Cholinergic Agonists

Lecture 4

CHOLINERGIC AGONISTS

- Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action.
- The **preganglionic** fibers terminating in the **adrenal medulla**, the **autonomic ganglia** (both parasympathetic and sympathetic), and the **postganglionic fibers** of the parasympathetic division use ACh as a neurotransmitter (Figure 1).
- The postganglionic sympathetic division of sweat glands also uses **acetylcholine**.
- In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in the central nervous system (CNS)

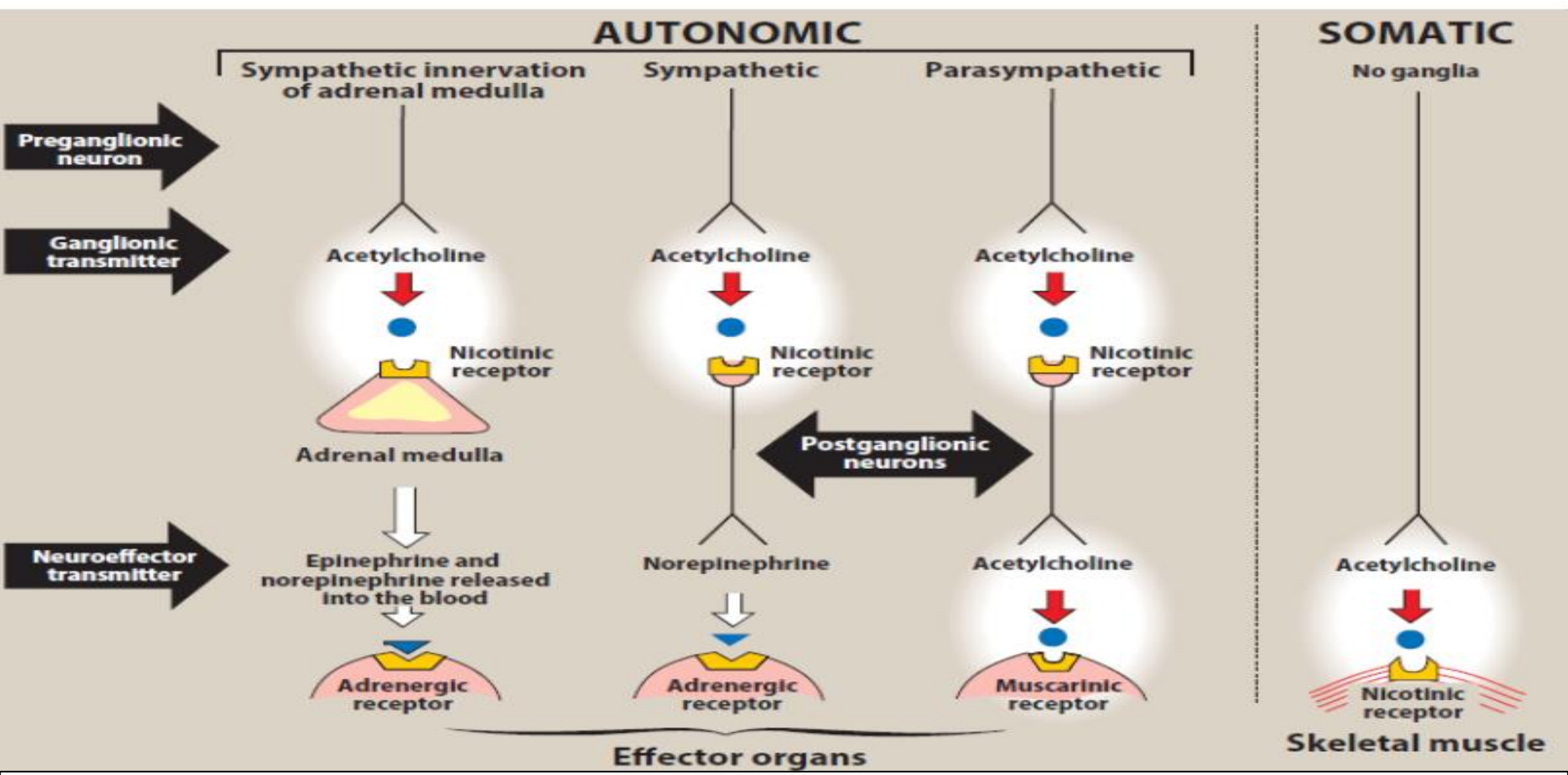


Figure 1: Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems

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 (Figure 2)

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 postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors.
- The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (Figure 1).
- 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 (Figure 2).

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.

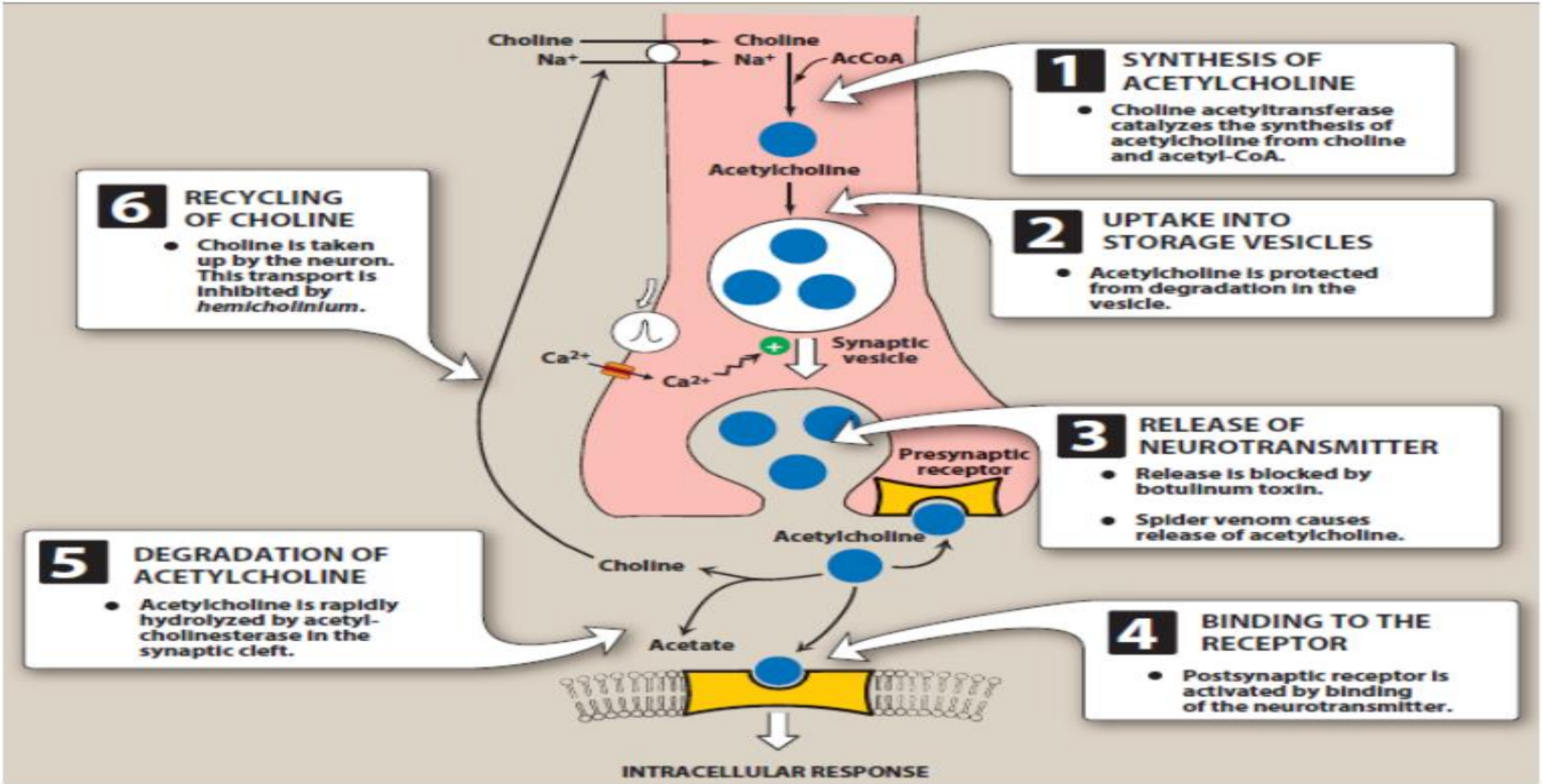


Figure 2: Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

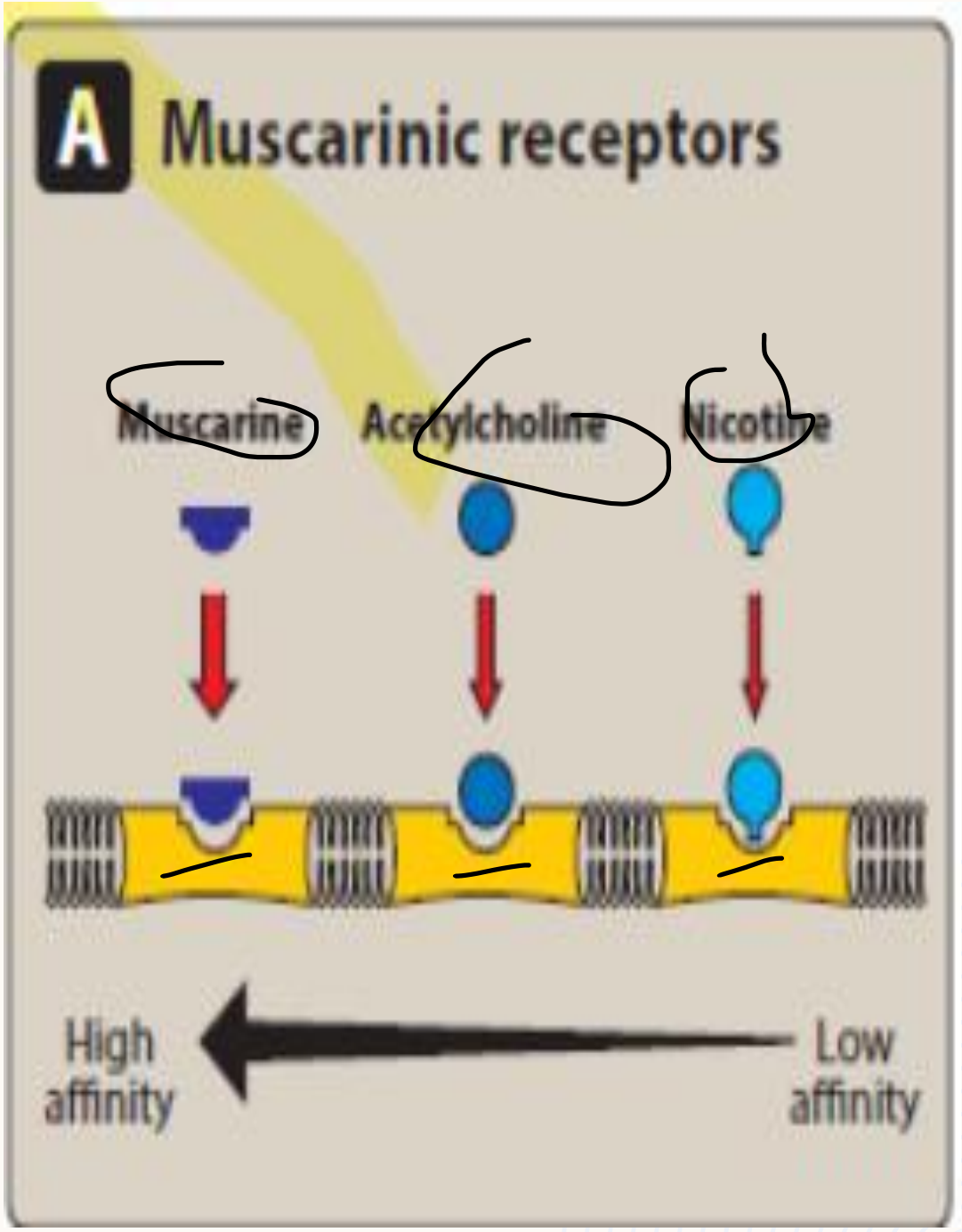
Cholinergic Receptors (Cholinoceptors)

- Two families of cholinoceptors, designated
  - A-muscarinic and
  - B-nicotinic receptors,

: 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:

- belong to the class of G protein–coupled receptors (metabotropic receptors).
- These receptors, in addition to binding 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 (Figure 3A).
- There are five subclasses of muscarinic receptors. However, only M1, M2, and M3 receptors have been functionally characterized.



A. 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, and 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). 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.

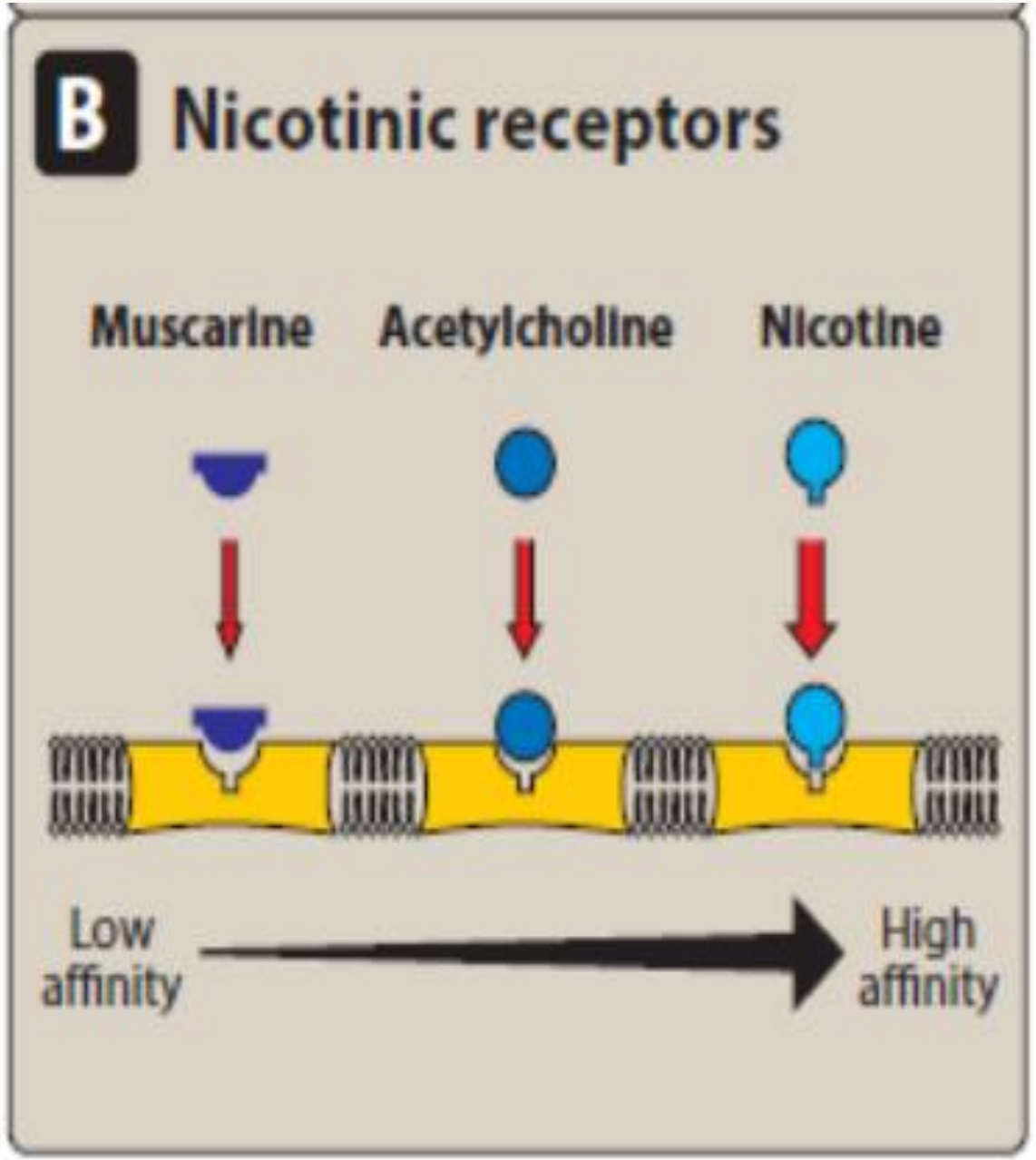
3. Muscarinic agonists:

1- **Pilocarpine:**

- is an example of a non-selective 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 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 (Figure 3B).
- The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel.
- Binding of two ACh molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell.
- Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor.
- Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.
- Those at the NMJ are sometimes designated NM, and the others, NN.
- 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.**

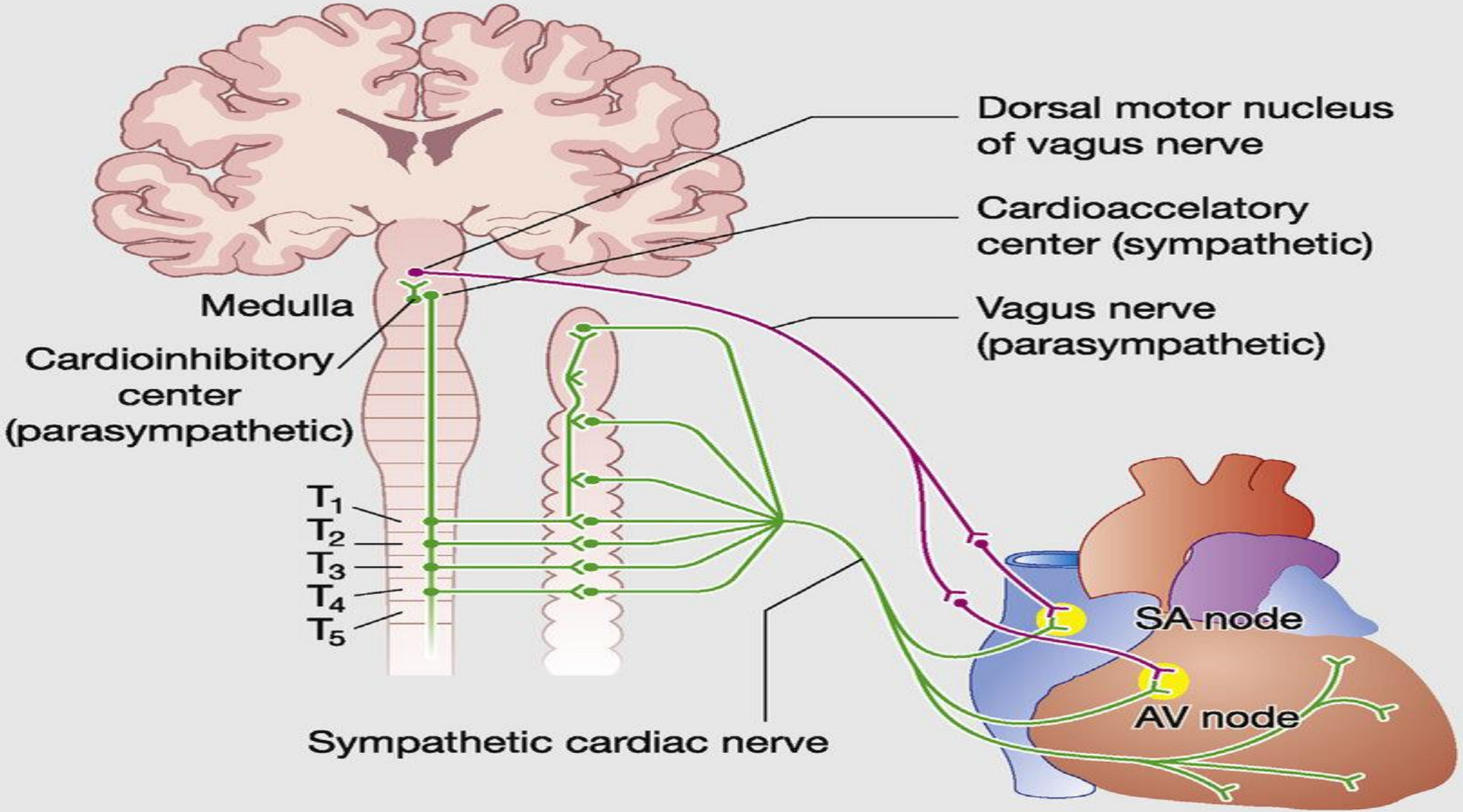


Directly-acting Cholinergic Agonists (cholino-mimetics)

- 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 (Figure 4).
- 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:

- ❑ 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 its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases.
- ❑ ACh has both muscarinic and nicotinic activity.
- ❑ Its actions include the following:
- ❖ **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].


Dorsal motor nucleus of vagus nerve
Cardioaccelatory center (sympathetic)
Vagus nerve (parasympathetic)
Medulla
Cardioinhibitory center (parasympathetic)
T1
T2
T3
T4
T5
SA node
AV node
Sympathetic cardiac nerve

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.
- 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.

3. Other actions of Ach:

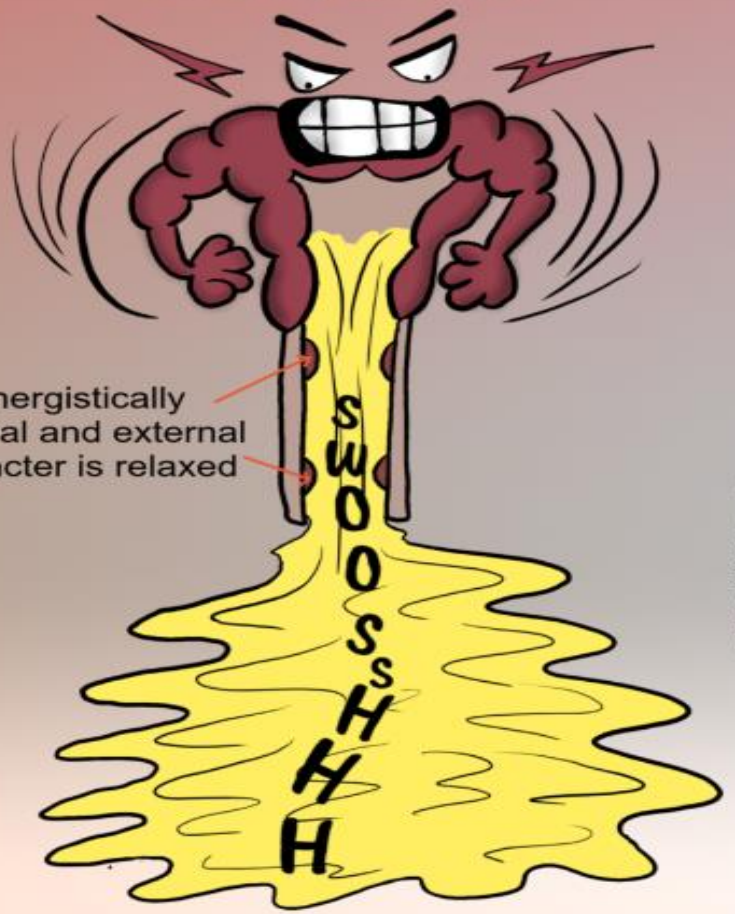
- In the gastrointestinal {GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility.
- It also enhances bronchiolar secretions and causes bronchoconstriction. [Note: Methacholine, a direct-acting cholinergic agonist, is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

When bladder is full

Parasympathetic system stimulate

Detrusor Contraction

Urine is pushed out



Successful Micturition

Under control of
Autonomic system

Smooth Muscle

Detrusor
The bladder wall muscle

I am autonomic powerful, significant muscle for urination...

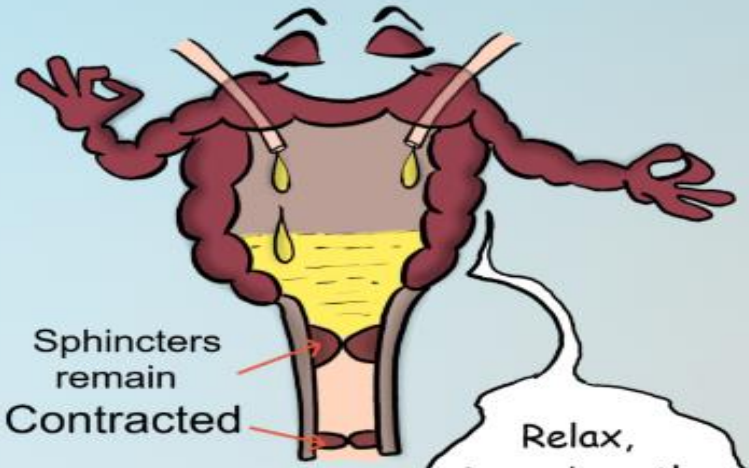
I am smooth as silk...

When Bladder is Empty

Sympathetic System relaxes Detrusor

Detrusor Muscle Relaxation

Bladder Stores Urine



No micturition
Urine is Stored

Relax,
Deep breath...

Allow yourself to **store** more urine.

Relax, chill and fill.

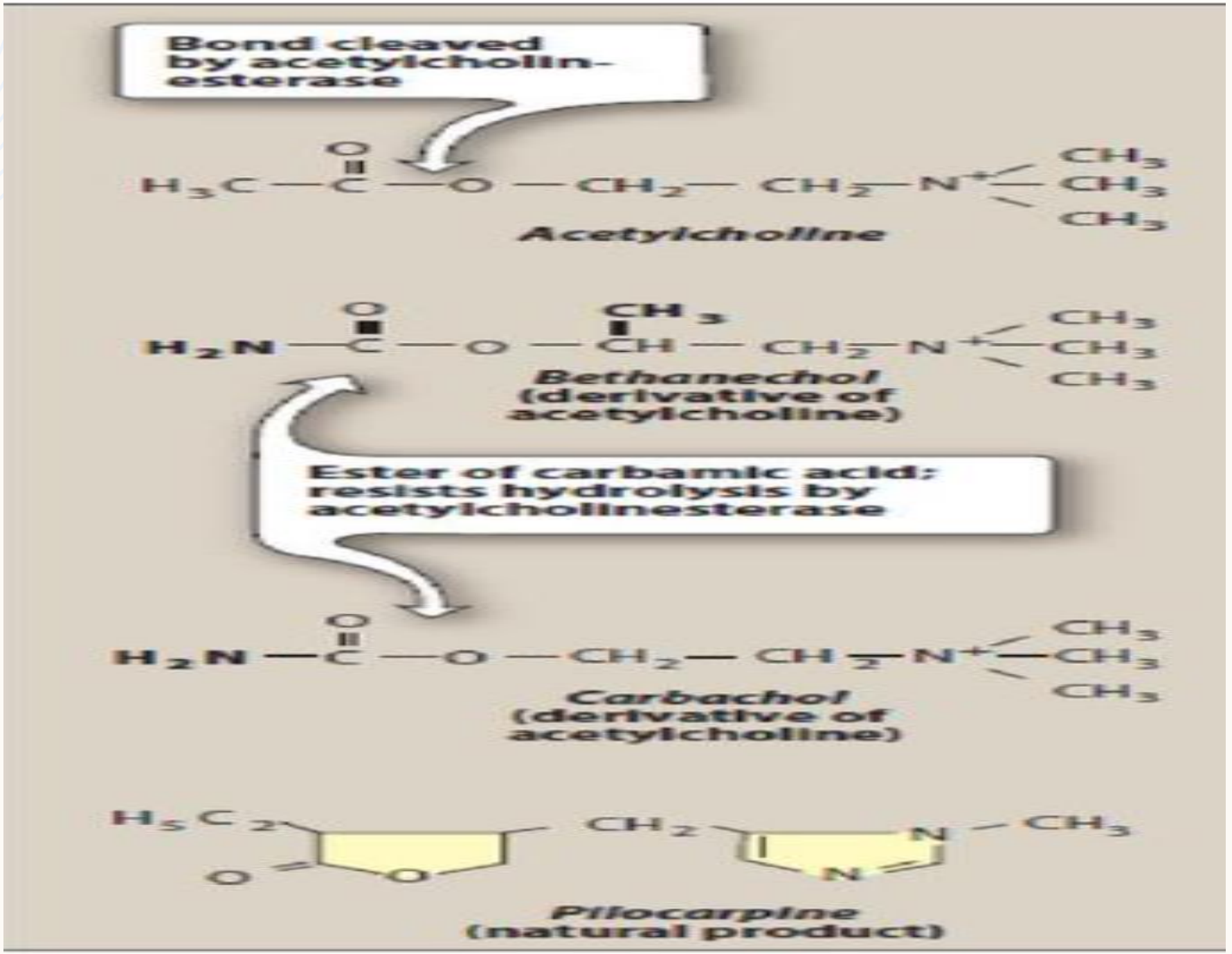
B. **Bethanechol:**

- ❑ is an unsubstituted carbamoyl ester, structurally related to ACh (Figure 4).
- ❑ It is not hydrolyzed by AChE 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 and GI tract.
- ❑ It has about a 1-hour duration of action.

1. Actions: Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects produce urination.
2. 2. Therapeutic applications: In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, non-obstructive urinary retention

- 3. Adverse effects of bethanechol:
- Bethanechol causes the effects of generalized cholinergic stimulation (Figure 5).
- These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
- Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.


Bond cleaved by acetylcholin-esterase
Acetylcholine
Bethanechol (derivative of acetylcholine)
Ester of carbamic acid: resists hydrolysis by acetylcholinesterase
Carbachol (derivative of acetylcholine)
Pilocarpine (natural product)

C. Carbachol (carbamylcholine):

- Carbachol has both muscarinic and nicotinic actions (non-selective). Like bethanechol, carbachol is an ester of carbamic acid (Figure 4) and a poor substrate for AChE.
- It is biotransformed by other esterases, but at a much slower rate.

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.

2. **Therapeutic uses of carbachol**:

- Because of its 1-high potency, 2-receptor non-selectivity, and 3-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 (Figure 4).
- 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.

1. **Actions**: Applied topically to the eye, pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. 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**

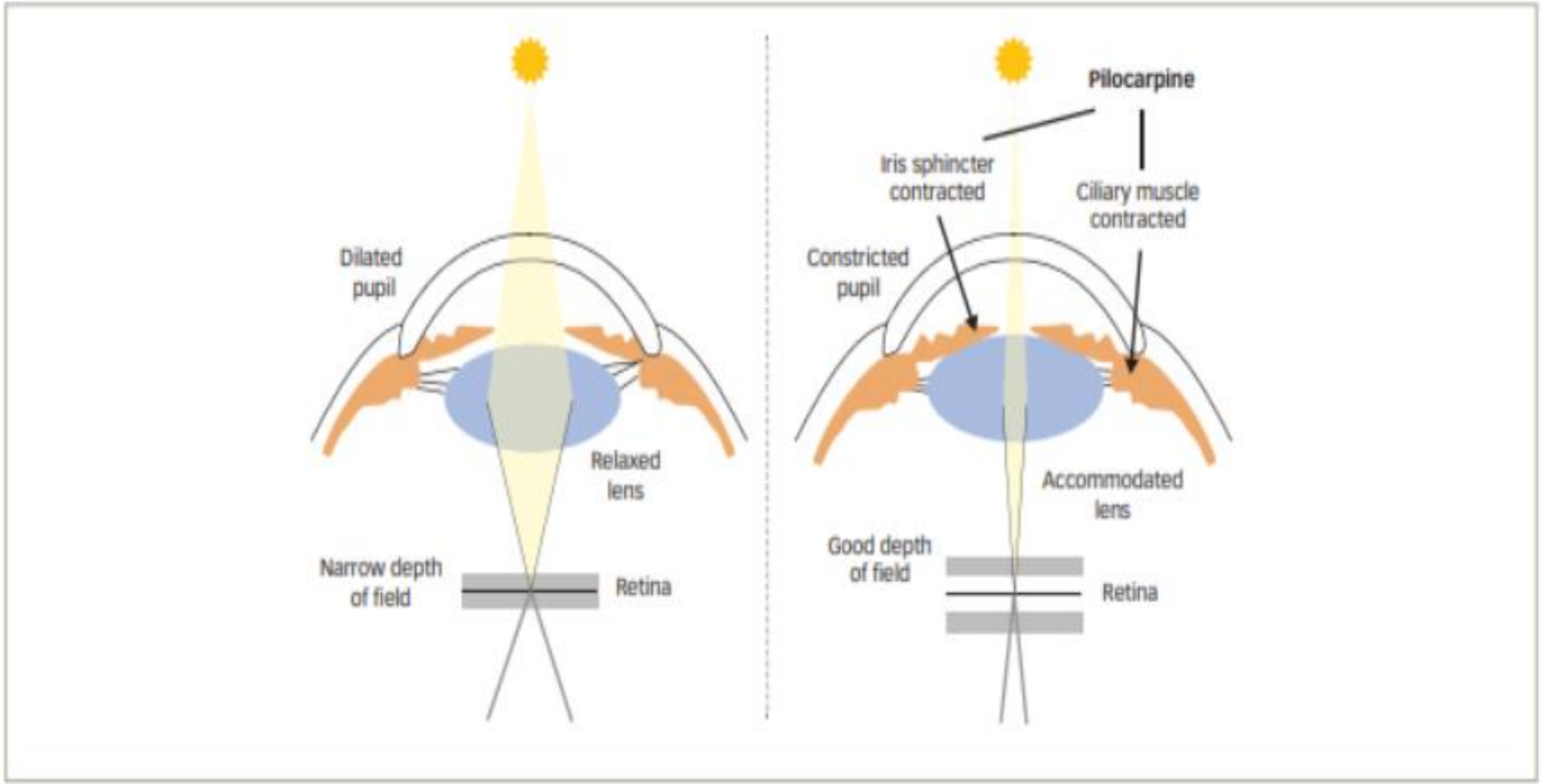
2. Therapeutic use in glaucoma:

- **Pilocarpine** is used: 1-to treat glaucoma 2-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.
- [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.].**

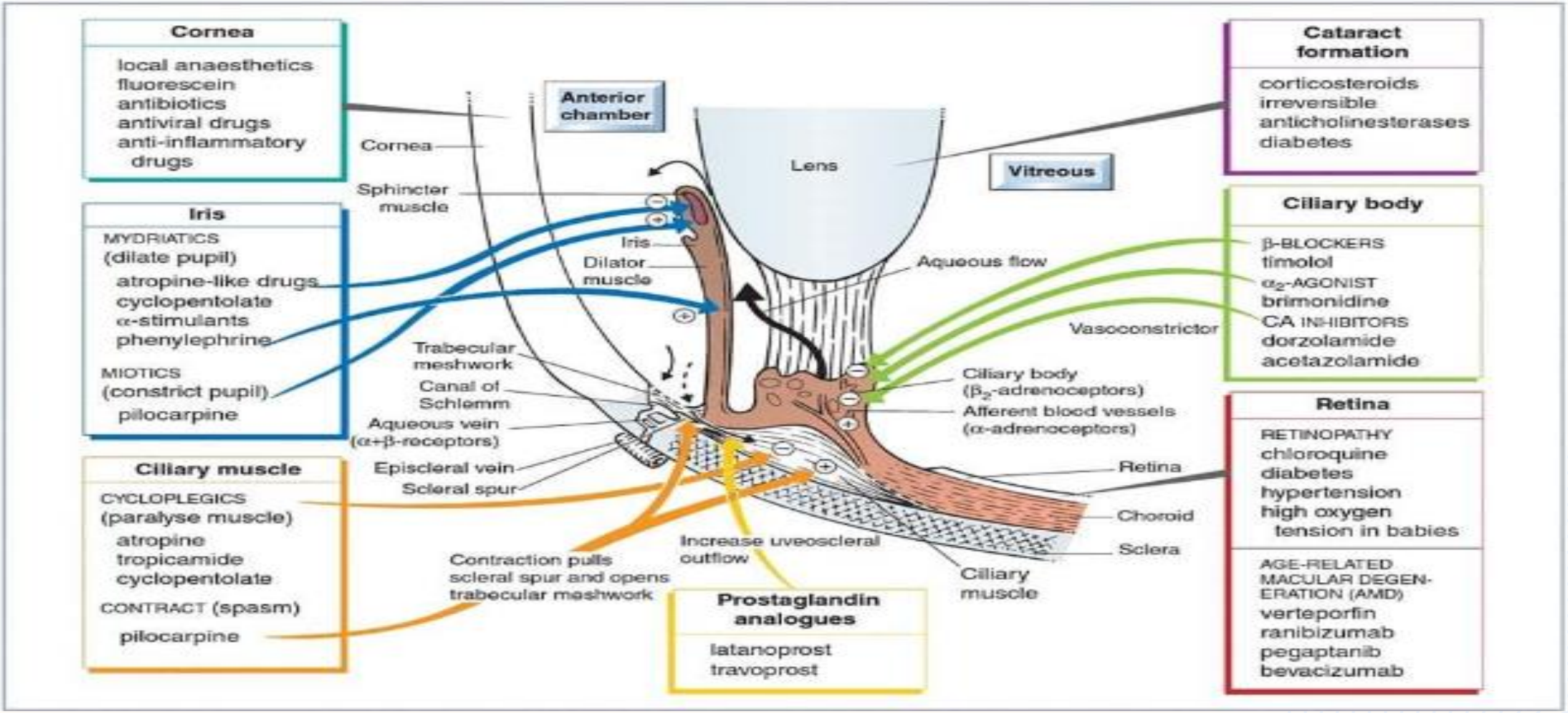
- **The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.**

- The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. **Sjogren syndrome [متلازمة شوغرن]**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.

Figure 1: Pilocarpine mechanism of action

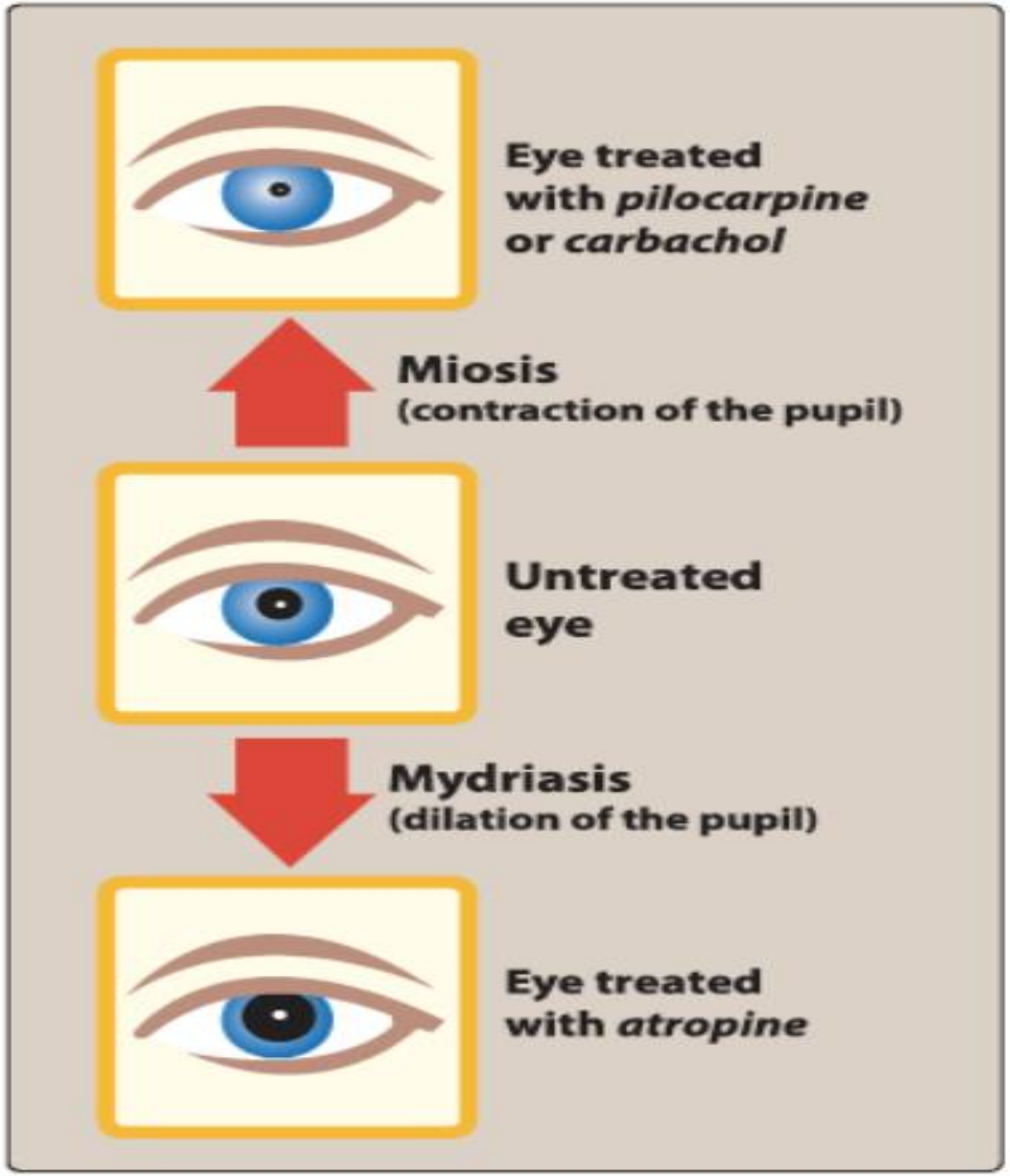


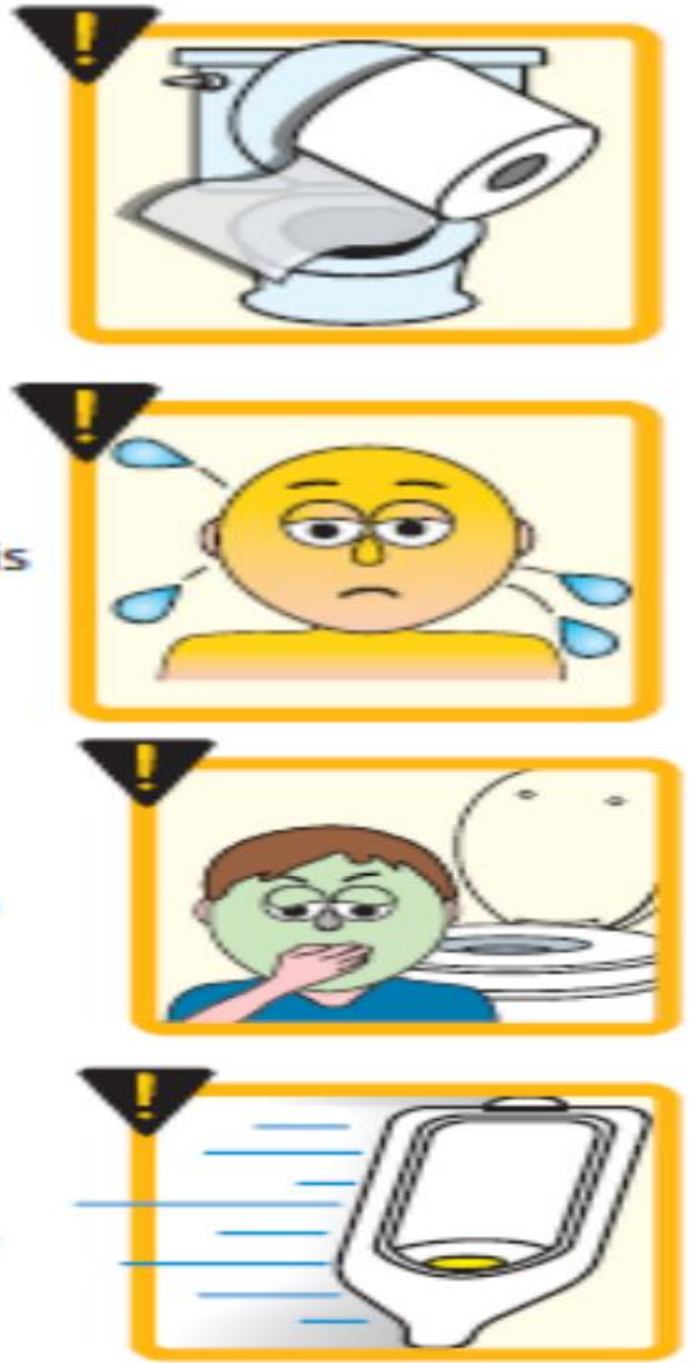
10 Ocular pharmacology



3. Adverse effects:

- Pilocarpine can cause blurred vision, night blindness, and brow ache.
- Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation.
- Figure 5: Some adverse effects observed with cholinergic agonists. The effects are similar to those produced by consumption of mushrooms of the **genus Inocybe**, which contain muscarine.
- Parenteral atropine, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of pilocarpine


Eye treated with *pilocarpine* or *carbachol*
Miosis
(contraction of the pupil)
Untreated eye
Mydriasis
(dilation of the pupil)
Eye treated with *atropine*


Diarrhea
Diaphoresis
Nausea
Urinary urgency

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (REVERSIBLE)

- Acetyl chloine 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 (Figure 6). 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.
- The reversible AChE inhibitors can be broadly classified as short acting or intermediate-acting agents.

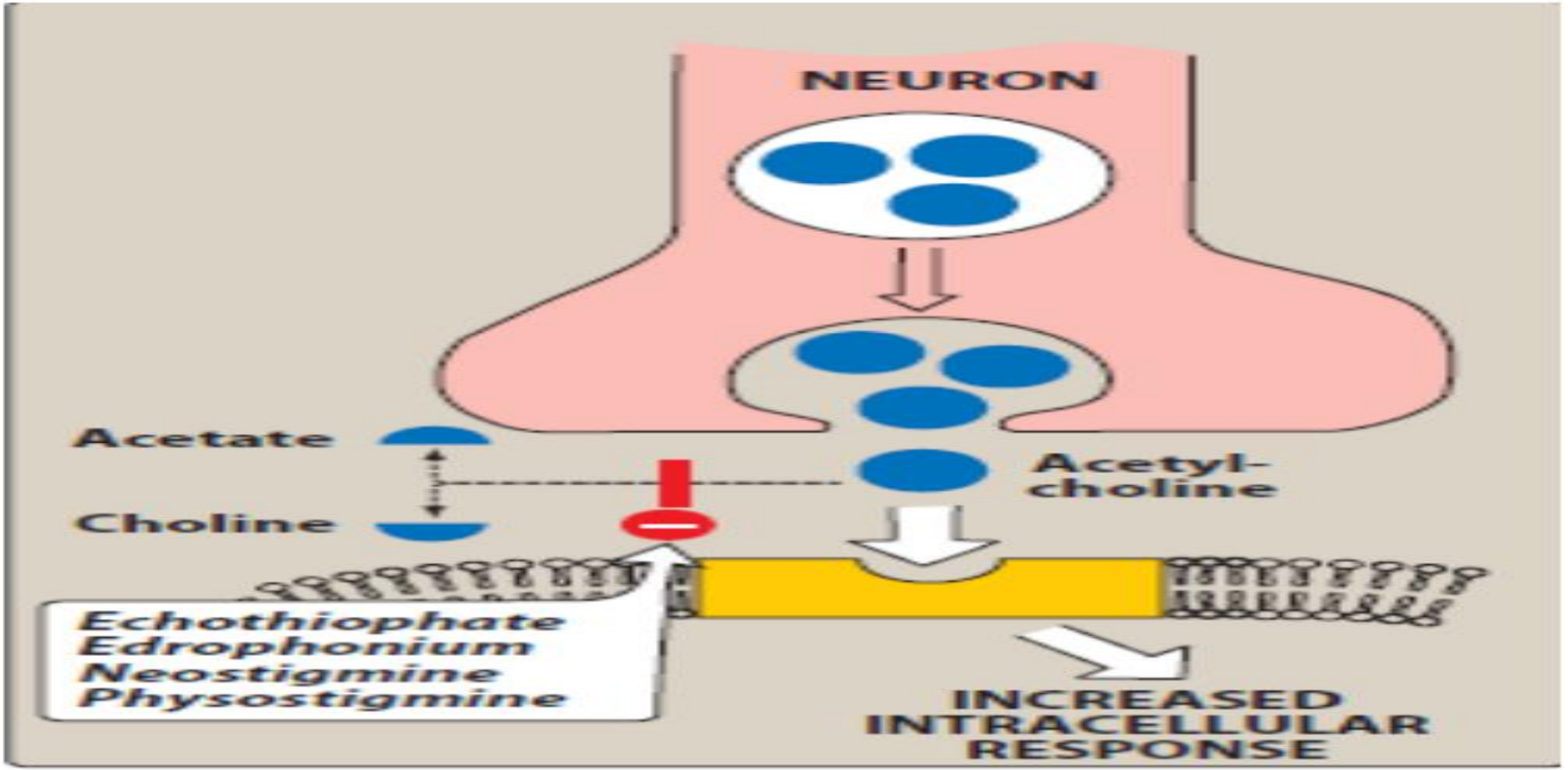


Figure 6: Mechanisms of action of indirect cholinergic agonists

A. Edrophonium:

- is the prototype short-acting 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.***
- 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**).
- (**Figure 6: Mechanisms of action of indirect cholinergic agonists**)
- Edrophonium may also be used to: assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of non-depolarizing neuromuscular blockers (NMBs) after surgery.
- Due to the availability of other agents, edrophonium use has become limited.

B. 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.

1. Actions: Physostigmine has a wide range of effects and

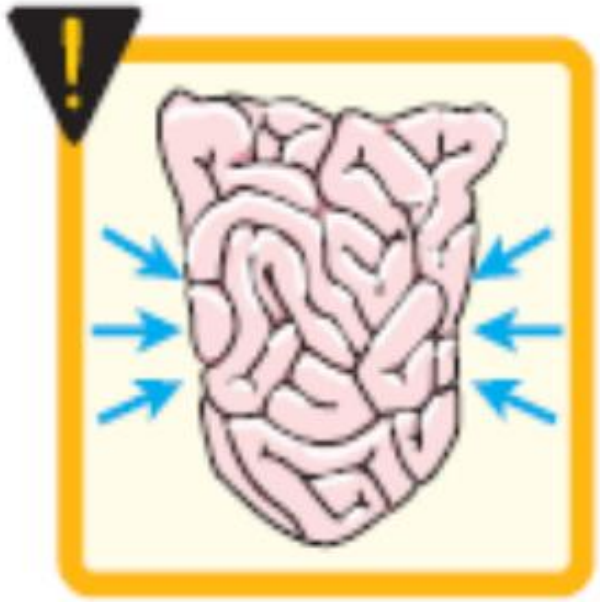
- ❖ stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ.
- ❖ Muscarinic stimulation can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension (Figure 7).
- ❖ Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses).
- ❖ Its duration of action is about 30 minutes to 2 hours, and it is considered an intermediate-acting agent.
- ❖ **Physostigmine can enter and stimulate the cholinergic sites in the CNS**.****

2. **Therapeutic uses of Physostigmine:**

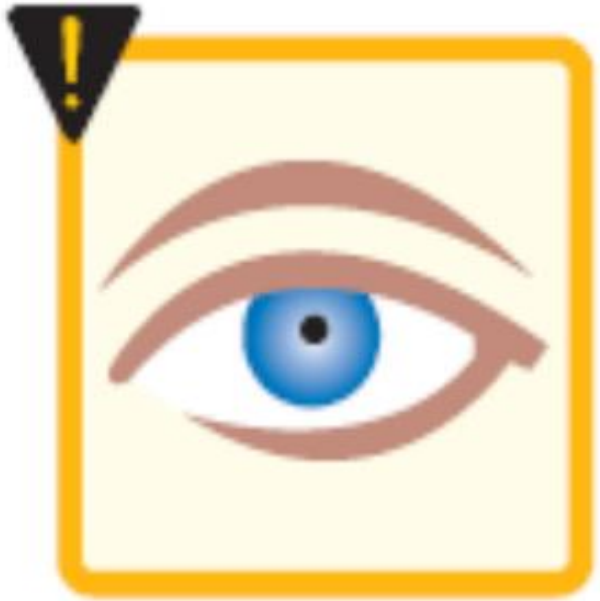
is used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, and to reverse the effects of NMBs.

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****.



Contraction o
visceral smoo
muscle



Miosis

Hypotension

Bradycardia

Figure 7: Some actions of physostigmine.

C. 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.
- Figure 7: Some actions of physostigmine.
- 1. Actions: Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS.
- 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 minutes to 2 hours.
- 2. Therapeutic uses: It is used to: 1) stimulate the bladder and GI tract and 2)also as an antidote for competitive neuromuscular-blocking agents.3) Neostigmine is also used 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:

- 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.

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

A. Echothiopate:

1. Mechanism of action:

- is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 8).
- Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules.
- 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.

2. **Actions of Echothiopate** :

- 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.

3. Therapeutic uses of Echothiopate :

- 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.

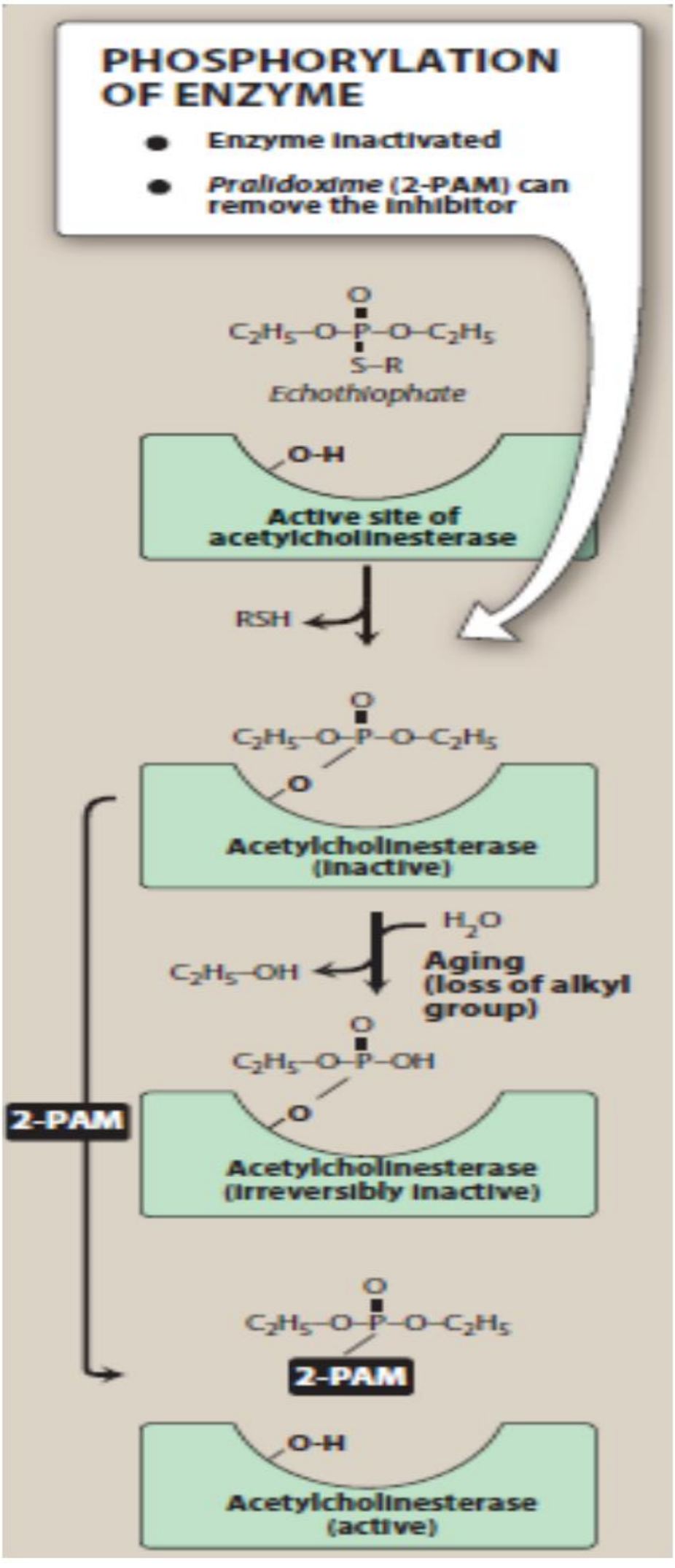


Figure 8: Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime*.

TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

- Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides , 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:

- ❑ : **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.
- ❑ 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).

Other treatments:

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

THANK for Listening

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