SECTION II AUTONOMIC DRUGS

CHAPTER 6

Introduction to Autonomic Pharmacology

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CASE STUDY

A teenage boy is seen at the office of a dental surgeon for extraction of an impacted wisdom tooth. He is so nervous that the dentist decides to administer a sedative to calm the boy. After intravenous administration of the sedative (promethazine), the boy relaxes and the extraction is accomplished with no complications. However, when the boy stands up from the dental chair, he turns very pale and faints. Lying on the floor, he rapidly regains consciousness, but has a rapid heart rate of 120 bpm and a blood pressure of only 110/70 mm Hg. When he sits up, his heart rate increases to 140 bpm, his pressure drops to 80/40 mm Hg, and he complains of faintness. He is helped to a couch in the reception area, where he rests for 30 minutes. At the end of this time the boy is able to sit up without symptoms and, after an additional 15 minutes, is able to stand without difficulty. What autonomic effects might promethazine have that would explain the patient's signs and symptoms? Why did his heart rate increase when his blood pressure dropped?

The nervous system is conventionally divided into the central nervous system (CNS; the brain and spinal cord) and the peripheral nervous system (PNS; neuronal tissues outside the CNS). The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic. The **autonomic nervous system (ANS)** is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life. Evidence is accumulating that the ANS, especially the vagus nerve, also influences immune function and some CNS functions such as seizure discharge. The **somatic** subdivision is largely concerned with consciously controlled functions such as movement, respiration, and posture. Both systems have important afferent (sensory) inputs that provide information regarding the internal and external environments and modify motor output through reflex arcs of varying size and complexity.

The nervous system has several properties in common with the endocrine system, which is the other major system for control of body function. These include high-level integration in the brain, the ability to influence processes in distant regions of the body, and extensive use of negative feedback. Both systems use chemicals for the transmission of information. In the nervous system, chemical transmission occurs between nerve cells and between nerve cells and their effector cells. Chemical transmission takes place through the release of small amounts of transmitter substances from the nerve terminals into the synaptic cleft. The transmitter crosses the cleft by diffusion and activates or inhibits the postsynaptic cell by binding to a specialized receptor molecule. In a few cases, *retrograde* transmission may occur from the postsynaptic cell to the presynaptic neuron terminal and modify its subsequent activity.

By using drugs that mimic or block the actions of chemical transmitters, we can selectively modify many autonomic functions. These functions involve a variety of effector tissues, including cardiac muscle, smooth muscle, vascular endothelium, exocrine glands, and presynaptic nerve terminals. Autonomic drugs are useful in many clinical conditions. Unfortunately, a very large number of drugs used for other purposes have unwanted effects on autonomic function (see Case Study).

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

The ANS lends itself to division on anatomic grounds into two major portions: the **sympathetic (thoracolumbar)** division and the **parasympathetic (craniosacral)** division (Figure 6–1). Neurons in both divisions originate in nuclei within the CNS and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. The sympathetic preganglionic

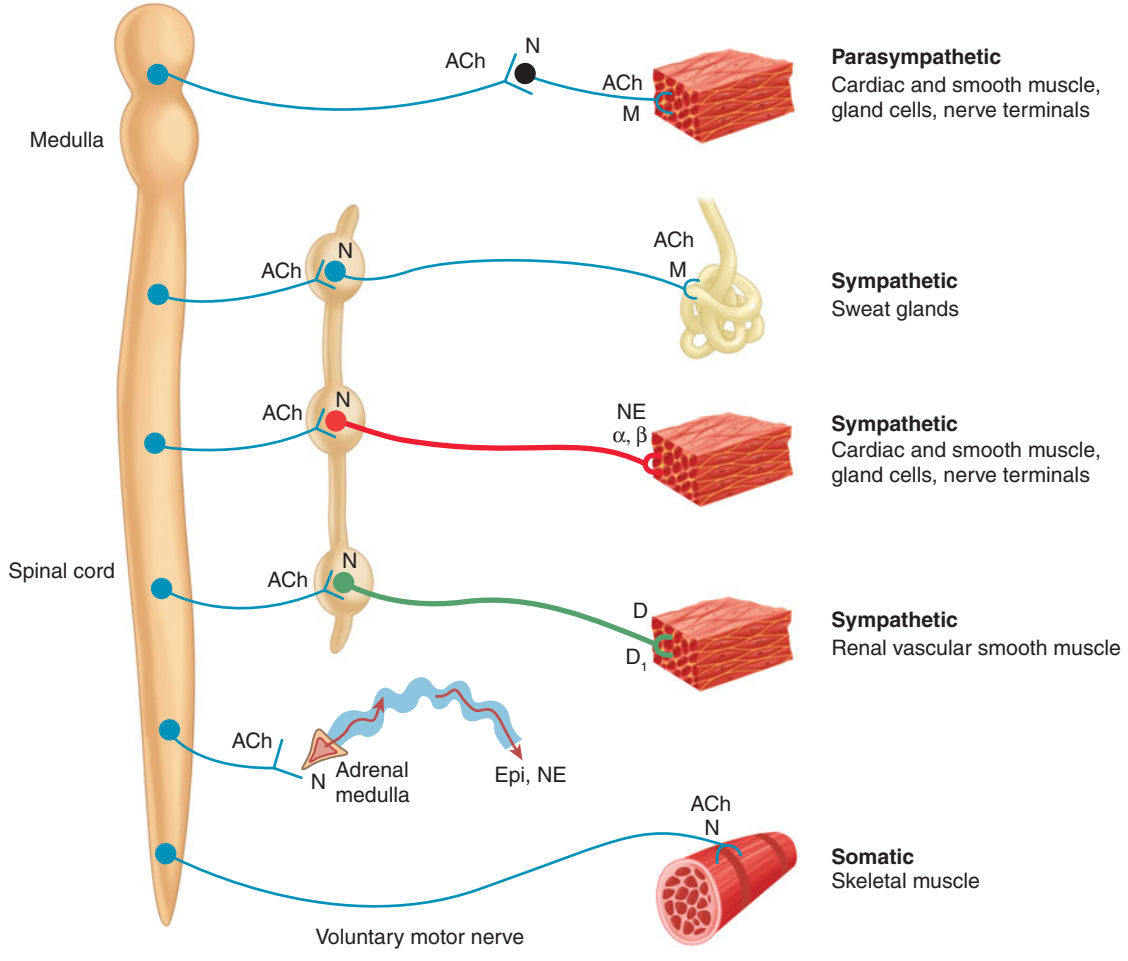

FIGURE 6–1 Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Cholinergic nerves are shown in blue; noradrenergic in red; and dopaminergic in green. Note that some sympathetic postganglionic fibers release acetylcholine or dopamine rather than norepinephrine. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases epinephrine and norepinephrine into the blood. ACh, acetylcholine; D, dopamine; Epi, epinephrine; M, muscarinic receptors; N, nicotinic receptors; NE, norepinephrine.

fibers leave the CNS through the thoracic and lumbar spinal nerves. The parasympathetic preganglionic fibers leave the CNS through the cranial nerves (especially the third, seventh, ninth, and tenth) and the third and fourth sacral spinal nerve roots.

Most sympathetic preganglionic fibers are short and terminate in ganglia located in the **paravertebral** chains that lie on either side of the spinal column. The remaining sympathetic preganglionic fibers are somewhat longer and terminate in **prevertebral ganglia,** which lie in front of the vertebrae, usually on the ventral surface of the aorta. From the ganglia, postganglionic sympathetic fibers run to the tissues innervated. Some preganglionic parasympathetic fibers terminate in parasympathetic ganglia located outside the organs innervated: the **ciliary, pterygopalatine, submandibular, otic,** and several **pelvic ganglia.** However, the majority of parasympathetic preganglionic fibers terminate on ganglion cells distributed diffusely or in networks in the walls of the innervated organs. Note that the terms "sympathetic" and "parasympathetic" are anatomic designations and do not depend on the type of transmitter chemical released from the nerve endings nor on the kind of effect—excitatory or inhibitory—evoked by nerve activity.

In addition to these clearly defined peripheral motor portions of the ANS, large numbers of afferent fibers run from the periphery to integrating centers, including the enteric plexuses in the gut, the autonomic ganglia, and the CNS. Many of the sensory pathways that end in the CNS terminate in the integrating centers of the hypothalamus and medulla and evoke reflex motor activity that is carried to the effector cells by the efferent fibers described previously. There is increasing evidence that some of these sensory fibers also have peripheral motor functions.

The **enteric nervous system (ENS)** is a large and highly organized collection of neurons located in the walls of the gastrointestinal (GI) system (Figure 6–2). It is sometimes considered a third

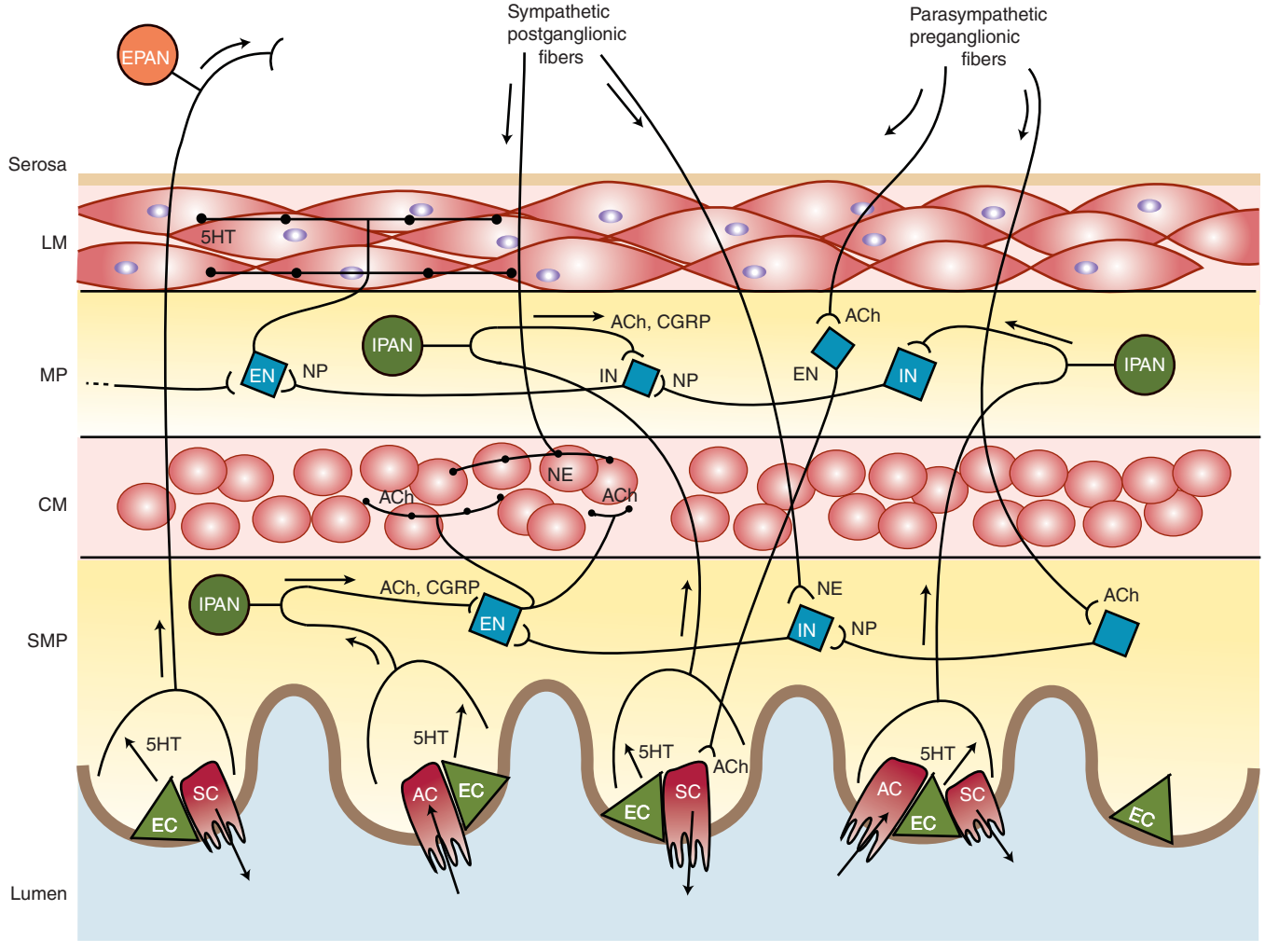

FIGURE 6–2 A highly simplified diagram of the intestinal wall and some of the circuitry of the enteric nervous system (ENS). The ENS receives input from both the sympathetic and the parasympathetic systems and sends afferent impulses to sympathetic ganglia and to the central nervous system. Many transmitter or neuromodulator substances have been identified in the ENS; see Table 6–1. ACh, acetylcholine; AC, absorptive cell; CM, circular muscle layer; EC, enterochromaffin cell; EN, excitatory neuron; EPAN, extrinsic primary afferent neuron; 5HT, serotonin; IN, inhibitory neuron; IPAN, intrinsic primary afferent neuron; LM, longitudinal muscle layer; MP, myenteric plexus; NE, norepinephrine; NP, neuropeptides; SC, secretory cell; SMP, submucosal plexus.

division of the ANS. It is found in the wall of the GI tract from the esophagus to the distal colon and is involved in both motor and secretory activities of the gut. It is particularly critical in the motor activity of the colon. The ENS includes the **myenteric plexus** (the plexus of Auerbach) and the **submucous plexus** (the plexus of Meissner). These neuronal networks receive preganglionic fibers from the parasympathetic system and postganglionic sympathetic axons. They also receive sensory input from within the wall of the gut. Fibers from the neuronal cell bodies in these plexuses travel forward, backward, and in a circular direction to the smooth muscle of the gut to control motility and to secretory cells in the mucosa. Sensory fibers transmit chemical and mechanical information from the mucosa and from stretch receptors to motor neurons in the plexuses and to postganglionic neurons in the sympathetic ganglia. The parasympathetic and sympathetic fibers that synapse on enteric plexus neurons appear to play a modulatory role, as indicated by the observation that deprivation of input from both ANS divisions does not abolish GI activity. In fact, selective denervation may result in greatly enhanced motor activity.

The ENS functions in a semiautonomous manner, utilizing input from the motor outflow of the ANS for modulation of GI activity and sending sensory information back to the CNS. The ENS also provides the necessary synchronization of impulses that, for example, ensures forward, not backward, propulsion of gut contents and relaxation of sphincters when the gut wall contracts.

The anatomy of autonomic synapses and junctions determines the localization of transmitter effects around nerve endings. Classic synapses such as the mammalian neuromuscular junction and most neuron-neuron synapses are relatively "tight" in that the nerve terminates in small boutons very close to the tissue innervated, so that the diffusion path from nerve terminal to postsynaptic receptors is very short. The effects are thus relatively rapid and localized. In contrast, junctions between autonomic neuron terminals and effector cells (smooth muscle, cardiac muscle, glands) differ from classic synapses in that transmitter is often released from a chain of varicosities in the postganglionic nerve fiber in the region of the smooth muscle cells rather than from boutons, and autonomic junctional clefts are wider than somatic synaptic clefts. Effects are thus slower in onset and discharge of a single motor fiber often activates or inhibits many effector cells.

NEUROTRANSMITTER CHEMISTRY OF THE AUTONOMIC NERVOUS SYSTEM

An important traditional classification of autonomic nerves is based on the primary transmitter molecules—acetylcholine or norepinephrine—released from their terminal boutons and varicosities. A large number of peripheral ANS fibers synthesize and release acetylcholine; they are **cholinergic** fibers; that is, they work by releasing acetylcholine. As shown in Figure 6–1, these include all preganglionic efferent autonomic fibers and the somatic (nonautonomic) motor fibers to skeletal muscle as well. Thus, almost all efferent fibers leaving the CNS are cholinergic. In addition, most parasympathetic postganglionic and a few sympathetic postganglionic fibers are cholinergic. A significant number of parasympathetic postganglionic neurons utilize nitric oxide or peptides as the primary transmitter or cotransmitters.

Most postganglionic sympathetic fibers release norepinephrine (also known as noradrenaline); they are **noradrenergic** (often called simply "adrenergic") fibers; that is, they work by releasing norepinephrine (noradrenaline). These transmitter characteristics are presented schematically in Figure 6–1. As noted, some sympathetic fibers release acetylcholine. Dopamine is a very important transmitter in the CNS, and there is evidence that it may be released by some peripheral sympathetic fibers. Adrenal medullary cells, which are embryologically analogous to postganglionic sympathetic neurons, release a mixture of epinephrine and norepinephrine. Finally, most autonomic nerves also release several **cotransmitter** substances (described in the text that follows), in addition to the primary transmitters just described.

Five key features of neurotransmitter function provide potential targets for pharmacologic therapy: **synthesis, storage, release,** and **termination of action** of the transmitter, and **receptor effects.** These processes are discussed next.

Cholinergic Transmission

The terminals and varicosities of cholinergic neurons contain large numbers of small membrane-bound vesicles concentrated near the synaptic portion of the cell membrane (Figure 6–3) as well as a smaller number of large dense-cored vesicles located farther from the synaptic membrane. The large vesicles contain a high concentration of peptide cotransmitters (Table 6–1), whereas the smaller clear vesicles contain most of the acetylcholine. Vesicles are initially synthesized in the neuron cell body and carried to the terminal by axonal transport. They may also be recycled several times within the terminal. Vesicles are provided with **vesicle-associated membrane proteins (VAMPs),** which serve to align them with release sites on the inner neuronal cell membrane and participate in triggering the release of transmitter. The release site on the inner surface of the nerve terminal membrane contains **synaptosomal nerve-associated proteins (SNAPs)**, which interact with VAMPs.

Acetylcholine is synthesized in the cytoplasm from acetyl-CoA and choline through the catalytic action of the enzyme **choline acetyltransferase (ChAT).** Acetyl-CoA is synthesized in mitochondria, which are present in large numbers in the nerve ending. Choline is transported from the extracellular fluid into the neuron terminal by a sodium-dependent membrane **choline transporter** (**CHT**; Figure 6–3). This symporter can be blocked by a group of research drugs called **hemicholiniums.** Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by a **vesicle-associated transporter (VAT)** that is driven by proton efflux (Figure 6–3). This antiporter can be blocked by the research drug **vesamicol.** Acetylcholine synthesis is a rapid process capable of supporting a very high rate of transmitter release. Storage of acetylcholine is accomplished by the packaging of "quanta" of acetylcholine molecules (usually 1000 to 50,000 molecules in each vesicle). Most of the vesicular acetylcholine (ACh) is bound to negatively charged **vesicular proteoglycan (VPG).**

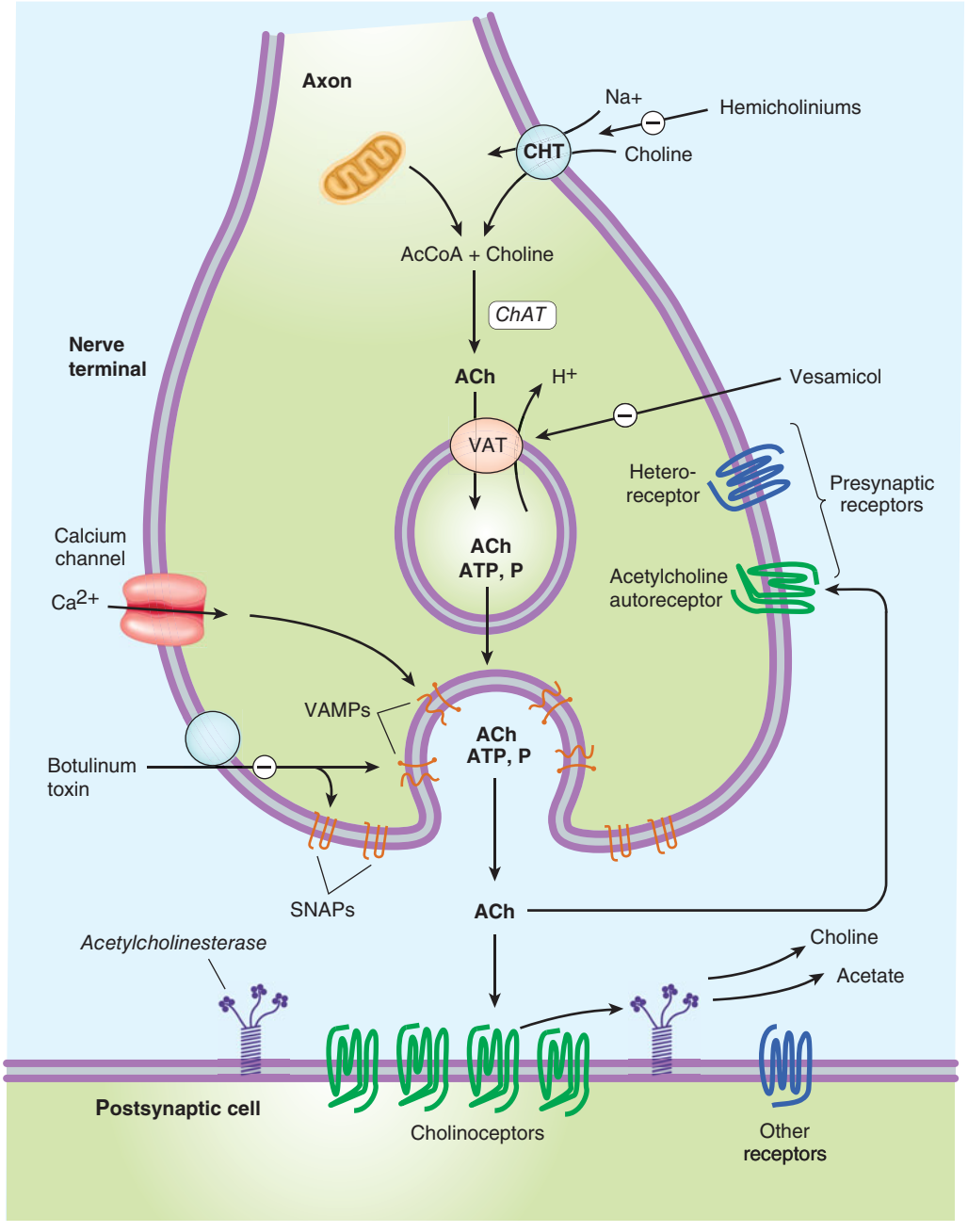

FIGURE 6–3 Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (CHT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine is then transported into the storage vesicle by a second carrier, the vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release. SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

Vesicles are concentrated on the inner surface of the nerve terminal facing the synapse through the interaction of so-called SNARE proteins on the vesicle (a subgroup of VAMPs called v-SNAREs, especially **synaptobrevin**) and on the inside of the terminal cell membrane (SNAPs called t-SNAREs, especially **syntaxin** and **SNAP-25**). Physiologic release of transmitter from the vesicles is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient

TABLE 6–1 Some of the transmitter substances found in autonomic nervous system, enteric nervous system, and nonadrenergic, noncholinergic neurons.[1]

Substance	Probable Roles
Acetylcholine (ACh)	The primary transmitter at ANS ganglia, at the somatic neuromuscular junction, and at parasympathetic postganglionic nerve endings. A primary excitatory transmitter to smooth muscle and secretory cells in the ENS. Probably also the major neuron-to-neuron ("ganglionic") transmitter in the ENS.
Adenosine triphosphate (ATP)	Acts as a transmitter or cotransmitter at many ANS-effector synapses.
Calcitonin gene-related peptide (CGRP)	Found with substance P in cardiovascular sensory nerve fibers. Present in some secretomotor ENS neurons and interneurons. A cardiac stimulant.
Cholecystokinin (CCK)	May act as a cotransmitter in some excitatory neuromuscular ENS neurons.
Dopamine	A modulatory transmitter in some ganglia and the ENS. Probably a postganglionic sympathetic transmitter in renal blood vessels.
Enkephalin and related opioid peptides	Present in some secretomotor and interneurons in the ENS. Appear to inhibit ACh release and thereby inhibit peristalsis. May *stimulate* secretion.
Galanin	Present in secretomotor neurons; may play a role in appetite-satiety mechanisms.
GABA (γ-aminobutyric acid)	May have presynaptic effects on excitatory ENS nerve terminals. Has some relaxant effect on the gut. Probably not a major transmitter in the ENS.
Gastrin-releasing peptide (GRP)	Extremely potent excitatory transmitter to gastrin cells. Also known as mammalian bombesin.
Neuropeptide Y (NPY)	Found in many noradrenergic neurons. Present in some secretomotor neurons in the ENS and may inhibit secretion of water and electrolytes by the gut. Causes long-lasting vasoconstriction. It is also a cotransmitter in some parasympathetic postganglionic neurons.
Nitric oxide (NO)	A cotransmitter at inhibitory ENS and other neuromuscular junctions; may be especially important at sphincters. Cholinergic nerves innervating blood vessels appear to activate the synthesis of NO by vascular endothelium. NO is synthesized on demand by nitric oxide synthase, NOS, not stored; see Chapter 19.
Norepinephrine (NE)	The primary transmitter at most sympathetic postganglionic nerve endings.
Serotonin (5-HT)	An important transmitter or cotransmitter at excitatory neuron-to-neuron junctions in the ENS.
Substance P, related tachykinins	Substance P is an important sensory neuron transmitter in the ENS and elsewhere. Tachykinins appear to be excitatory cotransmitters with ACh at ENS neuromuscular junctions. Found with CGRP in cardiovascular sensory neurons. Substance P is a vasodilator (probably via release of nitric oxide).
Vasoactive intestinal peptide (VIP)	Excitatory secretomotor transmitter in the ENS; may also be an inhibitory ENS neuromuscular cotransmitter. A probable cotransmitter in many cholinergic neurons. A vasodilator (found in many perivascular neurons) and cardiac stimulant.

[1]See Chapter 21 for transmitters found in the central nervous system.

influx of calcium ions via N-type calcium channels. Calcium interacts with the VAMP **synaptotagmin** on the vesicle membrane and triggers fusion of the vesicle membrane with the terminal membrane and opening of a pore into the synapse. The opening of the pore and inrush of cations results in release of the acetylcholine from the proteoglycan and exocytotic expulsion into the synaptic cleft. One depolarization of a somatic motor nerve may release several hundred quanta into the synaptic cleft. One depolarization of an autonomic postganglionic nerve varicosity or terminal probably releases less and releases it over a larger area. In addition to acetylcholine, several cotransmitters are released at the same time (Table 6–1). The acetylcholine vesicle release process is blocked by **botulinum toxin** through the enzymatic removal of two amino acids from one or more of the fusion proteins.

After release from the presynaptic terminal, acetylcholine molecules may bind to and activate an acetylcholine receptor (**cholinoceptor**). Eventually (and usually very rapidly), all of the acetylcholine released diffuses within range of an **acetylcholinesterase (AChE)** molecule. AChE very efficiently splits acetylcholine into choline and acetate, neither of which has significant transmitter effect, and thereby terminates the action of the transmitter (Figure 6–3). Most cholinergic synapses are richly supplied with acetylcholinesterase; the half-life of acetylcholine molecules in the synapse is therefore very short (a fraction of a second). Acetylcholinesterase is also found in other tissues, eg, red blood cells. (Other cholinesterases with a lower specificity for acetylcholine, including butyrylcholinesterase [pseudocholinesterase], are found in blood plasma, liver, glia, and many other tissues.)

Adrenergic Transmission

Adrenergic neurons (Figure 6–4) transport a precursor amino acid (tyrosine) into the nerve ending, then synthesize the catecholamine transmitter (Figure 6–5), and finally store it in membrane-bound vesicles. In most sympathetic postganglionic neurons, norepinephrine is the final product. In the adrenal medulla and certain areas of the brain, some norepinephrine is further converted to epinephrine. In dopaminergic neurons, synthesis terminates with

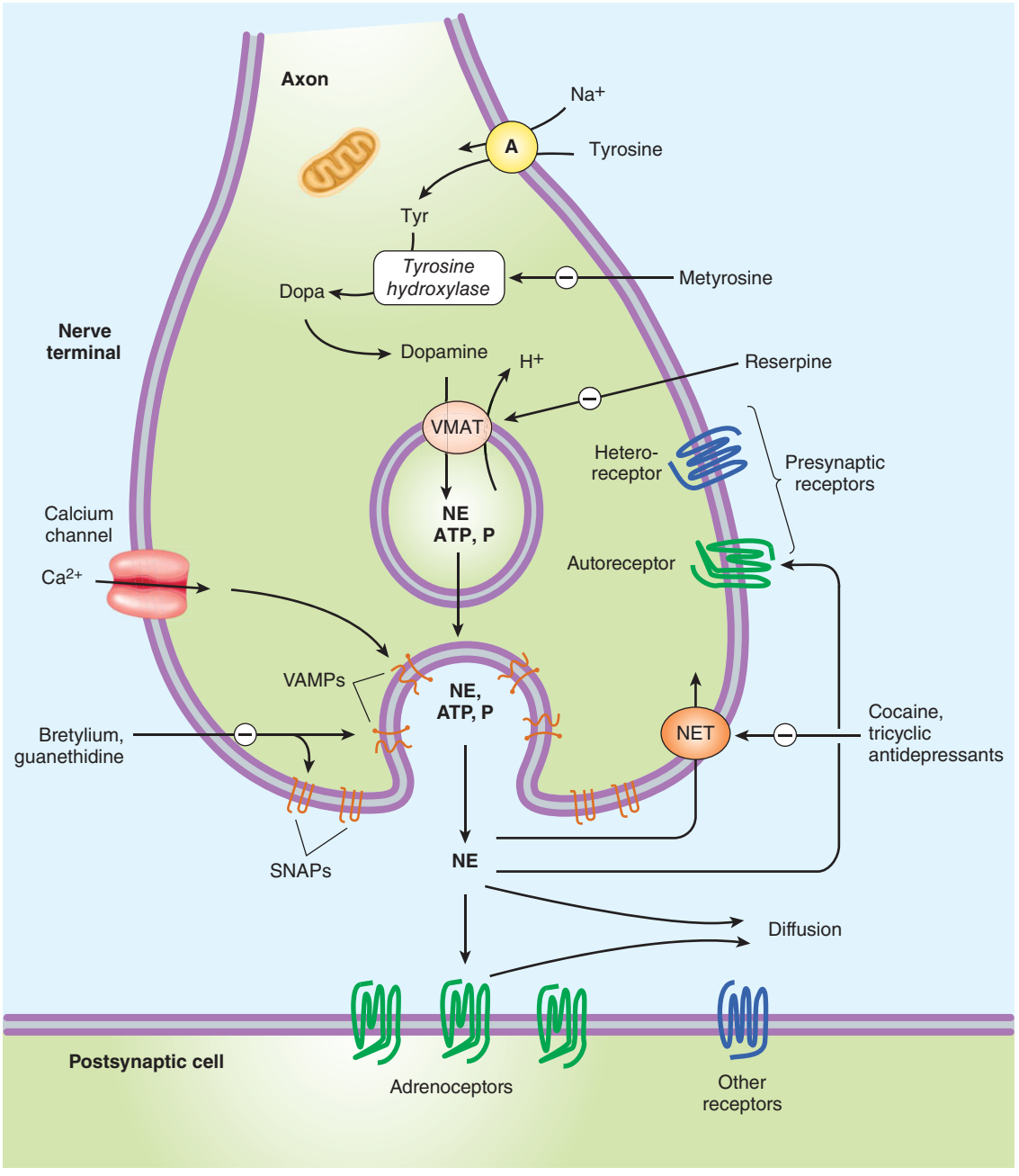

FIGURE 6–4 Schematic diagram of a generalized noradrenergic junction (not to scale). Tyrosine is transported into the noradrenergic ending or varicosity by a sodium-dependent carrier (A). Tyrosine is converted to dopamine (see Figure 6–5 for details), and transported into the vesicle by the vesicular monoamine transporter (VMAT), which can be blocked by reserpine. The same carrier transports norepinephrine (NE) and several other amines into these granules. Dopamine is converted to NE in the vesicle by dopamine-β-hydroxylase. Physiologic release of transmitter occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Fusion of vesicles with the surface membrane results in expulsion of norepinephrine, cotransmitters, and dopamine-β-hydroxylase. Release can be blocked by drugs such as guanethidine and bretylium. After release, norepinephrine diffuses out of the cleft or is transported into the cytoplasm of the terminal by the norepinephrine transporter (NET), which can be blocked by cocaine and tricyclic antidepressants, or into postjunctional or perijunctional cells. Regulatory receptors are present on the presynaptic terminal. SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

dopamine. Several processes in these nerve terminals are potential sites of drug action. One of these, the conversion of tyrosine to dopa, is the rate-limiting step in catecholamine transmitter synthesis. It can be inhibited by the tyrosine analog **metyrosine.** A high-affinity antiporter for catecholamines located in the wall of the storage vesicle **(vesicular monoamine transporter, VMAT)** can be inhibited by the **reserpine** alkaloids. Reserpine causes depletion of transmitter stores. Another transporter **(norepinephrine transporter, NET)** carries norepinephrine and similar molecules back into the cell cytoplasm from the synaptic cleft

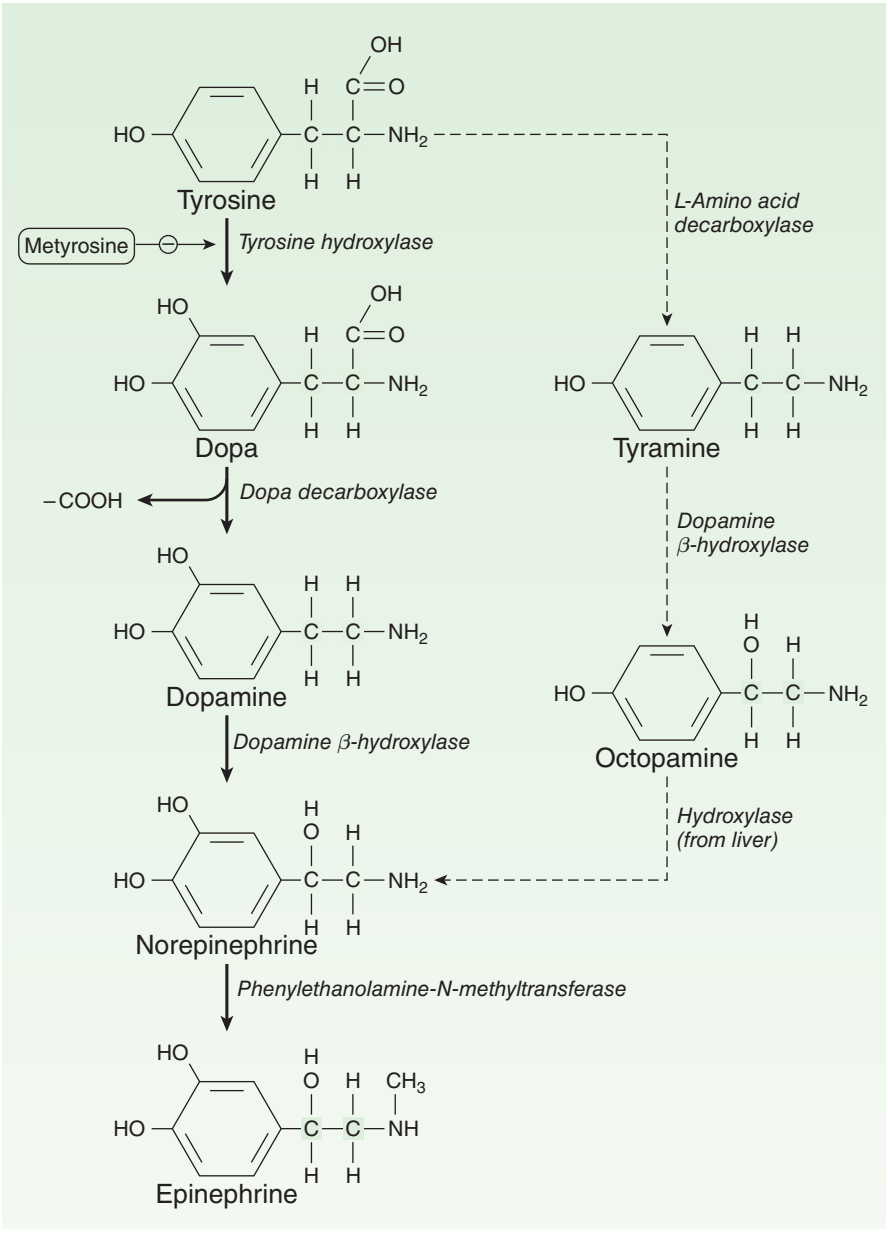

FIGURE 6–5 Biosynthesis of catecholamines. The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α-methyltyrosine). The alternative pathway shown by the dashed arrows has not been found to be of physiologic significance in humans. However, tyramine and octopamine may accumulate in patients treated with monoamine oxidase inhibitors. (Reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology,* 7th ed. McGraw-Hill, 2003.)

(Figure 6–4; NET). NET is also commonly called uptake 1 or reuptake 1 and is partially responsible for the termination of synaptic activity. NET can be inhibited by **cocaine** and **tricyclic antidepressant** drugs, resulting in an increase of transmitter activity in the synaptic cleft (see Box: Neurotransmitter Uptake Carriers).

Release of the vesicular transmitter store from noradrenergic nerve endings is similar to the calcium-dependent process previously described for cholinergic terminals. In addition to the primary transmitter (norepinephrine), adenosine triphosphate (ATP), dopamine-β-hydroxylase, and peptide cotransmitters are also released into the synaptic cleft. Indirectly acting and mixed sympathomimetics, eg, **tyramine, amphetamines,** and **ephedrine,** are capable of releasing stored transmitter from noradrenergic nerve endings by a calcium-independent process. These drugs are poor agonists (some are inactive) at adrenoceptors, but they are excellent substrates for monoamine transporters. As a result, they are avidly taken up into noradrenergic nerve endings by NET. In the nerve ending, they are then transported by VMAT into the vesicles, displacing norepinephrine, which is subsequently expelled into the synaptic space by reverse transport via NET. Amphetamines

Neurotransmitter Uptake Carriers

As noted in Chapter 1, several large families of transport proteins have been identified. The most important of these are the ABC (ATP-Binding Cassette) and SLC (SoLute Carrier) transporter families. As indicated by the name, the ABC carriers utilize ATP for transport. The SLC proteins are cotransporters and in most cases, use the movement of sodium down its concentration gradient as the energy source. Under some circumstances, they also transport transmitters in the reverse direction in a sodium-independent fashion.

NET, SLC6A2, the norepinephrine transporter, is a member of the SLC family, as are similar transporters responsible for the reuptake of dopamine (**DAT,** SLC6A3) and 5-HT (serotonin, **SERT,** SLC6A4) into the neurons that release these transmitters. These transport proteins are found in peripheral tissues and in the CNS wherever neurons utilizing these transmitters are located.

NET is important in the peripheral actions of cocaine and the amphetamines. In the CNS, NET and SERT are important targets of several antidepressant drug classes (see Chapter 30). The most important inhibitory transmitter in the CNS, γ-aminobutyric acid (GABA), is the substrate for at least three SLC transporters: GAT1, GAT2, and GAT3. GAT1 is the target of an antiseizure medication (see Chapter 24). Other SLC proteins transport glutamate, the major excitatory CNS transmitter.

also inhibit monoamine oxidase and have other effects that result in increased norepinephrine activity in the synapse. Their action does not require vesicle exocytosis.

Norepinephrine and epinephrine can be metabolized by several enzymes, as shown in Figure 6–6. Because of the high activity of monoamine oxidase in the mitochondria of the nerve terminal, there is significant turnover of norepinephrine even in the resting terminal. Since the metabolic products are excreted in the urine, an estimate of catecholamine turnover can be obtained from laboratory analysis of total metabolites (sometimes referred to as "VMA and metanephrines") in a 24-hour urine sample. However, metabolism is not the primary mechanism for termination of action of norepinephrine physiologically released from noradrenergic nerves. Termination of noradrenergic transmission results from two processes: simple diffusion away from the receptor site (with eventual metabolism in the plasma or liver) and reuptake into the nerve terminal by NET (Figure 6–4) or into perisynaptic glia or other cells.

Cotransmitters in Cholinergic & Adrenergic Nerves

As previously noted, the vesicles of both cholinergic and adrenergic nerves contain other substances in addition to the primary transmitter, sometimes in the same vesicles and sometimes in a separate vesicle population. Some of the substances identified to date are listed in Table 6–1. Many of these substances are also *primary* transmitters in the nonadrenergic, noncholinergic nerves described in the text that follows. They appear to play several roles in the function of nerves that release acetylcholine or norepinephrine. In some cases, they provide a faster or slower action to supplement or modulate the effects of the primary transmitter. They also participate in feedback inhibition of the same and nearby nerve terminals.

AUTONOMIC RECEPTORS

Historically, structure-activity analyses, with careful comparisons of the potency of series of autonomic agonist and antagonist analogs, led to the definition of different autonomic receptor subtypes, including muscarinic and nicotinic cholinoceptors, and α, β, and dopamine adrenoceptors (Table 6–2). Subsequently, binding of isotope-labeled ligands permitted the purification and characterization of several of the receptor molecules. Molecular biology now provides techniques for the discovery and expression of genes that code for related receptors within these groups (see Chapter 2).

The primary acetylcholine receptor subtypes were named after the alkaloids originally used in their identification: muscarine and nicotine, thus **muscarinic** and **nicotinic receptors.** In the case of receptors associated with noradrenergic nerves, the use of the names of the agonists (noradrenaline, phenylephrine, isoproterenol, and others) was not practicable. Therefore, the term **adrenoceptor** is widely used to describe receptors that respond to catecholamines such as norepinephrine. By analogy, the term **cholinoceptor** denotes receptors (both muscarinic and nicotinic) that respond to acetylcholine. In North America, receptors were colloquially named after the nerves that usually innervate them; thus, **adrenergic** (or noradrenergic) **receptors** and **cholinergic receptors.** The general class of adrenoceptors can be further subdivided into **α-adrenoceptor, β-adrenoceptor,** and **dopamine-receptor** types on the basis of both agonist and antagonist selectivity and on genomic grounds. Development of more selective blocking drugs has led to the naming of subclasses within these major types; for example, within the α-adrenoceptor class, α_1 and α_2 receptors differ in both agonist and antagonist selectivity. Specific examples of such selective drugs are given in the chapters that follow.

NONADRENERGIC, NONCHOLINERGIC (NANC) NEURONS

It has been known for many years that autonomic effector tissues (eg, gut, airways, bladder) contain nerve fibers that do not show the histochemical characteristics of either cholinergic or adrenergic fibers. Both motor and sensory NANC fibers are present. Although peptides are the most common transmitter substances found in these nerve endings, other substances, eg, nitric oxide synthase and purines, are also present in many nerve terminals (Table 6–1). Capsaicin, a neurotoxin derived from chili peppers, can cause the

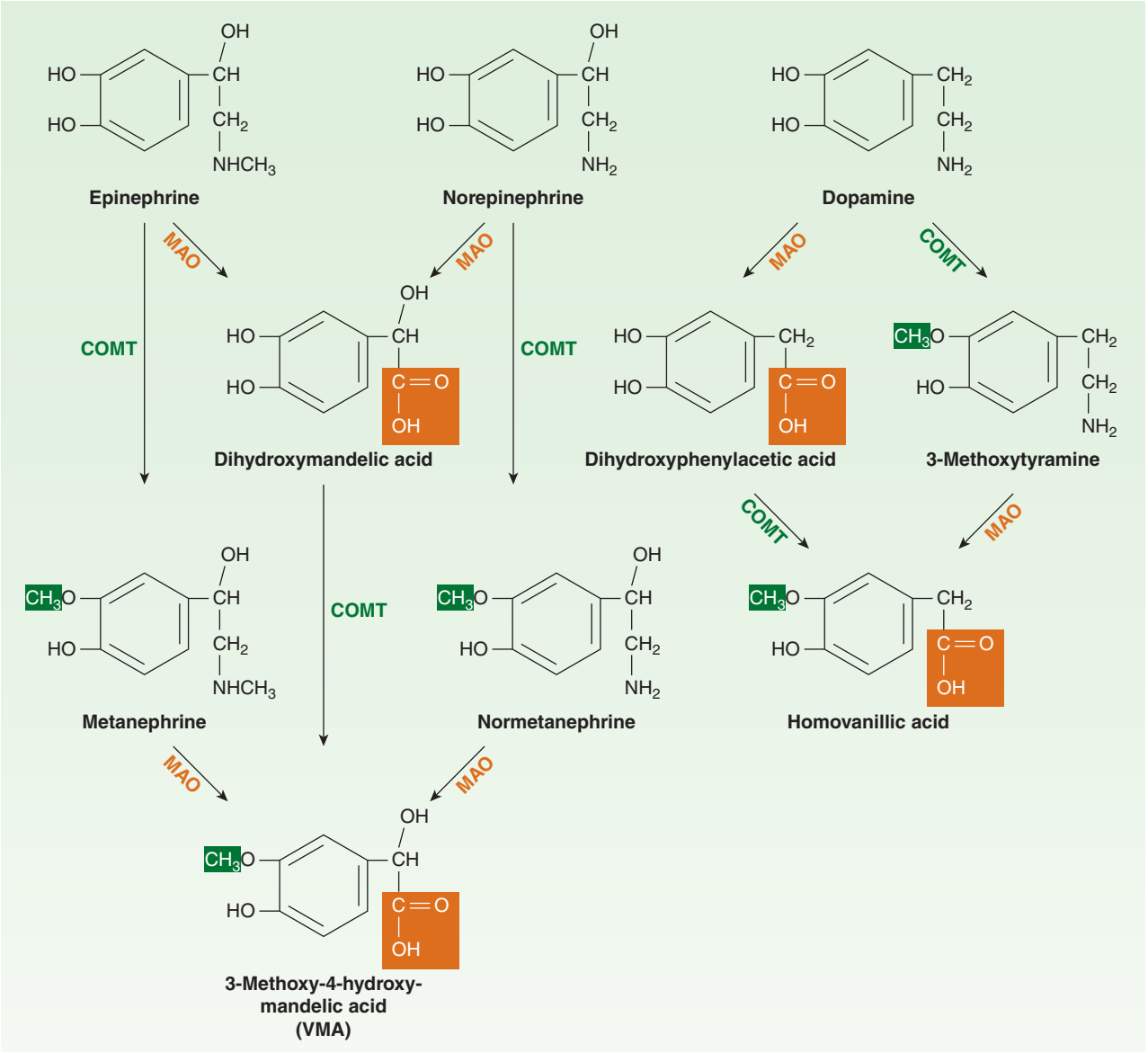

FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Modified and reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology,* 7th ed. McGraw-Hill, 2003.)

release of transmitter (especially substance P) from such neurons and, if given in high doses, destruction of the neuron.

The enteric system in the gut wall (Figure 6–2) is the most extensively studied system containing NANC neurons in addition to cholinergic and adrenergic fibers. In the small intestine, for example, these neurons contain one or more of the following: nitric oxide synthase (which produces nitric oxide; NO), calcitonin gene-related peptide, cholecystokinin, dynorphin, enkephalins, gastrin-releasing peptide, 5-hydroxytryptamine (serotonin), neuropeptide Y, somatostatin, substance P, and vasoactive intestinal peptide (VIP). Some neurons contain as many as five different transmitters.

The sensory fibers in the nonadrenergic, noncholinergic systems are probably better termed "sensory-efferent" or "sensory-local effector" fibers because, when activated by a sensory input, they are capable of releasing transmitter peptides from the sensory ending itself, from local axon branches, and from collaterals that terminate in the autonomic ganglia. These peptides are potent agonists in many autonomic effector tissues.

FUNCTIONAL ORGANIZATION OF AUTONOMIC ACTIVITY

Autonomic function is integrated and regulated at many levels, from the CNS to the effector cells. Most regulation uses negative feedback, but several other mechanisms have been identified. Negative feedback is particularly important in the responses of the ANS to the administration of autonomic drugs.

TABLE 6–2 Major autonomic receptor types.

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals; receptors typically contain two $\alpha 3$ and one $\beta 4$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular end plates; receptors typically contain two $\alpha 1$ and $\beta 1$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization
Adrenoceptors		
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP[1]
Dopamine receptors		
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D_3	Brain	Inhibition of adenylyl cyclase
D_4	Brain, cardiovascular system	Inhibition of adenylyl cyclase

[1]Cardiac β_3-receptor function is poorly understood, but activation does *not* appear to result in stimulation of rate or force.

Central Integration

At the highest level—midbrain and medulla—the two divisions of the ANS and the endocrine system are integrated with each other, with sensory input, and with information from higher CNS centers, including the cerebral cortex. These interactions are such that early investigators called the parasympathetic system a **trophotropic** one (ie, leading to growth) used to "rest and digest" and the sympathetic system an **ergotropic** one (ie, leading to energy expenditure), which is activated for "fight or flight." Although such terms offer little insight into the mechanisms involved, they do provide simple descriptions applicable to many of the actions of the systems (Table 6–3). For example, slowing of the heart and stimulation of digestive activity are typical energy-conserving and storing actions of the parasympathetic system. In contrast, cardiac stimulation, increased blood sugar, and cutaneous vasoconstriction are responses produced by sympathetic discharge that are suited to fighting or surviving attack.

At a more subtle level of interactions in the brain stem, medulla, and spinal cord, there are important cooperative interactions between the parasympathetic and sympathetic systems. For some organs, sensory fibers associated with the parasympathetic system exert reflex control over motor outflow in the sympathetic system. Thus, the sensory carotid sinus baroreceptor fibers in the glossopharyngeal nerve have a major influence on sympathetic outflow from the vasomotor center. This example is described in greater detail in the following text. Similarly, parasympathetic sensory fibers in the wall of the urinary bladder significantly influence sympathetic inhibitory outflow to that organ. Within the ENS, sensory fibers from the wall of the gut synapse on both preganglionic and postganglionic motor cells that control intestinal smooth muscle and secretory cells (Figure 6–2).

Integration of Cardiovascular Function

Autonomic reflexes are particularly important in understanding cardiovascular responses to autonomic drugs. As indicated in Figure 6–7, the primary controlled variable in cardiovascular function is **mean arterial pressure.** Changes in any variable contributing to mean arterial pressure (eg, a drug-induced increase in peripheral vascular resistance) evoke powerful **homeostatic** secondary responses that tend to compensate for the directly evoked

TABLE 6–3 Direct effects of autonomic *nerve* activity on some organ systems. Autonomic *drug* effects are similar but not identical (see text).

	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	***Action*[1]**	***Receptor*[2]**	***Action***	***Receptor*[2]**
Eye				
Iris radial muscle	Contracts	α_1	…	…
Iris circular muscle	…	…	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	…	…
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	…	…
Skeletal muscle vessels	Relaxes	β_2	…	…
	[Contracts]	α	…	…
	Relaxes[3]	M_3	…	…
Endothelium of vessels in heart, brain, viscera	…	…	Synthesizes and releases EDRF[4]	M_3, M_5[5]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2, [6]β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	…	…	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	…	…
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α	…	…
Sweat glands			…	…
Eccrine	Increases	M	…	…
Apocrine (stress)	Increases	α	…	…
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	…	…
Liver	Glycogenolysis	β_2, α	…	…
Fat cells	Lipolysis	β_3	…	…
Kidney	Renin release	β_1	…	…

[1]Less important actions are shown in brackets.

[2]Specific receptor type: α, alpha; β, beta; M, muscarinic.

[3]Vascular smooth muscle in skeletal muscle has sympathetic cholinergic dilator fibers.

[4]The endothelium of most blood vessels releases EDRF (endothelium-derived relaxing factor), which causes marked vasodilation, in response to muscarinic stimuli. Parasympathetic fibers innervate muscarinic receptors in vessels in the viscera and brain, and sympathetic cholinergic fibers innervate skeletal muscle blood vessels. The muscarinic receptors in the other vessels of the peripheral circulation are not innervated and respond only to circulating muscarinic agonists.

[5]Cerebral blood vessels dilate in response to M_5 receptor activation.

[6]Probably through presynaptic inhibition of parasympathetic activity.

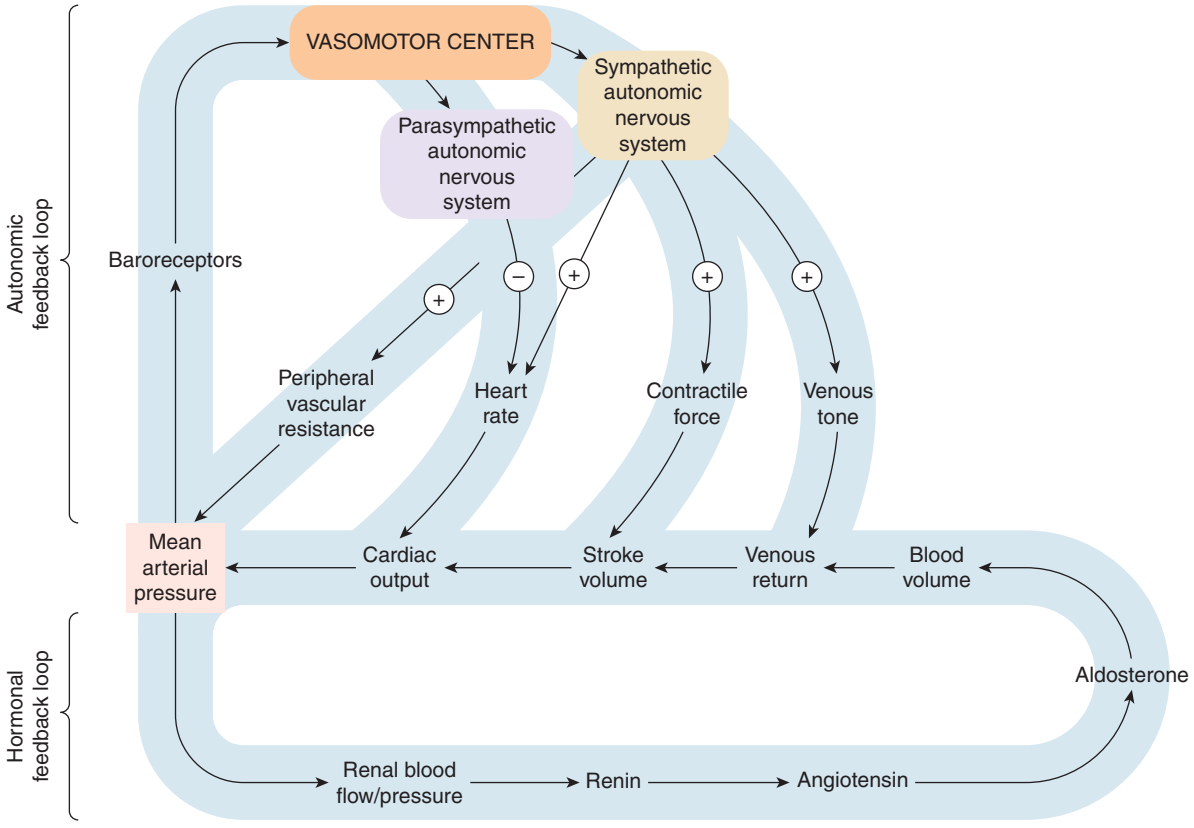

FIGURE 6–7 Autonomic and hormonal control of cardiovascular function. Note that two feedback loops are present: the autonomic nervous system loop and the hormonal loop. The sympathetic nervous system directly influences four major variables: peripheral vascular resistance, heart rate, force, and venous tone. It also directly modulates renin production (not shown). The parasympathetic nervous system directly influences heart rate. In addition to its role in stimulating aldosterone secretion, angiotensin II directly increases peripheral vascular resistance and facilitates sympathetic effects (not shown). The net feedback effect of each loop is to compensate for changes in arterial blood pressure. Thus, decreased blood pressure due to blood loss would evoke increased sympathetic outflow and renin release. Conversely, elevated pressure due to the administration of a vasoconstrictor drug would cause reduced sympathetic outflow, reduced renin release, and increased parasympathetic (vagal) outflow.

change. The homeostatic response may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate. A slow infusion of norepinephrine provides a useful example. This agent produces direct effects on both vascular and cardiac muscle. It is a powerful vasoconstrictor and, by increasing peripheral vascular resistance, increases mean arterial pressure. In the absence of reflex control—in a patient who has had a heart transplant, for example—the drug's effect on the heart is also stimulatory; that is, it increases heart rate and contractile force. However, in a subject with intact reflexes, the negative feedback response to increased mean arterial pressure causes decreased sympathetic outflow to the heart and a powerful increase in parasympathetic (vagus nerve) discharge at the cardiac pacemaker. This response is mediated by increased firing by the baroreceptor nerves of the carotid sinus and the aortic arch. Increased baroreceptor activity causes the changes mentioned in central sympathetic and vagal outflow. As a result, the *net* effect of ordinary pressor doses of norepinephrine in a normal subject is to produce a marked increase in peripheral vascular resistance, an increase in mean arterial pressure, and a consistent *slowing* of heart rate. Bradycardia, the reflex compensatory response elicited by this agent, is the *exact opposite* of the drug's direct action; yet it is completely predictable if the integration of cardiovascular function by the ANS is understood.

Presynaptic Regulation

The principle of negative feedback control is also found at the presynaptic level of autonomic function. Important presynaptic feedback inhibitory control mechanisms have been shown to exist at most nerve endings. A well-documented mechanism involves the α_2 receptor located on noradrenergic nerve terminals. This receptor is activated by norepinephrine and similar molecules; activation diminishes further release of norepinephrine from these nerve endings (Table 6–4). The mechanism of this G protein-mediated effect involves inhibition of the inward calcium current that causes vesicular fusion and transmitter release. Conversely, a presynaptic β receptor appears to facilitate the release of norepinephrine from some adrenergic neurons. Presynaptic receptors

TABLE 6–4 Autoreceptor, heteroreceptor, and modulatory effects on nerve terminals in peripheral synapses.[1]

Transmitter/Modulator	Receptor Type	Neuron Terminals Where Found
Inhibitory effects		
Acetylcholine	M_2, M_1	Adrenergic, enteric nervous system
Norepinephrine	$Alpha_2$	Adrenergic
Dopamine	D_2; less evidence for D_1	Adrenergic
Serotonin (5-HT)	5-HT_1, 5-HT_2, 5-HT_3	Cholinergic preganglionic
ATP and adenosine	P_2 (ATP), P_1 (adenosine)	Adrenergic autonomic and ENS cholinergic neurons
Histamine	H_3, possibly H_2	H_3 type identified on CNS adrenergic and serotonergic neurons
Enkephalin	Delta (also mu, kappa)	Adrenergic, ENS cholinergic
Neuropeptide Y	Y_1, Y_2 (NPY)	Adrenergic, some cholinergic
Prostaglandin E_1, E_2	EP_3	Adrenergic
Excitatory effects		
Epinephrine	$Beta_2$	Adrenergic, somatic motor cholinergic
Acetylcholine	N_M	Somatic motor cholinergic
Angiotensin II	AT_1	Adrenergic

[1]A provisional list. The number of transmitters and locations will undoubtedly increase with additional research.

that respond to the primary transmitter substance released by the nerve ending are called **autoreceptors.** Autoreceptors are usually inhibitory, but in addition to the excitatory β receptors on noradrenergic fibers, many cholinergic fibers, especially somatic motor fibers, have excitatory nicotinic autoreceptors.

Control of transmitter release is not limited to modulation by the transmitter itself. Nerve terminals also carry regulatory receptors that respond to many other substances. Such **heteroreceptors** may be activated by substances released from other nerve terminals that synapse with the nerve ending. For example, some vagal fibers in the myocardium synapse on sympathetic noradrenergic nerve terminals and inhibit norepinephrine release. Alternatively, the ligands for these receptors may diffuse to the receptors from the blood or from nearby tissues. Some of the transmitters and receptors identified to date are listed in Table 6–4. Presynaptic regulation by a variety of endogenous chemicals probably occurs in all nerve fibers.

Postsynaptic Regulation

Postsynaptic regulation can be considered from two perspectives: modulation by previous activity at the primary receptor (which may up- or down-regulate receptor number or desensitize receptors; see Chapter 2), and modulation by other simultaneous events.

The first mechanism has been well documented in several receptor-effector systems. Up-regulation and down-regulation are known to occur in response to decreased or increased activation, respectively, of the receptors. An extreme form of up-regulation occurs after denervation of some tissues, resulting in **denervation supersensitivity** of the tissue to activators of that receptor type. In skeletal muscle, for example, nicotinic receptors are normally restricted to the end-plate regions underlying somatic motor nerve terminals. Surgical denervation results in marked proliferation of nicotinic cholinoceptors over all parts of the fiber, including areas not previously associated with any motor nerve junctions. A pharmacologic supersensitivity related to denervation supersensitivity occurs in autonomic effector tissues after administration of drugs that deplete transmitter stores and prevent activation of the postsynaptic receptors for a sufficient period of time. For example, prolonged administration of large doses of reserpine, a norepinephrine depleter, can cause increased sensitivity of the smooth muscle and cardiac muscle effector cells served by the depleted sympathetic fibers.

The second mechanism involves modulation of the primary transmitter-receptor event by events evoked by the same or other transmitters acting on different postsynaptic receptors. Ganglionic transmission is a good example of this phenomenon (Figure 6–8). The postganglionic cells are activated (depolarized) as a result of binding of an appropriate ligand to a neuronal nicotinic (N_N) acetylcholine receptor. The resulting fast **excitatory postsynaptic potential (EPSP)** evokes a propagated action potential if threshold is reached. This event is often followed by a small and slowly developing but longer-lasting hyperpolarizing afterpotential—a slow **inhibitory postsynaptic potential (IPSP).** This hyperpolarization involves opening of potassium channels by M_2 cholinoceptors. The IPSP is followed by a small, slow excitatory postsynaptic potential caused by closure of potassium channels linked to M_1 cholinoceptors. Finally, a late, very slow EPSP may be evoked by peptides released from other fibers. These slow potentials serve to modulate the responsiveness of the postsynaptic cell to subsequent primary

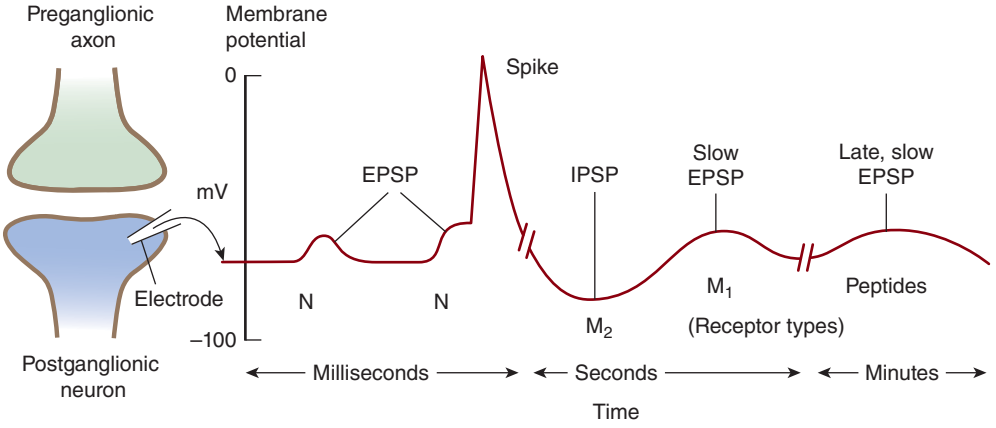

FIGURE 6–8 Excitatory and inhibitory postsynaptic potentials (EPSP and IPSP) in an autonomic ganglion cell. The postganglionic neuron shown at the left with a recording electrode might undergo the membrane potential changes shown schematically in the recording. The response begins with two EPSP responses to nicotinic (N) receptor activation, the first not reaching threshold. The second, suprathreshold, EPSP evokes an action potential, which is followed by an IPSP, probably evoked by M_2 receptor activation (with possible participation from dopamine receptor activation). The IPSP is, in turn, followed by a slower, M_1-dependent EPSP, and this is sometimes followed by a still slower peptide-induced excitatory postsynaptic potential.

excitatory presynaptic nerve activity. (See Chapter 21 for additional examples.)

PHARMACOLOGIC MODIFICATION OF AUTONOMIC FUNCTION

Because transmission involves different mechanisms in different segments of the ANS, some drugs produce highly specific effects, whereas others are much less selective in their actions. A summary of the steps in transmission of impulses, from the CNS to the autonomic effector cells, is presented in Table 6–5. Drugs that block action potential propagation (local anesthetics and some natural toxins) are very nonselective in their action, since they act on a process that is common to all neurons. On the other hand, drugs that act on the biochemical processes involved in transmitter synthesis and storage are more selective, since the biochemistry of each transmitter differs, eg, norepinephrine synthesis is very different from acetylcholine synthesis. Activation or blockade of effector cell receptors offers maximum

Pharmacology of the Eye

The eye is a good example of an organ with multiple autonomic functions, controlled by several autonomic receptors. As shown in Figure 6–9, the anterior chamber is the site of several autonomic effector tissues. These tissues include three muscles (pupillary dilator and constrictor muscles in the iris and the ciliary muscle) and the secretory epithelium of the ciliary body.

Parasympathetic nerve activity and muscarinic cholinomimetics mediate contraction of the circular pupillary constrictor muscle and of the ciliary muscle. Contraction of the pupillary constrictor muscle causes miosis, a reduction in pupil size. Miosis is usually present in patients exposed to large systemic or small topical doses of cholinomimetics, especially organophosphate cholinesterase inhibitors. Ciliary muscle contraction causes accommodation of focus for near vision. Marked contraction of the ciliary muscle, which often occurs with cholinesterase inhibitor intoxication, is called *cyclospasm*. Ciliary muscle contraction also puts tension on the trabecular meshwork, opening its pores and facilitating outflow of the aqueous humor into the canal of Schlemm. Increased outflow reduces intraocular pressure, a very useful result in patients with glaucoma. All of these effects are prevented or reversed by muscarinic blocking drugs such as atropine.

Alpha adrenoceptors mediate contraction of the radially oriented pupillary dilator muscle fibers in the iris and result in mydriasis. This occurs during sympathetic discharge and when α-agonist drugs such as phenylephrine are placed in the conjunctival sac. Beta adrenoceptors on the ciliary epithelium facilitate the secretion of aqueous humor. Blocking these receptors (with β-blocking drugs) reduces the secretory activity and reduces intraocular pressure, providing another therapy for glaucoma.

TABLE 6–5 Steps in autonomic transmission: Effects of drugs.

Process Affected	Drug Example	Site	Action
Action potential propagation	Local anesthetics, tetrodotoxin,[1] saxitoxin[2]	Nerve axons	Block voltage-gated sodium channels; block conduction
Transmitter synthesis	Hemicholiniums	Cholinergic nerve terminals: membrane	Block uptake of choline and slow synthesis
	α-Methyltyrosine (metyrosine)	Adrenergic nerve terminals and adrenal medulla: cytoplasm	Inhibits tyrosine hydroxylase and blocks synthesis of catecholamines
Transmitter storage	Vesamicol	Cholinergic terminals: VAT on vesicles	Prevents storage, depletes
	Reserpine	Adrenergic terminals: VMAT on vesicles	Prevents storage, depletes
Transmitter release	Many[3]	Nerve terminal membrane receptors	Modulate release
	ω-Conotoxin GVIA[4]	Nerve terminal calcium channels	Reduces transmitter release
	Botulinum toxin	Cholinergic vesicles	Prevents release
	α-Latrotoxin[5]	Cholinergic and adrenergic vesicles	Causes explosive transmitter release
	Tyramine, amphetamine	Adrenergic nerve terminals	Promote transmitter release
Transmitter reuptake after release	Cocaine, tricyclic antidepressants	Adrenergic nerve terminals, NET	Inhibit uptake; increase transmitter effect on postsynaptic receptors
Receptor activation or blockade	Norepinephrine	Receptors at adrenergic junctions	Binds α receptors; causes contraction
	Phentolamine	Receptors at adrenergic junctions	Binds α receptors; prevents activation
	Isoproterenol	Receptors at adrenergic junctions	Binds β receptors; activates adenylyl cyclase
	Propranolol	Receptors at adrenergic junctions	Binds β receptors; prevents activation
	Nicotine	Receptors at nicotinic cholinergic junctions (autonomic ganglia, neuromuscular end plates)	Binds nicotinic receptors; opens ion channel in postsynaptic membrane
	Tubocurarine	Neuromuscular end plates	Prevents activation
	Bethanechol	Receptors, parasympathetic effector cells (smooth muscle, glands)	Binds and activates muscarinic receptors
	Atropine	Receptors, parasympathetic effector cells	Binds muscarinic receptors; prevents activation
Enzymatic inactivation of transmitter	Neostigmine	Cholinergic synapses (acetylcholinesterase)	Inhibits enzyme; prolongs and intensifies transmitter action
	Tranylcypromine	Adrenergic nerve terminals (monoamine oxidase)	Inhibits enzyme; increases stored transmitter pool

[1]Toxin of puffer fish, California newt.

[2]Toxin of *Gonyaulax* (red tide organism).

[3]Norepinephrine, dopamine, acetylcholine, angiotensin II, various prostaglandins, etc.

[4]Toxin of marine snails of the genus *Conus*.

[5]Black widow spider venom.

VAT, vesicle-associated transporter; VMAT, vesicular monoamine transporter; NET, norepinephrine transporter.

flexibility and selectivity of effect attainable with currently available drugs: adrenoceptors are easily distinguished from cholinoceptors. Furthermore, individual receptor subgroups can often be selectively activated or blocked within each major type. Some examples are given in the Box: Pharmacology of the Eye. Even greater selectivity may be attainable in the future using drugs that target post-traditional receptor processes, eg, receptors for second messengers.

The next four chapters provide many more examples of this useful diversity of autonomic control processes.

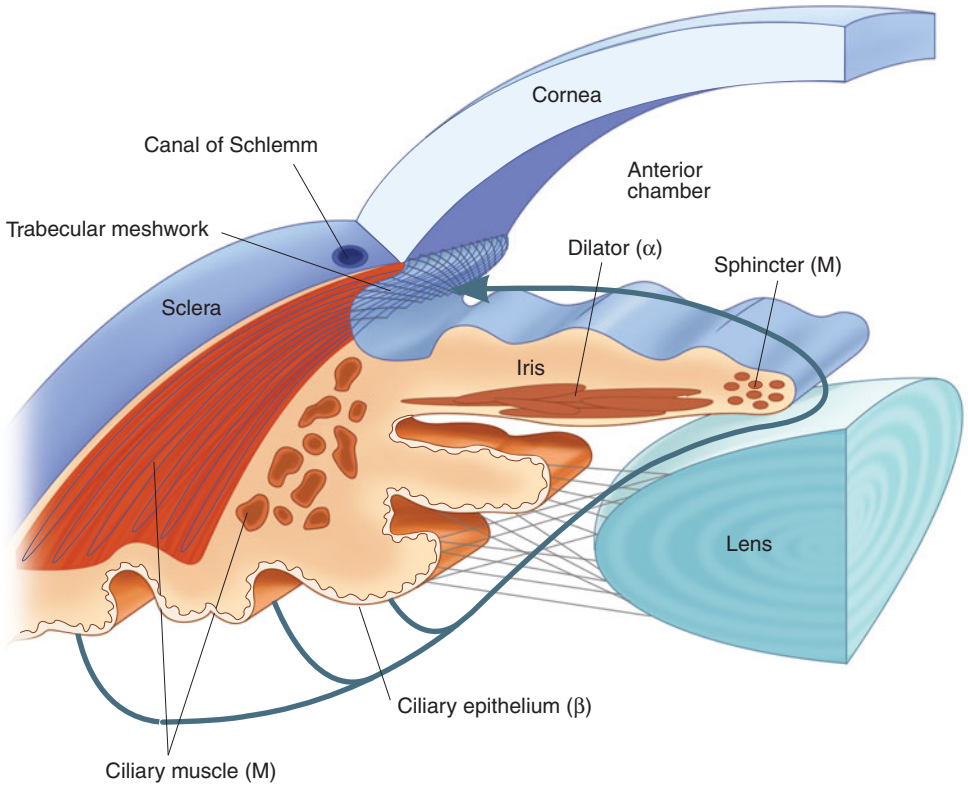

FIGURE 6–9 Structures of the anterior chamber of the eye. Tissues with significant autonomic functions and the associated ANS receptors are shown in this schematic diagram. Aqueous humor is secreted by the epithelium of the ciliary body, flows into the space in front of the iris, flows through the trabecular meshwork, and exits via the canal of Schlemm (*arrow*). Blockade of the β adrenoceptors associated with the ciliary epithelium causes decreased secretion of aqueous. Blood vessels (not shown) in the sclera are also under autonomic control and influence aqueous drainage.

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CASE STUDY ANSWER

Promethazine has potent α-adrenoceptor blocking activity in addition to its sedative, antianxiety effect. As a result, the normal autonomic response to postural change (sympathetic vasoconstriction upon standing up) was temporarily lost in the patient in this case. Marked orthostatic hypotension and syncope resulted with transient recovery upon lying down. The heart rate increased when the baroreceptors detected the drop in blood pressure because promethazine blocks α receptors (dominant in the vessels) but not β receptors (dominant in the heart).

CHAPTER 7

Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs

Achilles J. Pappano, PhD

CASE STUDY

In mid-afternoon, a coworker brings 43-year-old JM to the emergency department because he is unable to continue picking vegetables. His gait is unsteady and he walks with support from his colleague. JM has difficulty speaking and swallowing, his vision is blurred, and his eyes are filled with tears. His coworker notes that JM was working in a field that had been sprayed early in the morning with a material that had the odor of sulfur. Within 3 hours after starting his work, JM complained of tightness in his chest that made breathing difficult, and he called for help before becoming disoriented.

How would you proceed to evaluate and treat JM? What should be done for his coworker?

Acetylcholine-receptor stimulants and cholinesterase inhibitors make up a large group of drugs that mimic acetylcholine (cholinomimetic agents) (Figure 7–1). Cholinoceptor stimulants are classified pharmacologically by their spectrum of action, depending on the type of receptor—muscarinic or nicotinic—that is activated. Cholinomimetics are also classified by their mechanism of action because some bind directly to (and activate) cholinoceptors whereas others act indirectly by inhibiting the hydrolysis of endogenous acetylcholine.

SPECTRUM OF ACTION OF CHOLINOMIMETIC DRUGS

Early studies of the parasympathetic nervous system showed that the alkaloid **muscarine** mimicked the effects of parasympathetic nerve discharge; that is, the effects were **parasympathomimetic.** Application of muscarine to ganglia and to autonomic effector tissues (smooth muscle, heart, exocrine glands) showed that the parasympathomimetic action of the alkaloid occurred through an action on receptors at effector cells, not those in ganglia. The effects of acetylcholine itself and of other cholinomimetic drugs at autonomic neuroeffector junctions are called *parasympathomimetic effects* and are mediated by **muscarinic receptors.** In contrast, low concentrations of the alkaloid **nicotine** stimulated autonomic ganglia and skeletal muscle neuromuscular junctions but not autonomic effector cells. The ganglion and skeletal muscle receptors were therefore labeled nicotinic. When acetylcholine was later identified as the physiologic transmitter at both muscarinic and **nicotinic receptors,** both receptors were recognized as cholinoceptor subtypes.

Cholinoceptors are members of either G protein–linked (muscarinic) or ion channel (nicotinic) families on the basis of their transmembrane signaling mechanisms. Muscarinic receptors contain seven transmembrane domains whose third cytoplasmic loop is coupled to G proteins that function as transducers (see Figure 2–11). These receptors regulate the production of intracellular second messengers and modulate certain ion channels via their G proteins. Agonist selectivity is determined by the subtypes of muscarinic receptors and G proteins that are present in a given cell (Table 7–1). When expressed in cells, muscarinic receptors form dimers or oligomers that are thought to function in receptor movement between the endoplasmic reticulum and plasma membrane. Conceivably, agonist or antagonist ligands could signal by changing the ratio of monomeric to oligomeric receptors. Muscarinic receptors are located on plasma membranes of cells in the central nervous system, in organs innervated by parasympathetic

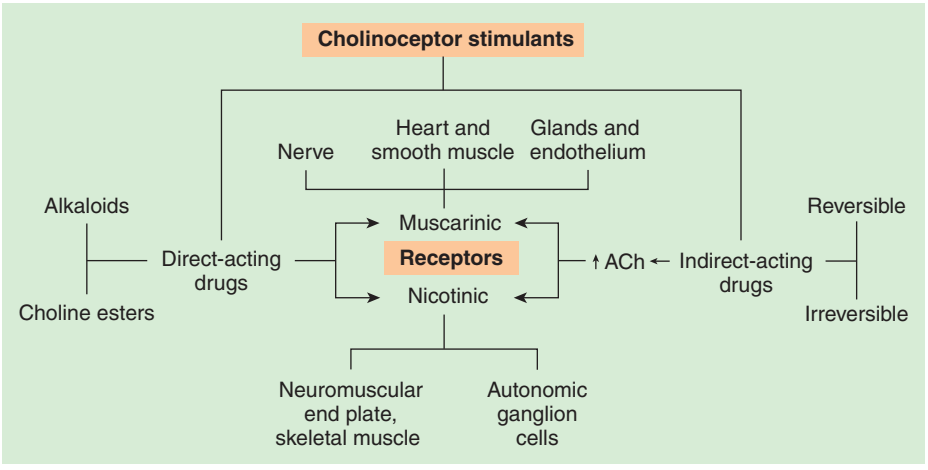

FIGURE 7–1 The major groups of cholinoceptor-activating drugs, receptors, and target tissues. ACh, acetylcholine.

nerves as well as on some tissues that are not innervated by these nerves, eg, endothelial cells (Table 7–1), and on those tissues innervated by postganglionic sympathetic cholinergic nerves.

Nicotinic receptors are part of a transmembrane polypeptide whose subunits form cation-selective ion channels (see Figure 2–9). These receptors are located on plasma membranes of postganglionic cells in all autonomic ganglia, of muscles innervated by somatic motor fibers, and of some central nervous system neurons (see Figure 6–1).

Nonselective cholinoceptor stimulants in sufficient dosage can produce very diffuse and marked alterations in organ system function because acetylcholine has multiple sites of action where it initiates both excitatory and inhibitory effects. Fortunately, drugs are available that have a degree of selectivity, so that desired effects can often be achieved while avoiding or minimizing adverse effects.

Selectivity of action is based on several factors. Some drugs stimulate either muscarinic receptors or nicotinic receptors selectively. Some agents stimulate nicotinic receptors at neuromuscular junctions preferentially and have less effect on nicotinic receptors in ganglia. Organ selectivity can also be achieved by using appropriate routes of administration ("pharmacokinetic selectivity"). For example, muscarinic stimulants can be administered topically to the surface of the eye to modify ocular function while minimizing systemic effects.

TABLE 7–1 Subtypes and characteristics of cholinoceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M_1		Nerves	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_2	Cardiac M_2	Heart, nerves, smooth muscle	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production, activation of K^+ channels
M_3		Glands, smooth muscle, endothelium	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_4		CNS	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production
M_5		CNS	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
N_M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer[1] $[(\alpha1)_2\beta1\delta\gamma)]$	Na^+, K^+ depolarizing ion channel
N_N	Neuronal type, ganglion receptor	CNS, postganglionic cell body, dendrites	Pentamer[1] with α and β subunits only, eg, $(\alpha4)_2(\beta2)_3$ (CNS) or $\alpha3\alpha5(\beta2)_3$ (ganglia)	Na^+, K^+ depolarizing ion channel

[1]Pentameric structure in *Torpedo* electric organ and fetal mammalian muscle has two α1 subunits and one each of β1, δ, and γ subunits. The stoichiometry is indicated by subscripts, eg, $[(\alpha1)_2\beta1\delta\gamma]$. In adult muscle, the γ subunit is replaced by an ε subunit. There are twelve neuronal nicotinic receptors with nine α (α2-α10) subunits and three (β2-β4) subunits. The subunit composition varies among different mammalian tissues.

DAG, diacylglycerol; IP_3, inositol trisphosphate.

Data from Millar NS: Assembly and subunit diversity of nicotinic acetylcholine receptors. Biochem Soc Trans 2003;31:869.

MODE OF ACTION OF CHOLINOMIMETIC DRUGS

Direct-acting cholinomimetic agents bind to and activate muscarinic or nicotinic receptors (Figure 7–1). Indirect-acting agents produce their primary effects by inhibiting acetylcholinesterase, which hydrolyzes acetylcholine to choline and acetic acid (see Figure 6–3). By inhibiting acetylcholinesterase, the indirect-acting drugs increase the endogenous acetylcholine concentration in synaptic clefts and neuroeffector junctions. The excess acetylcholine, in turn, stimulates cholinoceptors to evoke increased responses. These drugs act primarily where acetylcholine is physiologically released and are thus *amplifiers* of endogenous acetylcholine.

Some cholinesterase inhibitors also inhibit butyrylcholinesterase (pseudocholinesterase). However, inhibition of butyrylcholinesterase plays little role in the action of indirect-acting cholinomimetic drugs because this enzyme is not important in the physiologic termination of synaptic acetylcholine action. Some quaternary cholinesterase inhibitors also have a modest direct action as well, eg, neostigmine, which activates neuromuscular nicotinic cholinoceptors directly in addition to blocking cholinesterase.

■ BASIC PHARMACOLOGY OF THE DIRECT-ACTING CHOLINOCEPTOR STIMULANTS

The direct-acting cholinomimetic drugs can be divided on the basis of chemical structure into esters of choline (including acetylcholine) and alkaloids (such as muscarine and nicotine). Many of these drugs have effects on both receptors; acetylcholine is typical. A few of them are highly selective for the muscarinic or for the nicotinic receptor. However, none of the clinically useful drugs is selective for receptor subtypes in either class.

Chemistry & Pharmacokinetics

A. Structure

Four important choline esters that have been studied extensively are shown in Figure 7–2. Their permanently charged quaternary ammonium group renders them relatively insoluble in lipids. Many naturally occurring and synthetic cholinomimetic drugs that are not choline esters have been identified; a few of these are shown in Figure 7–3. The muscarinic receptor is strongly stereoselective: *(S)*-bethanechol is almost 1000 times more potent than *(R)*-bethanechol.

B. Absorption, Distribution, and Metabolism

Choline esters are poorly absorbed and poorly distributed into the central nervous system because they are hydrophilic. Although all are hydrolyzed in the gastrointestinal tract (and less active by the oral route), they differ markedly in their susceptibility to hydrolysis by cholinesterase. Acetylcholine is very rapidly hydrolyzed (see Chapter 6); large amounts must be infused intravenously to achieve concentrations sufficient to produce detectable effects. A large intravenous bolus injection has a brief effect, typically 5–20 seconds, whereas intramuscular and subcutaneous injections produce only local effects. Methacholine is more resistant to hydrolysis, and the carbamic acid esters carbachol and bethanechol are still more resistant to hydrolysis by cholinesterase and have correspondingly longer durations of action. The β-methyl group (methacholine, bethanechol) reduces the potency of these drugs at nicotinic receptors (Table 7–2).

The tertiary natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline; Figure 7–3) are well absorbed from most sites of administration. Nicotine, a liquid, is sufficiently lipid-soluble to be absorbed across the skin. Muscarine, a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested—eg, in certain mushrooms—and it even enters the brain. Lobeline is a plant derivative similar to nicotine. These amines are excreted chiefly by the kidneys. Acidification of the urine accelerates clearance of the tertiary amines (see Chapter 1).

Pharmacodynamics

A. Mechanism of Action

Activation of the parasympathetic nervous system modifies organ function by two major mechanisms. First, acetylcholine released

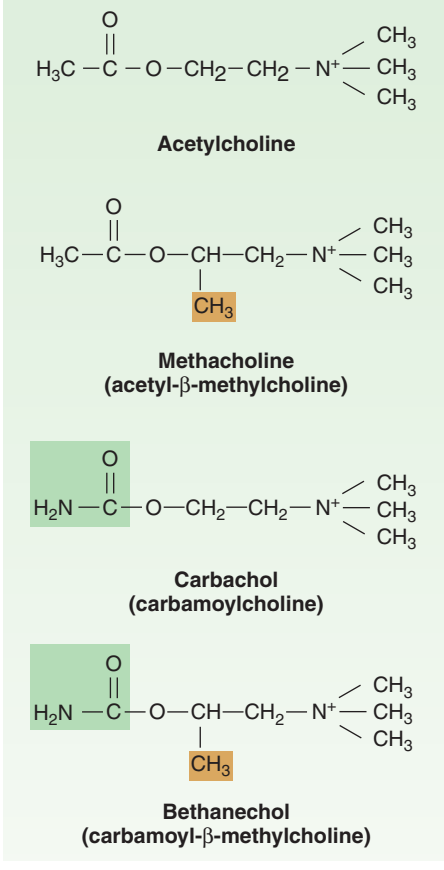

FIGURE 7–2 Molecular structures of four choline esters. Acetylcholine and methacholine are acetic acid esters of choline and β-methylcholine, respectively. Carbachol and bethanechol are carbamic acid esters of the same alcohols.

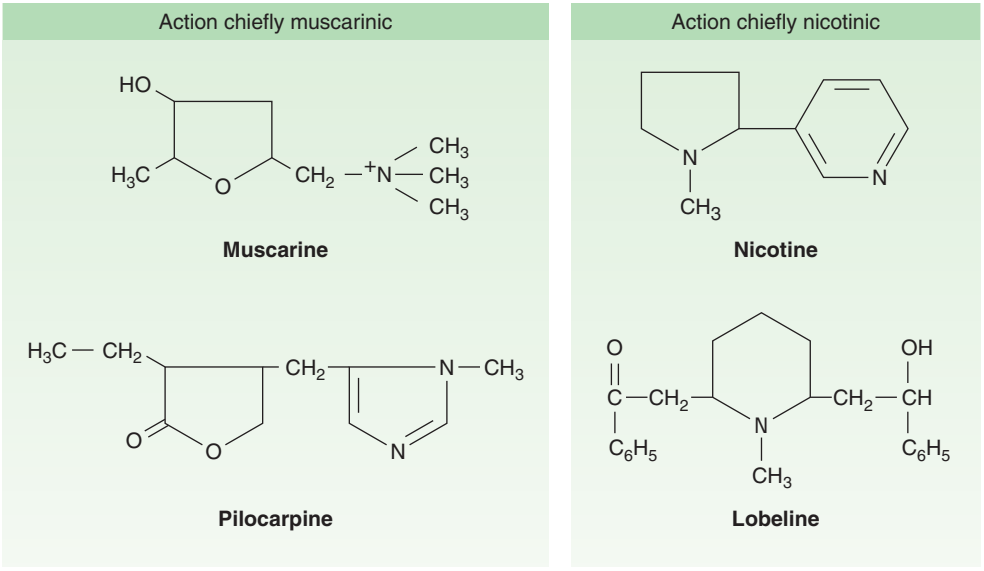

FIGURE 7–3 Structures of some cholinomimetic alkaloids.

from parasympathetic nerves activates muscarinic receptors on effector cells to alter organ function directly. Second, acetylcholine released from parasympathetic nerves interacts with muscarinic receptors on nerve terminals to inhibit the release of their neurotransmitter. By this mechanism, acetylcholine release and circulating muscarinic agonists indirectly alter organ function by modulating the effects of the parasympathetic and sympathetic nervous systems and perhaps nonadrenergic, noncholinergic (NANC) systems.

As indicated in Chapter 6, muscarinic receptor subtypes have been characterized by binding studies and cloned. Several cellular events occur when muscarinic receptors are activated, one or more of which might serve as second messengers for muscarinic activation. All muscarinic receptors appear to be of the G protein-coupled type (see Chapter 2 and Table 7–1). Muscarinic agonist binding activates the inositol trisphosphate (IP_3), diacylglycerol (DAG) cascade. Some evidence implicates DAG in the opening of smooth muscle calcium channels; IP_3 releases calcium from endoplasmic and sarcoplasmic reticulum. Muscarinic agonists also increase cellular cGMP concentrations. Activation of muscarinic receptors also increases potassium flux across cardiac cell membranes (Figure 7–4A) and decreases it in ganglion and smooth muscle cells. This effect is mediated by the binding of an activated G protein βγ subunit directly to the channel. Finally, muscarinic receptor activation in some tissues (eg, heart, intestine) inhibits adenylyl cyclase activity. Moreover, muscarinic agonists attenuate the activation of adenylyl cyclase and modulate the increase in cAMP levels induced by hormones such as catecholamines. These muscarinic effects on cAMP generation reduce the physiologic response of the organ to stimulatory hormones.

TABLE 7–2 Properties of choline esters.

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

The mechanism of nicotinic receptor activation has been studied in great detail, taking advantage of three factors: (1) the receptor is present in extremely high concentration in the membranes of the electric organs of electric fish; (2) α-bungarotoxin, a component of certain snake venoms, binds tightly to the receptors and is readily labeled as a marker for isolation procedures; and (3) receptor activation results in easily measured electrical and ionic changes in the cells involved. The nicotinic receptor in muscle tissues is a pentamer of four types of glycoprotein subunits (one monomer occurs twice) with a total molecular weight of about 250,000 (Figure 7–4B). The neuronal nicotinic receptor consists of α and β subunits only (Table 7–1). Each subunit has four transmembrane segments. The nicotinic receptor has two agonist binding sites at the interfaces formed by the two α subunits and two adjacent subunits (β, γ, ε). Agonist binding to the receptor sites causes a conformational change in the protein (channel opening) that allows sodium and potassium ions to diffuse rapidly down their concentration gradients (calcium ions may also carry charge through the nicotinic receptor ion channel). Binding of an agonist molecule by one of the two receptor sites only modestly increases the probability of channel opening; simultaneous binding of agonist by both of the receptor sites

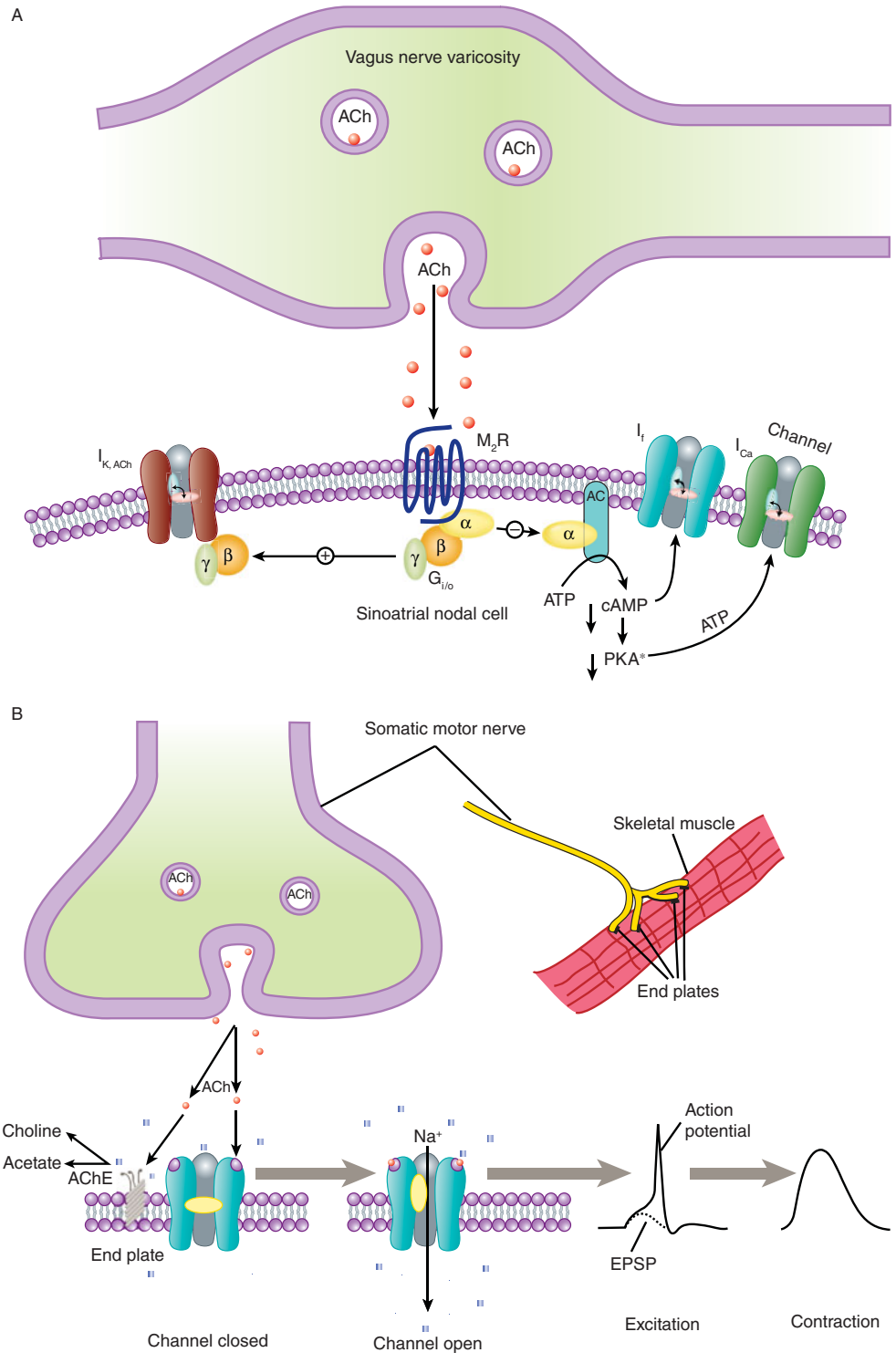

FIGURE 7–4 Muscarinic and nicotinic signaling. **A:** Muscarinic transmission to the sinoatrial node in heart. Acetylcholine (ACh) released from a varicosity of a postganglionic cholinergic axon interacts with a muscarinic receptor (M_2R) linked via $G_{i/o}$ to K^+ channel opening, which causes hyperpolarization, and to inhibition of cAMP synthesis. Reduced cAMP causes voltage-dependent opening of pacemaker channels (I_f) to shift to more negative potentials, and reduces the phosphorylation and availability of L-type Ca^{2+} channels (I_{Ca}). **B:** Nicotinic transmission at the skeletal neuromuscular junction. ACh released from the motor nerve terminal interacts with subunits of the pentameric nicotinic receptor to open it, allowing Na^+ influx to produce an excitatory postsynaptic potential (EPSP). The EPSP depolarizes the muscle membrane, generating an action potential, and triggering contraction. Acetylcholinesterase (AChE) in the extracellular matrix hydrolyzes ACh.

greatly enhances opening probability. Nicotinic receptor activation causes depolarization of the nerve cell or neuromuscular end plate membrane. In skeletal muscle, the depolarization initiates an action potential that propagates across the muscle membrane and causes contraction (Figure 7–4B).

Prolonged agonist occupancy of the nicotinic receptor abolishes the effector response; that is, the postganglionic neuron stops firing (ganglionic effect), and the skeletal muscle cell relaxes (neuromuscular end plate effect). Furthermore, the continued presence of the nicotinic agonist prevents electrical recovery of the postjunctional membrane. Thus, a state of "depolarizing blockade" occurs initially during persistent agonist occupancy of the receptor. Continued agonist occupancy is associated with return of membrane voltage to the resting level. The receptor becomes desensitized to agonist, and this state is refractory to reversal by other agonists. As described in Chapter 27, this effect can be exploited for producing muscle paralysis.

B. Organ System Effects

Most of the direct organ system effects of muscarinic cholinoceptor stimulants are readily predicted from knowledge of the effects of parasympathetic nerve stimulation (see Table 6–3) and the distribution of muscarinic receptors. Effects of a typical agent such as acetylcholine are listed in Table 7–3. The effects of nicotinic agonists are similarly predictable from knowledge of the physiology of the autonomic ganglia and skeletal muscle motor end plate.

1. Eye—Muscarinic agonists instilled into the conjunctival sac cause contraction of the smooth muscle of the iris sphincter (resulting in miosis) and of the ciliary muscle (resulting in accommodation). As a result, the iris is pulled away from the angle of the anterior chamber, and the trabecular meshwork at the base of the ciliary muscle is opened. Both effects facilitate aqueous humor outflow into the canal of Schlemm, which drains the anterior chamber.

2. Cardiovascular system—The primary cardiovascular effects of muscarinic agonists are reduction in peripheral vascular resistance and changes in heart rate. The direct effects listed in Table 7–3 are modified by important homeostatic reflexes, as described in Chapter 6 and depicted in Figure 6–7. Intravenous infusions of minimally effective doses of acetylcholine in humans (eg, 20–50 mcg/min) cause vasodilation, resulting in a reduction in blood pressure, often accompanied by a reflex increase in heart rate. Larger doses of acetylcholine produce bradycardia and decrease atrioventricular node conduction velocity in addition to hypotension.

The direct cardiac actions of muscarinic stimulants include the following: (1) an increase in a potassium current ($I_{K(ACh)}$) in the cells of the sinoatrial and atrioventricular nodes, in Purkinje cells, and also in atrial and ventricular muscle cells; (2) a decrease in the slow inward calcium current (I_{Ca}) in heart cells; and (3) a reduction in the hyperpolarization-activated current (I_f) that underlies diastolic depolarization (Figure 7–4A). All these actions are mediated by M_2 receptors and contribute to slowing the pacemaker rate. Effects (1) and (2) cause hyperpolarization, reduce action potential duration, and decrease the contractility of atrial and ventricular cells. Predictably, knockout of M_2 receptors eliminates the bradycardic effect of vagal stimulation and the negative chronotropic effect of carbachol on sinoatrial rate.

The direct slowing of sinoatrial rate and atrioventricular conduction that is produced by muscarinic agonists is often opposed by reflex sympathetic discharge, elicited by the decrease in blood pressure (see Figure 6–7). The resultant sympathetic-parasympathetic interaction is complex because muscarinic modulation of sympathetic influences occurs by inhibition of norepinephrine release and by postjunctional cellular effects. Muscarinic receptors that are present on postganglionic parasympathetic nerve terminals allow neurally released acetylcholine to inhibit its own secretion. The neuronal muscarinic receptors need not be the same subtype as found on effector cells. Therefore, the net effect on heart rate depends on local concentrations of the agonist in the heart and in the vessels and on the level of reflex responsiveness.

TABLE 7–3 Effects of direct-acting cholinoceptor stimulants.*

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

EDRF, endothelium-derived relaxing factor.

*Only the direct effects are indicated; homeostatic responses to these direct actions may be important (see text).

Parasympathetic innervation of the ventricles is much less extensive than that of the atria; activation of ventricular muscarinic receptors causes much less physiologic effect than that seen in atria. However, the effects of muscarinic agonists on ventricular function are clearly evident during sympathetic nerve stimulation because of muscarinic modulation of sympathetic effects ("accentuated antagonism").

In the intact organism, intravascular injection of muscarinic agonists produces marked vasodilation. However, earlier studies of isolated blood vessels often showed a contractile response to these agents. It is now known that acetylcholine-induced vasodilation arises from activation of M_3 receptors and requires the presence of intact endothelium (Figure 7–5). Muscarinic agonists release endothelium-derived relaxing factor (EDRF), identified as nitric oxide (NO), from the endothelial cells. The NO diffuses to adjacent vascular smooth muscle, where it activates guanylyl cyclase and increases cGMP, resulting in relaxation (see Figure 12–2). Isolated vessels prepared with the endothelium preserved consistently reproduce the vasodilation seen in the intact organism. The relaxing effect of acetylcholine was maximal at 3×10^{-7} M (Figure 7–5). This effect was eliminated in the absence of endothelium, and acetylcholine, at concentrations greater than 10^{-7} M, then caused contraction. This results from a direct effect of acetylcholine on vascular smooth muscle in which activation of M_3 receptors stimulates IP_3 production and releases intracellular calcium.

Parasympathetic nerves can regulate arteriolar tone in vascular beds in thoracic and abdominal visceral organs. Acetylcholine released from postganglionic parasympathetic nerves relaxes coronary arteriolar smooth muscle via the NO/cGMP pathway in humans as described above. Damage to the endothelium, as occurs with atherosclerosis, eliminates this action, and acetylcholine is then able to contract arterial smooth muscle and produce vasoconstriction. Parasympathetic nerve stimulation also causes vasodilation in cerebral blood vessels; however, the effect often appears as a result of NO released either from NANC (nitrergic) neurons or as a cotransmitter from cholinergic nerves. The relative contributions of cholinergic and NANC neurons to the vascular effects of parasympathetic nerve stimulation are not known for most viscera. Skeletal muscle receives sympathetic cholinergic vasodilator nerves, but the view that acetylcholine causes vasodilation in this vascular bed has not been verified experimentally. Nitric oxide, rather than acetylcholine, may be released from these neurons. However, this vascular bed responds to exogenous choline esters because of the presence of M_3 receptors on endothelial and smooth muscle cells.

The cardiovascular effects of all the choline esters are similar to those of acetylcholine—the main difference being in their potency and duration of action. Because of the resistance of methacholine, carbachol, and bethanechol to acetylcholinesterase, lower doses given intravenously are sufficient to produce effects similar to those of acetylcholine, and the duration of action of these synthetic choline esters is longer. The cardiovascular effects of most of the cholinomimetic natural alkaloids and the synthetic analogs are also generally similar to those of acetylcholine.

Pilocarpine is an interesting exception to the above statement. If given intravenously (an experimental exercise), it may produce hypertension after a brief initial hypotensive response. The longer-lasting hypertensive effect can be traced to sympathetic ganglionic discharge caused by activation of postganglionic cell membrane M_1 receptors, which close K^+ channels and elicit slow excitatory (depolarizing) postsynaptic potentials. This effect, like the hypotensive effect, can be blocked by atropine, an antimuscarinic drug.

3. Respiratory system—Muscarinic stimulants contract the smooth muscle of the bronchial tree. In addition, the glands of the tracheobronchial mucosa are stimulated to secrete. This combination of effects can occasionally cause symptoms, especially in individuals with asthma. The bronchoconstriction caused by muscarinic agonists is eliminated in knockout animals in which the M_3 receptor has been mutated.

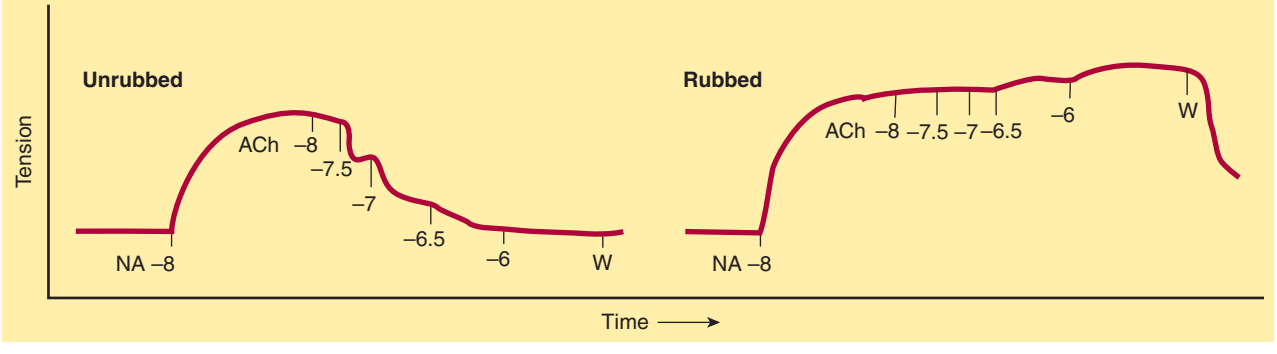

FIGURE 7–5 Activation of endothelial cell muscarinic receptors by acetylcholine (Ach) releases endothelium-derived relaxing factor (nitric oxide), which causes relaxation of vascular smooth muscle precontracted with norepinephrine, 10^{-8} M. Removal of the endothelium by rubbing eliminates the relaxant effect and reveals contraction caused by direct action of Ach on vascular smooth muscle. (NA, noradrenaline [norepinephrine]. Numbers indicate the log concentration applied at the time indicated.) (Modified and reproduced, with permission, from Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373.)

4. Gastrointestinal tract—Administration of muscarinic agonists, as in parasympathetic nervous system stimulation, increases the secretory and motor activity of the gut. The salivary and gastric glands are strongly stimulated; the pancreas and small intestinal glands are stimulated less so. Peristaltic activity is increased throughout the gut, and most sphincters are relaxed. Stimulation of contraction in this organ system involves depolarization of the smooth muscle cell membrane and increased calcium influx. Muscarinic agonists do not cause contraction of the ileum in mutant mice lacking M_2 and M_3 receptors. The M_3 receptor is required for direct activation of smooth muscle contraction, whereas the M_2 receptor reduces cAMP formation and relaxation caused by sympathomimetic drugs.

5. Genitourinary tract—Muscarinic agonists stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding. The function of M_2 and M_3 receptors in the urinary bladder appears to be the same as in intestinal smooth muscle. The human uterus is not notably sensitive to muscarinic agonists.

6. Miscellaneous secretory glands—Muscarinic agonists stimulate secretion by thermoregulatory sweat, lacrimal, and nasopharyngeal glands.

7. Central nervous system—The central nervous system contains both muscarinic and nicotinic receptors, the brain being relatively richer in muscarinic sites and the spinal cord containing a preponderance of nicotinic sites. The physiologic roles of these receptors are discussed in Chapter 21.

All five muscarinic receptor subtypes have been detected in the central nervous system. The roles of M_1 through M_3 have been analyzed by means of experiments in knockout mice. The M_1 subtype is richly expressed in brain areas involved in cognition. Knockout of M_1 receptors was associated with impaired neuronal plasticity in the forebrain, and pilocarpine did not induce seizures in M_1 mutant mice. The central nervous system effects of the synthetic muscarinic agonist oxotremorine (tremor, hypothermia, and antinociception) were lacking in mice with homozygously mutated M_2 receptors. Animals lacking M_3 receptors, especially those in the hypothalamus, had reduced appetite and diminished body fat mass.

In spite of the smaller ratio of nicotinic to muscarinic receptors, nicotine and lobeline (Figure 7–3) have important effects on the brain stem and cortex. Activation of nicotinic receptors occurs at presynaptic and postsynaptic loci. Presynaptic nicotinic receptors allow acetylcholine and nicotine to regulate the release of several neurotransmitters (glutamate, serotonin, GABA, dopamine, and norepinephrine). Acetylcholine regulates norepinephrine release via $\alpha3\beta4$ nicotinic receptors in the hippocampus and inhibits acetylcholine release from neurons in the hippocampus and cortex. The $\alpha4\beta2$ oligomer is the most abundant nicotinic receptor in the brain. Chronic exposure to nicotine has a dual effect at nicotinic receptors: activation (depolarization) followed by desensitization. The former effect is associated with greater release of dopamine in the mesolimbic system. This effect is thought to contribute to the mild alerting action and the addictive property of nicotine absorbed from tobacco. When the $\beta2$ subunits are deleted in reconstitution experiments, acetylcholine binding is reduced, as is the release of dopamine. The later desensitization of the nicotinic receptor is accompanied by increased high-affinity agonist binding and an upregulation of nicotinic binding sites, especially those of the $\alpha4\beta2$ oligomer. Sustained desensitization may contribute to the benefits of nicotine replacement therapy in smoking cessation regimens. In high concentrations, nicotine induces tremor, emesis, and stimulation of the respiratory center. At still higher levels, nicotine causes convulsions, which may terminate in fatal coma. The lethal effects on the central nervous system and the fact that nicotine is readily absorbed form the basis for the use of nicotine as an insecticide.

8. Peripheral nervous system—Autonomic ganglia are important sites of nicotinic synaptic action. The nicotinic agents shown in Figure 7–3 cause marked activation of these nicotinic receptors and initiate action potentials in postganglionic neurons (see Figure 6–8). Nicotine itself has a somewhat greater affinity for neuronal than for skeletal muscle nicotinic receptors. The action is the same on both parasympathetic and sympathetic ganglia. The initial response therefore often resembles simultaneous discharge of both the parasympathetic and the sympathetic nervous systems. In the case of the cardiovascular system, the effects of nicotine are chiefly sympathomimetic. Dramatic hypertension is produced by parenteral injection of nicotine; sympathetic tachycardia may alternate with a bradycardia mediated by vagal discharge. In the gastrointestinal and urinary tracts, the effects are largely parasympathomimetic: nausea, vomiting, diarrhea, and voiding of urine are commonly observed. Prolonged exposure may result in depolarizing blockade of the ganglia.

Neuronal nicotinic receptors are present on sensory nerve endings—especially afferent nerves in coronary arteries and the carotid and aortic bodies as well as on the glomus cells of the latter. Activation of these receptors by nicotinic stimulants and of muscarinic receptors on glomus cells by muscarinic stimulants elicits complex medullary responses, including respiratory alterations and vagal discharge.

9. Neuromuscular junction—The nicotinic receptors on the neuromuscular end plate apparatus are similar but not identical to the receptors in the autonomic ganglia (Table 7–1). Both types respond to acetylcholine and nicotine. (However, as noted in Chapter 8, the receptors differ in their structural requirements for nicotinic blocking drugs.) When a nicotinic agonist is applied directly (by iontophoresis or by intra-arterial injection), an immediate depolarization of the end plate results, caused by an increase in permeability to sodium and potassium ions (Figure 7–4). The contractile response varies from disorganized fasciculations of independent motor units to a strong contraction of the entire muscle depending on the synchronization of depolarization of end plates throughout the muscle. Depolarizing nicotinic agents that are not rapidly hydrolyzed (like nicotine itself) cause rapid development of depolarization blockade; transmission

blockade persists even when the membrane has repolarized (discussed further in Chapters 8 and 27). This latter phase of block is manifested as flaccid paralysis in the case of skeletal muscle.

■ BASIC PHARMACOLOGY OF THE INDIRECT-ACTING CHOLINOMIMETICS

The actions of acetylcholine released from autonomic and somatic motor nerves are terminated by enzymatic hydrolysis of the molecule. Hydrolysis is accomplished by the action of acetylcholinesterase, which is present in high concentrations in cholinergic synapses. The indirect-acting cholinomimetics have their primary effect at the active site of this enzyme, although some also have direct actions at nicotinic receptors. The chief differences between members of the group are chemical and pharmacokinetic—their pharmacodynamic properties are almost identical.

Chemistry & Pharmacokinetics

A. Structure

There are three chemical groups of cholinesterase inhibitors: (1) simple alcohols bearing a quaternary ammonium group, eg, edrophonium; (2) carbamic acid esters of alcohols having quaternary or tertiary ammonium groups (carbamates, eg, neostigmine); and (3) organic derivatives of phosphoric acid (organophosphates, eg, echothiophate). Examples of the first two groups are shown in Figure 7–6. Edrophonium, neostigmine, and pyridostigmine are synthetic quaternary ammonium agents used in medicine. Physostigmine (eserine) is a naturally occurring tertiary amine of greater lipid solubility that is also used in therapeutics. Carbaryl (carbaril) is typical of a large group of carbamate insecticides designed for very high lipid solubility, so that absorption into the insect and distribution to its central nervous system are very rapid.

A few of the estimated 50,000 organophosphates are shown in Figure 7–7. Many of the organophosphates (echothiophate is an exception) are highly lipid-soluble liquids. Echothiophate, a thiocholine derivative, is of clinical value because it retains the very long duration of action of other organophosphates but is more stable in aqueous solution. Soman is an extremely potent "nerve gas." Parathion and malathion are thiophosphate (sulfur-containing phosphate) prodrugs that are inactive as such; they are converted to the phosphate derivatives in animals and plants and are used as insecticides.

B. Absorption, Distribution, and Metabolism

Absorption of the quaternary carbamates from the conjunctiva, skin, gut and lungs is predictably poor, since their permanent charge renders them relatively insoluble in lipids. Thus, much larger doses are required for oral administration than for parenteral injection. Distribution into the central nervous system is negligible. Physostigmine, in contrast, is well absorbed from all sites and can be used topically in the eye (Table 7–4). It is distributed into the central nervous system and is more toxic than the more polar quaternary carbamates. The carbamates are relatively stable in aqueous solution but can be metabolized by nonspecific esterases in the body as well as by cholinesterase. However, the duration of their effect is determined chiefly by the stability of the inhibitor-enzyme complex (see Mechanism of Action, below), not by metabolism or excretion.

The organophosphate cholinesterase inhibitors (except for echothiophate) are well absorbed from the skin, lung, gut, and

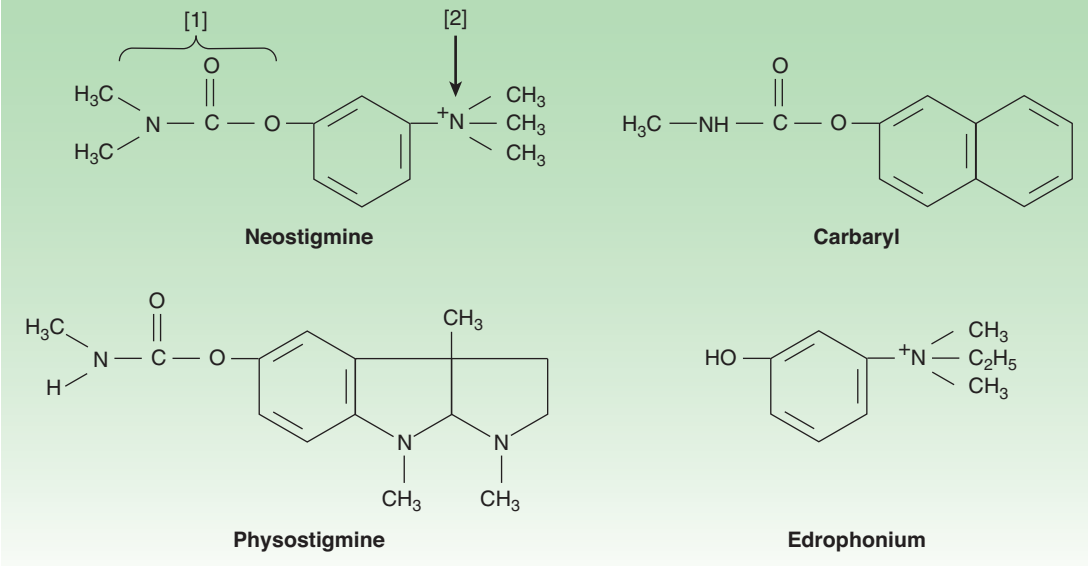

FIGURE 7–6 Cholinesterase inhibitors. Neostigmine exemplifies the typical ester composed of carbamic acid ([1]) and a phenol bearing a quaternary ammonium group ([2]). Physostigmine, a naturally occurring carbamate, is a tertiary amine. Edrophonium is not an ester but binds to the active site of the enzyme. Carbaryl is used as an insecticide.

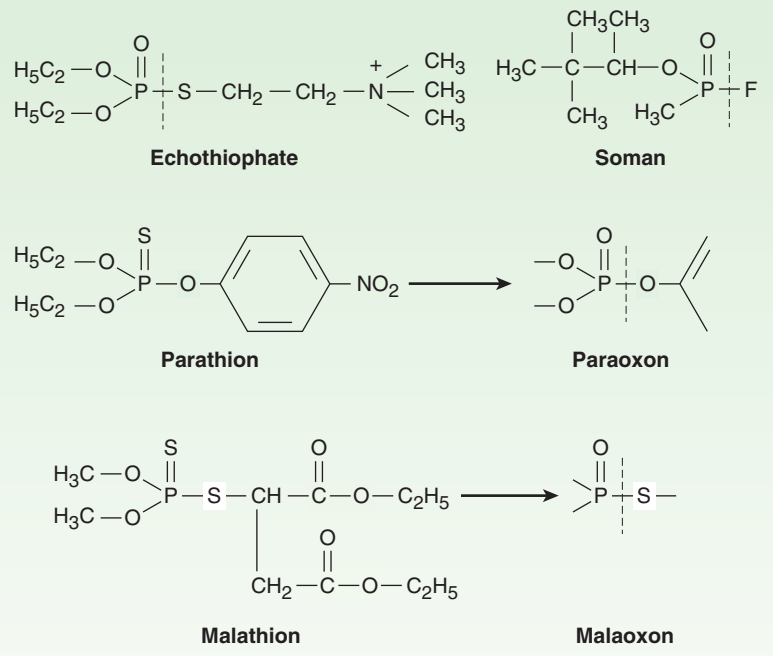

FIGURE 7–7 Structures of some organophosphate cholinesterase inhibitors. The dashed lines indicate the bond that is hydrolyzed in binding to the enzyme. The shaded ester bonds in malathion represent the points of detoxification of the molecule in mammals and birds.

conjunctiva—thereby making them dangerous to humans and highly effective as insecticides. They are relatively less stable than the carbamates when dissolved in water and thus have a limited half-life in the environment (compared with another major class of insecticides, the halogenated hydrocarbons, eg, DDT). Echothiophate is highly polar and more stable than most other organophosphates. When prepared in aqueous solution for ophthalmic use, it retains activity for weeks.

The thiophosphate insecticides (parathion, malathion, and related compounds) are quite lipid-soluble and are rapidly absorbed by all routes. They must be activated in the body by conversion to the oxygen analogs (Figure 7–7), a process that occurs rapidly in both insects and vertebrates. Malathion and a few other organophosphate insecticides are also rapidly metabolized by other pathways to inactive products in birds and mammals but not in insects; these agents are therefore considered safe enough for sale to the general public. Unfortunately, fish cannot detoxify malathion, and significant numbers of fish have died from the heavy use of this agent on and near waterways. Parathion is not detoxified effectively in vertebrates; thus, it is considerably more dangerous than malathion to humans and livestock and is not available for general public use in the USA.

All the organophosphates except echothiophate are distributed to all parts of the body, including the central nervous system. Therefore, central nervous system toxicity is an important component of poisoning with these agents.

Pharmacodynamics

A. Mechanism of Action

Acetylcholinesterase is the primary target of these drugs, but butyrylcholinesterase is also inhibited. Acetylcholinesterase is an extremely active enzyme. In the initial catalytic step, acetylcholine binds to the enzyme's active site and is hydrolyzed, yielding free choline and the acetylated enzyme. In the second step, the covalent acetyl-enzyme bond is split, with the addition of water (hydration). The entire process occurs in approximately 150 microseconds.

All the cholinesterase inhibitors increase the concentration of endogenous acetylcholine at cholinoceptors by inhibiting acetylcholinesterase. However, the molecular details of their interaction with the enzyme vary according to the three chemical subgroups mentioned above.

TABLE 7–4 Therapeutic uses and durations of action of cholinesterase inhibitors.

	Uses	Approximate Duration of Action
Alcohols		
Edrophonium	Myasthenia gravis, ileus, arrhythmias	5–15 minutes
Carbamates and related agents		
Neostigmine	Myasthenia gravis, ileus	0.5–2 hours
Pyridostigmine	Myasthenia gravis	3–6 hours
Physostigmine	Glaucoma	0.5–2 hours
Ambenonium	Myasthenia gravis	4–8 hours
Demecarium	Glaucoma	4–6 hours
Organophosphates		
Echothiophate	Glaucoma	100 hours

The first group, of which edrophonium is the example, consists of quaternary alcohols. These agents reversibly bind electrostatically and by hydrogen bonds to the active site, thus preventing access of acetylcholine. The enzyme-inhibitor complex does not involve a covalent bond and is correspondingly short-lived (on the order of 2–10 minutes). The second group consists of carbamate esters, eg, neostigmine and physostigmine. These agents undergo a two-step hydrolysis sequence analogous to that described for acetylcholine. However, the covalent bond of the *carbamoylated* enzyme is considerably more resistant to the second (hydration) process, and this step is correspondingly prolonged (on the order of 30 minutes to 6 hours). The third group consists of the organophosphates. These agents also undergo initial binding and hydrolysis by the enzyme, resulting in a *phosphorylated* active site. The covalent phosphorus-enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours). After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging.** This process apparently involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond. The rate of aging varies with the particular organophosphate compound. For example, aging occurs within 10 minutes with the chemical warfare agent soman, but as much as 48 hours later with the drug VX. If given before aging has occurred, strong nucleophiles like pralidoxime are able to break the phosphorus-enzyme bond and can be used as "cholinesterase regenerator" drugs for organophosphate insecticide poisoning (see Chapter 8). Once aging has occurred, the enzyme-inhibitor complex is even more stable and is more difficult to break, even with oxime regenerator compounds.

The organophosphate inhibitors are sometimes referred to as "irreversible" cholinesterase inhibitors, and edrophonium and the carbamates are considered "reversible" inhibitors because of the marked differences in duration of action. However, the molecular mechanisms of action of the three groups do not support this simplistic description.

B. Organ System Effects

The most prominent pharmacologic effects of cholinesterase inhibitors are on the cardiovascular and gastrointestinal systems, the eye, and the skeletal muscle neuromuscular junction (as described in the Case Study). Because the primary action is to amplify the actions of endogenous acetylcholine, the effects are similar (but not always identical) to the effects of the direct-acting cholinomimetic agonists.

1. Central nervous system—In low concentrations, the lipid-soluble cholinesterase inhibitors cause diffuse activation on the electroencephalogram and a subjective alerting response. In higher concentrations, they cause generalized convulsions, which may be followed by coma and respiratory arrest.

2. Eye, respiratory tract, gastrointestinal tract, urinary tract—The effects of the cholinesterase inhibitors on these organ systems, all of which are well innervated by the parasympathetic nervous system, are qualitatively quite similar to the effects of the direct-acting cholinomimetics (Table 7–3).

3. Cardiovascular system—The cholinesterase inhibitors can increase activity in both sympathetic and parasympathetic ganglia supplying the heart and at the acetylcholine receptors on neuroeffector cells (cardiac and vascular smooth muscles) that receive cholinergic innervation.

In the heart, the effects on the parasympathetic limb predominate. Thus, cholinesterase inhibitors such as edrophonium, physostigmine, or neostigmine mimic the effects of vagal nerve activation on the heart. Negative chronotropic, dromotropic, and inotropic effects are produced, and cardiac output falls. The fall in cardiac output is attributable to bradycardia, decreased atrial contractility, and some reduction in ventricular contractility. The latter effect occurs as a result of prejunctional inhibition of norepinephrine release as well as inhibition of postjunctional cellular sympathetic effects.

Cholinesterase inhibitors have minimal effects by direct action on vascular smooth muscle because most vascular beds lack cholinergic innervation (coronary vasculature is an exception). At moderate doses, cholinesterase inhibitors cause an increase in systemic vascular resistance and blood pressure that is initiated at sympathetic ganglia in the case of quaternary nitrogen compounds and also at central sympathetic centers in the case of lipid-soluble agents. Atropine, acting in the central and peripheral nervous systems, can prevent the increase of blood pressure and the increased plasma norepinephrine.

The *net* cardiovascular effects of moderate doses of cholinesterase inhibitors therefore consist of modest bradycardia, a fall in cardiac output, and an increased vascular resistance that results in a rise in blood pressure. (Thus, in patients with Alzheimer's disease who have hypertension, treatment with cholinesterase inhibitors requires that blood pressure be monitored to adjust antihypertensive therapy.) At high (toxic) doses of cholinesterase inhibitors, marked bradycardia occurs, cardiac output decreases significantly, and hypotension supervenes.

4. Neuromuscular junction—The cholinesterase inhibitors have important therapeutic and toxic effects at the skeletal muscle neuromuscular junction. Low (therapeutic) concentrations moderately prolong and intensify the actions of physiologically released acetylcholine. This increases the strength of contraction, especially in muscles weakened by curare-like neuromuscular blocking agents or by myasthenia gravis. At higher concentrations, the accumulation of acetylcholine may result in fibrillation of muscle fibers. Antidromic firing of the motor neuron may also occur, resulting in fasciculations that involve an entire motor unit. With marked inhibition of acetylcholinesterase, depolarizing neuromuscular blockade occurs and that may be followed by a phase of nondepolarizing blockade as seen with succinylcholine (see Table 27–2 and Figure 27–7).

Some quaternary carbamate cholinesterase inhibitors, eg, neostigmine, have an additional *direct* nicotinic agonist effect at the neuromuscular junction. This may contribute to the effectiveness of these agents as therapy for myasthenia.

CLINICAL PHARMACOLOGY OF THE CHOLINOMIMETICS

The major therapeutic uses of the cholinomimetics are to treat diseases of the eye (glaucoma, accommodative esotropia), the gastrointestinal and urinary tracts (postoperative atony, neurogenic bladder), and the neuromuscular junction (myasthenia gravis, curare-induced neuromuscular paralysis), and to treat patients with Alzheimer's disease. Cholinesterase inhibitors are occasionally used in the treatment of atropine overdosage and, very rarely, in the therapy of certain atrial arrhythmias.

Clinical Uses

A. The Eye

Glaucoma is a disease characterized by increased intraocular pressure. Muscarinic stimulants and cholinesterase inhibitors reduce intraocular pressure by causing contraction of the ciliary body so as to facilitate outflow of aqueous humor and perhaps also by diminishing the rate of its secretion (see Figure 6–9). In the past, glaucoma was treated with either direct agonists (pilocarpine, methacholine, carbachol) or cholinesterase inhibitors (physostigmine, demecarium, echothiophate, isoflurophate). For chronic glaucoma, these drugs have been largely replaced by topical β blockers and prostaglandin derivatives.

Acute angle-closure glaucoma is a medical emergency that is frequently treated initially with drugs but usually requires surgery for permanent correction. Initial therapy often consists of a combination of a direct muscarinic agonist and a cholinesterase inhibitor (eg, pilocarpine plus physostigmine) as well as other drugs. Once the intraocular pressure is controlled and the danger of vision loss is diminished, the patient can be prepared for corrective surgery (iridectomy). Open-angle glaucoma and some cases of secondary glaucoma are chronic diseases that are not amenable to traditional surgical correction, although newer laser techniques appear to be useful. Other treatments for glaucoma are described in the Box, Treatment of Glaucoma in Chapter 10.

Accommodative esotropia (strabismus caused by hypermetropic accommodative error) in young children is sometimes diagnosed and treated with cholinomimetic agonists. Dosage is similar to or higher than that used for glaucoma.

B. Gastrointestinal and Urinary Tracts

In clinical disorders that involve depression of smooth muscle activity without obstruction, cholinomimetic drugs with direct or indirect muscarinic effects may be helpful. These disorders include postoperative ileus (atony or paralysis of the stomach or bowel following surgical manipulation) and congenital megacolon. Urinary retention may occur postoperatively or postpartum or may be secondary to spinal cord injury or disease (neurogenic bladder). Cholinomimetics are also sometimes used to increase the tone of the lower esophageal sphincter in patients with reflux esophagitis. Of the choline esters, bethanechol is the most widely used for these disorders. For gastrointestinal problems, it is usually administered orally in a dose of 10–25 mg three or four times daily. In patients with urinary retention, bethanechol can be given subcutaneously in a dose of 5 mg and repeated in 30 minutes if necessary. Of the cholinesterase inhibitors, neostigmine is the most widely used for these applications. For paralytic ileus or atony of the urinary bladder, neostigmine can be given subcutaneously in a dose of 0.5–1 mg. If patients are able to take the drug by mouth, neostigmine can be given orally in a dose of 15 mg. In all of these situations, the clinician must be certain that there is no mechanical obstruction to outflow before using the cholinomimetic. Otherwise, the drug may exacerbate the problem and may even cause perforation as a result of increased pressure.

Pilocarpine has long been used to increase salivary secretion. Cevimeline, a quinuclidine derivative of acetylcholine, is a new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome and that caused by radiation damage of the salivary glands.

C. Neuromuscular Junction

Myasthenia gravis is an autoimmune disease affecting skeletal muscle neuromuscular junctions. In this disease, antibodies are produced against the main immunogenic region found on α1 subunits of the nicotinic receptor-channel complex. Antibodies are detected in 85% of myasthenic patients. The antibodies reduce nicotinic receptor function by (1) cross-linking receptors, a process that stimulates their internalization and degradation; (2) causing lysis of the postsynaptic membrane; and (3) binding to the nicotinic receptor and inhibiting function. Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness. Severe disease may affect all the muscles, including those necessary for respiration. The disease resembles the neuromuscular paralysis produced by *d*-tubocurarine and similar nondepolarizing neuromuscular blocking drugs (see Chapter 27). Patients with myasthenia are exquisitely sensitive to the action of curariform drugs and other drugs that interfere with neuromuscular transmission, eg, aminoglycoside antibiotics.

Cholinesterase inhibitors—but not direct-acting acetylcholine receptor agonists—are extremely valuable as therapy for myasthenia. Patients with ocular myasthenia may be treated with cholinesterase inhibitors alone (Figure 7–4B). Patients having more widespread muscle weakness are also treated with immunosuppressant drugs (steroids, cyclosporine, and azathioprine). In some patients, the thymus gland is removed; very severely affected patients may benefit from administration of immunoglobulins and from plasmapheresis.

Edrophonium is sometimes used as a diagnostic test for myasthenia. A 2 mg dose is injected intravenously after baseline muscle strength has been measured. If no reaction occurs after 45 seconds, an additional 8 mg may be injected. If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5 minutes can usually be observed.

Clinical situations in which severe myasthenia (myasthenic crisis) must be distinguished from excessive drug therapy (cholinergic crisis) usually occur in very ill myasthenic patients and must be managed in hospital with adequate emergency support systems (eg, mechanical ventilators) available. Edrophonium can be used to assess the adequacy of treatment with the longer-acting

cholinesterase inhibitors usually prescribed in patients with myasthenia gravis. If excessive amounts of cholinesterase inhibitor have been used, patients may become paradoxically weak because of nicotinic depolarizing blockade of the motor end plate. These patients may also exhibit symptoms of excessive stimulation of muscarinic receptors (abdominal cramps, diarrhea, increased salivation, excessive bronchial secretions, miosis, bradycardia). Small doses of edrophonium (1–2 mg intravenously) will produce no relief or even worsen weakness if the patient is receiving excessive cholinesterase inhibitor therapy. On the other hand, if the patient improves with edrophonium, an increase in cholinesterase inhibitor dosage may be indicated.

Long-term therapy for myasthenia gravis is usually accomplished with pyridostigmine; neostigmine or ambenonium are alternatives. The doses are titrated to optimum levels based on changes in muscle strength. These drugs are relatively short-acting and therefore require frequent dosing (every 6 hours for pyridostigmine and ambenonium and every 4 hours for neostigmine; Table 7–4). Sustained-release preparations are available but should be used only at night and if needed. Longer-acting cholinesterase inhibitors such as the organophosphate agents are not used, because the dose requirement in this disease changes too rapidly to permit smooth control of symptoms with long-acting drugs.

If muscarinic effects of such therapy are prominent, they can be controlled by the administration of antimuscarinic drugs such as atropine. Frequently, tolerance to the muscarinic effects of the cholinesterase inhibitors develops, so atropine treatment is not required.

Neuromuscular blockade is frequently produced as an adjunct to surgical anesthesia, using nondepolarizing neuromuscular relaxants such as pancuronium and newer agents (see Chapter 27). After surgery, it is usually desirable to reverse this pharmacologic paralysis promptly. This can be easily accomplished with cholinesterase inhibitors; neostigmine and edrophonium are the drugs of choice. They are given intravenously or intramuscularly for prompt effect.

D. Heart

The short-acting cholinesterase inhibitor edrophonium was used to treat supraventricular tachyarrhythmias, particularly paroxysmal supraventricular tachycardia. In this application, edrophonium has been replaced by newer drugs with different mechanisms (adenosine and the calcium channel blockers verapamil and diltiazem, see Chapter 14).

E. Antimuscarinic Drug Intoxication

Atropine intoxication is potentially lethal in children (see Chapter 8) and may cause prolonged severe behavioral disturbances and arrhythmias in adults. The tricyclic antidepressants, when taken in overdosage (often with suicidal intent), also cause severe muscarinic blockade (see Chapter 30). The muscarinic receptor blockade produced by all these agents is competitive in nature and can be overcome by increasing the amount of endogenous acetylcholine at the neuroeffector junctions. Theoretically, a cholinesterase inhibitor could be used to reverse these effects. Physostigmine has been used for this application because it enters the central nervous system and reverses the central as well as the peripheral signs of muscarinic blockade. However, as described below, physostigmine itself can produce dangerous central nervous system effects, and such therapy is therefore used only in patients with dangerous elevation of body temperature or very rapid supraventricular tachycardia (see also Chapter 58).

F. Central Nervous System

Tacrine is a drug with anticholinesterase and other cholinomimetic actions that has been used for the treatment of mild to moderate Alzheimer's disease. Tacrine's efficacy is modest, and hepatic toxicity is significant. Donepezil, galantamine, and rivastigmine are newer, more selective acetylcholinesterase inhibitors that appear to have the same modest clinical benefit as tacrine in treatment of cognitive dysfunction in Alzheimer's patients. Donepezil may be given once daily because of its long half-life, and it lacks the hepatotoxic effect of tacrine. However, no trials comparing these newer drugs with tacrine have been reported. These drugs are discussed in Chapter 60.

Toxicity

The toxic potential of the cholinoceptor stimulants varies markedly depending on their absorption, access to the central nervous system, and metabolism.

A. Direct-Acting Muscarinic Stimulants

Drugs such as pilocarpine and the choline esters cause predictable signs of muscarinic excess when given in overdosage. These effects include nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction. The effects are all blocked competitively by atropine and its congeners.

Certain mushrooms, especially those of the genus *Inocybe*, contain muscarinic alkaloids. Ingestion of these mushrooms causes typical signs of muscarinic excess within 15–30 minutes. These effects can be very uncomfortable but are rarely fatal. Treatment is with atropine, 1–2 mg parenterally. (*Amanita muscaria,* the first source of muscarine, contains very low concentrations of the alkaloid.)

B. Direct-Acting Nicotinic Stimulants

Nicotine itself is the only common cause of this type of poisoning. (Varenicline toxicity is discussed elsewhere in this chapter.) The acute toxicity of the alkaloid is well defined but much less important than the chronic effects associated with smoking. In addition to tobacco products, nicotine is also used in insecticides.

1. Acute toxicity—The fatal dose of nicotine is approximately 40 mg, or 1 drop of the pure liquid. This is the amount of nicotine in two regular cigarettes. Fortunately, most of the nicotine in cigarettes is destroyed by burning or escapes via the "sidestream" smoke. Ingestion of nicotine insecticides or of tobacco by infants and children is usually followed by vomiting, limiting the amount of the alkaloid absorbed.

The toxic effects of a large dose of nicotine are simple extensions of the effects described previously. The most dangerous are (1) central

stimulant actions, which cause convulsions and may progress to coma and respiratory arrest; (2) skeletal muscle end plate depolarization, which may lead to depolarization blockade and respiratory paralysis; and (3) hypertension and cardiac arrhythmias.

Treatment of acute nicotine poisoning is largely symptom-directed. Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with atropine. Central stimulation is usually treated with parenteral anticonvulsants such as diazepam. Neuromuscular blockade is not responsive to pharmacologic treatment and may require mechanical ventilation.

Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first 4 hours usually recover completely if hypoxia and brain damage have not occurred.

2. Chronic nicotine toxicity—The health costs of tobacco smoking to the smoker and its socioeconomic costs to the general public are still incompletely understood. However, the 1979 *Surgeon General's Report on Health Promotion and Disease Prevention* stated that "cigarette smoking is clearly the largest single preventable cause of illness and premature death in the United States." This statement has been supported by numerous subsequent studies. Unfortunately, the fact that the most important of the tobacco-associated diseases are delayed in onset reduces the health incentive to stop smoking.

Clearly, the addictive power of cigarettes is directly related to their nicotine content. It is not known to what extent nicotine per se contributes to the other well-documented adverse effects of chronic tobacco use. It appears highly probable that nicotine contributes to the increased risk of vascular disease and sudden coronary death associated with smoking. Also, nicotine probably contributes to the high incidence of ulcer recurrences in smokers with peptic ulcer.

There are several approaches to help patients stop smoking. One approach is replacement therapy with nicotine in the form of gum, transdermal patch, nasal spray, or inhaler. All these forms have low abuse potential and are effective in patients motivated to stop smoking. Their action derives from slow absorption of nicotine that occupies $\alpha4\beta2$ receptors in the central nervous system and reduces the desire to smoke and the pleasurable feelings of smoking.

Another quite effective agent for smoking cessation is **varenicline,** a synthetic drug with partial agonist action at $\alpha4\beta2$ nicotinic receptors. Varenicline also has antagonist properties that persist because of its long half-life; this prevents the stimulant effect of nicotine at presynaptic $\alpha4\beta2$ receptors that causes release of dopamine. However, its use is limited by nausea and insomnia and also by exacerbation of psychiatric illnesses, including anxiety and depression. Suicidal ideation has also been reported in some patients; this is currently being evaluated. The efficacy of varenicline is superior to that of bupropion, an antidepressant (see Chapter 30). Some of bupropion's efficacy in smoking cessation therapy stems from its noncompetitive antagonism (see Chapter 2) of nicotinic receptors where it displays some selectivity among neuronal subtypes.

C. Cholinesterase Inhibitors

The acute toxic effects of the cholinesterase inhibitors, like those of the direct-acting agents, are direct extensions of their pharmacologic actions. The major source of such intoxications is pesticide use in agriculture and in the home. Approximately 100 organophosphate and 20 carbamate cholinesterase inhibitors are available in pesticides and veterinary vermifuges used in the USA. Cholinesterase inhibitors used in agriculture can cause slowly or rapidly developing symptoms, as described in the Case Study, which persist for days. The cholinesterase inhibitors used as chemical warfare agents (soman, sarin, VX) induce effects rapidly because of the large concentrations present.

Acute intoxication must be recognized and treated promptly in patients with heavy exposure. The dominant initial signs are those of muscarinic excess: miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea. Central nervous system involvement (cognitive disturbances, convulsions, and coma) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade. Therapy always includes (1) maintenance of vital signs—respiration in particular may be impaired; (2) decontamination to prevent further absorption—this may require removal of all clothing and washing of the skin in cases of exposure to dusts and sprays; and (3) atropine parenterally in large doses, given as often as required to control signs of muscarinic excess. Therapy often also includes treatment with pralidoxime, as described in Chapter 8, and administration of benzodiazepines for seizures.

Preventive therapy for cholinesterase inhibitors used as chemical warfare agents has been developed to protect soldiers and civilians. Personnel are given autoinjection syringes containing a carbamate, pyridostigmine, and atropine. Protection is provided by pyridostigmine, which, by prior binding to the enzyme, impedes binding of organophosphate agents and thereby prevents prolonged inhibition of cholinesterase. The protection is limited to the peripheral nervous system because pyridostigmine does not readily enter the central nervous system. Enzyme inhibition by pyridostigmine dissipates within hours (Table 7–4), a duration of time that allows clearance of the organophosphate agent from the body.

Chronic exposure to certain organophosphate compounds, including some organophosphate cholinesterase inhibitors, causes delayed neuropathy associated with demyelination of axons. **Triorthocresyl phosphate,** an additive in lubricating oils, is the prototype agent of this class. The effects are not caused by cholinesterase inhibition but rather by neuropathy target esterase (NTE) inhibition whose symptoms (weakness of upper and lower extremities, unsteady gait) appear 1–2 weeks after exposure. Another nerve toxicity called intermediate syndrome occurs 1–4 days after exposure to organophosphate insecticides. This syndrome is also characterized by muscle weakness; its origin is not known but it appears to be related to cholinesterase inhibition.

SUMMARY Drugs Used for Cholinomimetic Effects

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIRECT-ACTING CHOLINE ESTERS				
• Bethanechol	Muscarinic agonist • negligible effect at nicotinic receptors	Activates M_1 through M_3 receptors in all peripheral tissues • causes increased secretion, smooth muscle contraction (except vascular smooth muscle relaxes), and changes in heart rate	Postoperative and neurogenic ileus and urinary retention	Oral and parenteral, duration ~ 30 min • does not enter central nervous system (CNS) • *Toxicity:* Excessive parasympathomimetic effects, especially bronchospasm in asthmatics • *Interactions:* Additive with other parasympathomimetics
• *Carbachol: Nonselective muscarinic and nicotinic agonist; otherwise similar to bethanechol; used topically almost exclusively for glaucoma*				
DIRECT-ACTING MUSCARINIC ALKALOIDS OR SYNTHETICS				
• Pilocarpine	Like bethanechol, partial agonist	Like bethanechol	Glaucoma; Sjögren's syndrome	Oral lozenge and topical • *Toxicity & interactions:* Like bethanechol
• *Cevimeline: Synthetic M_3-selective; similar to pilocarpine*				
DIRECT-ACTING NICOTINIC AGONISTS				
• Nicotine	Agonist at both N_N and N_M receptors	Activates autonomic postganglionic neurons (both sympathetic and parasympathetic) and skeletal muscle neuromuscular end plates • enters CNS and activates N_N receptors	Medical use in smoking cessation • nonmedical use in smoking and in insecticides	Oral gum, patch for smoking cessation • *Toxicity:* Increased gastrointestinal (GI) activity, nausea, vomiting, diarrhea acutely • increased blood pressure • high doses cause seizures • long-term GI and cardiovascular risk factor • *Interactions:* Additive with CNS stimulants
• *Varenicline: Selective partial agonist at α4β2 nicotinic receptors; used exclusively for smoking cessation*				
SHORT-ACTING CHOLINESTERASE INHIBITOR (ALCOHOL)				
• Edrophonium	Alcohol, binds briefly to active site of acetylcholinesterase (AChE) and prevents access of acetylcholine (ACh)	Amplifies all actions of ACh • increases parasympathetic activity and somatic neuromuscular transmission	Diagnosis and acute treatment of myasthenia gravis	Parenteral • quaternary amine • does not enter CNS • *Toxicity:* Parasympathomimetic excess • *Interactions:* Additive with parasympathomimetics
INTERMEDIATE-ACTING CHOLINESTERASE INHIBITORS (CARBAMATES)				
• Neostigmine	Forms covalent bond with AChE, but hydrolyzed and released	Like edrophonium, but longer-acting	Myasthenia gravis • postoperative and neurogenic ileus and urinary retention	Oral and parenteral; quaternary amine, does not enter CNS. Duration 2–4 h • *Toxicity & interactions:* Like edrophonium
• *Pyridostigmine: Like neostigmine, but longer-acting (4–6 h); used in myasthenia*				
• *Physostigmine: Like neostigmine, but natural alkaloid tertiary amine; enters CNS*				
LONG-ACTING CHOLINESTERASE INHIBITORS (ORGANOPHOSPHATES)				
• Echothiophate	Like neostigmine, but released more slowly	Like neostigmine, but longer-acting	Obsolete • was used in glaucoma	Topical only • *Toxicity:* Brow ache, uveitis, blurred vision
• *Malathion: Insecticide, relatively safe for mammals and birds because metabolized by other enzymes to inactive products; some medical use as ectoparasiticide*				
• *Parathion, others: Insecticide, dangerous for all animals; toxicity important because of agricultural use and exposure of farm workers (see text)*				
• *Sarin, others: "Nerve gas," used exclusively in warfare and terrorism*				

PREPARATIONS AVAILABLE

DIRECT-ACTING CHOLINOMIMETICS

Acetylcholine (Miochol-E)
Ophthalmic: 1% intraocular solution

Bethanechol (generic, Urecholine)
Oral: 5, 10, 25, 50 mg tablets
Parenteral: 5 mg/mL for SC injection

Carbachol
Ophthalmic (topical, Isopto Carbachol, Carboptic): 0.75, 1.5, 2.25, 3% solution
Ophthalmic (intraocular, Miostat, Carbastat): 0.01% solution

Cevimeline (Evoxac)
Oral: 30 mg capsules

Nicotine
Transdermal: 5-21 mg/day absorbed/patch
Inhalation: 0.5-4 mg/dose
Gum: 2-4 mg/dose

Pilocarpine (generic, Isopto Carpine)
Ophthalmic (topical): 0.5, 1, 2, 3, 4, 6, 8, 10% solutions, 4% gel
Ophthalmic sustained-release inserts (Ocusert Pilo-20, Ocusert Pilo-40): release 20 and 40 mcg pilocarpine per hour for 1 week, respectively
Oral (Salagen): 5 mg tablets

Varenicline (Chantix)
Oral: 0.5, 1 mg tablets

CHOLINESTERASE INHIBITORS

Ambenonium (Mytelase)
Oral: 10 mg tablets

Demecarium (Humorsol)
Ophthalmic: 0.125, 0.25% solution

Donepezil (Aricept)
Oral: 5, 10, 23 mg tablets

Echothiophate (Phospholine)
Ophthalmic: 1.5 mg powder to reconstitute for 0.03, 0.06, 0.125% solution

Edrophonium (generic, Tensilon)
Parenteral: 10 mg/mL for IM or IV injection

Galantamine (Reminyl, Razadyne)
Oral: 4, 8, 12 mg tablets; 8, 16, 24 mg extended-release capsules; 4 mg/mL solution

Neostigmine (generic, Prostigmin)
Oral: 15 mg tablets
Parenteral: 0.2, 0.5, 1, 2.5 mg/mL solution

Physostigmine (generic, Eserine)
Ophthalmic: 0.25% ointment; 0.25, 0.5% solution
Parenteral: 1 mg/mL for IM or slow IV injection

Pyridostigmine (Mestinon, Regonol)
Oral: 30, 60 mg tablets; 180 mg sustained-release tablets; 12 mg/mL syrup
Parenteral: 5 mg/mL for IM or slow IV injection

Rivastigmine (Exelon)
Oral: 1.5, 3, 4.5, 6 mg tablets; 2 mg/mL solution; transdermal patch 4.6 or 9.5 mg/24 h

Tacrine (Cognex)
Oral: 10, 20, 30, 40 mg tablets

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CASE STUDY ANSWER

The patient's presentation is characteristic of poisoning by organophosphate cholinesterase inhibitors. Ask the coworker if he can identify the agent used. Decontaminate the patient by removal of clothing and washing affected areas. Ensure an open airway and ventilate with oxygen. For muscarinic excess, administer atropine (0.5–5 mg) intravenously until signs of muscarinic excess (dyspnea, lacrimation, confusion) subside. To treat nicotinic excess, infuse 2-PAM (initially a 1–2% solution in 15–30 minutes) followed by infusion of 1% solution (200–500 mg/h) until muscle fasciculations cease. If needed, decontaminate the coworker and isolate all contaminated clothing.

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CHAPTER

8

Cholinoceptor-Blocking Drugs

Achilles J. Pappano, PhD

CASE STUDY

JH, a 63-year-old architect, complains of urinary symptoms to his family physician. He has hypertension, and during the last 8 years, he has been adequately managed with a thiazide diuretic and an angiotensin-converting enzyme inhibitor. During the same period, JH developed the signs of benign prostatic hypertrophy, which eventually required prostatectomy to relieve symptoms. He now complains that he has an increased urge to urinate as well as urinary frequency, and this has disrupted the pattern of his daily life. What do you suspect is the cause of JH's problem? What information would you gather to confirm your diagnosis? What treatment steps would you initiate?

Cholinoceptor antagonists, like agonists, are divided into muscarinic and nicotinic subgroups on the basis of their specific receptor affinities. Ganglion blockers and neuromuscular junction blockers make up the antinicotinic drugs. The ganglion-blocking drugs have little clinical use and are discussed at the end of this chapter. Neuromuscular blockers are discussed in Chapter 27. This chapter emphasizes drugs that block muscarinic cholinoceptors.

Five subtypes of muscarinic receptors have been identified, primarily on the basis of data from ligand-binding and cDNA-cloning experiments (see Chapters 6 and 7). A standard terminology (M_1 through M_5) for these subtypes is now in common use, and evidence—based mostly on selective agonists and antagonists—indicates that functional differences exist between several of these subtypes.

The M_1 receptor subtype is located on central nervous system (CNS) neurons, sympathetic postganglionic cell bodies, and many presynaptic sites. M_2 receptors are located in the myocardium, smooth muscle organs, and some neuronal sites. M_3 receptors are most common on effector cell membranes, especially glandular and smooth muscle cells. M_4 and M_5 receptors are less prominent and appear to play a greater role in the CNS than in the periphery.

BASIC PHARMACOLOGY OF THE MUSCARINIC RECEPTOR-BLOCKING DRUGS

Muscarinic antagonists are sometimes called parasympatholytic because they block the effects of parasympathetic autonomic discharge. However, they do not "lyse" parasympathetic nerves, and they have some effects that are not predictable from block of the parasympathetic nervous system. For these reasons, the term "antimuscarinic" is preferable.

Naturally occurring compounds with antimuscarinic effects have been known and used for millennia as medicines, poisons, and cosmetics. **Atropine** is the prototype of these drugs. Many similar plant alkaloids are known, and hundreds of synthetic antimuscarinic compounds have been prepared.

Chemistry & Pharmacokinetics

A. Source and Chemistry

Atropine and its naturally occurring congeners are tertiary amine alkaloid esters of tropic acid (Figure 8–1). Atropine (hyoscyamine) is found in the plant *Atropa belladonna*, or deadly nightshade, and

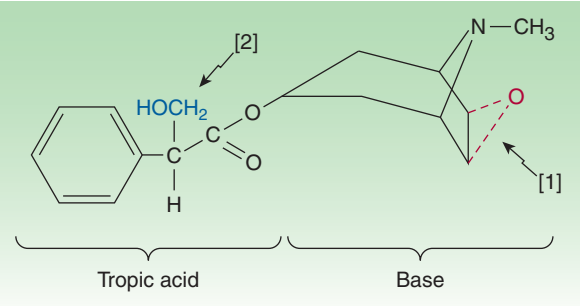


FIGURE 8–1 The structure of atropine (oxygen [red] at *[1]* is missing) or scopolamine (oxygen present). In homatropine, the hydroxymethyl at *[2]* is replaced by a hydroxyl group, and the oxygen at *[1]* is absent.

in *Datura stramonium*, also known as jimson-weed (Jamestown weed), sacred Datura, or thorn apple. **Scopolamine** (hyoscine) occurs in *Hyoscyamus niger*, or henbane, as the *l*(–) stereoisomer. Naturally occurring atropine is *l*(–)-hyoscyamine, but the compound readily racemizes, so the commercial material is racemic *d,l*-hyoscyamine. The *l*(–) isomers of both alkaloids are at least 100 times more potent than the *d*(+) isomers.

A variety of semisynthetic and fully synthetic molecules have antimuscarinic effects. The tertiary members of these classes (Figure 8–2) are often used for their effects on the eye or the CNS. Many antihistaminic (see Chapter 16), antipsychotic (see Chapter 29), and antidepressant (see Chapter 30) drugs have similar structures and, predictably, significant antimuscarinic effects.

Quaternary amine antimuscarinic agents (Figure 8–2) have been developed to produce more peripheral effects and reduced CNS effects.

B. Absorption

Natural alkaloids and most tertiary antimuscarinic drugs are well absorbed from the gut and conjunctival membranes. When applied in a suitable vehicle, some (eg, scopolamine) are even absorbed across the skin (transdermal route). In contrast, only 10–30% of a dose of a quaternary antimuscarinic drug is absorbed after oral administration, reflecting the decreased lipid solubility of the charged molecule.

C. Distribution

Atropine and the other tertiary agents are widely distributed in the body. Significant levels are achieved in the CNS within 30 minutes to 1 hour, and this can limit the dose tolerated when the drug is taken for its peripheral effects. Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs. In contrast, the quaternary derivatives are poorly taken up by the brain and therefore are relatively free—at low doses—of CNS effects.

D. Metabolism and Excretion

After administration, the elimination of atropine from the blood occurs in two phases: the $t_{½}$ of the rapid phase is 2 hours and that of the slow phase is approximately 13 hours. About 50% of the dose is excreted unchanged in the urine. Most of the rest appears in the urine as hydrolysis and conjugation products. The drug's effect on parasympathetic function declines rapidly in all organs except the eye. Effects on the iris and ciliary muscle persist for ≥ 72 hours.

Pharmacodynamics

A. Mechanism of Action

Atropine causes reversible (surmountable) blockade (see Chapter 2) of cholinomimetic actions at muscarinic receptors; that is, blockade by a small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist. Mutation experiments suggest that aspartate in the third transmembrane segment of the heptahelical receptor forms an ionic bond with the nitrogen atom of acetylcholine; this amino acid is also required for binding of antimuscarinic drugs. When atropine binds to the muscarinic receptor, it prevents actions such as the release of inositol trisphosphate (IP_3) and the inhibition of adenylyl cyclase that are caused by muscarinic agonists (see Chapter 7). Muscarinic antagonists were traditionally viewed as neutral compounds that occupied the receptor and prevented agonist binding. Recent evidence indicates that muscarinic receptors are constitutively active, and most drugs that block the actions of acetylcholine are inverse agonists (see Chapter 1) that shift the equilibrium to the inactive state of the receptor. Muscarinic blocking drugs that are inverse agonists include atropine, pirenzepine, trihexyphenidyl, AF-DX 116, 4-DAMP, ipratropium, glycopyrrolate, and a methyl derivative of scopolamine (Table 8–1).

The effectiveness of antimuscarinic drugs varies with the tissue and with the source of agonist. Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands. Secretion of acid by the gastric parietal cells is the least sensitive. In most tissues, antimuscarinic agents block exogenously administered cholinoceptor agonists more effectively than endogenously released acetylcholine.

Atropine is highly selective for muscarinic receptors. Its potency at nicotinic receptors is much lower, and actions at nonmuscarinic receptors are generally undetectable clinically.

Atropine does not distinguish among the M_1, M_2, and M_3 subgroups of muscarinic receptors. In contrast, other antimuscarinic drugs are moderately selective for one or another of these subgroups (Table 8–1). Most synthetic antimuscarinic drugs are considerably less selective than atropine in interactions with nonmuscarinic receptors. For example, some quaternary amine antimuscarinic agents have significant ganglion-blocking actions, and others are potent histamine receptor blockers. The antimuscarinic effects of other agents, eg, antipsychotic and antidepressant drugs, have been mentioned. Their relative selectivity for muscarinic receptor subtypes has not been defined.

B. Organ System Effects

1. Central nervous system—In the doses usually used, atropine has minimal stimulant effects on the CNS, especially the parasympathetic medullary centers, and a slower, longer-lasting sedative effect on the brain. Scopolamine has more marked central effects, producing

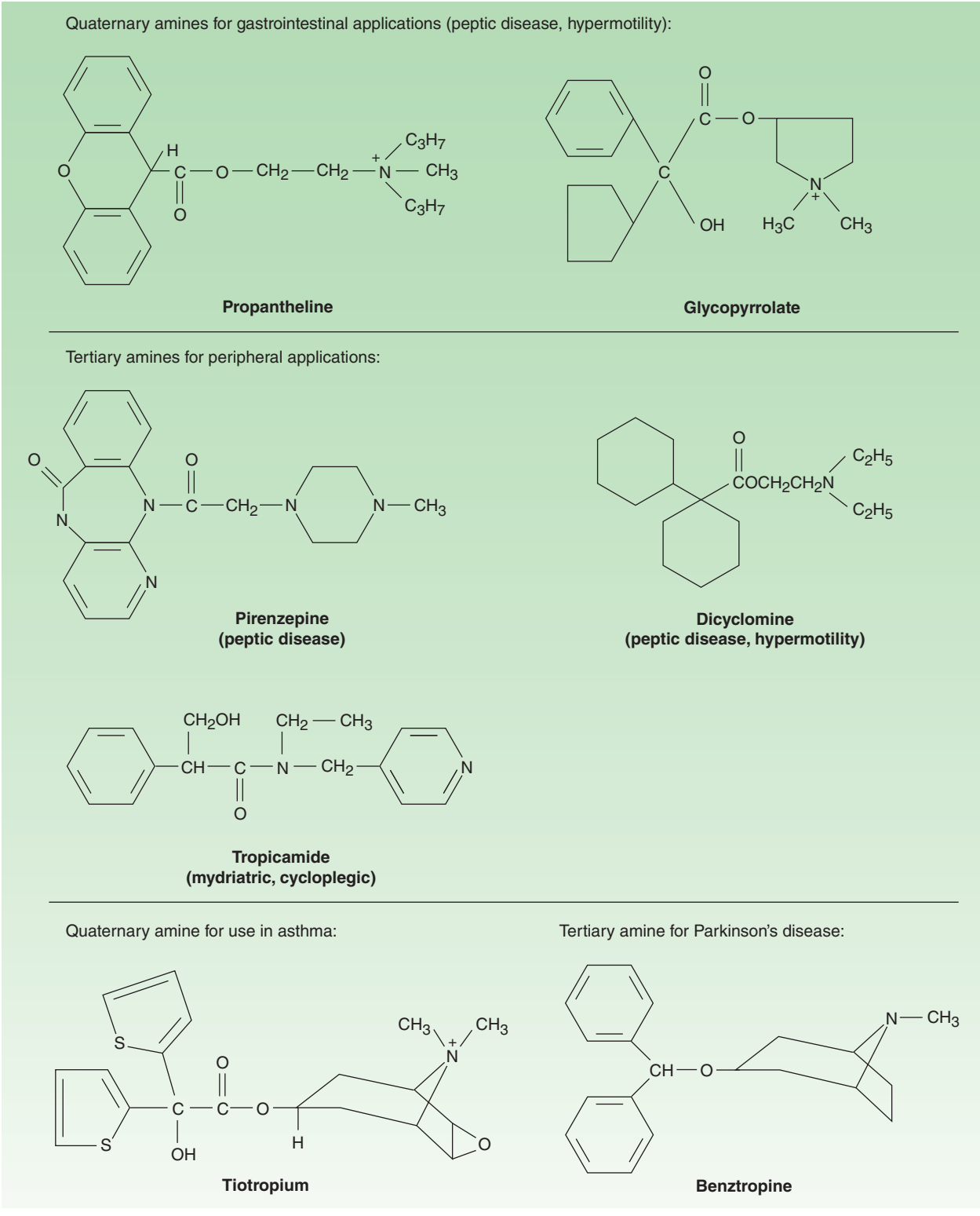


FIGURE 8–2 Structures of some semisynthetic and synthetic antimuscarinic drugs.

TABLE 8–1 Muscarinic receptor subgroups important in peripheral tissues and their antagonists.

	Subgroup		
Property	**M_1**	**M_2**	**M_3**
Primary locations	Nerves	Heart, nerves, smooth muscle	Glands, smooth muscle, endothelium
Dominant effector system	↑ IP_3, ↑ DAG	↓ cAMP, ↑ K^+ channel current	↑ IP_3, ↑ DAG
Antagonists	Pirenzepine, telenzepine, dicyclomine,[2] trihexyphenidyl[3]	Gallamine,[1] methoctramine, AF-DX 116[4]	4-DAMP, darifenacin, solifenacin, oxybutynin, tolterodine
Approximate dissociation constant[5]			
Atropine	1	1	1
Pirenzepine	25	300	500
AF-DX 116	2000	65	4000
Darifenacin	70	55	8

[1]In clinical use as a neuromuscular blocking agent (obsolete).

[2]In clinical use as an intestinal antispasmodic agent.

[3]In clinical use in the treatment of Parkinson's disease.

[4]Compound used in research only.

[5]Relative to atropine. Smaller numbers indicate higher affinity.

AF-DX 116, 11-({2-[(diethylamino)methyl]-1-piperidinyl}acetyl)-5,11-dihydro-6*H*-pyrido-[2,3-*b*](1,4)benzodiazepine-6-one; DAG, diacylglycerol; IP_3, inositol trisphosphate; 4-DAMP, 4-diphenylacetoxy-*N*-methylpiperidine.

drowsiness when given in recommended dosages and amnesia in sensitive individuals. In toxic doses, scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma.

The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine—in the form of belladonna extract—was one of the first drugs used in the therapy of this disease. As discussed in Chapter 28, parkinsonian tremor and rigidity seem to result from a *relative* excess of cholinergic activity because of a deficiency of dopaminergic activity in the basal ganglia-striatum system. The combination of an antimuscarinic agent with a dopamine precursor drug (levodopa) can sometimes provide more effective therapy than either drug alone.

Vestibular disturbances, especially motion sickness, appear to involve muscarinic cholinergic transmission. Scopolamine is often effective in preventing or reversing these disturbances.

2. Eye—The pupillary constrictor muscle (see Figure 6–9) depends on muscarinic cholinoceptor activation. This activation is blocked by topical atropine and other tertiary antimuscarinic drugs and results in unopposed sympathetic dilator activity and **mydriasis** (Figure 8–3). Dilated pupils were considered cosmetically desirable during the Renaissance and account for the name belladonna (Italian, "beautiful lady") applied to the plant and its active extract because of the use of the extract as eye drops during that time.

The second important ocular effect of antimuscarinic drugs is to weaken contraction of the ciliary muscle, or **cycloplegia.** Cycloplegia results in loss of the ability to accommodate; the fully atropinized eye cannot focus for near vision (Figure 8–3).

Both mydriasis and cycloplegia are useful in ophthalmology. They are also potentially hazardous, since acute glaucoma may be induced in patients with a narrow anterior chamber angle.

A third ocular effect of antimuscarinic drugs is to reduce lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes when receiving large doses of antimuscarinic drugs.

3. Cardiovascular system—The sinoatrial node is very sensitive to muscarinic receptor blockade. Moderate to high therapeutic doses of atropine cause tachycardia in the innervated and spontaneously beating heart by blockade of vagal slowing. However, lower doses often result in initial bradycardia before the effects of peripheral vagal block become manifest (Figure 8–4). This slowing may be due to block of prejunctional M_1 receptors (autoreceptors, see Figure 6–3) on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues. The same mechanisms operate in the atrioventricular node; in the presence of high vagal tone, atropine can significantly reduce the PR interval of the electrocardiogram by blocking muscarinic receptors in the atrioventricular node. Muscarinic effects on atrial muscle are similarly blocked, but these effects are of no clinical significance except in atrial flutter and fibrillation. The ventricles are less affected by antimuscarinic drugs at therapeutic levels because of a lesser degree of vagal control. In toxic concentrations, the drugs can cause intraventricular conduction block that has been attributed to a local anesthetic action.

Most blood vessels, except those in thoracic and abdominal viscera, receive no direct innervation from the parasympathetic system. However, parasympathetic nerve stimulation dilates coronary arteries, and sympathetic cholinergic nerves cause vasodilation in the skeletal muscle vascular bed (see Chapter 6). Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation (see Chapter 7). These receptors are readily blocked by antimuscarinic

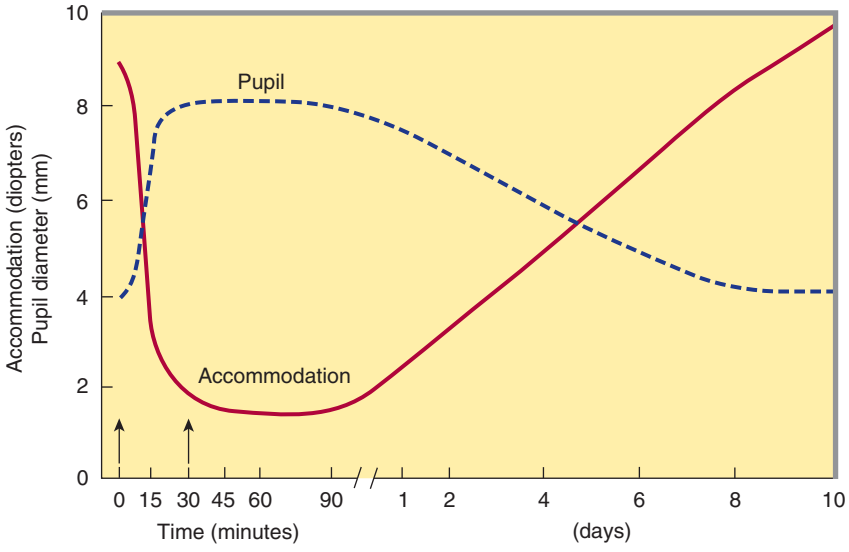


FIGURE 8–3 Effects of topical scopolamine drops on pupil diameter (mm) and accommodation (diopters) in the normal human eye. One drop of 0.5% solution of drug was applied at zero time, and a second drop was administered at 30 minutes (*arrows*). The responses of 42 eyes were averaged. Note the extremely slow recovery. (Redrawn from Marron J: Cycloplegia and mydriasis by use of atropine, scopolamine, and homatropine-paredrine. Arch Ophthalmol 1940;23:340.)

drugs. At toxic doses, and in some individuals at normal doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. The mechanism is unknown.

The net cardiovascular effects of atropine in patients with normal hemodynamics are not dramatic: tachycardia may occur, but there is little effect on blood pressure. However, the cardiovascular effects of administered direct-acting muscarinic agonists are easily prevented.

4. Respiratory system—Both smooth muscle and secretory glands of the airway receive vagal innervation and contain muscarinic receptors. Even in normal individuals, administration of atropine can cause some bronchodilation and reduce secretion. The effect is more significant in patients with airway disease, although the antimuscarinic drugs are not as useful as the β-adrenoceptor stimulants in the treatment of asthma (see Chapter 20). The effectiveness of nonselective antimuscarinic drugs in treating chronic obstructive

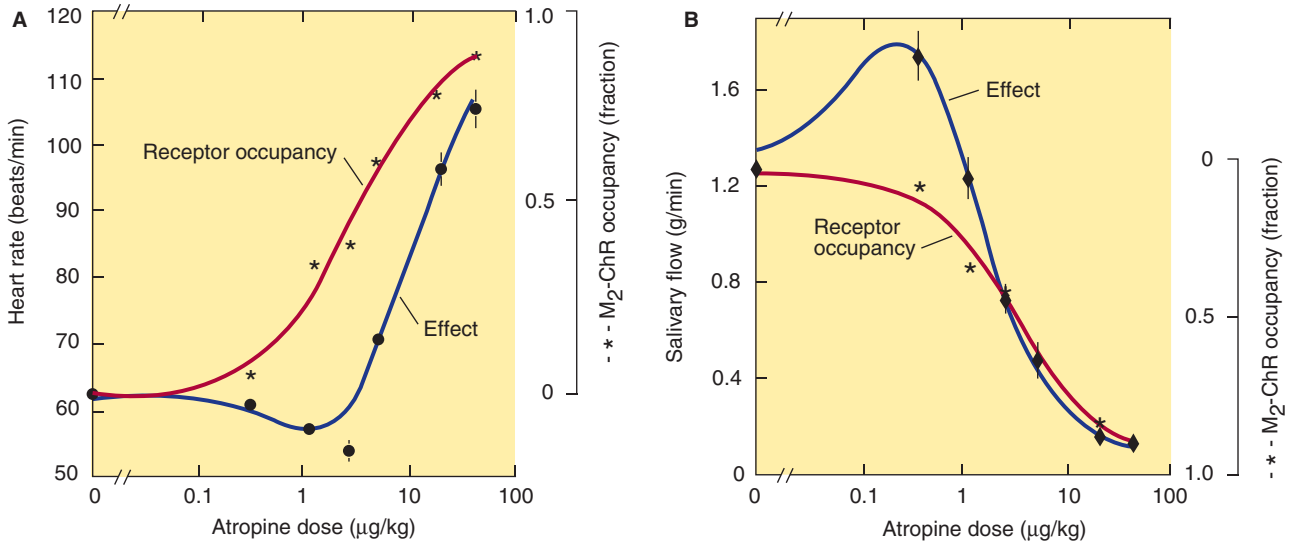


FIGURE 8–4 Effects of increasing doses of atropine on heart rate (**A**) and salivary flow (**B**) compared with muscarinic receptor occupancy in humans. The parasympathomimetic effect of low-dose atropine is attributed to blockade of prejunctional muscarinic receptors that suppress acetylcholine release. (Modified and reproduced, with permission, from Wellstein A, Pitschner HF: Complex dose-response curves of atropine in man explained by different functions of M_1 and M_2 cholinoceptors. Naunyn Schmiedebergs Arch Pharmacol 1988;338:19.)

pulmonary disease (COPD) is limited because block of autoinhibitory M_2 receptors on postganglionic parasympathetic nerves can oppose the bronchodilation caused by block of M_3 receptors on airway smooth muscle. Nevertheless, antimuscarinic agents are valuable in some patients with asthma or COPD.

Antimuscarinic drugs are frequently used before the administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

5. Gastrointestinal tract—Blockade of muscarinic receptors has dramatic effects on motility and some of the secretory functions of the gut. However, even complete muscarinic block cannot totally abolish activity in this organ system, since local hormones and noncholinergic neurons in the enteric nervous system (see Chapters 6 and 62) also modulate gastrointestinal function. As in other tissues, exogenously administered muscarinic stimulants are more effectively blocked than are the effects of parasympathetic (vagal) nerve activity. The removal of autoinhibition, a negative feedback mechanism by which neural acetylcholine suppresses its own release, might explain the lower efficacy of antimuscarinic drugs against the effects of endogenous acetylcholine.

Antimuscarinic drugs have marked effects on salivary secretion; dry mouth occurs frequently in patients taking antimuscarinic drugs for Parkinson's disease or urinary conditions (Figure 8–5). Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required. Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol. Pirenzepine and a more potent analog, telenzepine, reduce gastric acid secretion with fewer adverse effects than atropine and other less selective agents. This was thought to result from a selective blockade of excitatory M_1 muscarinic receptors on vagal ganglion cells innervating the stomach, as suggested by their high ratio of M_1 to M_3 affinity (Table 8–1). However, carbachol was found to stimulate gastric acid secretion in animals with M_1 receptors knocked out; M_3 receptors were implicated and pirenzepine opposed this effect of carbachol, an indication that pirenzepine is selective but not specific for M_1 receptors. The mechanism of vagal regulation of gastric acid secretion likely involves multiple muscarinic receptor-dependent pathways. Pirenzepine and telenzepine are investigational in the USA. Pancreatic and intestinal secretion are little affected by atropine; these processes are primarily under hormonal rather than vagal control.

Gastrointestinal smooth muscle motility is affected from the stomach to the colon. In general, the walls of the viscera are relaxed, and both tone and propulsive movements are diminished. Therefore, gastric emptying time is prolonged, and intestinal transit time is lengthened. Diarrhea due to overdosage with parasympathomimetic agents is readily stopped, and even diarrhea caused by nonautonomic agents can usually be temporarily controlled. However, intestinal "paralysis" induced by antimuscarinic drugs is temporary; local mechanisms within the enteric nervous system usually reestablish at least some peristalsis after 1–3 days of antimuscarinic drug therapy.

6. Genitourinary tract—The antimuscarinic action of atropine and its analogs relaxes smooth muscle of the ureters and bladder wall and slows voiding (Figure 8–5). This action is useful in the treatment of spasm induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have prostatic hyperplasia (see following section, Clinical Pharmacology of the Muscarinic Receptor-Blocking Drugs). The antimuscarinic drugs have no significant effect on the uterus.

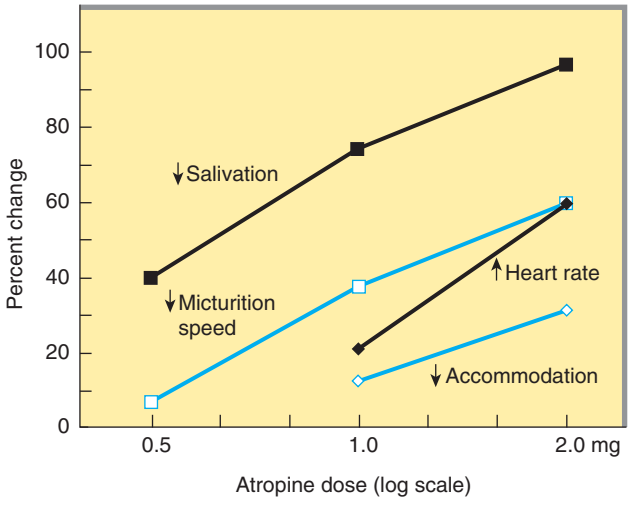


FIGURE 8–5 Effects of subcutaneous injection of atropine on salivation, speed of micturition (voiding), heart rate, and accommodation in normal adults. Note that salivation is the most sensitive of these variables, accommodation the least. (Data from Herxheimer A: Br J Pharmacol 1958;13:184.)

7. Sweat glands—Atropine suppresses thermoregulatory sweating. Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drugs. In adults, body temperature is elevated by this effect only if large doses are administered, but in infants and children even ordinary doses may cause "atropine fever."

CLINICAL PHARMACOLOGY OF THE MUSCARINIC RECEPTOR-BLOCKING DRUGS

Therapeutic Applications

The antimuscarinic drugs have applications in several of the major organ systems and in the treatment of poisoning by muscarinic agonists.

A. Central Nervous System Disorders

1. Parkinson's disease—The treatment of Parkinson's disease is often an exercise in polypharmacy, since no single agent is fully effective over the course of the disease. Most antimuscarinic drugs promoted for this application (see Table 28–1) were developed before levodopa became available. Their use is accompanied by all of the adverse effects described below, but the drugs remain useful as adjunctive therapy in some patients.

2. Motion sickness—Certain vestibular disorders respond to antimuscarinic drugs (and to antihistaminic agents with antimuscarinic effects). Scopolamine is one of the oldest remedies for seasickness and is as effective as any more recently introduced agent. It can be given by injection or by mouth or as a transdermal patch. The patch formulation produces significant blood levels over 48–72 hours. Useful doses by any route usually cause significant sedation and dry mouth.

B. Ophthalmologic Disorders

Accurate measurement of refractive error in uncooperative patients, eg, young children, requires ciliary paralysis. Also, ophthalmoscopic examination of the retina is greatly facilitated by mydriasis. Therefore, antimuscarinic agents, administered topically as eye drops or ointment, are very helpful in doing a complete examination. For adults and older children, the shorter-acting drugs are preferred (Table 8–2). For younger children, the greater efficacy of atropine is sometimes necessary, but the possibility of antimuscarinic poisoning is correspondingly increased. Drug loss from the conjunctival sac via the nasolacrimal duct into the nasopharynx can be diminished by the use of the ointment form rather than drops. Formerly, ophthalmic antimuscarinic drugs were selected from the tertiary amine subgroup to ensure good penetration after conjunctival application. Recent experiments in animals, however, suggest that glycopyrrolate, a quaternary agent, is as rapid in onset and as long-lasting as atropine.

Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, eg, phenylephrine, produce a short-lasting mydriasis that is usually sufficient for funduscopic examination (see Chapter 9).

A second ophthalmologic use is to prevent synechia (adhesion) formation in uveitis and iritis. The longer-lasting preparations, especially homatropine, are valuable for this indication.

C. Respiratory Disorders

The use of atropine became part of routine preoperative medication when anesthetics such as ether were used, because these irritant anesthetics markedly increased airway secretions and were associated with frequent episodes of laryngospasm. Preanesthetic injection of atropine or scopolamine could prevent these hazardous effects. Scopolamine also produces significant amnesia for the events associated with surgery and obstetric delivery, a side effect that was considered desirable. On the other hand, urinary retention and intestinal hypomotility following surgery were often exacerbated by antimuscarinic drugs. Newer inhalational anesthetics are far less irritating to the airways.

Patients with **COPD,** a condition that occurs more frequently in older patients, particularly chronic smokers, benefit from bronchodilators, especially antimuscarinic agents. **Ipratropium** and **tiotropium** (see Figure 8–2), synthetic analogs of atropine, are used as inhalational drugs in COPD. The aerosol route of administration has the advantage of maximal concentration at the bronchial target tissue with reduced systemic effects. This application is discussed in greater detail in Chapter 20. Tiotropium has a longer bronchodilator action than ipratropium and can be given once daily because it dissociates slowly from M_3 receptors. It has a terminal elimination $t_{1/2}$ of 5–6 days; steady-state plasma levels are achieved in about 25 days with single daily administration. Tiotropium reduces the incidence of COPD exacerbations and is a useful adjunct to pulmonary rehabilitation in increasing exercise tolerance. The hyperactive neural bronchoconstrictor reflex present in most individuals with **asthma** is mediated by the vagus, acting on muscarinic receptors on bronchial smooth muscle cells. Ipratropium and tiotropium are also used as inhalational drugs in asthma.

D. Cardiovascular Disorders

Marked reflex vagal discharge sometimes accompanies the pain of myocardial infarction (eg, vasovagal attack) and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. Parenteral atropine or a similar antimuscarinic drug is appropriate therapy in this situation. Rare individuals without other detectable cardiac disease have hyperactive carotid sinus reflexes and may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck, eg, from a tight collar. Such individuals may benefit from the judicious use of atropine or a related antimuscarinic agent.

Pathophysiology can influence muscarinic activity in other ways as well. Circulating autoantibodies against the second extracellular loop of cardiac M_2 muscarinic receptors have been detected in some patients with idiopathic dilated cardiomyopathy and those afflicted with Chagas' disease caused by the protozoan *Trypanosoma cruzi.* Patients with Graves' disease (hyperthyroidism) also have such autoantibodies that may facilitate the development of atrial fibrillation. These antibodies exert parasympathomimetic actions on the heart that are prevented by atropine. In animals immunized with a peptide from the second extracellular loop of the M_2 receptor, the antibody is an allosteric modulator of the receptor. Although their role in the pathology of heart diseases is unknown, these antibodies should provide clues to the molecular basis of receptor activation because their site of action differs from the orthosteric site where acetylcholine binds (see Chapter 2).

E. Gastrointestinal Disorders

Antimuscarinic agents are now rarely used for peptic ulcer disease in the USA (see Chapter 62). Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild or self-limited conditions of hypermotility. They are

TABLE 8–2 Antimuscarinic drugs used in ophthalmology.

Drug	Duration of Effect (days)	Usual Concentration (%)
Atropine	7–10	0.5–1
Scopolamine	3–7	0.25
Homatropine	1–3	2–5
Cyclopentolate	1	0.5–2
Tropicamide	0.25	0.5–1

often combined with an opioid antidiarrheal drug, an extremely effective therapy. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent. The classic combination of atropine with diphenoxylate, a nonanalgesic congener of meperidine, is available under many names (eg, Lomotil) in both tablet and liquid form (see Chapter 62).

F. Urinary Disorders

Atropine and other antimuscarinic drugs have been used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders (Table 8–3). However, specific antimicrobial therapy is essential in bacterial cystitis. In the human urinary bladder, M_2 and M_3 receptors are expressed predominantly with the M_3 subtype mediating direct activation of contraction. As in intestinal smooth muscle, the M_2 subtype appears to act indirectly by inhibiting relaxation by norepinephrine and epinephrine.

Receptors for acetylcholine on the urothelium (the epithelial lining of the urinary tract) and on afferent nerves as well as the detrusor muscle provide a broad basis for the action of antimuscarinic drugs in the treatment of overactive bladder. **Oxybutynin,** which is somewhat selective for M_3 receptors, is used to relieve bladder spasm after urologic surgery, eg, prostatectomy. It is also valuable in reducing involuntary voiding in patients with neurologic disease, eg, children with meningomyelocele. Oral oxybutynin or instillation of the drug by catheter into the bladder in such patients appears to improve bladder capacity and continence and to reduce infection and renal damage. Transdermally applied oxybutynin or its oral extended-release formulation reduces the need for multiple daily doses. **Trospium,** a nonselective antagonist, has been approved and is comparable in efficacy and side effects to oxybutynin. **Darifenacin** and **solifenacin** are recently approved antagonists that have greater selectivity for M_3 receptors than oxybutynin or trospium. Darifenacin and solifenacin have the advantage of once-daily dosing because of their long half-lives. **Tolterodine** and **fesoterodine,** M_3-selective antimuscarinics, are available for use in adults with urinary incontinence. They have many of the qualities of darifenacin and solifenacin and are available in extended-release tablets. The convenience of the newer and longer-acting drugs has not been accompanied by improvements in overall efficacy or by reductions in side effects such as dry mouth. An alternative treatment for urinary incontinence refractory to antimuscarinic drugs is intrabladder injection of botulinum toxin A. Botulinum toxin is reported to reduce urinary incontinence for several months after a single treatment by interfering with the co-release of ATP with neuronal acetylcholine (see Figure 6–3). Blockade of the activation of sensory nerves in the urothelium by ATP may account for a large part of this effect of botulinum toxin. This approach is not an FDA-approved indication at present.

Imipramine, a tricyclic antidepressant drug with strong antimuscarinic actions, has long been used to reduce incontinence in institutionalized elderly patients. It is moderately effective but causes significant CNS toxicity. **Propiverine,** a newer antimuscarinic agent, has been approved for this purpose.

Antimuscarinic agents have also been used in urolithiasis to relieve the painful ureteral smooth muscle spasm caused by passage of the stone. However, their usefulness in this condition is debatable.

TABLE 8–3 Antimuscarinic drugs used in gastrointestinal and genitourinary conditions.

Drug	Usual Dosage
Quaternary amines	
Anisotropine	50 mg tid
Clidinium	2.5 mg tid–qid
Glycopyrrolate	1 mg bid–tid
Isopropamide	5 mg bid
Mepenzolate	25–50 mg qid
Methantheline	50–100 mg qid
Methscopolamine	2.5 mg qid
Oxyphenonium	5–10 mg qid
Propantheline	15 mg qid
Tridihexethyl	25–50 mg tid–qid
Trospium	20 mg bid
Tertiary amines	
Atropine	0.4 mg tid–qid
Darifenacin	7.5 mg qd
Dicyclomine	10–20 mg qid
Oxybutynin	5 mg tid
Oxyphencyclimine	10 mg bid
Propiverine	15 mg bid–tid
Scopolamine	0.4 mg tid
Solifenacin	5 mg qd
Tolterodine	2 mg bid

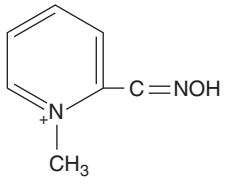
G. Cholinergic Poisoning

Severe cholinergic excess is a medical emergency, especially in rural communities where cholinesterase inhibitor insecticides are commonly used and in cultures where wild mushrooms are frequently eaten. The potential use of cholinesterase inhibitors as chemical warfare "nerve gases" also requires an awareness of the methods for treating acute poisoning (see Chapter 58).

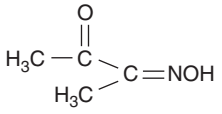
1. Antimuscarinic therapy—Both the nicotinic and the muscarinic effects of the cholinesterase inhibitors can be life-threatening. Unfortunately, there is no effective method for directly blocking the nicotinic effects of cholinesterase inhibition, because nicotinic agonists *and* antagonists cause blockade of transmission (see Chapter 27). To reverse the muscarinic effects, a tertiary (not quaternary) amine drug must be used (preferably atropine) to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors. Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion

and chemical warfare nerve gases: 1–2 mg of atropine sulfate may be given intravenously every 5–15 minutes until signs of effect (dry mouth, reversal of miosis) appear. The drug may have to be given many times, since the acute effects of the cholinesterase inhibitor may last 24–48 hours or longer. In this life-threatening situation, as much as 1 g of atropine per day may be required for as long as 1 month for full control of muscarinic excess.

2. Cholinesterase regenerator compounds—A second class of compounds, composed of substituted oximes capable of regenerating active enzyme from the organophosphorus-cholinesterase complex, is also available to treat organophosphorus poisoning. These oxime agents include pralidoxime (PAM), diacetylmonoxime (DAM), obidoxime, and others.



Pralidoxime



Diacetylmonoxime

Organophosphates cause phosphorylation of the serine OH group at the active site of cholinesterase. The oxime group (═NOH) has a very high affinity for the phosphorus atom, for which it competes with serine OH. These oximes can hydrolyze the phosphorylated enzyme and regenerate active enzyme from the organophosphorus-cholinesterase complex if the complex has not "aged" (see Chapter 7). Pralidoxime is the most extensively studied—in humans—of the agents shown and the only one available for clinical use in the USA. It is most effective in regenerating the cholinesterase associated with skeletal muscle neuromuscular junctions. Pralidoxime and obidoxime are ineffective in reversing the central effects of organophosphate poisoning because each has positively charged quaternary ammonium groups that prevent entry into the CNS. Diacetylmonoxime, on the other hand, crosses the blood-brain barrier and, in experimental animals, can regenerate some of the CNS cholinesterase.

Pralidoxime is administered by intravenous infusion, 1–2 g given over 15–30 minutes. In spite of the likelihood of aging of the phosphate-enzyme complex, recent reports suggest that administration of multiple doses of pralidoxime over several days may be useful in severe poisoning. In excessive doses, pralidoxime can induce neuromuscular weakness and other adverse effects. Pralidoxime is *not* recommended for the reversal of inhibition of acetylcholinesterase by carbamate inhibitors. Further details of treatment of anticholinesterase toxicity are given in Chapter 58.

A third approach to protection against excessive acetylcholinesterase inhibition is *pretreatment* with reversible enzyme inhibitors to prevent binding of the irreversible organophosphate inhibitor. This prophylaxis can be achieved with pyridostigmine but is reserved for situations in which possibly lethal poisoning is anticipated, eg, chemical warfare (see Chapter 7). Simultaneous use of atropine is required to control muscarinic excess.

Mushroom poisoning has traditionally been divided into rapid-onset and delayed-onset types. The rapid-onset type is usually apparent within 30 minutes to 2 hours after ingestion of the mushrooms, and can be caused by a variety of toxins. Some of these produce simple upset stomach; others can have disulfiram-like effects; some cause hallucinations; and a few mushrooms (eg, Inocybe species) can produce signs of muscarinic excess: nausea, vomiting, diarrhea, urinary urgency, sweating, salivation, and sometimes bronchoconstriction. Parenteral atropine, 1–2 mg, is effective treatment in such intoxications. Despite its name, *Amanita muscaria* contains not only muscarine (the alkaloid was named after the mushroom), but also numerous other alkaloids, including antimuscarinic agents, and ingestion of *A muscaria* often causes signs of atropine poisoning, not muscarine excess.

Delayed-onset mushroom poisoning, usually caused by *Amanita phalloides, A virosa, Galerina autumnalis,* or *G marginata,* manifests its first symptoms 6–12 hours after ingestion. Although the initial symptoms usually include nausea and vomiting, the major toxicity involves hepatic and renal cellular injury by amatoxins that inhibit RNA polymerase. Atropine is of no value in this form of mushroom poisoning (see Chapter 58).

H. Other Applications

Hyperhidrosis (excessive sweating) is sometimes reduced by antimuscarinic agents. However, relief is incomplete at best, probably because apocrine rather than eccrine glands are usually involved.

Adverse Effects

Treatment with atropine or its congeners directed at one organ system almost always induces undesirable effects in other organ systems. Thus, mydriasis and cycloplegia are adverse effects when an antimuscarinic agent is used to reduce gastrointestinal secretion or motility, even though they are therapeutic effects when the drug is used in ophthalmology.

At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug *in adults.* Atropine poisoning has occurred as a result of attempted suicide, but most cases are due to attempts to induce hallucinations. Poisoned individuals manifest dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week. Body temperature is frequently elevated. These effects are memorialized in the adage, "dry as a bone, blind as a bat, red as a beet, mad as a hatter."

Unfortunately, children, especially infants, are very sensitive to the hyperthermic effects of atropine. Although accidental administration of over 400 mg has been followed by recovery, deaths have followed doses as small as 2 mg. Therefore, atropine should be considered a highly dangerous drug when overdose occurs in infants or children.

Overdoses of atropine or its congeners are generally treated symptomatically (see Chapter 58). Poison control experts discourage the use of physostigmine or another cholinesterase inhibitor to reverse the effects of atropine overdose because symptomatic management is more effective and less dangerous. When physostigmine is deemed necessary, *small* doses are given *slowly* intravenously

(1–4 mg in adults, 0.5–1 mg in children). Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam.

Poisoning caused by high doses of quaternary antimuscarinic drugs is associated with all of the peripheral signs of parasympathetic blockade but few or none of the CNS effects of atropine. These more polar drugs may cause significant ganglionic blockade, however, with marked orthostatic hypotension (see below). Treatment of the antimuscarinic effects, if required, can be carried out with a quaternary cholinesterase inhibitor such as neostigmine. Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine.

Recent evidence indicates that some centrally acting drugs (tricyclic antidepressants, selective serotonin reuptake inhibitors, anti-anxiety agents) with antimuscarinic actions impair memory and cognition in older patients.

Contraindications

Contraindications to the use of antimuscarinic drugs are relative, not absolute. Obvious muscarinic excess, especially that caused by cholinesterase inhibitors, can always be treated with atropine.

Antimuscarinic drugs are contraindicated in patients with glaucoma, especially angle-closure glaucoma. Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers.

In elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.

Because the antimuscarinic drugs slow gastric emptying, they may *increase* symptoms in patients with gastric ulcer. Nonselective antimuscarinic agents should never be used to treat acid-peptic disease (see Chapter 62).

■ BASIC & CLINICAL PHARMACOLOGY OF THE GANGLION-BLOCKING DRUGS

Ganglion-blocking agents competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some members of the group also block the ion channel that is gated by the nicotinic cholinoceptor. The ganglion-blocking drugs are important and used in pharmacologic and physiologic research because they can block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.

Chemistry & Pharmacokinetics

All ganglion-blocking drugs of interest are synthetic amines. **Tetraethylammonium (TEA),** the first to be recognized as having this action, has a very short duration of action. **Hexamethonium ("C6")** was developed and was introduced clinically as the first drug effective for management of hypertension. As shown in Figure 8–6, there is an obvious relationship between the structures of the agonist acetylcholine and the nicotinic antagonists tetraethylammonium and hexamethonium. Decamethonium, the "C10" analog of hexamethonium, is a depolarizing neuromuscular blocking agent.

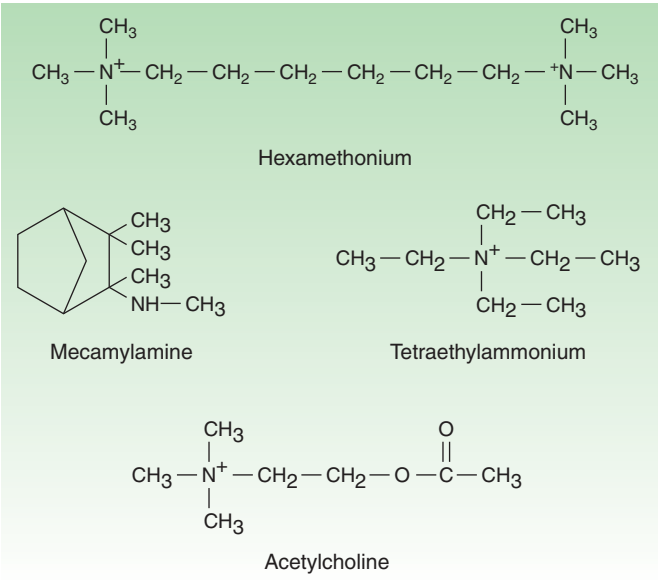


FIGURE 8–6 Some ganglion-blocking drugs. Acetylcholine is shown for reference.

Mecamylamine, a secondary amine, was developed to improve the degree and extent of absorption from the gastrointestinal tract because the quaternary amine ganglion-blocking compounds were poorly and erratically absorbed after oral administration. **Trimethaphan,** a short-acting ganglion blocker, is inactive orally and is given by intravenous infusion.

Pharmacodynamics

A. Mechanism of Action

Ganglionic nicotinic receptors, like those of the skeletal muscle neuromuscular junction, are subject to both depolarizing and nondepolarizing blockade (see Chapters 7 and 27). Nicotine itself, carbamoylcholine, and even acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.

Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists. However, hexamethonium actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinoceptor itself. In contrast, trimethaphan appears to block the nicotinic receptor, not the channel pore. Blockade can be surmounted by increasing the concentration of an agonist, eg, acetylcholine.

B. Organ System Effects

1. Central nervous system—Mecamylamine, unlike the quaternary amine agents and trimethaphan, crosses the blood-brain barrier and readily enters the CNS. Sedation, tremor, choreiform movements, and mental aberrations have been reported as effects of mecamylamine.

2. Eye—The ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation because the ciliary muscle receives innervation primarily from the parasympathetic nervous system. The effect on the pupil is not so easily predicted, since the iris receives both sympathetic innervation (mediating pupillary dilation) and parasympathetic innervation (mediating pupillary constriction). Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

3. Cardiovascular system—Blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a marked decrease in arteriolar and venomotor tone. The blood pressure may fall precipitously because both peripheral vascular resistance and venous return are decreased (see Figure 6–7). Hypotension is especially marked in the upright position (orthostatic or postural hypotension), because postural reflexes that normally prevent venous pooling are blocked.

Cardiac effects include diminished contractility and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

4. Gastrointestinal tract—Secretion is reduced, although not enough to effectively treat peptic disease. Motility is profoundly inhibited, and constipation can be marked.

5. Other systems—Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function. Therefore, ganglionic blockade causes hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia. Sexual function is impaired in that both erection and ejaculation may be prevented by moderate doses.

Thermoregulatory sweating is reduced by the ganglion-blocking drugs. However, hyperthermia is not a problem except in very warm environments, because cutaneous vasodilation is usually sufficient to maintain a normal body temperature.

6. Response to autonomic drugs—Patients receiving ganglion-blocking drugs are fully responsive to autonomic drugs acting on muscarinic, α-, and β-adrenergic receptors because these effector cell receptors are not blocked. In fact, responses may be exaggerated or even reversed (eg, intravenously administered norepinephrine may cause tachycardia rather than bradycardia), because homeostatic reflexes, which normally moderate autonomic responses, are absent.

Clinical Applications & Toxicity

Ganglion blockers are used infrequently because more selective autonomic blocking agents are available. Mecamylamine blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to reduce nicotine craving in patients attempting to quit smoking. Trimethaphan is occasionally used in the treatment of hypertensive emergencies and dissecting aortic aneurysm; in producing hypotension, which can be of value in neurosurgery to reduce bleeding in the operative field; and in the treatment of patients undergoing electroconvulsive therapy. The toxicity of the ganglion-blocking drugs is limited to the autonomic effects already described. For most patients, these effects are intolerable except for acute use.

SUMMARY Drugs with Anticholinergic Actions

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
MOTION SICKNESS DRUGS				
• Scopolamine	Unknown mechanism in CNS	Reduces vertigo, postoperative nausea	Prevention of motion sickness and postoperative nausea and vomiting	Transdermal patch used for motion sickness • IM injection for postoperative use • *Toxicity:* Tachycardia, blurred vision, xerostomia, delirium • *Interactions:* With other antimuscarinics
GASTROINTESTINAL DISORDERS				
• Dicyclomine	Competitive antagonism at M_3 receptors	Reduces smooth muscle and secretory activity of gut	Irritable bowel syndrome, minor diarrhea	Available in oral and parenteral forms • short $t_{½}$ but action lasts up to 6 hours • *Toxicity:* Tachycardia, confusion, urinary retention, increased intraocular pressure • *Interactions:* With other antimuscarinics
• *Hyoscyamine: Longer duration of action*				
• *Glycopyrrolate: Similar to dicyclomine*				
OPHTHALMOLOGY				
• Atropine	Competitive antagonism at all M receptors	Causes mydriasis and cycloplegia	Retinal examination; prevention of synechiae after surgery	Used as drops • long (5–6 days) action • *Toxicity:* Increased intraocular pressure in closed-angle glaucoma • *Interactions:* With other antimuscarinics
• *Scopolamine: Faster onset of action than atropine*				
• *Homatropine: Shorter duration of action (12–24 h)*				
• *Cyclopentolate: Shorter duration of action (3–6 h)*				
• *Tropicamide: Shortest duration of action (15–60 min)*				
RESPIRATORY (ASTHMA, COPD)				
• Ipratropium	Competitive, nonselective antagonist at M receptors	Reduces or prevents bronchospasm	Prevention and relief of acute episodes of bronchospasm	Aerosol canister, up to qid • *Toxicity:* Xerostomia, cough • *Interactions:* With other antimuscarinics
• *Tiotropium: Longer duration of action; used qd*				
URINARY				
• Oxybutynin	Slightly M_3-selective muscarinic antagonist	Reduces detrusor smooth muscle tone, spasms	Urge incontinence; postoperative spasms	Oral, IV, patch formulations • *Toxicity:* Tachycardia, constipation, increased intraocular pressure, xerostomia • Patch: Pruritus • *Interactions:* With other antimuscarinics
• *Darifenacin, solifenacin, and tolterodine: Tertiary amines with somewhat greater selectivity for M_3 receptors*				
• *Trospium: Quaternary amine with less CNS effect*				
CHOLINERGIC POISONING				
• Atropine	Nonselective competitive antagonist at all muscarinic receptors in CNS and periphery	Blocks muscarinic excess at exocrine glands, heart, smooth muscle	Mandatory antidote for severe cholinesterase inhibitor poisoning	Intravenous infusion until antimuscarinic signs appear • continue as long as necessary • *Toxicity:* Insignificant as long as AChE inhibition continues
• Pralidoxime	Very high affinity for phosphorus atom but does not enter CNS	Regenerates active AChE; can relieve skeletal muscle end plate block	Usual antidote for early-stage (48 h) cholinesterase inhibitor poisoning	Intravenous every 4–6 h • *Toxicity:* Can cause muscle weakness in overdose

AChE, acetylcholinesterase; CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

PREPARATIONS AVAILABLE

ANTIMUSCARINIC ANTICHOLINERGIC DRUGS*

Atropine (generic)
Oral: 0.4, 0.6 mg tablets
Parenteral: 0.05, 0.1, 0.4, 0.5, 1 mg/mL for injection; Atropen: 0.25, 0.5, 2 mg pen injectors
Ophthalmic (generic, Isopto Atropine): 0.5, 1, 2% drops; 0.5, 1% ointments

Belladonna alkaloids, extract or tincture (generic)
Oral: 0.27–0.33 mg/mL liquid

Clidinium (generic, Quarzan, others)
Oral: 2.5, 5 mg capsules

Cyclopentolate (generic, Cyclogyl, others)
Ophthalmic: 0.5, 1, 2% solution

Darifenacin (Enablex)
Oral: 7.5, 15 mg tablets (extended release)

Dicyclomine (generic, Bentyl, others)
Oral: 10, 20 mg capsules; 20 mg tablets; 10 mg/5 mL syrup
Parenteral: 10 mg/mL for intramuscular injection

Fesoterodine (Toviaz)
Oral: 4, 8 mg extended-release tablets

Flavoxate (Urispas)
Oral: 100 mg tablets

Glycopyrrolate (generic, Robinul)
Oral: 1, 2 mg tablets
Parenteral: 0.2 mg/mL for injection

Homatropine (generic, Isopto Homatropine, others)
Ophthalmic: 2, 5% solution

l-Hyoscyamine (Anaspaz, Cystospaz-M, Levsin, others)
Oral: 0.125, 0.25 mg tablets; 0.375, 0.75 mg timed-release capsules; 0.125 mg/5 mL oral elixir and solution
Parenteral: 0.5 mg/mL for injection

Ipratropium (generic, Atrovent)
Aerosol: 200 dose metered-dose inhaler (0.17 mg/dose)
Solution for nebulizer: 0.02%
Nasal spray: 0.03, 0.06%

Mepenzolate (Cantil)
Oral: 25 mg tablets

Methantheline (Banthine)
Oral: 50 mg tablets

Methscopolamine (generic, Pamine)
Oral: 2.5, 5 mg tablets

Oxybutynin (generic, Ditropan)
Oral: 5 mg tablets; 5, 10 mg extended-release tablets; patch (3.9 mg/day); 5 mg/5 mL syrup
Topical: 10% gel

Propantheline (generic, Pro-Banthine, others)
Oral: 7.5, 15 mg tablets

Scopolamine (generic)
Oral: 0.4 mg tablets
Parenteral: 0.4 mg/mL for injection
Ophthalmic (Isopto Hyoscine): 0.25% solution
Transdermal (Transderm Scop): 1.5 mg (delivers 0.5 mg/24 h)patch; extended-release patch (delivers 0.33 mg/24 h)

Solifenacin (Vesicare)
Oral: 5, 10 mg tablets

Tiotropium (Spiriva)
Aerosol: 18 mcg tablet for inhaler

Tolterodine (Detrol)
Oral: 1, 2 mg tablets; 2, 4 mg extended-release capsules

Tridihexethyl (Pathilon)
Oral: 25 mg tablets

Tropicamide (generic, Mydriacyl Ophthalmic, others)
Ophthalmic: 0.5, 1% drops

Trospium (Spasmex, Sanctura)
Oral: 20 mg tablets; 60 mg extended-release capsule
Suppository: 0.75, 1.0 mg
Parenteral: 0.6 mg/mL

GANGLION BLOCKERS

Mecamylamine (Inversine)
Oral: 2.5, 10 mg tablets

Trimethaphan (Arfonad)
Parenteral: 50 mg/mL

CHOLINESTERASE REGENERATOR

Pralidoxime (generic, Protopam)
Parenteral: 1 g vial with 20 mL diluent for IV administration; 600 mg in 2 mL autoinjector

*Antimuscarinic drugs used in parkinsonism are listed in Chapter 28.

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CASE STUDY ANSWER

JH's symptoms are often displayed by patients following prostatectomy to relieve significant obstruction of bladder outflow. Urge incontinence can occur in patients whose prostatic hypertrophy caused instability of the detrusor muscle. He should be advised that urinary incontinence and urinary frequency can diminish with time after prostatectomy as detrusor muscle instability subsides. JH can be helped by daily administration of a single tablet of extended-release tolterodine (4 mg/day) or oxybutynin (5–10 mg/day). A transdermal patch containing oxybutynin (3.9 mg/day) is also available.

CHAPTER 9

Adrenoceptor Agonists & Sympathomimetic Drugs

Italo Biaggioni, MD, & David Robertson, MD*

CASE STUDY

A 68-year-old man presents with a complaint of light-headedness on standing that is worse after meals and in hot environments. Symptoms started about 4 years ago and have slowly progressed to the point that he is disabled. He has fainted several times, but always recovers consciousness almost as soon as he falls. Review of symptoms reveals slight worsening of constipation, urinary retention out of proportion to prostate size, and decreased sweating. He is otherwise healthy with no history of hypertension, diabetes, or Parkinson's disease. Because of his urinary retention, he was placed on the α_1 antagonist tamsulosin but he could not tolerate it because of worsening of orthostatic hypotension. Physical examination revealed a blood pressure of 167/84 mm Hg supine and 106/55 mm Hg standing. There was an inadequate compensatory increase in heart rate (from 84 to 88 bpm), considering the degree of orthostatic hypotension. Physical examination is otherwise unremarkable with no evidence of peripheral neuropathy or parkinsonian features. Laboratory examinations are negative except for plasma norepinephrine, which is low at 98 pg/mL (normal is 250–400 pg/mL for his age). A diagnosis of pure autonomic failure is made, based on the clinical picture and the absence of drugs that could induce orthostatic hypotension and diseases commonly associated with autonomic neuropathy (eg, diabetes, Parkinson's disease). What precautions should this patient observe in using sympathomimetic drugs? Can such drugs be used in his treatment?

The sympathetic nervous system is an important regulator of virtually all organ systems. This is particularly evident in the regulation of blood pressure. As illustrated in the case study, the autonomic nervous system is crucial for the maintenance of blood pressure even under relatively minor situations of stress (eg, the gravitational stress of standing).

The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals, which then activates adrenoceptors on postsynaptic sites (see Chapter 6). Also, in response to a variety of stimuli such as stress, the adrenal medulla releases epinephrine, which is transported in the blood to target tissues. In other words, epinephrine acts as a hormone, whereas norepinephrine acts as a neurotransmitter.

Drugs that mimic the actions of epinephrine or norepinephrine have traditionally been termed **sympathomimetic drugs.** The sympathomimetics can be grouped by mode of action and by the spectrum of receptors that they activate. Some of these drugs (eg, norepinephrine and epinephrine) are *direct* agonists; that is, they directly interact with and activate adrenoceptors. Others are *indirect* agonists because their actions are dependent on their ability to enhance the actions of endogenous catecholamines. These indirect agents may have either of two different mechanisms: (1) they may displace stored catecholamines from the adrenergic nerve ending (eg, the mechanism of action of tyramine), or they may decrease the clearance of released norepinephrine either by (2a) inhibiting reuptake of catecholamines already released (eg, the mechanism of action of cocaine and tricyclic antidepressants) or (2b) preventing the enzymatic metabolism of norepinephrine (monoamine oxidase and catechol-*O*-methyltransferase inhibitors). Some drugs have both direct and indirect actions. Both

*The authors thank Drs. Vsevolod Gurevich and Randy Blakely for helpful comments.

types of sympathomimetics, direct and indirect, ultimately cause activation of adrenoceptors, leading to some or all of the characteristic effects of endogenous catecholamines.

The pharmacologic effects of direct agonists depend on the route of administration, their relative affinity for adrenoreceptor subtypes, and the relative expression of these receptor subtypes in target tissues. The pharmacologic effects of indirect sympathomimetics are greater under conditions of increased sympathetic activity and norepinephrine storage and release.

MOLECULAR PHARMACOLOGY UNDERLYING THE ACTIONS OF SYMPATHOMIMETIC DRUGS

The effects of catecholamines are mediated by cell-surface receptors. Adrenoceptors are typical G protein-coupled receptors (GPCRs; see Chapter 2). The receptor protein has an extracellular N-terminus, traverses the membrane seven times (transmembrane domains) forming three extracellular and three intracellular loops, and has an intracellular C-terminus (Figure 9–1). G protein-coupled receptors are coupled by G proteins to the various effector proteins whose activities are regulated by those receptors. Each G protein is a heterotrimer consisting of α, β, and γ subunits. G proteins are classified on the basis of their distinctive α subunits. G proteins of particular importance for adrenoceptor function include G_s, the stimulatory G protein of adenylyl cyclase; G_i and G_o, the inhibitory G proteins of adenylyl cyclase; and G_q and G_{11}, the G proteins coupling α receptors to phospholipase C. The activation of G protein-coupled receptors by catecholamines promotes the dissociation of guanosine diphosphate (GDP) from the α subunit of the appropriate G protein. Guanosine triphosphate (GTP) then binds to this G protein, and the α subunit dissociates from the β-γ unit. The activated GTP-bound α subunit then regulates the activity of its effector. Effectors of adrenoceptor-activated α subunits include adenylyl cyclase, cGMP phosphodiesterase, phospholipase C, and ion channels. The α subunit is inactivated by hydrolysis of the bound GTP to GDP and phosphate, and the subsequent reassociation of the α subunit with the β-γ subunit. The β-γ subunits have additional independent effects, acting on a variety of effectors such as ion channels and enzymes.

Adrenoreceptors were initially characterized pharmacologically, with α receptors having the comparative potencies epinephrine ≥ norepinephrine >> isoproterenol, and β receptors having the comparative potencies isoproterenol > epinephrine ≥ norepinephrine. The development of selective antagonists revealed the presence of subtypes of these receptors, which were finally characterized by

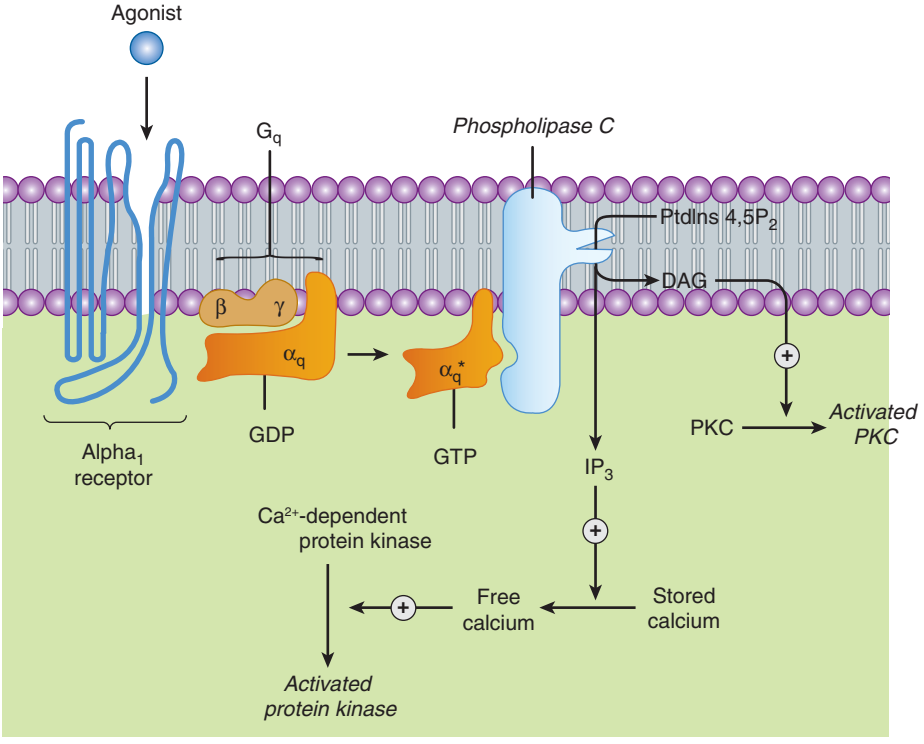

FIGURE 9–1 Activation of α_1 responses. Stimulation of α_1 receptors by catecholamines leads to the activation of a G_q-coupling protein. The activated α subunit (α_q*) of this G protein activates the effector, phospholipase C, which leads to the release of IP_3 (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol) from phosphatidylinositol 4,5-bisphosphate (PtdIns 4,5P_2). IP_3 stimulates the release of sequestered stores of calcium, leading to an increased concentration of cytoplasmic Ca^{2+}. Ca^{2+} may then activate Ca^{2+}-dependent protein kinases, which in turn phosphorylate their substrates. DAG activates protein kinase C (PKC). GTP, guanosine triphosphate; GDP, guanosine diphosphate. See text for additional effects of α_1-receptor activation.

TABLE 9–1 Adrenoceptor types and subtypes.

Receptor	Agonist	Antagonist	G Protein	Effects	Gene on Chromosome
α_1 type	Phenylephrine	Prazosin	G_q	↑ IP3, DAG common to all	
α_{1A}					C8
α_{1B}					C5
α_{1D}					C20
α_2 type	Clonidine	Yohimbine	G_i	↓ cAMP common to all	
α_{2A}	Oxymetazoline				C10
α_{2B}		Prazosin			C2
α_{2C}		Prazosin			C4
β type	Isoproterenol	Propranolol	G_s	↑ cAMP common to all	
β_1	Dobutamine	Betaxolol			C10
β_2	Albuterol	Butoxamine			C5
β_3					C8
Dopamine type	Dopamine				
D_1	Fenoldopam		G_s	↑ cAMP	C5
D_2	Bromocriptine		G_i	↓ cAMP	C11
D_3			G_i	↓ cAMP	C3
D_4		Clozapine	G_i	↓ cAMP	C11
D_5			G_s	↑ cAMP	C4

molecular cloning. We now know that unique genes encode the receptor subtypes listed in Table 9–1.

Likewise, the endogenous catecholamine dopamine produces a variety of biologic effects that are mediated by interactions with specific dopamine receptors (Table 9–1). These receptors are distinct from α and β receptors and are particularly important in the brain (see Chapters 21 and 29) and in the splanchnic and renal vasculature. Molecular cloning has identified several distinct genes encoding five receptor subtypes, two D_1-like receptors (D_1 and D_5) and three D_2-like (D_2, D_3, and D_4). Further complexity occurs because of the presence of introns within the coding region of the D_2-like receptor genes, which allows for alternative splicing of the exons in this major subtype. There is extensive polymorphic variation in the D_4 human receptor gene. These subtypes may have importance for understanding the efficacy and adverse effects of novel antipsychotic drugs (see Chapter 29).

Receptor Types

A. Alpha Receptors

$Alpha_1$ receptors are coupled via G proteins in the G_q family to phospholipase C. This enzyme hydrolyzes polyphosphoinositides, leading to the formation of **inositol 1,4,5-trisphosphate (IP_3)** and **diacylglycerol (DAG)** (Table 9–1, Figure 9–1). IP_3 promotes the release of sequestered Ca^{2+} from intracellular stores, which increases the cytoplasmic concentration of free Ca^{2+} and the activation of various calcium-dependent protein kinases. Activation of these receptors may also increase influx of calcium across the cell's plasma membrane. IP_3 is sequentially dephosphorylated, which ultimately leads to the formation of free inositol. DAG activates protein kinase C, which modulates activity of many signaling pathways. In addition, α_1 receptors activate signal transduction pathways that were originally described for peptide growth factor receptors that activate tyrosine kinases. For example, α_1 receptors have been found to activate mitogen-activated kinases (MAP kinases) and polyphosphoinositol-3-kinase (PI-3-kinase). These pathways may have importance for the α_1-receptor–mediated stimulation of cell growth and proliferation through the regulation of gene expression.

$Alpha_2$ receptors inhibit adenylyl cyclase activity and cause intracellular cyclic adenosine monophosphate (cAMP) levels to decrease. $Alpha_2$-receptor–mediated inhibition of adenylyl cyclase activity is transduced by the inhibitory regulatory protein, G_i (Figure 9–2). It is likely that not only α, but also the β-γ subunits of G_i contribute to inhibition of adenylyl cyclase. $Alpha_2$ receptors use other signaling pathways, including regulation of ion channel activities and the activities of important enzymes involved in signal transduction. Indeed, some of the effects of α_2 adrenoceptors are independent of their ability to inhibit adenylyl cyclase; for example, α_2-receptor agonists cause platelet aggregation and a decrease in platelet cAMP levels, but it is not clear whether aggregation is the result of the decrease in cAMP or other mechanisms involving G_i-regulated effectors.

B. Beta Receptors

Activation of all three receptor subtypes (β_1, β_2, and β_3) results in stimulation of adenylyl cyclase and increased conversion of

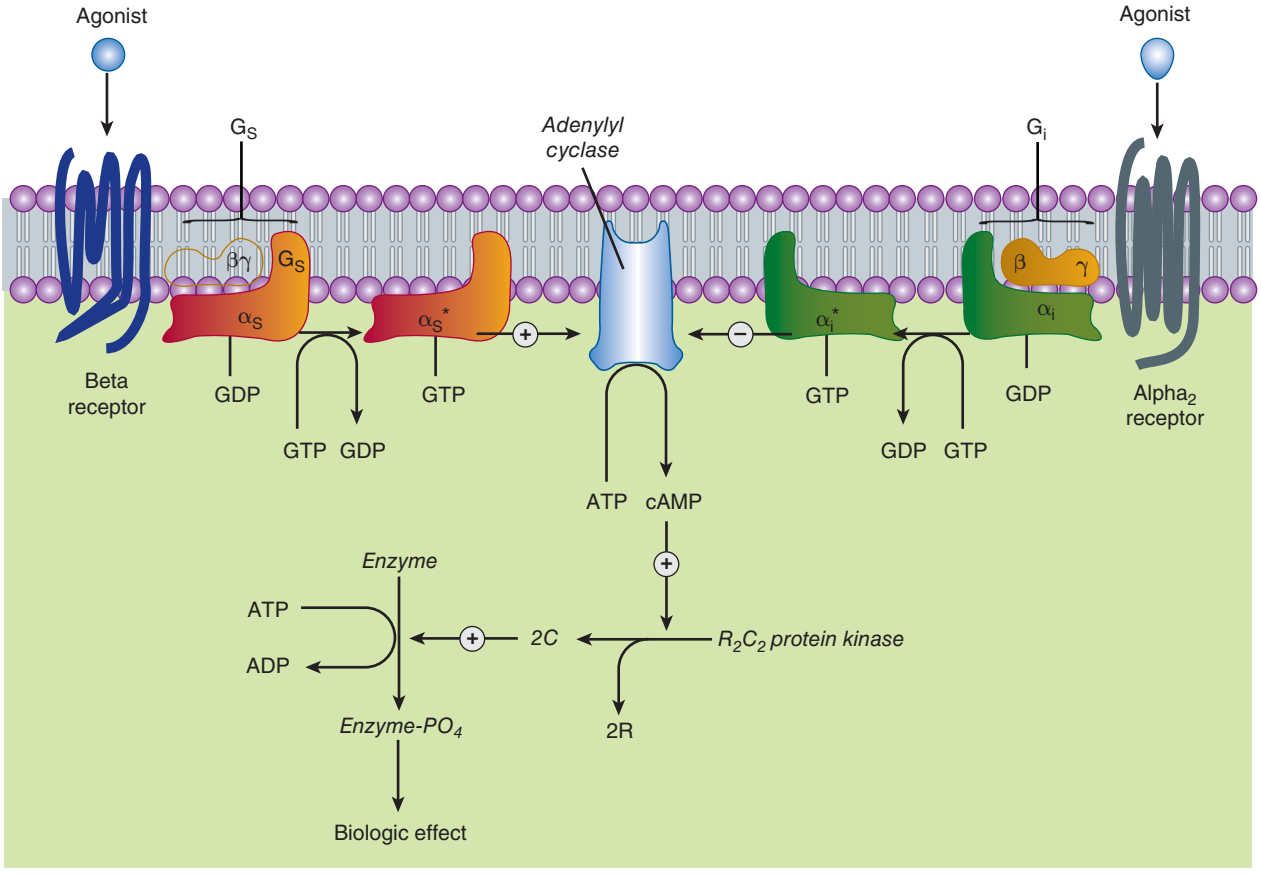

FIGURE 9–2 Activation and inhibition of adenylyl cyclase by agonists that bind to catecholamine receptors. Binding to β adrenoceptors stimulates adenylyl cyclase by activating the stimulatory G protein, G_s, which leads to the dissociation of its α subunit charged with GTP. This activated α_s subunit directly activates adenylyl cyclase, resulting in an increased rate of synthesis of cAMP. Alpha$_2$-adrenoceptor ligands inhibit adenylyl cyclase by causing dissociation of the inhibitory G protein, G_i, into its subunits; ie, an activated α_i subunit charged with GTP and a β-γ unit. The mechanism by which these subunits inhibit adenylyl cyclase is uncertain. cAMP binds to the regulatory subunit (*R*) of cAMP-dependent protein kinase, leading to the liberation of active catalytic subunits (*C*) that phosphorylate specific protein substrates and modify their activity. These catalytic units also phosphorylate the cAMP response element binding protein (CREB), which modifies gene expression. See text for other actions of β and α_2 adrenoceptors.

adenosine triphosphate (ATP) to cAMP (Table 9–1, Figure 9–2). Activation of the cyclase enzyme is mediated by the stimulatory coupling protein G_s. Cyclic AMP is the major second messenger of β-receptor activation. For example, in the liver of many species, β-receptor–activated cAMP synthesis leads to a cascade of events culminating in the activation of glycogen phosphorylase. In the heart, β-receptor–activated cAMP synthesis increases the influx of calcium across the cell membrane and its sequestration inside the cell. Beta-receptor activation also promotes the relaxation of smooth muscle. Although the mechanism of the smooth muscle effect is uncertain, it may involve the phosphorylation of myosin light-chain kinase to an inactive form (see Figure 12–1). Beta adrenoceptors may activate voltage-sensitive calcium channels in the heart via G_s-mediated enhancement independently of changes in cAMP concentration. Under certain circumstances, β_2 receptors may couple to G_q proteins. These receptors have been demonstrated to activate additional kinases, such as MAP kinases, by forming multi-subunit complexes within cells, which contain multiple signaling molecules.

The β_3 adrenoreceptor is a lower affinity receptor compared with β_1 and β_2 receptors but is more resistant to desensitization. It is found in several tissues, but its physiologic or pathologic role in humans is not clear. Selective agonists and antagonists have been developed but are not clinically available.

C. Dopamine Receptors

The D_1 receptor is typically associated with the stimulation of adenylyl cyclase (Table 9–1); for example, D_1-receptor–induced smooth muscle relaxation is presumably due to cAMP accumulation in the smooth muscle of those vascular beds in which dopamine is a vasodilator. D_2 receptors have been found to inhibit adenylyl cyclase activity, open potassium channels, and decrease calcium influx.

Receptor Selectivity

Many clinically available adrenergic agonists have selectivity for the major (α_1 and α_2 versus β) adrenoreceptor types, but not for the subtypes of these major groups. Examples of clinically useful sympathomimetic agonists that are relatively selective for α_1-, α_2-, and β-adrenoceptor subgroups are compared with some nonselective agents in Table 9–2. Selectivity means that a drug may preferentially bind to one subgroup of receptors at concentrations too low to interact extensively with another subgroup. However, selectivity is not usually absolute (nearly absolute selectivity has been termed "specificity"), and at higher concentrations, a drug may also interact with related classes of receptors. The effects of a given drug may depend not only on its selectivity to adrenoreceptor types, but also to the relative expression of receptor subtypes in a given tissue. (see Box: Receptor Selectivity and Physiologic Functions of Adrenoceptor Subtypes).

Receptor Regulation

Responses mediated by adrenoceptors are not fixed and static. The number and function of adrenoceptors on the cell surface and their responses may be regulated by catecholamines themselves, other hormones and drugs, age, and a number of disease states (see Chapter 2). These changes may modify the magnitude of a tissue's physiologic response to catecholamines and can be important clinically during the course of treatment. One of the best-studied examples of receptor regulation is the **desensitization** of adrenoceptors that may occur after exposure to catecholamines and other sympathomimetic drugs. After a cell or tissue has been exposed for a period of time to an agonist, that tissue often becomes less responsive to further stimulation by that agent (see Figure 2–12).

TABLE 9–2 Relative receptor affinities.

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

[1]See text.

Receptor Selectivity and Physiologic Functions of Adrenoceptor Subtypes: Lessons from Knockout Mice

Since pharmacologic tools used to evaluate the function of adrenoceptor subtypes have some limitations, a number of knockout mice have been developed with one or more adrenoceptor genes subjected to loss of function mutations, as described in Chapter 1 (see Box: Pharmacology & Genetics). These models have their own complexities, and extrapolations from mice to humans may be uncertain. Nonetheless, these studies have yielded some novel insights. For example, α-adrenoceptor subtypes play an important role in cardiac responses, the α_{2A}-adrenoceptor subtype is critical in transducing the effects of α_2 agonists on blood pressure control, and β_1 receptors play a predominant role in directly increasing heart rate in the mouse heart.

Other terms such as tolerance, refractoriness, and tachyphylaxis have also been used to denote desensitization. This process has potential clinical significance because it may limit the therapeutic response to sympathomimetic agents.

Many mechanisms have been found to contribute to desensitization. Some mechanisms function relatively slowly, over the course of hours or days, and these typically involve transcriptional or translational changes in the receptor protein level, or its migration to the cell surface. Other mechanisms of desensitization occur quickly, within minutes. Rapid modulation of receptor function in desensitized cells may involve critical covalent modification of the receptor, especially by phosphorylation on specific amino acid residues, association of these receptors with other proteins, or changes in their subcellular location.

There are two major categories of desensitization of responses mediated by G protein-coupled receptors. **Homologous** desensitization refers to loss of responsiveness exclusively of the receptors that have been exposed to repeated or sustained activation by an agonist. **Heterologous** desensitization refers to the process by which desensitization of one receptor by its agonists also results in desensitization of another receptor that has not been directly activated by the agonist in question.

A major mechanism of desensitization that occurs rapidly involves phosphorylation of receptors by members of the **G protein-coupled receptor kinase (GRK)** family, of which there are seven members. Specific adrenoceptors become substrates for these kinases only when they are bound to an agonist. This mechanism is an example of homologous desensitization because it specifically involves only agonist-occupied receptors.

Phosphorylation of these receptors enhances their affinity for **arrestins,** a family of four widely expressed proteins. Upon binding of arrestin, the capacity of the receptor to activate G proteins is blunted, presumably as a result of steric hindrance

(see Figure 2–12). Arrestin then interacts with clathrin and clathrin adaptor AP2, leading to endocytosis of the receptor. In addition to blunting responses requiring the presence of the receptor on the cell surface, these regulatory processes may also contribute to novel mechanisms of receptor signaling via intracellular pathways.

Receptor desensitization may also be mediated by second-messenger feedback. For example, β adrenoceptors stimulate cAMP accumulation, which leads to activation of protein kinase A; protein kinase A can phosphorylate residues on β receptors, resulting in inhibition of receptor function. For the β_2 receptor, phosphorylation occurs on serine residues both in the third cytoplasmic loop and in the carboxyl terminal tail of the receptor. Similarly, activation of protein kinase C by G_q-coupled receptors may lead to phosphorylation of this class of G protein-coupled receptors. This second-messenger feedback mechanism has been termed heterologous desensitization because activated protein kinase A or protein kinase C may phosphorylate any structurally similar receptor with the appropriate consensus sites for phosphorylation by these enzymes.

Adrenoceptor Polymorphisms

Since elucidation of the sequences of the genes encoding the α_1, α_2, and β subtypes of adrenoceptors, it has become clear that there are relatively common genetic polymorphisms for many of these receptor subtypes in humans. Some of these may lead to changes in critical amino acid sequences that have pharmacologic importance. Often, distinct polymorphisms occur in specific combinations termed **haplotypes.** Some polymorphisms have been shown to alter susceptibility to diseases such as heart failure, others to alter the propensity of a receptor to desensitize, and still others to alter therapeutic responses to drugs in diseases such as asthma. This remains an area of active research because studies have reported inconsistent results as to the pathophysiologic importance of some polymorphisms.

The Norepinephrine Transporter

When norepinephrine is released into the synaptic cleft, it binds to postsynaptic adrenoceptors to elicit the expected physiologic effect. However, just as the release of neurotransmitters is a tightly regulated process, the mechanisms for removal of neurotransmitter must also be highly effective. The norepinephrine transporter (NET) is the principal route by which this occurs. It is particularly efficient in the synapses of the heart, where up to 90% of released norepinephrine is removed by the NET. Remaining synaptic norepinephrine may escape into the extrasynaptic space and enter the bloodstream or be taken up into extraneuronal cells and metabolized by catecholamine-*N*-methyltransferase. In other sites such as the vasculature, where synaptic structures are less well developed, removal may still be 60% or more by NET. The NET, often situated on the presynaptic neuronal membrane, pumps the synaptic norepinephrine back into the neuron cell cytoplasm. In the cell, this norepinephrine may reenter the vesicles or undergo metabolism through monoamine oxidase to dihydroxyphenylglycol (DHPG). Elsewhere in the body similar transporters remove dopamine (dopamine transporter, DAT), serotonin (serotonin transporter, SERT), and other neurotransmitters. The NET, surprisingly, has equivalent affinity for dopamine as for norepinephrine, and it can sometimes clear dopamine in brain areas where DAT is low, like the cortex.

Blockade of the NET, eg, by the nonselective psychostimulant cocaine or the NET selective agents atomoxetine or reboxetine, impairs this primary site of norepinephrine removal and thus synaptic norepinephrine levels rise, leading to greater stimulation of α and β adrenoceptors. In the periphery this effect may produce a clinical picture of sympathetic activation, but it is often counterbalanced by concomitant stimulation of α_2 adrenoceptors in the brainstem that reduces sympathetic activation.

However, the function of the norepinephrine and dopamine transporters is complex, and drugs can interact with the NET to actually reverse the direction of transport and induce the release of intraneuronal neurotransmitter. This is illustrated in Figure 9–3. Under normal circumstances (panel A), presynaptic NET (red) inactivates and recycles norepinephrine (NE, red) released by vesicular fusion. In panel B, amphetamine (black) acts as both an NET substrate and a reuptake blocker, eliciting reverse transport and blocking normal uptake, thereby increasing NE levels in and beyond the synaptic cleft. In panel C, agents such as methylphenidate and cocaine (hexagons) block NET-mediated NE reuptake and enhance NE signaling.

MEDICINAL CHEMISTRY OF SYMPATHOMIMETIC DRUGS

Phenylethylamine may be considered the parent compound from which sympathomimetic drugs are derived (Figure 9–4). This compound consists of a benzene ring with an ethylamine side chain. Substitutions may be made on (1) the benzene ring, (2) the terminal amino group, and (3) the α or β carbons of the ethylamino chain. Substitution by –OH groups at the 3 and 4 positions yields sympathomimetic drugs collectively known as catecholamines. The effects of modification of phenylethylamine are to change the affinity of the drugs for α and β receptors, spanning the range from almost pure α activity (methoxamine) to almost pure β activity (isoproterenol), as well as to influence the intrinsic ability to activate the receptors.

In addition to determining relative affinity to receptor subtype, chemical structure also determines the pharmacokinetic properties and bioavailability of these molecules.

A. Substitution on the Benzene Ring

Maximal α and β activity is found with catecholamines, ie, drugs having –OH groups at the 3 and 4 positions on the benzene ring. The absence of one or the other of these groups, particularly the hydroxyl at C_3, without other substitutions on the ring may dramatically reduce the potency of the drug. For example, phenylephrine (Figure 9–5) is much less potent than epinephrine;

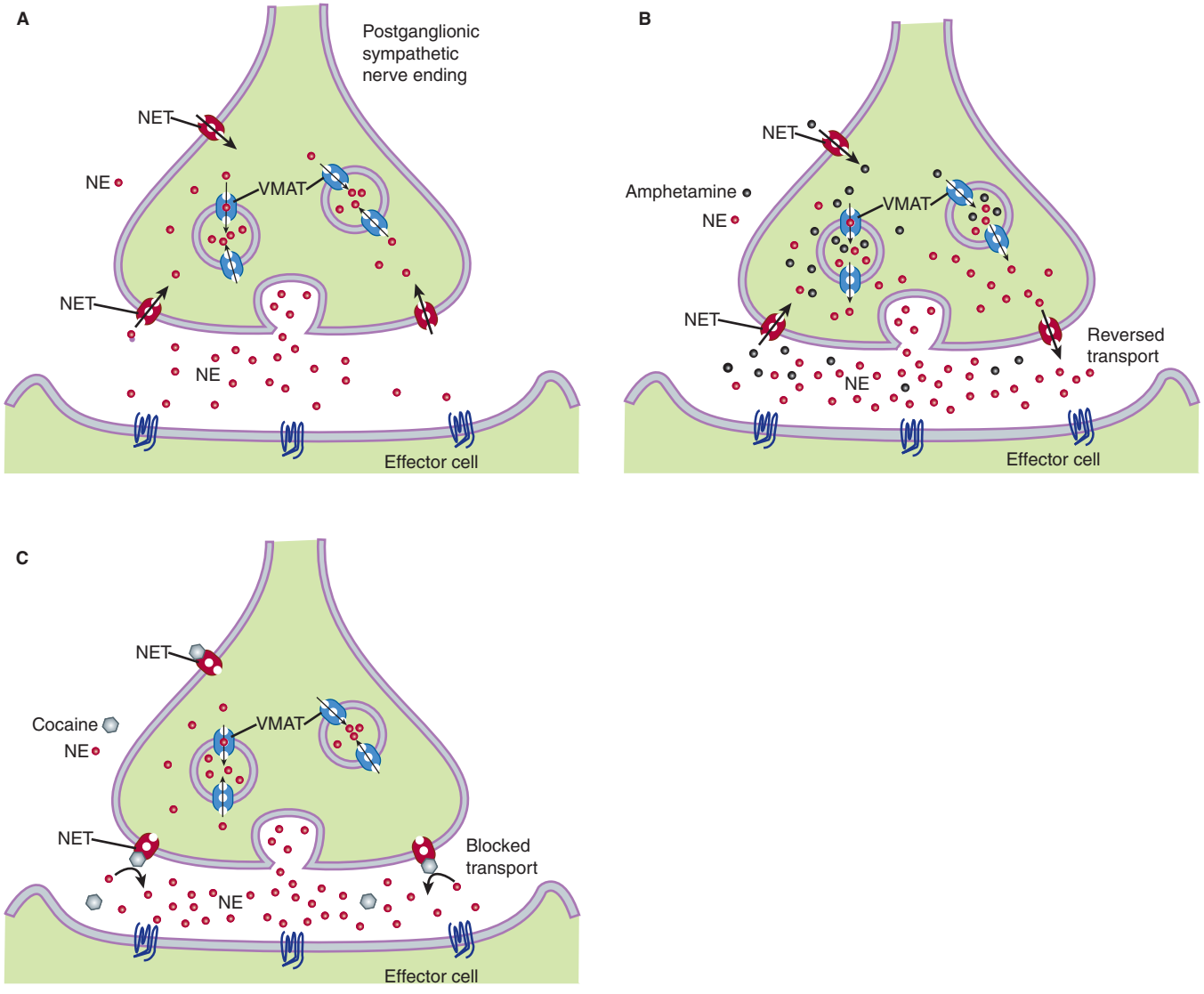

FIGURE 9–3 Pharmacologic targeting of monoamine transporters. Commonly used drugs such as antidepressants, amphetamines, and cocaine target monoamine (norepinephrine, dopamine, and serotonin) transporters with different potencies. **A** shows the mechanism of reuptake of norepinephrine (NE) back into the noradrenergic neuron via the norepinephrine transporter (NET), where a proportion is sequestered in presynaptic vesicles through the vesicular monoamine transporter (VMAT). **B** and **C** show the effects of amphetamine and cocaine on these pathways. See text for details.

indeed, α-receptor affinity is decreased about 100-fold and β activity is almost negligible except at very high concentrations. On the other hand, catecholamines are subject to inactivation by catechol-*O*-methyltransferase (COMT), and because this enzyme is found in the gut and liver, catecholamines are not active orally (see Chapter 6). Absence of one or both –OH groups on the phenyl ring increases the bioavailability after oral administration and prolongs the duration of action. Furthermore, absence of ring –OH groups tends to increase the distribution of the molecule to the central nervous system. For example, ephedrine and amphetamine (Figure 9–5) are orally active, have a prolonged duration of action, and produce central nervous system effects not typically observed with the catecholamines.

B. Substitution on the Amino Group

Increasing the size of alkyl substituents on the amino group tends to increase β-receptor activity. For example, methyl substitution on norepinephrine, yielding epinephrine, enhances activity at β_2 receptors. Beta activity is further enhanced with isopropyl substitution at the amino group (isoproterenol). $Beta_2$-selective agonists generally require a large amino substituent group. The larger the substituent on the amino group, the lower the activity at α receptors; for example, isoproterenol is very weak at α receptors.

C. Substitution on the Alpha Carbon

Substitutions at the α carbon block oxidation by monoamine oxidase (MAO) and prolong the action of such drugs, particularly the

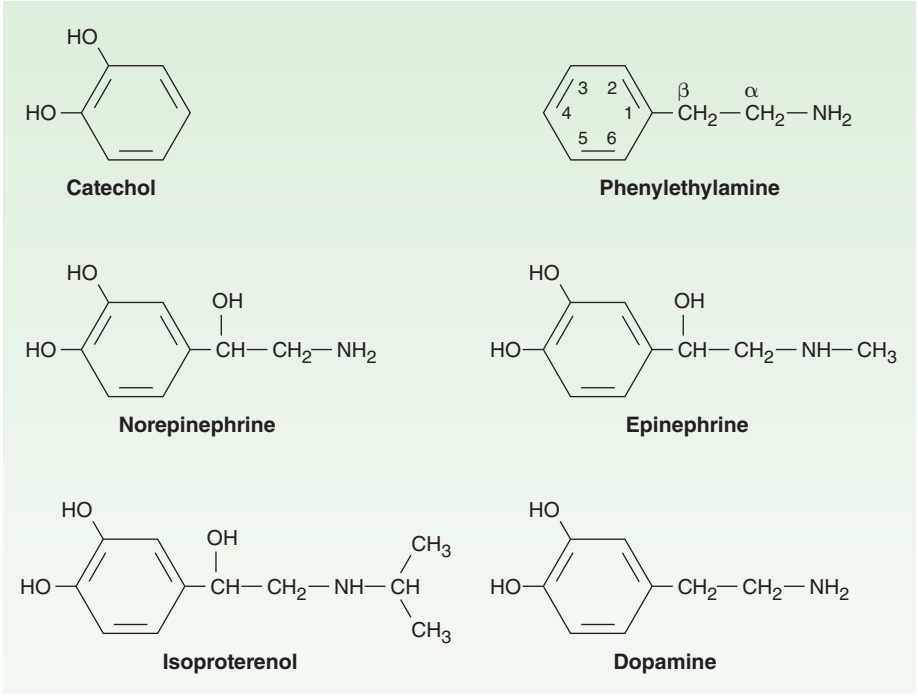

FIGURE 9–4 Phenylethylamine and some important catecholamines. Catechol is shown for reference.

noncatecholamines. Ephedrine and amphetamine are examples of α-substituted compounds (Figure 9–5). Alpha-methyl compounds are also called phenylisopropylamines. In addition to their resistance to oxidation by MAO, some phenylisopropylamines have an enhanced ability to displace catecholamines from storage sites in noradrenergic nerves (see Chapter 6). Therefore, a portion of their activity is dependent on the presence of normal norepinephrine stores in the body; they are indirectly acting sympathomimetics.

D. Substitution on the Beta Carbon

Direct-acting agonists typically have a β-hydroxyl group, although dopamine does not. In addition to facilitating activation of adrenoceptors, this hydroxyl group may be important for storage of sympathomimetic amines in neural vesicles.

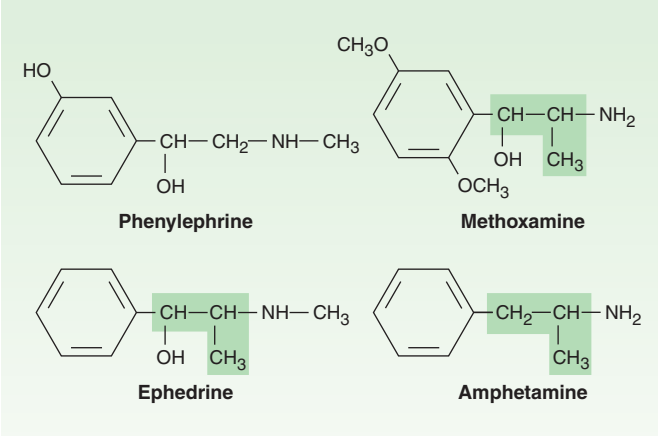

FIGURE 9–5 Some examples of noncatecholamine sympathomimetic drugs. The isopropyl group is highlighted in color.

ORGAN SYSTEM EFFECTS OF SYMPATHOMIMETIC DRUGS

Cardiovascular System

General outlines of the cellular actions of sympathomimetics are presented in Tables 6–3 and 9–3. Sympathomimetics have prominent cardiovascular effects because of widespread distribution of α and β adrenoceptors in the heart, blood vessels, and neural and hormonal systems involved in blood pressure regulation. The net effect of a given sympathomimetic in the intact organism depends not only on its relative selectivity for α or β adrenoceptors and its pharmacologic action at those receptors; any effect these agents have on blood pressure is counteracted by compensatory baroreflex mechanisms aimed at restoring homeostasis.

The effects of sympathomimetic drugs on blood pressure can be explained on the basis of their effects on heart rate, myocardial function, peripheral vascular resistance, and venous return (see Figure 6–7 and Table 9–4). The endogenous catecholamines, norepinephrine and epinephrine, have complex cardiovascular effects

TABLE 9–3 Distribution of adrenoceptor subtypes.

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

because they activate both α and β receptors. It is easier to understand these actions by first describing the cardiovascular effect of sympathomimetics that are selective for a given adrenoreceptor.

A. Effects of Alpha$_1$-Receptor Activation

Alpha$_1$ receptors are widely expressed in vascular beds, and their activation leads to arterial and venous vasoconstriction. Their direct effect on cardiac function is of relatively less importance. A relatively pure α agonist such as phenylephrine increases peripheral arterial resistance and decreases venous capacitance. The enhanced arterial resistance usually leads to a dose-dependent rise in blood pressure (Figure 9–6). In the presence of normal cardiovascular reflexes, the rise in blood pressure elicits a baroreceptor-mediated increase in vagal tone with slowing of the heart rate, which may be quite marked (Figure 9–7). However, cardiac output may not diminish in proportion to this reduction in rate, since increased venous return may increase stroke volume. Furthermore, direct α-adrenoceptor stimulation of the heart may have a modest positive inotropic action. The magnitude of the restraining effect of the baroreflex is quite dramatic. If baroreflex function is removed by pretreatment with the ganglionic blocker trimethaphan, the pressor effect of phenylephrine is increased approximately tenfold, and bradycardia is no longer observed (Figure 9–7), confirming that the decrease in heart rate associated with the increase in blood pressure induced by phenylephrine was reflex in nature rather than a direct effect of α_1-receptor activation.

Patients who have an impairment of autonomic function (due to pure autonomic failure as in the case study or to more common conditions such as diabetic autonomic neuropathy) exhibit this extreme hypersensitivity to most pressor and depressor stimuli, including medications. This is to a large extent due to failure of baroreflex buffering. Such patients may have exaggerated increases in heart rate or blood pressure when taking sympathomimetics with β- and α-adrenergic activity, respectively. This, however, can be used as an advantage in their treatment. The α agonist midodrine is commonly used to ameliorate orthostatic hypotension in these patients.

There are major differences in receptor types predominantly expressed in the various vascular beds (Table 9–4). The skin vessels have predominantly α receptors and constrict in response to epinephrine and norepinephrine, as do the splanchnic vessels. Vessels in skeletal muscle may constrict or dilate depending on whether α or β receptors are activated. The blood vessels of the nasal mucosa express α receptors, and local vasoconstriction induced by sympathomimetics explains their decongestant action (see Therapeutic Uses of Sympathomimetic Drugs).

B. Effects of Alpha$_2$-Receptor Activation

Alpha$_2$ adrenoceptors are present in the vasculature, and their activation leads to vasoconstriction. This effect, however, is observed only when α_2 agonists are given locally, by rapid intravenous injection or in very high oral doses. When given systemically, these vascular effects are obscured by the central effects of α_2 receptors, which lead to inhibition of sympathetic tone and blood pressure. Hence, α_2 agonists are used as *sympatholytics* in the treatment of hypertension (see Chapter 11). In patients with pure autonomic failure, characterized by neural degeneration of postganglionic noradrenergic fibers, clonidine may increase blood pressure because the central sympatholytic effects of clonidine become irrelevant, whereas the peripheral vasoconstriction remains intact.

C. Effects of Beta-Receptor Activation

The blood pressure response to a β-adrenoceptor agonist depends on its contrasting effects on the heart and the vasculature. Stimulation of β receptors in the heart increases cardiac output by increasing contractility and by direct activation of the sinus node to increase heart rate. Beta agonists also decrease peripheral resistance by activating β_2 receptors, leading to vasodilation in certain vascular beds (Table 9–4). Isoproterenol is a nonselective β agonist; it activates both β_1 and β_2 receptors. The net effect is to maintain or slightly increase systolic pressure and to lower diastolic pressure, so that mean blood pressure is decreased (Figure 9–6).

Direct effects on the heart are determined largely by β_1 receptors, although β_2 and to a lesser extent α receptors are also involved, especially in heart failure. Beta-receptor activation results in increased calcium influx in cardiac cells. This has both

TABLE 9–4 Cardiovascular responses to sympathomimetic amines.

	Phenylephrine	Epinephrine	Isoproterenol
Vascular resistance (tone)			
Cutaneous, mucous membranes (α)	↑↑	↑↑	0
Skeletal muscle (β_2, α)	↑	↓ or ↑	↓↓
Renal (α, D_1)	↑	↑	↓
Splanchnic (α, β)	↑↑	↓ or ↑[1]	↓
Total peripheral resistance	↑↑↑	↓ or ↑[1]	↓↓
Venous tone (α, β)	↑	↑	↓
Cardiac			
Contractility (β_1)	0 or ↑	↑↑↑	↑↑↑
Heart rate (predominantly β_1)	↓↓ (vagal reflex)	↑ or ↓	↑↑↑
Stroke volume	0, ↓, ↑	↑	↑
Cardiac output	↓	↑	↑↑
Blood pressure			
Mean	↑↑	↑	↓
Diastolic	↑↑	↓ or ↑[1]	↓↓
Systolic	↑↑	↑↑	0 or ↓
Pulse pressure	0	↑↑	↑↑

[1]Small doses decrease, large doses increase.

↑ = increase; ↓ = decrease; 0 = no change.

electrical and mechanical consequences. Pacemaker activity—both normal (sinoatrial node) and abnormal (eg, Purkinje fibers)—is increased (**positive chronotropic** effect). Conduction velocity in the atrioventricular node is increased (**positive dromotropic** effect), and the refractory period is decreased. Intrinsic contractility is increased (**positive inotropic** effect), and relaxation is accelerated. As a result, the twitch response of isolated cardiac muscle is increased in tension but abbreviated in duration. In the intact heart, intraventricular pressure rises and falls more rapidly, and ejection time is decreased. These direct effects are easily demonstrated in the absence of reflexes evoked by changes in blood pressure, eg, in isolated myocardial preparations and in patients with ganglionic blockade. In the presence of normal reflex activity, the direct effects on heart rate may be dominated by a reflex response to blood pressure changes. Physiologic stimulation of the heart by catecholamines tends to increase coronary blood flow. Expression of β_3 adrenoreceptors has been detected in the human heart and may be upregulated in disease states, but its relevance to human disease is unclear.

D. Effects of Dopamine-Receptor Activation

Intravenous administration of dopamine promotes vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels, via activation of D_1 receptors. Activation of the D_1 receptors in the renal vasculature may also induce natriuresis. The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output). The activation of presynaptic D_2 receptors suppresses norepinephrine release, but it is unclear if this contributes to cardiovascular effects of dopamine. In addition, dopamine activates β_1 receptors in the heart. At low doses, peripheral resistance may decrease. At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed. Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

Noncardiac Effects of Sympathomimetics

Adrenoceptors are distributed in virtually all organ systems. This section focuses on the activation of adrenoceptors that are responsible for the therapeutic effects of sympathomimetics or that explain their adverse effects. A more detailed description of the therapeutic use of sympathomimetics is given later in this chapter.

Activation of β_2 receptors in **bronchial smooth muscle** leads to bronchodilation, and β_2 agonists are important in the treatment of asthma (see Chapter 20 and Table 9–3).

In the **eye,** the radial pupillary dilator muscle of the iris contains α receptors; activation by drugs such as phenylephrine causes mydriasis (see Figure 6–9). Alpha stimulants also have important effects on intraocular pressure. Alpha agonists increase the outflow of aqueous humor from the eye and can be used clinically to reduce intraocular pressure. In contrast, β agonists have little effect, but β *antagonists* decrease the production of aqueous humor. These effects are important in the treatment of glaucoma (see Chapter 10), a leading cause of blindness.

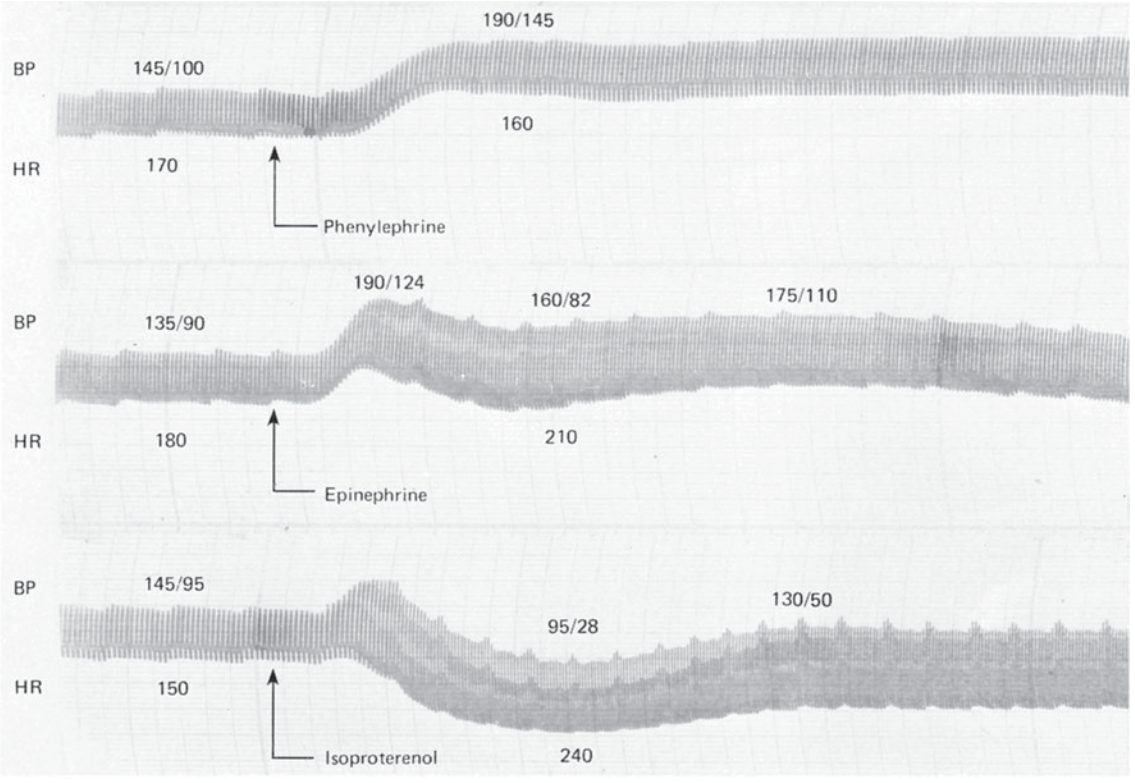

FIGURE 9–6 Effects of an α-selective (phenylephrine), β-selective (isoproterenol), and nonselective (epinephrine) sympathomimetic, given as an intravenous bolus injection to a dog. Reflexes are blunted but not eliminated in this anesthetized animal. BP, blood pressure; HR, heart rate.

In **genitourinary** organs, the bladder base, urethral sphincter, and prostate contain α receptors that mediate contraction and therefore promote urinary continence. The specific subtype of α_1 receptor involved in mediating constriction of the bladder base and prostate is uncertain, but α_{1A} receptors probably play an important role. This effect explains why urinary retention is a potential adverse effect of administration of the α_1 agonist midodrine.

Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation. The detumescence of erectile tissue that normally follows ejaculation is also brought about by norepinephrine (and possibly neuropeptide Y) released from sympathetic nerves. Alpha activation appears to have a similar detumescent effect on erectile tissue in female animals.

The **salivary glands** contain adrenoceptors that regulate the secretion of amylase and water. However, certain sympathomimetic drugs, eg, clonidine, produce symptoms of dry mouth. The mechanism of this effect is uncertain; it is likely that central nervous system effects are responsible, although peripheral effects may contribute.

The **apocrine sweat glands,** located on the palms of the hands and a few other areas, respond to adrenoceptor stimulants with increased sweat production. These are the apocrine nonthermoregulatory glands usually associated with psychological stress. (The diffusely distributed thermoregulatory eccrine sweat glands are regulated by *sympathetic cholinergic* postganglionic nerves that activate muscarinic cholinoceptors; see Chapter 6.)

Sympathomimetic drugs have important effects on intermediary **metabolism.** Activation of β adrenoceptors in fat cells leads to increased lipolysis with enhanced release of free fatty acids and glycerol into the blood. $Beta_3$ adrenoceptors play a role in mediating this response in animals, but their role in humans is probably minor. Human fat cells also contain α_2 receptors that inhibit lipolysis by decreasing intracellular cAMP. Sympathomimetic drugs enhance glycogenolysis in the liver, which leads to increased glucose release into the circulation. In the human liver, the effects of catecholamines are probably mediated mainly by β receptors, though α_1 receptors may also play a role. Catecholamines in high concentration may also cause metabolic acidosis. Activation of β_2 adrenoceptors by endogenous epinephrine or by sympathomimetic drugs promotes the uptake of potassium into cells, leading to a fall in extracellular potassium. This may result in a fall in the plasma potassium concentration during stress or protect against a rise in plasma potassium during exercise. Blockade of these receptors may accentuate the rise in plasma potassium that occurs during exercise. On the other hand, epinephrine has been used to treat hyperkalemia in certain conditions, but other alternatives are more commonly used. Beta receptors and α_2 receptors that are expressed in pancreatic islets tend to increase and decrease insulin secretion, respectively, although the major regulator of insulin release is the plasma concentration of glucose.

Catecholamines are important endogenous regulators of **hormone secretion** from a number of glands. As mentioned above,

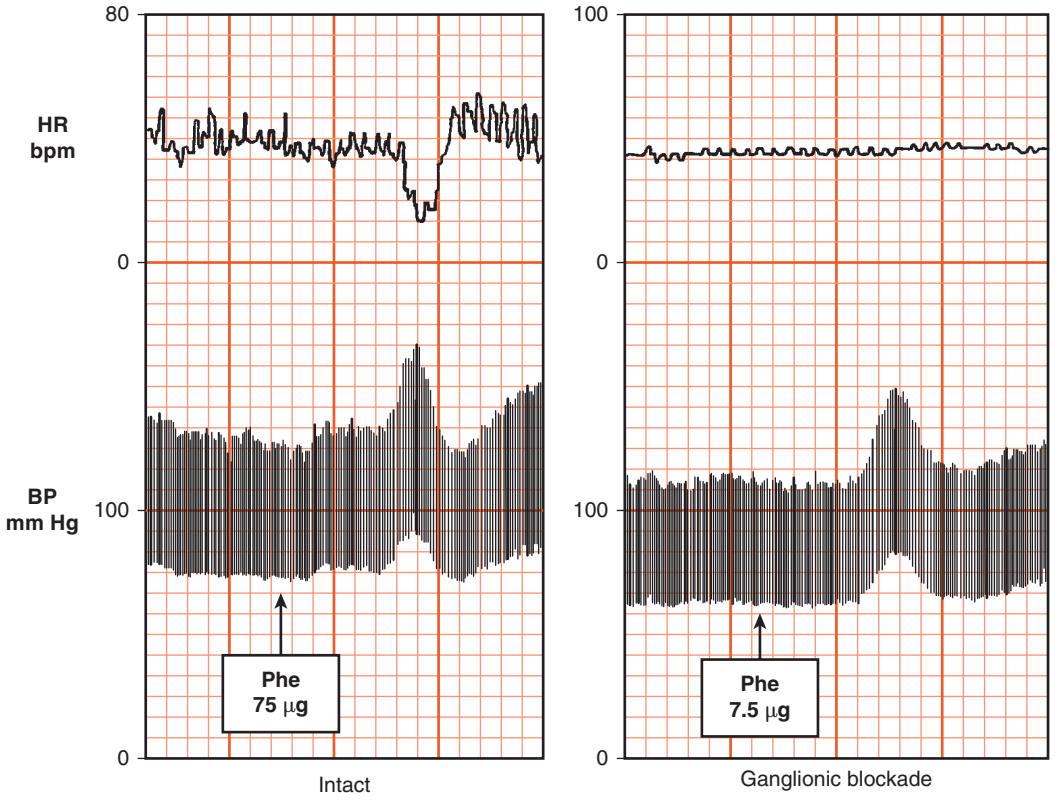

FIGURE 9–7 Effects of ganglionic blockade on the response to phenylephrine (Phe) in a human subject. **Left:** The cardiovascular effect of the selective α agonist phenylephrine when given as an intravenous bolus to a subject with intact autonomic baroreflex function. Note that the increase in blood pressure (BP) is associated with a baroreflex-mediated compensatory decrease in heart rate (HR). **Right:** The response in the same subject after autonomic reflexes were abolished by the ganglionic blocker trimethaphan. Note that resting blood pressure is decreased and heart rate is increased by trimethaphan because of sympathetic and parasympathetic withdrawal (HR scale is different). In the absence of baroreflex buffering, approximately a tenfold lower dose of phenylephrine is required to produce a similar increase in blood pressure. Note also the lack of compensatory decrease in heart rate.

insulin secretion is stimulated by β receptors and inhibited by α_2 receptors. Similarly, renin secretion is stimulated by β_1 and inhibited by α_2 receptors; indeed, β-receptor antagonist drugs may lower blood pressure in patients with hypertension at least in part by lowering plasma renin. Adrenoceptors also modulate the secretion of parathyroid hormone, calcitonin, thyroxine, and gastrin; however, the physiologic significance of these control mechanisms is probably limited. In high concentrations, epinephrine and related agents cause leukocytosis, in part by promoting demargination of sequestered white blood cells back into the general circulation.

The action of sympathomimetics on the **central nervous system** varies dramatically, depending on their ability to cross the blood-brain barrier. The catecholamines are almost completely excluded by this barrier, and subjective CNS effects are noted only at the highest rates of infusion. These effects have been described as ranging from "nervousness" to "an adrenaline rush" or "a feeling of impending disaster." Furthermore, peripheral effects of β-adrenoceptor agonists such as tachycardia and tremor are similar to the somatic manifestations of anxiety. In contrast, noncatecholamines with indirect actions, such as amphetamines, which readily enter the central nervous system from the circulation, produce qualitatively very different CNS effects. These actions vary from mild alerting, with improved attention to boring tasks; through elevation of mood, insomnia, euphoria, and anorexia; to full-blown psychotic behavior. These effects are not readily assigned to either α- or β-mediated actions and may represent enhancement of dopamine-mediated processes or other effects of these drugs in the CNS.

SPECIFIC SYMPATHOMIMETIC DRUGS

Endogenous Catecholamines

Epinephrine (adrenaline) is an agonist at both α and β receptors. It is therefore a very potent vasoconstrictor and cardiac stimulant. The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly β_1 receptors) and the vasoconstriction induced in many vascular beds (α receptors). Epinephrine also activates β_2 receptors in some vessels (eg, skeletal muscle blood vessels), leading to their dilation. Consequently, total peripheral resistance may actually fall, explaining

the fall in diastolic pressure that is sometimes seen with epinephrine injection (Figure 9–6; Table 9–4). Activation of β_2 receptors in skeletal muscle contributes to increased blood flow during exercise. Under physiologic conditions, epinephrine functions largely as a hormone; after release from the adrenal medulla into the blood, it acts on distant cells.

Norepinephrine (levarterenol, noradrenaline) is an agonist at both α_1 and α_2 receptors. Norepinephrine also activates β_1 receptors with similar potency as epinephrine, but has relatively little effect on β_2 receptors. Consequently, norepinephrine increases peripheral resistance and both diastolic and systolic blood pressure. Compensatory baroreflex activation tends to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained.

Dopamine is the immediate precursor in the synthesis of norepinephrine (see Figure 6–5). Its cardiovascular effects were described above. Endogenous dopamine may have more important effects in regulating sodium excretion and renal function. It is an important neurotransmitter in the central nervous system and is involved in the reward stimulus relevant to addiction. Its deficiency in the basal ganglia leads to Parkinson's disease, which is treated with its precursor levodopa. Dopamine receptors are also targets for antipsychotic drugs.

Direct-Acting Sympathomimetics

Phenylephrine was discussed previously when describing the actions of a relatively pure α_1 agonist (Table 9–2). Because it is not a catechol derivative (Figure 9–4), it is not inactivated by COMT and has a longer duration of action than the catecholamines. It is an effective mydriatic and decongestant and can be used to raise the blood pressure (Figure 9–6).

Midodrine is a prodrug that is enzymatically hydrolyzed to desglymidodrine, a selective α_1-receptor agonist. The peak concentration of desglymidodrine is achieved about 1 hour after midodrine is administered. The primary indication for midodrine is the treatment of orthostatic hypotension, typically due to impaired autonomic nervous system function. Although the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, it may cause hypertension when the subject is supine. The Food and Drug Administration considered withdrawing approval of this drug in 2010 because required postapproval studies that verify the clinical benefit of the drug had not been done. Action was suspended in response to prescriber and patient requests.

Methoxamine acts pharmacologically like phenylephrine, since it is predominantly a direct-acting α_1-receptor agonist. It may cause a prolonged increase in blood pressure due to vasoconstriction; it also causes a vagally mediated bradycardia. Methoxamine is available for parenteral use, but clinical applications are rare and limited to hypotensive states.

Alpha$_2$-selective agonists have an important ability to decrease blood pressure through actions in the central nervous system even though direct application to a blood vessel may cause vasoconstriction. Such drugs (eg, **clonidine, methyldopa, guanfacine, guanabenz**) are useful in the treatment of hypertension (and some other conditions) and are discussed in Chapter 11. Sedation is a recognized side effect of these drugs, and newer α_2-agonists (with activity also at imidazoline receptors) with fewer central nervous system side effects are available outside the USA for the treatment of hypertension (**moxonidine,** rilmenidine). On the other hand, the primary indication of **dexmedetomidine** is for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. It also reduces the requirements for opioids in pain control. Finally, **tizanidine** is used as a central muscle relaxant.

Xylometazoline and **oxymetazoline** are direct-acting α agonists. These drugs have been used as topical decongestants because of their ability to promote constriction of the nasal mucosa. When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect (see Chapter 11). Oxymetazoline has significant affinity for α_{2A} receptors.

Isoproterenol (isoprenaline) is a very potent β-receptor agonist and has little effect on α receptors. The drug has positive chronotropic and inotropic actions; because isoproterenol activates β receptors almost exclusively, it is a potent vasodilator. These actions lead to a marked increase in cardiac output associated with a fall in diastolic and mean arterial pressure and a lesser decrease or a slight increase in systolic pressure (Table 9–4; Figure 9–6).

Beta-selective agonists are very important because the separation of β_1 and β_2 effects (Table 9–2), although incomplete, is sufficient to reduce adverse effects in several clinical applications.

Beta$_1$-selective agents include **dobutamine** and a partial agonist, **prenalterol** (Figure 9–8). Because they are less effective in activating vasodilator β_2 receptors, they may increase cardiac output with less reflex tachycardia than occurs with nonselective β agonists such as isoproterenol. **Dobutamine** was initially considered a relatively β_1-selective agonist, but its actions are more complex. Its chemical structure resembles dopamine, but its actions are mediated mostly by activation of α and β receptors. Clinical preparations of dobutamine are a racemic mixture of (–) and (+) isomers, each with contrasting activity at α_1 and α_2 receptors. The (+) isomer is a potent β_1 agonist and an α_1-receptor antagonist. The (–) isomer is a potent α_1 agonist, which is capable of causing significant vasoconstriction when given alone. The resultant cardiovascular effects of dobutamine reflect this complex pharmacology. Dobutamine has a positive inotropic action caused by the isomer with predominantly β-receptor activity. It has relatively greater inotropic than chronotropic effect compared with isoproterenol. Activation of α_1 receptors probably explains why peripheral resistance does not decrease significantly.

Beta$_2$-selective agents have achieved an important place in the treatment of asthma and are discussed in Chapter 20. An additional application is to achieve uterine relaxation in premature labor (ritodrine; see below). Some examples of β_2-selective drugs currently in use are shown in Figures 9–8 and 20–4; many more are available or under investigation.

Mixed-Acting Sympathomimetics

Ephedrine occurs in various plants and has been used in China for over 2000 years; it was introduced into Western medicine in 1924 as the first orally active sympathomimetic drug. It is found

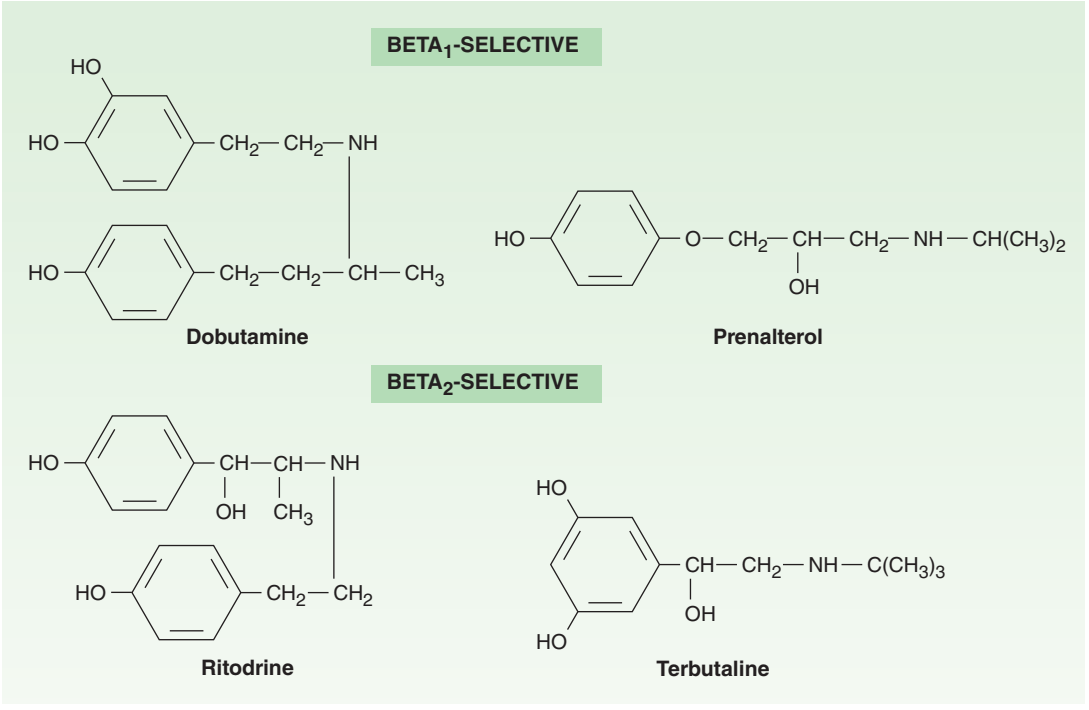

FIGURE 9–8 Examples of β_1- and β_2-selective agonists.

in ma huang, a popular herbal medication (see Chapter 64). Ma huang contains multiple ephedrine-like alkaloids in addition to ephedrine. Because ephedrine is a noncatechol phenylisopropylamine (Figure 9–5), it has high bioavailability and a relatively long duration of action—hours rather than minutes. As with many other phenylisopropylamines, a significant fraction of the drug is excreted unchanged in the urine. Since it is a weak base, its excretion can be accelerated by acidification of the urine.

Ephedrine has not been extensively studied in humans despite its long history of use. Its ability to activate β receptors probably accounted for its earlier use in asthma. Because it gains access to the central nervous system, it is a mild stimulant. Ingestion of ephedrine alkaloids contained in ma huang has raised important safety concerns. **Pseudoephedrine,** one of four ephedrine enantiomers, has been available over the counter as a component of many decongestant mixtures. However, the use of pseudoephedrine as a precursor in the illicit manufacture of methamphetamine has led to restrictions on its sale.

Phenylpropanolamine was a common component in over-the-counter appetite suppressants. It was removed from the market because its use was associated with hemorrhagic strokes in young women. The mechanism of this potential adverse effect is unknown, but the drug can increase blood pressure in patients with impaired autonomic reflexes.

Indirect-Acting Sympathomimetics

As noted previously, indirect-acting sympathomimetics can have one of two different mechanisms (Figure 9–3). First, they may enter the sympathetic nerve ending and displace stored catecholamine transmitter. Such drugs have been called amphetamine-like or "displacers." Second, they may inhibit the reuptake of released transmitter by interfering with the action of the norepinephrine transporter, NET.

A. Amphetamine-Like

Amphetamine is a racemic mixture of phenylisopropylamine (Figure 9–5) that is important chiefly because of its use and misuse as a central nervous system stimulant (see Chapter 32). Pharmacokinetically, it is similar to ephedrine; however, amphetamine even more readily enters the central nervous system, where it has marked stimulant effects on mood and alertness and a depressant effect on appetite. Its D-isomer is more potent than the L-isomer. Amphetamine's actions are mediated through the release of norepinephrine and, to some extent, dopamine.

Methamphetamine (*N*-methylamphetamine) is very similar to amphetamine with an even higher ratio of central to peripheral actions. **Phenmetrazine** is a variant phenylisopropylamine with amphetamine-like effects. It has been promoted as an anorexiant and is also a popular drug of abuse. **Methylphenidate** is an amphetamine variant whose major pharmacologic effects and abuse potential are similar to those of amphetamine. Methylphenidate may be effective in some children with attention deficit hyperactivity disorder (see Therapeutic Uses of Sympathomimetic Drugs). **Modafinil** is a psychostimulant that differs from amphetamine in structure, neurochemical profile, and behavioral effects. Its mechanism of action is not fully known. It

inhibits both norepinephrine and dopamine transporters, and it increases synaptic concentrations not only of norepinephrine and dopamine, but also of serotonin and glutamate, while decreasing GABA levels. It is used primarily to improve wakefulness in narcolepsy and some other conditions. It is often associated with increases in blood pressure and heart rate, though these are usually mild (see Therapeutic Uses of Sympathomimetic Drugs).

Tyramine (see Figure 6–5) is a normal by product of tyrosine metabolism in the body and can be produced in high concentrations in protein-rich foods by decarboxylation of tyrosine during fermentation (Table 9–5). It is readily metabolized by MAO in the liver and is normally inactive when taken orally because of a very high first-pass effect, ie, low bioavailability. If administered parenterally, it has an indirect sympathomimetic action caused by the release of stored catecholamines. Consequently, tyramine's spectrum of action is similar to that of norepinephrine. In patients treated with MAO inhibitors—particularly inhibitors of the MAO-A isoform—this effect of tyramine may be greatly intensified, leading to marked increases in blood pressure. This occurs because of increased bioavailability of tyramine and increased neuronal stores of catecholamines. Patients taking MAO inhibitors must be very careful to avoid tyramine-containing foods. There are differences in the effects of various MAO inhibitors on tyramine bioavailability, and isoform-specific or reversible enzyme antagonists may be safer (see Chapters 28 and 30).

TABLE 9–5 Foods reputed to have a high content of tyramine or other sympathomimetic agents.

Food	Tyramine Content of an Average Serving
Beer	4–45 mg
Broad beans, fava beans	Negligible (but contains dopamine)
Cheese, natural or aged	Nil to 130 mg (cheddar, Gruyère, and Stilton especially high)
Chicken liver	Nil to 9 mg
Chocolate	Negligible (but contains phenylethylamine)
Sausage, fermented (eg, salami, pepperoni, summer sausage)	Nil to 74 mg
Smoked or pickled fish (eg, pickled herring)	Nil to 198 mg
Snails	(No data found)
Wine (red)	Nil to 3 mg
Yeast (eg, dietary brewer's yeast supplements)	2–68 mg

Note: In a patient taking an irreversible monoamine oxidase (MAO) inhibitor drug, 20–50 mg of tyramine in a meal may increase the blood pressure significantly (see also Chapter 30: Antidepressant Agents). Note that only cheese, sausage, pickled fish, and yeast supplements contain sufficient tyramine to be consistently dangerous. This does not rule out the possibility that some preparations of other foods might contain significantly greater than average amounts of tyramine. Amounts in mg as per regular food portion.

B. Catecholamine Reuptake Inhibitors

Many inhibitors of the amine transporters for norepinephrine, dopamine, and serotonin are used clinically. Although specificity is not absolute, some are highly selective for one of the transporters. Many antidepressants, particularly the older tricyclic antidepressants, can inhibit norepinephrine and serotonin reuptake to different degrees. This may lead to orthostatic tachycardia as a side effect. Some antidepressants of this class, particularly imipramine, can induce orthostatic hypotension presumably by their clonidine-like effect or by blocking α_1 receptors, but the mechanism remains unclear.

Atomoxetine is a selective inhibitor of the norepinephrine reuptake transporter. Its actions, therefore, are mediated by potentiation of norepinephrine levels in noradrenergic synapses. It is used in the treatment of attention deficit disorders (see below). Atomoxetine has surprisingly little cardiovascular effect because it has a clonidine-like effect in the central nervous system to decrease sympathetic outflow while at the same time potentiating the effects of norepinephrine in the periphery. However, it may increase blood pressure in some patients. Norepinephrine reuptake is particularly important in the heart, especially during sympathetic stimulation, and this explains why atomoxetine and other norepinephrine reuptake inhibitors frequently cause orthostatic tachycardia. **Reboxetine** has similar characteristics as atomoxetine. **Sibutramine** is a serotonin and norepinephrine reuptake inhibitor and was initially approved by the FDA as an appetite suppressant for long-term treatment of obesity. It has been taken off the market in the United States and several other countries because it has been associated with a small increase in cardiovascular events including strokes in patients with a history of cardiovascular disease, which outweighed the benefits gained by modest weight reduction. **Duloxetine** is a widely used antidepressant with balanced serotonin and norepinephrine reuptake inhibitory effects (see Chapter 30). Increased cardiovascular risk has not been reported with duloxetine. Duloxetine and **milnacipran,** another serotonin and norepinephrine transporter blocker, are approved for the treatment of pain in fibromyalgia (see Chapter 30).

Cocaine is a local anesthetic with a peripheral sympathomimetic action that results from inhibition of transmitter reuptake at noradrenergic synapses (Figure 9-3). It readily enters the central nervous system and produces an amphetamine-like psychological effect that is shorter lasting and more intense than amphetamine. The major action of cocaine in the central nervous system is to inhibit dopamine reuptake into neurons in the "pleasure centers" of the brain. These properties and the fact that a rapid onset of action can be obtained when smoked, snorted into the nose, or injected, has made cocaine a heavily abused drug (see Chapter 32). It is interesting that dopamine-transporter knockout mice still self-administer cocaine, suggesting that cocaine may have additional pharmacologic targets.

Dopamine Agonists

Levodopa, which is converted to dopamine in the body, and **dopamine agonists** with central actions are of considerable value in the treatment of Parkinson's disease and prolactinemia. These agents are discussed in Chapters 28 and 37.

Fenoldopam is a D_1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds. The primary indication for fenoldopam is in the intravenous treatment of severe hypertension (see Chapter 11).

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

Cardiovascular Applications

In keeping with the critical role of the sympathetic nervous system in the control of blood pressure, a major area of application of the sympathomimetics is in cardiovascular conditions.

A. Treatment of Acute Hypotension

Acute hypotension may occur in a variety of settings such as severe hemorrhage, decreased blood volume, cardiac arrhythmias, neurologic disease or accidents, adverse reactions or overdose of medications such as antihypertensive drugs, and infection. If cerebral, renal, and cardiac perfusion is maintained, hypotension itself does not usually require vigorous direct treatment. Rather, placing the patient in the recumbent position and ensuring adequate fluid volume while the primary problem is determined and treated is usually the correct course of action. The use of sympathomimetic drugs merely to elevate a blood pressure that is not an immediate threat to the patient may increase morbidity. Sympathomimetic drugs may be used in a hypotensive emergency to preserve cerebral and coronary blood flow. The treatment is usually of short duration while the appropriate intravenous fluid or blood is being administered. Direct-acting α agonists such as **norepinephrine, phenylephrine,** and **methoxamine** have been used in this setting when vasoconstriction is desired.

Shock is a complex acute cardiovascular syndrome that results in a critical reduction in perfusion of vital tissues and a wide range of systemic effects. Shock is usually associated with hypotension, an altered mental state, oliguria, and metabolic acidosis. If untreated, shock usually progresses to a refractory deteriorating state and death. The three major mechanisms responsible for shock are hypovolemia, cardiac insufficiency, and altered vascular resistance. Volume replacement and treatment of the underlying disease are the mainstays of the treatment of shock. Although sympathomimetic drugs have been used in the treatment of virtually all forms of shock, their efficacy is unclear.

In most forms of shock, intense vasoconstriction, mediated by reflex sympathetic nervous system activation, is present. Indeed, efforts aimed at reducing rather than increasing peripheral resistance may be more fruitful to improve cerebral, coronary, and renal perfusion. A decision to use vasoconstrictors or vasodilators is best made on the basis of information about the underlying cause. Their use may require invasive monitoring.

Cardiogenic shock and acute heart failure, usually due to massive myocardial infarction, has a poor prognosis. Mechanically assisted perfusion and emergency cardiac surgery have been utilized in some settings. Optimal fluid replacement requires monitoring of pulmonary capillary wedge pressure and other parameters of cardiac function. Positive inotropic agents such as dopamine or dobutamine may provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction. In low to moderate doses, these drugs may increase cardiac output and, compared with norepinephrine, cause relatively little peripheral vasoconstriction. Isoproterenol increases heart rate and work more than either dopamine or dobutamine. See Chapter 13 for a discussion of shock associated with myocardial infarction.

Unfortunately, the patient with shock may not respond to any of these therapeutic maneuvers; the temptation is then to use vasoconstrictors to maintain blood pressure. Coronary perfusion may be improved, but this gain may be offset by increased myocardial oxygen demands as well as more severe vasoconstriction in blood vessels to the abdominal viscera. Therefore, the goal of therapy in shock should be to optimize tissue perfusion, not blood pressure.

B. Chronic Orthostatic Hypotension

On standing, gravitational forces induce venous pooling, resulting in decreased venous return. Normally, a decrease in blood pressure is prevented by reflex sympathetic activation with increased heart rate, and peripheral arterial and venous vasoconstriction. Impairment of autonomic reflexes that regulate blood pressure can lead to chronic orthostatic hypotension. This is more often due to medications that can interfere with autonomic function (eg, imipramine and other tricyclic antidepressants, α blockers for the treatment of urinary retention, and diuretics) diabetes, and other diseases causing peripheral autonomic neuropathies, and less commonly, primary degenerative disorders of the autonomic nervous system, as in the case study described at the beginning of the chapter.

Increasing peripheral resistance is one of the strategies to treat chronic orthostatic hypotension, and drugs activating α receptors can be used for this purpose. Midodrine, an orally active α_1 agonist, is frequently used for this indication. Other sympathomimetics, such as oral ephedrine or phenylephrine, can be tried.

C. Cardiac Applications

Catecholamines such as isoproterenol and epinephrine have been used in the temporary emergency management of complete heart block and cardiac arrest. Epinephrine may be useful in cardiac arrest in part by redistributing blood flow during cardiopulmonary resuscitation to coronaries and to the brain. However, electronic pacemakers are both safer and more effective in heart block and should be inserted as soon as possible if there is any indication of continued high-degree block.

Dobutamine injection is used as a pharmacologic **cardiac stress test.** Dobutamine augments myocardial contractility and promotes coronary and systemic vasodilation. These actions lead to increased heart rate and increased myocardial work and can reveal areas of ischemia in the myocardium that are detected by echocardiogram or nuclear medicine techniques. Dobutamine is often used in patients unable to exercise during the stress test.

D. Inducing Local Vasoconstriction

Reduction of local or regional blood flow is desirable for achieving hemostasis in surgery, for reducing diffusion of local anesthetics

away from the site of administration, and for reducing mucous membrane congestion. In each instance, α-receptor activation is desired, and the choice of agent depends on the maximal efficacy required, the desired duration of action, and the route of administration.

Effective pharmacologic hemostasis, often necessary for facial, oral, and nasopharyngeal surgery, requires drugs of high efficacy that can be administered in high concentration by local application. Epinephrine is usually applied topically in nasal packs (for epistaxis) or in a gingival string (for gingivectomy). Cocaine is still sometimes used for nasopharyngeal surgery because it combines a hemostatic effect with local anesthesia. Occasionally, cocaine is mixed with epinephrine for maximum hemostasis and local anesthesia.

Combining α agonists with some local anesthetics greatly prolongs the duration of infiltration nerve block; the total dose of local anesthetic (and the probability of toxicity) can therefore be reduced. Epinephrine, 1:200,000, is the favored agent for this application, but norepinephrine, phenylephrine, and other α agonists have also been used. Systemic effects on the heart and peripheral vasculature may occur even with local drug administration but are usually minimal. Use of epinephrine with local anesthesia of acral vascular beds (digits, nose, and ears) has not been advised because of fear of ischemic necrosis. Recent studies suggest that it can be used (with caution) for this indication.

Mucous membrane decongestants are α agonists that reduce the discomfort of hay fever and, to a lesser extent, the common cold by decreasing the volume of the nasal mucosa. These effects are probably mediated by α_1 receptors. Unfortunately, rebound hyperemia may follow the use of these agents, and repeated topical use of high drug concentrations may result in ischemic changes in the mucous membranes, probably as a result of vasoconstriction of nutrient arteries. Constriction of these vessels may involve activation of α_2 receptors, and phenylephrine is often used in nasal decongestant sprays. A longer duration of action—at the cost of much lower local concentrations and greater potential for cardiac and central nervous system effects—can be achieved by the oral administration of agents such as ephedrine or one of its isomers, pseudoephedrine. Long-acting topical decongestants include xylometazoline and oxymetazoline. Most of these mucous membrane decongestants are available as over-the-counter products.

Pulmonary Applications

One of the most important uses of sympathomimetic drugs is in the therapy of bronchial asthma. Beta$_2$-selective drugs (albuterol, metaproterenol, terbutaline) are used for this purpose. Short-acting preparations can be used only transiently for acute treatment of asthma symptoms. For chronic asthma treatment in adults, long-acting β_2 agonists should only be used as an addition to steroids because they may increase morbidity if used alone. There is less agreement about their benefit in children. Long-acting β_2 agonists are also used in patients with chronic obstructive pulmonary disease (COPD). Nonselective drugs are now rarely used because they are likely to have more adverse effects than the selective drugs. The use of β agonists for the management of asthma is discussed in Chapter 20.

Anaphylaxis

Anaphylactic shock and related immediate (type I) IgE-mediated reactions affect both the respiratory and the cardiovascular systems. The syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of **epinephrine,** 0.3–0.5 mg (0.3–0.5 mL of a 1:1000 epinephrine solution). Intramuscular injection may be the preferred route of administration, since skin blood flow (and hence systemic drug absorption from subcutaneous injection) is unpredictable in hypotensive patients. In some patients with impaired cardiovascular function, intravenous injection of epinephrine may be required. Glucocorticoids and antihistamines (both H_1- and H_2-receptor antagonists) may be useful as secondary therapy in anaphylaxis. The use of these agents precedes the era of controlled clinical trials, but extensive experimental and clinical experience supports the use of epinephrine as the agent of choice in anaphylaxis, presumably because epinephrine activates α, β_1, and β_2 receptors, all of which may be important in reversing the pathophysiologic processes underlying anaphylaxis. It is recommended that patients at risk for insect sting hypersensitivity, severe food allergies, or other types of anaphylaxis carry epinephrine in an autoinjector (EpiPen) for self-administration.

Ophthalmic Applications

Phenylephrine is an effective mydriatic agent frequently used to facilitate examination of the retina. It is also a useful decongestant for minor allergic hyperemia and itching of the conjunctival membranes. Sympathomimetics administered as ophthalmic drops are also useful in localizing the lesion in Horner's syndrome. (See Box: An Application of Basic Pharmacology to a Clinical Problem.)

Glaucoma responds to a variety of sympathomimetic and sympathoplegic drugs. (See Box, The Treatment of Glaucoma, in Chapter 10.) Epinephrine and its prodrug dipivefrin are now rarely used, but β-blocking agents are among the most important therapies. **Apraclonidine** and **brimonidine** are α_2-selective agonists that also lower intraocular pressure and are approved for use in glaucoma. The mechanism of action of these drugs in treating glaucoma is still uncertain; direct neuroprotective effects may be involved in addition to the benefits of lowering intraocular pressure.

Genitourinary Applications

As noted above, β_2-selective agents relax the pregnant uterus. **Ritodrine, terbutaline,** and similar drugs have been used to suppress premature labor. The goal is to defer labor long enough to ensure adequate maturation of the fetus. These drugs may delay labor for several days. This may afford time to administer corticosteroid drugs, which decrease the incidence of neonatal respiratory distress syndrome. However, meta-analysis of older trials and a randomized study suggest that β-agonist therapy may have no significant benefit on perinatal infant mortality and may increase maternal morbidity.

Oral sympathomimetic therapy is occasionally useful in the treatment of stress incontinence. Ephedrine or pseudoephedrine may be tried.

An Application of Basic Pharmacology to a Clinical Problem

Horner's syndrome is a condition—usually unilateral—that results from interruption of the sympathetic nerves to the face. The effects include vasodilation, ptosis, miosis, and loss of sweating on the affected side. The syndrome can be caused by either a preganglionic or a postganglionic lesion, such as a tumor. Knowledge of the location of the lesion (preganglionic or postganglionic) helps determine the optimal therapy.

A localized lesion in a nerve causes degeneration of the distal portion of that fiber and loss of transmitter contents from the degenerated nerve ending—without affecting neurons innervated by the fiber. Therefore, a preganglionic lesion leaves the postganglionic adrenergic neuron intact, whereas a postganglionic lesion results in degeneration of the adrenergic nerve endings and loss of stored catecholamines from them. Because indirectly acting sympathomimetics require normal stores of catecholamines, such drugs can be used to test for the presence of normal adrenergic nerve endings. The iris, because it is easily visible and responsive to topical sympathomimetics, is a convenient assay tissue in the patient.

If the lesion of Horner's syndrome is postganglionic, indirectly acting sympathomimetics (eg, cocaine, hydroxyamphetamine) will not dilate the abnormally constricted pupil because catecholamines have been lost from the nerve endings in the iris. In contrast, the pupil dilates in response to phenylephrine, which acts directly on the α receptors on the smooth muscle of the iris. A patient with a preganglionic lesion, on the other hand, shows a normal response to both drugs, since the postganglionic fibers and their catecholamine stores remain intact in this situation.

Central Nervous System Applications

The amphetamines have a mood-elevating (euphoriant) effect; this effect is the basis for the widespread abuse of this drug group (see Chapter 32). The amphetamines also have an alerting, sleep-deferring action that is manifested by improved attention to repetitive tasks and by acceleration and desynchronization of the electroencephalogram. A therapeutic application of this effect is in the treatment of narcolepsy. **Modafinil,** a new amphetamine substitute, is approved for use in narcolepsy and is claimed to have fewer disadvantages (excessive mood changes, insomnia, and abuse potential) than amphetamine in this condition. The appetite-suppressing effect of these agents is easily demonstrated in experimental animals. In obese humans, an encouraging initial response may be observed, but there is no evidence that long-term improvement in weight control can be achieved with amphetamines alone, especially when administered for a relatively short course. A final application of the central nervous system-active sympathomimetics is in the attention deficit hyperactivity disorder (ADHD), a behavioral syndrome consisting of short attention span, hyperkinetic physical behavior, and learning problems. Some patients with this syndrome respond well to low doses of **methylphenidate** and related agents. Extended-release formulations of methylphenidate may simplify dosing regimens and increase adherence to therapy, especially in school-age children. Slow or continuous-release preparations of the α_2 agonists clonidine and guanfacine are also effective in children with ADHD. Clinical trials suggest that modafinil may also be useful in ADHD, but because the safety profile in children has not been defined, it has not gained approval by the FDA for this indication.

Additional Therapeutic Uses

Although the primary use of the α_2 agonist **clonidine** is in the treatment of hypertension (see Chapter 11), the drug has been found to have efficacy in the treatment of diarrhea in diabetics with autonomic neuropathy, perhaps because of its ability to enhance salt and water absorption from the intestine. In addition, clonidine has efficacy in diminishing craving for narcotics and alcohol during withdrawal and may facilitate cessation of cigarette smoking. Clonidine has also been used to diminish menopausal hot flushes and is being used experimentally to reduce hemodynamic instability during general anesthesia. **Dexmedetomidine** is an α_2 agonist used for sedation under intensive care circumstances and during anesthesia (see Chapter 25). It blunts the sympathetic response to surgery, which may be beneficial in some situations. It lowers opioid requirements for pain control and does not depress ventilation. Clonidine is also sometimes used as a premedication before anesthesia. **Tizanidine** is an α_2 agonist that is used as a muscle relaxant (see Chapter 27).

SUMMARY Sympathomimetic Drugs

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α_1 AGONISTS				
• Midodrine	Activates phospholipase C, resulting in increased intracellular calcium and vasoconstriction	Vascular smooth muscle contraction increasing blood pressure (BP)	Orthostatic hypotension	Oral • prodrug converted to active drug with a 1-h peak effect • *Toxicity:* Supine hypertension, piloerection (goose bumps), and urinary retention
• *Phenylephrine: Can be used IV for short-term maintenance of BP in acute hypotension and intranasally to produce local vasoconstriction as a decongestant*				
α_2 AGONISTS				
• Clonidine	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Vasoconstriction is masked by central sympatholytic effect, which lowers BP	Hypertension	Oral • transdermal • peak effect 1–3 h • half-life of oral drug ~12 h • produces dry mouth and sedation
• *α-Methyldopa, guanfacine, and guanabenz: Also used as central sympatholytics*				
• *Dexmedetomidine: Prominent sedative effects and used in anesthesia*				
• *Tizanidine: Used as a muscle relaxant*				
• *Apraclonidine and brimonidine: Used in glaucoma to reduce intraocular pressure*				
β_1 AGONISTS				
• Dobutamine[1]	Activates adenylyl cyclase, increasing myocardial contractility	Positive inotropic effect	Cardiogenic shock, acute heart failure	IV • requires dose titration to desired effect
B_2 AGONISTS				
• Albuterol	Activates adenylyl cyclase	Bronchial smooth muscle dilation	Asthma	Inhalation • duration 4–6 h • *Toxicity:* Tremor, tachycardia
• *See other β_2 agonists in Chapter 20*				
DOPAMINE				
D_1 Agonists				
• Fenoldopam	Activates adenylyl cyclase	Vascular smooth muscle relaxation	Hypertension	Requires dose titration to desired effect
D_2 Agonists				
• Bromocriptine	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Mimics dopamine actions in the central nervous system	Parkinson's disease, prolactinemia	Oral • *Toxicity:* Nausea, headache, orthostatic hypotension
• *See other D_2 agonists in Chapters 28 and 37*				

[1] *Dobutamine has other actions in addition to β_1-agonist effect. See text for details.*

PREPARATIONS AVAILABLE[1]

Amphetamine, racemic mixture (generic)
(attention deficit hyperactivity disorder [ADHD], narcolepsy)
Oral: 5, 10 mg tablets
Oral (Adderall): 1:1:1:1 mixtures of amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine saccharate, formulated to contain a total of 5, 7.5, 10, 12.5, 15, 20, or 30 mg in tablets; or 10, 20, or 30 mg in capsules

Apraclonidine (Iopidine)
(glaucoma)
Topical: 0.5, 1% ophthalmic solutions

Armodafinil (Nuvigil)
(narcolepsy)
Oral: 50, 150, 250 mg tablets

Brimonidine (Alphagan)
(glaucoma)
Topical: 0.15, 0.2% ophthalmic solution

Dexmedetomidine (Precedex)
(sedation)
Parenteral: 100 mcg/mL

Dexmethylphenidate (Focalin)
(ADHD)
Oral: 2.5, 5, 10 mg tablets
Oral sustained release: 5, 10, 15, 20, 30 mg capsules

Dextroamphetamine (generic, Dexedrine)
(ADHD, narcolepsy)
Oral: 5, 10 mg tablets
Oral sustained release: 5, 10, 15 mg capsules
Oral mixtures with amphetamine: see Amphetamine (Adderall)

Dobutamine (generic, Dobutrex)
(hypotension)
Parenteral: 12.5 mg/mL in 20 mL vials for injection

Dopamine (generic, Intropin)
(hypotension)
Parenteral: 40, 80, 160 mg/mL for injection; 80, 160, 320 mg/100 mL in 5% D/W for injection

Ephedrine (generic)
(hypotension, asthma)
Oral: 25 mg capsules
Parenteral: 50 mg/mL for injection

Epinephrine (generic, Adrenalin Chloride, others)
(anaphylaxis, hypotension, asthma)
Parenteral: 1:1000 (1 mg/mL), 1:2000 (0.5 mg/mL), 1:10,000 (0.1 mg/mL), 1:100,000 (0.01 mg/mL) for injection
Parenteral autoinjector (EpiPen): 1:1000 (1 mg/mL), 1:2000 (0.5 mg/mL)
Ophthalmic: 0.1, 0.5, 1, 2% drops
Nasal: 0.1% drops and spray
Aerosol for bronchospasm (Primatene Mist, Bronkaid Mist): 0.22 mg/spray
Solution for nebulizer aerosol: 1:100

Fenoldopam (Corlopam)
(hypertension)
Parenteral: 10 mg/mL for IV infusion

Hydroxyamphetamine (Paremyd)
(mydriatic)
Ophthalmic: 1% drops (includes 0.25% tropicamide)

Isoproterenol (generic, Isuprel)
(bradycardia)
Parenteral: 1:5000 (0.2 mg/mL), 1:50,000 (0.02 mg/mL) for injection

Metaraminol (Aramine)
(hypotension)
Parenteral: 10 mg/mL for injection

Methamphetamine (Desoxyn)
(ADHD)
Oral: 5 mg tablets

Methylphenidate (generic, Ritalin, Ritalin-SR)
(ADHD, narcolepsy)
Oral: 5, 10, 20 mg tablets
Oral sustained release: 10, 18, 20, 27, 36, 54 mg tablets; 20, 30, 40 mg capsules

Midodrine (ProAmatine)
(hypotension)
Oral: 2.5, 5, 10 mg tablets

Modafinil (Provigil)
(narcolepsy)
Oral: 100, 200 mg tablets

Naphazoline (generic, Privine)
(decongestant)
Nasal: 0.05% drops and spray
Ophthalmic: 0.012, 0.02, 0.03, 0.1% drops

Norepinephrine (generic, Levophed)
(hypotension)
Parenteral: 1 mg/mL for injection

Oxymetazoline (generic, Afrin, Neo-Synephrine 12 Hour, Visine LR)
(decongestant)
Nasal: 0.05% spray
Ophthalmic: 0.025% drops

Phenylephrine (generic, Neo-Synephrine)
(hypotension, decongestant)
Oral: 10 mg chewable tablets
Parenteral: 10 mg/mL for injection
Nasal: 0.125, 0.16, 0.25, 0.5, 1% drops and spray
Ophthalmic: 0.12, 2.5, 10% solution

Pseudoephedrine (generic, Sudafed)
(decongestant)
Oral: 30, 60 mg tablets; 30, 60 mg capsules; 15, 30 mg/5 mL syrups; 7.5 mg/0.8 mL drops
Oral extended release: 120, 240 mg tablets, capsules

Tetrahydrozoline (generic, Visine)
(decongestant)
Nasal: 0.05, 0.1% drops
Ophthalmic: 0.05% drops

Tizanidine (Zanaflex)
(muscle relaxant)
Oral: 2, 4, 6 mg capsules; 2, 4 mg tablets

Xylometazoline (generic, Otrivin)
(decongestant)
Nasal: 0.05, 0.1% drops

[1]Primary clinical indications are given in parentheses. α_2 agonists used in hypertension are listed in Chapter 11. β_2 Agonists used in asthma are listed in Chapter 20. Norepinephrine transporter inhibitors are listed in Chapter 30. The primary clinical indications are given in parentheses.

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CASE STUDY ANSWER

The clinical picture is that of autonomic failure. The best indicator of this is the profound drop in orthostatic blood pressure without an adequate compensatory increase in heart rate. Pure autonomic failure is a neurodegenerative disorder selectively affecting peripheral autonomic fibers. Patients' blood pressure is critically dependent on whatever residual sympathetic tone they have, hence the symptomatic worsening of orthostatic hypotension that occurred when this patient was given the α blocker tamsulosin. Conversely, these patients are hypersensitive to the pressor effects of α agonists and other sympathomimetics. For example, the α agonist midodrine can increase blood pressure significantly at doses that have no effect in normal subjects and can be used to treat their orthostatic hypotension. Caution should be observed in the use of sympathomimetics (including over-the-counter agents) and sympatholytic drugs.

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CHAPTER

10

Adrenoceptor Antagonist Drugs

David Robertson, MD, & Italo Biaggioni, MD*

CASE STUDY

A 46-year-old woman sees her physician because of palpitations and headaches. She enjoyed good health until 1 year ago when spells of rapid heartbeat began. These became more severe and were eventually accompanied by throbbing headaches and drenching sweats. Physical examination revealed a blood pressure of 150/90 mm Hg and heart rate of 88 bpm. During the physical examination, palpation of the abdomen elicited a sudden and typical episode, with a rise in blood pressure to 210/120 mm Hg, heart rate to 122 bpm, profuse sweating, and facial pallor. This was accompanied by severe headache. What is the likely cause of her episodes? What caused the blood pressure and heart rate to rise so high during the examination? What treatments might help this patient?

Catecholamines play a role in many physiologic and pathophysiologic responses as described in Chapter 9. Drugs that block their receptors therefore have important effects, some of which are of great clinical value. These effects vary dramatically according to the drug's selectivity for α and β receptors. The classification of adrenoceptors into α_1, α_2, and β subtypes and the effects of activating these receptors are discussed in Chapters 6 and 9. Blockade of peripheral dopamine receptors is of minor clinical importance at present. In contrast, blockade of central nervous system dopamine receptors is very important; drugs that act on these receptors are discussed in Chapters 21 and 29. This chapter deals with pharmacologic antagonist drugs whose major effect is to occupy α_1, α_2, or β receptors outside the central nervous system and prevent their activation by catecholamines and related agonists.

For pharmacologic research, α_1- and α_2-adrenoceptor antagonist drugs have been very useful in the experimental exploration of autonomic nervous system function. In clinical therapeutics, nonselective α antagonists are used in the treatment of pheochromocytoma (tumors that secrete catecholamines), and α_1-selective antagonists are used in primary hypertension and benign prostatic hyperplasia. Beta-receptor antagonist drugs are useful in a much wider variety of clinical conditions and are firmly established in the treatment of hypertension, ischemic heart disease, arrhythmias, endocrinologic and neurologic disorders, glaucoma, and other conditions.

*The authors thank Dr Randy Blakely for helpful comments, Dr Brett English for improving tables, and our students at Vanderbilt for advice on conceptual clarity.

BASIC PHARMACOLOGY OF THE ALPHA-RECEPTOR ANTAGONIST DRUGS

Mechanism of Action

Alpha-receptor antagonists may be reversible or irreversible in their interaction with these receptors. Reversible antagonists dissociate from receptors, and the block can be surmounted with sufficiently high concentrations of agonists; irreversible drugs do not dissociate and cannot be surmounted. Phentolamine and prazosin (Figure 10–1) are examples of reversible antagonists. These drugs and labetalol—drugs used primarily for their antihypertensive effects—as well as several ergot derivatives (see Chapter 16) are also reversible α-adrenoceptor antagonists or partial agonists. Phenoxybenzamine, an agent related to the nitrogen mustards,

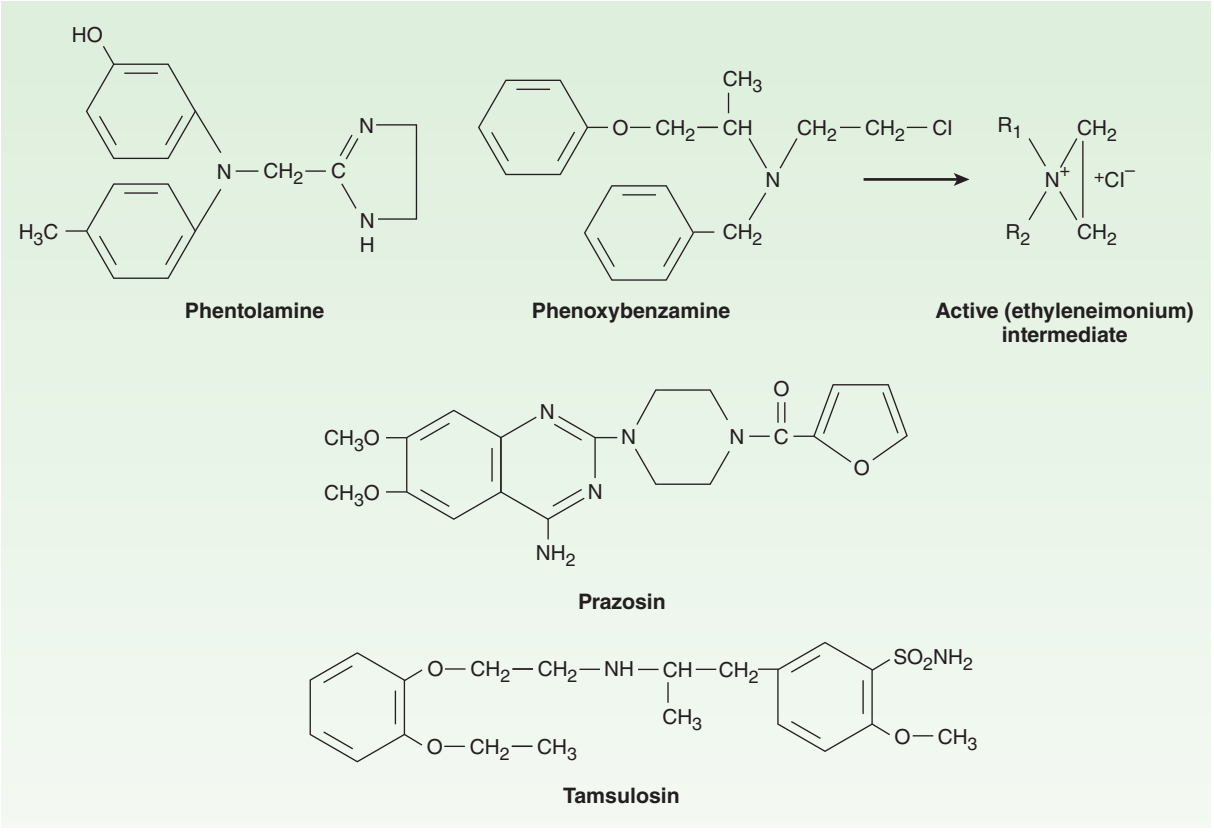

FIGURE 10–1 Structure of several α-receptor–blocking drugs.

forms a reactive ethyleneimonium intermediate (Figure 10–1) that covalently binds to α receptors, resulting in irreversible blockade. Figure 10–2 illustrates the effects of a reversible drug in comparison with those of an irreversible agent.

As discussed in Chapters 1 and 2, the duration of action of a reversible antagonist is largely dependent on the half-life of the drug in the body and the rate at which it dissociates from its receptor: The shorter the half-life of the drug in the body, the less time it takes for the effects of the drug to dissipate. In contrast, the effects of an irreversible antagonist may persist long after the drug has been cleared from the plasma. In the case of phenoxybenzamine, the restoration of tissue responsiveness after extensive α-receptor blockade is dependent on synthesis of new receptors, which may take several days. The rate of return of α_1-adrenoceptor responsiveness may be particularly important in patients having a sudden cardiovascular event or who become candidates for urgent surgery.

Pharmacologic Effects

A. Cardiovascular Effects

Because arteriolar and venous tone are determined to a large extent by α receptors on vascular smooth muscle, α-receptor antagonist drugs cause a lowering of peripheral vascular resistance and blood pressure (Figure 10–3). These drugs can prevent the pressor effects of usual doses of α agonists; indeed, in the case of agonists with both α and β_2 effects (eg, epinephrine), selective α-receptor antagonism may convert a pressor to a depressor response (Figure 10–3). This change in response is called **epinephrine reversal;** it illustrates how the activation of both α and β receptors in the vasculature may lead to opposite responses. Alpha-receptor antagonists often cause orthostatic hypotension and reflex tachycardia; nonselective ($\alpha_1 = \alpha_2$, Table 10–1) blockers usually cause significant tachycardia if blood pressure is lowered below normal. Orthostatic hypotension is due to antagonism of sympathetic nervous system stimulation of α_1 receptors in vascular smooth muscle; contraction of veins is an important component of the normal capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery. Constriction of arterioles in the legs also contributes to the normal orthostatic response. Tachycardia may be more marked with agents that block α_2-presynaptic receptors in the heart, since the augmented release of norepinephrine will further stimulate β receptors in the heart.

B. Other Effects

Blockade of α receptors in other tissues elicits miosis (small pupils) and nasal stuffiness. $Alpha_1$ receptors are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine. Alpha blockers, therefore, are used

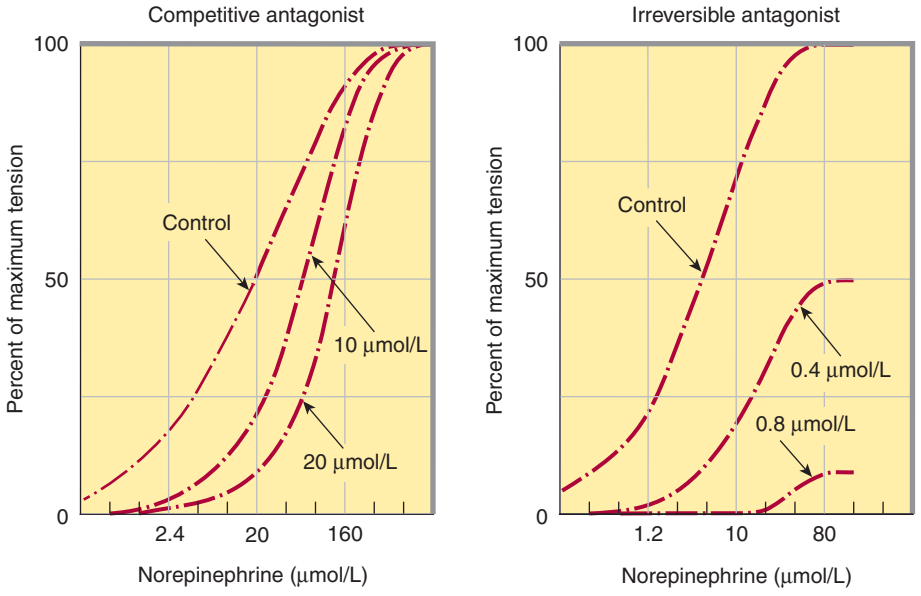

FIGURE 10–2 Dose-response curves to norepinephrine in the presence of two different α-adrenoceptor–blocking drugs. The tension produced in isolated strips of cat spleen, a tissue rich in α receptors, was measured in response to graded doses of norepinephrine. **Left:** Tolazoline, a reversible blocker, shifted the curve to the right without decreasing the maximum response when present at concentrations of 10 and 20 µmol/L. **Right:** Dibenamine, an analog of phenoxybenzamine and irreversible in its action, reduced the maximum response attainable at both concentrations tested. (Modified and reproduced, with permission, from Bickerton RK: The response of isolated strips of cat spleen to sympathomimetic drugs and their antagonists. J Pharmacol Exp Ther 1963;142:99.)

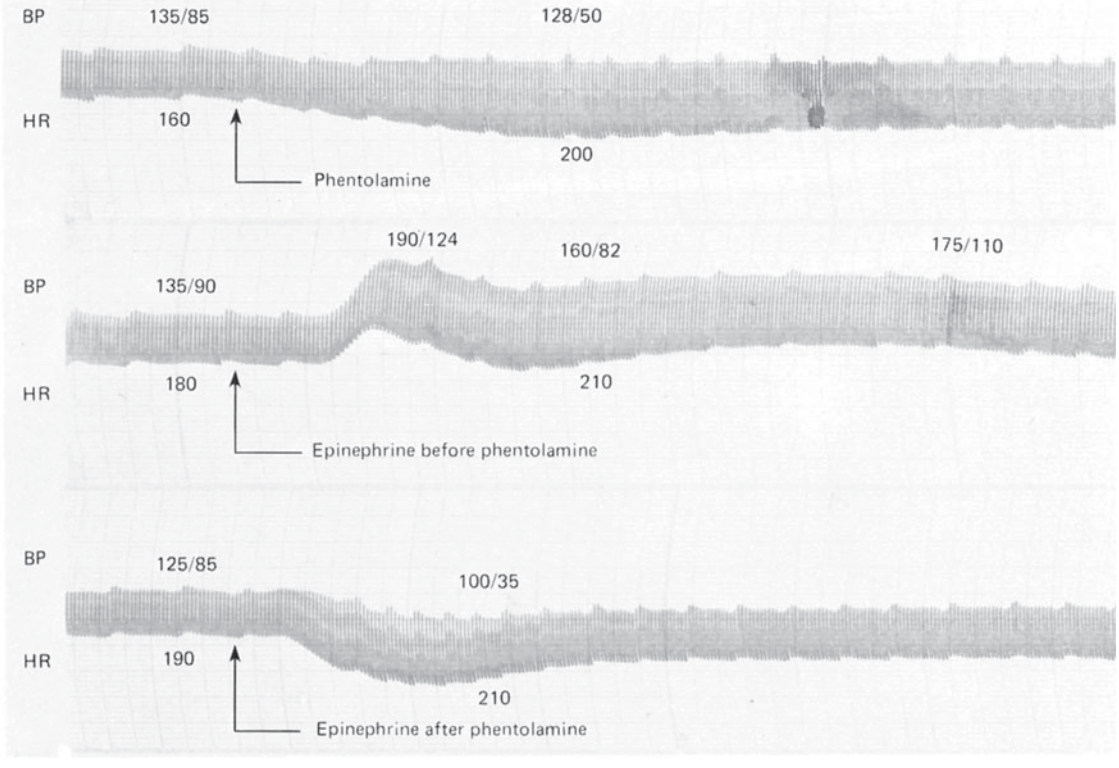

FIGURE 10–3 **Top:** Effects of phentolamine, an α-receptor–blocking drug, on blood pressure in an anesthetized dog. Epinephrine reversal is demonstrated by tracings showing the response to epinephrine before **(middle)** and after **(bottom)** phentolamine. All drugs given intravenously. BP, blood pressure; HR, heart rate.

TABLE 10–1 Relative selectivity of antagonists for adrenoceptors.

	Receptor Affinity
Alpha antagonists	
Prazosin, terazosin, doxazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Yohimbine, tolazoline	$\alpha_2 >> \alpha_1$
Mixed antagonists	
Labetalol, carvedilol	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$
Beta antagonists	
Metoprolol, acebutolol, alprenolol, atenolol, betaxolol, celiprolol, esmolol, nebivolol	$\beta_1 >>> \beta_2$
Propranolol, carteolol, penbutolol, pindolol, timolol	$\beta_1 = \beta_2$
Butoxamine	$\beta_2 >>> \beta_1$

therapeutically for the treatment of urinary retention due to prostatic hyperplasia (see below). Individual agents may have other important effects in addition to α-receptor antagonism (see below).

SPECIFIC AGENTS

Phenoxybenzamine binds covalently to α receptors, causing irreversible blockade of long duration (14–48 hours or longer). It is somewhat selective for α_1 receptors but less so than prazosin (Table 10–1). The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. Phenoxybenzamine blocks histamine (H_1), acetylcholine, and serotonin receptors as well as α receptors (see Chapter 16).

The pharmacologic actions of phenoxybenzamine are primarily related to antagonism of α-receptor–mediated events. The most significant effect is attenuation of catecholamine-induced vasoconstriction. While phenoxybenzamine causes relatively little fall in blood pressure in normal supine individuals, it reduces blood pressure when sympathetic tone is high, eg, as a result of upright posture or because of reduced blood volume. Cardiac output may be increased because of reflex effects and because of some blockade of presynaptic α_2 receptors in cardiac sympathetic nerves.

Phenoxybenzamine is absorbed after oral administration, although bioavailability is low and its kinetic properties are not well known. The drug is usually given orally, starting with dosages of 10 mg/d and progressively increasing the dose until the desired effect is achieved. A dosage of less than 100 mg/d is usually sufficient to achieve adequate α-receptor blockade. The major use of phenoxybenzamine is in the treatment of pheochromocytoma (see below).

Most adverse effects of phenoxybenzamine derive from its α-receptor–blocking action; the most important are orthostatic hypotension and tachycardia. Nasal stuffiness and inhibition of ejaculation also occur. Since phenoxybenzamine enters the central nervous system, it may cause less specific effects, including fatigue, sedation, and nausea. Because phenoxybenzamine is an alkylating agent, it may have other adverse effects that have not yet been characterized.

Phentolamine is a potent competitive antagonist at both α_1 and α_2 receptors (Table 10–1). Phentolamine reduces peripheral resistance through blockade of α_1 receptors and possibly α_2 receptors on vascular smooth muscle. Its cardiac stimulation is due to antagonism of presynaptic α_2 receptors (leading to enhanced release of norepinephrine from sympathetic nerves) and sympathetic activation from baroreflex mechanisms. Phentolamine also has minor inhibitory effects at serotonin receptors and agonist effects at muscarinic and H_1 and H_2 histamine receptors. Phentolamine's principal adverse effects are related to cardiac stimulation, which may cause severe tachycardia, arrhythmias, and myocardial ischemia. Phentolamine has been used in the treatment of pheochromocytoma. In addition it is sometimes used to reverse local anesthesia in soft tissue sites; local anesthetics are often given with vasoconstrictors that slow their removal. Local phentolamine permits reversal at the end of the procedure. Unfortunately oral and intravenous formulations of phentolamine are no longer consistently available in the United States.

Prazosin is a piperazinyl quinazoline effective in the management of hypertension (see Chapter 11). It is highly selective for α_1 receptors and typically 1000-fold less potent at α_2 receptors. This may partially explain the relative absence of tachycardia seen with prazosin compared with that of phentolamine and phenoxybenzamine. Prazosin relaxes both arterial and venous vascular smooth muscle, as well as smooth muscle in the prostate, due to blockade of α_1 receptors. Prazosin is extensively metabolized in humans; because of metabolic degradation by the liver, only about 50% of the drug is available after oral administration. The half-life is normally about 3 hours.

Terazosin is another reversible α_1-selective antagonist that is effective in hypertension (see Chapter 11); it is also approved for use in men with urinary symptoms due to benign prostatic hyperplasia (BPH). Terazosin has high bioavailability but is extensively metabolized in the liver, with only a small fraction of unchanged drug excreted in the urine. The half-life of terazosin is 9–12 hours.

Doxazosin is efficacious in the treatment of hypertension and BPH. It differs from prazosin and terazosin in having a longer half-life of about 22 hours. It has moderate bioavailability and is extensively metabolized, with very little parent drug excreted in urine or feces. Doxazosin has active metabolites, although their contribution to the drug's effects is probably small.

Tamsulosin is a competitive α_1 antagonist with a structure quite different from that of most other α_1-receptor blockers. It has high bioavailability and a half-life of 9–15 hours. It is metabolized extensively in the liver. Tamsulosin has higher affinity for α_{1A} and α_{1D} receptors than for the α_{1B} subtype. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction

in *prostate* smooth muscle versus *vascular* smooth muscle compared with other α_1-selective antagonists. The drug's efficacy in BPH suggests that the α_{1A} subtype may be the most important α subtype mediating prostate smooth muscle contraction. Furthermore, compared with other antagonists, tamsulosin has less effect on standing blood pressure in patients. Nevertheless, caution is appropriate in using any α antagonist in patients with diminished sympathetic nervous system function. Patients receiving oral tamsulosin and undergoing cataract surgery are at increased risk of the intraoperative floppy iris syndrome (IFIS), characterized by the billowing of a flaccid iris, propensity for iris prolapse, and progressive intraoperative pupillary constriction. These effects increase the risk of cataract surgery, and complications are more likely in the ensuing 14 days if patients are taking these agents.

OTHER ALPHA-ADRENOCEPTOR ANTAGONISTS

Alfuzosin is an α_1-selective quinazoline derivative that is approved for use in BPH. It has a bioavailability of about 60%, is extensively metabolized, and has an elimination half-life of about 5 hours. It may increase risk of QT prolongation in susceptible individuals. **Silodosin** resembles tamsulosin in blocking the α_{1A} receptor and is used in treatment of BPH. **Indoramin** is another α_1-selective antagonist that also has efficacy as an antihypertensive. It is not available in the USA. **Urapidil** is an α_1 antagonist (its primary effect) that also has weak α_2-agonist and 5-HT_{1A}-agonist actions and weak antagonist action at β_1 receptors. It is used in Europe as an antihypertensive agent and for benign prostatic hyperplasia. **Labetalol** has both α_1-selective and β-antagonistic effects; it is discussed below. Neuroleptic drugs such as **chlorpromazine** and **haloperidol** are potent dopamine receptor antagonists but are also antagonists at α receptors. Their antagonism of α receptors probably contributes to some of their adverse effects, particularly hypotension. Similarly, the antidepressant **trazodone** has the capacity to block α_1 receptors. Ergot derivatives, eg, **ergotamine** and **dihydroergotamine,** cause reversible α-receptor blockade, probably via a partial agonist action (see Chapter 16).

Yohimbine, an indole alkaloid, is an α_2-selective antagonist. It is sometimes used in the treatment of orthostatic hypotension because it promotes norepinephrine release through blockade of α_2 receptors in both the central nervous system and the periphery. This increases central sympathetic activation and also promotes increased norepinephrine release in the periphery. It was once widely used to treat male erectile dysfunction but has been superseded by phosphodiesterase-5 inhibitors like sildenafil (see Chapter 12). Yohimbine can greatly elevate blood pressure if administered to patients receiving norepinephrine transport blocking drugs. Yohimbine reverses the antihypertensive effects of α_2-adrenoceptor agonists such as clonidine. It is used in veterinary medicine to reverse anesthesia produced by xylazine, an α_2 agonist used to calm animals. Although yohimbine has been taken off the market in the USA solely for financial reasons, it is available as a "nutritional" supplement.

CLINICAL PHARMACOLOGY OF THE ALPHA-RECEPTOR–BLOCKING DRUGS

Pheochromocytoma

Pheochromocytoma is a tumor of the adrenal medulla or sympathetic ganglion cells. The tumor secretes catecholamines, especially norepinephrine and epinephrine. The patient in the case study at the beginning of this chapter had a left adrenal pheochromocytoma that was identified by imaging. In addition, she had elevated plasma and urinary norepinephrine, epinephrine, and their metabolites, normetanephrine and metanephrine.

The diagnosis of pheochromocytoma is confirmed on the basis of elevated plasma or urinary levels of catecholamines, metanephrine, and normetanephrine (see Chapter 6). Once diagnosed biochemically, techniques to localize a pheochromocytoma include computed tomography and magnetic resonance imaging scans and scanning with radiomarkers such as ^{131}I-meta-iodobenzylguanidine (MIBG), a norepinephrine transporter substrate that is taken up by tumor cells.

The major clinical use of phenoxybenzamine is in the management of pheochromocytoma. Patients have many symptoms and signs of catecholamine excess, including intermittent or sustained hypertension, headaches, palpitations, and increased sweating.

Release of stored catecholamines from pheochromocytomas may occur in response to physical pressure, chemical stimulation, or spontaneously. When it occurs during operative manipulation of pheochromocytoma, the resulting hypertension may be controlled with α-receptor blockade or nitroprusside. Nitroprusside is preferred because its effects can be more readily titrated and it has a shorter duration of action.

Alpha-receptor antagonists are most useful in the preoperative management of patients with pheochromocytoma (Figure 10–4). Administration of phenoxybenzamine in the preoperative period helps to control hypertension and tends to reverse chronic changes resulting from excessive catecholamine secretion such as plasma volume contraction, if present. Furthermore, the patient's operative course may be simplified. Oral doses of 10 mg/d can be increased at intervals of several days until hypertension is controlled. Some physicians give phenoxybenzamine to patients with pheochromocytoma for 1–3 weeks before surgery. Other surgeons prefer to operate on patients in the absence of treatment with phenoxybenzamine, counting on modern anesthetic techniques to control blood pressure and heart rate during surgery. Phenoxybenzamine can be very useful in the chronic treatment of inoperable or metastatic pheochromocytoma. Although there is less experience with alternative drugs, hypertension in patients with pheochromocytoma may also respond to reversible α_1-selective antagonists or to conventional calcium channel antagonists. Beta-receptor antagonists may be required after α-receptor blockade has been instituted to reverse the cardiac effects of excessive catecholamines. Beta antagonists should not be used prior to establishing effective α-receptor blockade, since unopposed

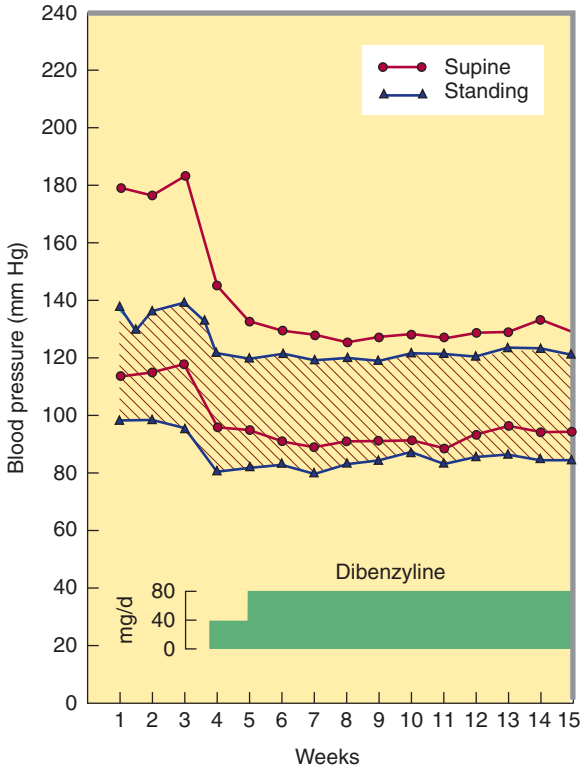

FIGURE 10–4 Effects of phenoxybenzamine (Dibenzyline) on blood pressure in a patient with pheochromocytoma. Dosage of the drug was begun in the fourth week as shown by the shaded bar. Supine systolic and diastolic pressures are indicated by the circles, and the standing pressures by triangles and the hatched area. Note that the α-blocking drug dramatically reduced blood pressure. The reduction in orthostatic hypotension, which was marked before treatment, is probably due to normalization of blood volume, a variable that is sometimes markedly reduced in patients with longstanding pheochromocytoma-induced hypertension. (Redrawn and reproduced, with permission, from Engelman E, Sjoerdsma A: Chronic medical therapy for pheochromocytoma. Ann Intern Med 1961;61:229.)

β-receptor blockade could theoretically cause blood pressure elevation from increased vasoconstriction.

Pheochromocytoma is sometimes treated with **metyrosine** (α-methyltyrosine), the α-methyl analog of tyrosine. This agent is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of dopamine, norepinephrine, and epinephrine (see Figure 6–5). Metyrosine is especially useful in symptomatic patients with inoperable or metastatic pheochromocytoma. Because it has access to the central nervous system, metyrosine can cause extrapyramidal effects due to reduced dopamine levels.

Hypertensive Emergencies

The α-adrenoceptor antagonist drugs have limited application in the management of hypertensive emergencies, but labetalol has been used in this setting (see Chapter 11). In theory, α-adrenoceptor antagonists are most useful when increased blood pressure reflects excess circulating concentrations of α agonists, eg, in pheochromocytoma, overdosage of sympathomimetic drugs, or clonidine withdrawal. However, other drugs are generally preferable, since considerable experience is necessary to use α-adrenoceptor antagonist drugs safely in these settings.

Chronic Hypertension

Members of the prazosin family of α_1-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension (see Chapter 11). They are generally well tolerated, but they are not usually recommended as monotherapy for hypertension because other classes of antihypertensives are more effective in preventing heart failure. Their major adverse effect is orthostatic hypotension, which may be severe after the first few doses but is otherwise uncommon. Nonselective α antagonists are not used in primary systemic hypertension. Prazosin and related drugs may also be associated with dizziness. Orthostatic changes in blood pressure should be checked routinely in any patient being treated for hypertension.

It is interesting that the use of α-adrenoceptor antagonists such as prazosin has been found to be associated with either no changes in plasma lipids or increased concentrations of high-density lipoproteins (HDL), which could be a favorable alteration. The mechanism for this effect is not known.

Peripheral Vascular Disease

Alpha-receptor–blocking drugs do not seem to be effective in the treatment of peripheral vascular occlusive disease characterized by morphologic changes that limit flow in the vessels. Occasionally, individuals with Raynaud's phenomenon and other conditions involving excessive reversible vasospasm in the peripheral circulation do benefit from prazosin or phenoxybenzamine, although calcium channel blockers may be preferable for most patients.

Urinary Obstruction

Benign prostatic hyperplasia is common in elderly men. Various surgical treatments are effective in relieving the urinary symptoms of BPH; however, drug therapy is efficacious in many patients. The mechanism of action in improving urine flow involves partial reversal of smooth muscle contraction in the enlarged prostate and in the bladder base. It has been suggested that some α_1-receptor antagonists may have additional effects on cells in the prostate that help improve symptoms.

Prazosin, doxazosin, and terazosin are all efficacious in patients with BPH. These drugs are particularly useful in patients who also have hypertension. Considerable interest has focused on which α_1-receptor subtype is most important for smooth muscle contraction in the prostate: *subtype-selective* α_{1A}-receptor antagonists may have improved efficacy and safety in treating this disease. As indicated above, tamsulosin is also efficacious in BPH and has relatively minor effects on blood pressure at a low dose. This drug may be preferred in patients who have experienced orthostatic hypotension with other α_1-receptor antagonists.

Erectile Dysfunction

A combination of phentolamine with the nonspecific smooth muscle relaxant papaverine, when injected directly into the penis, may cause erections in men with sexual dysfunction. Long-term administration may result in fibrotic reactions. Systemic absorption

may lead to orthostatic hypotension; priapism may require direct treatment with an α-adrenoceptor agonist such as phenylephrine. Alternative therapies for erectile dysfunction include prostaglandins (see Chapter 18), sildenafil and other cGMP phosphodiesterase inhibitors (see Chapter 12), and apomorphine.

Applications of Alpha$_2$ Antagonists

Alpha$_2$ antagonists have relatively little clinical usefulness. They have limited benefit in male erectile dysfunction. There has been experimental interest in the development of highly selective antagonists for treatment of type 2 diabetes (α_2 receptors inhibit insulin secretion), and for treatment of psychiatric depression. It is likely that better understanding of the subtypes of α_2 receptors will lead to development of clinically useful subtype-selective new drugs.

BASIC PHARMACOLOGY OF THE BETA-RECEPTOR ANTAGONIST DRUGS

Beta-receptor antagonists share the common feature of antagonizing the effects of catecholamines at β adrenoceptors. Beta-blocking drugs occupy β receptors and competitively reduce receptor occupancy by catecholamines and other β agonists. (A few members of this group, used only for experimental purposes, bind irreversibly to β receptors.) Most β-blocking drugs in clinical use are pure antagonists; that is, the occupancy of a β receptor by such a drug causes no activation of the receptor. However, some are partial agonists; that is, they cause partial activation of the receptor, albeit less than that caused by the full agonists epinephrine and isoproterenol. As described in Chapter 2, partial agonists inhibit the activation of β receptors in the presence of high catecholamine concentrations but moderately activate the receptors in the absence of endogenous agonists. Finally, evidence suggests that some β blockers (eg, betaxolol, metoprolol) are *inverse agonists*—drugs that reduce constitutive activity of β receptors—in some tissues. The clinical significance of this property is not known.

The β-receptor–blocking drugs differ in their relative affinities for β_1 and β_2 receptors (Table 10–1). Some have a higher affinity for β_1 than for β_2 receptors, and this selectivity may have important clinical implications. Since none of the clinically available β-receptor antagonists are absolutely specific for β_1 receptors, the selectivity is dose-related; it tends to diminish at higher drug concentrations. Other major differences among β antagonists relate to their pharmacokinetic characteristics and local anesthetic membrane-stabilizing effects.

Chemically, most β-receptor antagonist drugs (Figure 10–5) resemble isoproterenol to some degree (see Figure 9–4).

Pharmacokinetic Properties of the Beta-Receptor Antagonists

A. Absorption

Most of the drugs in this class are well absorbed after oral administration; peak concentrations occur 1–3 hours after ingestion. Sustained-release preparations of propranolol and metoprolol are available.

B. Bioavailability

Propranolol undergoes extensive hepatic (first-pass) metabolism; its bioavailability is relatively low (Table 10–2). The proportion of drug reaching the systemic circulation increases as the dose is increased, suggesting that hepatic extraction mechanisms may become saturated. A major consequence of the low bioavailability of propranolol is that oral administration of the drug leads to much lower drug concentrations than are achieved after intravenous injection of the same dose. Because the first-pass effect varies among individuals, there is great individual variability in the plasma concentrations achieved after oral propranolol. For the same reason, bioavailability is limited to varying degrees for most β antagonists with the exception of betaxolol, penbutolol, pindolol, and sotalol.

C. Distribution and Clearance

The β antagonists are rapidly distributed and have large volumes of distribution. Propranolol and penbutolol are quite lipophilic and readily cross the blood-brain barrier (Table 10–2). Most β antagonists have half-lives in the range of 3–10 hours. A major exception is esmolol, which is rapidly hydrolyzed and has a half-life of approximately 10 minutes. Propranolol and metoprolol are extensively metabolized in the liver, with little unchanged drug appearing in the urine. The cytochrome P450 2D6 (CYP2D6) genotype is a major determinant of interindividual differences in metoprolol plasma clearance (see Chapter 4). Poor metabolizers exhibit threefold to tenfold higher plasma concentrations after administration of metoprolol than extensive metabolizers. Atenolol, celiprolol, and pindolol are less completely metabolized. Nadolol is excreted unchanged in the urine and has the longest half-life of any available β antagonist (up to 24 hours). The half-life of nadolol is prolonged in renal failure. The elimination of drugs such as propranolol may be prolonged in the presence of liver disease, diminished hepatic blood flow, or hepatic enzyme inhibition. It is notable that the pharmacodynamic effects of these drugs are sometimes prolonged well beyond the time predicted from half-life data.

Pharmacodynamics of the Beta-Receptor Antagonist Drugs

Most of the effects of these drugs are due to occupation and blockade of β receptors. However, some actions may be due to other effects, including partial agonist activity at β receptors and local anesthetic action, which differ among the β blockers (Table 10–2).

A. Effects on the Cardiovascular System

Beta-blocking drugs given chronically lower blood pressure in patients with hypertension (see Chapter 11). The mechanisms involved are not fully understood but probably include suppression of renin release and effects in the central nervous system. These drugs do *not* usually cause hypotension in healthy individuals with normal blood pressure.

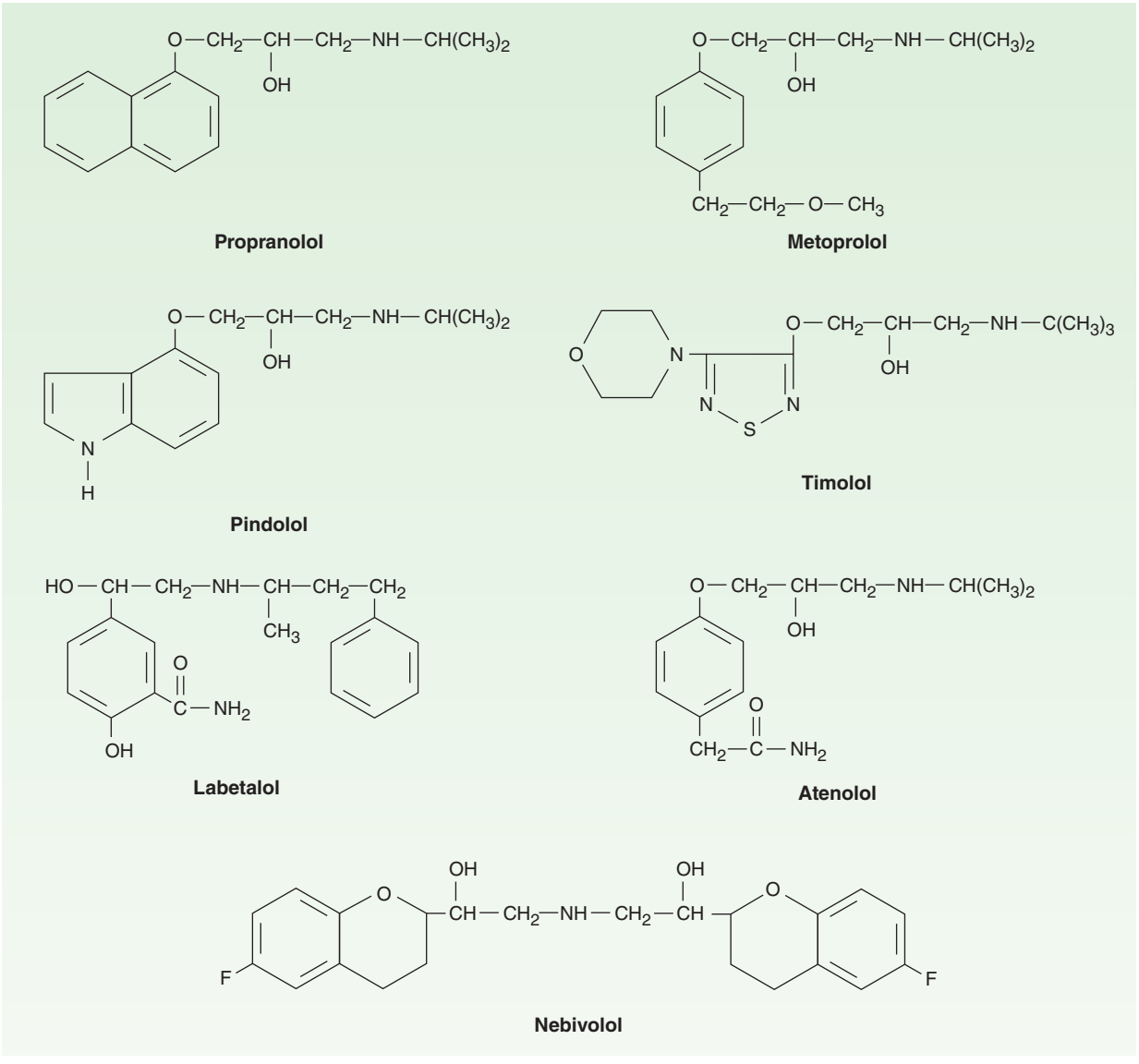

FIGURE 10–5 Structures of some β-receptor antagonists.

Beta-receptor antagonists have prominent effects on the heart (Figure 10–6) and are very valuable in the treatment of angina (see Chapter 12) and chronic heart failure (see Chapter 13) and following myocardial infarction (see Chapter 14). The negative inotropic and chronotropic effects reflect the role of adrenoceptors in regulating these functions. Slowed atrioventricular conduction with an increased PR interval is a related result of adrenoceptor blockade in the atrioventricular node. In the vascular system, β-receptor blockade opposes β_2-mediated vasodilation. This may acutely lead to a rise in peripheral resistance from unopposed α-receptor–mediated effects as the sympathetic nervous system discharges in response to lowered blood pressure due to the fall in cardiac output. Nonselective and β_1-blocking drugs antagonize the release of renin caused by the sympathetic nervous system.

Overall, although the acute effects of these drugs may include a rise in peripheral resistance, chronic drug administration leads to a fall in peripheral resistance in patients with hypertension.

B. Effects on the Respiratory Tract

Blockade of the β_2 receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma. Beta$_1$-receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective β antagonists when blockade of β_1 receptors in the heart is desired and β_2-receptor blockade is undesirable. However, no currently available β_1-selective antagonist is sufficiently specific to *completely* avoid interactions with β_2 adrenoceptors. Consequently, these drugs should generally be avoided in patients with asthma. On the other

TABLE 10–2 Properties of several beta-receptor–blocking drugs.

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-life	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4 hours	50
Atenolol	β_1	No	No	Low	6–9 hours	40
Betaxolol	β_1	No	Slight	Low	14–22 hours	90
Bisoprolol	β_1	No	No	Low	9–12 hours	80
Carteolol	None	Yes	No	Low	6 hours	85
Carvedilol[1]	None	No	No	Moderate	7–10 hours	25–35
Celiprolol	β_1	Yes	No	Low	4–5 hours	70
Esmolol	β_1	No	No	Low	10 minutes	0
Labetalol[1]	None	Yes	Yes	Low	5 hours	30
Metoprolol	β_1	No	Yes	Moderate	3–4 hours	50
Nadolol	None	No	No	Low	14–24 hours	33
Nebivolol	β_1	?[2]	No	Low	11–30 hours	12–96
Penbutolol	None	Yes	No	High	5 hours	>90
Pindolol	None	Yes	Yes	Moderate	3–4 hours	90
Propranolol	None	No	Yes	High	3.5–6 hours	30[3]
Sotalol	None	No	No	Low	12 hours	90
Timolol	None	No	No	Moderate	4–5 hours	50

[1]Carvedilol and labetalol also cause α_1-adrenoceptor blockade.

[2]β_3 agonist.

[3]Bioavailability is dose-dependent.

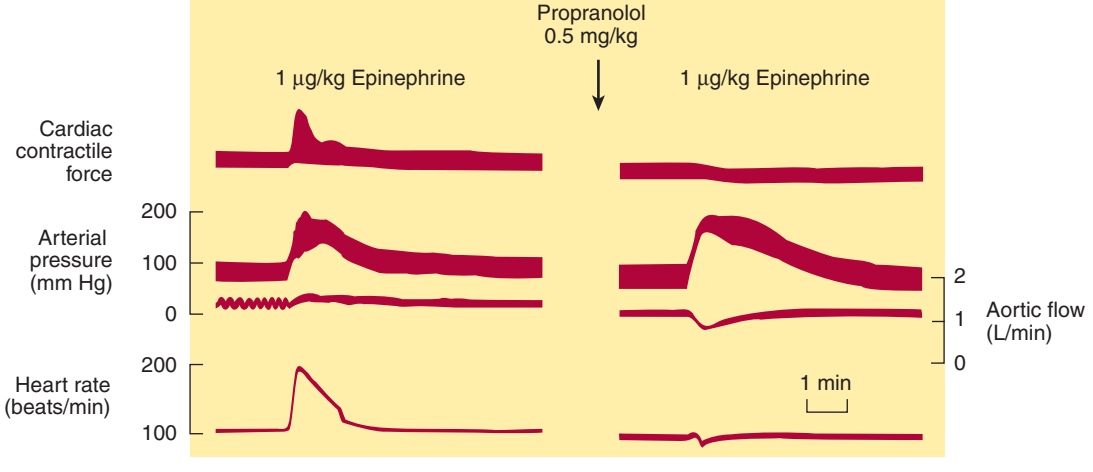

FIGURE 10–6 The effect in an anesthetized dog of the injection of epinephrine before and after propranolol. In the presence of a β-receptor–blocking agent, epinephrine no longer augments the force of contraction (measured by a strain gauge attached to the ventricular wall) nor increases cardiac rate. Blood pressure is still elevated by epinephrine because vasoconstriction is not blocked. (Reproduced, with permission, from Shanks RG: The pharmacology of β sympathetic blockade. Am J Cardiol 1966;18:312.)

hand, many patients with chronic obstructive pulmonary disease (COPD) may tolerate these drugs quite well and the benefits, for example in patients with concomitant ischemic heart disease, may outweigh the risks.

C. Effects on the Eye

Beta-blocking agents reduce intraocular pressure, especially in glaucoma. The mechanism usually reported is decreased aqueous humor production. (See Clinical Pharmacology and Box: The Treatment of Glaucoma.)

D. Metabolic and Endocrine Effects

Beta-receptor antagonists such as propranolol inhibit sympathetic nervous system stimulation of lipolysis. The effects on carbohydrate metabolism are less clear, though glycogenolysis in the human liver is at least partially inhibited after β_2-receptor blockade. Glucagon is the primary hormone used to combat hypoglycemia; it is unclear to what extent β antagonists impair recovery from hypoglycemia, but they should be used with caution in insulin-dependent diabetic patients. This may be particularly important in diabetic patients with inadequate glucagon reserve and in pancreatectomized patients since catecholamines may be the major factors in stimulating glucose release from the liver in response to hypoglycemia. $Beta_1$-receptor–selective drugs may be less prone to inhibit recovery from hypoglycemia. Beta-receptor antagonists are much safer in those type 2 diabetic patients who do not have hypoglycemic episodes.

The chronic use of β-adrenoceptor antagonists has been associated with increased plasma concentrations of very-low-density lipoproteins (VLDL) and decreased concentrations of HDL cholesterol. Both of these changes are potentially unfavorable in terms of risk of cardiovascular disease. Although low-density lipoprotein (LDL) concentrations generally do not change, there is a variable decline in the HDL cholesterol/LDL cholesterol ratio that may increase the risk of coronary artery disease. These changes tend to occur with both selective and nonselective β blockers, though they may be less likely to occur with β blockers possessing intrinsic sympathomimetic activity (partial agonists). The mechanisms by which β-receptor antagonists cause these changes are not understood, though changes in sensitivity to insulin action may contribute.

E. Effects Not Related to Beta-Blockade

Partial β-agonist activity was significant in the first β-blocking drug synthesized, dichloroisoproterenol. It has been suggested that retention of some intrinsic sympathomimetic activity is desirable to prevent untoward effects such as precipitation of asthma or excessive bradycardia. Pindolol and other partial agonists are noted in Table 10–2. It is not yet clear to what extent partial agonism is clinically valuable. Furthermore, these drugs may not be as effective as the pure antagonists in secondary prevention of myocardial infarction. However, they may be useful in patients who develop symptomatic bradycardia or bronchoconstriction in response to pure antagonist β-adrenoceptor drugs, but only if they are strongly indicated for a particular clinical indication.

The Treatment of Glaucoma

Glaucoma is a major cause of blindness and of great pharmacologic interest because the chronic form often responds to drug therapy. The primary manifestation is increased intraocular pressure not initially associated with symptoms. Without treatment, increased intraocular pressure results in damage to the retina and optic nerve, with restriction of visual fields and, eventually, blindness. Intraocular pressure is easily measured as part of the routine ophthalmologic examination. Two major types of glaucoma are recognized: open-angle and closed-angle (also called narrow-angle). The closed-angle form is associated with a shallow anterior chamber, in which a dilated iris can occlude the outflow drainage pathway at the angle between the cornea and the ciliary body (see Figure 6–9). This form is associated with acute and painful increases of pressure, which must be controlled on an emergency basis with drugs or prevented by surgical removal of part of the iris (iridectomy). The open-angle form of glaucoma is a chronic condition, and treatment is largely pharmacologic. Because intraocular pressure is a function of the balance between fluid input and drainage out of the globe, the strategies for the treatment of open-angle glaucoma fall into two classes: reduction of aqueous humor secretion and enhancement of aqueous outflow. Five general groups of drugs—cholinomimetics, α agonists, β blockers, prostaglandin $F_{2\alpha}$ analogs, and diuretics—have been found to be useful in reducing intraocular pressure and can be related to these strategies as shown in Table 10–3. Of the five drug groups listed in Table 10–3, the prostaglandin analogs and the β blockers are the most popular. This popularity results from convenience (once- or twice-daily dosing) and relative lack of adverse effects (except, in the case of β blockers, in patients with asthma or cardiac pacemaker or conduction pathway disease). Other drugs that have been reported to reduce intraocular pressure include prostaglandin E_2 and marijuana. The use of drugs in acute closed-angle glaucoma is limited to cholinomimetics, acetazolamide, and osmotic agents preceding surgery. The onset of action of the other agents is too slow in this situation.

Local anesthetic action, also known as "membrane-stabilizing" action, is a prominent effect of several β blockers (Table 10–2). This action is the result of typical local anesthetic blockade of sodium channels (see Chapter 26) and can be demonstrated experimentally in isolated neurons, heart muscle, and skeletal muscle membrane. However, it is unlikely that this effect is important after systemic administration of these drugs, since the concentration in plasma usually achieved by these routes is too low for the anesthetic effects to be evident. The membrane-stabilizing β blockers are not used topically on the eye, because local anesthesia of the cornea would be highly undesirable. Sotalol

TABLE 10–3 Drugs used in open-angle glaucoma.

	Mechanism	Methods of Administration
Cholinomimetics		
Pilocarpine, carbachol, physostigmine, echothiophate, demecarium	Ciliary muscle contraction, opening of trabecular meshwork; increased outflow	Topical drops or gel; plastic film slow-release insert
Alpha agonists		
Nonselective	Increased outflow	Topical drops
Epinephrine, dipivefrin		
Alpha$_2$-selective	Decreased aqueous secretion	
Apraclonidine		Topical, postlaser only
Brimonidine		Topical
Beta blockers		
Timolol, betaxolol, carteolol, levobunolol, metipranolol	Decreased aqueous secretion from the ciliary epithelium	Topical drops
Carbonic anhydrase inhibitors		
Dorzolamide, brinzolamide	Decreased aqueous secretion due to lack of HCO_3^-	Topical
Acetazolamide, dichlorphenamide, methazolamide		Oral
Prostaglandins		
Latanoprost, bimatoprost, travoprost, unoprostone	Increased outflow	Topical

is a nonselective β-receptor antagonist that lacks local anesthetic action but has marked class III antiarrhythmic effects, reflecting potassium channel blockade (see Chapter 14).

SPECIFIC AGENTS (SEE TABLE 10–2)

Propranolol is the prototypical β-blocking drug. As noted above, it has low and dose-dependent bioavailability. A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period. The drug has negligible effects at α and muscarinic receptors; however, it may block some serotonin receptors in the brain, though the clinical significance is unclear. It has no detectable partial agonist action at β receptors.

Metoprolol, atenolol, and several other drugs (Table 10–2) are members of the β_1-selective group. These agents may be safer in patients who experience bronchoconstriction in response to propranolol. Since their β_1 selectivity is rather modest, they should be used with great caution, if at all, in patients with a history of asthma. However, in selected patients with COPD the benefits may exceed the risks, eg, in patients with myocardial infarction. Beta$_1$-selective antagonists may be preferable in patients with diabetes or peripheral vascular disease when therapy with a β blocker is required, since β_2 receptors are probably important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

Nebivolol is the most highly selective β_1-adrenergic receptor blocker, though some of its metabolites do not have this level of specificity. Nebivolol has the additional quality of eliciting vasodilation. This is due to an action of the drug on endothelial nitric oxide production. Nebivolol may increase insulin sensitivity and does not adversely affect lipid profile.

Nadolol is noteworthy for its very long duration of action; its spectrum of action is similar to that of timolol. **Timolol** is a nonselective agent with no local anesthetic activity. It has excellent ocular hypotensive effects when administered topically in the eye. **Levobunolol** (nonselective) and **betaxolol** (β_1-selective) are also used for topical ophthalmic application in glaucoma; the latter drug may be less likely to induce bronchoconstriction than nonselective antagonists. **Carteolol** is a nonselective β-receptor antagonist.

Pindolol, acebutolol, carteolol, bopindolol,* oxprenolol,* celiprolol,* and **penbutolol** are of interest because they have partial β-agonist activity. They are effective in the major cardiovascular applications of the β-blocking group (hypertension and angina). Although these partial agonists may be less likely to cause bradycardia and abnormalities in plasma lipids than are antagonists, the overall clinical significance of intrinsic sympathomimetic activity remains uncertain. Pindolol, perhaps as a result of actions on serotonin signaling, may potentiate the action of traditional antidepressant medications. Celiprolol is a β_1-selective antagonist with a modest capacity to activate β_2 receptors.

There is limited evidence suggesting that celiprolol may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation. Acebutolol is also a β_1-selective antagonist.

*Not available in the USA

Labetalol is a reversible adrenoceptor antagonist available as a racemic mixture of two pairs of chiral isomers (the molecule has two centers of asymmetry). The (*S,S*)- and (*R,S*)-isomers are nearly inactive, the (*S,R*)-isomer is a potent α blocker, and the (*R,R*)-isomer is a potent β blocker. Labetalol's affinity for α receptors is less than that of phentolamine, but labetalol is α_1-selective. Its β-blocking potency is somewhat lower than that of propranolol. Hypotension induced by labetalol is accompanied by less tachycardia than occurs with phentolamine and similar α blockers.

Carvedilol, medroxalol,* and **bucindolol*** are nonselective β-receptor antagonists with some capacity to block α_1-adrenergic receptors. Carvedilol antagonizes the actions of catecholamines more potently at β receptors than at α_1 receptors. The drug has a half-life of 6–8 hours. It is extensively metabolized in the liver, and stereoselective metabolism of its two isomers is observed. Since metabolism of (*R*)-carvedilol is influenced by polymorphisms in CYP2D6 activity and by drugs that inhibit this enzyme's activity (such as quinidine and fluoxetine, see Chapter 4), drug interactions may occur. Carvedilol also appears to attenuate oxygen free radical–initiated lipid peroxidation and to inhibit vascular smooth muscle mitogenesis independently of adrenoceptor blockade. These effects may contribute to the clinical benefits of the drug in chronic heart failure (see Chapter 13).

Esmolol is an ultra-short–acting β_1-selective adrenoceptor antagonist. The structure of esmolol contains an ester linkage; esterases in red blood cells rapidly metabolize esmolol to a metabolite that has a low affinity for β receptors. Consequently, esmolol has a short half-life (about 10 minutes). Therefore, during continuous infusions of esmolol, steady-state concentrations are achieved quickly, and the therapeutic actions of the drug are terminated rapidly when its infusion is discontinued. Esmolol may be safer to use than longer-acting antagonists in critically ill patients who require a β-adrenoceptor antagonist. Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients.

Butoxamine is a research drug selective for β_2 receptors. Selective β_2-blocking drugs have not been actively sought because there is no obvious clinical application for them; none is available for clinical use.

■ CLINICAL PHARMACOLOGY OF THE BETA-RECEPTOR–BLOCKING DRUGS

Hypertension

The β-adrenoceptor–blocking drugs have proved to be effective and well tolerated in hypertension. Although many hypertensive patients respond to a β blocker used alone, the drug is often used with either a diuretic or a vasodilator. In spite of the short half-life of many β antagonists, these drugs may be administered once or twice daily and still have an adequate therapeutic effect. Labetalol, a competitive α and β antagonist, is effective in hypertension, though its ultimate role is yet to be determined. Use of these agents is discussed in greater detail in Chapter 11. There is some evidence that drugs in this class may be less effective in the elderly and in individuals of African ancestry. However, these differences are relatively small and may not apply to an individual patient. Indeed, since effects on blood pressure are easily measured, the therapeutic outcome for this indication can be readily detected in any patient.

Ischemic Heart Disease

Beta-adrenoceptor blockers reduce the frequency of anginal episodes and improve exercise tolerance in many patients with angina (see Chapter 12). These actions relate to the blockade of cardiac β receptors, resulting in decreased cardiac work and reduction in oxygen demand. Slowing and regularization of the heart rate may contribute to clinical benefits (Figure 10–7). Multiple large-scale prospective studies indicate that the long-term use of **timolol, propranolol,** or **metoprolol** in patients who have had a myocardial infarction prolongs survival (Figure 10–8). At the present time, data are less compelling for the use of other than the three mentioned β-adrenoceptor antagonists for this indication. It is significant that surveys in many populations have indicated that β-receptor antagonists are underused, leading to unnecessary morbidity and mortality. In addition, β-adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction. In this setting, relative contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease. It has been suggested that certain polymorphisms in β_2-adrenoceptor genes may influence survival among patients receiving antagonists after acute coronary syndromes.

Cardiac Arrhythmias

Beta antagonists are often effective in the treatment of both supraventricular and ventricular arrhythmias (see Chapter 14). It has been suggested that the improved survival following myocardial infarction in patients using β antagonists (Figure 10–8) is due to suppression of arrhythmias, but this has not been proved. By increasing the atrioventricular nodal refractory period, β antagonists slow ventricular response rates in atrial flutter and fibrillation. These drugs can also reduce ventricular ectopic beats, particularly if the ectopic activity has been precipitated by catecholamines. Sotalol has antiarrhythmic effects involving ion channel blockade in addition to its β-blocking action; these are discussed in Chapter 14.

Heart Failure

Clinical trials have demonstrated that at least three β antagonists—metoprolol, bisoprolol, and carvedilol—are effective in reducing mortality in selected patients with chronic heart failure. Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life. Although mechanisms are uncertain, there appear to be beneficial effects on

*Not available in the USA.

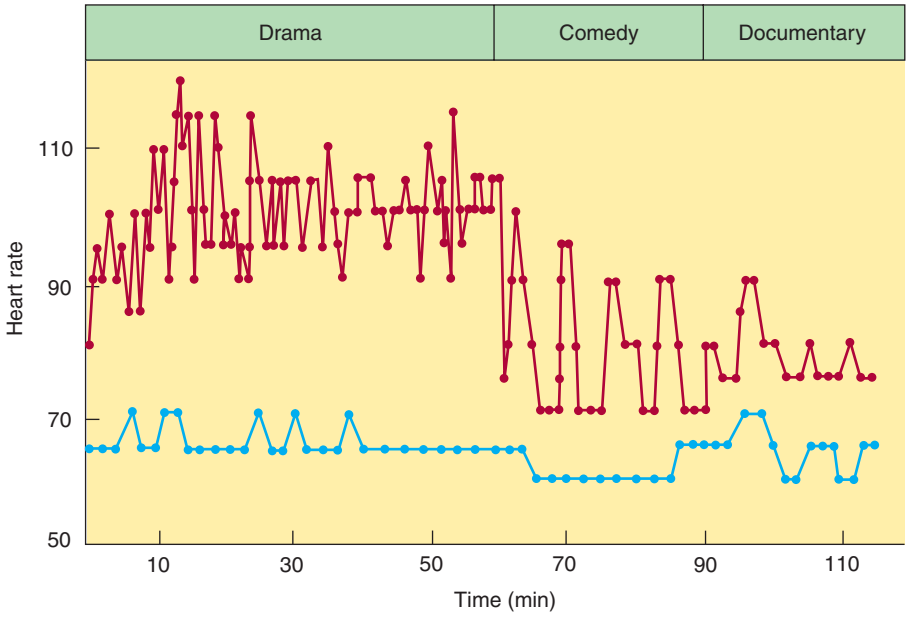

FIGURE 10–7 Heart rate in a patient with ischemic heart disease measured by telemetry while watching television. Measurements were begun 1 hour after receiving placebo (*upper line, red*) or 40 mg of oxprenolol (*lower line, blue*), a nonselective β antagonist with partial agonist activity. Not only was the heart rate decreased by the drug under the conditions of this experiment, it also varied much less in response to stimuli. (Modified and reproduced, with permission, from Taylor SH: Oxprenolol in clinical practice. Am J Cardiol 1983;52:34D.)

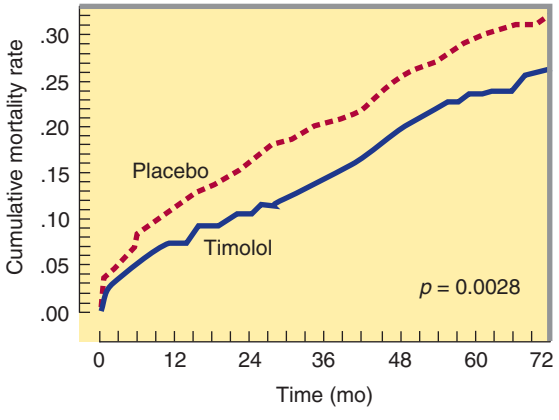

FIGURE 10–8 Effects of β-blocker therapy on life-table cumulated rates of mortality from all causes over 6 years among 1884 patients surviving myocardial infarctions. Patients were randomly assigned to treatment with placebo (*dashed red line*) or timolol (*solid blue line*). (Reproduced, with permission, from Pederson TR: Six-year follow-up of the Norwegian multicenter study on timolol after acute myocardial infarction. N Engl J Med 1985;313:1055.)

myocardial remodeling and in decreasing the risk of sudden death (see Chapter 13).

Other Cardiovascular Disorders

Beta-receptor antagonists have been found to increase stroke volume in some patients with obstructive cardiomyopathy. This beneficial effect is thought to result from the slowing of ventricular ejection and decreased outflow resistance. Beta antagonists are useful in dissecting aortic aneurysm to decrease the rate of development of systolic pressure. Beta antagonists are also useful in selected at-risk patients in the prevention of adverse cardiovascular outcomes resulting from noncardiac surgery.

Glaucoma (See Box: The Treatment of Glaucoma)

Systemic administration of β-blocking drugs for other indications was found serendipitously to reduce intraocular pressure in patients with glaucoma. Subsequently, it was found that topical administration also reduces intraocular pressure. The mechanism appears to involve reduced production of aqueous humor by the ciliary body, which is physiologically activated by cAMP. Timolol and related β antagonists are suitable for local use in the eye because they lack local anesthetic properties. Beta antagonists appear to have an efficacy comparable to that of epinephrine or pilocarpine in open-angle glaucoma and are far better tolerated by most patients. While the maximal daily dose applied locally (1 mg) is small compared with the systemic doses commonly used in the treatment of hypertension or angina (10–60 mg), sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals. Topical timolol may interact with orally administered verapamil and increase the risk of heart block.

Betaxolol, carteolol, levobunolol, and metipranolol are also approved for the treatment of glaucoma. Betaxolol has the potential advantage of being β_1-selective; to what extent this potential

advantage might diminish systemic adverse effects remains to be determined. The drug apparently has caused worsening of pulmonary symptoms in some patients.

Hyperthyroidism

Excessive catecholamine action is an important aspect of the pathophysiology of hyperthyroidism, especially in relation to the heart (see Chapter 38). The β antagonists are beneficial in this condition. The effects presumably relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine. The latter action may vary from one β antagonist to another. Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism); it is used cautiously in patients with this condition to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases

Propranolol reduces the frequency and intensity of **migraine headache**. Other β-receptor antagonists with preventive efficacy include metoprolol and probably also atenolol, timolol, and nadolol. The mechanism is not known. Since sympathetic activity may enhance skeletal muscle tremor, it is not surprising that β antagonists have been found to reduce certain **tremors** (see Chapter 28). The somatic manifestations of anxiety may respond dramatically to low doses of propranolol, particularly when taken prophylactically. For example, benefit has been found in musicians with **performance anxiety ("stage fright").** Propranolol may contribute to the symptomatic treatment of alcohol withdrawal in some patients.

Miscellaneous

Beta-receptor antagonists have been found to diminish portal vein pressure in patients with cirrhosis. There is evidence that both propranolol and nadolol decrease the incidence of the first episode of bleeding from esophageal varices and decrease the mortality rate associated with bleeding in patients with cirrhosis. Nadolol in combination with isosorbide mononitrate appears to be more efficacious than sclerotherapy in preventing rebleeding in patients who have previously bled from esophageal varices. Variceal band ligation in combination with a β antagonist may be more efficacious.

CHOICE OF A BETA-ADRENOCEPTOR ANTAGONIST DRUG

Propranolol is the standard against which newer β antagonists developed for systemic use have been compared. In many years of very wide use, propranolol has been found to be a safe and effective drug for many indications. Since it is possible that some actions of a β-receptor antagonist may relate to some other effect of the drug, these drugs should not be considered interchangeable for all applications. For example, only β antagonists known to be effective in stable heart failure or in prophylactic therapy after myocardial infarction should be used for those indications. It is possible that the beneficial effects of one drug in these settings might not be shared by another drug in the same class. The possible advantages and disadvantages of β-receptor antagonists that are partial agonists have not been clearly defined in clinical settings, although current evidence suggests that they are probably less efficacious in secondary prevention after a myocardial infarction compared with pure antagonists.

CLINICAL TOXICITY OF THE BETA-RECEPTOR ANTAGONIST DRUGS

Many adverse effects have been reported for propranolol but most are minor. Bradycardia is the most common adverse cardiac effect of β-blocking drugs. Sometimes patients note coolness of hands and feet in winter. Central nervous system effects include mild sedation, vivid dreams, and rarely, depression. Discontinuing the use of β blockers in any patient who develops psychiatric depression should be seriously considered if clinically feasible. It has been claimed that β-receptor antagonist drugs with low lipid solubility are associated with a lower incidence of central nervous system adverse effects than compounds with higher lipid solubility (Table 10–2). Further studies designed to compare the central nervous system adverse effects of various drugs are required before specific recommendations can be made, though it seems reasonable to try the hydrophilic drugs nadolol or atenolol in a patient who experiences unpleasant central nervous system effects with other β blockers.

The major adverse effects of β-receptor antagonist drugs relate to the predictable consequences of β blockade. $Beta_2$-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction without having these consequences in normal individuals. Indeed, relatively trivial asthma may become severe after β blockade. However, because of their lifesaving potential in cardiovascular disease, strong consideration should be given to individualized therapeutic trials in some classes of patients, eg, those with chronic obstructive pulmonary disease who have appropriate indications for β blockers. While β_1-selective drugs may have less effect on airways than nonselective β antagonists, they must be used very cautiously in patients with reactive airway disease. $Beta_1$-selective antagonists are generally well tolerated in patients with mild to moderate peripheral vascular disease, but caution is required in patients with severe peripheral vascular disease or vasospastic disorders.

Beta-receptor blockade depresses myocardial contractility and excitability. In patients with abnormal myocardial function, cardiac output may be dependent on sympathetic drive. If this stimulus is removed by β blockade, cardiac decompensation may ensue. Thus, caution must be exercised in starting a β-receptor antagonist in patients with compensated heart failure even though long-term use of these drugs in these patients may prolong life. A life-threatening adverse cardiac effect of a β antagonist may be overcome directly with isoproterenol or with glucagon (glucagon

stimulates the heart via glucagon receptors, which are not blocked by β antagonists), but neither of these methods is without hazard. A very small dose of a β antagonist (eg, 10 mg of propranolol) may provoke severe cardiac failure in a susceptible individual. Beta blockers may interact with the calcium antagonist verapamil; severe hypotension, bradycardia, heart failure, and cardiac conduction abnormalities have all been described. These adverse effects may even arise in susceptible patients taking a topical (ophthalmic) β blocker and oral verapamil.

Patients with ischemic heart disease or renovascular hypertension may be at increased risk if β blockade is suddenly interrupted. The mechanism of this effect might involve up-regulation of the number of β receptors. Until better evidence is available regarding the magnitude of the risk, prudence dictates the gradual tapering rather than abrupt cessation of dosage when these drugs are discontinued, especially drugs with short half-lives, such as propranolol and metoprolol.

The incidence of hypoglycemic episodes exacerbated by β-blocking agents in diabetics is unknown. Nevertheless, it is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions if alternative therapies are available. Beta$_1$-selective antagonists offer some advantage in these patients, since the rate of recovery from hypoglycemia may be faster compared with that in diabetics receiving nonselective β-adrenoceptor antagonists. There is considerable potential benefit from these drugs in diabetics after a myocardial infarction, so the balance of risk versus benefit must be evaluated in individual patients.

SUMMARY Sympathetic Antagonists

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ALPHA-ADRENOCEPTOR ANTAGONISTS				
• Phenoxybenzamine	Irreversibly blocks α_1 and α_2• indirect baroreflex activation	Lowers blood pressure (BP) • heart rate (HR) rises due to baroreflex activation	Pheochromocytoma • high catecholamine states	Irreversible blocker • duration > 1 day • *Toxicity*: Orthostatic hypotension • tachycardia • myocardial ischemia
• Phentolamine	Reversibly blocks α_1 and α_2	Blocks α-mediated vasoconstriction, lowers BP, increases HR (baroreflex)	Pheochromocytoma	Half-life ~45 min after IV injection
• Prazosin • Doxazosin • Terazosin	Block α_1, but not α_2	Lower BP	Hypertension • benign prostatic hyperplasia	Larger depressor effect with first dose may cause orthostatic hypotension
• Tamsulosin	Tamsulosin is slightly selective for α_{1A}	α_{1A} Blockade may relax prostatic smooth muscles more than vascular smooth muscle	Benign prostatic hyperplasia	Orthostatic hypotension may be less common with this subtype
• Yohimbine	Blocks α_2• elicits increased central sympathetic activity • increased norepinephrine release	Raises BP and HR	Male erectile dysfunction • hypotension	May cause anxiety • excess pressor effect if norepinephrine transporter is blocked
• Labetalol (see carvedilol section below)	$\beta > \alpha_1$ block	Lowers BP with limited HR increase	Hypertension	Oral, parenteral • *Toxicity:* Less tachycardia than other α_1 agents
BETA-ADRENOCEPTOR ANTAGONISTS				
• Propranolol • Nadolol • Timolol	Block β_1 and β_2	Lower HR and BP • reduce renin	Hypertension • angina pectoris • arrhythmias • migraine • hyperthyroidism	Oral, parenteral • *Toxicity:* Bradycardia • worsened asthma • fatigue • vivid dreams • cold hands
• Metoprolol • Atenolol • Alprenolol • Betaxolol • Nebivolol	Block $\beta_1 > \beta_2$	Lower HR and BP • reduce renin • may be safer in asthma	Angina pectoris • hypertension • arrhythmias	*Toxicity:* Bradycardia • fatigue • vivid dreams • cold hands

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
• Butoxamine[1]	Blocks $\beta_2 > \beta_1$	Increases peripheral resistance	No clinical indication	*Toxicity:* Asthma provocation
• Pindolol • Acebutolol • Carteolol • Bopindolol[1] • Oxprenolol[1] • Celiprolol[1] • Penbutolol	β_1, β_2, with intrinsic sympathomimetic (partial agonist) effect	Lowers BP • modestly lower HR	Hypertension • arrhythmias • migraine • may avoid worsening of bradycardia	Oral • *Toxicity:* Fatigue • vivid dreams • cold hands
• Carvedilol • Medroxalol[1] • Bucindolol[1] (see labetalol above)	$\beta > \alpha_1$ block		Heart failure	Oral, long half-life • *Toxicity:* Fatigue
• Esmolol	$\beta_1 > \beta_2$	Very brief cardiac β blockade	Rapid control of BP and arrhythmias, thyrotoxicosis and myocardial ischemia intraoperatively	Parenteral only • half-life ~ 10 min • *Toxicity:* Bradycardia • hypotension
TYROSINE HYDROXYLASE INHIBITOR				
• Metyrosine	Blocks tyrosine hydroxylase • reduces synthesis of dopamine, norepinephrine, and epinephrine	Lowers BP • in central nervous system may elicit extrapyramidal effects (due to low dopamine)	Pheochromocytoma	*Toxicity:* Extrapyramidal symptoms • orthostatic hypotension • crystalluria

[1]Not available in the USA.

PREPARATIONS AVAILABLE*

ALPHA BLOCKERS

Alfuzosin (Uroxatral)
Oral: 10 mg tablets (extended release)

Doxazosin (generic, Cardura)
Oral: 1, 2, 4, 8 mg tablets; 4, 8 mg extended-release tablets

Phenoxybenzamine (Dibenzyline)
Oral: 10 mg capsules

Phentolamine (generic)
Parenteral: 5 mg/vial for injection

Prazosin (generic, Minipress)
Oral: 1, 2, 5 mg capsules

Silodosin (Rapaflow)
Oral: 4, 8 mg capsules

Tamsulosin (Flomax)
Oral: 0.4 mg capsule

Terazosin (generic, Hytrin)
Oral: 1, 2, 5, 10 mg tablets, capsules

Tolazoline (Priscoline)
Parenteral: 25 mg/mL for injection

BETA BLOCKERS

Acebutolol (generic, Sectral)
Oral: 200, 400 mg capsules

Atenolol (generic, Tenormin)
Oral: 25, 50, 100 mg tablets
Parenteral: 0.5 mg/mL for IV injection

Betaxolol
Oral (Kerlone): 10, 20 mg tablets
Ophthalmic (generic, Betoptic): 0.25%, 0.5% drops

Bisoprolol (generic, Zebeta)
Oral: 5, 10 mg tablets

Carteolol
Oral (Cartrol): 2.5, 5 mg tablets
Ophthalmic (generic, Ocupress): 1% drops

Carvedilol (Coreg)
Oral: 3.125, 6.25, 12.5, 25 mg tablets; 10, 20, 40, 80 mg extended-release capsules

Esmolol (Brevibloc)
Parenteral: 10 mg/mL for IV injection; 250 mg/mL for IV infusion

*In the USA

Labetalol (generic, Normodyne, Trandate)
Oral: 100, 200, 300 mg tablets
Parenteral: 5 mg/mL for injection

Levobunolol (Betagan Liquifilm, others)
Ophthalmic: 0.25, 0.5% drops

Metipranolol (Optipranolol)
Ophthalmic: 0.3% drops

Metoprolol (generic, Lopressor, Toprol)
Oral: 50, 100 mg tablets
Oral sustained release: 25, 50, 100, 200 mg tablets
Parenteral: 1 mg/mL for injection

Nadolol (generic, Corgard)
Oral: 20, 40, 80, 120, 160 mg tablets

Nebivolol (Bystolic)
Oral: 2.5, 5, 10 mg tablets

Penbutolol (Levatol)
Oral: 20 mg tablets

Pindolol (generic, Visken)
Oral: 5, 10 mg tablets

Propranolol (generic, Inderal)
Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8, 80 mg/mL solutions
Oral sustained release: 60, 80, 120, 160 mg capsules
Parenteral: 1 mg/mL for injection

Sotalol (generic, Betapace)
Oral: 80, 120, 160, 240 mg tablets

Timolol
Oral (generic, Blocadren): 5, 10, 20 mg tablets
Ophthalmic (generic, Timoptic): 0.25, 0.5% drops, gel

TYROSINE HYDROXYLASE INHIBITOR

Metyrosine (Demser)
Oral: 250 mg capsules

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CASE STUDY ANSWER

The patient had a pheochromocytoma. The tumor secretes catecholamines, especially norepinephrine and epinephrine, resulting in increases in blood pressure (via α_1 receptors) and heart rate (via β_1 receptors). The pheochromocytoma was in the left adrenal gland and was identified by MIBG imaging, which labels tissues that have norepinephrine transporters on their cell surface (see text). In addition, she had elevated plasma and urinary norepinephrine, epinephrine, and their metabolites, normetanephrine and metanephrine. The catecholamines made the blood pressure surge and the heart rate increase, producing a typical episode during her examination, perhaps set off in this case by external pressure as the physician palpated the abdomen. Her profuse sweating was typical and partly due to α_1 receptors, though the large magnitude of drenching sweats in pheochromocytoma has never been fully explained. Treatment would consist of preoperative control of blood pressure and normalization of blood volume if reduced, followed by surgical resection of the tumor. Control of blood pressure extremes might be necessary during surgery, probably with nitroprusside.