Cholinergic Agonists

4

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I. OVERVIEW

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in the mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors 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 cholinergic agonists discussed in this chapter.

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

Figure 4.1
Summary of cholinergic agonists.

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 ACh. In addition, cholinergic neurons innervate the muscles of the somatic system and 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 of ACh, 2) storage, 3) release, 4) binding of ACh to the receptor, 5) degradation of ACh in the synaptic cleft (the space between the nerve endings and adjacent receptors on nerves or effector organs), and 6) recycling of choline (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.

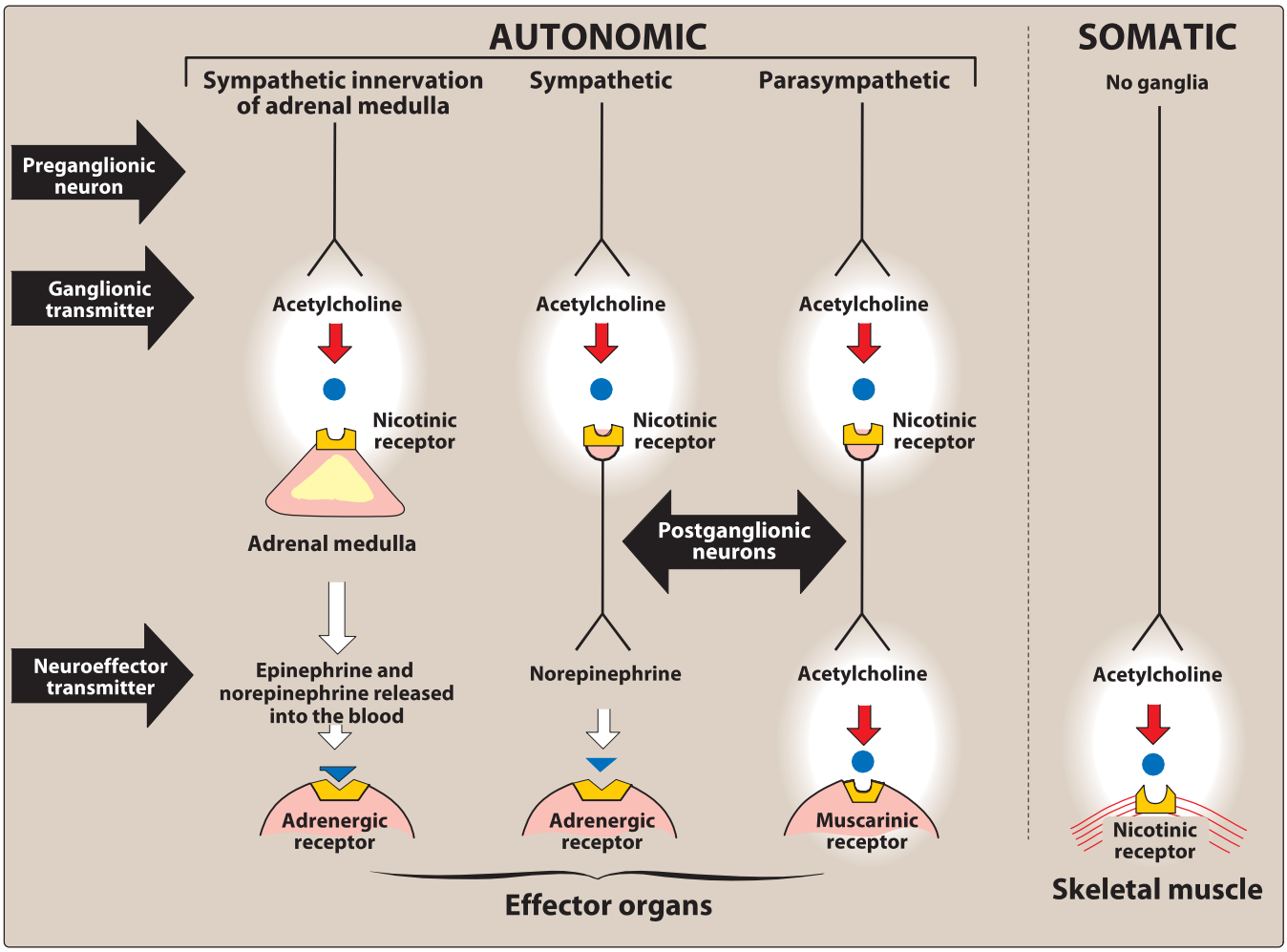

Figure 4.2
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

2. **Storage of acetylcholine in vesicles:** ACh is packaged and stored into presynaptic vesicles by an active transport process. The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan. 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 (here, ATP) that increases or decreases the effect of the primary neurotransmitter.

3. **Release of acetylcholine:** When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of 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.

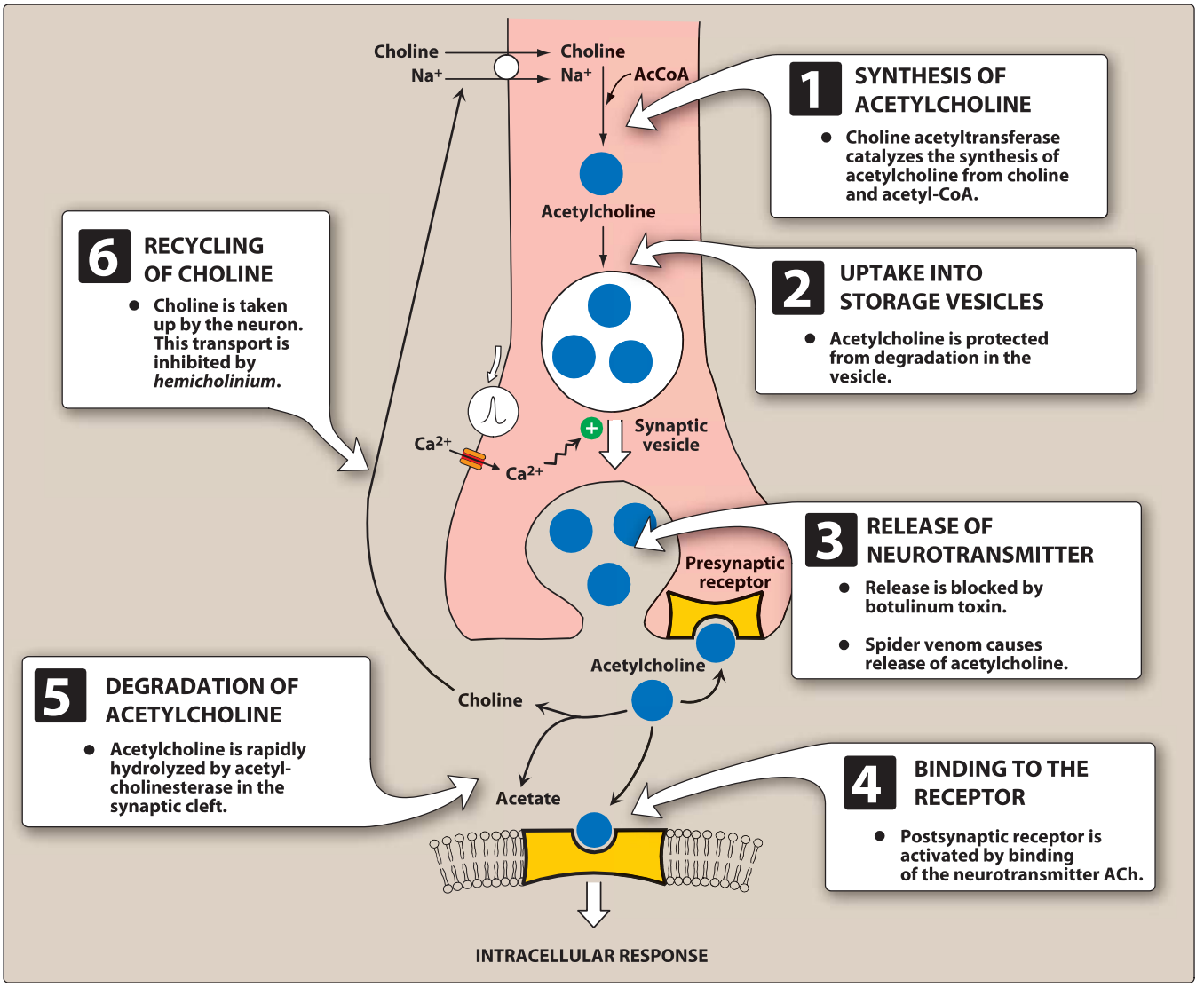

Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

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 ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of 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.

6. **Recycling of choline:** Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoceptors, 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 in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for *nicotine*, an alkaloid found in tobacco and other plants (Figure 4.4A). There are five subclasses of muscarinic receptors; however, only M_1, M_2, and M_3 receptors have been functionally characterized.

1. **Location of muscarinic receptors:** These receptors are found on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands. Although all five subtypes are found on neurons, M_1 receptors are also found on gastric parietal cells, M_2 receptors on cardiac cells and smooth muscle, and M_3 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. **Mechanism of acetylcholine signal transduction:** A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when M_1 or M_3 receptors are activated, the receptor undergoes a conformational change and interacts with a G-protein that activates phospholipase C. This ultimately leads to production of second messengers inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 causes an increase in intracellular Ca^{2+}. Calcium can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. DAG activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell. In contrast, activation of the M_2 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.

3. **Muscarinic agonists:** *Pilocarpine* is a nonselective muscarinic agonist used to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agents that are directed against specific receptor subtypes.

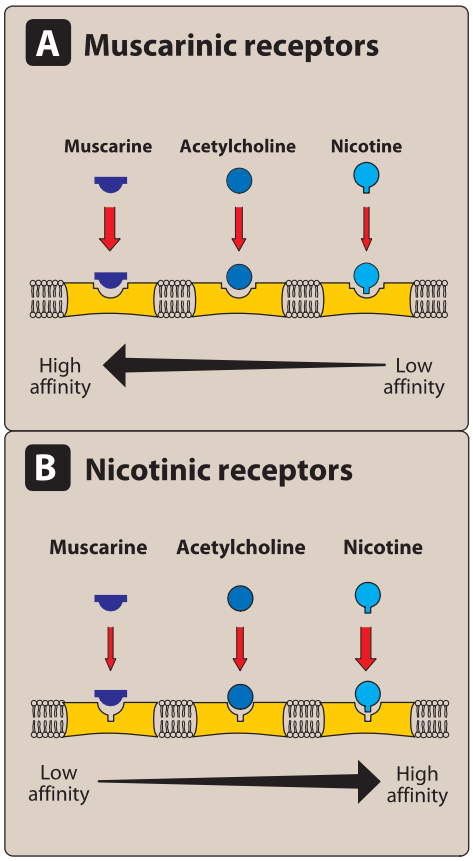

Figure 4.4
Types of cholinergic receptors.

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 (ionotropic receptor). 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_M, and the others, N_N. 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 cholinoceptors (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* (Figure 4.5). 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.

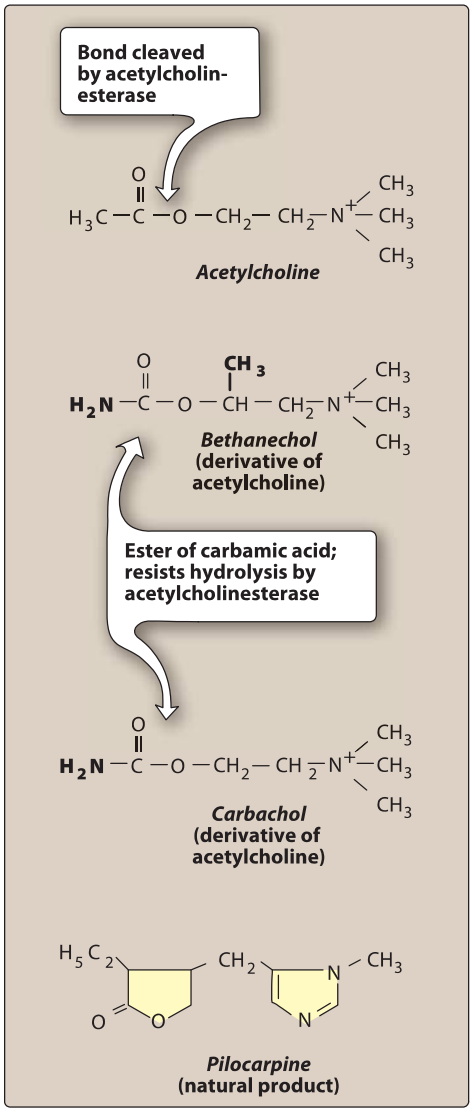

Figure 4.5
Comparison of the structures of some cholinergic agonists.

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 (bradycardia) and cardiac output, mainly because 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_3 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, increases gastric acid secretion, and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions and causes bronchoconstriction. [Note: *Methacholine*, a direct-acting cholinergic agonist, is used to assist in the diagnosis of asthma due to its bronchoconstricting properties.] In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

B. Bethanechol

Bethanechol [be-THAN-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 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 (Figure 4.6), 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.

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.

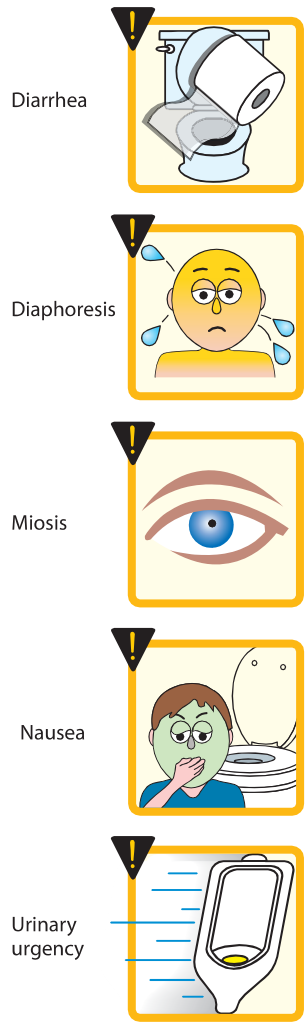

Figure 4.6
Some adverse effects observed with cholinergic agonists.

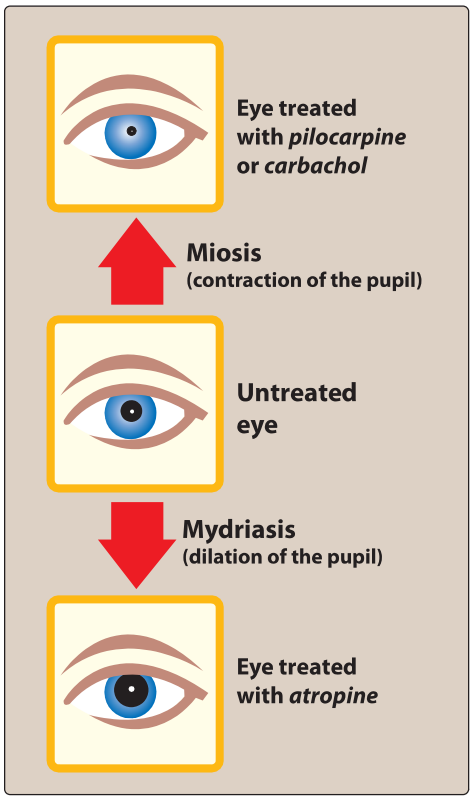

Figure 4.7
Actions of *pilocarpine*, *carbachol*, and *atropine* on the iris and ciliary muscle of the eye.

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 (Figure 4.7). [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).

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

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 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 cholinoceptors, 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 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 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). *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 (NMBs) 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 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,

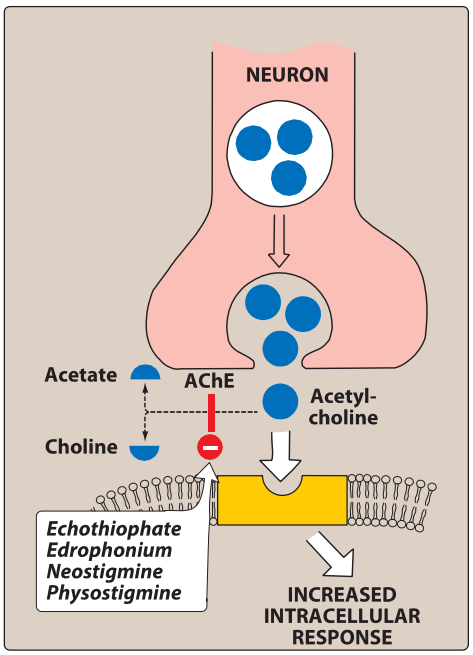

Figure 4.8
Mechanisms of action of indirect cholinergic agonists. AChE = acetylcholinesterase.

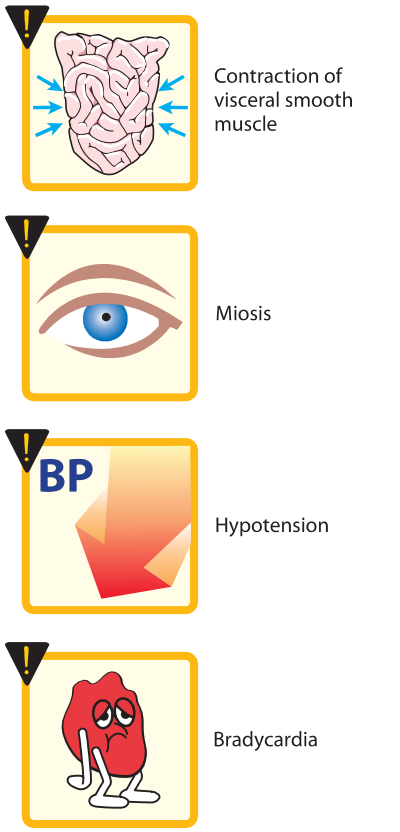

Figure 4.9
Some actions of *physostigmine*.

bradycardia, and hypotension (Figure 4.9). 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.

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 *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.

D. Pyridostigmine

Pyridostigmine [peer-id-oh-STIG-meen] is another cholinesterase inhibitor used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3 to 6 hours) but longer than that of *neostigmine*. Adverse effects are similar to those of *neostigmine*.

E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* [TAK-reen], the first agent

in this category, 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 disease, none can stop its progression. GI distress is their primary adverse effect (see Chapter 8).

VI. 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.

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 cataracts. Figure 4.11 summarizes actions of some cholinergic agonists.

VII. TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as sarin are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.

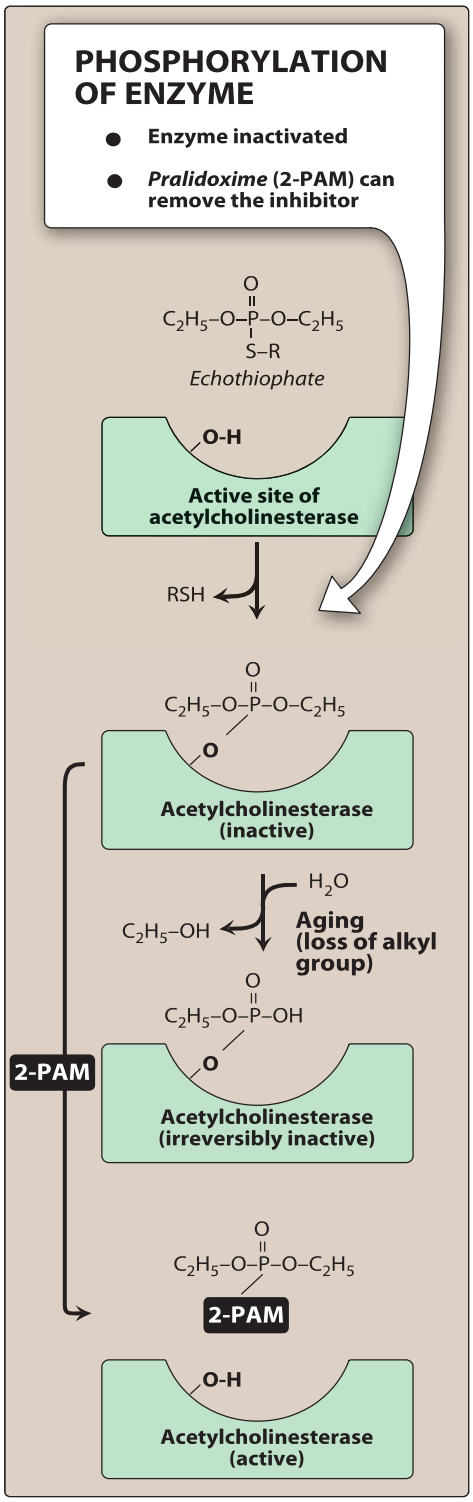

Figure 4.10
Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime* (2-PAM). R = $(CH_3)_3N^+–CH_2–CH_2–$; RSH = $(CH_3)_3N^+–CH_2–CH_2–S–H$.

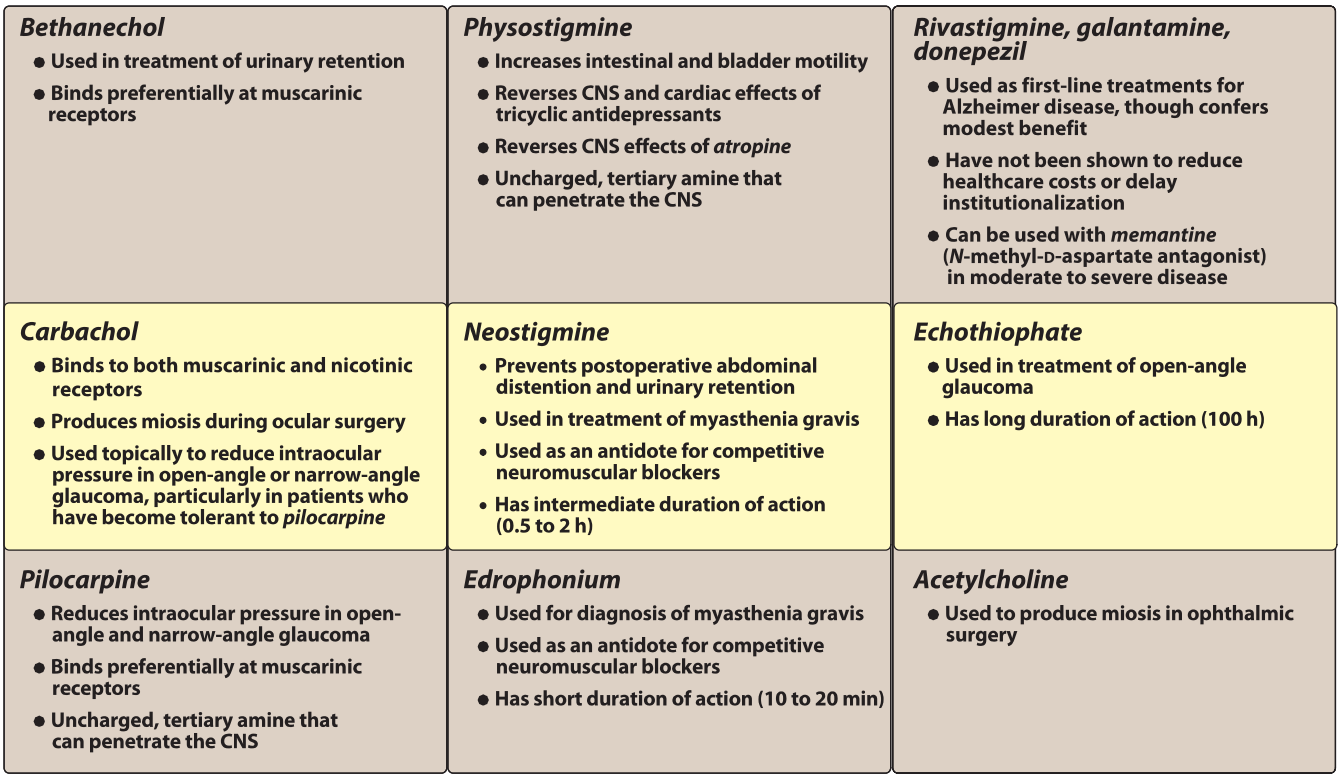

Figure 4.11
Summary of actions of some cholinergic agonists. CNS = central nervous system.

A. Reactivation of acetylcholinesterase

Pralidoxime [pral-i-DOX-eem] (2-PAM) can reactivate inhibited AChE (Figure 4.10). 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. In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*).

B. Other treatments

Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. *Diazepam* is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

STUDY QUESTIONS

Choose the ONE best answer.

4.1 Botulinum toxin blocks the release of acetylcholine from cholinergic nerve terminals. Which 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.

4.2 A patient develops urinary retention after an abdominal surgery. Urinary obstruction was ruled out in this patient. Which strategy would be helpful in promoting urination?

A. Activating nicotinic receptors
B. Inhibiting the release of acetylcholine
C. Inhibiting cholinesterase enzyme
D. Blocking muscarinic receptors

Correct answer = C. Activation of muscarinic receptors in the detrusor muscle of the urinary bladder can promote urination in patients where the tone of detrusor muscle is low. Inhibiting cholinesterase enzyme increases the levels of acetylcholine, and acetylcholine can increase the tone of the detrusor muscle. There are no nicotinic receptors in the detrusor muscle; therefore, activation of nicotinic receptors is not helpful. Inhibiting the release of acetylcholine or blocking muscarinic receptors worsens urinary retention.

4.3 Which of the following drugs could theoretically improve asthma symptoms?

A. Bethanechol
B. Pilocarpine
C. Pyridostigmine
D. Atropine

Correct answer = D. Muscarinic agonists and drugs that increase acetylcholine levels cause constriction of bronchial smooth muscles and could exacerbate asthma symptoms. Bethanechol and pilocarpine are muscarinic agonists, and pyridostigmine is a cholinesterase inhibitor that increases levels of acetylcholine. Atropine is a muscarinic antagonist and therefore does not exacerbate asthma. Theoretically, it should relieve symptoms of asthma (not used clinically for this purpose).

4.4 If an ophthalmologist wants to dilate the pupils for an eye examination, which drug/class of drugs is theoretically useful?

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

Correct answer = B. Muscarinic agonists (for example, pilocarpine) contract the circular smooth muscles in the iris sphincter and constrict the pupil (miosis). Anticholinesterases (for example, neostigmine, physostigmine) also cause miosis by increasing the level of ACh. Muscarinic antagonists, on the other hand, relax the circular smooth muscles in the iris sphincter and cause dilation of the pupil (mydriasis).

4.5 In Alzheimer disease, there is a deficiency of cholinergic neuronal function in the brain. Theoretically, which strategy is useful in treating symptoms of Alzheimer 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. Because there is already a deficiency in brain cholinergic function in Alzheimer disease, inhibiting cholinergic receptors or inhibiting the release of ACh worsens the condition. Activating the acetylcholinesterase enzyme increases the degradation of ACh, which also worsens the condition. However, inhibiting the acetylcholinesterase enzyme helps to increase the levels of ACh in the brain and thereby relieve the symptoms of Alzheimer disease.

4.6 An elderly female who lives in a farmhouse 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.

Correct answer = A. The symptoms are consistent with that of cholinergic crisis. Since the elderly female lives on a farm and the symptoms are consistent with a 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.

4.7 A patient who received a nondepolarizing neuromuscular blocker (NMB) for skeletal muscle relaxation during surgery is experiencing mild skeletal muscle paralysis after the surgery. Which drug could reverse this effect of NMBs?

A. Pilocarpine
B. Bethanechol
C. Neostigmine
D. Atropine

Correct answer = C. Neuromuscular blockers act by blocking nicotinic receptors on the skeletal muscles. Increasing the levels of ACh in the neuromuscular junctions can reverse the effects of NMBs. Therefore, neostigmine, a cholinesterase inhibitor, could reverse the effects of NMBs. Pilocarpine and bethanechol are preferentially muscarinic agonists and have no effects on the nicotinic receptors. Atropine is a muscarinic antagonist and has no effects on nicotinic receptors.

4.8 A 60-year-old female who had a cancerous growth in the neck region underwent radiation therapy. Her salivary secretion was reduced due to radiation and she suffers from dry mouth (xerostomia). Which drug would be most useful in treating xerostomia in this patient?

A. Acetylcholine
B. Pilocarpine
C. Echothiophate
D. Atropine

Correct answer = B. Salivary secretion may be enhanced by activating muscarinic receptors in the salivary glands. This can be achieved in theory by using a muscarinic agonist or an anticholinesterase agent. Pilocarpine is a muscarinic agonist administered orally for this purpose. Acetylcholine has similar effects as that of pilocarpine; however, it cannot be used therapeutically as it is rapidly destroyed by cholinesterase in the body. Echothiophate is an irreversible cholinesterase inhibitor, but it cannot be used therapeutically because of its toxic effects. Atropine is a muscarinic antagonist and worsens dry mouth.

4.9 A 40-year-old male presents to his family physician with drooping eyelids, difficulty chewing and swallowing, and muscle fatigue even on mild exertion. Which agent could be used to diagnose myasthenia gravis in this patient?

A. Atropine
B. Edrophonium
C. Pralidoxime
D. Echothiophate

Correct answer = B. The function of nicotinic receptors in skeletal muscles is diminished in myasthenia gravis due to the development of antibodies to nicotinic receptors (autoimmune disease). Any drug that increases levels of ACh in the neuromuscular junction can improve symptoms in myasthenia gravis. Thus, edrophonium, a reversible cholinesterase inhibitor with a short duration of action can temporarily improve skeletal muscle weakness in myasthenia gravis, serving as a diagnostic tool. Atropine is a muscarinic antagonist and has no role in skeletal muscle function. Pralidoxime is a drug that is used to reverse the binding of irreversible cholinesterase inhibitors with cholinesterase enzyme and helps to reactivate cholinesterase enzyme. Hence, pralidoxime will not be useful in improving skeletal muscle function in myasthenia gravis.

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

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

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