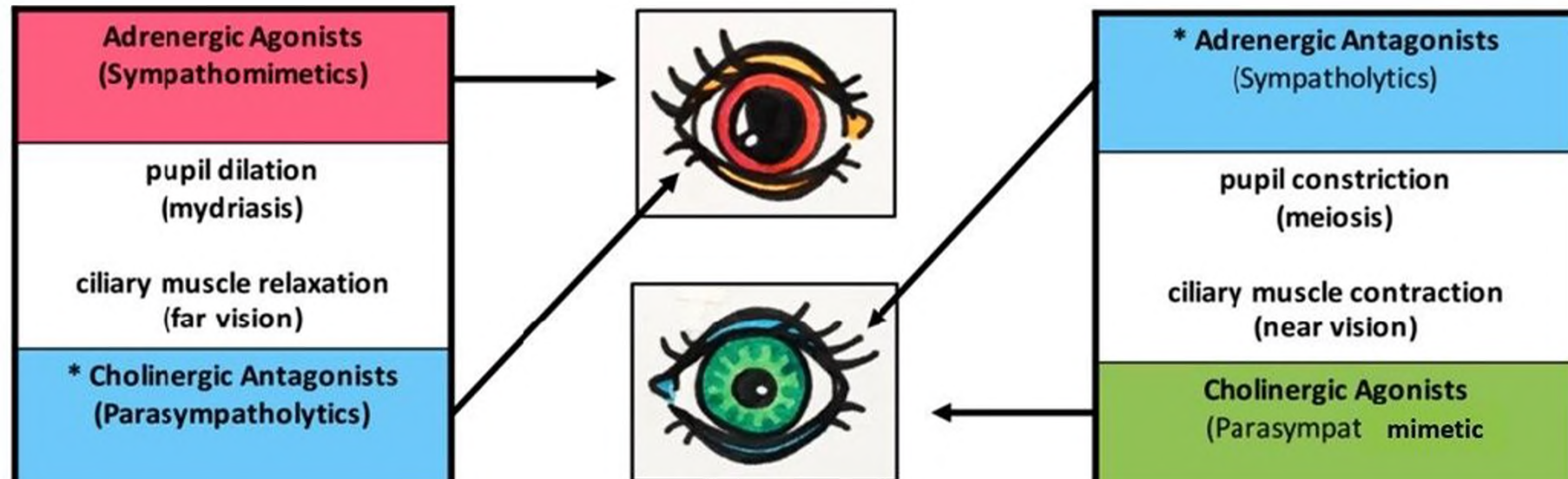


Autonomic drugs parasympathomimetics & parasympatholytics sympathomimetics & sympatholytics

Dr.Samaher
Jaber Younis
BCPS



Cholinergic Agonists

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

DIRECT ACTING

Acetylcholine

Bethanechol (oral)

Carbachol

Nicotine

Pilocarpine

Methacholine

INDIRECT ACTING (REVERSIBLE)

Short acting

Edrophonium

Medium acting

Neostigmine

Physostigmine

Pyridostigmine

INDIRECT ACTING USED FOR ALZHEIMER'D DISEASE

Tacrine (not used clinically due to ADR profile)

Donepezil

Galantamine

Rivastigmine

INDIRECT ACTING (IRREVERSIBLE)

Echothiophate

Organophosphates

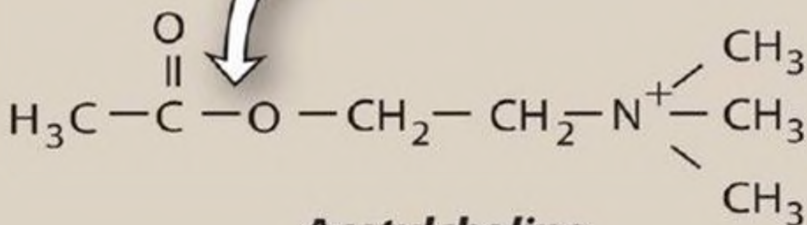
REACTIVATION OF ACETYLCHOLINESTERASE

Pralidoxime

1. Direct-Acting Cholinergic Agonists

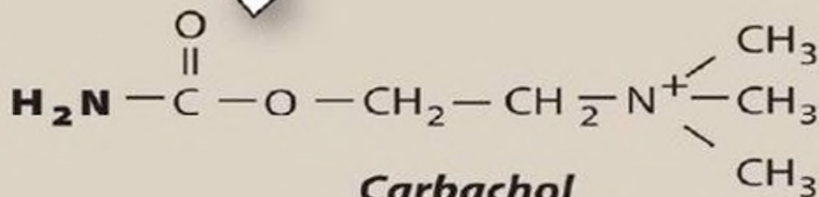
- Cholinergic agonists mimic the effects of ACh by binding directly to cholinergic receptors (muscarinic or nicotinic). These agents may be broadly classified into two groups: 1) choline esters, which include endogenous ACh and synthetic esters of choline, such as ***carbachol*** and ***bethanechol***, and 2) naturally occurring alkaloids, such as ***nicotine*** and ***pilocarpine***. All 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 clinical usefulness.

**Bond cleaved
by acetylcholin-
esterase**

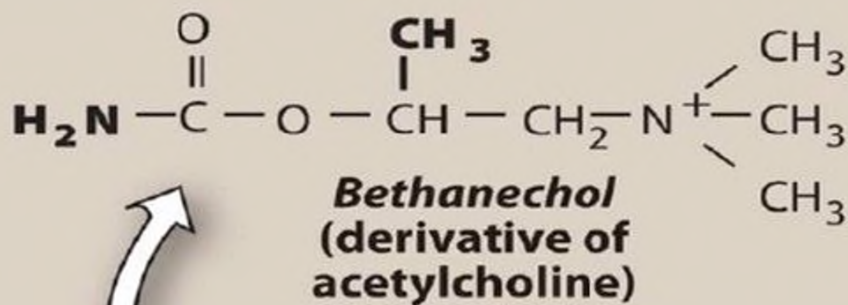


Acetylcholine

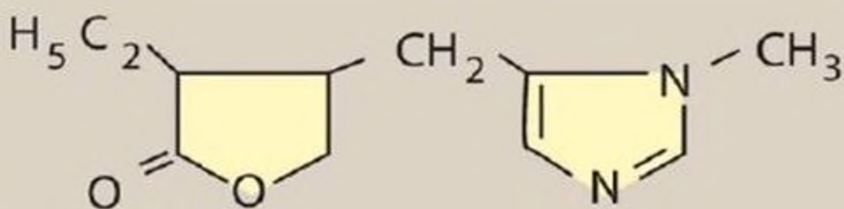
**Ester of carbamic acid;
resists hydrolysis by
acetylcholinesterase**



***Carbachol*
(derivative of
acetylcholine)**



**Ester of carbamic acid;
resists hydrolysis by
acetylcholinesterase**



Pilocarpine
(natural product)

- **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 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 stimulate urination.

- **2. Therapeutic uses**

- 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* can cause **generalized cholinergic stimulation, with sweating, salivation, flushing, decreased blood pressure (with reflex tachycardia), nausea, abdominal pain, diarrhea, and bronchospasm**. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent

- **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. The vision becomes fixed at some particular distance, making it impossible to focus. [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye.]
- **2. Therapeutic uses**
- Because of its high **potency**, receptor nonselectivity, and relatively long duration of action, *carbachol* is **rarely used**. **Intraocular use provides miosis** for eye surgery and lowers intraocular pressure in the treatment of **glaucoma**.
- **3. Adverse effects**
- With ophthalmologic use, few adverse effects occur due to lack of systemic penetration (quaternary amine).

- **Pilocarpine**

- The alkaloid *pilocarpine* is a tertiary amine and is stable to hydrolysis by AChE . 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.

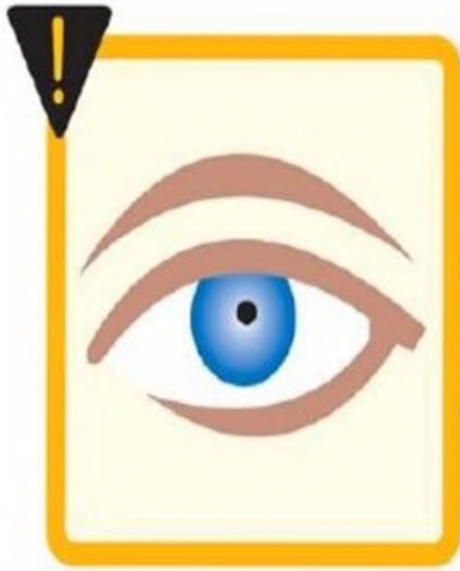
- **2. Therapeutic uses**

- *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. [Note: Topical carbonic anhydrase inhibitors, such as **dorzolamide** and β -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. **Sjögren 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**.

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

Miosis



Diarrhea



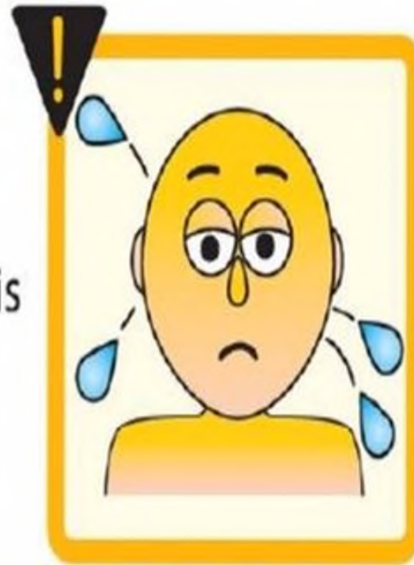
Urinary
urgency

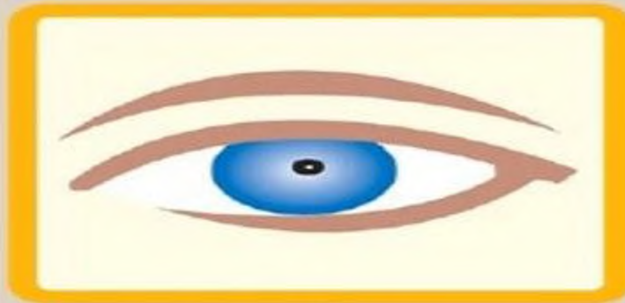


Nausea



Diaphoresis

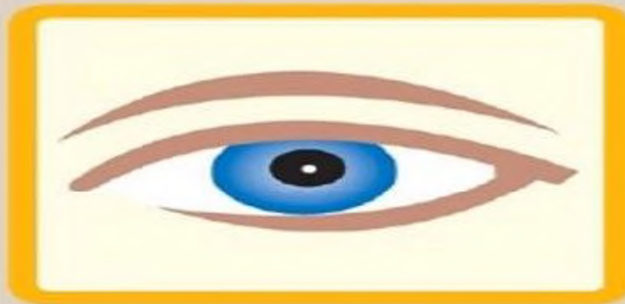




Eye treated
with *pilocarpine*
or *carbachol*



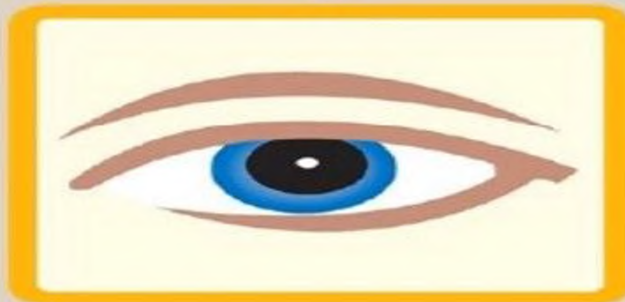
Miosis
(contraction of the pupil)



**Untreated
eye**



Mydriasis
(dilation of the pupil)



Eye treated
with *atropine*

2. Indirect-Acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)

- Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide 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 cholinergic receptors, 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.

Acetate

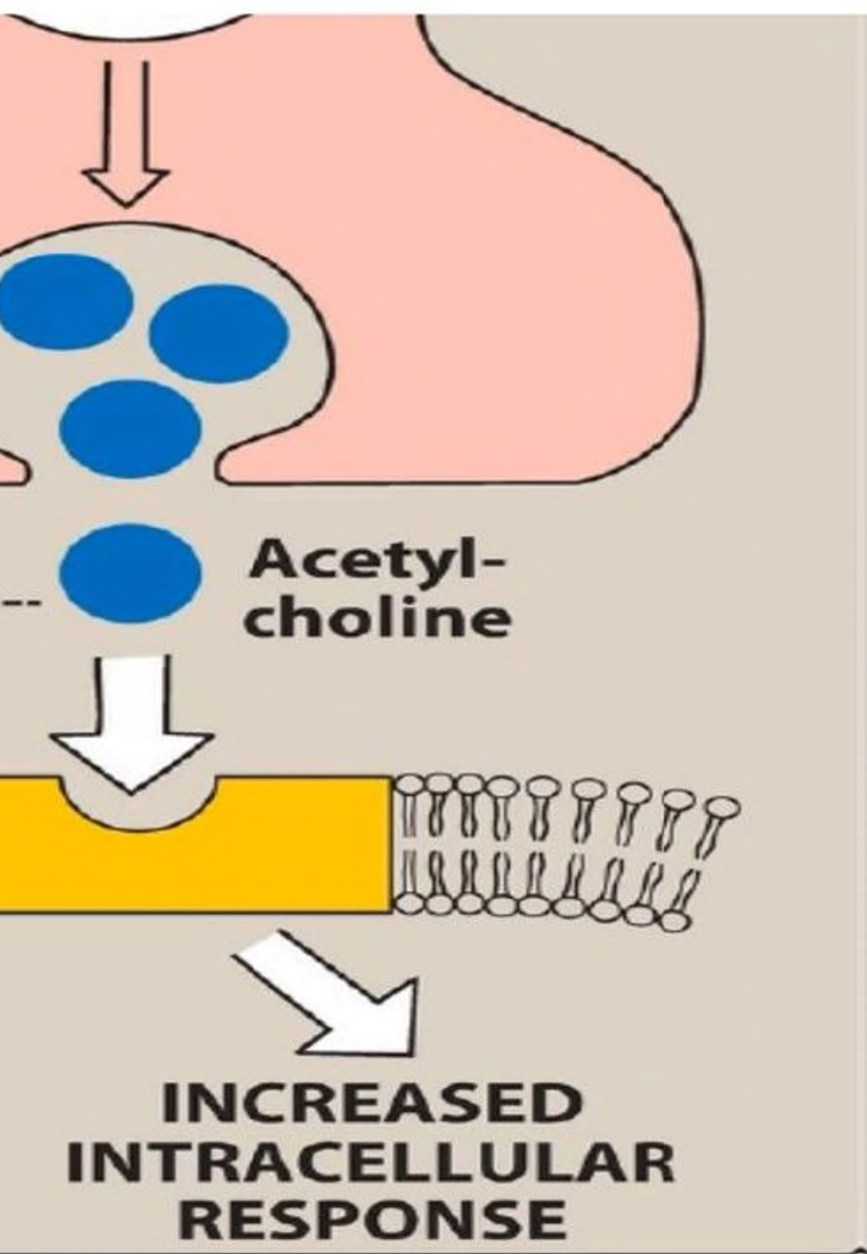


AChE

Choline



Echothiophate
Edrophonium
Neostigmine
Physostigmine



- **Edrophonium**

- *Edrophonium* is the prototype **short-acting AChE inhibitor**. *Edrophonium* binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It 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** (**historical**), an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, 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). For reversing the effects of nondepolarizing neuromuscular blockers (NMBs) after surgery. Due to the availability of other agents, *edrophonium* use has become **limited**.

- **Physostigmine**
- *Physostigmine* 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**. 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**
- *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

- **Neostigmine**
- *Neostigmine* is a synthetic compound that reversibly inhibits AChE in a manner similar to *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 *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 as **an antidote for competitive neuromuscular-blocking agents**. *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

- **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*
- ***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 ability 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.
- **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.

- **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 (no use)**

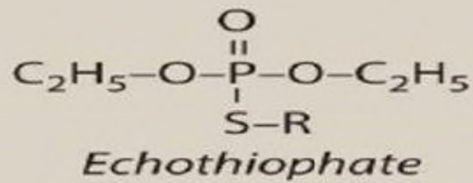
- A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. However, *echothiophate* is rarely used due to its side effect profile, which includes the risk of cataracts.

- **Reactivation of acetylcholinesterase**

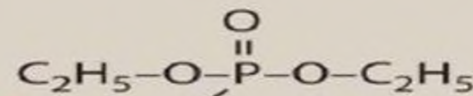
- *Pralidoxime (2-PAM)* can reactivate inhibited AChE. However, it is unable to penetrate into the CNS and therefore is not useful in treating the CNS effects of organophosphates. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate 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.

PHOSPHORYLATION OF ENZYME

- Enzyme inactivated
- *Pralidoxime* (2-PAM) can remove the inhibitor



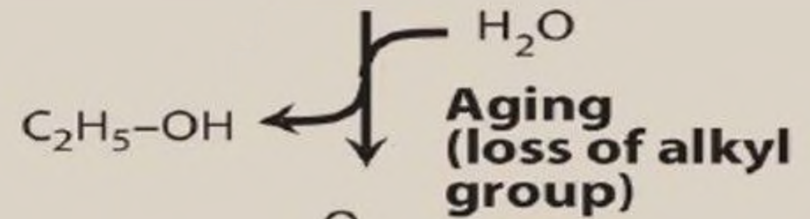
RSH



Acetylcholinesterase (inactive)

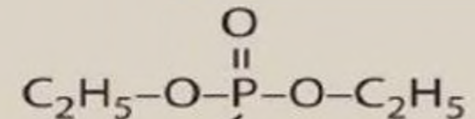
AGING

2-PAM



2-PAM NOT EFFECTIVE

Acetylcholinesterase (irreversibly inactive)



2-PAM

O-H

Acetylcholinesterase (active)

2-PAM

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

Cholinergic Antagonists

- Cholinergic antagonist is a general term for agents that bind to cholinceptors (**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**. They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), **antimuscarinic agents** (more accurate terminology), or **parasympatholytics**. The effects of parasympathetic innervation are thus, interrupted by these agents, and the actions of sympathetic innervation are left unopposed. A second group of drugs, the **ganglionic blockers**, shows a preference for nicotinic receptors of the sympathetic and parasympathetic ganglia. **Clinically, they are the least important 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.

AUTONOMIC

SOMATIC

Sympathetic innervation of adrenal medulla

Sympathetic

Parasympathetic

No ganglia

Preganglionic neuron

Ganglionic transmitter

Acetylcholine

Acetylcholine

Acetylcholine

Nicotinic receptor

Nicotinic receptor

Nicotinic receptor

Sites of action of ganglionic blockers

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

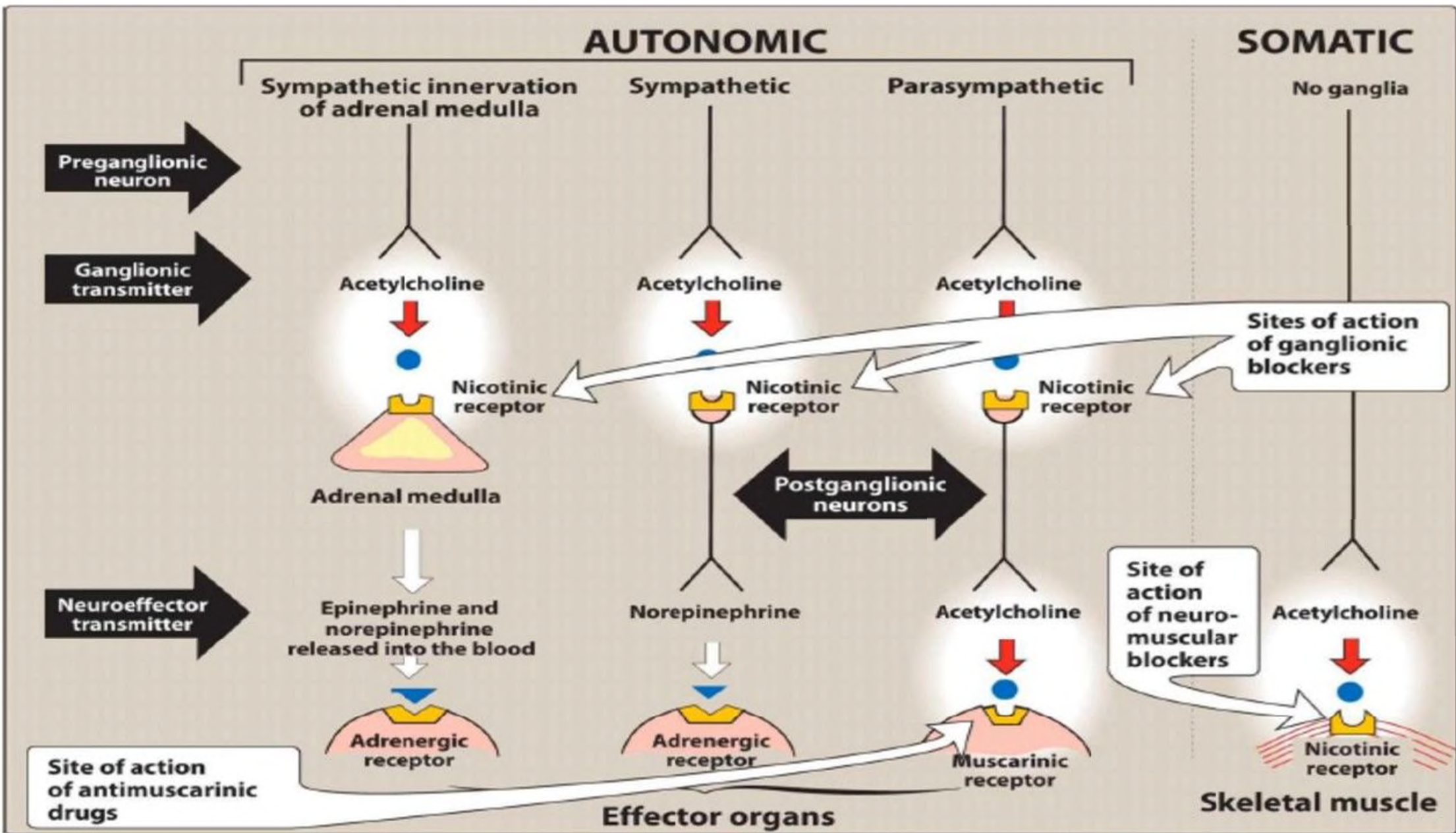
Muscarinic receptor

Nicotinic receptor

Site of action of antimuscarinic drugs

Effector organs

Skeletal muscle



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 SCOP

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. [Note: A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.]

- **Atropine**
- *Atropine* is a tertiary amine extracted from belladonna alkaloid. It has a high affinity for muscarinic receptors and binds competitively to prevent ACh from binding. *Atropine* acts both **centrally and peripherally**. General actions last about 4 hours; however, effects of topical administration in the **eye may persist for days**. Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are seen in **bronchial tissue, salivary and sweat glands, and the heart**.
- **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.
- **b. Gastrointestinal (GI)**
- *Atropine* (as the active isomer, *L-hyoscyamine*) 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 ulcers**. Doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.
- **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 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 M2 receptors on the sinoatrial node.

Dose of atropine

> 10.0 mg

5.0 mg

2.0 mg

0.5 mg





Hallucinations and delirium; coma

Rapid heart rate; palpitations; marked dryness of the mouth; dilation of pupil; some blurring of near vision

Slight cardiac slowing; some dryness of the mouth; inhibition of sweating

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. [Note: Inhibition of secretions of sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

2. Therapeutic uses

a. 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).

b. Antispasmodic

Atropine is used as an antispasmodic agent to relax the GI tract.

c. Cardiovascular

Injectable *atropine* is used to treat **bradycardia of varying etiologies**.

d. Antisecretory

Atropine is sometimes used as an **antisecretory agent** to block secretions in the respiratory tract prior to surgery.

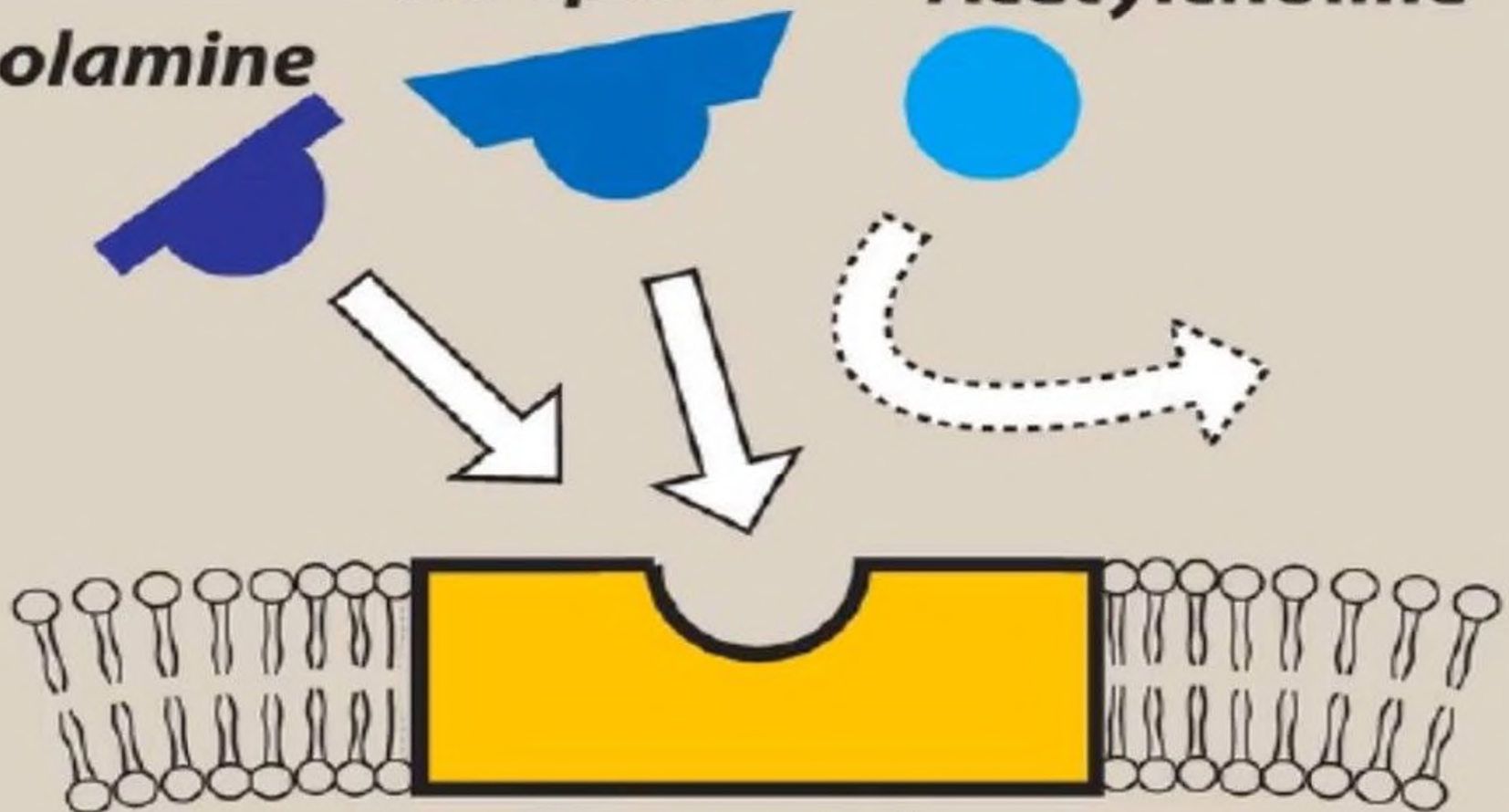
e. Antidote for cholinergic agonists

Atropine is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of 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 injectable *atropine* may be required over a long period 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.

Scopolamine

Atropine

Acetylcholine



**Muscarinic
receptor**

Scopolamine

- *Scopolamine*, another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS (unlike *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action as compared to *atropine*. It has some special actions as indicated below.
- **1. Actions**
- *Scopolamine* is one of the most effective drugs available for **motion sickness**. It also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces **sedation**, but at higher doses, it can produce **excitement**. *Scopolamine* may produce euphoria and is susceptible to abuse.

Aclidinium, glycopyrrolate, ipratropium, and tiotropium

- *Ipratropium* and *tiotropium* are quaternary derivatives of *tropine*, and *glycopyrrolate* and *aclidinium* are synthetic quaternary compounds.
- *Ipratropium* is classified as a short-acting muscarinic antagonist (SAMA), while *glycopyrrolate*, *tiotropium*, and *aclidinium* are classified as long-acting muscarinic antagonists (LAMAs) based on the duration of action.
- These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). *Ipratropium* and *tiotropium* are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively. All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

Tropicamide and cyclopentolate

- These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.
- ***Benztropine and trihexyphenidyl***
- *Benztropine* and *trihexyphenidyl* are useful as adjuncts with other **antiparkinson agents to treat Parkinson disease** and other types of parkinsonian syndromes, including antipsychotic-induced **extrapyramidal symptoms**.

Oxybutynin and other antimuscarinic agents for overactive bladder

- *Oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, and trospium* are synthetic *atropine*-like drugs with antimuscarinic actions.
- **1. Actions**
 - By competitively blocking muscarinic (M3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Antimuscarinic actions at M3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. *Darifenacin* and *solifenacin* are relatively more selective M3 muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.
- **2. Therapeutic uses**
 - These agents are used for management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.
- **4. Adverse effects**
 - Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents. Extended release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated. *Trospium* is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia.

Drug

Therapeutic uses

Muscarinic blockers

Trihexyphenidyl
Benztropine

- Treatment of Parkinson disease
- Management of antipsychotic-induced extrapyramidal effects

Darifenacin
Fesoterodine
Oxybutynin
Solifenacin
Tolterodine
Trospium

- Treatment of overactive urinary bladder

Cyclopentolate
Tropicamide
*Atropine**

- In ophthalmology, to produce mydriasis and cycloplegia prior to refraction

*Atropine**

- To treat spastic disorders of the GI tract
- To treat organophosphate poisoning
- To suppress respiratory secretions prior to surgery
- To treat bradycardia

Scopolamine

● To prevent motion sickness

Aclidinium
Glycopyrrolate
Ipratropium
Tiotropium

● Treatment of COPD

Ganglionic blockers

Nicotine

● Smoking cessation

Neuromuscular Blocking Agents



- These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle. They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers (NMBs) are clinically useful to facilitate rapid intubation when needed due to respiratory failure (rapid sequence intubation).
- During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses. This increases the safety of anesthesia by allowing patients to recover quickly and completely.
- NMBs should not substitute for inadequate anesthesia. NMBs are also used in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.

Adrenergic Agonists

- The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline).
- These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed Sympathomimetics, and drugs that block activation of adrenergic receptors are termed sympatholytics.
- Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists),
- while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists).

DIRECT-ACTING AGENTS

Albuterol ACCUNEB, PROAIR, VENTOLIN

Arformoterol BROVANA

Clonidine CATAPRES, DURACLON

Dobutamine* GENERIC ONLY

Dopamine* GENERIC ONLY

Epinephrine* ADRENALIN, EPIPEN

Fenoldopam CORLOPAM

Formoterol FORADIL, PERFOROMIST

Guanfacine INTUNIV, TENEX

Indacaterol ARCAPTA

Isoproterenol* ISUPREL

Metaproterenol GENERIC ONLY

Midodrine GENERIC ONLY

Mirabegron MYRBETRIQ

Norepinephrine* LEVOPHED

Oxymetazoline AFRIN, VISINE

Phenylephrine NEO-SYNEPHRINE, SUDAFED PE

Salmeterol SEREVENT

Terbutaline GENERIC ONLY

INDIRECT-ACTING AGENTS

Amphetamine ADDERALL

Cocaine GENERIC ONLY

DIRECT AND INDIRECT ACTING (mixed action) AGENTS

Ephedrine AKOVAZ

Pseudoephedrine SUDAFED

- **Mechanism of action of adrenergic agonists**

- **1. Direct-acting agonists**

- These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of *epinephrine* from the adrenal medulla. Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, *dopamine*, and *phenylephrine*

- **2. Indirect-acting agonists**

- These agents may block the **reuptake of *norepinephrine*** or cause the release of *norepinephrine* from the cytoplasmic pools or vesicles of the adrenergic neuron. The *norepinephrine* then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause *norepinephrine* release include ***cocaine* and *amphetamine***, respectively

- **3. Mixed-action agonists**

- ***Ephedrine*** and its stereoisomer, ***pseudoephedrine***, both stimulate adrenoceptors directly and enhance release of *norepinephrine* from the adrenergic neuron

- **Epinephrine**

- *Epinephrine* is one of the four catecholamines (*epinephrine*, *norepinephrine*, *dopamine*, and *dobutamine*) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*, which is stored in chromaffin cells along with *norepinephrine*. On stimulation, the adrenal medulla releases about 80% *epinephrine* and 20% *norepinephrine* directly into the circulation. ***Epinephrine* interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.**

- **1. Actions**

- **a. Cardiovascular**

- The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (**positive inotrope: β_1 action**) and increases its rate of contraction (**positive chronotrope: β_1 Action**). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. *Epinephrine* activates β_1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β_2 effects). These combined effects result in a decrease in renal blood flow. Therefore, the **cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β_2 receptor-mediated vasodilation in the skeletal muscle vascular bed**

b. Respiratory

Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). It also inhibits the release of allergy mediators such as **histamine from mast cells**

c. Hyperglycemia

Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2 effect), increased release of **glucagon** (β_2 effect), and a decreased release of **insulin** (α_2 effect).

d. Lipolysis

Epinephrine initiates lipolysis through agonist activity on the β receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

2. Therapeutic uses

a. Bronchospasm

Epinephrine is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of anaphylactic shock, *epinephrine* is the drug of choice and can be lifesaving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves.

a. Anaphylactic shock

Epinephrine is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.

a. Cardiac arrest

Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.

d. Local anesthesia

Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of *epinephrine*. *Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. *Epinephrine* also reduces systemic absorption of the local anesthetic and promotes local hemostasis.

e. Intraocular surgery

Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

- **Pharmacokinetics**

- *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route for anaphylaxis in the outpatient setting is **intramuscular** (anterior thigh) due to rapid absorption. In emergencies, ***epinephrine* is given intravenously (IV) for the most rapid onset of action.** It may also be given **subcutaneously, by endotracheal tube, or by inhalation.** It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and **vanillylmandelic acid** are excreted in urine.

- **Adverse effects**

- *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger **cardiac arrhythmias**, particularly if the patient is receiving *digoxin*. *Epinephrine* can also induce **pulmonary edema** due to increased afterload caused by vasoconstrictive properties of the drug. Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to an enhanced response to *epinephrine*, and the dose must be reduced in these individuals. **Inhalation anesthetics also sensitize the heart to the effects of *epinephrine*,** which may lead to tachycardia. *Epinephrine* increases the release of endogenous stores of glucose. In diabetic patients, dosages of *insulin* may have to be increased. Nonselective β -blockers prevent vasodilatory effects of *epinephrine* on β_2 receptors, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

- **Norepinephrine**

- Because *norepinephrine* is the neurotransmitter in the adrenergic neurons, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the **α - adrenergic** receptor is most affected.

- **1. Cardiovascular actions**

- **a. Vasoconstriction**

- *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α_1 effect). Both systolic and diastolic blood pressures increase. [Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β_2 receptors on blood vessels supplying skeletal muscles. The weak β_2 activity of *norepinephrine* also explains why it is not useful in the treatment **of bronchospasm or anaphylaxis.**]

- **Dopamine**

- *Dopamine*, the immediate metabolic precursor of *norepinephrine*, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate α - and β -adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α_1 receptors, whereas at lower doses, it stimulates β_1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors, distinct from the α - and β -adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with *norepinephrine* release.

- **1. Actions**

- **Cardiovascular**

- *Dopamine* exerts a stimulatory effect on the β_1 receptors of the heart, having both positive inotropic and chronotropic effects . At very high doses, *dopamine* activates α_1 receptors on the vasculature, resulting in vasoconstriction.
- Dose:
 - 1-5 mcg/kg/min iv (renal dose, low dose)
 - 5-15 mcg/kg/min iv (cardiac dose, medium dose)
 - >20 mcg/kg/min iv (vascular dose, high dose)

- **Fenoldopam**

- *Fenoldopam* is an agonist of peripheral *dopamine* D1 receptors. It is used as a rapid-acting vasodilator to treat **severe hypertension** in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. *Fenoldopam* is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a **10-minute elimination half-life** after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may occur with this agent.

- **Dobutamine**

- *Dobutamine* is a synthetic, direct-acting catecholamine that is primarily a β_1 receptor agonist with minor β_2 and α_1 effects. It increases heart rate and cardiac output with few vascular effects. *Dobutamine* is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not elevate oxygen demands of the myocardium as much as other sympathomimetic drugs. *Dobutamine* should be used with caution in atrial fibrillation, because it increases atrioventricular (AV) conduction. Other adverse effects are similar to *epinephrine*. Tolerance may develop with prolonged use.

- **Phenylephrine**

- *Phenylephrine* is a direct-acting, synthetic adrenergic drug that binds primarily to α_1 receptors. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally, making it useful in the treatment of paroxysmal supraventricular tachycardia. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate). Large doses can cause hypertensive headache and cardiac irregularities. *Phenylephrine* acts as a **nasal decongestant** when applied topically or taken orally. Although data suggest it may not be as effective, *phenylephrine* has replaced *pseudoephedrine* in many oral decongestants, since *pseudoephedrine* has been misused to make *methamphetamine*. *Phenylephrine* is also used in ophthalmic solutions for mydriasis.

- **Midodrine**

- *Midodrine*, a prodrug, is metabolized to the pharmacologically active desglymidodrine. It is a selective α_1 agonist, which acts in the periphery to increase arterial and venous tone. *Midodrine* is indicated for the treatment of orthostatic hypotension. The drug should be given three times daily, with doses at 3- or 4-hour intervals. To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

- **Clonidine**

- *Clonidine* is an α_2 agonist used for the treatment of hypertension. It can also be used to minimize symptoms of **withdrawal from opiates, tobacco smoking, and benzodiazepines**. Both *clonidine* and the α_2 agonist **guanfacine** may be used in the management of **attention deficit hyperactivity disorder**. *Clonidine* acts centrally on presynaptic α_2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are **lethargy, sedation, constipation, and xerostomia**. Abrupt discontinuation must be avoided to prevent rebound hypertension

- **Albuterol, metaproterenol, and terbutaline**

- *Albuterol, metaproterenol, and terbutaline* are short-acting β_2 agonists (SABAs) used primarily as bronchodilators and administered by a metered-dose inhaler. *Albuterol* is the SABA of choice for the management of acute asthma symptoms, because it is more selective for β_2 receptors than *metaproterenol*. Inhaled *terbutaline* is no longer available in the United States, but is still used in other countries. **Injectable terbutaline** is used off-label as a uterine relaxant to **suppress premature labor**, and use for this indication should not exceed 72 hours. One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β_1 receptor activation), especially in patients with underlying cardiac disease. **Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided**

- **Salmeterol, formoterol, and indacaterol**
- *Salmeterol, formoterol, arformoterol* (the [R,R]-enantiomer of *formoterol*), and *indacaterol* are long-acting β_2 selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol*. Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action. LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthma-related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.
- **Mirabegron**
- *Mirabegron* is a β_3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder. *Mirabegron* may increase blood pressure and should not be used in patients with uncontrolled hypertension. It increases levels of *digoxin* and inhibits the CYP2D6 isozyme, which may enhance the effects of other medications metabolized by this pathway (for example, *metoprolol*).
- **Tyramine**
- *Tyramine* is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. Like ***amphetamines***, ***tyramine can enter the nerve terminal and displace stored norepinephrine***. The released catecholamine then acts on adrenoreceptors.

Adrenergic Antagonists

- The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous or exogenous agonists. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

α BLOCKERS

Alfuzosin UROXATRAL

Doxazosin CARDURA

Phenoxybenzamine DIBENZYLINE

Phentolamine GENERIC ONLY

Prazosin MINIPRESS

Silodosin RAPAFLO

Tamsulosin FLOMAX

Terazosin GENERIC ONLY

Yohimbine YOCON

β BLOCKERS

Acebutolol GENERIC ONLY

Atenolol TENORMIN

Betaxolol BETOPTIC-S

Bisoprolol GENERIC ONLY

Carteolol GENERIC ONLY

Carvedilol COREG, COREG CR

Esmolol BREVIBLOC

Labetalol GENERIC ONLY

Levobunolol BETAGAN

Metipranolol GENERIC ONLY

Metoprolol LOPRESSOR, TOPROL-XL

Nadolol CORGARD

Nebivolol BYSTOLIC

Pindolol GENERIC ONLY

Propranolol INDERAL LA, INNOPRAN XL

Timolol BETIMOL, ISTALOL, TIMOPTIC

- **α -Adrenergic Blocking Agents**

- α -Adrenergic blocking agents antagonize the subtype(s) of α -adrenergic receptors (α_1 or α_2), depending on the specificity of the agent for the receptor subtype(s). Drugs that block α_1 -adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α_1 -adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This lowered blood pressure induces reflex tachycardia. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. Selective α_2 -adrenergic blockers have limited clinical utility.

Phenoxybenzamine (α)

Phentolamine (α)

**Doxazocin, Prazocin, Trazocin,
Alfuzocin, Tamsulosin(α_1)**

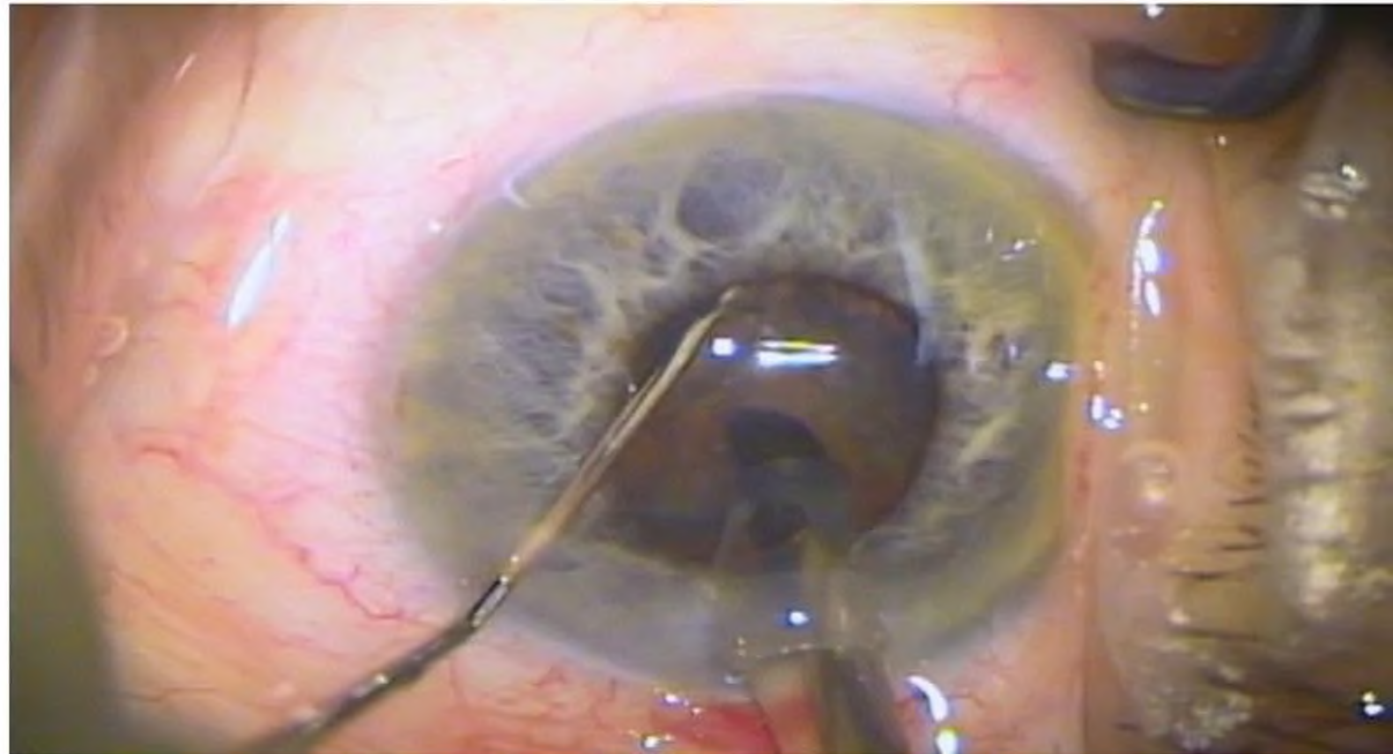
Vasodilation, ↓ peripheral Resistance, Reflex tachycardia, ↓ BP, Epinephrine Reversal. Used in Pheochromocytoma, Ranaud's Disease. Adverse: postural hypotension, nasal stuffiness, nausea, and vomiting, Sexual dysfunction

Vasodilation, ↓ peripheral Resistance, Reflex tachycardia, ↓ BP, Epinephrine Reversal. Used in Pheochromocytoma, Impotence, Ranaud's Disease. Adverse: Postural hypotension, nasal stuffiness, nausea, and vomiting, Sexual dysfunction, arrhythmias, anginal pain

Vasodilation, ↓ peripheral Resistance, ↓ BP 1st three are used in Hypertension, 1st dose effect. other 2 are used in benign prostatic hyperplasia or BPH Adverse: dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension

- the first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.
- α 1-Blockers such as *prazosin* and *doxazosin* may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). An additive antihypertensive effect occurs when α 1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, *sildenafil*), thereby necessitating cautious dose titration and use at the lowest possible doses. These agents may cause “**floppy iris syndrome**,” a condition in which the iris billows in response to intraoperative eye surgery

- a triad of intraoperative signs beyond poor pupil dilation: iris billowing and floppiness; **iris prolapse** to the main and side incisions; and progressive miosis. Particularly if such iris behavior is unexpected, the rate of complications such as posterior capsule rupture, vitreous loss, and iris trauma is increased.



- **β -Adrenergic Blocking Agents**

- All of the clinically available β -blockers are competitive antagonists. Nonselective β -blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors. These drugs also differ in intrinsic sympathomimetic activity (ISA), CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics. Although all β -blockers lower blood pressure, they do not induce postural hypotension, because the α -adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β -Blockers are effective in treating systemic as well as portal hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma.
- They are also used for the prophylaxis of migraine headaches. [Note: The names of all β -blockers end in “-olol” except for *labetalol* and *carvedilol*.]

Propranolol(β)	Actions: $\downarrow$HR, $\downarrow$HT, $\downarrow$Heart O₂ Demand, $\downarrow$BP, no Postural Hypotension due to Peripheral Vasoconstriction, Bronchoconstriction, $\downarrow$Renal Flow due to $\downarrow$BP results in Na Retention, disturbances in glucose metabolism, blocks action of Isoproterenol. Uses: Hypertension, glaucoma, angina, hyperthyroidism, Myocardial Infarction, Migraine prophylaxis Adverse: Bronchoconstriction, Arrhythmias, Sexual impairment, Disturbances in metabolism.
Timolol, Nadolol (β)	more potent than propranolol, with longer duration of action. Used in Glaucoma, & occasionally, for systemic treatment of hypertension
Acebutolol, Atenolol, Esmolol, Metoprolol(β_1)	antagonize β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors. $\downarrow$BP in hypertension and increase exercise tolerance in angina. Esmolol has a very short lifetime. little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism useful in hypertensive patients with impaired pulmonary function, & Diabetes. Atenolol (Glaucoma) Adverse: dizziness, drowsiness, fatigue, bradycardia

Acebutolol, Pindolol(β_1 -ISA)

intrinsic sympathomimetic activity, i.e, stimulate $\beta_1, 2$.effective in hypertensive patients with moderate bradycardia

Labetolol, Carvedilol(α, β)

Peripheral vasodilation, $\downarrow$ BP, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable.Labetalol may be employed as an alternative to methyldopa in the treatment of pregnancy-induced hypertension.Adverse:Orthostatic hypotension and dizziness