Al-Mustaqbal University College

Pharmacology I 3rd stage

Cholinergic Agonists

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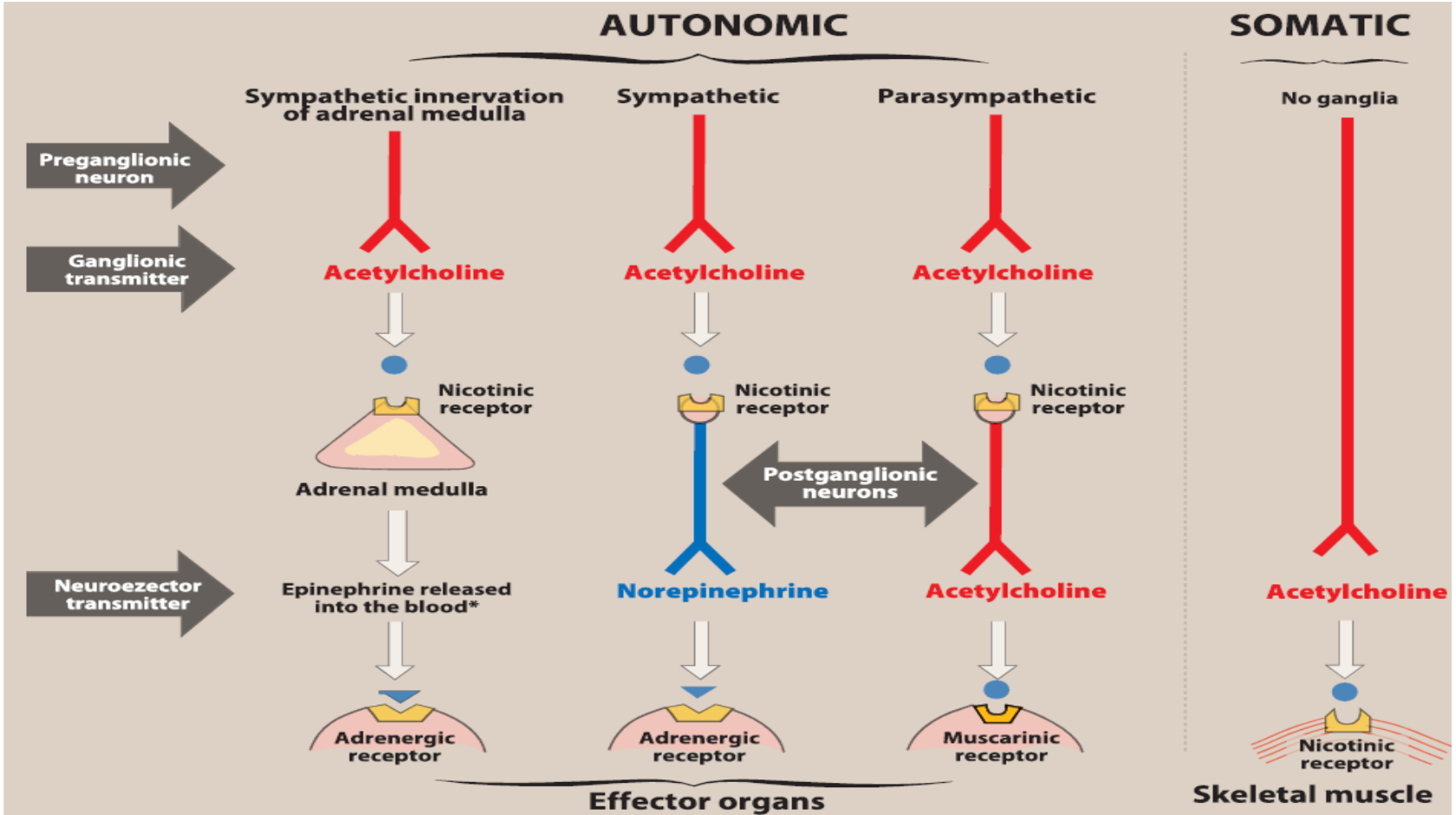
Cholinergic Agonists

The cholinergic drugs act on receptors activated by acetylcholine (ACh)

THE CHOLINERGIC NEURON



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

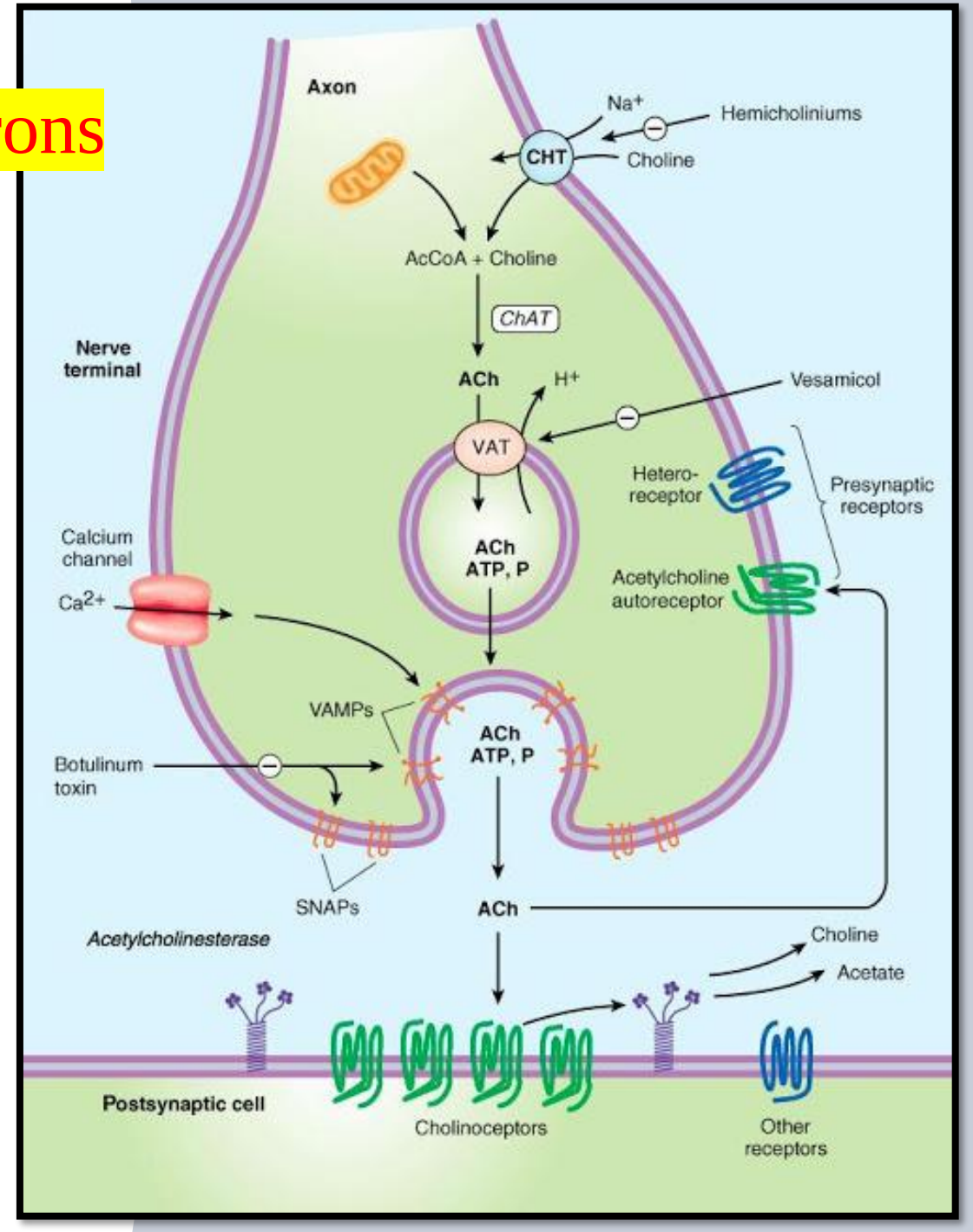
REACTIVATION OF ACETYLCHOLINESTERASE

Pralidoxime PROTOPAM

Neurotransmission at Cholinergic neurons

1-Synthesis of acetylcholine:

Choline is up taken from the extracellular fluid into the cytoplasm of the cholinergic neuron (can be inhibited by the drug hemicholinium). 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: The acetylcholine is packaged into presynaptic vesicles. The mature vesicle contains acetylcholine and adenosine triphosphate (ATP) as cotransmitter that increases or decreases the effect of the primary neurotransmitter.

3. Release of acetylcholine:

When an action potential propagated by the action of 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 release of their contents into the synaptic space. **This release can be blocked by botulinum toxin.**

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 (which may be muscarinic or nicotinic receptor) leading to initiate response.

2- presynaptic receptors on the membrane of the neuron that released ACh.

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.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

A.Muscarinic receptors :

These receptors, in addition to binding **acetylcholine**, also recognize **muscarine**, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for **nicotine**.

They are G- protein coupled receptors, and there are five subclasses of muscarinic receptors: M1, M2, M3, M4, and M5. Only M1, M2 and M3, receptors have been functionally characterized.

M1 receptors are found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle.

Mechanism of acetylcholine signal transduction:

Activation of M1 or M3 cholinergic receptors causes increasing an intracellular concentration of second messenger like (IP3) or diacylglycerol (DAG) or Ca^{2+} ions while activation of the M2 subtype on the cardiac muscle stimulates a G-protein that inhibits adenylyl cyclase and increases K^{+} conductance. The heart responds with a decrease in rate and force of contraction.

Muscarinic agonists: Pilocarpine is a nonselective muscarinic agonist used to treat xerostomia and glaucoma.

B. Nicotinic receptors: These receptors, in addition to binding acetylcholine, also recognize nicotine but show only a weak affinity for muscarine.

It functions as a ligand-gated ion channel. Binding of acetylcholine molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine (or acetylcholine) initially stimulates and then blocks the receptor.

Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction.

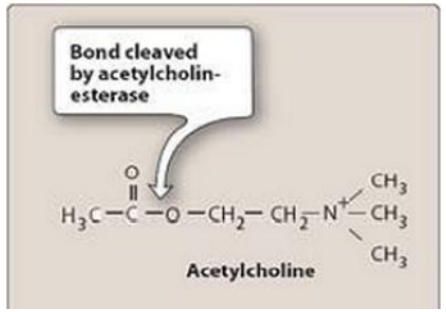
Direct-Acting Cholinergic Agonists

Cholinergic agonists (parasympathomimetics) mimic the effects of acetylcholine by binding directly to cholinoceptors (muscarinic or nicotinic). These agents may be broadly classified into two groups:

A. choline esters: which include **acetylcholine and synthetic esters of choline**, such as **carbachol and bethanechol**.

B. Naturally occurring alkaloids: **such as pilocarpine**.

All of the direct-acting cholinergic drugs have longer durations of action than acetylcholine.



1 . 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 is therapeutically of no importance because of its multiplicity of actions (leading to diffuse effect) and its rapid inactivation by the cholinesterases. Acetylcholine has both muscarinic and nicotinic activity.

Actions of Acetylcholine include:

1. Decrease in heart rate and cardiac output:

Acetylcholine, if injected intravenously, 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: It should be remembered that normal vagal activity regulates the heart by the release of acetylcholine at the SA node.]

2.Decrease in blood pressure:

Injection of acetylcholine causes vasodilation and lowering of blood pressure by an indirect mechanism of action: (through M2 receptor activation then nitric oxide which relaxing smooth muscles of blood vessels.

3. Other actions:

- It increases salivary secretion and stimulates intestinal secretions and motility.
- It causes bronchoconstriction and enhances bronchiolar secretions.
- ACh increases the tone of the detrusor muscle, causing urination.
- In the eye, stimulating ciliary muscle contraction for near vision and causing miosis (marked constriction of the pupil). Acetylcholine (1% solution used to produce miosis during ophthalmic surgery)

B. Bethanechol [be-THAN-e-kole] is structurally related to Ach.
It is not hydrolyzed by AChE but by another enzyme.
It lacks nicotinic actions but does have strong muscarinic activity.
It has about a 1-hour duration of action.

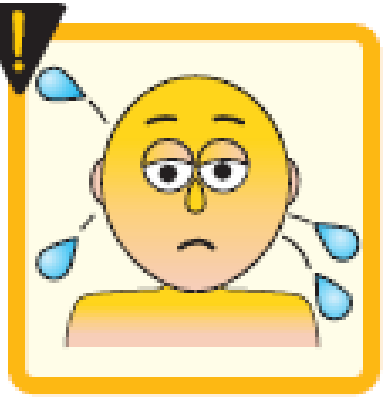
1. Actions: increased intestinal motility and tone.
It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects stimulate urination

2. Therapeutic uses: It is used to stimulate the atonic bladder, in postpartum or postoperative. It may be used to treat neurogenic atony as well as megacolon.

Adverse effects: Bethanechol causes the effects of generalized cholinergic stimulation. These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

Diarrhea

Diaphoresis



Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

Urinary urgency

Nausea

3. Carbachol

Carbachol has both muscarinic as well as nicotinic actions, it is a poor substrate for acetylcholinesterase. A single administration can last as long as 1 hour.

Actions: Carbachol has profound effects on both the cardiovascular system and the gastrointestinal system. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. In the eye, it causes miosis.

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.

Adverse effects: At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration.

3-Pilocarpine

Pilocarpine is stable to hydrolysis by acetylcholinesterase. It is less potent when compared with acetylcholine and its derivatives, but it is uncharged and will penetrate the CNS at therapeutic doses. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

Actions:

- Applied topically to the cornea, pilocarpine produces a rapid miosis and contraction of the ciliary muscle.
- Pilocarpine is a potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck.

Therapeutic use:

in glaucoma: Pilocarpine is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (also called closed-angle) and wide-angle (also called open-angle) glaucoma, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor.

Adverse effects: Pilocarpine can enter the brain and cause CNS disturbances. It stimulates profuse sweating and salivation.

Indirect-Acting Cholinergic Agonsists:

Anticholinesterases (Reversible)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions.

It is located both pre- and postsynaptically in the nerve terminal.

Inhibitors of acetylcholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings. This results in the accumulation of acetylcholine in the synaptic space.

A- Physostigmine

Physostigmine is found naturally in plants. It is a substrate for acetylcholinesterase, and inactivates it reversibly. The result is potentiation of cholinergic activity throughout the body.

Actions: Physostigmine has effects at muscarinic and nicotinic sites of the autonomic nervous system and the nicotinic receptors of the neuromuscular junction. Its duration of action is about 2 to 4 hours. Physostigmine can enter and stimulate the cholinergic sites in the CNS.

Therapeutic uses:

- The drug increases intestinal and bladder motility, it's used in the treatment of atony of either organ.
- Placed topically in the eye, it produces miosis and lowering of intraocular pressure. It is used to treat glaucoma.
- Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, phenothiazines, and tricyclic antidepressants.

Adverse effects:

- on the CNS may lead to convulsions when high doses are used.
- Bradycardia and a fall in cardiac output.
- Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of acetylcholine and, ultimately, results in paralysis of skeletal muscle.

B- Neostigmine

Neostigmine is a synthetic compound that reversibly inhibits acetylcholinesterase in a manner similar to that of physostigmine. It is more polar and does not enter the CNS. On skeletal muscle it can stimulate contractility before it paralyzes. Neostigmine has a moderate duration of action, usually 30 minutes to 2 hours.

Therapeutic uses:

- It is used to stimulate the bladder and GI tract
- Neostigmine has found use in symptomatic treatment of **myasthenia gravis**, an autoimmune disease caused by antibodies to the nicotinic receptor at neuromuscular junctions. This causes their degradation and, thus, makes fewer receptors available for interaction with the neurotransmitter.

Adverse effects of neostigmine

include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

C. Pyridostigmine and ambenomium

Pyridostigmine and ambenomium 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.

D- Demecarium

Demecarium is another cholinesterase inhibitor used to treat chronic open-angle glaucoma (primarily in patients refractory to other agents). Mechanisms of actions and side effects are similar to those of neostigmine.

E- Edrophonium

The actions of edrophonium are similar to those of neostigmine, except that it is more rapidly absorbed and has a short duration of action of 10 to 20 minutes. Edrophonium is used in the diagnosis of myasthenia gravis. Intravenous injection of edrophonium leads to a rapid increase in muscle strength.

F- Tacrine, donepezil, rivastigmine, and galantamine

patients with Alzheimer's disease have a deficiency of cholinergic neurons in the CNS. Anticholinesterases can be used as possible remedies for the loss of cognitive function.

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

Despite the ability of donepezil, rivastigmine, and galantamine to delay the progression of the disease, none can stop its progression.

Gastrointestinal distress is their primary adverse effect.

Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Irreversible)

A number of synthetic organophosphate compounds have the capacity to bind covalently to acetylcholinesterase. The result is a long-lasting increase in acetylcholine at all sites where it is released.

Echothiophate

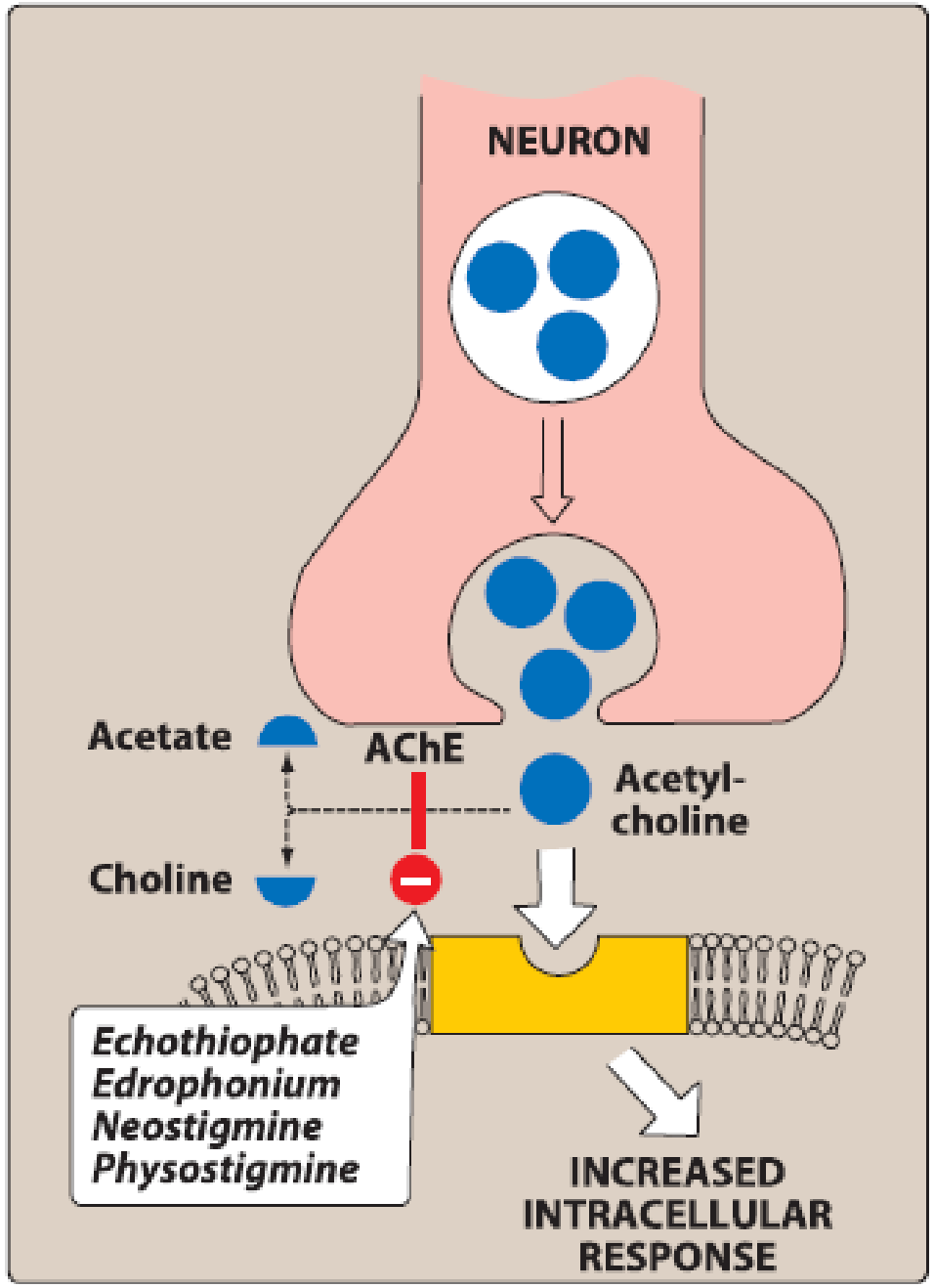
Mechanism of action: Echothiophate is an organophosphate that covalently binds via its phosphate group to the OH group at the active site of acetylcholinesterase. Once this occurs, the enzyme is permanently inactivated, and restoration of acetylcholinesterase activity requires the synthesis of new enzyme molecules. After that aging occurs (which is the release of ethyl group from the phosphorylated enzyme) this makes it impossible to break the bond between the remaining drug and the enzyme.

Actions:

Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. Echothiophate also produces intense miosis.

Therapeutic uses:

An ophthalmic solution of the drug is used directly in the eye for the chronic treatment of open-angle glaucoma. The potential risk for causing cataracts limits the use of echothiophate.



- **Reactivation of acetylcholinesterase:**
- **Pralidoxime** can reactivate inhibited acetylcholinesterase. However, it is unable to penetrate into the CNS. it displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of echothiophate, except for those in the CNS. After aging, pralidoxime is less effective.

Other treatments of organophosphate poisoning

Atropine is administered to prevent muscarinic side effects of these agents.

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you