Pharmacology I

Cholinergic Agonists

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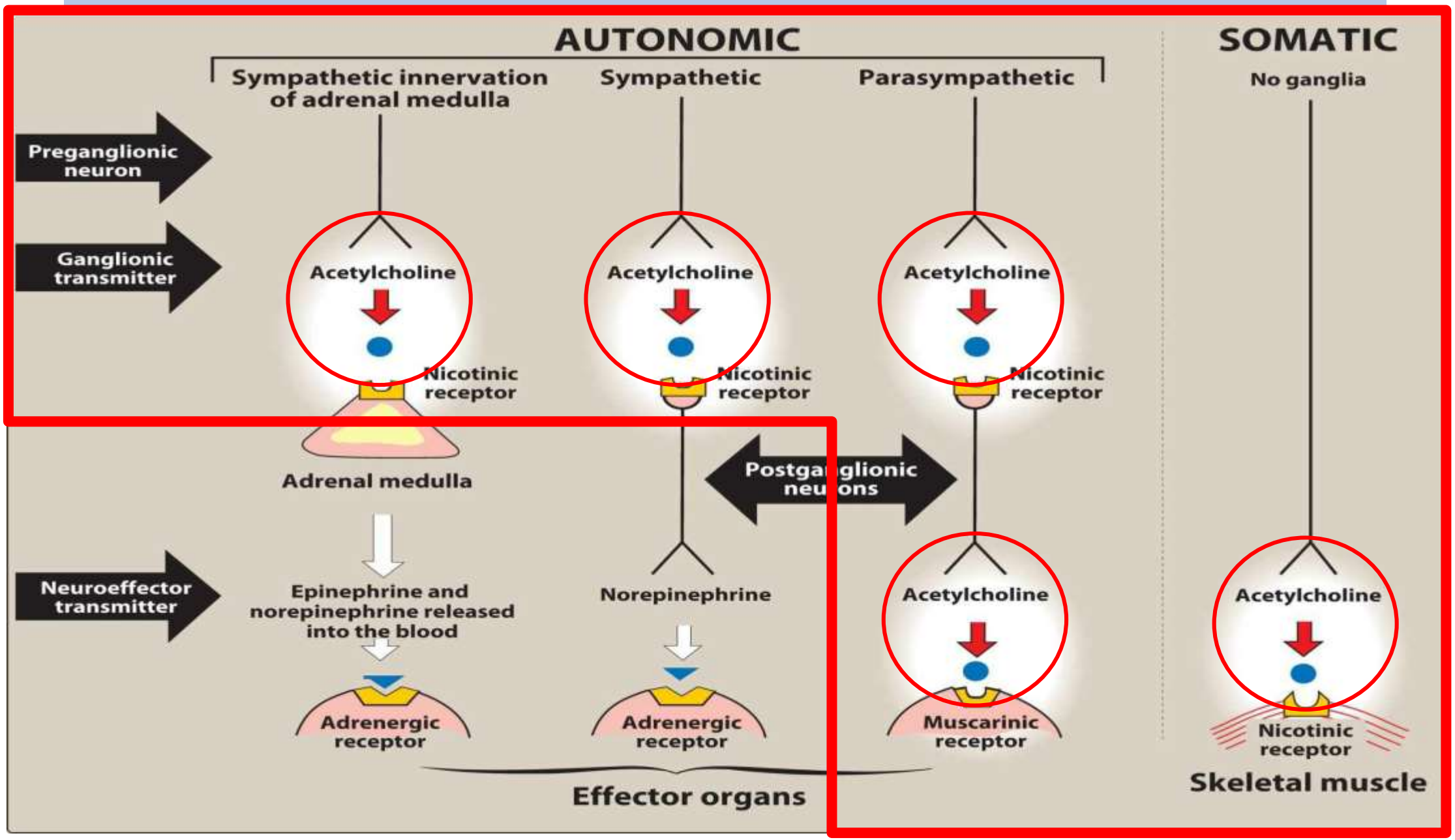
Lecture No. : 4

- Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in the mechanism of action.
- **The cholinergic drugs** act on receptors activated by **acetylcholine** (ACh),
- **The adrenergic drugs** act on receptors stimulated by **norepinephrine** or **epinephrine**.
- Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS.

The Cholinergic Neuron

1. The preganglionic fibers terminating in the **adrenal medulla**,
2. The **autonomic ganglia** (both parasympathetic and sympathetic), and
3. The **postganglionic fibers of the parasympathetic** division use **ACh as a neurotransmitter** (Figure 1).
4. The **postganglionic sympathetic division of sweat glands** also uses **acetylcholine**.
5. In addition, **cholinergic neurons innervate the muscles (NMJ)** of the somatic system and play an important role in the **CNS**.

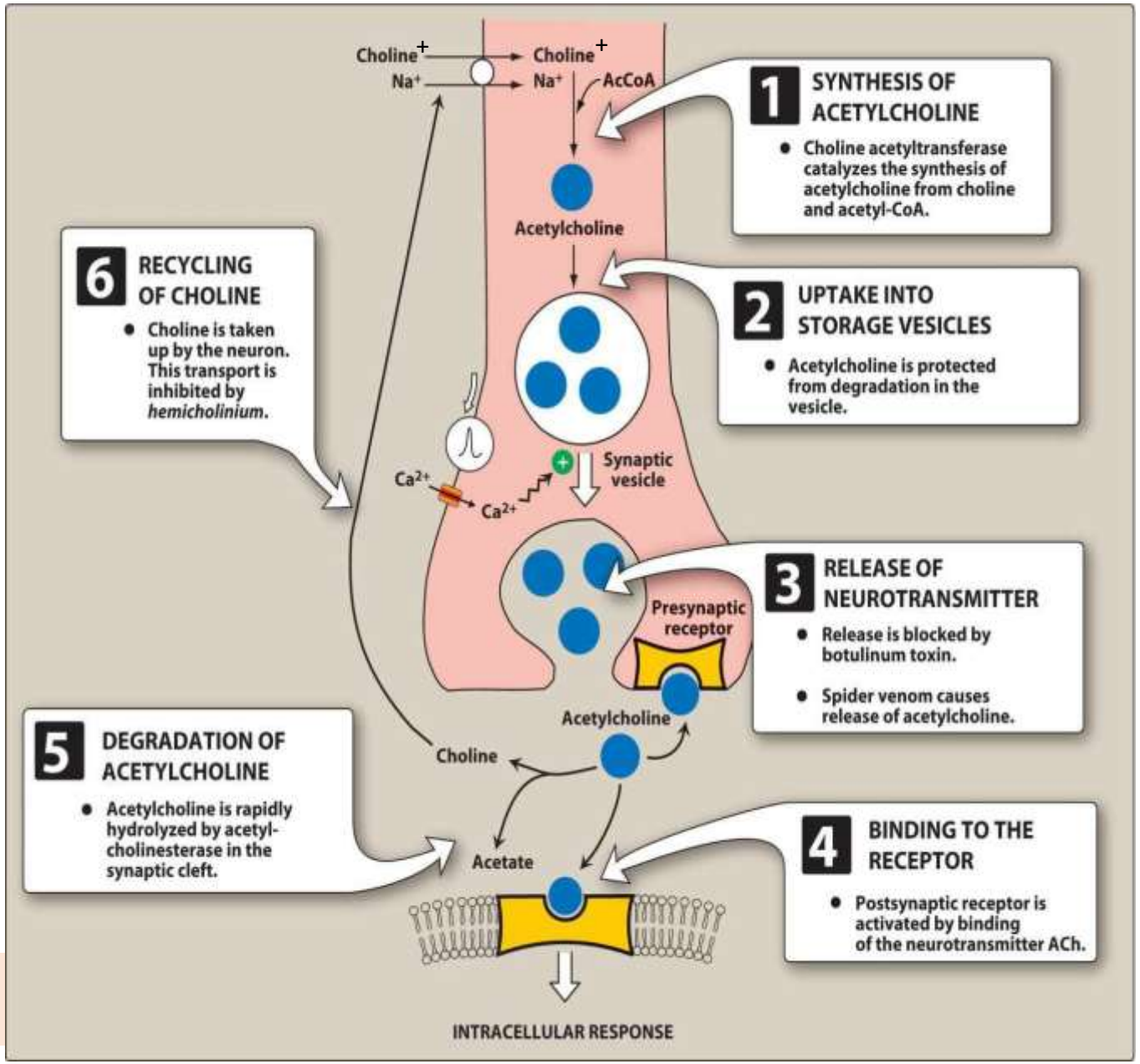
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.



A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps:

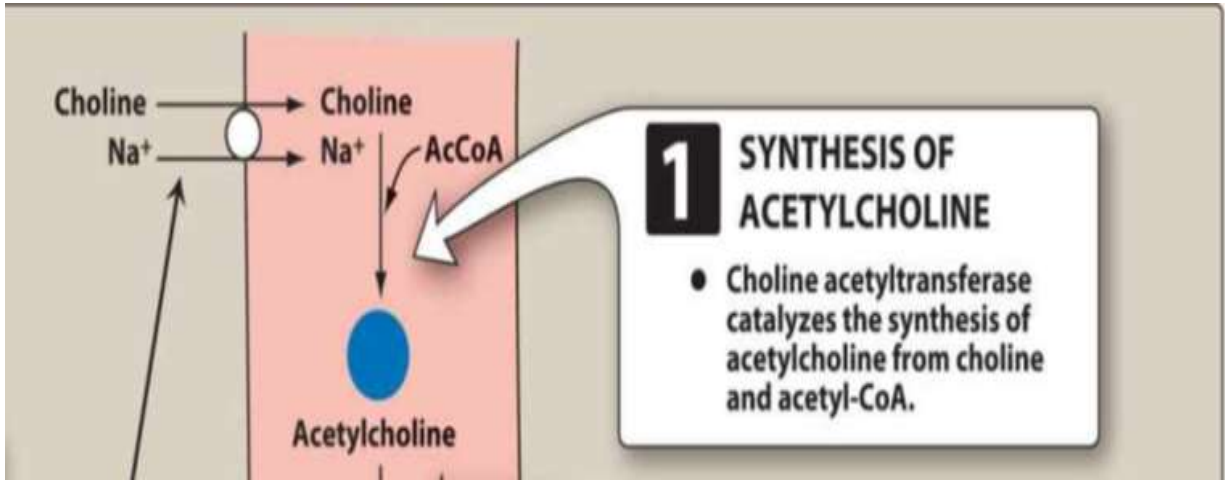
1) Synthesis
2) Storage
3) Release
4) Binding of **Ach** to a receptor
5) Degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs)
6) Recycling of choline and acetate



Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

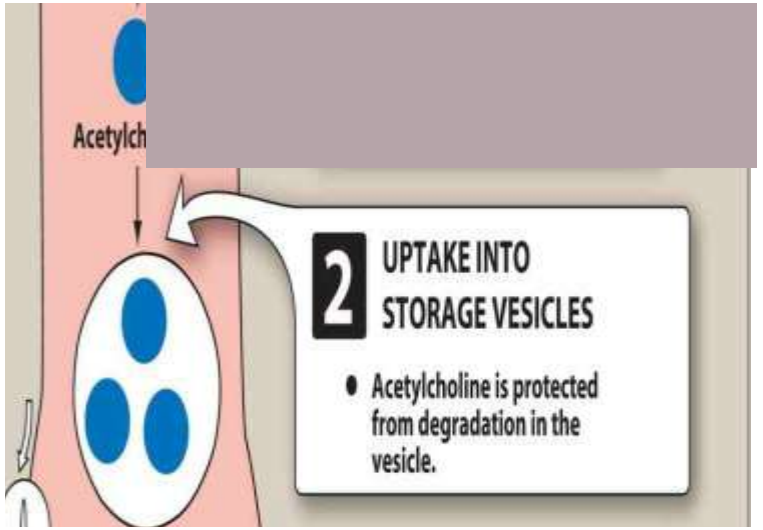
1. Synthesis of acetylcholine

- Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an **energy-dependent carrier system** that cotransports sodium and can be inhibited by the drug ***hemicholinium***.
- [Note: *Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane*.]
- The uptake of choline is the **rate limiting step** in ACh synthesis.
- **Choline acetyltransferase catalyzes** the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.



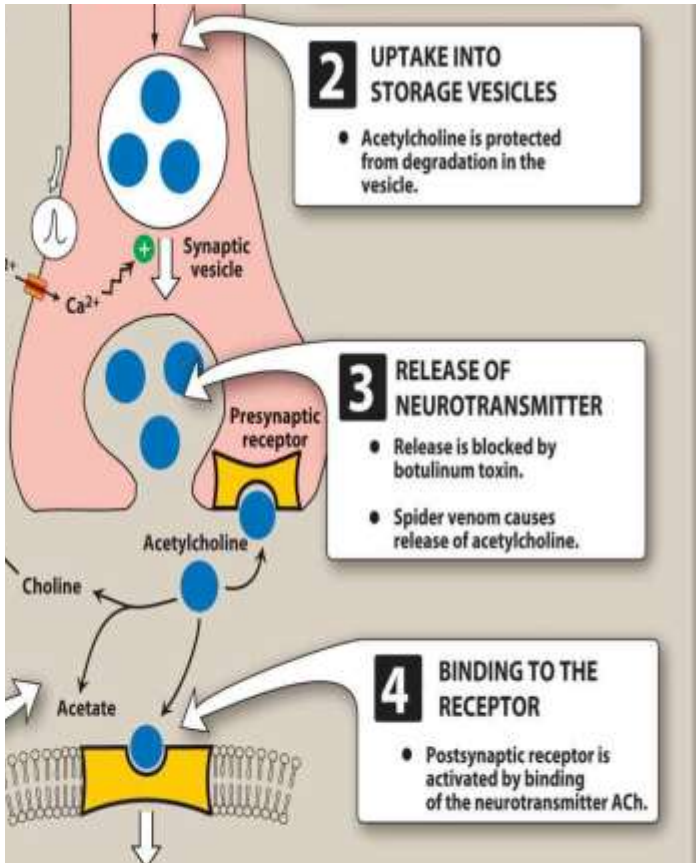
2. Storage of acetylcholine in vesicles

- ACh is packaged and stored into **presynaptic vesicles** by an **active transport process**.
- The mature vesicle contains not only ACh but also **adenosine triphosphate (ATP)** and **proteoglycan**.
- **Co-transmission** from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles contain the **primary neurotransmitter** (here, ACh) as well as a **co-transmitter** (here, ATP) that increases or decreases the effect of the primary neurotransmitter.



3. Release of acetylcholine

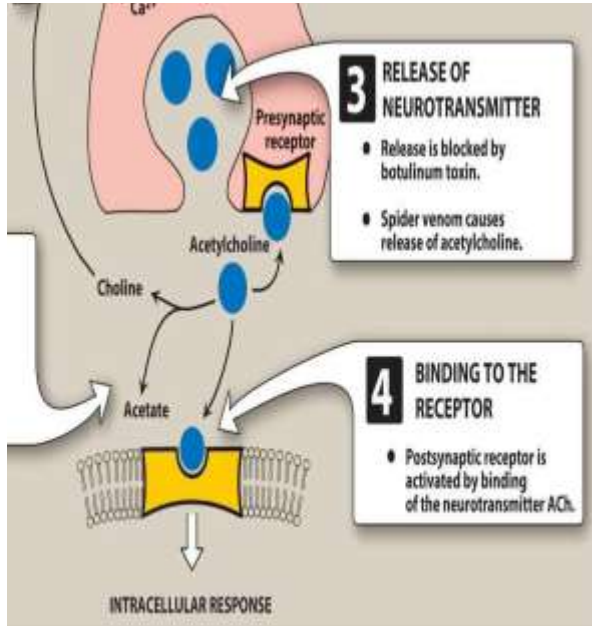
- When an action potential propagated by **voltage-sensitive sodium channels** arrives at a nerve ending, **voltage-sensitive calcium channels** on the presynaptic membrane **open**, causing an **increase** **in the concentration of intracellular calcium**.
- Elevated calcium levels **promote the fusion** of synaptic vesicles with the cell membrane and the **release of their contents into the synaptic space**.
- This release can be **blocked by botulinum toxin**. In contrast, the toxin in **black widow spider** venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.



4. Binding to the receptor

- ACh released from the synaptic vesicles diffuses across the synaptic space and binds to:

1. **Postsynaptic receptors** on the target cell, or
2. **Presynaptic receptors** on the membrane of the neuron that released the ach, or
3. To other **Targeted presynaptic receptors**.



- The postsynaptic cholinergic receptors on the surface of the effector organs are **divided into two classes**: **muscarinic and nicotinic.**
- Binding to a receptor leads to a biologic response within the cell, such as the **initiation of a nerve impulse in a postganglionic fiber** or **activation of specific enzymes** in effector cells, as mediated by second messenger molecules.

5. Degradation of acetylcholine

- The signal at the postjunctional effector site is rapidly terminated, because **Acetylcholinesterase** (AChE) cleaves ACh to choline and acetate in the synaptic cleft .

6. Recycling of choline

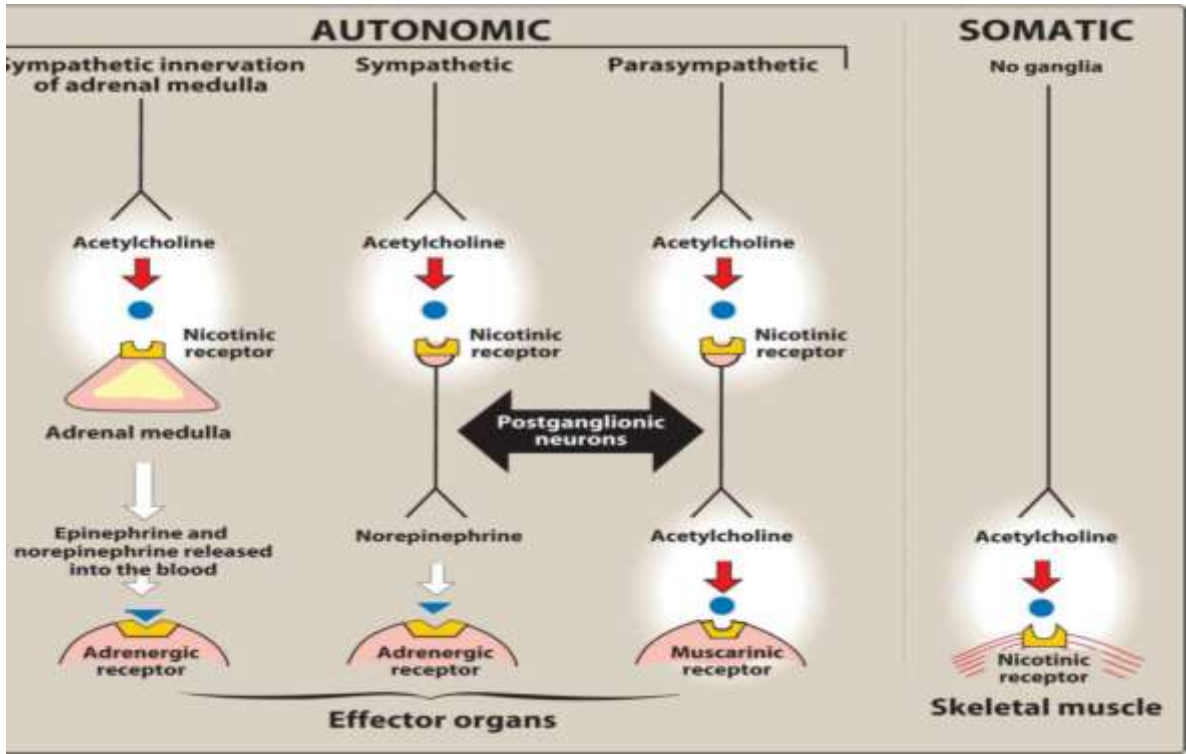
- Choline may be recaptured by **a sodium-coupled, high-affinity uptake system** that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

Cholinergic Receptors (Cholinoceptors)

- Two families of cholinoceptors, designated

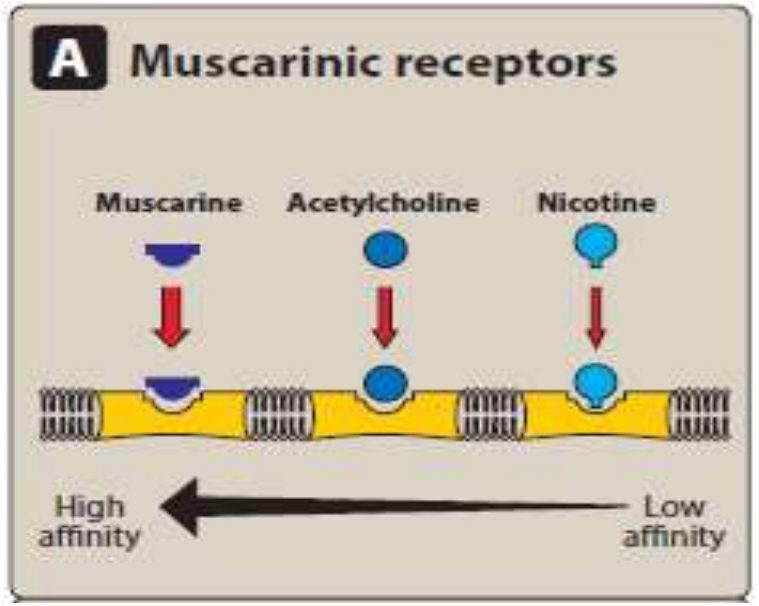
1. **Muscarinic receptors**
2. **Nicotinic receptors**

- They can be **distinguished** from each other **on the basis** of their different **affinities** for **agents** that mimic the action of ACh (**cholinomimetic agents**).



A. Muscarinic receptors

- **Muscarinic receptors** belong to the class of **G protein–coupled receptors (metabotropic receptors)**.
- These receptors, in addition to **binding to ACh**, also recognize **muscarine**, an alkaloid that is present in certain poisonous mushrooms.
- In contrast, the **muscarinic receptors** show only a **weak** affinity for **nicotine**.
- There are **five subclasses** of muscarinic receptors. However, only **M1, M2, and M3 receptors** have been functionally characterized.



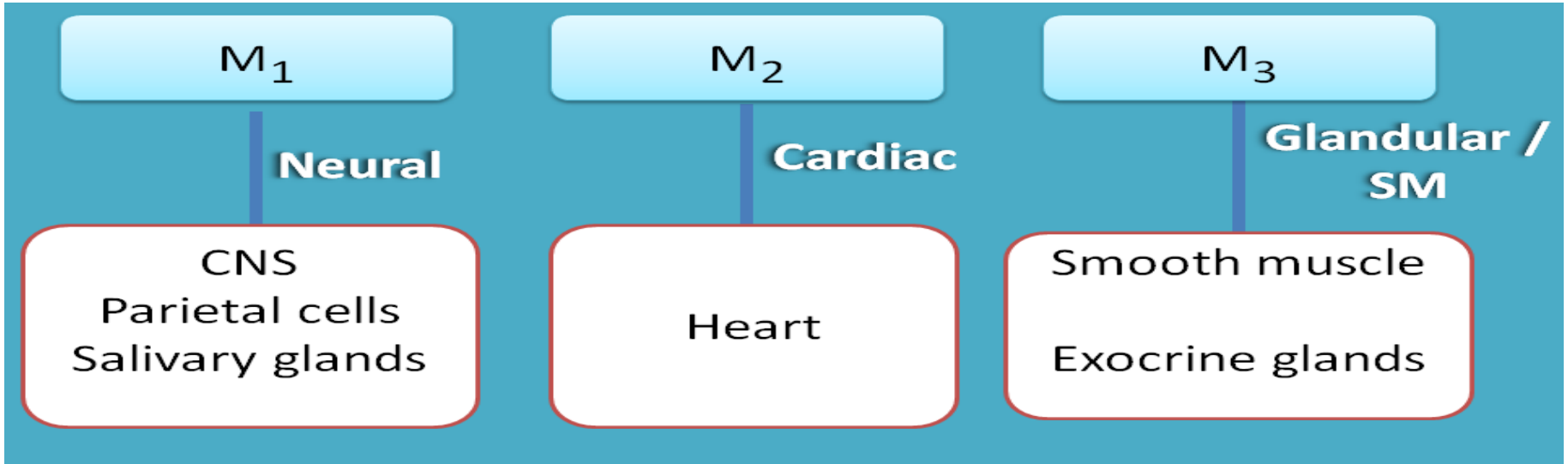
1. Locations of muscarinic receptors

- These receptors are found on the **autonomic effector organs**, such as the heart, smooth muscle, brain, and exocrine glands.
- Although all five subtypes are found on neurons,

✓ **M1 receptors** are also found on **gastric parietal cells**

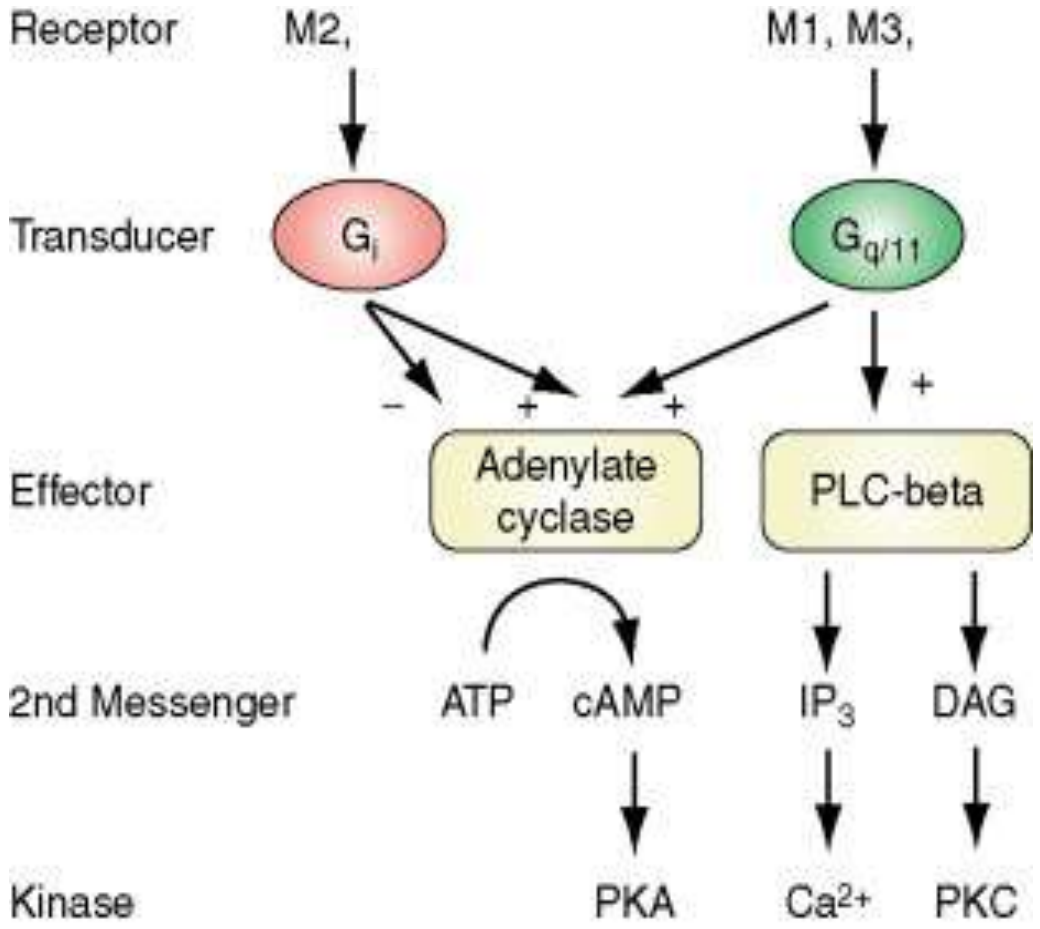
✓ **M2 receptors** on **cardiac cells** and **smooth muscle**

✓ **M3 receptors** on the **bladder**, **exocrine glands**, and **smooth muscle**.



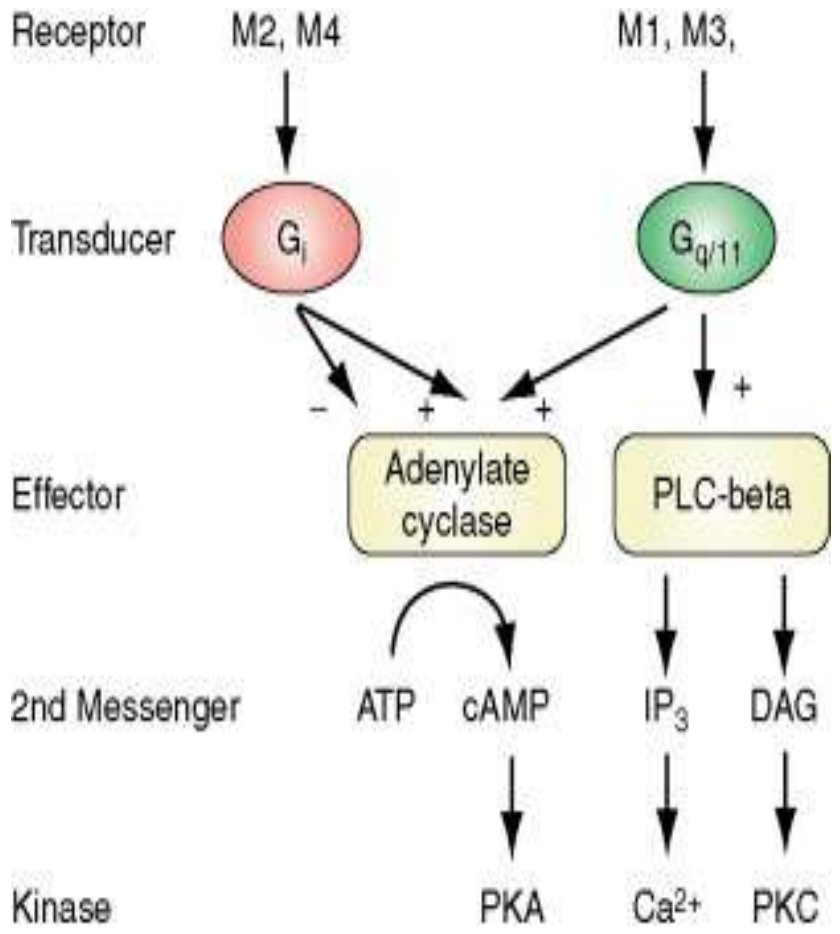
2-Mechanisms of acetylcholine signal transduction

- A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor.
- For example, **when M1 or M3 receptors are activated**, the receptor undergoes a conformational change and interacts with a **G protein**, **designated Gq**, that in turn **activates phospholipase C**.
- This ultimately leads to the production of the **second messenger inositol-1,4,5-trisphosphate** (IP3) and **diacylglycerol** (DAG).



2-Mechanisms of acetylcholine signal transduction

- **IP3** causes an **increase** in **intracellular Ca2+.** Calcium can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction.
- **Diacylglycerol** activates **protein kinase C**, an enzyme that phosphorylates numerous proteins within the cell.
- **In contrast**, activation of the **M2 subtype** on the **cardiac** muscle **stimulates a G protein**, designated **Gi**, that **inhibits adenylyl cyclase** and **increases K+ conductance**. The **heart responds** with a **decrease in rate and force of contraction**.

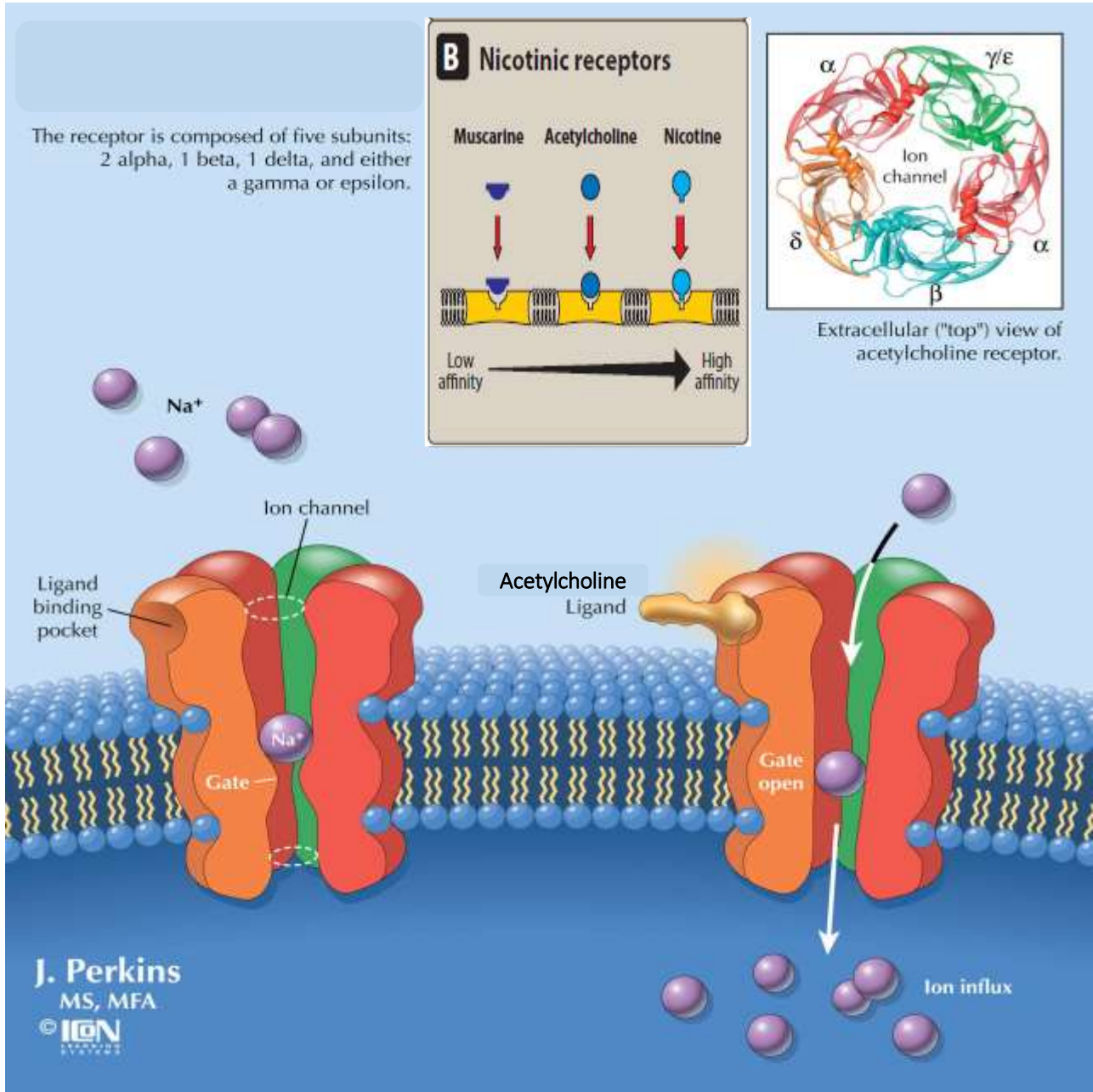


3. Muscarinic agonists

- **Pilocarpine** is an example of a **nonselective muscarinic agonist.** **Used in clinical practice** to treat **xerostomia and glaucoma**.
- Attempts are currently underway to **develop** muscarinic agonists and antagonists that are directed against **specific receptor subtypes.**
- **M1 receptor agonists** are being investigated for the treatment of **Alzheimer's disease** and
- **M3 receptor antagonists** **(tiotropium)** for the treatment of **chronic obstructive pulmonary disease**.

B. Nicotinic receptors

- These receptors, in addition to binding ACh, also recognize **nicotine** but **show only a weak affinity for muscarine**.
- The nicotinic receptor is **composed of five subunits**, and it functions as a **ligand-gated ion channel**.
- Binding of two ACh molecules produces a **conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell**.



B. Nicotinic receptors

- **Nicotine at low concentration stimulates the receptor**, whereas **nicotine at high concentration blocks the receptor**.

- **Nicotinic receptors** are **located** in the:

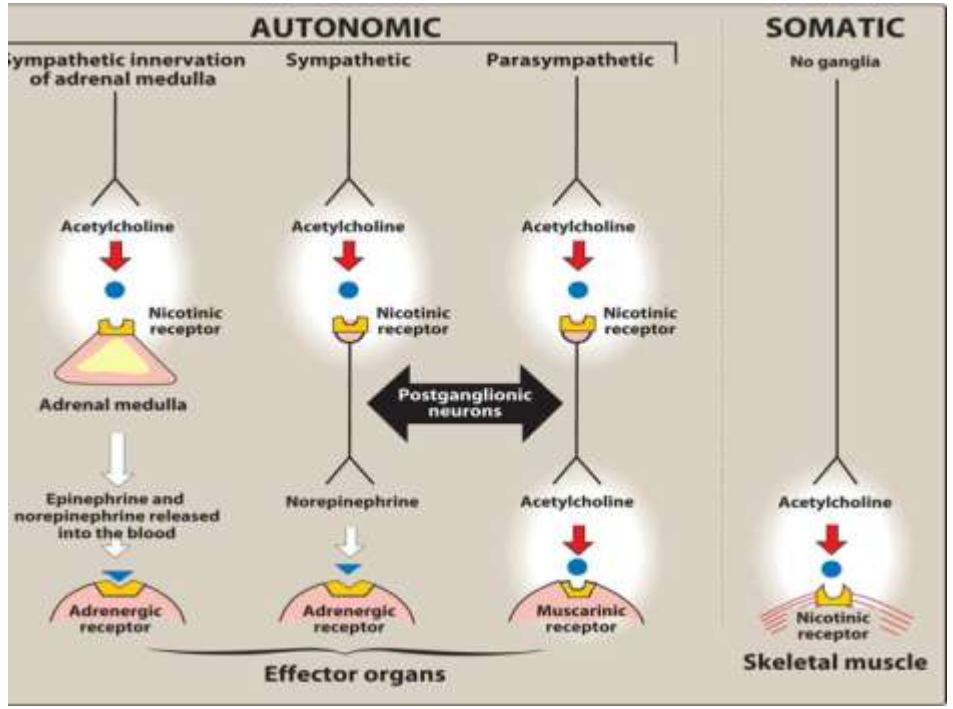
  1) CNS,

  2) The adrenal medulla,

  3) Autonomic ganglia,

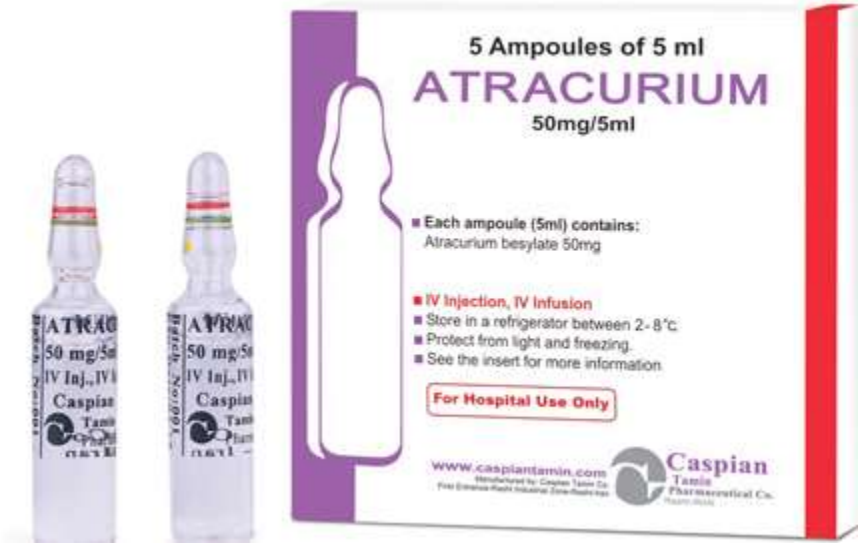
  4) The neuromuscular junction (NMJ) in skeletal muscles.

- Those at the NMJ are sometimes designated NM, and the others, NN.

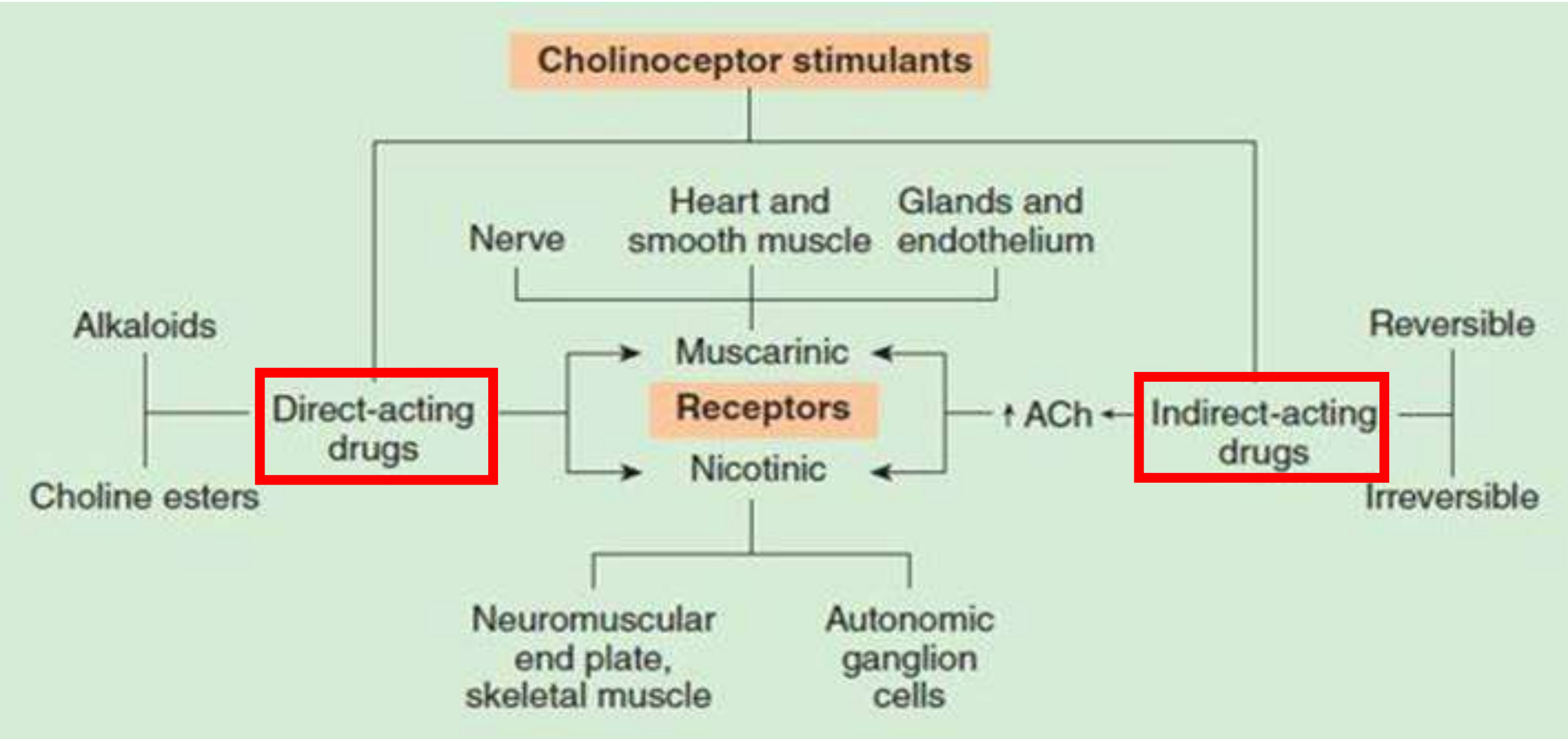


B. Nicotinic receptors

- The nicotinic receptors of **autonomic ganglia** differ from those of the **NMJ**.
- For example, **ganglionic receptors** are selectively **blocked** by **mecamylamine**, whereas **NMJ receptors** are specifically **blocked** by **atracurium**.



Cholinergic agents



Cholinergic Agonists

DIRECT ACTING

Acetylcholine MIOCHOL-E
Bethanechol URECHOLINE
Carbachol MIOSTAT, ISOPTO CARBACHOL
Cevimeline EVOXAC
Methacholine PROVOCHOLINE
Nicotine NICORETTE
Pilocarpine SALAGEN, ISOPTO CARPINE

INDIRECT ACTING (reversible)

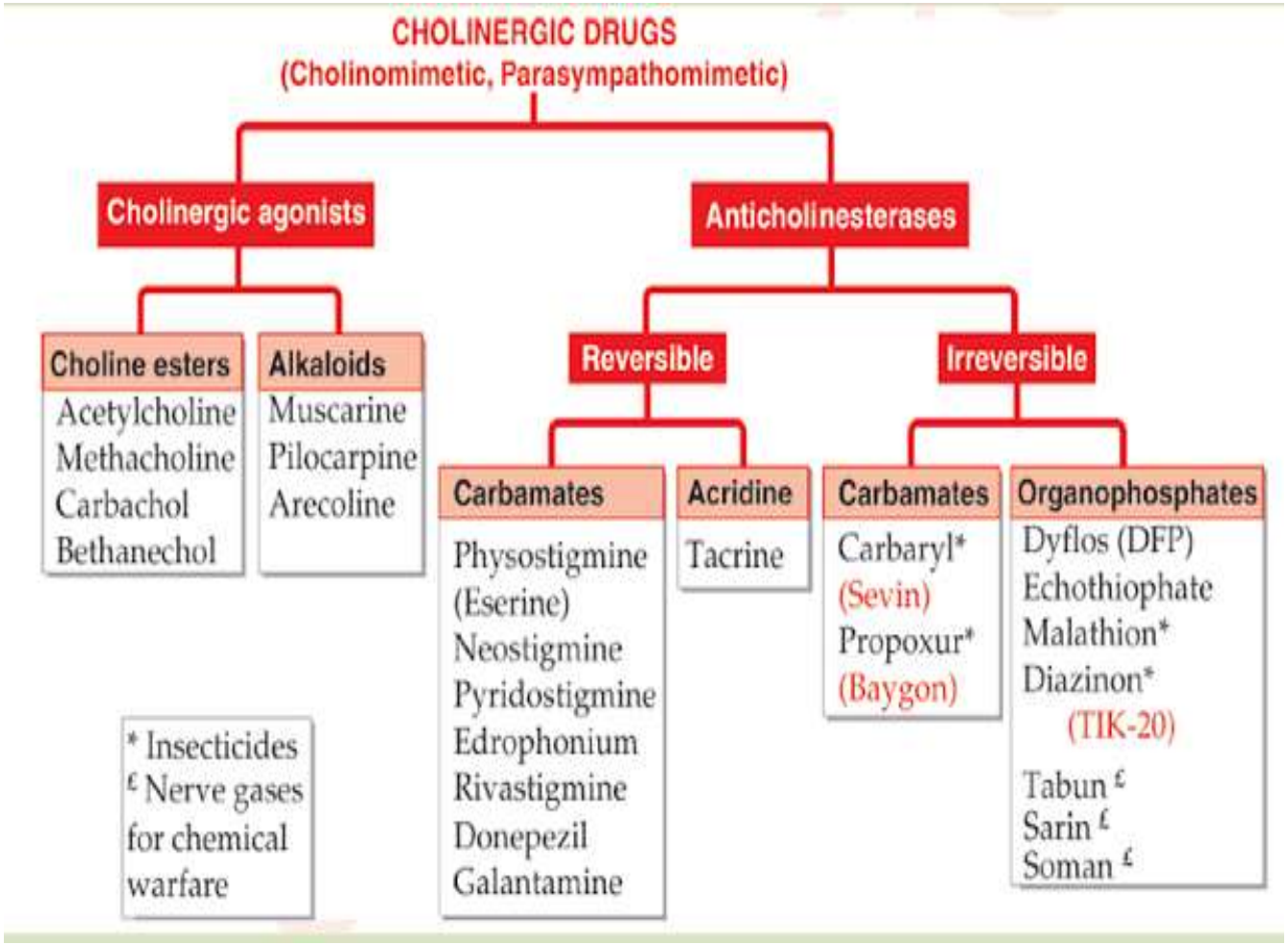
Donepezil ARICEPT
Edrophonium ENLON
Galantamine RAZADYNE
Neostigmine BLOXIVERZ
Physostigmine GENERIC ONLY
Pyridostigmine MESTINON
Rivastigmine EXELON

INDIRECT ACTING (irreversible)

Echothiophate PHOSPHOLINE IODIDE

REACTIVATION OF ACETYLCHOLINESTERASE

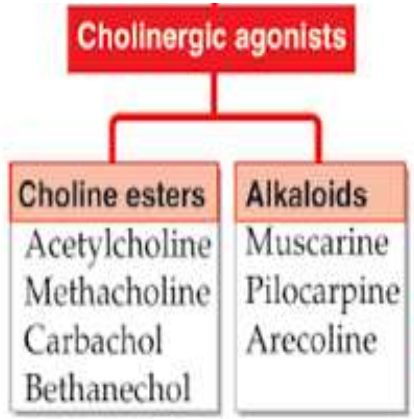
Pralidoxime PROTOPAM

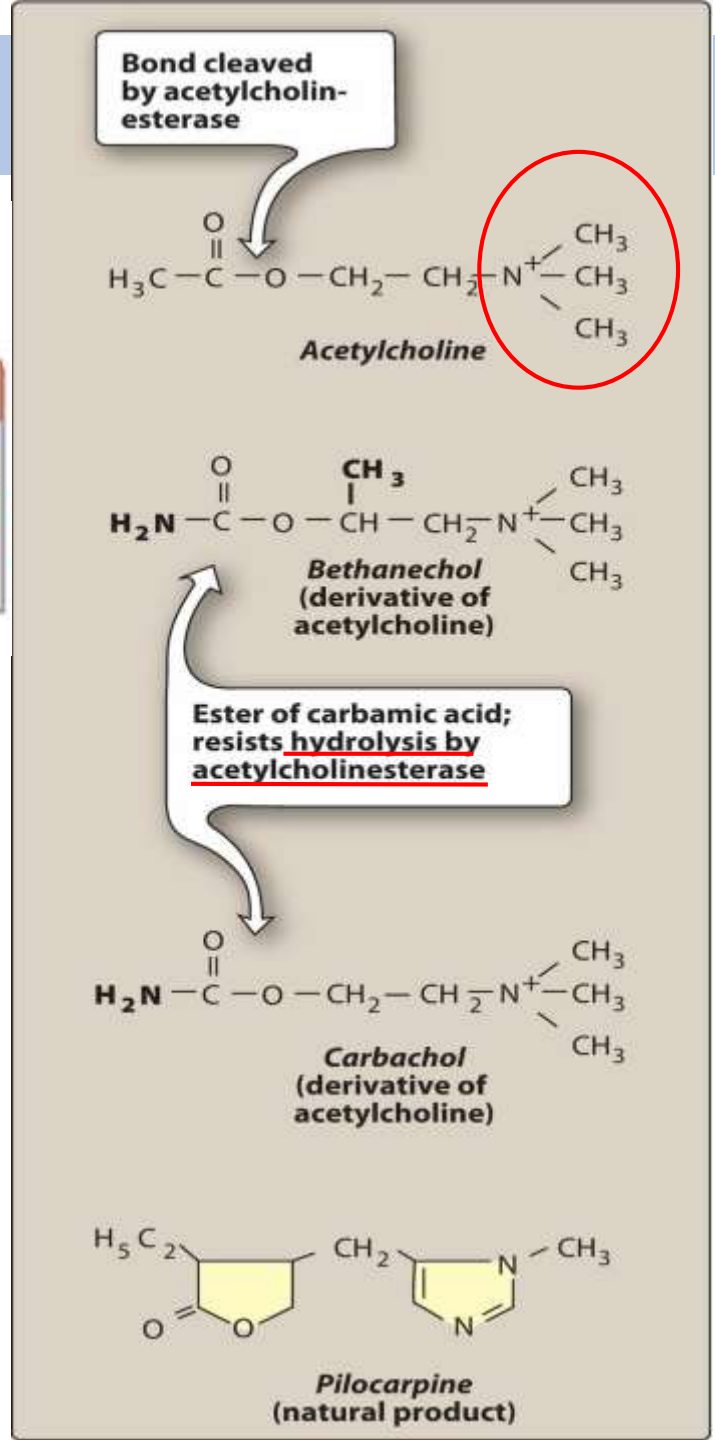


Direct-acting Cholinergic Agonists

- **Cholinergic agonists** mimic the effects of ACh by binding **directly** to **Cholinoceptors** (muscarinic or nicotinic). These agents may be broadly classified into two groups:

1. **Endogenous choline esters**, which include **Ach** and **synthetic esters of choline**, such as **carbachol** and **bethanechol**, and
2. **Naturally occurring alkaloids**, such as **nicotine** and **pilocarpine** .





Direct-acting Cholinergic Agonists

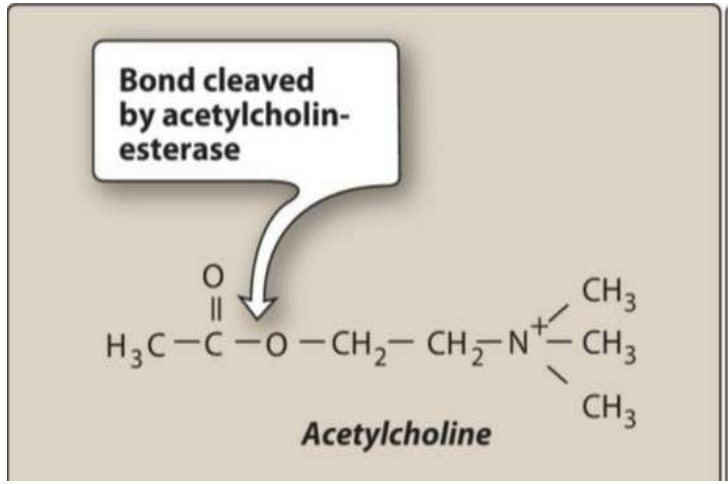
- **All** of the direct-acting cholinergic drugs have a **longer duration of action** than **ACh**.
- The **more therapeutically useful** drugs (pilocarpine and bethanechol) preferentially bind to **muscarinic receptors** and are sometimes referred to as **muscarinic agents**.
- However, as a group, ***the direct-acting agonists show little specificity in their actions***, **which limits their clinical usefulness**.

A. Acetylcholine

- **Acetylcholine** is a **quaternary ammonium** compound that cannot penetrate membranes.
- Although it is the neurotransmitter of **parasympathetic** and somatic nerves as well as autonomic ganglia,
- ***It lacks therapeutic importance*** **because** *of:*

1. *Its multiplicity of actions (leading to diffuse effects) and*
2. *Its rapid inactivation by the cholinesterases.*

- ACh has both **muscarinic** and **nicotinic** activity.



A. Acetylcholine

- Its actions include the following:

1. **Decrease** in heart rate and cardiac output
2. **Decrease** in blood pressure
3. Other actions on GIT, GUT, Respiratory and Eye

1. Decrease in heart rate and cardiac output

- **The actions of Ach on the heart mimic *the effects of vagal stimulation*.**
- **For example**, if injected intravenously, *ACh produces a brief **decrease** in cardiac rate* (negative chronotropy) and *stroke volume* as a result of a *reduction* in the *rate of firing at the sinoatrial (SA) node*.
- [**Note**: Normal vagal activity regulates the heart by the release of ACh at the **SA node**.]

1897 TW Engelmann described:

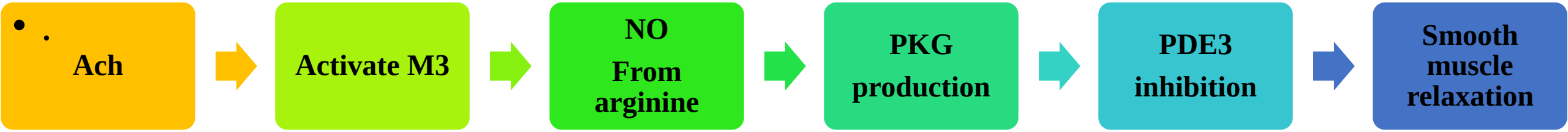
- **Inotropy:** Contractility
- **Chronotropy:** Rate (SA node)
- **Dromotropy:** Conduction (AV node)
- **Bathmotropy:** Excitability

1982 described:

- **Lusitropy:** Relaxation (active)

2. Decrease in blood pressure

- Injection of ACh causes **vasodilation and lowering of blood pressure** by an indirect mechanism of action. **ACh activates M3 receptors** found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of **nitric oxide from arginine**.
- **Nitric oxide** then diffuses to vascular smooth muscle cells to stimulate **protein kinase G production**, leading to **hyperpolarization and smooth muscle relaxation** via **phosphodiesterase-3 inhibition**.



2. Decrease in blood pressure

- In the **absence** of administered cholinergic agents, the vascular **cholinergic receptors** have no known function, ***because ACh is never released into the blood in significant quantities***.
- **Atropine** blocks these **muscarinic receptors** and prevents ACh from producing **vasodilation**.

Atropine may act as **antidote** direct antidote physiologically by antagonizing the muscarinic receptor's actions

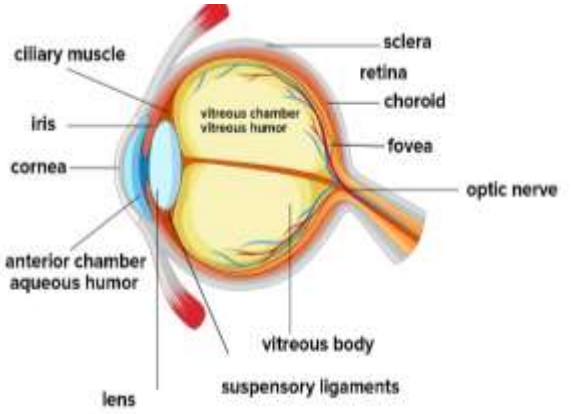
3. Other actions

- **In the gastrointestinal {GI) tract**, acetylcholine **increases salivary secretion**, **increases gastric acid secretion**, and **stimulates intestinal secretions and motility**.
- **Respiratory tract : It also enhances bronchiolar secretions** and **causes bronchoconstriction.**
- [Note: **Methacholine**, a direct-acting cholinergic agonist, is used to assist in the **diagnosis** of asthma due to its **bronchoconstricting** properties.]

A non-selective muscarinic receptor agonist

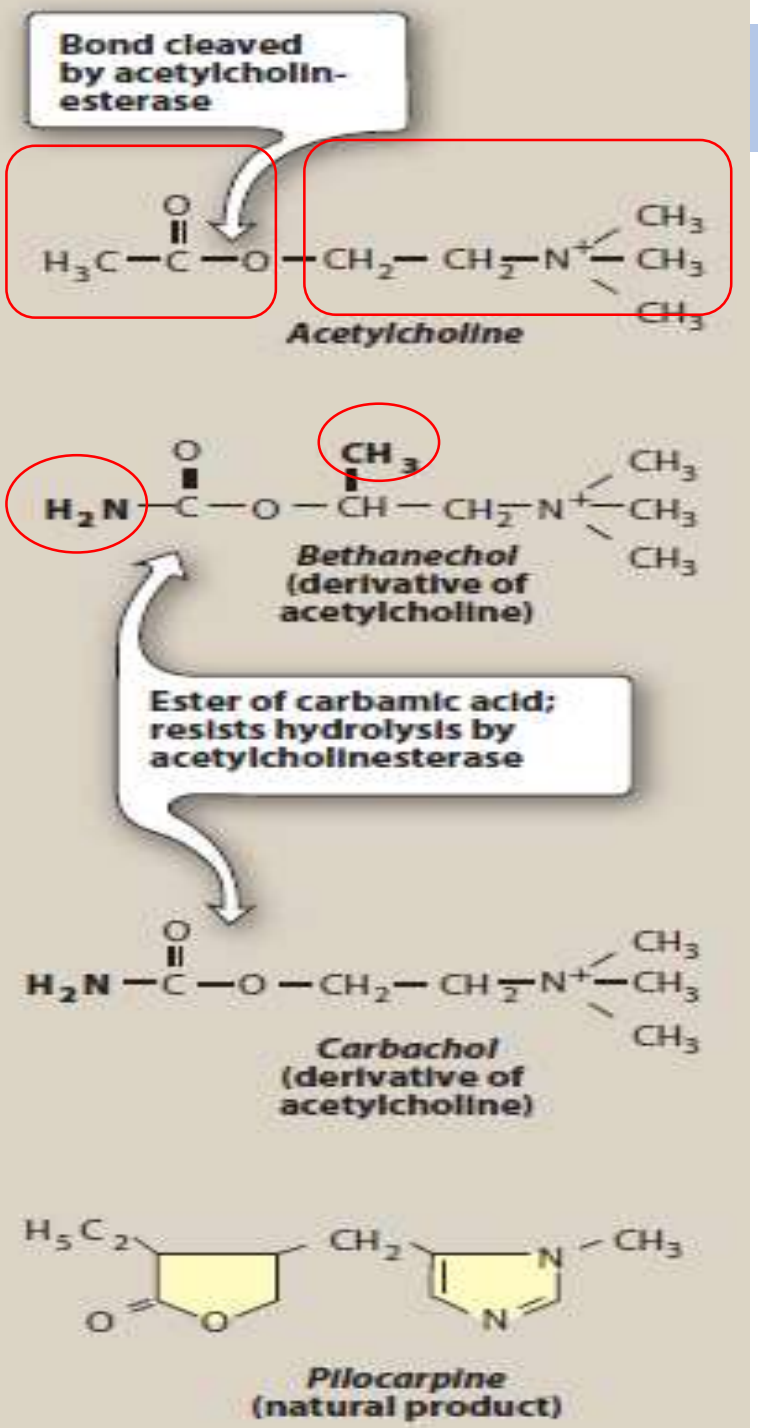
3. Other actions

- **In the genitourinary tract**, Ach increases the tone of the detrusor muscle, causing **urination**.
- **In the eye**, ACh is involved in **stimulation** of **ciliary muscle contraction** for near vision and in the **constriction** of the pupillae sphincter muscle, causing **miosis** (marked constriction of the pupil).
- ACh {1% solution) is instilled into the anterior chamber of the eye to produce **miosis during ophthalmic surgery**.



B. Bethanechol (M1,M3)

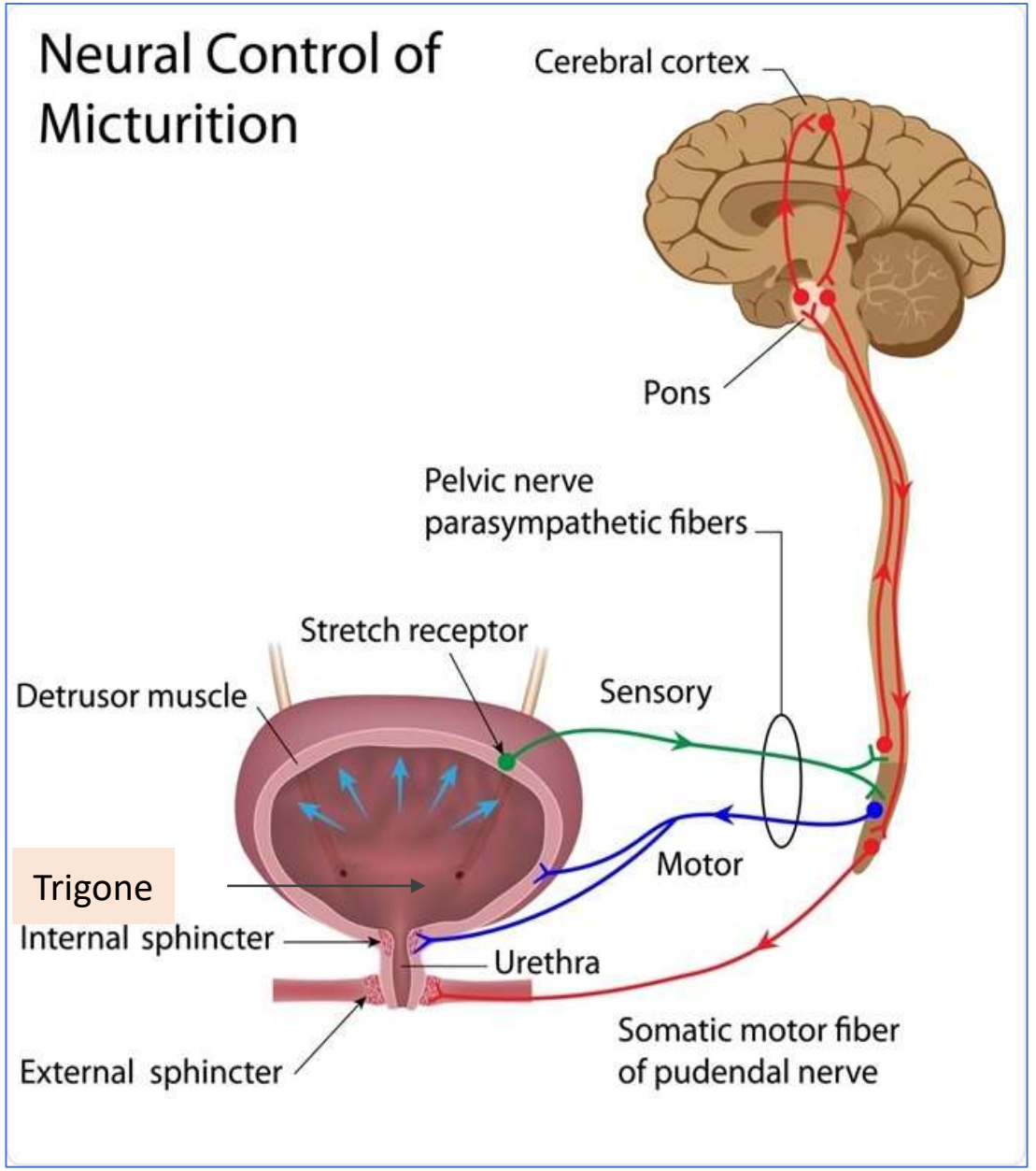
- **Bethanechol** is an unsubstituted carbamoyl ester, structurally related to ACh .
- It is **not hydrolyzed by Ach Estrase** due to the esterification of carbamic acid, although it is inactivated through hydrolysis by other **esterases**.
- It ***lacks*** ***nicotinic*** *actions* (due to the addition of the methyl group) but does have **strong muscarinic activity**.
- Its major actions are on the **smooth musculature** of the **bladder (M3) and GI tract (M1)**.
- It has about a **1-hour duration of action**.



B. Bethanechol

Actions: *Bethanechol* **directly stimulates muscarinic receptors**, causing:

1. ***Increased*** *intestinal motility* and *tone*.
2. ***Stimulates*** *the* ***detrusor muscle*** of the **bladder**, whereas the ***trigone*** *and sphincter muscles are* ***relaxed.*** These effects produce **urination**.



B. Bethanechol

- **Therapeutic applications**: In urologic treatment, bethanechol is used to stimulate the **Atonic bladder**, particularly in **postpartum** or **postoperative**, **non-obstructive urinary retention**.

Bethanechol

- **Used in treatment of urinary retention**
- **Binds preferentially at muscarinic receptors**

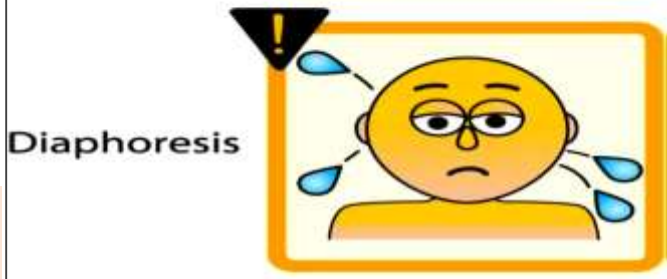
Atonic bladder refers to a condition where the detrusor muscle in the bladder loses its ability to contract, making emptying the bladder difficult.

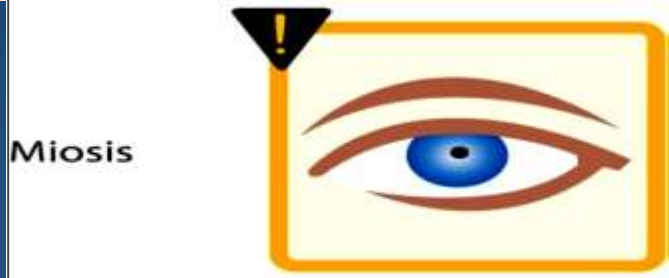
B. Bethanechol

3.Adverse effects: *Bethanechol* causes the effects of generalized cholinergic stimulation. These include:

1. Sweating, (diaphoresis)
2. Salivation,
3. Flushing,
4. Decreased blood pressure,
5. Nausea, abdominal pain, diarrhea,
6. Bronchospasm
7. Miosis
8. Urinary urgency

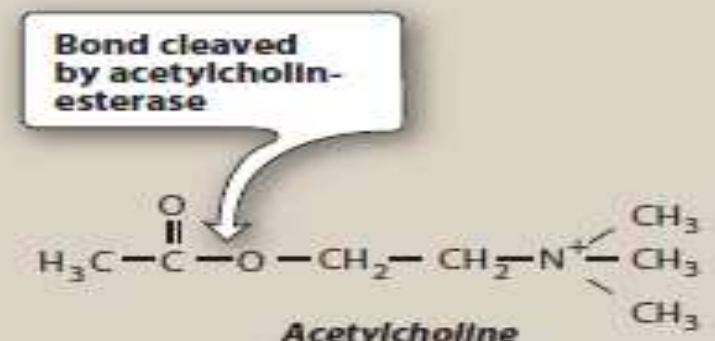
- ***Antidote is Atropine sulfate*** may be administered to overcome severe **cardiovascular** or **bronchoconstrictor** responses to this agent.

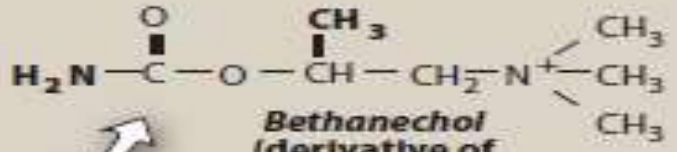


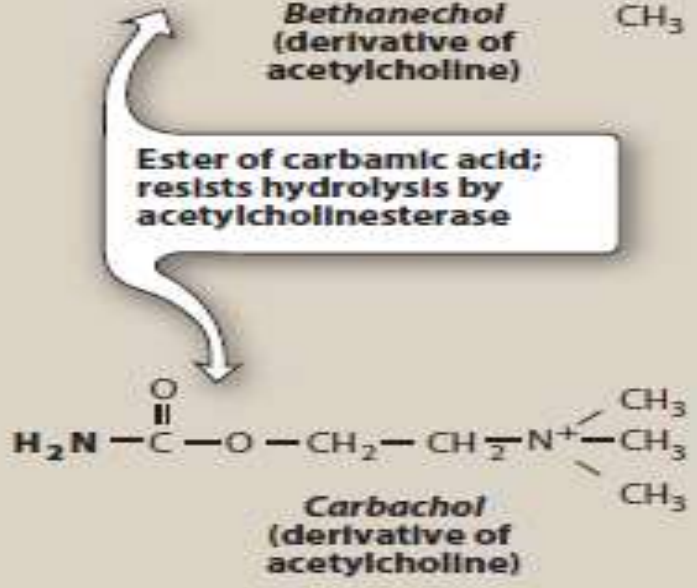


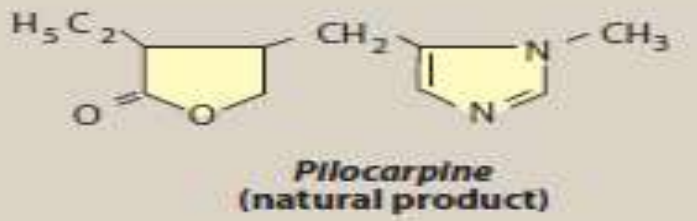
C. Carbachol (carbamylcholine)(M,N)

- **Carbachol** has **both muscarinic and nicotinic actions**.
- Like bethanechol, carbachol is an ester of carbamic acid and **a poor substrate for AChE**.
- It is biotransformed by other **esterases**, but at a much **slower rate**.









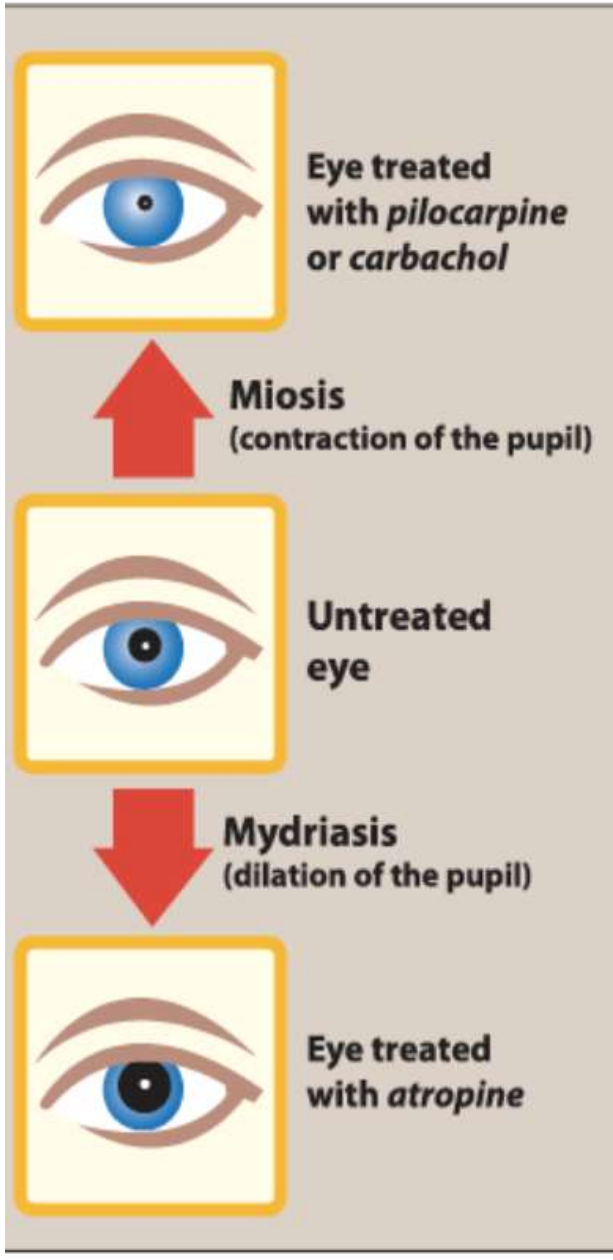
Carbachol

- Binds to both muscarinic and nicotinic receptors
- Produces miosis during ocular surgery
- Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*

C. Carbachol Eye Drop (carbamylcholine)

1.Actions: Carbachol has profound effects on both the **cardiovascular and GI systems** because of its ganglion-stimulating activity, and *it may first stimulate and then depress these systems*.

- It can cause release of epinephrine from the **adrenal medulla** by its nicotinic action.
- Locally instilled **into the eye**, it mimics the effects of ACh, *causing miosis and a spasm of accommodation* in which the ciliary muscle of the eye remains in a **constant state of contraction**. *The vision becomes fixed at some particular distance, making it impossible to focus*.



C. Carbachol (carbamylcholine)

2. Therapeutic uses: Because of its high **potency**, **receptor non-selectivity**, and relatively **long duration of action**, carbachol is **rarely used therapeutically except** in the **eye** as a **miotic agent** to **treat glaucoma** **by causing pupillary contraction and a decrease in intraocular pressure**.

3. Adverse effects: At doses used ophthalmologically, **little or no side effects** occur due to lack of systemic penetration (quaternary amine).

D. Pilocarpine

- The alkaloid pilocarpine is a **tertiary amine** and is stable to hydrolysis by AChE.
- Compared with ACh and its derivatives, it is far ***less potent*** but is **uncharged** and **can penetrate the CNS** at therapeutic doses.
- Pilocarpine exhibits **muscarinic activity** and is used primarily in **ophthalmology**.

D. Pilocarpine

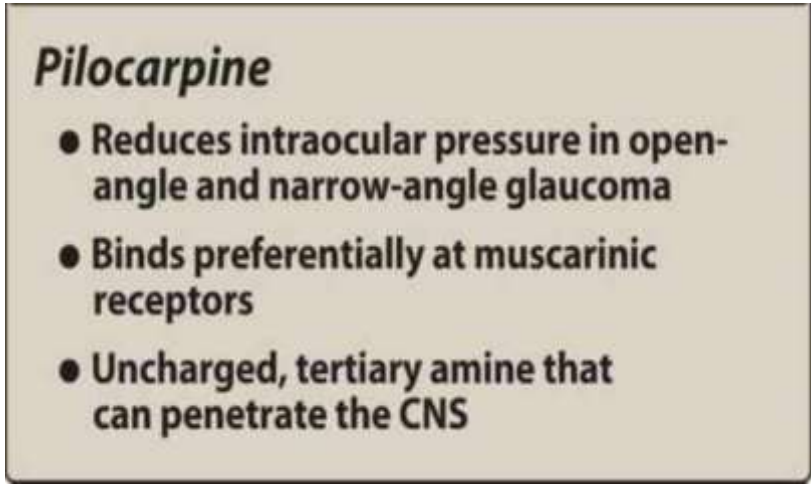
1. **Actions:** Applied topically **to the eye**, pilocarpine produces **rapid miosis**, **contraction of the ciliary muscle**, and **spasm of accommodation**.
2. Pilocarpine is one of the most **potent stimulators of secretions** such as sweat, tears, and saliva, but its use for producing these effects has been limited due ***to its lack of selectivity***.

D. Pilocarpine

2. **Therapeutic use in glaucoma:**

1. Pilocarpine is used to **treat glaucoma** and is the **drug of choice** for **emergency** **lowering of intraocular pressure** of both open-angle and angle-closure glaucoma.

- Pilocarpine is extremely effective in **opening** the **trabecular meshwork** around the **Schlemm canal**, causing an **immediate drop in intraocular pressure** because of the **increased drainage of aqueous humor**.
- This action occurs within **a few minutes**, **lasts 4 to 8 hours**, and can be repeated.



D. Pilocarpine

- **Therapeutic use in glaucoma:**
- [Note: **Topical carbonic anhydrase inhibitors**, such as dorzolamide and **B-adrenergic blockers** such as timolol, are effective in treating glaucoma but are not **used for emergency lowering of intraocular pressure**.]

2. The miotic action of pilocarpine is also useful in reversing **mydriasis** due to **atropine**.
3. The drug is beneficial in (1) **promoting salivation in patients with xerostomia** resulting from irradiation of the head and neck. (2) **Sjogren syndrome**, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and **Cevimeline**, a cholinergic drug that also has the drawback of being nonspecific.

D. Pilocarpine

3. Adverse effects: Pilocarpine can cause

1. Blurred vision,
2. Night blindness, and
3. Brow ache.
4. **Poisoning** with this agent is characterized by **exaggeration of various parasympathetic effects**, including profuse sweating (diaphoresis) and salivation.

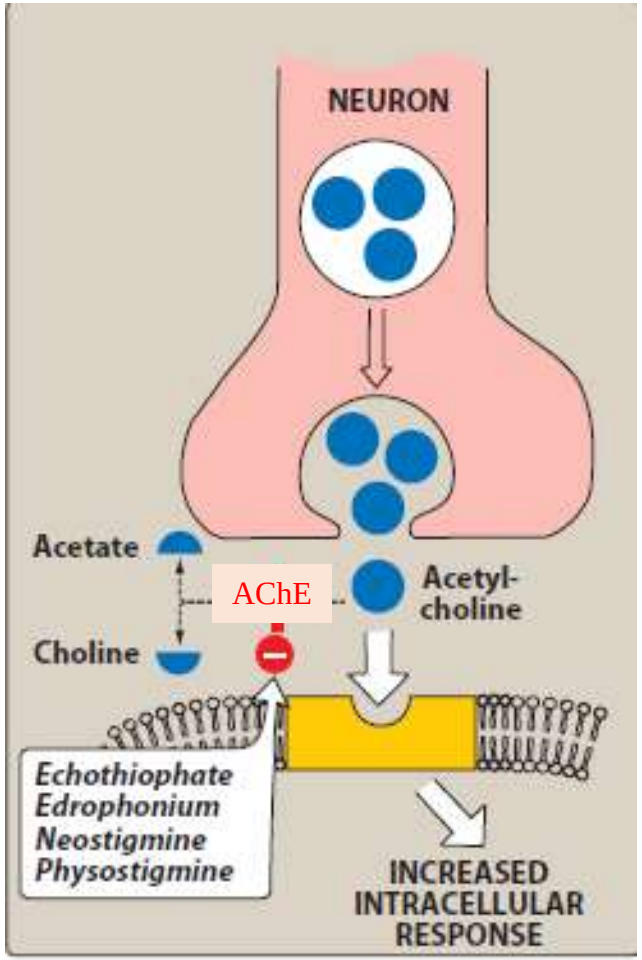
- The effects are similar to those produced by consumption of mushrooms of the genus lnocybe, which contain muscarine.
- **Parenteral atropine**, at doses that can cross the blood-brain barrier, is administered to counteract the **toxicity of pilocarpine**.

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)

INDIRECT ACTING (reversible)
Donepezil ARICEPT
Edrophonium ENLON
Galantamine RAZADYNE
Neostigmine BLOXIVERZ
Physostigmine GENERIC ONLY
Pyridostigmine MESTINON
Rivastigmine EXELON

Anticholinesterase Agents (Reversible)

- **Acetylcholine esterase AChE** is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions.
- It is **located both pre- and postsynaptically** in the nerve terminal where it is membrane bound.
- Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) **indirectly** provide a **cholinergic action** by preventing the degradation of ACh. This results in an **accumulation** of ACh in the synaptic space.
- Therefore, these drugs can provoke a response at **all cholinoceptors in the body**, including both **muscarinic** and **nicotinic** receptors of the ANS, as well as at the NMJ and in the brain.



Anticholinesterase Agents (Reversible)

- **The reversible AChE inhibitors can be broadly classified as**

1. **Short acting agents**
2. **Intermediate acting Agents.**

A. Edrophonium

- ***Edrophonium*** is the ***prototype*** **short-acting** ***reversible*** AChE inhibitor.
- ***Edrophonium*** binds reversibly to the active center of AChE, preventing hydrolysis of ACh.
- It is ***rapidly absorbed and has a short duration of action*** of **10 to 20 minutes** due to rapid renal elimination.
- *Edrophonium* is a ***quaternary amine***, and its actions are **limited to the periphery**. (**doesn't enter the CNS**)

A. Edrophonium

- **Uses**

1. It is used in the **diagnosis of myasthenia gravis**, *an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes their degradation, making fewer receptors available for interaction with Ach.*

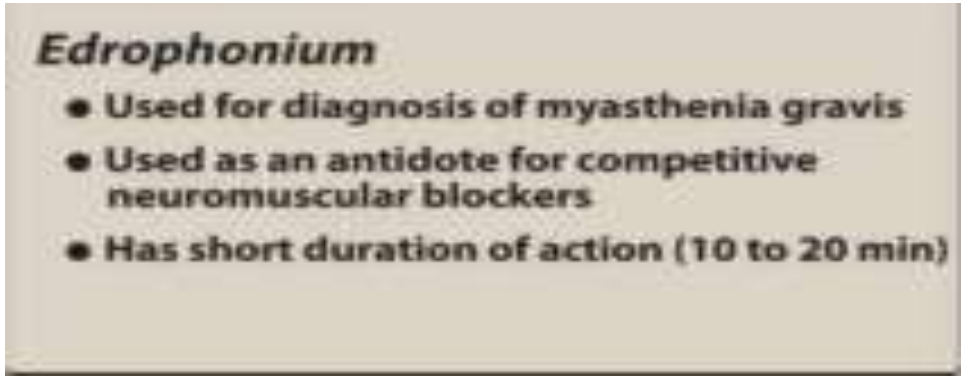
- Intravenous injection of **edrophonium** leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (**atropine is the antidote**).

2. Edrophonium may also be **used to assess cholinesterase inhibitor therapy**, for differentiating **cholinergic and myasthenic crises**, and

3. It is used in **reversing** the effects of **nondepolarizing neuromuscular blockers** (NMBs) after surgery.

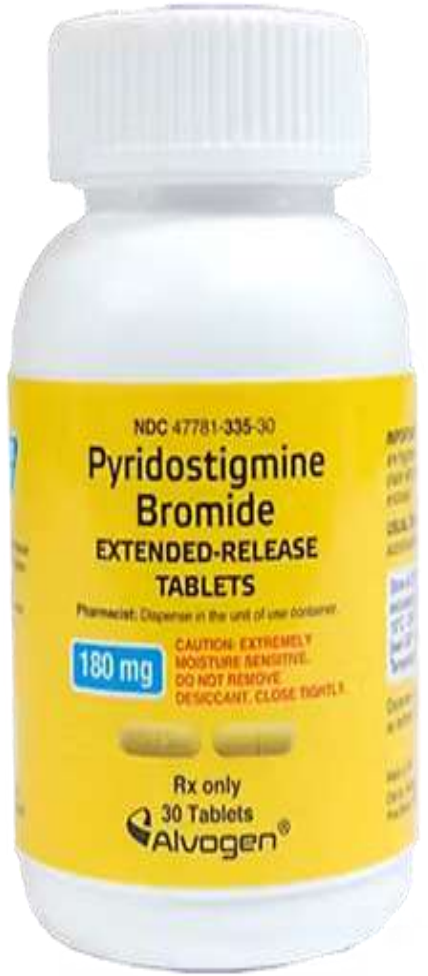
- Due to the availability of other agents,

Edrophonium use has become limited.



B. Physostigmine (3º amine)

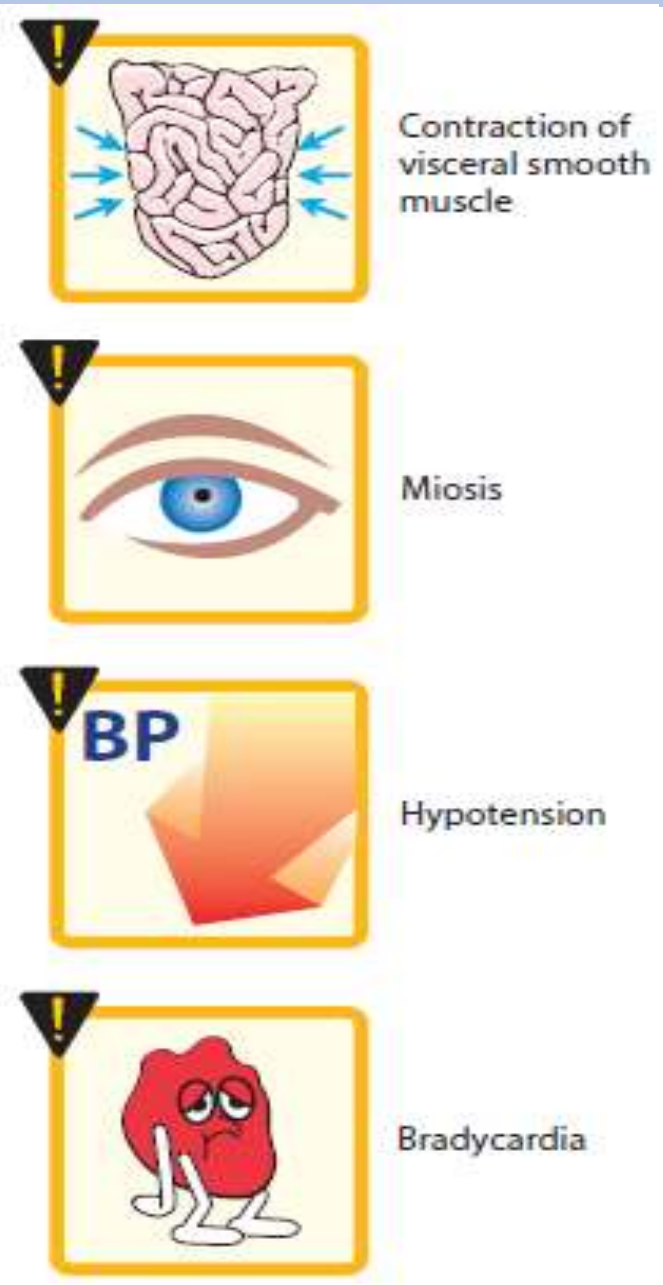
- Physostigmine is a nitrogenous **carbamic acid ester** found naturally in plants and is a **tertiary amine**.
- It is a **substrate** for AChE, and it forms a relatively stable **carbamoylated intermediate** with the enzyme, which then becomes **reversibly inactivated**.
- The result is **potentiation** of cholinergic activity throughout the body.



B. Physostigmine

1. **Actions**: **Physostigmine** has a wide range of effects and **stimulates** not only the **muscarinic** and **nicotinic** sites of the **ANS**, but also the **nicotinic** receptors of the **NMJ. (and CNS)**
2. **Muscarinic stimulation** can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension.
3. **Nicotinic stimulation** can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses).

- ***Its duration*** of action is about ***30 min to 2 hrs***, and it is considered an **intermediate-acting agent.**
- **Physostigmine** can ***enter and stimulate the cholinergic sites in the CNS***.



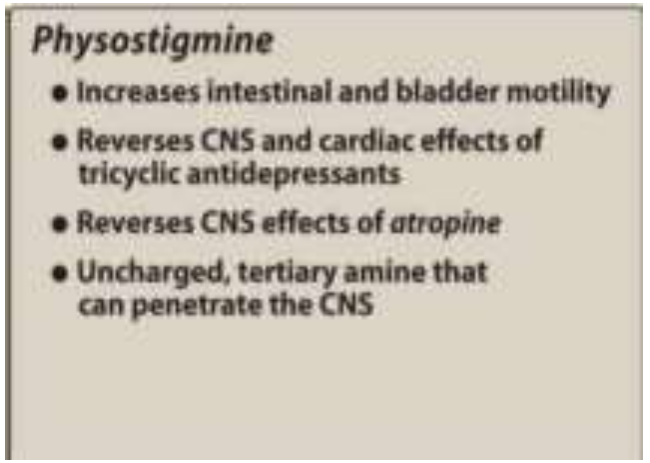
Fasciculations are involuntary rapid muscle twitches

B. Physostigmine

2. **Therapeutic uses**: it is **used in the treatment of:**

   a) Overdoses of drugs with **anticholinergic** actions, such as atropine, and

   b) To **reverse** the effects of **NMBs**.



3. **Adverse effects**: **High** doses of physostigmine may lead to **convulsions**. **Bradycardia** and a **fall in cardiac output** may also occur. Inhibition of AChE at the NMJ causes the accumulation of Ach and, ultimately through continuous **depolarization**, results in **paralysis** of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

C. Neostigmine

- **Neostigmine** is a synthetic compound that is also a **carbamic acid ester**, and it **reversibly inhibits AChE** in a manner similar to that of physostigmine.

❑Actions:

- Unlike physostigmine, **Neostigmine** has a **quaternary nitrogen**. Therefore,

1. It is more **polar**,
2. It is absorbed **poorly** from the GI tract, and
3. **It does not enter the CNS**.
4. Its **effect on skeletal muscle** is **greater** than that of physostigmine, and it can stimulate contractility before it paralyzes.

- Neostigmine has an **intermediate duration of action**, usually **30 min to 2 hrs**

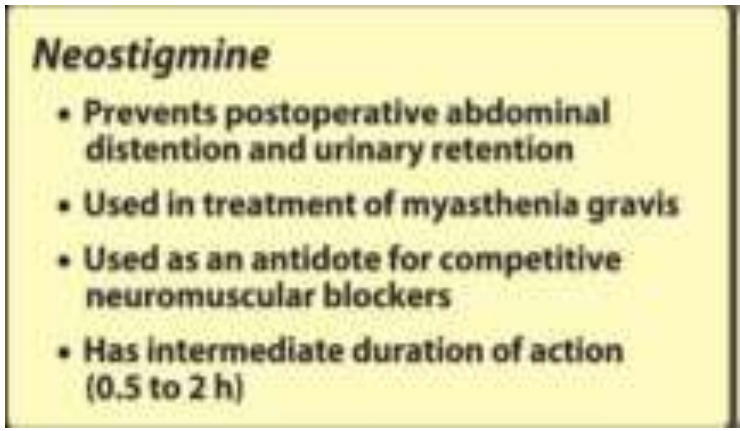
C. Neostigmine

2. Therapeutic uses: It is used to

a) Stimulate the bladder and GI tract

b) As an **antidote for competitive neuromuscular-blocking agents**.

c) To **manage symptoms of myasthenia gravis**.



3. Adverse effects: Adverse effects of neostigmine include those of **generalized cholinergic stimulation**, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. **Neostigmine does not cause CNS side effects** and is **not used** to overcome **toxicity** of central-acting antimuscarinic agents such as **atropine**.

- Neostigmine is **contraindicated** when **intestinal or urinary bladder obstruction** is present.

D. Pyridostigmine

- Pyridostigmine is another cholinesterase inhibitor used in the chronic management of **myasthenia gravis**.
- Its duration of **action is intermediate** (3 to 6 hours) but longer than that of neostigmine.
- Adverse effects are similar to those of neostigmine.

E. **Tacrine, donepezil, rivastigmine, and galantamine**

- Patients with **Alzheimer disease** have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of **anticholinesterases** as possible remedies for **the loss of cognitive function**.
- **Tacrine**, the first agent in this category, has been replaced by others because of its **hepatotoxicity**.
- Despite the ability of donepezil, rivastigmine, and galantamine to **delay the progression** of Alzheimer disease, **none can stop its progression**.
- **GI distress** is their primary adverse effect

E. Tacrine, donepezil, rivastigmine, and galantamine

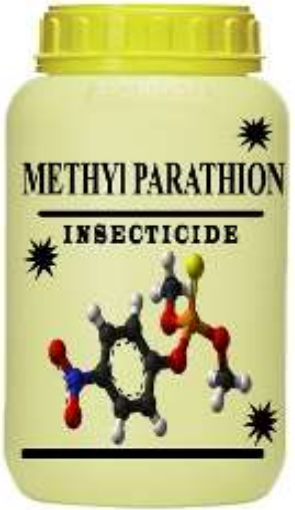
Rivastigmine, galantamine, donepezil

- Used as first-line treatments for Alzheimer disease, though confers modest benefit
- Have not been shown to reduce healthcare costs or delay institutionalization
- Can be used with *memantine* (*N*-methyl-D-aspartate antagonist) in moderate to severe disease

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Irreversible)

- A number of synthetic **organophosphate compounds** have the capacity to bind covalently to AChE.
- The result is a **long-lasting increase** in Ach at all sites where it is released.
- Many of these drugs are **extremely toxic** and were developed by the **military as nerve agents**.
- Related compounds, such as *parathion* and *malathion*, are used as **insecticides**.

INDIRECT ACTING (irreversible)
Echothiophate PHOSPHOLINE IODIDE
REACTIVATION OF ACETYLCHOLINESTERASE
Pralidoxime PROTOPAM

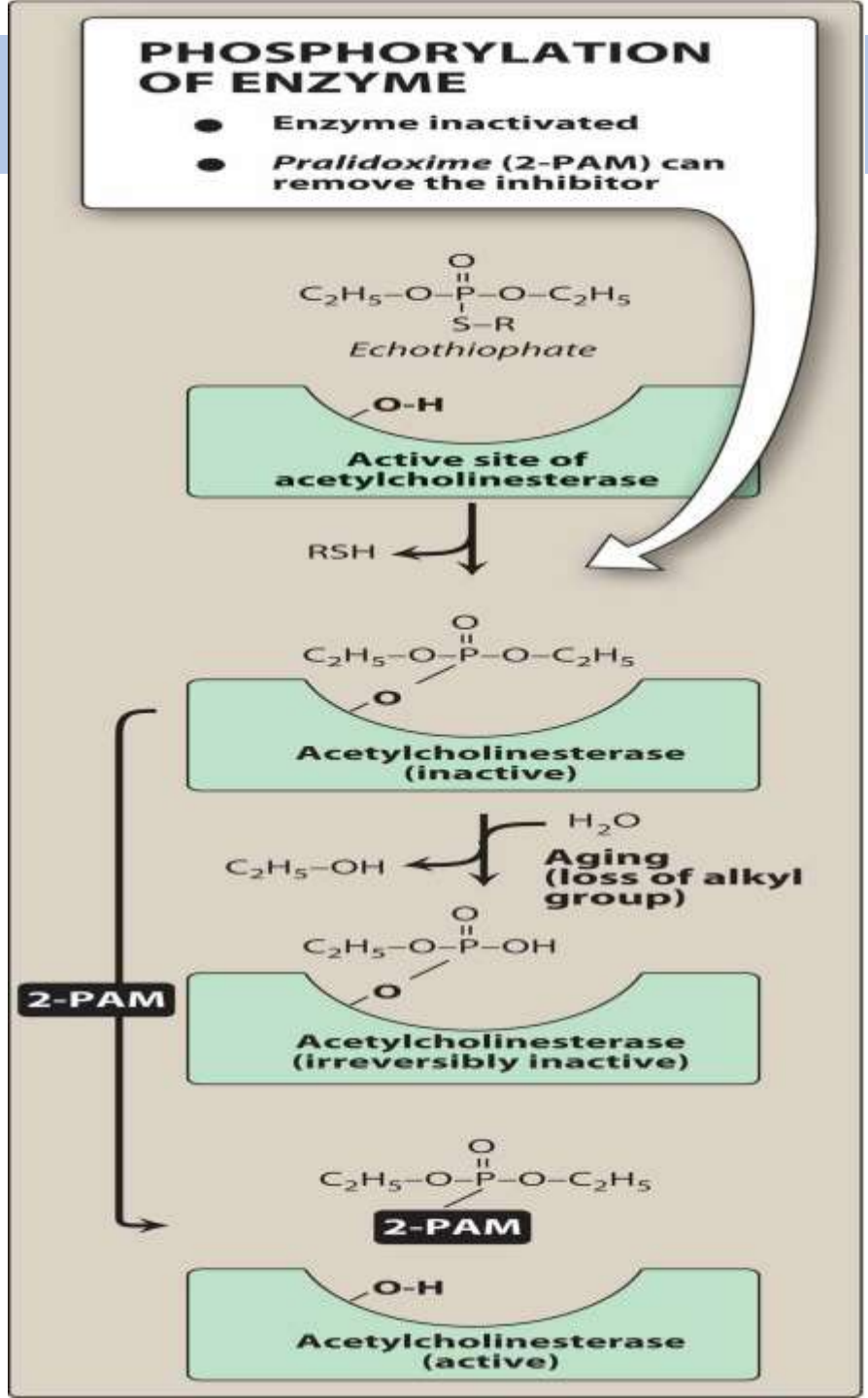


A. Echothiophate

1. **Mechanism of action:** Echothiophate is an **organophosphate** that **covalently** binds via its phosphate group at the **active site of AChE**. Once this occurs, the enzyme is **permanently inactivated**, and **restoration** of AChE activity requires the synthesis of **new enzyme** molecules.

A. Echothiophate

- Following covalent modification of AChE, the phosphorylated enzyme slowly **releases** one of its **ethyl groups**.
- The loss of an alkyl group, which is called **aging**, makes it impossible for chemical **reactivators**, such as **pralidoxime**, to break the bond between the remaining drug and the enzyme.



A. Echothiophate

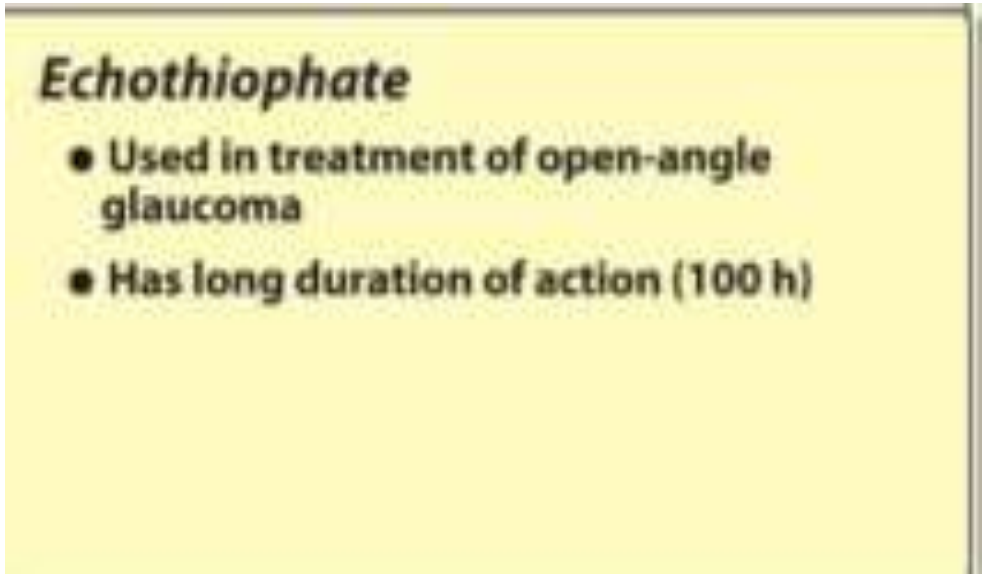
2.Actions: Actions include generalized **cholinergic stimulation**, **paralysis of motor function** (causing breathing difficulties), and convulsions.

- Echothiophate produces intense **miosis** and, thus, has found therapeutic use.
- **Intraocular pressure falls** from the facilitation of outflow of aqueous humor.
- **Atropine** in high dosages can reverse **many** of the peripheral and **some** of the **central** muscarinic effects of echothiophate.

Echothiophate

3. Therapeutic uses:

- **A topical ophthalmic solution** of the drug is available for the treatment of **open-angle glaucoma**.
- However, echothiophate is **rarely used** due to **its side effect profile**, which includes the risk of **cataracts**.



Toxicology of anticholinesterase agents

- Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as **agricultural insecticides** in the United States, which has led to numerous cases of **accidental poisoning** with these agents.
- In addition, they are frequently used for **suicidal and homicidal purposes**.
- **Organophosphate** nerve gases such as **sarin** are used as agents of **warfare and chemical terrorism**.
- Toxicity with these agents is manifested as **nicotinic and muscarinic** signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.

Reactivation of acetylcholinesterase

1. **Pralidoxime (2-PAM)** can reactivate inhibited AChE.

- However, it is **unable** to **penetrate into the CNS** and therefore is not useful in treating the CNS effects of organophosphates.
- The presence of a **charged group** allows it to approach an **anionic site** on the **enzyme**, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme.
- **If given before aging** of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects.

Reactivation of acetylcholinesterase

- With the **newer nerve agents** that produce **aging** of the enzyme complex within **seconds**, *pralidoxime* is less effective.
- *Pralidoxime* is a weak **AChE inhibitor** and, at higher doses, may cause side effects similar to other AChE inhibitors.
- In addition, it cannot overcome toxicity of **reversible AChE inhibitors** (for example, *physostigmine*).

Reactivation of acetylcholinesterase

- **Other treatments**:

2. **Atropine** is administered to **prevent muscarinic side effects** of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia.

3. **Diazepam** is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

Bethanechol

- Used in treatment of urinary retention
- Binds preferentially at muscarinic receptors

Physostigmine

- Increases intestinal and bladder motility
- Reverses CNS and cardiac effects of tricyclic antidepressants
- Reverses CNS effects of *atropine*
- Uncharged, tertiary amine that can penetrate the CNS

Rivastigmine, galantamine, donepezil

- Used as first-line treatments for Alzheimer disease, though confers modest benefit
- Have not been shown to reduce healthcare costs or delay institutionalization
- Can be used with *memantine* (*N*-methyl-D-aspartate antagonist) in moderate to severe disease

Carbachol

- Binds to both muscarinic and nicotinic receptors
- Produces miosis during ocular surgery
- Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*

Neostigmine

- Prevents postoperative abdominal distention and urinary retention
- Used in treatment of myasthenia gravis
- Used as an antidote for competitive neuromuscular blockers
- Has intermediate duration of action (0.5 to 2 h)

Echothiophate

- Used in treatment of open-angle glaucoma
- Has long duration of action (100 h)

Pilocarpine

- Reduces intraocular pressure in open-angle and narrow-angle glaucoma
- Binds preferentially at muscarinic receptors
- Uncharged, tertiary amine that can penetrate the CNS

Edrophonium

- Used for diagnosis of myasthenia gravis
- Used as an antidote for competitive neuromuscular blockers
- Has short duration of action (10 to 20 min)

Acetylcholine

- Used to produce miosis in ophthalmic surgery

Pharmacology I

Cholinergic Antagonists

Dr. Marwan Al-Zubeidy

Cholinergic Antagonists

- **Cholinergic antagonist** is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.
- *The most clinically useful of these agents are* ***selective blockers of muscarinic receptors.***
- First group: They are commonly known as **anticholinergic agents** (a misnomer, as they antagonize only muscarinic receptors), **antimuscarinic agents** (more accurate terminology), or **parasympatholytics.**

- **A second group of drugs**, **the ganglionic blockers**, shows a preference for the **nicotinic** receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the **least important of the cholinergic antagonists**.
- **A third family of compounds**, **the neuromuscular blocking agents** (mostly **nicotinic** antagonists), interfere with transmission of efferent impulses to skeletal muscles. These drugs are used as **skeletal muscle relaxants** in surgical anesthesia and as agents to **facilitate intubation** in surgical and critical care patients.

ANTIMUSCARINIC AGENTS

Aclidinium TUDORZA
Atropine GENERIC ONLY
Benztropine COGENTIN
Cyclopentolate AKPENTOLATE, CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Glycopyrrolate ROBINUL, SEEBRI
Hyoscyamine LEVSIN, OSCIMIN, SYMAX
Ipratropium ATROVENT HFA
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA RESPIMAT
Tolterodine DETROL
Trihexyphenidyl GENERIC ONLY
Tropicamide MYDRIACYL, TROPICACYL
Trospium GENERIC ONLY

GANGLIONIC BLOCKERS

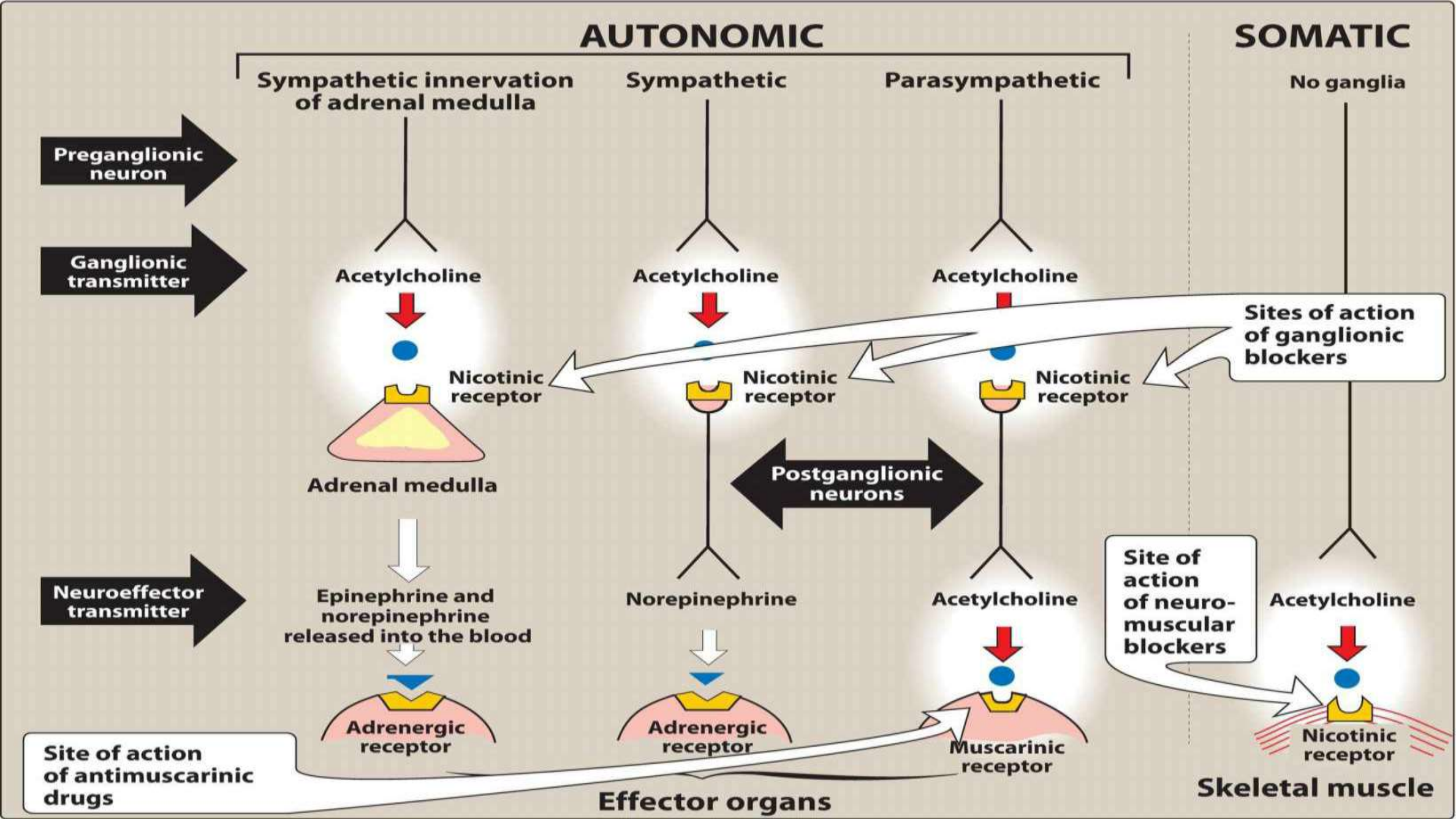
Nicotine NICODERM, NICORETTE, NICOTROL

NEUROMUSCULAR BLOCKERS

Cisatracurium NIMBEX
Mivacurium MIVACRON
Pancuronium GENERIC ONLY
Rocuronium GENERIC ONLY
Succinylcholine ANECTINE, QUELICIN
Vecuronium GENERIC ONLY

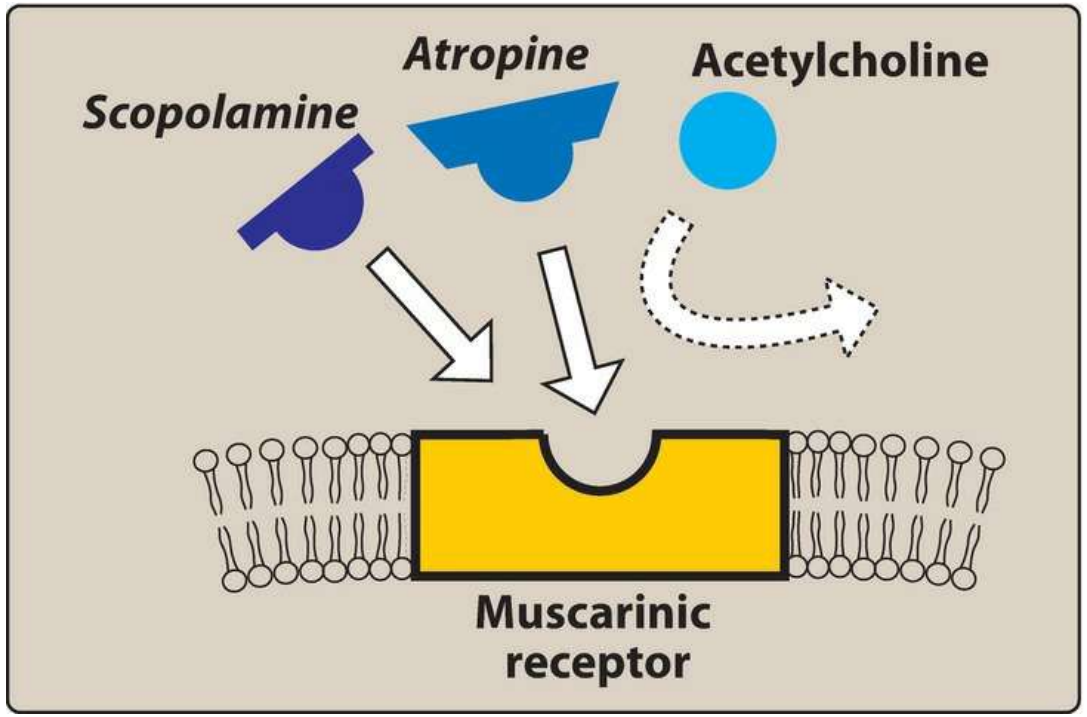
Antimuscarinic Agents

- Commonly known as **anticholinergic drugs**, these agents (for example, **atropine** and **scopolamine**) **block muscarinic receptors**, causing inhibition of muscarinic functions.
- In addition, these **drugs block** the few **exceptional sympathetic neurons** that are cholinergic, **such as those innervating the salivary and sweat glands.**
- **Because they do not block nicotinic receptors**, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia.
- The anticholinergic drugs are beneficial in a variety of clinical situations.


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
No ganglia
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
Sites of action of ganglionic blockers
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine and norepinephrine released into the blood
Norepinephrine
Acetylcholine
Site of action of neuro-muscular blockers
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Site of action of antimuscarinic drugs
Effector organs
Skeletal muscle

A. Atropine:

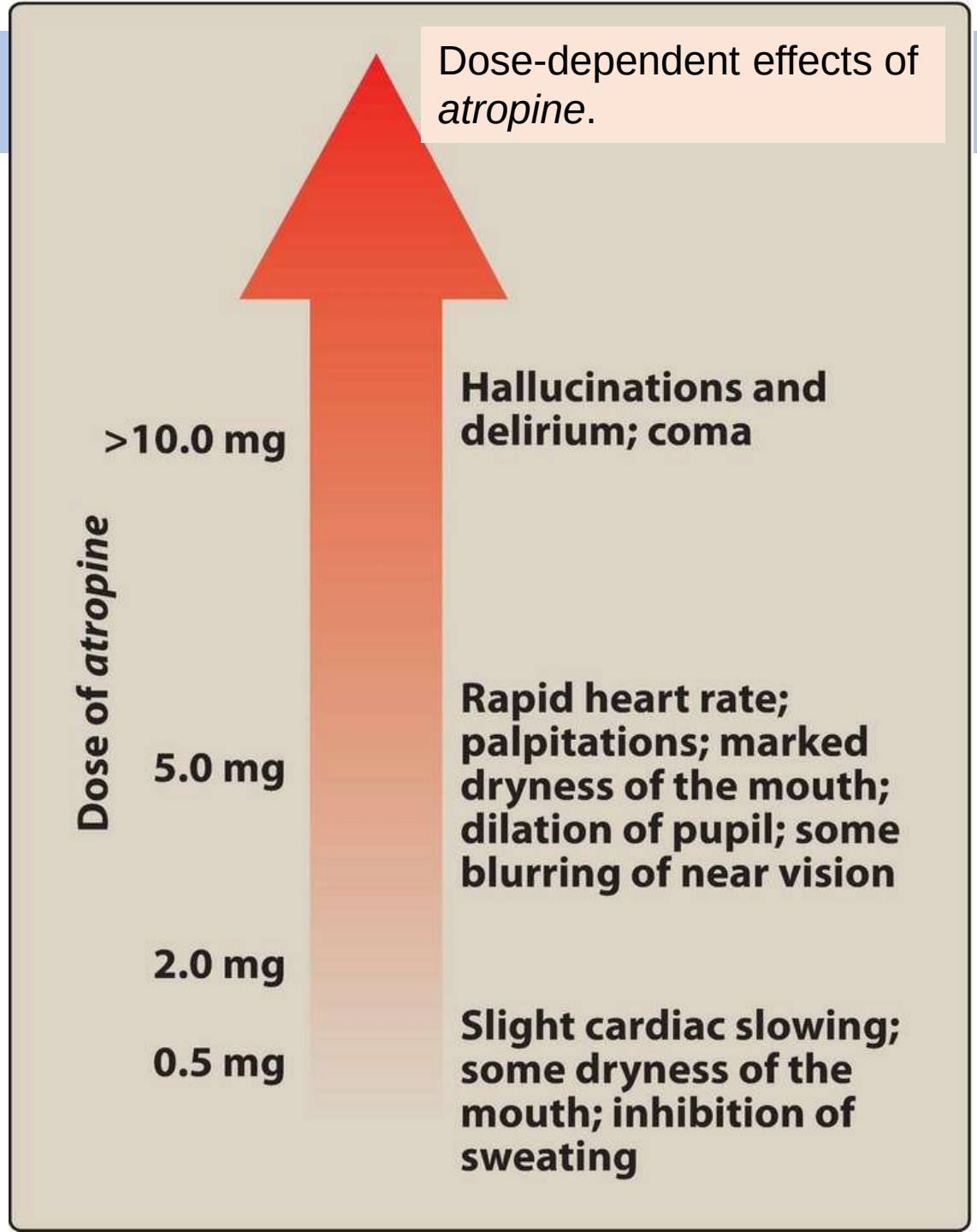
- **Atropine** is a **tertiary amine belladonna alkaloid** with a high affinity for **muscarinic** receptors.
- It binds **competitively** and prevents ACh from binding to those sites.



Competition of *atropine* and *scopolamine* with *acetylcholine* for the muscarinic receptor

A. Atropine:

- Atropine acts **both centrally and peripherally**.
- Its general **actions** **last about 4 hours**, **except** when placed topically **in the eye**, where the action may last **for days**.
- Neuroeffector organs have varying sensitivity to atropine.
- **The greatest inhibitory effects** are on **bronchial tissue** and the **secretion** of **sweat** and **saliva** and the **heart**.



A. Atropine:

1. Actions:

a. Eye: Atropine **blocks muscarinic** activity in the eye, resulting in **mydriasis** (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision).

- In patients with **angle-closure glaucoma**, intraocular pressure may rise **dangerously**.

A. Atropine:

1. Actions:

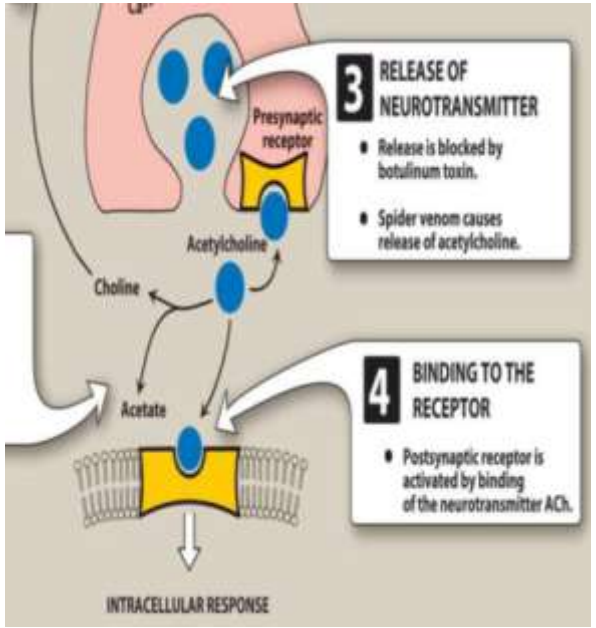
b. Gastrointestinal (GI): Atropine can be used as an **antispasmodic** to reduce activity of the GI tract.

- **Atropine and scopolamine** are probably the **most potent antispasmodic** drugs available.
- Although gastric motility is reduced, **hydrochloric acid** production **is not** significantly affected. Thus, atropine **is not effective** for the treatment of peptic ulcer.
- Doses of atropine that reduce spasms also **reduce saliva secretion**, **ocular accommodation**, and **urination**.
- These effects **decrease compliance** with atropine.

A. Atropine:

1. Actions:

c. Cardiovascular: Atropine produces **divergent** effects on the cardiovascular system, depending on the dose.



- **At low doses,** the predominant effect is a slight decrease in heart rate. This effect results from **blockade of the M1 receptors** on the **inhibitory prejunctional (or presynaptic)** neurons, thus permitting increased Ach release.
- **Higher doses of atropine** cause a progressive **increase** in heart rate by blocking **the M2 receptors** on the sinoatrial node.

A. Atropine:

1. Actions:

d. Secretions: Atropine **blocks muscarinic** receptors in **the salivary glands**, producing **dryness of the mouth** (xerostomia). The salivary glands are exquisitely sensitive to atropine.

- **Sweat** and **lacrimal glands** are similarly affected.

A. Atropine:

Therapeutic uses:

1. **Ophthalmic:** Topical atropine exerts both **mydriatic and cycloplegic** effects, and it **permits** the measurement of refractive errors without interference by the accommodative capacity of the eye.

- **Shorter-acting antimuscarinics** (**cyclopentolate** and **tropicamide**) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents).

A. Atropine:

Therapeutic uses:

2. **Antispasmodic:** Atropine is used as an antispasmodic agent to relax the GI tract.

3. **Cardiovascular:** The drug is used to treat **bradycardia** of varying etiologies.

4. **Antisecretory:** Atropine is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

A. Atropine:

Therapeutic uses:

5. **Antidote for cholinergic agonists**: Atropine is used for the **treatment** of :
   - **Organophosphate** (insecticides, nerve gases) **poisoning**,
   - **Overdose** of clinically used **anticholinesterases** such as **physostigmine**, and
   - In some types of **mushroom poisoning** (certain mushrooms contain cholinergic substances that block cholinesterases).

- **Massive doses of atropine** may be required **over a long period** of time to counteract the poisons.
- The ability of atropine to **enter the central nervous system** (CNS) is of particular importance in treating central toxic effects of anticholinesterases.