postganglionic parasympathetic)*

Cholinergic nervous system:.





Chloinergic transmission:

Definition **:**transmission and delivery of the impulses between cholinergic nerves . either between : preganglionic and postganglionic neurons , or between : post ganglionic neuron and the effector organ .

Mechanism :

1- The action potential reaches the nerve terminal, carrying depolarization with it.
2- Depolarization causes opening of calcium channels, and so calcium enters the nerve terminal
3- Entry of calcium ions causes release of neurotransmitters *like Ach.* (see the following steps)

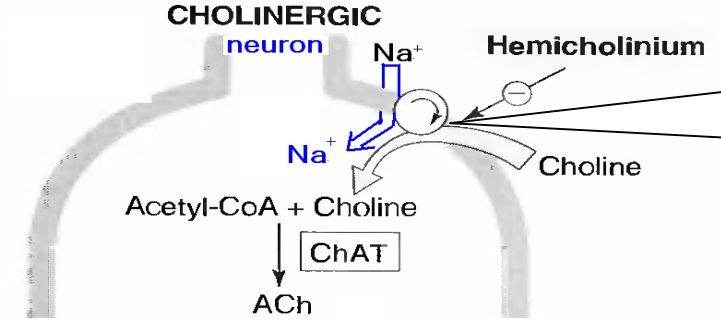
STEPS of signal transduction

1. Synthesis of acetylcholine
2. Storage in specific vesicles
3. Release
4. Binding to receptors
5. Metabolism (fate)
6. Recycling of the choline

*N.B: cholinergic nerves are motor (efferent) nerves.

1. Synthesis:

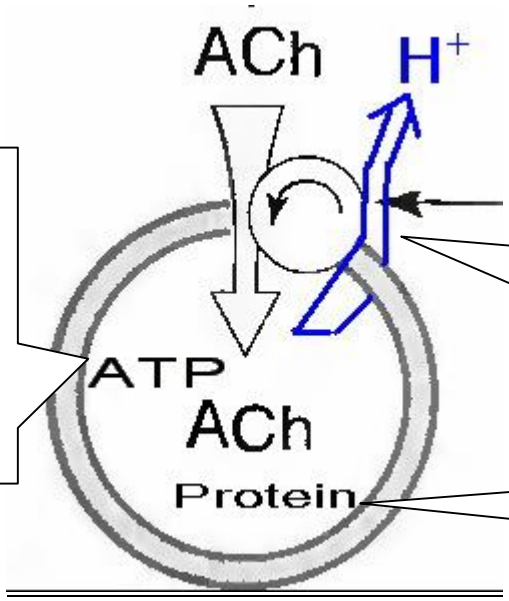
- Choline + Acetyl coA → Ach + CoA
- The enzyme for this reaction is **choline acetyltransferase**
    - The synthesis enzyme is inhibited by **Bromoacetyl CoA**, one of Ach analogues.
- Acetyl CoA comes **from mitochondria**
- **Sources of choline:** reused choline, diet, and synthesized (de novo) in liver
- Choline reuptake into the cytoplasm of cholinergic presynaptic nerve terminals is by special carriers.



Choline transport into the cell which mediated by a carrier (**rate limiting step in synthesis of choline**)

- Inhibitor of choline reuptake : **Hemicholimium**.

2. Storage:



ATP is inside the vesicle with Ach. Function: **modify** action of Ach and **Considered as a Co- transmitter during exocytosis.**

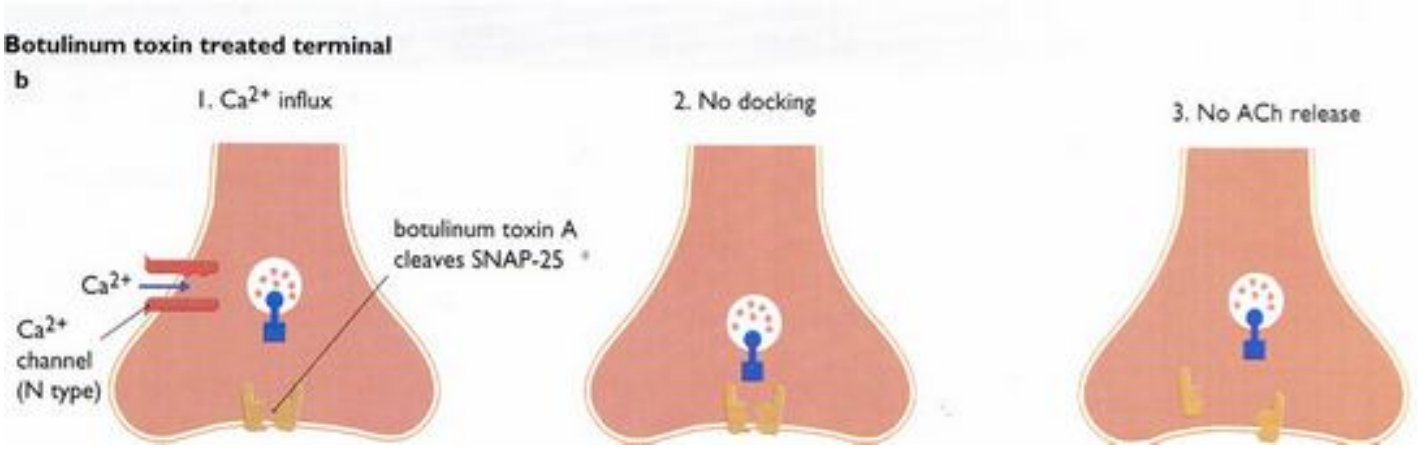
entry into vesicle is mediated by a vesicular associated transporter (antiporter: enter of Ach and exit of H^+)

Participate in **triggering** the release of transmitter

- Ach is transported into the storage vesicles by **active transport system.**
- Inhibition by **vesamicol.**

3. Release:

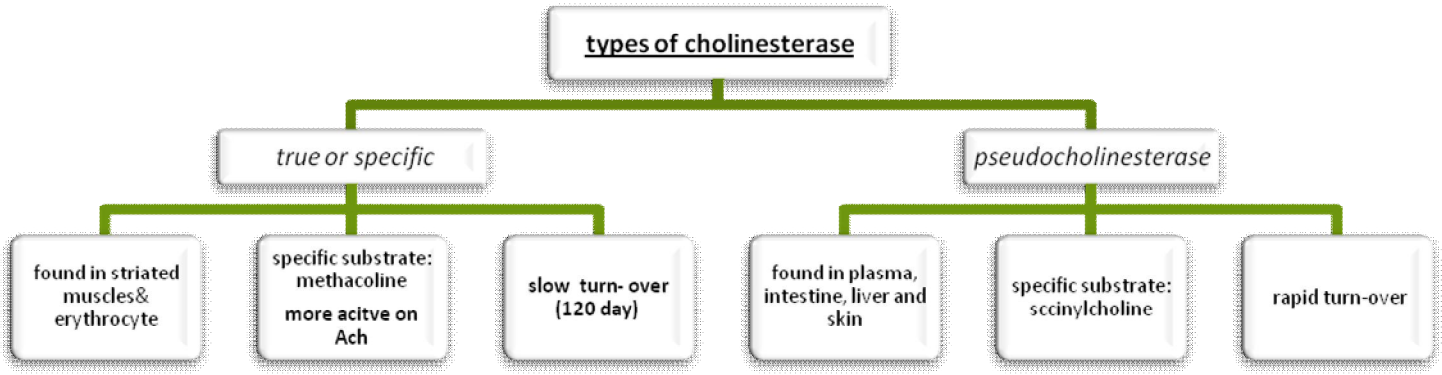
- Ach is released upon nerve stimulation ⟶ influx of Ca^{2+} ⟶ exocytosis ⟶ Ach release into synaptic cleft.
- Inhibition by **Mg, aminoglycosides** *(antibiotic).*
- Also inhibited by drug called **botulinum toxin** produced by **Clostridium botulinum**
    - Botulinum toxins cause **removal of two amino acids from fusion (docking) protein SNAP-25**
- Botulinum toxin, also known as Botox, causes prevention of transmission and agglutination of RBC



Clinical Applications: Botulinum is used in some cases as muscle relaxant

4. Hydrolysis of Acetylcholine:

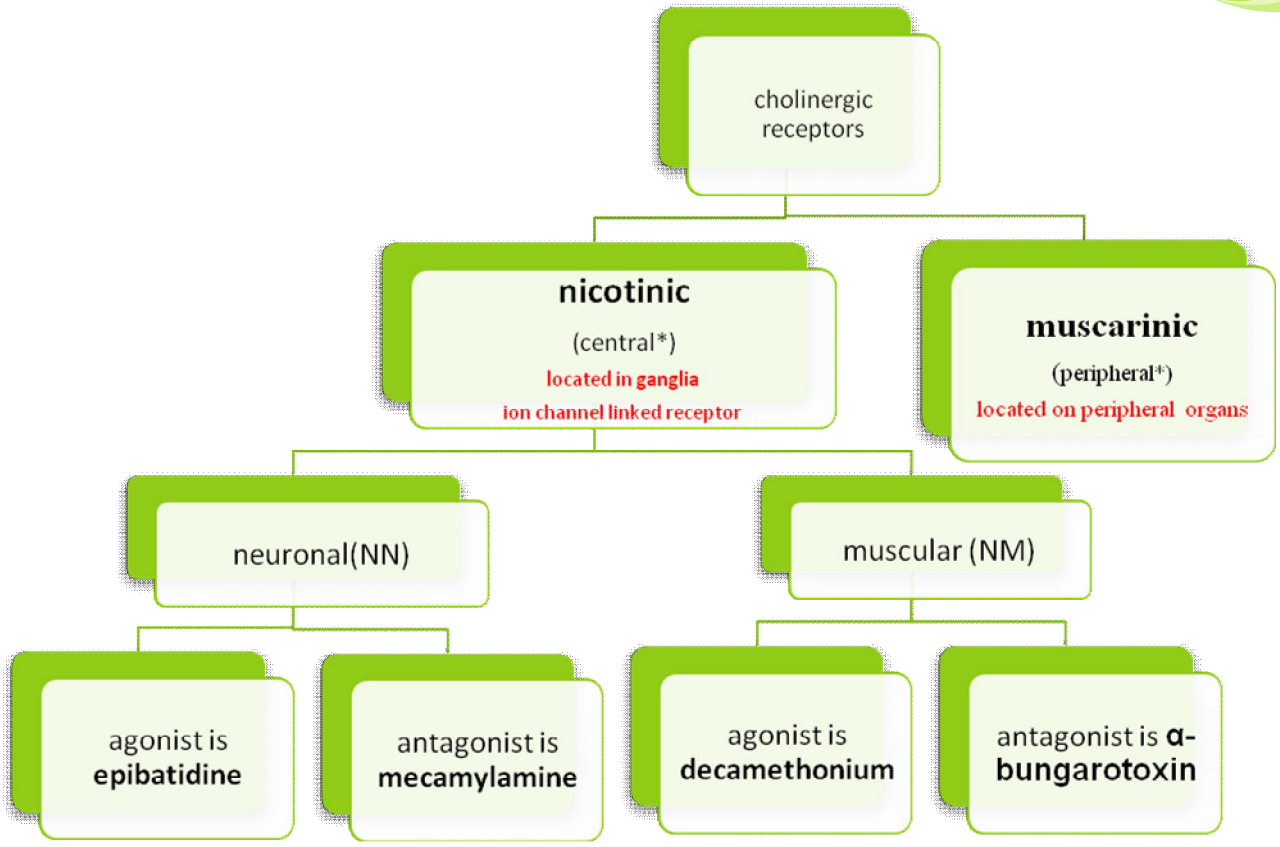
By **Acetylcholine esterase.**



<u>They both act on Ach</u>

Cholinesterase is inhibited by **neostigmine.**

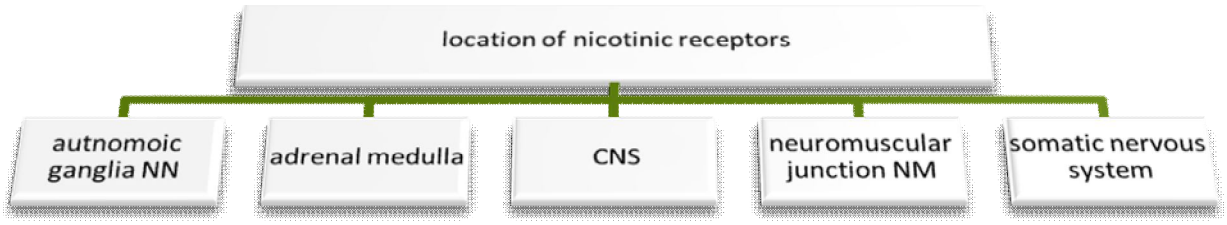
Cholinergic receptors:



N.B:[their location depends on type of stimulation].

* central = in the center i.e. between pre-post ganglionic neurons.

** prepheral = in the periphery i.e. between postganglionic neuron - organ



Muscarinic (peripheral) receptors:

- G-protein linked receptors.(so they're type 2 receptors)
- Five subclasses(M1-M5)
  - **M1(neuronal):**
    - ✓ Located in: CNS, PNS, Parietal cells of stomach.
    - ✓ Lead to formation of IP_3 , DAG, and Ca^+ .
    - ✓ Antagonist is **pirenzepine, which is used to treat ulcers.**

- **M2(Cardiac):**
  - ✓ Cause opening of K^+ channels and inhibition of adenylyl cyclase (cAMP)
  - ✓ ↓ heart rate.
  - ✓ Antagonist is **gallamine**.

- **M3:**
  - ✓ In glands and smooth muscle.
  - ✓ In smooth muscle of blood vessels → nitric oxide release (NO) → dilation
  - ✓ antagonist is **hexahydrosiladifenol** [HHSD]

- **M5:** in cerebral blood vessels → vasodilation

- M1, M3,M5 are EXCITATORY in function by increasing IP_3 and DAG.
- M2, M4 are INHIBITORY in function by inhibiting adenylyl cyclase.

What are the actions of cholinergic system activation

1. Nicotinic action.
2. Muscarinic action.
3. CNS.

- *There is no parasympathetic supply to the ventricles and blood vessels.*
- Endothelium of blood vessels respond only to cholinomimetic drugs (exogenous)

Nicotinic actions of ACH :

1. *Skeletal muscle :*

- Stimulation ⟶ muscle fasciculation (twitching) .
- High concentration ⟶ persistent of depolarization and paralysis

2. *Ganglia :*

- Stimulation of sympathetic and parasympathetic ganglia

3. *Adrenal medulla :*

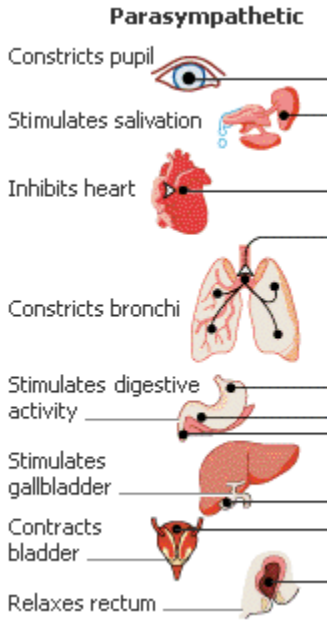
- Release of catecholamines (epinephrine, norepinephrine) .

CNS actions:

a. Nicotinic actions:
- ADH secretion from hypothalamus.
- Inhibition of motor fibers.

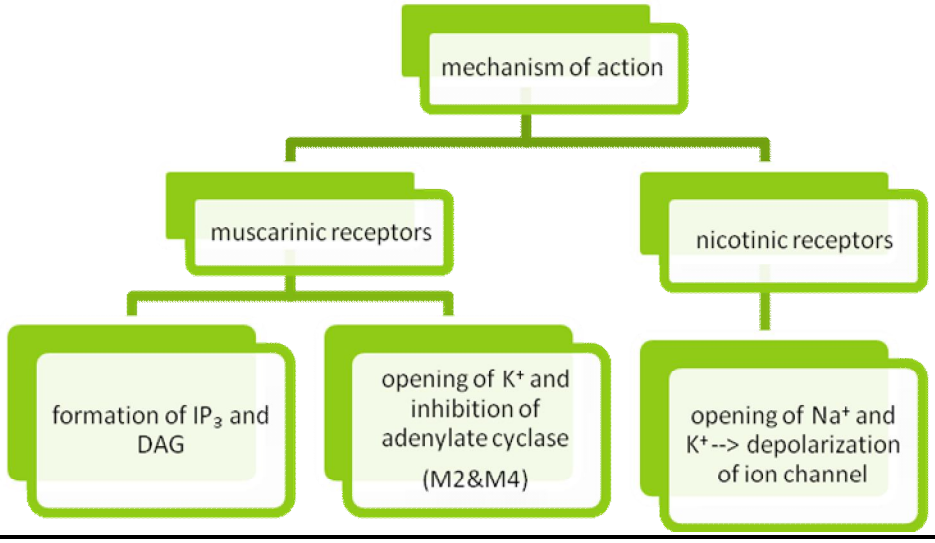
b. Muscarinic action: Ach is involved in memory and arousal.
- Parkinsonism (due to the increase in the cholinergic activity and decrease in dopaminergic activity (Ach is more than dopamine).
- Dementia of Alzheimer: loss of cholinergic neurons.

Muscarinic Actions



Organ	Action	Receptor
Eye: Iris sphincter muscle Ciliary muscle	Contraction (miosis) *They eye contracts for near vision.*	M_3
Heart SA node Atria AV node Ventricle	 -Decrease in heart rate (-ve chronotropy) -Decrease in contractility strength& refractory period (-ve ionotropy) -Decrease in conduction velocity (-ve dromotropy) -Small decrease in contractile strength	M_2
Blood vessels	Indirect dilation by action of EDRF Nitric oxide (NO)	M_3
Respiratory system Smooth muscle glands	 -Contraction (bronchoconstriction) -↑secretion	M_3
Sweat, lacrimal, and nasopharyngeal glands	↑secretion	M_3
GIT: Glands Sphincters Smooth muscle wall	 ↑Secretion Relaxation Contraction (↑Peristalsis)	M_3
Genitourinary: Bladder wall (detrusor) Sphincter (trigone) Uterus	 Contraction Relaxation Insensitive	M_3

MECHANISM OF ACTION



Cholinomimetics (parasympathomimetics) :

These drugs **produce actions similar to cholinergic system** stimulation.

Types :

1. ***Direct cholinomimetics :*** act by direct stimulation of nicotinic & muscarinic receptors .
2. ***Indirect cholinomimetics***: (anticholenesterase) they act indirectly by inhibiting acetylcholinesterase → preventing the degradation of Ach → ↑life span of Ach → amplifying the action of endogenous Ach.

Mechanism of action of cholinomimetics:

1) Muscarinic agonists

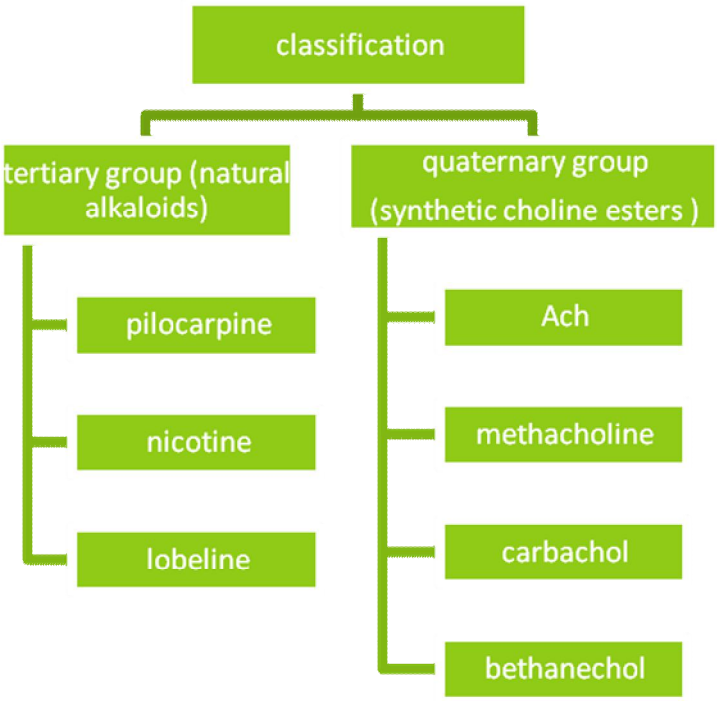
- Activation of phospholipase C ⟶ ↑ IP3 & DAG ⟶contraction of smooth muscles
- Increase cGMP ⟶NO release ⟶relaxation
- Inhibition of adenyl cyclase (cAMP)
- Opening of K channels ⟶Hyperpolarization

2)Nicotinic agonists

- Opening of ion channels ⟶Depolarization

Their type of action and mechanism resemble acetylcholine (in the table and diagram above)

Direct cholinomimetics drugs :



1. Tertiary: Naturally occurring alkaloids:

- bases
- non-polar (can cros BBB) (lipid soluble)
- easily excreted by kidney
- ↑clearance by acidification of urine; e.g. ingesting ascorbate acid
- Nicotine is lipid soluble and can be absorbed by the **skin**
- Nicotine is used as insecticide

Example: Pilocarpine: *(tertiary amine, basic)*

- **Pharmacokinetics**: * It is well absorbed orally
  * Good distribution
  * Not degraded by cholinesterase.
  * Long duration of action
  * Excreted unchanged (it doesn't undergo phase 1 in metabolism) in urine
- **Pharmacodynamics**:
  1. Direct muscarinic agonist mainly act on the eye as well as on secretions (saliva, tears, sweat)
  2. **No nictonic action**
  3. CNS actions
- **Uses**:
  1. Xerostomia (dry mouth)
  2. To counteract mydriatics after fundus examination.
  3. Treating glaucoma (see below)

2. Quaternary: choline esters:

Acetylcholine & synthetic choline esters (Methacholine, Carbachol, Bethanechol)

Acetylcholine:

- Quaternary ammonium compound.
- ↓lipid solubility, doesn't cross blood brain barrier
- Usually , esters are polar → ionized →increased water solubility ..
- Not absorbed orally (hydrolyzed by GIT enzymes)
- Muscarinic and nicotinic agonist.
- Not used due to :*non selective *(wide range of actions)* (because it acts on nicotinc & muscarinic receptors)
  *short half life (because it is degraded by pseudocholinesterase in plasma)

Synthetic choline esters: Quaternary ammonium compound

1. **Methacholine** (acetyl β-**methyl** choline)
2. **Bethanechol** (carbamoyl –β- **methyl**choline).
3. **Carbachol** (carbamoyl choline)

They have methyl group that can:
1- **Inhibit degradation** (can act for a longer duration)
2- **Act mainly on muscarinic receptors**

Pharmacokinetics :

- polar
- poor distribution
- cannot cross BBB
- All synthetic cholinesters are resistant in variable degrees to hydrolysis by chloinestrase.

What are the differences between Ach and synthetic choline esters?

Synthetic choline esters are:-

1. More specific.
2. **Less or not metabolized by acetylcholinesterase .**
3. Have longer duration of action.
4. ***Never*** given I.V or I.M because they might cause severe bradycardia; However they can be given subcutaneously.

Methacholine(Muscarinic Agonist):

- Taken orally or SC
- Metabolized only by **TRUE** choline-estrase
- Muscarinic acts more on CVS than GIT & UT.
- **Has very mild** Nicotinic action
- Used for:
  1. Peripheral vascular disease
  2. Paroxysmal atrial tachycardia

Carbachol (Muscarinic & Nicotinic):

- **Not** a substrate for Ach-estrase
- Longer duration than Ach
- Both **Muscarinic & Nicotinic action**
- Muscarinic actions mainly on eyes, GIT & Urinary tract
- Used for:
    a. Glaucoma
    b. Urinary retention, paralytic ileus

Bethanechol (Muscarinic Agonist):

- Similar to Carbachol but it has **no effect** on Nicotinic receptors
- Orally or SC

Uses of Choline synthetic esters :

- Glaucoma → pilocarpine
- Urinary retention → bethancol & carbachol
- Paralytic ileum → bethancol & carbachol

	Ach	methacholine	Carbachol	bethanechol
Absorbtion	Not absorbed	Irregular	Better	Better
Degradation by acetylcholinesterase	+++ by True & Pseudo	+ True only	None (resistant)	None (resistant)
Duration	Very short	Longer (+)	Longer (++)	Longer (++)
Administration	I.V	Oral , S.C	Oral , S.C Eye drops	Oral , S.C
Muscarinic	+++	+++	+++	+++
Selectivity	Not	More on CVS than GIT and urinary bladder	Eye, GIT Urinary bladder	GIT Urinary Bladder
Nicotinic	+++	*very mild*	+++	No
Uses	No	• Paroxysmal atrial tachycardia •Peripheral vascular disease	•Glaucoma •Urinary retention •Paralytic ileus	•Urinary retention •Paralytic ileus

Muscarine:

- Toxic comes from mushroom (Amanita muscaria)
- Will cause:
    1. Vomiting
    2. Diarrhea
    3. nausea

Contraindications:

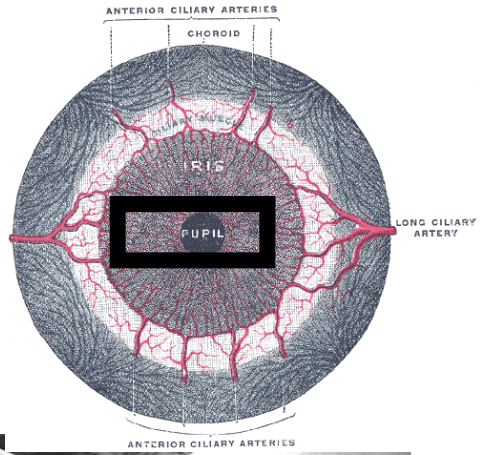
1. Bronchial asthma
2. Peptic ulcer
3. Angina pectoris

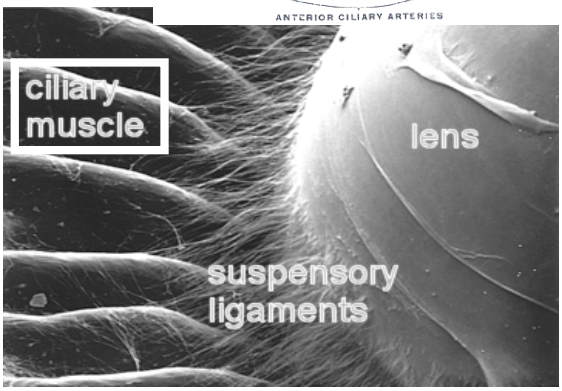
System organ effects:

1- Eye.

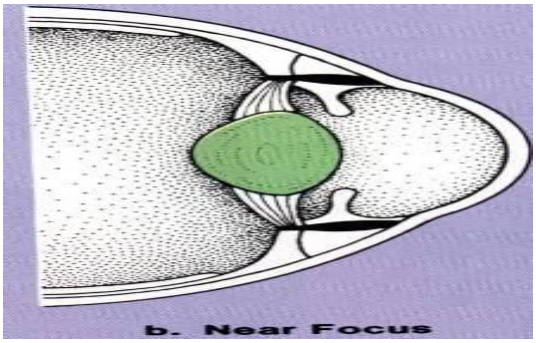
Physiology of the eye:

- Parasympathetic controls the action of the iris, sphincter pupillae, muscle→ cause constriction of the pupil
- Pupil functions are:
  a) Control light intensity
  b) Regulation of intraocular pressure.
- Constriction of pupil is called **(miosis).**
- Parasympathetic stimulation also controls **ciliary muscle.**

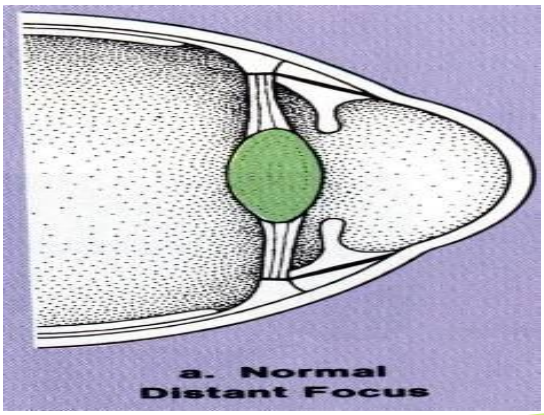




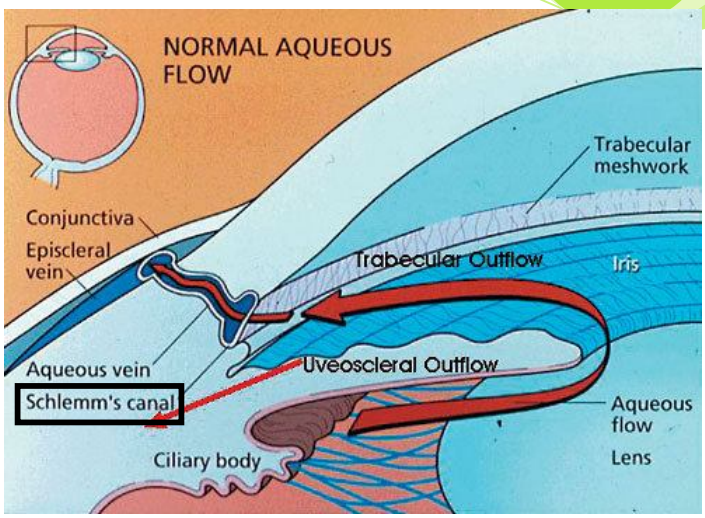
- When the ciliary muscle contracts → the lens becomes more globular and focuses on near objects



When the ciliary muscle relaxes → the lens becomes flattened and starts focusing on distant objects.



Pathology of the eye:



- Aqueous humor is drained by Schlemm's canal.
  - In case of iris relaxation → the folding of iris will close the canal→↑aqueous humor→severe pain due to↑**intraocular pressure (<u>glaucoma)</u>**→damage to the optic nerve.
  - Muscarinic agonist will:
    1. Contract the iris
    2. Expose the trabecular meshwork.

2- Cardiovascular system:

- Same action of the table above .
- Lead to hypotension followed by reflex sympathetic discharge.

3- Respiratory system:

- May lead to asthma.

4- Central nervous system:

- Nicotine and lobeline→ causes alertness
- High level of nicotine→convulsion and coma

5- Peripheral nervous system:

- Act on ganglia (activate both sympathetic and parasympathetic)
- In case of CVS the sympathetic dominates → tachycardia
- In case of GIT the parasympathetic dominates → nausea, diarrhea, and voiding urine.
- Nicotinic receptors in aortic and carotid bodies→ stimulation of respiration and vagal discharges.

MCQs

1. **Major neurotransmitter released at end organ effectors of the thoracolumbar division of the autonomic nervous system:-**
   a. dopamine
   b. Adrenaline
   c. noradrenaline
   d. Acetylcholine

2. **Preganglionic fibers terminating on adrenal medullary chromaffin cells release:-**
   a. noradrenaline
   b. adrenaline
   c. acetylcholine
   d. dopamine

3. **Activation of the sympathetic nervous system will cause which change in the skeletal muscle versus cutaneous vascular beds?**
   a. vasoconstriction,vasoconstriction
   b. vasodilatation, vasodilatation
   c. vasodilatation, vasoconstriction
   d. vasoconstriction, vasodilation

4. **Rate-limiting step in acetylcholine synthesis:-**
   a. choline acetyltransferase activity.
   b. vesicular protein synthesis.
   c. choline uptake.
   d. acetylcholinesterase activity
   e. availability of acetate

5. **Inhibits choline transport into cholinergic vesicles:-**
   a. bretylium
   b. vesamicol
   c. reserpine
   d. atropine

6. **Influx of this ion promotes fusion between axoplasmic membrane and nearby vesicles:-**
   a. sodium
   b. potassium
   c. calcium
   d. Chloride
   e. Clostridium toxins inhibit:-

7. **Acetylcholinesterase**
   a. prevent reuptake of choline .
   b. inhibit vesicular acetylcholine release.
   c. prevent calcium influx

1.c	2.c	3.c	4.c	5.b
6.c	7. None is true			

8. True" acetylcholinesterase is found in:-

a. intestine
b. liver
c. erythrocytes
d. plasma

9. Cholinergic receptor type that mediates the decrease in heart rate by activating potassium channels:-

a. M1– muscarinic
b. M2-muscarinic
c. M3-muscarinic
d. nicotinic

10. Cholinergic receptor type that mediates vasodilation following low-dose i.v. acetylcholine administration:-

a. a nicotinic
b. muscarinic
c. nitric oxide receptor
d. substance P receptor

11. Factors that limit CNS effects of systemic acetylcholine administration:-

a. poor CNS penetration
b. inactivation by plasma cholinesterase
c. both
d. neither

12. Choline ester most susceptible to hydrolysis by acetylcholinesterase:-

a. carbachol
b. acetylcholine
c. methacholine
d. pilocarpine

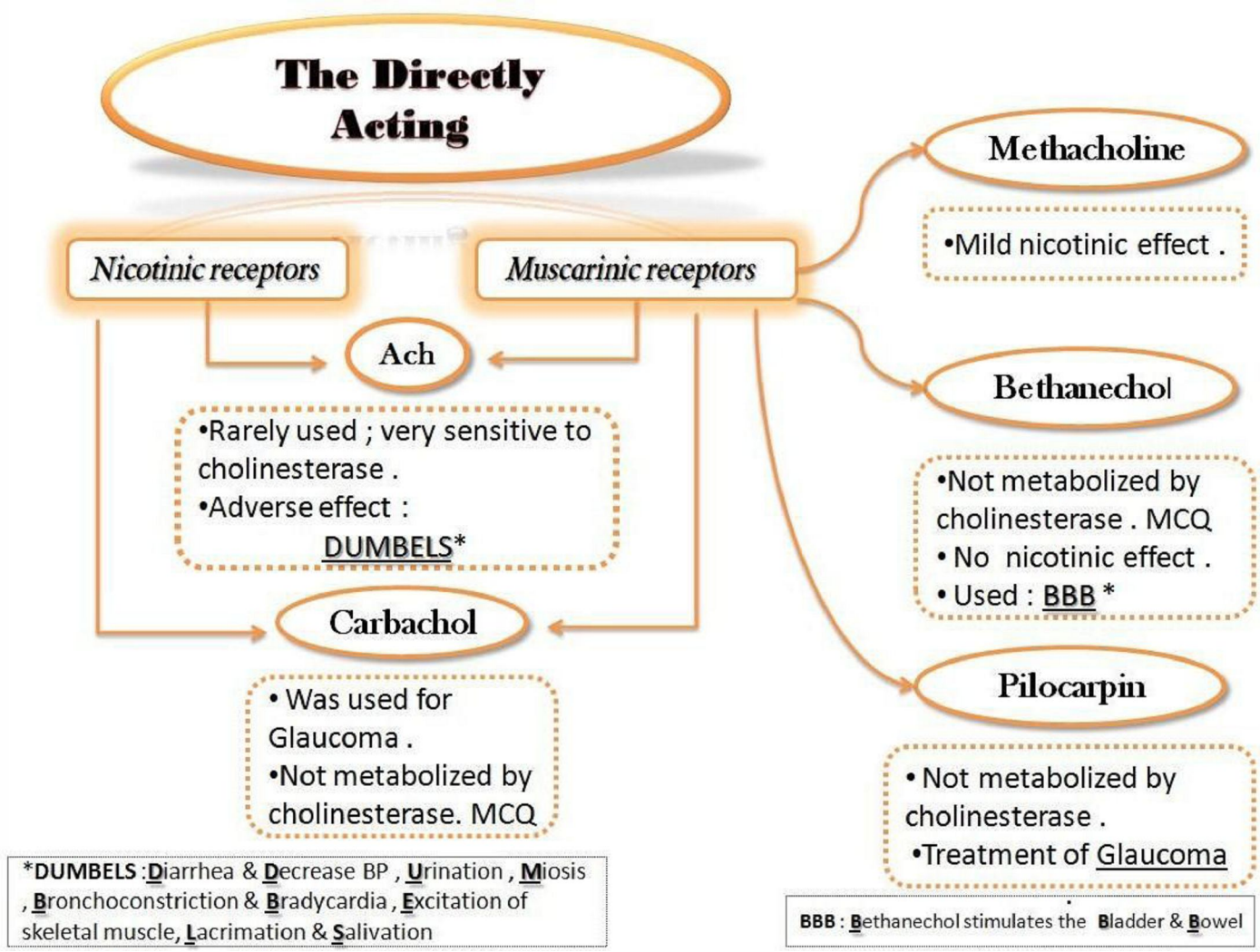
13. Drugs which have no nicotinic activity, and are resistant to the activity of acetylcholinesterase include:-

a. acetylcholine
b. pilocarpine
c. carbachol
d. bethanechol

14. Associated with parasympathetic activation (direct effects):-

a. increase heart rate
b. decreased GI motility
c. decrease cardiac contractility
d. Miosis

8.c	9.b	10.b	11.c	12.b
13.b,d	14. c			



By: Naif Fnais

Indirect cholinomimetics:

Mechanism of action :

- Inhibiting acetylcholinesterase action, thus increasing the Ach concentration at cholinergic receptors, at **both nicotinic & muscarinic receptors.**
  - they indirectly provide a cholinergic action by prolonging the lifetime of Ach produced endogenously at the cholinergic nerve endings.

Degradation of Ach by acetylcholinesterase:

1. **Hydrolysis of Ach occurs after it binds to the active site of the enzyme**
   Acetyl choline (Ach) → choline + acetylated enzyme (Binding)
2. **Acetylated enzyme's bond is broken by hydration**
   Acetylated enzyme → cholinesterase enzyme + Acetic acid (Hydration) **3.**
3. Anticholinesterase competes with Ach at the active site of the enzyme → accumulation of Ach in the synaptic cleft.

Cholinesterase enzyme has 2 binding sites:

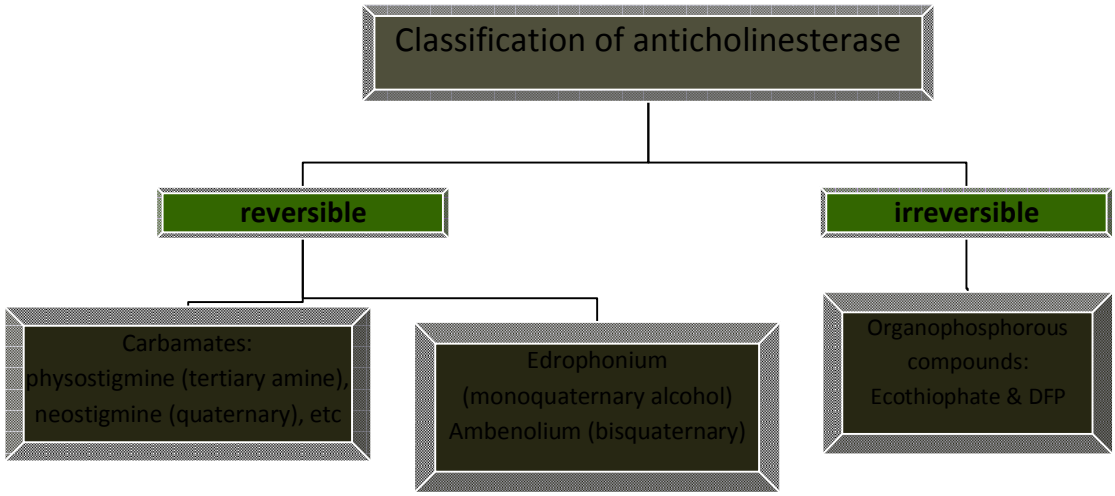
1. **ANIONIC** →N+
2. **ESTERIC SITE** → ester link

Pharmacological effects of anticholinesterase :

1. **Nicotinic action:** same action of Ach and cholinomimetics (direct & indirect)
2. **Muscarinic action**
3. **Action on CNS:** excitation, convulsion, respiratory failure, coma.

Classification of anticholinesterase:

- Anticholinesterase are divided into reversible and irreversible according to the ability of them to bind to the receptors .
- Reversible anticholinestrase : bind to the enzyme for short time .
- Irreversible : bind for long time by stable covalent bond .



Edrophonium (monoquaternary alcohol):

- Simple alcohol
- Polar , quaternary
- Reversible anticholinestrase
- Not substrate for the enzyme (not degraded by cholinesterase)
- Attach mainly to **anionic** site by electrostatic forces.
- Has a very short duration of action, 5-15 minutes, more than Ach but less than the others.

Pharmacokinetics:

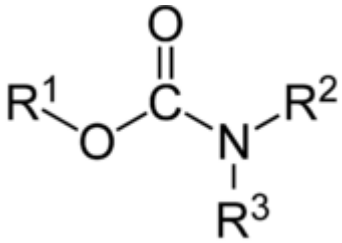
- Polar.
- ↓lipid solubility
- ↓distribution in CNS
- Not absorbed orally (should be given by injection).
- Not hydrolyzed by cholinesterase (because it doesn't have ester, so it cannot bind properly to cholinesterase).
- Excreted unchanged in urine.
- Used in diagnosis of myasthenia gravis (see below)

Carbamates:

- Attach to <u>both</u> sites of cholinesterase enzymes (esteric and anionic site) by covalent bond (have ester group).
- Hydrolyzed at a <u>slower</u> rate than Ach.
- Substrate for <u>TRUE</u> cholinesterase enzyme & <u>non specific esterases.</u>
- Long half life (30 minutes-8 hours).
- All polar <u>except Physostigmine</u>.

Physostigmine:

Tertiary ammonium compound, reversible anticholinesterase.



Pharmacokinetics :

- Non- polar: Good lipid solubility. Good BBB penetration.
- Good oral absorption.
- Hydrolyzed by cholinesterase (true & pseudo)

Pharmacodynamics :

- Attach to both sides of the enzyme (anionic + esteric)
- Has intermediate duration of action.
- Has CNS stimulation action.
- No direct action on NMJ.
- Has muscarinic and nicotinic action

Uses :

- Glaucoma
- To counteract the effect of mydiatrics.
- Atropine intoxication (I.V)
  (atropine is a muscarinic blocker)

mydriatics :are drugs that cause eye mydreasis which is dilation of the pupil of the eye.

Neostigmine:

Quaternary ammonium reversibl anticholinesterase.

Pharmacokinetics :

- Polar compound: Poor lipid solubility.
- Can be taken orally.
- No BBB penetration (no CNS effect).
- Has intermediate duration of action.
- Hydrolyzed by cholinesterase (true & pseudo)

Pharmacodynamics :

1. Indirect action:
   - Has both muscarinic and nicotinic action.
   - More prominent on GIT and urinary tract than CVS.

2. Direct action *on NMJ*.

Uses :

- Used for treatment of myasthenia gravis, *combined with* ***atropine***
  - Atropine will block muscarinic receptors . so that neostigmine works selectively ONLY on Nicotinic receptors which are found in skeletal muscles (NMJ)
- Curare intoxication, *(curare is a muscle relaxant)*
- Paralytic ileus + urinary retention

Ambenonium and Pyridostigmine :

- Reversible anticholinestrase
- Similar to neostigmine (in pharmacodynamics & kinetics)
- Used for treatment of myasthenia gravis

Organophosphorous compounds:

- All are highly lipid soluble except echothiophate.
- Have long duration of action.

Thiophosphate (sulfur containing phosphate) :

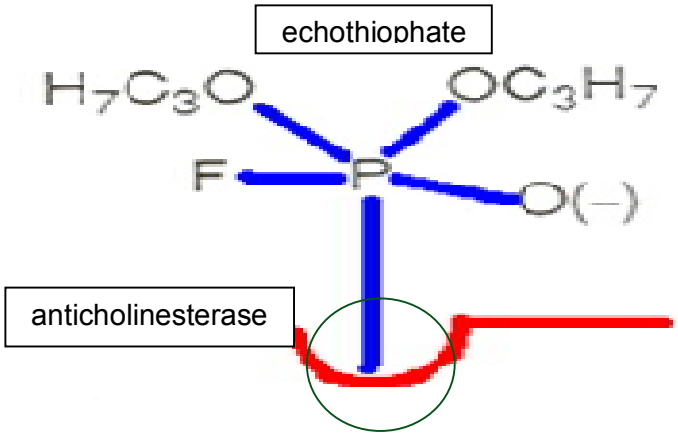
- They are prodrugs.
- *E.g. Malathion, Parathion.*
- Used as insecticides.
- Malathion is converted to sarin which is a toxic nerve gas .

Echothiophate and Isoflurophate:

- Irreversible drugs
- Well absorbed from skin, lung, gut, conjunctiva except ecothiophate.
- Toxic and has no clinical application.

mechanism :

- Work indirectly by inhibition of cholinesterase .
- Binds to esteratic site of cholinesterase forming covalent bond (the phosphorus atom). (that's why it has very long duration of action)
- Aging makes the bond extremely stable .(can't be cleaved)
  - In aging: O^- will fall making the bond between P and the enzyme stronger.
  - Organophosphorus drugs are reversible before the formation of the aging bond



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+ Diisopropylflourophosphate (DFP)
//

Pharmacological effects of organophosphorus compounds:

1. **Muscarinic action. (check the table)**
2. **Nicotinic action**. (Ganglia, NMJ):
   - Therapeutic dose >>> increase action of Ach (increase force of contraction)
   - Toxic dose: muscle twitching, fibrillation, and paralysis.
3. **CNS:** makes the parasympathetic limp predominate.

Organophosphorus compounds toxicity:

- Severe bradycardia, hypotension.
- Bronchospasm
- Increased GIT motility →cramps and diarrhea.
- CNS effects →convulsions, coma and respiratory failure.
- Twitching of skeletal muscles → depolarization block →muscle weakness,fatigue, and paralysis.

Treatment of organophosphorous toxicity:

1. Prevent further absorption
2. Support respiration
3. Cholinesterase reactivation (see next paragraph)
4. Atropine (block muscarinic and central actions)

Cholinesterase reactivation (Oximes)

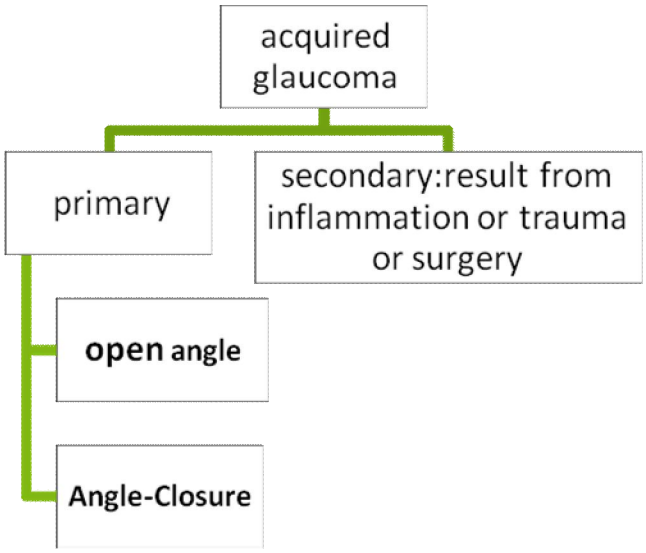
Pralidoxime (PAM) & obidixime

- Accelerate the hydrolytic regeneration of cholinesterase enzyme
- They activate recently inhibited enzymes before aging (useless after aging)
- **Uses:** IV ⟶ over 15-30 min for organophosphorous intoxication (cannot be used as a single dose, must be multiple because its duration is very long)

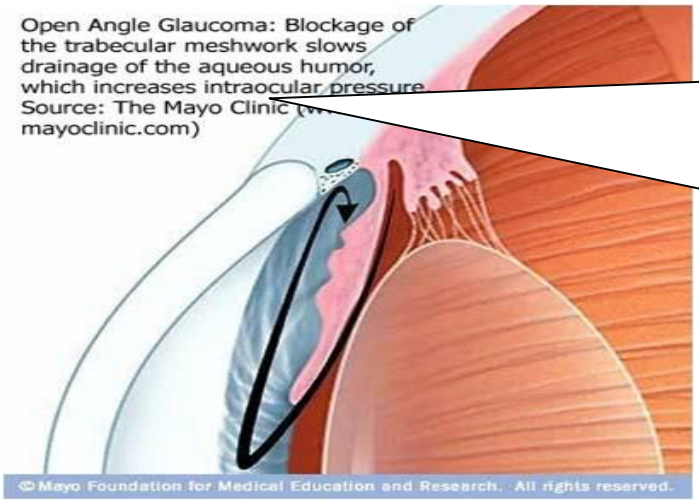
Clinical uses of cholinergic drugs

In this section we will talk about some diseases and how the drugs will manage them.

1. Glaucoma



Open angle glaucoma



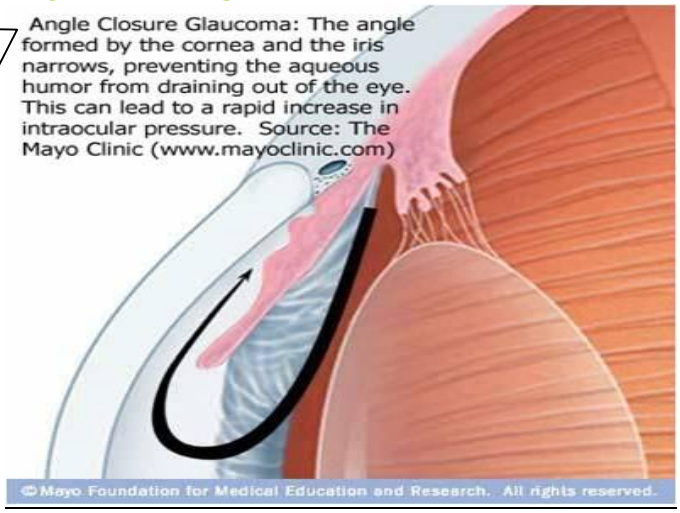
- 80% of the cases
- Chronic disease , No symptoms thus called "thieve of the night".
- **Can't** treated with traditional surgical correction

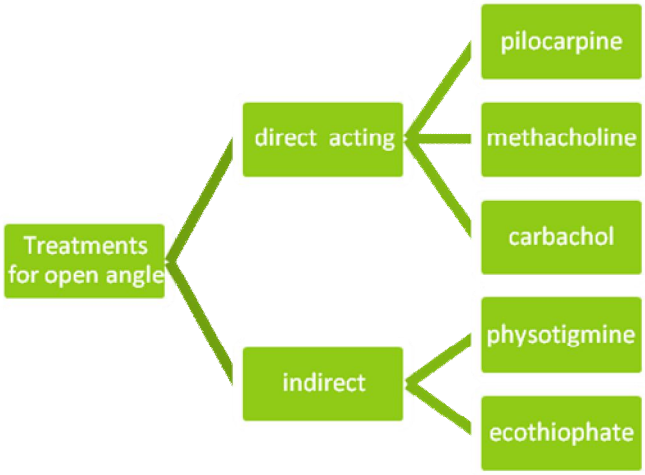
- Muscarinic stimulants ↑outflow of aqueous humor and ↓secretion.

- acute angle closure requires surgery for permanent correction.

Initially treated with drugs . Once the intraocular pressure is controlled and the danger of vision loss is diminished, the patient can be prepared for **corrective surgery.**

Angle-closure glaucoma



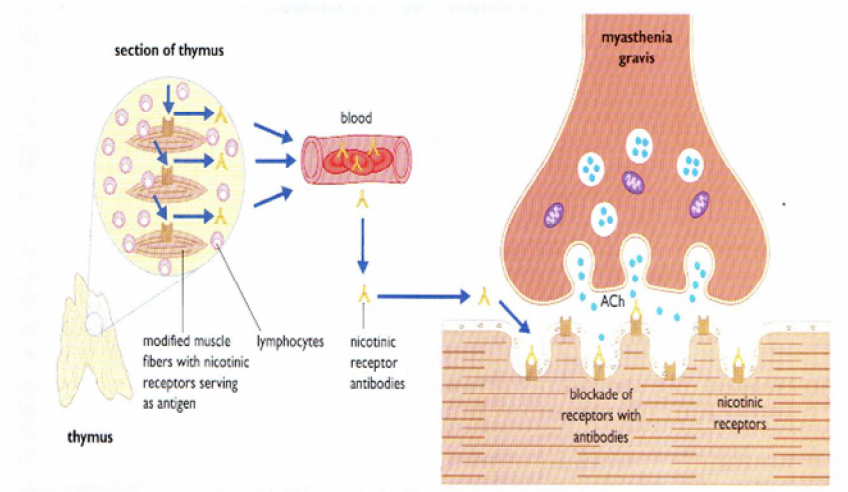


2- Post operative ileus "atony":

- After surgery smooth muscle in the stomach will paralyze in some patients leading to nausea and vomiting.
- Using of the drugs leading to contraction of smooth muscles and ↑peristalsis
- <u>We don't use drugs in case of anatomic obstruction</u> (because the food will accumulate behind the spot of obstruction causing distention then bursting)
- The same might happen in case of urinary bladder. We use cholinergic drugs to contract the smooth muscle and relax the sphincter.
- The drugs used
    1. Neostigmine of choline esterase inhibitor.
    2. Bethanechol of choline ester.
    3. Carbachol (less favored)

3- Myasthenia gravis:

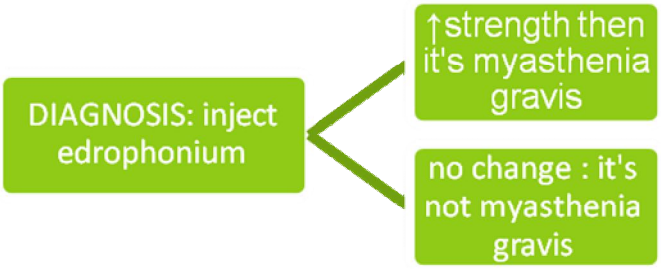
- Autoimmune disease.
- Due to release of antibody from the thymus against nicotinic receptors in the neuromuscular junction. This phenomenon is detected in 85% of patients.
- Mechanism:
    1. Cross – linking receptor , (internalization and degradation of receptor)
    2. Lysis of postsynaptic membrane ; or
    3. Binds to nicotinic receptor and inhibit their function.



Signs :

1. Ptosis (dropping of eyelid)
2. Diplopia (double vision)
3. Difficulty in speaking and swollowing

Diagnosis : by edrophonium



Treatment

- **Neostigmine** (CHOLINESTERASE inhibitor) + immunosupressent due to side effect on other muscaricinic receptor we use an antimuscarinic drug e.g. atropine.
- If we use excessive amount of neostigmine → depolarization block (paralysis) this case is called **cholinergic crisis.**
- Severe myasthenia → paralysis of muscle (**myasthenic crisis).**
    - We use edrophonium to differentiate between them.
- We use edrophonium to assess the adequacy of drugs :
    I. If the muscle strength improves then the drug of use was inadequate. And increase of the dose is necessary.
    II. If there is no change then muscle weakness is attributed to the toxicity of drug in use, which in turn causes a depolarization blockade.
- Some patients undergo surgery, thymectomy, for myasthenia gravis.

4- Reverse pharmacological paralysis:

- In surgeries we use neuromuscular blocker e.g. d-tubocurarine for anesthesia.
- Use of d-tubocurarine → respiratory depression
- During surgery; the patient is capable of breathing mechanically.
- Since d-tubocurarine is reversible and surmountable, we use neostigmine after the surgical operation to overcome the effect of d-tubocurarine.

5- Supraventricular tachycardia:

- In this case ↓pumping efficiency of the heart as a result of decreased time needed to fill the ventricle with blood.
- **Treatment:** edrophonium → decrease conduction.

6- Antimuscarinic drug intoxication:

- Excess use of anti muscarinic drugs.
- Atropine can cause hyperthermia because it decreases sweating and shunts cutaneous blood supply.
- Maybe lethal in children.
- Treatment: physostigmine.
- Why? Because it crosses the blood brain barrier and reverses the effect of atropine in CNS and in PNS.

7- Alzheimer disease.

- **Cause:** reduced synthesis of acetylcholine in brain
- First treatment: tacrine (anti cholinesterase) side effect: hepatotoxic
- Treatment now is donepezil non hepatotoxic.(both are given orally)

8- Sjorgren's syndrome:

- Autoimmune disorder where immune cells attack exocrine glands.
- Treatment of dry mouth that result from the disease: cevimline.
- Cevimline:
  I. New cholinomimetic drug.
  II. Directly acting
  III. Given orally

9- Smoking cessation:

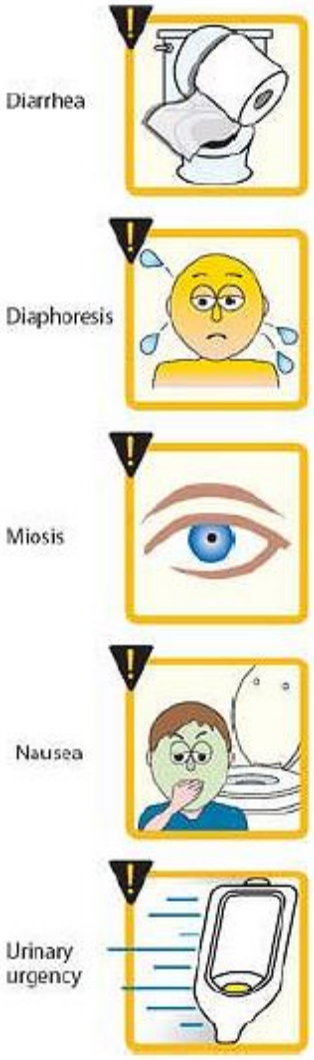
- Smoking cessation drugs are medicines that help people stop smoking cigarettes or using other forms of tobacco
- *E.g. varennicline*

Toxicity of cholinergic drugs

We are going to talk about excessive use of cholinergic drugs and effect of that on some organs

A. Directly acting muscarinic stimulants (e.g. methacoline)

- Lead to nausea, vomiting, diarrhea, salivation, cutaneous vasodilation, bronchial constriction.



B. Directly acting nicotinic stimulants (e.g. nicotine, acetylcholine, carbachol):

a. Acute toxicity:

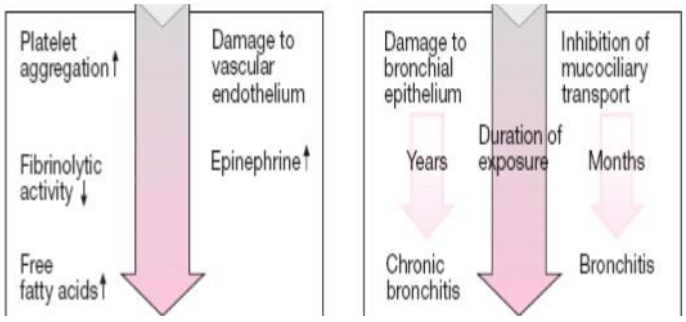
- Action on CNS: leading to convulsion and coma
- Skeletal muscle depolarization (paralysis)
- Hypertenstion & cardiac arrhythmias because the action will be on nicotinic receptor in ganglion → activation of sympathetic system → ↑cardiac output →hypertension.

Treatment:

i. Atropine
ii. Anticonvulsant drug (diazepam)
iii. Mechanical respiration

a. Chronic toxicity:

- Lead to increased risk for vascular disease
- Increase peptic ulcer.



C. Cholinesterase inhibitors:

- Intoxication comes from pesticide and veterinary vermifuge (drugs that kill worms).
- Initial signs of intoxication: similar to those in directly acting muscarinic stimulants.
- Initial signs are followed by CNS involvement
- Accompanied by peripheral nicotinic effect.

Therapy:

1. Maintenance of vital signs
2. Decontamination: removal of clothes and washing to prevent further absorption.
3. Atropine
4. In case of organophosphorus intoxication we use pralidoxime.

MCQs

15. Classes of anticholinesterase drugs:-

a. reversible, short-acting
b. intermediate, carbamylating
c. long-acting, phosphorylate agents
d. A & B
e. A, B & C

16. Anticholinesterase agent; quaternary ammonium compound; intermediate-duration, carbamylating agent::

a. physostigmine
b. neostigmine
c. edrophonium
d. tacrine

17. Indirect-acting cholinomimetic:-

a. atropine
b. edrophonium
c. carbachol
d. acetylcholine
e. Ephedri ne

18. Consequences of acetylcholinesterase inhibitor application to the conjunctiva:-

a. relaxation of the pupillary sphincter muscle.
b. relaxation of the ciliary muscle .
c. both

19. Your pharmacology laboratory has been given an unknown compound for screening. It is found to contract the sphincter muscle of the eye, decrease the heart rate, increase bronchial gland secretions and causes sweating. You would classify this compound as (an):

a. alpha agonist
b. alpha antagonist
c. beta antagonist
d. Muscarinic

20. Which type of glaucoma response to anticholinesterase treatment?

a. Angle closure
b. secondary
c. congenital
d. Open angle

15. e	16. B	17. B	18. C	19.c
20. D	21. d			

21. Probable cause of myasthenia gravis:-

a. excessive synthesis of cholinergic receptors .
b. inadequate synthesis of acetylcholine
c. failure of acetylcholine reuptake system.
d. 'binding of anti--muscarinic receptor antibodies to the muscarinic cholinergic receptor .
e. binding of anti-nicotinic receptor antibodies to the nicotinic cholinergic receptor

22. Your pharmacology laboratory has received a new compound for screening. Initial experimentation with the compound yields the following findings: It causes contraction of the detrusor muscle of the urinary bladder, contraction of the sphincter muscle of the iris, and secretion of lacrimal glands. With this information you might initially classify the compound as a(an):

a. alpha agonist
b. muscarinic agonist
c. beta agonist
d. anticholinergic
e. alpha antagonist

23. Rationale for prescribing anticholinesterase drugs to patients with myasthenia gravis:-

a. increase acetylcholine turnover
b. increase receptor number
c. increase amount of acetylcholine available for neuromuscular junctions .
d. reduce choline reuptake

24. Symptom appears in 'cholinergic crisis' and an acute exacerbation of myasthenia gravis is:-

a. increased salivation
b. muscle fasciculations (twitching)
c. profuse sweating
d. muscle weakness

25. All of the following statements concerning physostigmine and neostigmine are true EXCEPT:

a. physostigmine and neostigmine are classified as reversible cholinesterase inhibitors
b. neostigmine stimulates nicotinic receptors at ganglia and neuromuscular junctions unlike physostigmine
c. physostigmine is well absorbed orally
d. a major problem encountered with neostigmine is the unpleasant central nervous system effects which result from its administration
e. physostigmine is a tertiary amine and is able to penetrate the central nervous system

21. e	22. B	23. C	24. D	25. D

26. Clinical uses of bethanecol:-

a. management of postoperative abdominal distention.
b. management of Alzheimer's disease.
c. Treatment of cholinergic blockers intoxication
d. treatment of reduced salivation secondary to radiation therapy

27. All of the following are clinical uses of anticholienestrases except :

a. reversal of neuromuscular blockade produced by nondepolarizing neuromuscular-blocking drugs.
b. myasthenia gravis management
c. glaucoma treatment
d. treatment of paralytic ileus and urinary bladder atony

28. In organophosphate poisoning, this agent may be capable of re-activating inhibited acetylcholinesterase:-

a. atropine
b. pilocarpine
c. Mecamylamine
d. PAM

29. Symptoms following diisopropylfluorophosphate exposure :-

a. constipation
b. salivation
c. decreased gastric acid secretion
d. bronchodilatation.

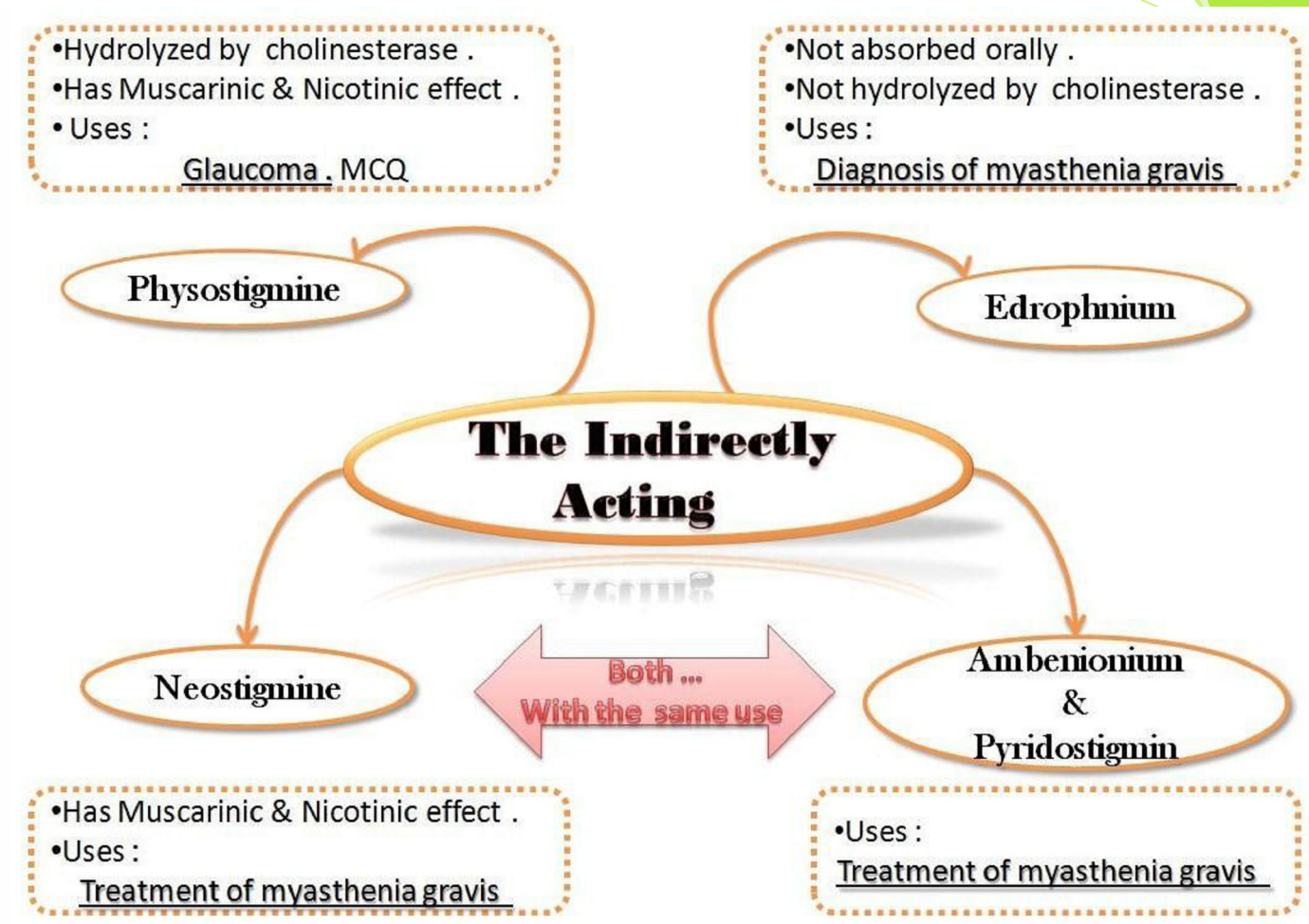
30. All of the following are contraindication of muscarinic agonist except

a. asthma
b. glaucoma
c. peptic ulcer
d. coronary vascular disease
e. obstruction of the bladder
f. marked bradycardia

31. A patient is given a medication which stimulates bladder contractions to increase urination. What type of receptors have been stimulated?

a. Adrenergic
b. Sympathetic
c. Muscarinic

26. a	27.E	28. B	29. B	30.b	31. c



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