DRUGS THAT ACT IN THE ANS

07/03/2019

Dr Karamallah S. Mahmood

PhD Clinical Pharmacology

The cholinergic drugs

DIRECT ACTING

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

INDIRECT ACTING (reversible)

Ambenonium MYTELASE
Donepezil ARICEPT
Galantamine RAZADYNE
Neostigmine PROSTIGMIN
Physostigmine ANTILIRIUM
Pyridostigmine MESTINON
Rivastigmine EXELON
Tacrine COGNEX

INDIRECT ACTING (irreversible)

Echothiophate PHOSPHOLINE IODIDE

REACTIVATION OF ACETYLCHOLINESTERASE

Pralidoxime PROTOPAM

B. Bethanechol

Bethanechol is an unsubstituted carbamoyl ester, structurally related to ACh.

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 an 1-hour duration of action

B. Bethanechol

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. Therapeutic applications: In urologic treatment, bethanechol is used to stimulate the **atonic bladder**, particularly in postpartum or postoperative, **nonobstructive urinary retention**. Bethanechol may also be used to treat neurogenic atony as well as **megacolon**.

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

C. Carbachol (carbamylcholine)

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.

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.

C. Carbachol (carbamylcholine)

2. Therapeutic uses: Because of its high potency, receptor nonselectivity, 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.

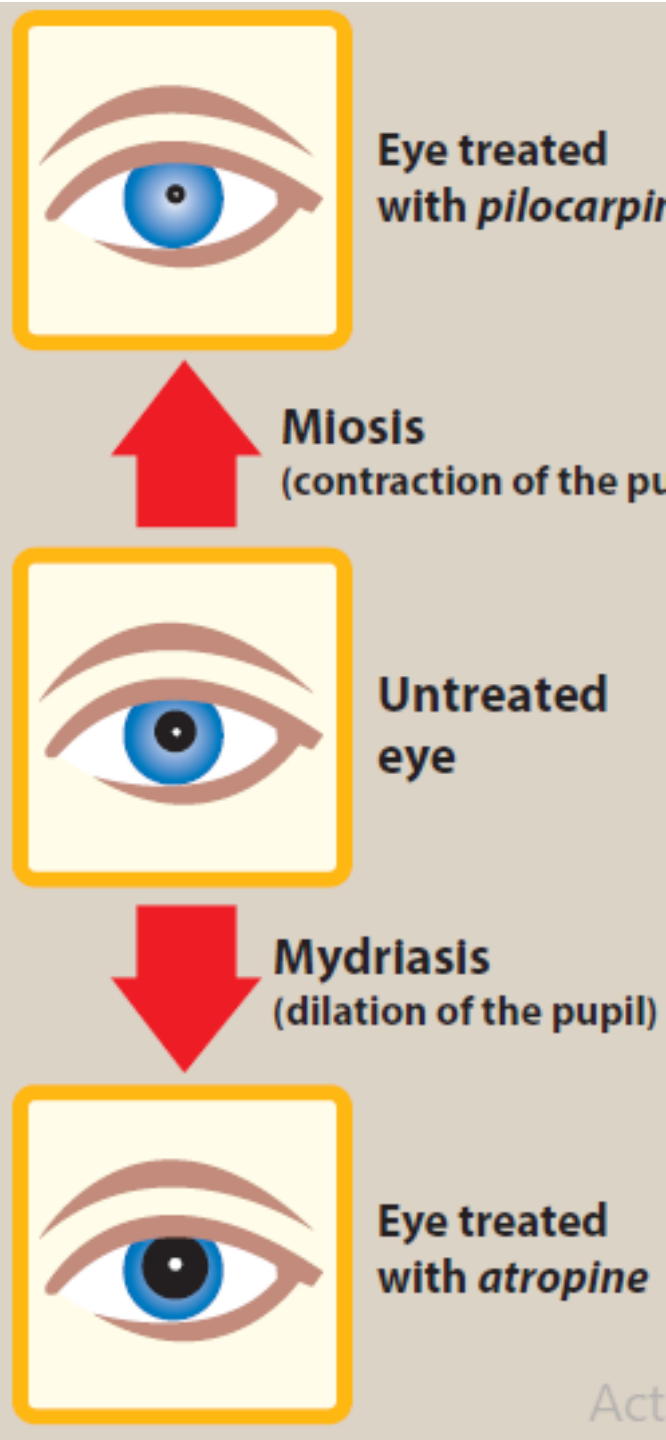
3. Adverse effects: At doses used ophthalmologically, **little or no side** effects occur due to lack of systemic penetration (quaternary amine).

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

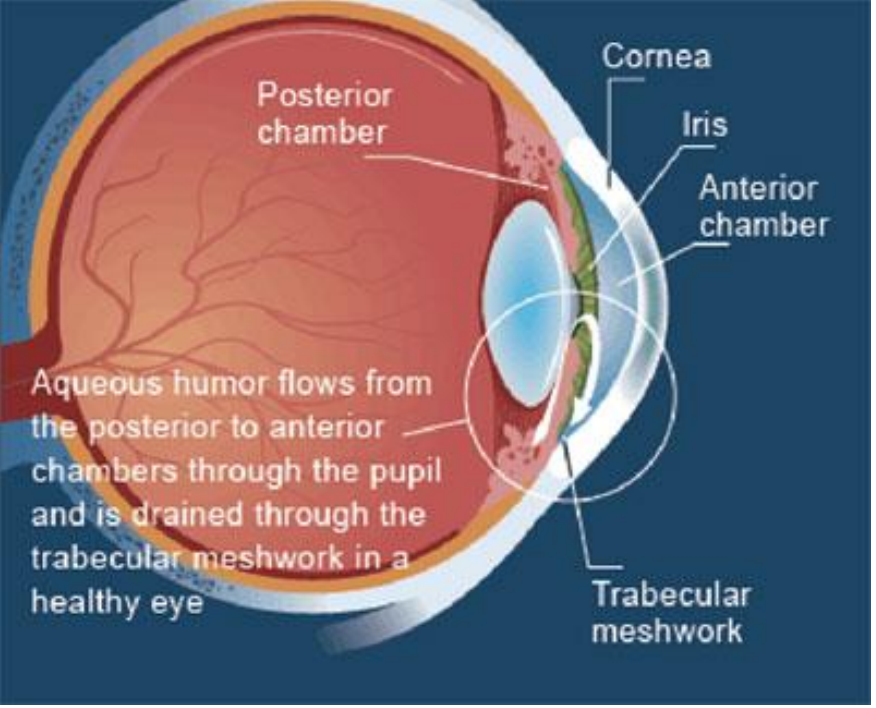
1. Actions: Applied topically to the eye, pilocarpine produces rapid miosis and contraction of the ciliary muscle.

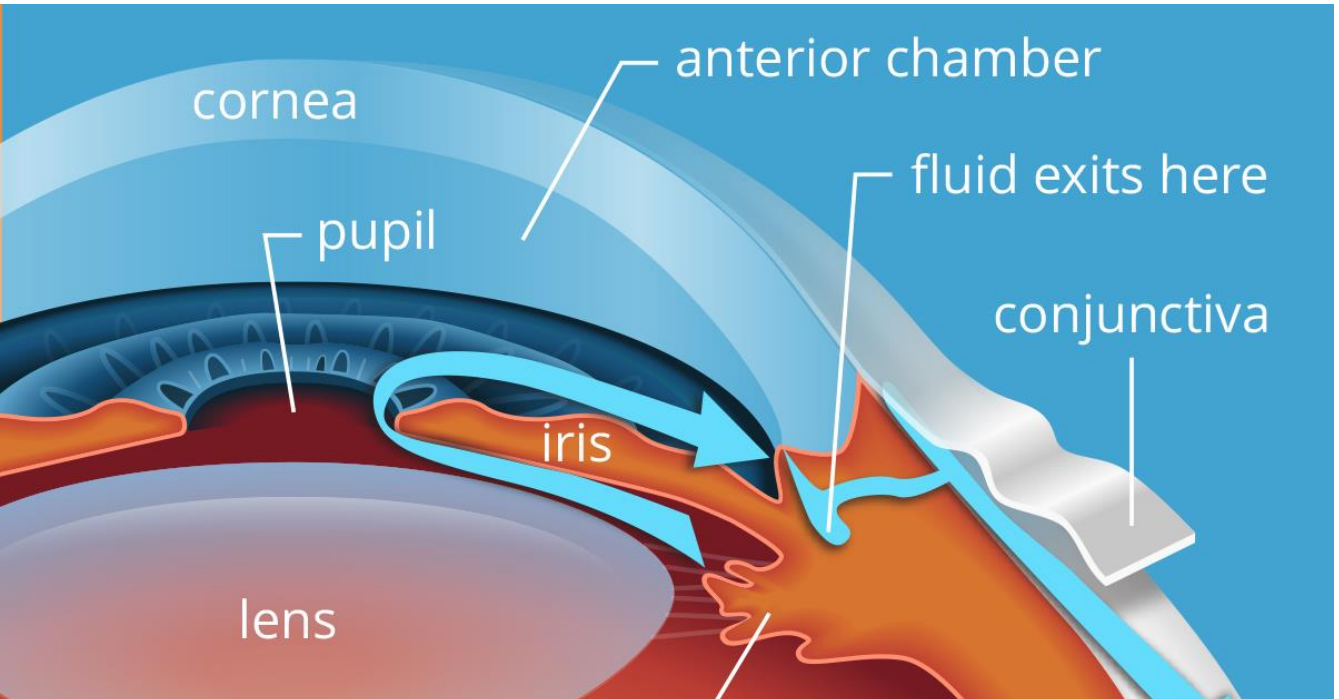
When the eye undergoes this miosis, it experiences a spasm of accommodation.

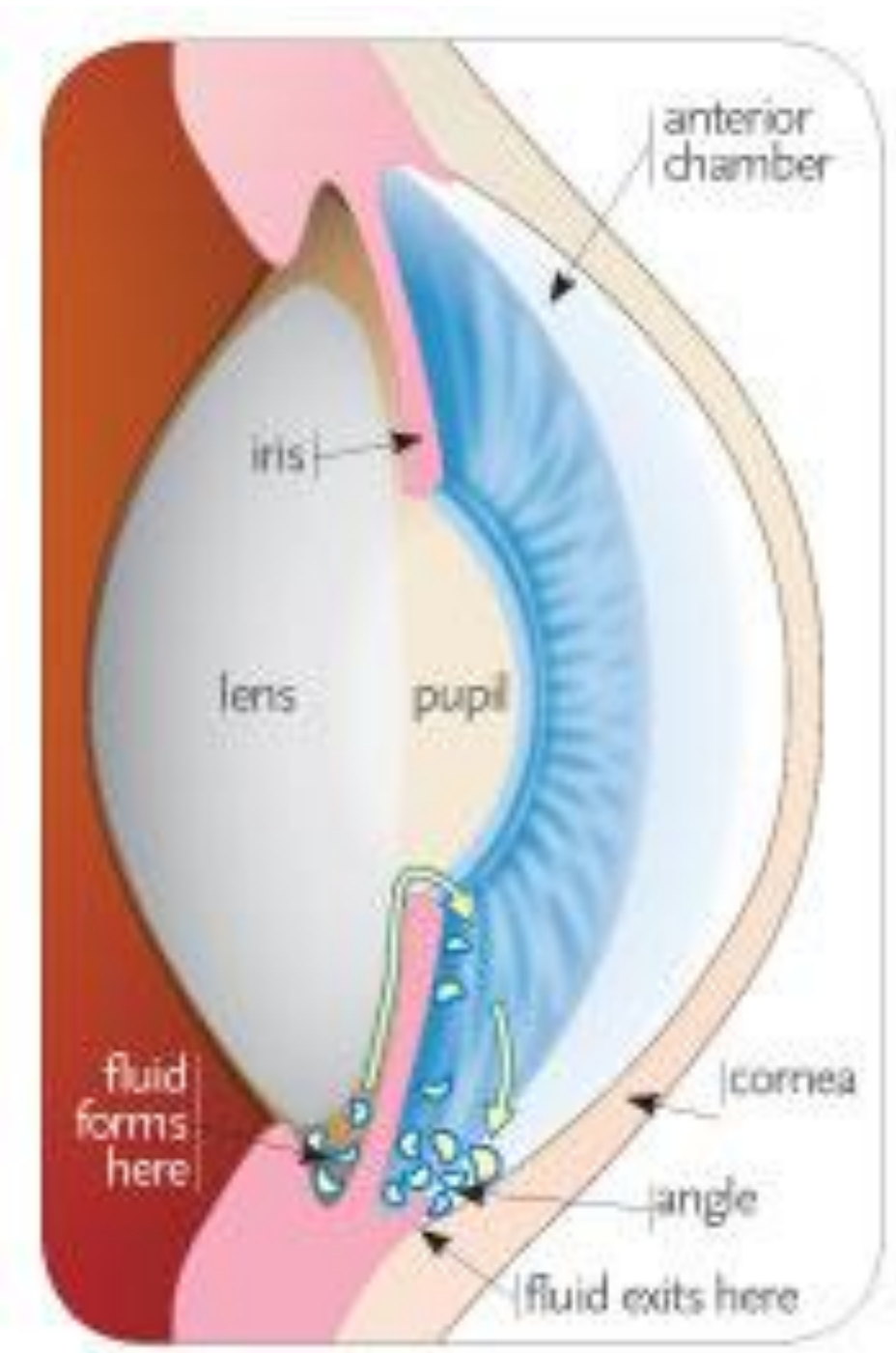
The vision becomes fixed at some particular distance, making it impossibleto focus.

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.

The drug is beneficial in promoting salivation in patients with **xerostomia** resulting from irradiation of the head and neck.


Posterior chamber
Cornea
Iris
Anterior chamber
Aqueous humor flows from the posterior to anterior chambers through the pupil and is drained through the trabecular meshwork in a healthy eye
Trabecular meshwork


anterior chamber
cornea
fluid exits here
pupil
conjunctiva
iris
lens


anterior chamber
iris
lens
pupil
fluid forms here
cornea
angle
fluid exits here

D. Pilocarpine

2. Therapeutic use in glaucoma: 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 as a result of the increased drainage of aqueous humor.

This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated.

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

D. Pilocarpine

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.

Parenteral atropine, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of pilocarpine.

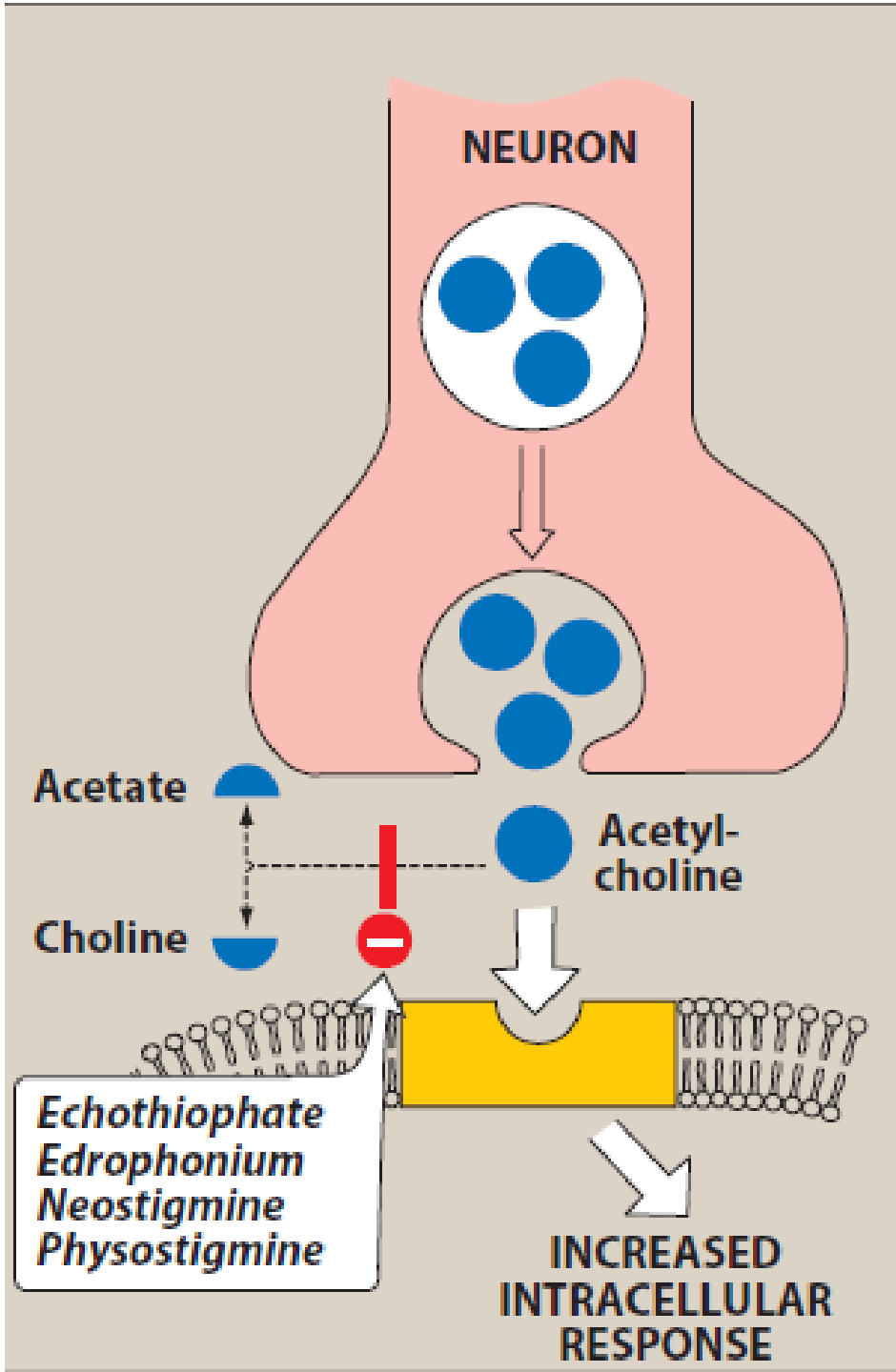
Anticholinesterase Agents

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.



A. Edrophonium

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. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote).

A. Edrophonium

Edrophonium may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing **neuromuscular blockers** after surgery.

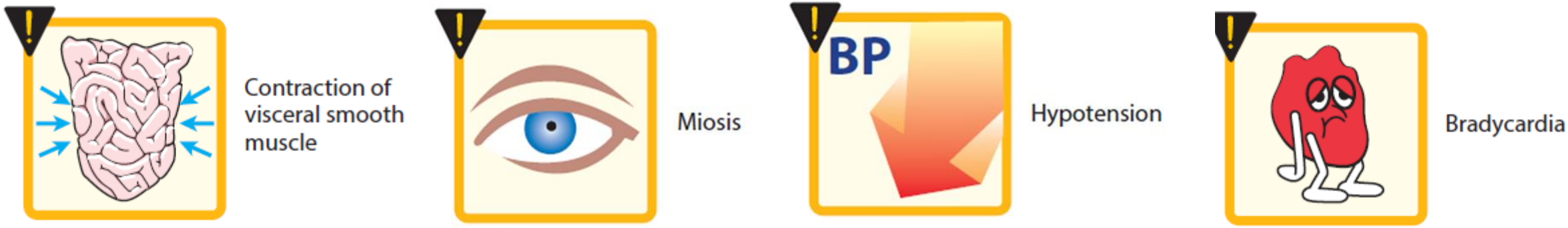
Due to the availability of other agents, edrophonium use has become limited.

B. Physostigmine

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 as a result of its action and stimulates not only the **muscarinic** and **nicotinic** sites of the ANS but also the nicotinic receptors of the **NMJ**.

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.

B. Physostigmine

2. Therapeutic uses: The drug increases **intestinal and bladder motility**, which serves as its therapeutic action in atony of either organ.

Physostigmine is also used in the treatment of **overdoses** of drugs with anticholinergic actions, such as atropine.

3. Adverse effects: The effects of physostigmine on the **CNS** may lead to convulsions when high doses are used.

Bradycardia and a fall in cardiac output may also occur.

Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, 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.

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 stimulate the **bladder and GI** tract and also as an antidote for **competitive neuromuscular-blocking agents**.

Neostigmine is also used to manage symptoms of **myasthenia gravis**.

C. Neostigmine

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 and ambenonium

Pyridostigmine and ambenonium are other cholinesterase inhibitors that are used in the chronic management of **myasthenia gravis**.

Their durations of action are **intermediate** (3 to 6 hours and 4 to 8 hours, respectively) but longer than that of neostigmine.

Adverse effects of these agents are similar to those of neostigmine.

E. Tacrine, donepezil, rivastigmine and galantamine

Patients with Alzheimer's disease have a deficiency of cholinergic neurons in the CNS.
This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function.

Tacrine was the first to become available, but it has been replaced by others because of its hepatotoxicity.

Despite the ability of donepezil, rivastigmine, and galantamine to delay the progression of Alzheimer's 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.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)/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.

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.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)/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.

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 causing cataracts.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)/A. Echothiophate

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's 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) with moderate to severe disease

Carbachol

- 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 hrs)

Echothiophate

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

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

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.

A. 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.

A. 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).

B. 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