I. OVERVIEW

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 cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine (ACh), whereas the adrenergic drugs (Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS. Figure 4.1 summarizes the cholinergic agonists discussed in this chapter.

II. THE CHOLINERGIC NEURON

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 4.2). The postganglionic sympathetic division of sweat glands also uses acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and also play an important role in the central nervous system (CNS).

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), and 6) recycling of choline and acetate (Figure 4.3).

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 coupled to the efflux of protons. The mature vesicle contains not only ACh but also adenosine triphosphate and proteoglycan. Cotransmission 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 cotransmitter 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.
II. The Cholinergic Neuron

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 4.2). 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 4.3). [Note: Butyrylcholinesterase, sometimes called...]

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Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.
pseudocholinesterase, is found in the plasma, but does not play a significant role in the termination of the effect of ACh in the synapse.]

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 acetylated into ACh that is stored until released by a subsequent action potential.

III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoreceptors, designated muscarinic and 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

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 4.4A). There are five sub-classes of muscarinic receptors. However, only M₁, M₂, and M₃ receptors have been functionally characterized.

1. Locations of muscarinic receptors: These receptors are found on ganglia of the peripheral nervous system and 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. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration, they may show some activity at nicotinic receptors.]

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 Gₐ, that in turn activates phospholipase C. This ultimately leads to the production of the second messengers 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: Pilocarpine is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic
agonists and antagonists that are directed against specific receptor subtypes. M<sub>3</sub> receptor agonists are being investigated for the treatment of Alzheimer’s disease and M<sub>3</sub> receptor antagonists for the treatment of chronic obstructive pulmonary disease. [Note: At present, no clinically important agents interact solely with the M<sub>3</sub> and M<sub>4</sub> receptors.]

**B. Nicotinic receptors**

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (Figure 4.4B). 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 N<sub>2</sub>, and the others, N<sub>3</sub>. 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.

**IV. DIRECT-ACTING CHOLINERGIC AGONISTS**

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoreceptors (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 4.5). 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. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

**A. Acetylcholine**

Acetylcholine [ah-see-teel-KOE-leen] 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.]

2. **Decrease in blood pressure:** Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates M<sub>r</sub> 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:** In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions. In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

**B. Bethanechol**

*Bethanechol* [be-TAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh (Figure 4.5). 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. **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 (Figure 4.6). 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.
C. Carbachol (carbamylcholine)

*Carbachol* [KAR-ba-kole] has both muscarinic and nicotinic actions. Like *bethanechol*, *carbachol* is an ester of carbamic acid (Figure 4.5) 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.

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* [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by AChE (Figure 4.5). 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 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 impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye.] *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. 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.

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. [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.

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

### V. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (REVERSIBLE)

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 4.8). Therefore, these drugs can provoke a response at all cholinoreceptors 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.

#### A. **Edrophonium**

*Edrophonium* [ed-row-FOE-nee-um] 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). *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* [fi-zoe-STIG-meen] 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 carbamo-ylated 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 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.

2. **Therapeutic uses:** The drug increases intestinal and bladder motility, which serves as its therapeutic action in atony of either organ (Figure 4.9). *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* [nee-oh-STIG-meen] 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.

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* [peer-id-oh-STIG-meen] and *ambenonium* [am-be-NOE-nee-um] 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 [TAK-reen] was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of donepezil [doe-NEP-e-zil], rivastigmine [ri-va-STIG-meen], and galantamine [ga-LAN-ta-meen] to delay the progression of Alzheimer’s disease, none can stop its progression. GI distress is their primary adverse effect (see Chapter 8).

VI. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTIMUSCARINIC 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. Echothiophate

1. Mechanism of action: Echothiophate [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 4.10). 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: 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. Figure 4.11 summarizes the actions of some of the cholinergic agonists.

VII. TOXICOLOGY OF ANTIMUSCARINIC 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.
### VII. Toxicology of Anticholinesterase Agents

<table>
<thead>
<tr>
<th><strong>Bethanechol</strong></th>
<th><strong>Physostigmine</strong></th>
<th><strong>Rivastigmine, galantamine, donepezil</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used in treatment of urinary retention</td>
<td>• Increases intestinal and bladder motility</td>
<td>• Used as first-line treatments for Alzheimer's disease, though confers modest benefit</td>
</tr>
<tr>
<td>• Binds preferentially at muscarinic receptors</td>
<td>• Reverses CNS and cardiac effects of tricyclic antidepressants</td>
<td>• Have not been shown to reduce healthcare costs or delay institutionalization</td>
</tr>
<tr>
<td></td>
<td>• Reverses CNS effects of atropine</td>
<td>• Can be used with memantine (N-methyl-D-aspartate antagonist) with moderate to severe disease</td>
</tr>
<tr>
<td></td>
<td>• Uncharged, tertiary amine that can penetrate the CNS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Carbachol</strong></th>
<th><strong>Neostigmine</strong></th>
<th><strong>Echothiophate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Produces miosis during ocular surgery</td>
<td>• Prevents postoperative abdominal distention and urinary retention</td>
<td>• Used in treatment of open-angle glaucoma</td>
</tr>
<tr>
<td>• Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to pilocarpine</td>
<td>• Used in treatment of myasthenia gravis</td>
<td>• Has long duration of action (100 hours)</td>
</tr>
<tr>
<td></td>
<td>• Used as an antidote for competitive neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Has intermediate duration of action (0.5 to 2 hrs)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pilocarpine</strong></th>
<th><strong>Edrophonium</strong></th>
<th><strong>Acetylcholine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduces intraocular pressure in open-angle and narrow-angle glaucoma</td>
<td>• Used for diagnosis of myasthenia gravis</td>
<td>• Used to produce miosis in ophthalmic surgery</td>
</tr>
<tr>
<td>• Binds preferentially at muscarinic receptors</td>
<td>• Used as an antidote for competitive neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td>• Uncharged, tertiary amine that can penetrate the CNS</td>
<td>• Has short duration of action (10 to 20 min)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.11**
Summary of actions of some cholinergic agonists. CNS = central nervous system.

### A. Reactivation of acetylcholinesterase

*Pralidoxime* [pral-i-DOX-eem] (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 (Figures 4.6 and 4.9). 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 patient airway, oxygen supply, and artificial respiration, may be necessary as well.
Study Questions

Choose the ONE best answer.

Botulinum toxin blocks the release of acetylcholine from cholinergic nerve terminals. Which of the following is a possible effect of botulinum toxin?

A. Skeletal muscle paralysis.
B. Improvement of myasthenia gravis symptoms.
C. Increased salivation.
D. Reduced heart rate.

Correct answer = A. Acetylcholine released by cholinergic neurons acts on nicotinic receptors in the skeletal muscle cells to cause contraction. Therefore, blockade of ACh release causes skeletal muscle paralysis. Myasthenia gravis is an autoimmune disease where antibodies are produced against nicotinic receptors and inactivate nicotinic receptors. A reduction in ACh release therefore worsens (not improves) the symptoms of this condition. Reduction in ACh release by botulinum toxin causes reduction in secretions including saliva (not increase in salivation) causing dry mouth and an increase (not reduction) in heart rate due to reduced vagal activity.

A dentist would like to reduce salivation in a patient in preparation for an oral surgical procedure. Which of the following strategies will be useful in reducing salivation?

A. Activate nicotinic receptors in the salivary glands.
B. Block nicotinic receptors in the salivary glands.
C. Activate muscarinic receptors in the salivary glands.
D. Block muscarinic receptors in the salivary glands.

Which of the following is a systemic effect of a muscarinic agonist?

A. Reduced heart rate (bradycardia).
B. Increased blood pressure.
C. Mydriasis (dilation of the pupil).
D. Reduced urinary frequency.
E. Constipation.

If an ophthalmologist wants to dilate the pupils for an eye examination, which of the following drugs/classes of drugs could be theoretically useful?

A. Muscarinic receptor activator (agonist).
B. Muscarinic receptor inhibitor (antagonist).
C. Acetylcholine.
D. Pilocarpine.
E. Neostigmine.

In Alzheimer’s disease, there is a deficiency of cholinergic neuronal function in the brain. Theoretically, which of the following strategies will be useful in treating the symptoms of Alzheimer’s disease?

A. Inhibiting cholinergic receptors in the brain.
B. Inhibiting the release of acetylcholine in the brain.
C. Inhibiting the acetylcholinesterase enzyme in the brain.
D. Activating the acetylcholinesterase enzyme in the brain.

Correct answer = C. Since there is already a deficiency in brain cholinergic function in Alzheimer’s disease, inhibiting cholinergic receptors or inhibiting the release of ACh will worsen the condition. Activating the acetylcholinesterase enzyme will increase the degradation of ACh, which will again worsen the condition. However, inhibiting the acetylcholinesterase enzyme will help to increase the levels of ACh in the brain and thereby help to relieve the symptoms of Alzheimer’s disease.
An elderly female who lives in a farm house was brought to the emergency room in serious condition after ingesting a liquid from an unlabeled bottle found near her bed, apparently in a suicide attempt. She presented with diarrhea, frequent urination, convulsions, breathing difficulties, constricted pupils (miosis), and excessive salivation. Which of the following is correct regarding this patient?

A. She most likely consumed an organophosphate pesticide.
B. The symptoms are consistent with sympathetic activation.
C. Her symptoms can be treated using an anticholinesterase agent.
D. Her symptoms can be treated using a cholinergic agonist.

Sarin is a volatile nerve agent that inhibits cholinesterase enzymes. Which of the following symptoms would you expect to see in a patient exposed to sarin?

A. Urinary retention.
B. Tachycardia.
C. Constriction of pupils (miosis).
D. Dilation of the pupils (mydriasis).
E. Dry mouth.

Head and neck irradiation in cancer patients can decrease salivary secretion and cause dry mouth. All of the following drugs or classes of drugs are theoretically useful in improving secretion of saliva in these patients except:

A. Muscarinic antagonists.
B. Muscarinic agonists.
C. Anticholinesterase agents.
D. Pilocarpine.
E. Neostigmine.

Which of the following drugs or classes of drugs will be useful in treating the symptoms of myasthenia gravis?

A. Nicotinic antagonists.
B. Muscarinic agonists.
C. Muscarinic antagonists.
D. Anticholinesterase agents.

Atropa belladonna is a plant that contains atropine (a muscarinic antagonist). Which of the following drugs or classes of drugs will be useful in treating poisoning with belladonna?

A. Malathion.
B. Physostigmine.
C. Muscarinic antagonists.
D. Nicotinic antagonists

Correct answer = A. The symptoms are consistent with that of cholinergic crisis. Since the elderly female lives on a farm and since the symptoms are consistent with that of cholinergic crisis (usually caused by cholinesterase inhibitors), it may be assumed that she has consumed an organophosphate pesticide (irreversible cholinesterase inhibitor). Assuming that the symptoms are caused by organophosphate poisoning, administering an anticholinesterase agent or a cholinergic agonist will worsen the condition. The symptoms are not consistent with that of sympathetic activation, as sympathetic activation will cause symptoms opposite to that of cholinergic crisis seen in this patient.

Correct answer = C. Sarin is an organophosphate nerve gas that inhibits cholinesterase enzymes and increases ACh levels. Therefore, symptoms of cholinergic crisis (increased urination, bradycardia, excessive secretions, constriction of pupils, etc.) should be expected in patients exposed to sarin. Urinary retention, tachycardia, mydriasis, and dry mouth are usually seen with muscarinic antagonists.

Correct answer = A. Activation of muscarinic receptors in the salivary glands causes secretion of saliva. This can be achieved in theory by using a muscarinic agonist such as pilocarpine or an anticholinesterase agent such as neostigmine (increases levels of ACh). Muscarinic agonists (anticholinergic drugs) will reduce salivary secretion and worsen dry mouth.

Correct answer = D. The function of nicotinic receptors in skeletal muscles is diminished in myasthenia gravis due to the development of antibodies to nicotinic receptors in the patient’s body (autoimmune disease). Any drug that can increase the levels of ACh in the neuromuscular junction can improve symptoms in myasthenia gravis. Thus, cholinesterase inhibitors help to improve the symptoms of myasthenia gravis. Muscarinic drugs have no role in myasthenia gravis, and nicotinic antagonists will worsen the symptoms.

Correct answer = B. Atropine is a competitive muscarinic receptor antagonist that causes anticholinergic effects. Muscarinic agonists or any other drugs that can increase the levels of ACh will be able to counteract the effects of atropine. Thus, anticholinesterases such as malathion and physostigmine can counteract the effects of atropine in theory. However, malathion being an irreversible inhibitor of acetylcholinesterase is not used for systemic treatment in patients. Muscarinic antagonists will worsen the toxicity of atropine. Nicotinic antagonists could worsen the toxicity by acting on parasympathetic ganglionic receptors and thus reducing the release of ACh.