occurred in 1989. Thus, 12 years had passed between project launch and approval for use in patients).

In 1999, worldwide sales of omeprazole were $5.9 billion. By 2001, sales were $5.7 billion, and the worldwide market for ulcer drugs exceeded 14 billion. There are now five benzimidazole compounds available from a number of companies. Omeprazole went off patent in 2001 and is now available as generic drug.

Section II. Autonomic Drugs

Chapter 6. Introduction to Autonomic Pharmacology

General

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 autonomous (independent) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions—cardiac output, blood flow to various organs, digestion, etc—that are necessary for life. The somatic division is largely concerned with consciously controlled functions such as movement, respiration, and posture. Both systems have important afferent (sensory) inputs that provide sensation 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.

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. Conversely, a very large number of drugs used for other purposes have unwanted effects on autonomic function.

Anatomy of the Autonomic Nervous System

The autonomic nervous system lends itself to division on anatomic grounds into two major portions: the sympathetic (thoracolumbar) division and the parasympathetic (craniosacral) division (Figure 6–1). Both divisions originate in nuclei within the central nervous system and give
rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. The sympathetic preganglionic fibers leave the central nervous system through the thoracic and lumbar spinal nerves. The parasympathetic preganglionic fibers leave the central nervous system through the cranial nerves (especially the third, seventh, ninth, and tenth) and the third and fourth sacral spinal roots.

Most of the sympathetic preganglionic fibers terminate in ganglia located in the paravertebral chains that lie on either side of the spinal column. The remaining sympathetic preganglionic fibers terminate in prevertebral ganglia, which lie in front of the vertebrae. 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. 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 ones 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 autonomic nervous system, there are large numbers of afferent fibers that run from the periphery to integrating centers, including the enteric plexuses in the gut, the autonomic ganglia, and the central nervous system. Many of the sensory neurons that end in the central nervous system 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 above. There is increasing evidence that some of these sensory fibers also have important peripheral motor functions (see Nonadrenergic, Noncholinergic Systems, below).

The enteric nervous system (ENS) is a large and highly organized collection of neurons located in the walls of the gastrointestinal system (Figure 6–2). It is sometimes considered a third division of the ANS. The enteric nervous system 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 as well as postganglionic sympathetic axons. They also receive sensory input from within the wall of the gut. Fibers from the cell bodies in these plexuses travel to the smooth muscle of the gut to control motility. Other motor fibers go to the secretory cells. Sensory fibers transmit 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 completely halt activity in the plexuses nor in the smooth muscle and glands innervated by them.

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. (LM, longitudinal muscle layer; MP, myenteric plexus; CM, circular muscle layer; SMP, submucosal plexus; ACh, acetylcholine; NE, norepinephrine; NO, nitric oxide; NP, neuropeptides; SP, substance P; 5-HT, serotonin.)

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 autonomic nervous system fibers synthesize and release acetylcholine; they are cholinergic fibers, ie, they act 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 central nervous system 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 for transmission. Most postganglionic sympathetic fibers release norepinephrine (noradrenaline); they are **noradrenergic** (often called simply "adrenergic") fibers—ie, they act by releasing norepinephrine. These transmitter characteristics are presented schematically in Figure 6–1. As noted above, a few sympathetic fibers release acetylcholine. Dopamine is a very important transmitter in the central nervous system, and there is evidence that it is 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 transmitter substances, or *cotransmitters*, in addition to the primary transmitter.

Five key features of neurotransmitter function represent potential targets of pharmacologic therapy: synthesis, storage, release, activation of receptors, and termination of action. These processes are discussed in detail below.

**Cholinergic Transmission**

The terminals 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), while the smaller clear vesicles contain most of the acetylcholine. Vesicles are initially synthesized in the neuron soma and transported to the terminal. They may also be recycled several times within the terminal.

![Figure 6–3.](image-url)
Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent carrier (A). This transport can be inhibited by hemicholinium drugs. ACh is transported into the storage vesicle by a second carrier (B) that can be inhibited by vesamicol. Peptides (P), 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 ACh and cotransmitters into the junctional cleft. This step is blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the
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 carrier (Figure 6–3, carrier A). This carrier can be blocked by a group of drugs called hemicholiniums. Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by an antiporter that removes protons (Figure 6–3, carrier B). This transporter can be blocked by 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 1000–50,000 molecules in each vesicle).

Release of transmitter is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions. The increased Ca²⁺ concentration "destabilizes" the storage vesicles by interacting with special proteins associated with the vesicular membrane. Fusion of the vesicular membranes with the terminal membrane occurs through the interaction of vesicular proteins (vesicle-associated membrane proteins, VAMPs), eg, synaptotagmin and synaptobrevin, with several proteins of the terminal membrane (synaptosome-associated proteins, SNAPs), eg, SNAP-25 and syntaxin. Fusion of the membranes results in exocytotic expulsion of—in the case of somatic motor nerves—several hundred quanta of acetylcholine into the synaptic cleft. The amount of transmitter released by one depolarization of an autonomic postganglionic nerve terminal is probably smaller. In addition to acetylcholine, several cotransmitters will be released at the same time (Table 6–1). The ACh vesicle release process is blocked by botulinum toxin through the enzymatic removal of two amino acids from one or more of the fusion proteins.

Table 6–1. Some of the Transmitter Substances Found in Autonomic Nervous System (ANS), Enteric Nervous System (ENS), and Nonadrenergic, Noncholinergic Neurons.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Probable Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (ACh)</td>
<td>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 (&quot;ganglionic&quot;) transmitter in the ENS.</td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP)</td>
<td>May act as a cotransmitter at inhibitory ENS neuromuscular junctions. Inhibits release of ACh and norepinephrine from ANS nerve endings. An excitatory transmitter in sympathetic–smooth muscle synapses.</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide</td>
<td>Found with substance P in cardiovascular sensory nerve fibers. Present in some secretomotor ENS neurons and interneurons. A cardiac stimulant.</td>
</tr>
<tr>
<td>(CGRP)</td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>May act as a cotransmitter in some excitatory neuromuscular ENS neurons.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>A possible postganglionic sympathetic transmitter in renal blood vessels.</td>
</tr>
<tr>
<td></td>
<td>Probably a modulatory transmitter in some ganglia and the ENS.</td>
</tr>
</tbody>
</table>
### 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)

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 many parasympathetic postganglionic neurons and sympathetic postganglionic noradrenergic vascular neurons.

### Nitric oxide (NO)

A cotransmitter at inhibitory ENS neuromuscular junctions; especially important at sphincters. Probable transmitter for parasympathetic vasodilation.

### Norepinephrine (NE)

The primary transmitter at most sympathetic postganglionic nerve endings.

### Serotonin (5-HT)

A major transmitter at excitatory neuron-to-neuron junctions in the ENS.

### Substance P (and 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.

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 will diffuse 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 in the synapse is therefore very short. Acetylcholinesterase is also found in other tissues, eg, red blood cells. (Another cholinesterase with a lower specificity for acetylcholine, butyrylcholinesterase [pseudocholinesterase], is found in blood plasma, liver, glia, and many other tissues.)

### Adrenergic Transmission

Adrenergic neurons (Figure 6–4) also transport a precursor molecule into the nerve ending, then synthesize the catecholamine transmitter, and finally store it in membrane-bound vesicles, but—as indicated in Figure 6–5—the synthesis of the catecholamine transmitters is more complex than that of acetylcholine. In most sympathetic postganglionic neurons, norepinephrine is the final product. In the adrenal medulla and certain areas of the brain, norepinephrine is further converted to epinephrine. Conversely, synthesis terminates with dopamine in the dopaminergic neurons of the central nervous system. Several important 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* (Figure
6–4). A high-affinity carrier for catecholamines located in the wall of the storage vesicle can be
inhibited by the *reserpine* alkaloids (Figure 6–4, carrier B). Depletion of transmitter stores results.
Another carrier transports norepinephrine and similar molecules into the cell cytoplasm (Figure 6–
4, carrier 1, commonly called uptake 1 or reuptake 1). It can be inhibited by *cocaine* and *tricyclic
antidepressant* drugs, resulting in an increase of transmitter activity in the synaptic cleft.

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), which is transported into the vesicle by a carrier (B) that 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-\(\beta\)-hydroxylase. 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-\(\beta\)-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 (uptake 1, blocked by cocaine, tricyclic antidepressants) or into the postjunctional cell (uptake 2). Regulatory receptors are present on the presynaptic terminal. (SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.)

Figure 6–5.
Biosynthesis of catecholamines. The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α-methyltyrosine). The alternative pathways shown by the dashed arrows have 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.)

Release of the vesicular transmitter store from noradrenergic nerve endings is similar to the calcium-dependent process described above for cholinergic terminals. In addition to the primary transmitter (norepinephrine), ATP, dopamine-β-hydroxylase, and peptide cotransmitters are also released into the synaptic cleft. Indirectly acting sympathomimetics—eg, tyramine and amphetamines—are capable of releasing stored transmitter from noradrenergic nerve endings. These drugs are poor agonists (some are inactive) at adrenoceptors but are taken up into noradrenergic nerve endings by uptake 1. In the nerve ending, they may displace norepinephrine from storage vesicles, inhibit monoamine oxidase, and have other effects that result in increased norepinephrine activity in the synapse. Their action does not require vesicle exocytosis and is not calcium-dependent.

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 a 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 several processes, including simple diffusion away from the receptor site (with eventual metabolism in the plasma or liver) and reuptake into the nerve terminal (uptake 1) or into perisynaptic glia or smooth muscle cells (uptake 2) (Figure 6–4).

Figure 6–6.
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. 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 below. Their roles in the function of nerves that release acetylcholine or norepinephrine are not yet fully understood. 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 $\alpha$, $\beta$, and dopamine adrenoceptors (Table 6–2). Molecular biology now provides techniques for the discovery and expression of genes that code for related receptors within these groups. (See Chapter 2: Drug Receptors & Pharmacodynamics, How Are New Receptors Discovered?)

<table>
<thead>
<tr>
<th>Receptor Name</th>
<th>Typical Locations</th>
<th>Result of Ligand Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinoceptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic $M_1$</td>
<td>CNS neurons, sympathetic postganglionic neurons, some presynaptic sites</td>
<td>Formation of IP$_3$ and DAG, increased intracellular calcium</td>
</tr>
<tr>
<td>Muscarinic $M_2$</td>
<td>Myocardium, smooth muscle, some presynaptic sites</td>
<td>Opening of potassium channels, inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>Muscarinic $M_3$</td>
<td>Exocrine glands, vessels (smooth muscle and endothelium)</td>
<td>Formation of IP$_3$ and DAG, increased intracellular calcium</td>
</tr>
<tr>
<td>Nicotinic $N_N$</td>
<td>Postganglionic neurons, some presynaptic cholinergic terminals</td>
<td>Opening of Na$^+$, K$^+$ channels, depolarization</td>
</tr>
<tr>
<td>Nicotinic $N_M$</td>
<td>Skeletal muscle neuromuscular end plates</td>
<td>Opening of Na$^+$, K$^+$ channels, depolarization</td>
</tr>
<tr>
<td><strong>Adrenoceptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>Postsynaptic effector cells, especially smooth muscle</td>
<td>Formation of IP$_3$ and DAG, increased intracellular calcium</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle</td>
<td>Inhibition of adenylyl cyclase, decreased cAMP</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals</td>
<td>Stimulation of adenylyl cyclase, increased cAMP</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Postsynaptic effector cells, especially smooth muscle and cardiac muscle</td>
<td>Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac</td>
</tr>
</tbody>
</table>
The primary acetylcholine receptor subtypes were named after the alkaloids originally used in their identification: muscarine and nicotine. These nouns are readily converted into adjectives—thus, muscarinic and nicotinic receptors. In the case of receptors associated with noradrenergic nerves, the coining of simple adjectives from the names of the agonists (noradrenaline, phenylephrine, isoproterenol, etc) was not practicable. Therefore, the term adrenoceptor is widely used to describe receptors that respond to catecholamines such as norepinephrine. By analogy, the term cholinoreceptor 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 adrenoceptors can be subdivided into α-adrenoceptor and β-adrenoceptor types on the basis of both agonist and antagonist selectivity. Development of more selective blocking drugs has led to the naming of subclasses within these major types; eg, within the α-adrenoceptor class, α₁ and α₂ receptors differ in both agonist and antagonist selectivity. Specific examples of such selective drugs are given in the chapters that follow.

Nonadrenergic, Noncholinergic 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 nonadrenergic, noncholinergic 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). Improved immunologic assay methods now permit accurate identification and quantitation of peptides stored in and released from the fiber terminals. Capsaicin, a neurotoxin derived from chili peppers, can cause the 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 nonadrenergic, noncholinergic 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,
calcitonin gene-related peptide, cholecystokinin, dynorphin, enkephalins, gastrin-releasing peptide, 
5-hydroxytryptamine (serotonin), neuropeptide Y, somatostatin, substance P, and vasoactive 
intestinal peptide. Some neurons contain as many as five different transmitters. The ENS functions 
in a semiautonomous manner, utilizing input from the motor outflow of the ANS for modulation of 
gastrointestinal activity and sending sensory information back to the central nervous system. The 
ENS 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 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 at many autonomic effector tissues.

Functional Organization of Autonomic Activity

A basic understanding of the interactions of autonomic nerves with each other and with their 
effector organs is essential for an appreciation of the actions of autonomic drugs, especially because 
of the significant reflex (compensatory) effects that may be evoked by these agents.

Central Integration

At the highest level—midbrain and medulla—the two divisions of the autonomic nervous system 
and the endocrine system are integrated with each other, with sensory input, and with information 
from higher central nervous system centers. 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) that is 
activated for "fight or flight." While 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 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.

<table>
<thead>
<tr>
<th>Effect of</th>
<th>Sympathetic Activity</th>
<th>Parasympathetic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>Action (^1)</td>
<td>Receptor (^2)</td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial muscle</td>
<td>Contracts</td>
<td>M(^1)</td>
</tr>
<tr>
<td>Circular muscle</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Table 6–3. Direct Effects of Autonomic Nerve Activity on Some Organ Systems.
<table>
<thead>
<tr>
<th></th>
<th>Relaxation</th>
<th>Activation</th>
<th>Effector</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ciliary muscle</strong></td>
<td>[Relaxes]</td>
<td>$\beta$</td>
<td>Contracts</td>
<td>$M_3$</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinoatrial node</td>
<td>Accelerates</td>
<td>$\beta_1,\beta_2$</td>
<td>Decelerates</td>
<td>$M_2$</td>
</tr>
<tr>
<td>Ectopic pacemakers</td>
<td>Accelerates</td>
<td>$\beta_1,\beta_2$</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Contractility</td>
<td>Increases</td>
<td>$\beta_1,\beta_2$</td>
<td>Decreases (atria)</td>
<td>$M_2$</td>
</tr>
<tr>
<td><strong>Blood vessels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin, splanchnic vessels</td>
<td>Contracts</td>
<td>. . .</td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle vessels</td>
<td>Relaxes</td>
<td>$\beta_2$</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>[Contracts]</td>
<td>$\alpha$</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>Relaxes</td>
<td>$M^3$</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td><strong>Endothelium</strong></td>
<td></td>
<td></td>
<td>Releases EDRF</td>
<td>$M_3^4$</td>
</tr>
<tr>
<td><strong>Bronchiolar smooth muscle</strong></td>
<td>Relaxes</td>
<td>$\beta_2$</td>
<td>Contracts</td>
<td>$M_3$</td>
</tr>
<tr>
<td><strong>Gastrointestinal tract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smooth muscle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walls</td>
<td>Relaxes</td>
<td>$\alpha_2,\beta_2$</td>
<td>Contracts</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Sphincters</td>
<td>Contracts</td>
<td>$\alpha_1$</td>
<td>Relaxes</td>
<td>$M_3$</td>
</tr>
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<td>Secretion</td>
<td>. . .</td>
<td>. . .</td>
<td>Increases</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Myenteric plexus</td>
<td></td>
<td></td>
<td>Activates</td>
<td>$M_1$</td>
</tr>
<tr>
<td><strong>Genitourinary smooth muscle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder wall</td>
<td>Relaxes</td>
<td>$\beta_2$</td>
<td>Contracts</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Sphincter</td>
<td>Contracts</td>
<td>$\alpha_1$</td>
<td>Relaxes</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Uterus, pregnant</td>
<td>Relaxes</td>
<td>$\beta_2$</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>Contracts</td>
<td>$\alpha$</td>
<td>Contracts</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Penis, seminal vesicles</td>
<td>Ejaculation</td>
<td>$\alpha$</td>
<td>Erection</td>
<td>$M$</td>
</tr>
<tr>
<td>Skin</td>
<td>Pilomotor smooth muscle</td>
<td>Contracts</td>
<td>( \alpha )</td>
<td>...</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-----</td>
</tr>
<tr>
<td>Skin</td>
<td>Sweat glands</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Skin</td>
<td>Thermoregulatory</td>
<td>Increases</td>
<td>M</td>
<td>...</td>
</tr>
<tr>
<td>Skin</td>
<td>Apocrine (stress)</td>
<td>Increases</td>
<td>( \alpha )</td>
<td>...</td>
</tr>
</tbody>
</table>

**Metabolic functions**

<table>
<thead>
<tr>
<th>Liver</th>
<th>Gluconeogenesis</th>
<th>( \beta_2, \alpha )</th>
<th>...</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Glycogenolysis</td>
<td>( \beta_2, \alpha )</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Fat cells</td>
<td>Lipolysis</td>
<td>( \beta_3 )</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renin release</td>
<td>( \beta_1 )</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Autonomic nerve endings**

<table>
<thead>
<tr>
<th>Sympathetic</th>
<th>...</th>
<th>...</th>
<th>Decreases NE release</th>
<th>( M^6 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic</td>
<td>Decreases ACh release</td>
<td>( \alpha )</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

1 Less important actions are shown in brackets.

2 Specific receptor type: \( \alpha = \) alpha, \( \beta = \) 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. However, unlike the receptors innervated by sympathetic cholinergic fibers in skeletal muscle blood vessels, these muscarinic receptors are not innervated and respond only to circulating muscarinic agonists.

5 Probably through presynaptic inhibition of parasympathetic activity.

6 Probably \( M_1 \) but \( M_2 \) may participate in some locations.

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 below. Similarly, parasympathetic sensory fibers in the wall of the urinary bladder significantly influence sympathetic inhibitory outflow to that organ. Within the enteric nervous system, 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) will evoke powerful **homeostatic** secondary responses that tend to compensate for the directly evoked 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; ie, it increases heart rate and contractile force. However, in a subject with intact reflexes, the negative feedback baroreceptor 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. As a result, the net effect of ordinary pressor doses of norepinephrine 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 autonomic nervous system is understood.

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. 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 and renin release and increased parasympathetic (vagal) outflow.

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 an \( \alpha_2 \) 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). Conversely, a presynaptic \( \beta \) receptor appears to facilitate the release of norepinephrine. Presynaptic receptors that respond to the transmitter substances released by the nerve ending are called autoreceptors. Autoreceptors are usually inhibitory, but many cholinergic fibers, especially somatic motor fibers, have excitatory nicotinic autoreceptors.

Table 6–4. Autoreceptor, Heteroreceptor, and Modulatory Effects in Peripheral Synapses.¹

<table>
<thead>
<tr>
<th>Transmitter/Modulator</th>
<th>Receptor Type</th>
<th>Neuron Terminals Where Found</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibitory effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>M₂</td>
<td>Adrenergic, enteric nervous system</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Alpha₂</td>
<td>Adrenergic</td>
</tr>
<tr>
<td>Dopamine</td>
<td>D₂; less evidence for D₁</td>
<td>Adrenergic</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>5-HT₁, 5-HT₂, 5-HT₃</td>
<td>Cholinergic preganglionic</td>
</tr>
<tr>
<td>ATP and adenosine</td>
<td>P₂ (ATP), P₁ (adenosine)</td>
<td>Adrenergic autonomic and ENS cholinergic neurons</td>
</tr>
<tr>
<td>Histamine</td>
<td>H₃, possibly H₂</td>
<td>H₃ type identified on CNS adrenergic and serotonergic neurons</td>
</tr>
<tr>
<td>Enkephalin</td>
<td>Delta (also mu, kappa)</td>
<td>Adrenergic, ENS cholinergic</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>NPY</td>
<td>Adrenergic, some cholinergic</td>
</tr>
</tbody>
</table>
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 the prior history of activity at the primary receptor (which may up- or down-regulate receptor number or desensitize receptors; see Chapter 2: Drug Receptors & Pharmacodynamics) and modulation by other temporally associated events.

The first mechanism has been well documented in several receptor-effector systems. Up- 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 cholinoreceptors 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, 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 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

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E₁, E₂</td>
<td>EP₃</td>
<td>Adrenergic</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Beta₂</td>
<td>Adrenergic, somatic motor cholinergic</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>NM</td>
<td>Somatic motor cholinergic, ANS cholinergic</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>AT₁</td>
<td>Adrenergic</td>
</tr>
</tbody>
</table>

¹A provisional list. The number of transmitters and locations will undoubtedly increase with additional research.
slowly developing but longer-lasting hyperpolarizing afterpotential—a slow inhibitory postsynaptic potential (IPSP). The hyperpolarization involves opening of potassium channels by M₂ cholinoceptors. The IPSP is followed by a small, slow excitatory postsynaptic potential caused by closure of potassium channels linked to M₁ 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 excitatory presynaptic nerve activity. (See Chapter 21: Introduction to the Pharmacology of CNS Drugs for additional examples.)

**Figure 6–8.**

<table>
<thead>
<tr>
<th>Preganglionic axon</th>
<th>Membrane potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrode</td>
<td>0 mV</td>
</tr>
<tr>
<td>Postganglionic axon</td>
<td>-100 mV</td>
</tr>
</tbody>
</table>

**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 achieving threshold. The action potential is followed by an IPSP, probably evoked by M₂ receptor activation (with possible participation from dopamine receptor activation). The IPSP is, in turn, followed by a slower M₁-dependent EPSP, and this is sometimes followed by a still slower peptide-induced excitatory postsynaptic potential.

**Pharmacologic Modification of Autonomic Function**

Because transmission involves different mechanisms in different segments of the autonomic nervous system, some drugs produce highly specific effects while others are much less selective in their actions. A summary of the steps in transmission of impulses, from the central nervous system to the autonomic effector cells, is presented in Table 6–5. Drugs that block action potential propagation (local anesthetics) 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 adrenergic transmission is very different from that of cholinergic transmission. Activation or blockade of effector cell receptors offers maximum flexibility and selectivity of effect: adrenoceptors are easily distinguished from cholinoceptors. Furthermore, individual subgroups can often be selectively activated or blocked within each major type. Some examples are given in Pharmacology of the Eye.
### Table 6–5. Steps in Autonomic Transmission: Effects of Drugs.

<table>
<thead>
<tr>
<th>Process</th>
<th>Drug Example</th>
<th>Site</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action potential propagation</td>
<td>Local anesthetics, tetrodotoxin&lt;sup&gt;1&lt;/sup&gt;, saxitoxin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Nerve axons</td>
<td>Block sodium channels; block conduction</td>
</tr>
<tr>
<td>Transmitter synthesis</td>
<td>Hemicholinium</td>
<td>Cholinergic nerve terminals: membrane</td>
<td>Blocks uptake of choline and slows synthesis</td>
</tr>
<tr>
<td></td>
<td>α-Methyltyrosine (metyrosine)</td>
<td>Adrenergic nerve terminals and adrenal medulla: cytoplasm</td>
<td>Blocks synthesis</td>
</tr>
<tr>
<td>Transmitter storage</td>
<td>Vesamicol</td>
<td>Cholinergic terminals: vesicles</td>
<td>Prevents storage, depletes</td>
</tr>
<tr>
<td></td>
<td>Reserpine</td>
<td>Adrenergic terminals: vesicles</td>
<td>Prevents storage, depletes</td>
</tr>
<tr>
<td>Transmitter release</td>
<td>Many&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Nerve terminal membrane receptors</td>
<td>Modulate release</td>
</tr>
<tr>
<td></td>
<td>α-Conotoxin GVIA&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Nerve terminal calcium channels</td>
<td>Blocks calcium channels, reduces transmitter release</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin</td>
<td>Cholinergic vesicles</td>
<td>Prevents release</td>
</tr>
<tr>
<td></td>
<td>Alpha-latrotoxin&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Cholinergic and adrenergic vesicles</td>
<td>Causes explosive release</td>
</tr>
<tr>
<td></td>
<td>Tyramine, amphetamine</td>
<td>Adrenergic nerve terminals</td>
<td>Promote transmitter release</td>
</tr>
<tr>
<td>Transmitter uptake after release</td>
<td>Cocaine, tricyclic antidepressants</td>
<td>Adrenergic nerve terminals</td>
<td>Inhibit uptake; increase transmitter effect on postsynaptic receptors</td>
</tr>
<tr>
<td></td>
<td>6-Hydroxydopamine</td>
<td>Adrenergic nerve terminals</td>
<td>Destroys the terminals</td>
</tr>
<tr>
<td>Receptor activation or blockade</td>
<td>Norepinephrine</td>
<td>Receptors at adrenergic junctions</td>
<td>Binds α&lt;sub&gt;1&lt;/sub&gt; receptors; causes activation</td>
</tr>
<tr>
<td></td>
<td>Phentolamine</td>
<td>Receptors at adrenergic junctions</td>
<td>Binds α&lt;sub&gt;2&lt;/sub&gt; receptors; prevents activation</td>
</tr>
<tr>
<td></td>
<td>Isoproterenol</td>
<td>Receptors at adrenergic junctions</td>
<td>Binds β&lt;sub&gt;1&lt;/sub&gt; receptors; activates adenylyl cyclase</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>Receptors at adrenergic junctions</td>
<td>Binds β&lt;sub&gt;2&lt;/sub&gt; receptors; prevents activation</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>Receptors at nicotinic cholinergic junctions (autonomic ganglia, neuromuscular end plates)</td>
<td>Binds nicotinic receptors; opens ion channel in</td>
</tr>
</tbody>
</table>
postsynaptic membrane

<table>
<thead>
<tr>
<th></th>
<th>Neuromuscular end plates</th>
<th>Prevents activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Receptors, parasympathetic effector cells (smooth muscle, glands)</th>
<th>Binds and activates muscarinic receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethanechol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Receptors, parasympathetic effector cells</th>
<th>Binds muscarinic receptors; prevents activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzymatic inactivation of transmitter</th>
<th>Cholinergic synapses (acetylcholinesterase)</th>
<th>Inhibits enzyme; prolongs and intensifies transmitter action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tranylcypromine</th>
<th>Adrenergic nerve terminals (monoamine oxidase)</th>
<th>Inhibits enzyme; increases stored transmitter pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Toxin of puffer fish, California newt.
2. Toxin of *Gonyaulax* (red tide organism).
3. Norepinephrine, dopamine, acetylcholine, peptides, various prostaglandins, etc.
4. Toxin of marine snails of the genus *Conus*.
5. Black widow spider venom.

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

**Pharmacology of the Eye**

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

**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 through the anterior chamber, and exits via the canal of Schlemm (arrow). Blockade of the 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.

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 alpha 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.

Chapter 7. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs

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, ie, 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 cholinoimmetic 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 intramembrane transducers (see Figure 2–11). In general, these receptors regulate the production of intracellular second messengers. Agonist selectivity is determined by the subtypes of muscarinic receptors and G proteins that are present in a given cell (Table 7–1). Muscarinic receptors are located on plasma membranes of cells in the central nervous system, in organs innervated by parasympathetic 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.

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Other Names</th>
<th>Location</th>
<th>Structural Features</th>
<th>Postreceptor Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>M₁a</td>
<td>Nerves</td>
<td>Seven transmembrane segments, G protein-linked</td>
<td>IP₃, DAG cascade</td>
</tr>
<tr>
<td>M₂</td>
<td>M₂α, cardiac M₂</td>
<td>Heart, nerves, smooth muscle</td>
<td>Seven transmembrane segments, G protein-linked</td>
<td>Inhibition of cAMP production, activation of K⁺ channels</td>
</tr>
<tr>
<td>M₃</td>
<td>M₂β, glandular</td>
<td>Glands, smooth</td>
<td>Seven transmembrane segments, G protein-linked</td>
<td>IP₃, DAG cascade</td>
</tr>
</tbody>
</table>
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).

Unselective cholinceptor 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.

Mode of Action of Cholinomimetic Drugs

Direct-acting cholinomimetic agents directly 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 neuroeffecter junctions, and the excess acetylcholine in turn stimulates cholinceptors to evoke increased responses. These drugs act primarily where acetylcholine is physiologically released and are amplifiers of endogenous acetylcholine.

<table>
<thead>
<tr>
<th></th>
<th>M₂</th>
<th>muscle, endothelium</th>
<th>segments, G protein-linked</th>
</tr>
</thead>
<tbody>
<tr>
<td>m₄¹</td>
<td>?CNS</td>
<td>Seven transmembrane segments, G protein-linked</td>
<td>Inhibition of cAMP production</td>
</tr>
<tr>
<td>m₅¹</td>
<td>?CNS</td>
<td>Seven transmembrane segments, G protein-linked</td>
<td>IP₃, DAG cascade</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Muscle type, end plate receptor</th>
<th>Skeletal muscle neuromuscular junction</th>
<th>Pentamer (αββγ)²</th>
<th>Na⁺, K⁺ depolarizing ion channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₇</td>
<td>Neuronal type, ganglion receptor</td>
<td>Postganglionic cell body, dendrites</td>
<td>α and β subunits only as α₂β₂ or α₂β₃</td>
<td>Na⁺, K⁺ depolarizing ion channel</td>
</tr>
</tbody>
</table>

¹Genes have been cloned, but functional receptors have not been incontrovertibly identified.

²Structure in *Torpedo* electric organ and fetal mammalian muscle. In adult muscle, the ρ subunit is replaced by an ε subunit. Several different α and β subunits have been identified in different mammalian tissues (Lukas et al, 1999).
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). A few of these drugs are highly selective for the muscarinic or for the nicotinic receptor. Many have effects on both receptors; acetylcholine is typical.

Chemistry & Pharmacokinetics

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.

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

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 in the body. Acetylcholine is very rapidly hydrolyzed (see Chapter 6: Introduction to Autonomic Pharmacology); large amounts must be infused intravenously to achieve concentrations high enough 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).

### Table 7–2. Properties of Choline Esters.

<table>
<thead>
<tr>
<th>Choline Ester</th>
<th>Susceptibility to Cholinesterase</th>
<th>Muscarinic Action</th>
<th>Nicotinic Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine chloride</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Methacholine chloride</td>
<td>+</td>
<td>+++</td>
<td>None</td>
</tr>
<tr>
<td>Carbachol chloride</td>
<td>Negligible</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bethanechol chloride</td>
<td>Negligible</td>
<td>++</td>
<td>None</td>
</tr>
</tbody>
</table>

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 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.

**Figure 7–3.**

[Structures of some cholinomimetic alkaloids.](#)
Pharmacodynamics

Mechanism of Action

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

The mechanisms by which muscarinic stimulants alter cellular function continue to be investigated. As indicated in Chapter 6: Introduction to Autonomic Pharmacology, 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: Drug Receptors & Pharmacodynamics and Table 7–1). Muscarinic agonist binding activates the IP₃, DAG cascade. Some evidence implicates DAG in the opening of smooth muscle calcium channels; IP₃ 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 and decreases it in ganglion and smooth muscle cells. This effect is mediated by the binding of an activated G protein directly to the channel. Finally, muscarinic receptor activation in some tissues (eg, heart, intestine) inhibits adenylyl cyclase activity. Moreover, muscarinic agonists can 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 cause a reduction of the physiologic response of the organ to stimulatory hormones.

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, is tightly bound to the receptors and 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 (see Figure 2–9). The neuronal nicotinic receptor consists of α and β subunits only (Table 7–1). Each subunit has four transmembrane segments. Each α subunit has a receptor site that, when occupied by a nicotinic agonist, causes a conformational change in the protein (channel opening) that allows sodium and potassium ions to diffuse rapidly down their concentration gradients. While binding of an agonist molecule by one of the two α subunit receptor sites only modestly increases the probability of channel opening, simultaneous binding of agonist by both of the receptor sites greatly enhances opening probability. The primary effect of nicotinic receptor activation is depolarization of the nerve cell or neuromuscular end plate membrane.

Prolonged agonist occupancy of the nicotinic receptor abolishes the effector response; ie, 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" is induced that is refractory to reversal by other agonists. As noted below, this effect can be exploited for producing muscle paralysis.
Organ System Effects

Most of the direct organ system effects of muscarinic cholinoreceptor stimulants are readily predicted from a 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 a knowledge of the physiology of the autonomic ganglia and skeletal muscle motor end plate.

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

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: Introduction to Autonomic Pharmacology and depicted in Figure 6–7. Intravenous infusions of minimal effective doses of acetylcholine in humans (eg, 20–50 \( \mu \)g/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 the hypotensive effect.

The direct cardiac actions of muscarinic stimulants include the following: (1) an increase in a potassium current (\( I_{K(ACh)} \)) in atrial muscle cells and in the cells of the sinoatrial and atrioventricular nodes as well; (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. All of these actions are mediated by \( M_2 \) receptors and contribute to slowing the pacemaker rate. Effects (1) and (2) cause hyperpolarization and decrease the contractility of atrial cells.

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. The resultant sympathetic-parasympathetic interaction is complex because of the muscarinic modulation of sympathetic influences that 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.

Parasympathetic innervation of the ventricles is much less extensive than that of the atria and activation of ventricular muscarinic receptors results in much less physiologic effect than that seen in atria. However, during sympathetic stimulation, the effects of muscarinic agonists on ventricular function are clearly evident because of muscarinic modulation of sympathetic effects ("accentuated antagonism"; Levy et al, 1994).

In the intact organism, muscarinic agonists produce marked vasodilation. However, in earlier studies, isolated blood vessels often showed a contractile response to these agents. It is now known that acetylcholine-induced vasodilation requires the presence of intact endothelium (Figure 7–4). Muscarinic agonists release a substance (endothelium-derived relaxing factor, or EDRF) from the endothelial cells that relaxes smooth muscle. Isolated vessels prepared with the endothelium preserved consistently reproduce the vasodilation seen in the intact organism. EDRF appears to be largely nitric oxide (NO). This substance activates guanylyl cyclase and increases cGMP in smooth muscle, resulting in relaxation (see Figure 12–2).

Figure 7–4.
Activation of endothelial cell muscarinic receptors by acetylcholine releases endothelium-derived relaxing factor (nitric oxide) (EDRF [NO]), which causes relaxation of vascular smooth muscle precontracted with norepinephrine. Removal of the endothelium by rubbing eliminates the relaxant effect and reveals contraction caused by direct action of acetylcholine on vascular smooth muscle. (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.)

The cardiovascular effects of all of 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 M1 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.

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.

Gastrointestinal Tract

Administration of muscarinic agonists, like 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 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.

Genitourinary Tract

Muscarinic agonists stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding. The human uterus is not notably sensitive to muscarinic agonists.

Miscellaneous Secretory Glands
Muscarinic agonists stimulate secretion by thermoregulatory sweat, lacrimal, and nasopharyngeal glands.

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: Introduction to the Pharmacology of CNS Drugs.

The role of muscarinic receptors in the central nervous system has been confirmed by experiments in knockout mice (see Chapter 1: Introduction). Predictably, carbachol did not inhibit atrial rate in animals with mutated M2 receptors. The central nervous system effects of the synthetic muscarinic agonist oxotremorine (tremor, hypothermia, and antinociception) were also lacking in mice with homozygously mutated M2 receptors. Knockout of M1 receptors is associated with different changes in the peripheral and central nervous systems. Oxotremorine did not suppress M current in sympathetic ganglia, and pilocarpine did not induce epileptic seizures in M1 mutant mice.

In spite of the smaller ratio of nicotinic to muscarinic receptors in the brain, nicotine and lobeline (Figure 7–3) have important effects on the brainstem and cortex. The mild alerting action of nicotine absorbed from inhaled tobacco smoke is the best-known of these effects. In larger 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. Dimethylphenylpiperazinium (DMPP), a synthetic nicotinic stimulant used in research is relatively free of these central effects because it does not cross the blood-brain barrier.

Peripheral Nervous System

The 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. 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 vagally mediated bradycardia. 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.

Neuromuscular Junction
The nicotinic receptors on the neuromuscular end plate apparatus are similar but not identical to the receptors in the autonomic ganglia (see Table 7–1). Both types respond to acetylcholine and nicotine. (However, as discussed in Chapter 8: Cholinoceptor-Blocking Drugs, 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. Depending on the synchronization of depolarization of end plates throughout the muscle, the contractile response will vary from disorganized fasciculations of independent motor units to a strong contraction of the entire 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). In the case of skeletal muscle, this block is manifested as flaccid paralysis.

Basic Pharmacology of the Indirect-Acting Cholinomimetics

The actions of acetylcholine released from autonomic and somatic motor nerves are terminated by enzymatic destruction 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

Structure

The commonly used cholinesterase inhibitors fall into three chemical groups: (1) simple alcohols bearing a quaternary ammonium group, eg, edrophonium; (2) carbamic acid esters of alcohols bearing 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 7–5. Edrophonium, neostigmine, and ambenonium 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.

Figure 7–5.
Cholinesterase inhibitors. Neostigmine exemplifies the typical compound that is an ester 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.

A few of the estimated 50,000 organophosphates are shown in Figure 7–6. 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 insecticides that are inactive as such; they are converted to the phosphate derivatives in animals and plants and are used as insecticides.

Figure 7–6.
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.

Absorption, Distribution, and Metabolism

Absorption of the quaternary carbamates from the conjunctiva, skin, and lungs is predictably poor, since their permanent charge renders them relatively insoluble in lipids. Similarly, 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.

Table 7–4. Therapeutic Uses and Durations of Action of Cholinesterase Inhibitors.

<table>
<thead>
<tr>
<th>Uses</th>
<th>Approximate Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohols</strong></td>
<td></td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Myasthenia gravis, ileus, arrhythmias</td>
</tr>
<tr>
<td><strong>Carbamates and related agents</strong></td>
<td></td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Myasthenia gravis, ileus</td>
</tr>
<tr>
<td>Drug</td>
<td>Condition</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Ambenonium</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Demecarium</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>

**Organophosphates**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echotiohate</td>
<td>Glaucoma</td>
<td>100 hrs</td>
</tr>
</tbody>
</table>

The organophosphate cholinesterase inhibitors (except for echotiohate) are well absorbed from the skin, lung, gut, and 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 the other major class of insecticides, the halogenated hydrocarbons, eg, DDT). Echotiohate is highly polar and more stable than most other organophosphates. It can be made up in aqueous solution for ophthalmic use and retains its 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 7–6), a process that occurs rapidly in both insects and vertebrates. Malathion and certain 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.

All of the organophosphates except echotiohate are distributed to all parts of the body, including the central nervous system. Poisoning with these agents therefore includes an important component of central nervous system toxicity.

### Pharmacodynamics

#### 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 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 takes place in approximately 150 microseconds.

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

The first group, of which edrophonium is the major 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. If given before aging has occurred, strong nucleophiles like pralidoxime are able to split the phosphorus-enzyme bond and can be used as "cholinesterase regenerator" drugs for organophosphate insecticide poisoning (see Chapter 8: Cholinoceptor-Blocking Drugs). Once aging has occurred, the enzyme-inhibitor complex is even more stable and is more difficult to split, even with oxime regenerator compounds.

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

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. 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.

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.

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.

Cardiovascular System

The cholinesterase inhibitors can increase activation 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 less marked effects on vascular smooth muscle and on blood pressure than direct-acting muscarinic agonists. This is because indirect-acting drugs can modify the tone of only those vessels that are innervated by cholinergic nerves and because the net effects on vascular tone may reflect activation of both the parasympathetic and sympathetic nervous systems. The cholinomimetic effect at the smooth muscle effector tissue is minimal since few vascular beds receive cholinergic innervation. Activation of sympathetic ganglia may increase vascular resistance.

The net cardiovascular effects of moderate doses of cholinesterase inhibitors therefore consist of modest bradycardia, a fall in cardiac output, and no change or a modest fall in blood pressure. Large (toxic) doses of these drugs cause more marked bradycardia (occasionally tachycardia) and hypotension.

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 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 27–6).

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 for diseases of the eye (glaucoma, accommodative esotropia), the gastrointestinal and urinary tracts (postoperative atony, neurogenic bladder), the neuromuscular junction (myasthenia gravis, curare-induced neuromuscular paralysis), and rarely, the heart (certain atrial arrhythmias). Cholinesterase inhibitors are occasionally used in the treatment of atropine overdosage. Several newer cholinesterase inhibitors are being used to treat patients with Alzheimer's disease.

Clinical Uses

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 section Treatment of Glaucoma in Chapter 10: Adrenoceptor Antagonist Drugs.

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.

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 prior to 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 is a new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome.

Neuromuscular Junction

Myasthenia gravis is a disease affecting skeletal muscle neuromuscular junctions. An autoimmune process causes production of antibodies that decrease the number of functional nicotinic receptors on the postjunctional end plates. 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: Skeletal Muscle Relaxants). 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. Almost all patients are also treated with immunosuppressant drugs and some with thymectomy.

Edrophonium is sometimes used as a diagnostic test for myasthenia. A 2 mg dose is injected intravenously after baseline measurements of muscle strength have been obtained. If no reaction occurs after 45 seconds, an additional 8 mg may be injected. Some clinicians divide the 8 mg dose into two doses of 3 and 5 mg given at 45-second intervals. If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5 minutes will usually be observed.

Edrophonium is also used to assess the adequacy of treatment with the longer-acting cholinesterase inhibitors 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. 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.

Long-term therapy for myasthenia gravis is usually accomplished with neostigmine, pyridostigmine, or ambenonium. The doses are titrated to optimum levels based on changes in muscle strength. These agents are relatively short-acting and therefore require frequent dosing (every 4 hours for neostigmine and every 6 hours for pyridostigmine and ambenonium; 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 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: Skeletal Muscle Relaxants). Following 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.

Heart

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

Antimuscarinic Drug Intoxication
Atropine intoxication is potentially lethal in children (see Chapter 8: Cholinooceptor-Blocking Drugs) 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: Antidepressant Agents). The muscarinic receptor blockade produced by all these agents is competitive in nature and can be overcome by increasing the amount of endogenous acetylcholine present 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 noted previously, 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.

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. Evidence for 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 comparative trials of these newer drugs and tacrine have been reported. These drugs are discussed in Chapter 61: Special Aspects of Geriatric Pharmacology.

Toxicity

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

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, 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. Treatment is with atropine, 1–2 mg parenterally. (*Amanita muscaria*, the first source of muscarine, contains very low concentrations of the alkaloid.)

Direct-Acting Nicotinic Stimulants

Nicotine itself is the only common cause of this type of poisoning. 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.

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 respiration.

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.

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 studies. Unfortunately, the fact that the most important of the tobacco-associated diseases are delayed in onset reduces the health incentive to stop smoking.

It is clear that 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. It is also probable that nicotine contributes to the high incidence of ulcer recurrences in smokers with peptic ulcer.

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.

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 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: Cholinoceptor-Blocking Drugs.

Chronic exposure to certain organophosphate compounds, including some organophosphate cholinesterase inhibitors, causes neuropathy associated with demyelination of axons.
**Triorthocresylphosphate**, an additive in lubricating oils, is the prototype agent of this class. The effects are not caused by cholinesterase inhibition.

Preparations Available

**Direct-Acting Cholinomimetics**

**Acetylcholine** (Miochol-E)

Ophthalmic: 1:100 (10 mg/mL) 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% drops

Ophthalmic (intraocular, Miostat, Carbastat): 0.01% solution

**Cevimeline** (Evoxac)

Oral: 30 mg capsules

**Pilocarpine** (generic, Isopto Carpine)

Ophthalmic (topical): 0.25, 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 μg pilocarpine per hour for 1 week, respectively

Oral (Salagen): 5 mg tablets

Cholinesterase Inhibitors

**Ambenonium** (Mytelase)

Oral: 10 mg tablets

**Demecarium** (Humorsol)

Ophthalmic: 0.125, 0.25% drops

**Donepezil** (Aricept)
Chapter 8. Cholinoceptor-Blocking Drugs

Cholinoceptor-Blocking Drugs: Introduction

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

As noted in Chapter 6: Introduction to Autonomic Pharmacology and Chapter 7: Cholinoreceptor-Activating & Cholinesterase-Inhibiting Drugs, five subtypes of muscarinic receptors have been described, primarily on the basis of data from ligand-binding and cDNA-cloning experiments. A standard terminology (M1 through M5) 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.

As suggested in Chapter 6: Introduction to Autonomic Pharmacology, the M1 receptor subtype appears to be located on central nervous system neurons, sympathetic postganglionic cell bodies, and many presynaptic sites. M2 receptors are located in the myocardium, smooth muscle organs, and some neuronal sites. M3 receptors are most common on effector cell membranes, especially glandular and smooth muscle cells.

Basic Pharmacology of the Muscarinic Receptor-Blocking Drugs

Muscarinic antagonists are often 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

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 in Datura stramonium, also known as jimsonweed (Jamestown weed) 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 central nervous system. Many antihistaminic (see Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids), antipsychotic (see Chapter 29: Antipsychotic Agents & Lithium), and antidepressant (see Chapter 30: Antidepressant Agents) drugs have similar structures and, predictably, significant antimuscarinic effects.

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

Quaternary amines for gastrointestinal applications (peptic disease, hypermotility):

- **Propantheline**
- **Glycopyrrolate**

Tertiary amines for peripheral applications:

- **Pirenzepine** *(peptic disease)*
- **Dicyclomine** *(peptic disease, hypermotility)*
- **Tropicamide** *(mydriatic, cycloplegic)*

Quaternary amine for use in asthma:

- **Ipratropium**

Tertiary amine for Parkinson’s disease:

- **Benztropine**

Structures of some semisynthetic and synthetic antimuscarinic drugs.
Quaternary amine antimuscarinic agents (Figure 8–2) have been developed to produce more peripheral effects with reduced central nervous system effects.

Absorption

The 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.

Distribution

Atropine and the other tertiary agents are widely distributed in the body. Significant levels are achieved in the central nervous system within 30 minutes to 1 hour, and this may limit the dose tolerated when the drug is taken for its peripheral effects. Scopolamine is rapidly and fully distributed into the central nervous system 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 central nervous system effects.

Metabolism and Excretion

Atropine disappears rapidly from the blood after administration, with a half-life of 2 hours. About 60% 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

Mechanism of Action

Atropine causes reversible (surmountable) blockade of cholinomimetic actions at muscarinic receptors—ie, blockade by a small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist. Mutation experiments suggest that a specific amino acid is required in the receptor to form the characteristic 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 the actions described in Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs such as the release of inositol trisphosphate (IP$_3$) and the inhibition of adenylyl cyclase that are caused by muscarinic agonists.

The effectiveness of antimuscarinic drugs varies with the tissue under study 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 between the M$_1$, M$_2$, and M$_3$ subgroups of muscarinic receptors. In contrast, other antimuscarinic drugs have moderate selectivity for one or another of these subgroups.
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 groups, eg, antipsychotic and antidepressant drugs, have been mentioned. Their relative selectivity for muscarinic receptor subtypes has not been defined.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Property</th>
<th>(M_1)</th>
<th>(M_2)</th>
<th>(M_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary locations</td>
<td>Nerves</td>
<td>Heart, nerves, smooth muscle</td>
<td>Glands, smooth muscle, endothelium</td>
<td></td>
</tr>
<tr>
<td>Dominant effector system</td>
<td>(\uparrow\text{IP}_3, \uparrow\text{DAG})</td>
<td>(\downarrow\text{cAMP}, \downarrow\text{K}^+) channel current</td>
<td>(\uparrow\text{IP}_3, \uparrow\text{DAG})</td>
<td></td>
</tr>
<tr>
<td>Antagonists</td>
<td>Pirenzepine, telenzepine</td>
<td>Gallamine,(^1) methoctramine, AF-DX 116</td>
<td>4-DAMP, HHSD, darifenacin</td>
<td></td>
</tr>
<tr>
<td>Approximate dissociation constant(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>10</td>
<td>50</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>AF-DX 116</td>
<td>800</td>
<td>100</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>HHSD</td>
<td>40</td>
<td>200</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)In clinical use as a neuromuscular blocking agent.

\(^2\)In clinical use as an intestinal antispasmodic agent.

\(^3\)In clinical use in the treatment of Parkinson's disease.

\(^4\)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)benzodiazepin-6-one; DAG, Diacylglycerol; IP\(_3\), Inositol trisphosphate; 4-DAMP, 4-Diphenylacetoxy-N-methylpiperidine; HHSD, Hexahydrosiladifenidol

Organ System Effects

Central Nervous System
In the doses usually used, atropine has minimal stimulant effects on the central nervous system, especially the parasympathetic medullary centers, and a slower, longer-lasting sedative effect on the brain. Scopolamine has more marked central effects, producing 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: Pharmacologic Management of Parkinsonism & Other Movement Disorders, 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) may 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.

Eye

The pupillary constrictor muscle (see Figure 6–9) depends on muscarinic cholinceptor 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.

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.)

The second important ocular effect of antimuscarinic drugs is weakening of contraction of the ciliary muscle, or cycloplegia. The result of cycloplegia is 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 precipitated in patients with a narrow anterior chamber angle.

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

Cardiovascular System

The sinoatrial node is very sensitive to muscarinic receptor blockade. The effect of moderate to high therapeutic doses of atropine in the innervated and spontaneously beating heart is a blockade of vagal slowing and a relative tachycardia. 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 presynaptic muscarinic receptors on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues. The same mechanisms operate in the control of atrioventricular node function; in the presence of high vagal tone, atropine can significantly reduce the PR interval of the ECG 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. Because of a lesser degree of muscarinic control, the ventricles are less affected by antimuscarinic drugs at therapeutic levels. In toxic concentrations, the drugs can cause intraventricular conduction block by an unknown mechanism.

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 M₁ and M₂ cholinoreceptors. Naunyn Schmiedebergs Arch Pharmacol 1988;338:19.)

Blood vessels receive no direct innervation from the parasympathetic nervous system. However, parasympathetic nerve stimulation dilates coronary arteries, and sympathetic cholinergic nerves cause vasodilation in the skeletal muscle vascular bed (see Chapter 6: Introduction to Autonomic Pharmacology). Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation (see Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs). These receptors are readily blocked by antimuscarinic 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 stimulants are easily prevented.

Respiratory System

Both smooth muscle and secretory glands of the airway receive vagal innervation and contain muscarinic receptors. Even in normal individuals, some bronchodilation and reduction of secretion can be measured after administration of atropine. The effect is more significant in patients with airway disease, although the antimuscarinic drugs are not as useful as the B-adrenoceptor stimulants in the treatment of asthma (see Chapter 20: Drugs Used in Asthma). The effectiveness of unselective antimuscarinic drugs in treating chronic obstructive pulmonary disease (COPD) is limited because block of autoinhibitory M₂ receptors on postganglionic parasympathetic nerves can oppose the bronchodilation caused by block of M₃ receptors on airway smooth muscle. Nevertheless, antimuscarinic agents are valuable in some patients with asthma or COPD.
Antimuscarinic drugs are frequently used prior to administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

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 63) also modulate gastrointestinal function. As in other tissues, exogenously administered muscarinic stimulants are more effectively blocked than 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 greater efficacy of antimuscarinic drugs against exogenous muscarinic stimulants.

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 results from a selective blockade of presynaptic excitatory muscarinic receptors on vagal nerve endings as suggested by their high ratio of \( M_1 \) to \( M_3 \) affinity (Table 8–1). 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.

Figure 8–5.

![Graph showing effects of atropine on salivation, micturition speed, heart rate, and accommodation](image)

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.)

| Table 8–2. Antimuscarinic Drugs Used in Ophthalmology. |
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 that 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 will usually reestablish at least some peristalsis after 1–3 days of antimuscarinic drug therapy.

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 elderly men, who may have prostatic hyperplasia (see following section, Clinical Pharmacology of the Muscarinic Receptor-Blocking Drugs). The antimuscarinic drugs have no significant effect on the uterus.

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

Central Nervous System Disorders

Parkinson's Disease

As described in Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders, 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.
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, by mouth, or as a transdermal patch. The patch formulation produces significant blood levels over 48–72 hours. Unfortunately, useful doses by any route usually cause significant sedation and dry mouth.

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 extremely 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 instead of drops. In the past, ophthalmic antimuscarinic drugs have been 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: Adrenoceptor-Activating & Other Sympathomimetic Drugs).

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.

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.

As described in Chapter 20: Drugs Used in Asthma, 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 (Figure 8–2), a synthetic analog of atropine, is used as an inhalational drug in asthma. The aerosol route of administration provides the advantages of maximal concentration at the bronchial target tissue with reduced systemic effects. This application is discussed in greater detail in Chapter 20: Drugs Used in Asthma. Ipratropium has also proved useful in COPD, a condition that occurs with higher frequency in older patients, particularly chronic smokers. Patients with COPD benefit from bronchodilators, especially antimuscarinic agents such as ipratropium. Investigational agents in this category include tiotropium, a long-acting quaternary aerosol antimuscarinic drug.
Cardiovascular Disorders

Marked reflex vagal discharge sometimes accompanies the pain of myocardial infarction and may result in sufficient depression of sinoatrial or atrioventricular node function 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 muscarinic receptors have been detected in some patients with idiopathic dilated cardiomyopathy. These antibodies exert parasympathomimetic actions on the heart that are prevented by atropine. Although their role in the pathology of heart failure is unknown, they should provide clues to the molecular basis of receptor activation.

Gastrointestinal Disorders

Antimuscarinic agents are now rarely used for peptic ulcer disease in the USA (see Chapter 63: Drugs Used in the Treatment of Gastrointestinal Diseases). 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 often combined with an opioid anti-diarrheal 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 63: Drugs Used in the Treatment of Gastrointestinal Diseases).

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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quaternary amines</strong></td>
<td></td>
</tr>
<tr>
<td>Anisotropine</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Clidinium</td>
<td>2.5 mg tid–qid</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>1 mg bid–tid</td>
</tr>
<tr>
<td>Isopropamide</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>Mepenzolate</td>
<td>25–50 mg qid</td>
</tr>
<tr>
<td>Methantheline</td>
<td>50–100 mg qid</td>
</tr>
<tr>
<td>Methscopolamine</td>
<td>2.5 mg qid</td>
</tr>
<tr>
<td>Oxyphenonium</td>
<td>5–10 mg qid</td>
</tr>
</tbody>
</table>
### Antimuscarinic Therapy

As noted in Chapter 7: Cholinesterase-Inhibiting & Cholinomimetic Drugs, both the
nicotinic and 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 blockers cause blockade of transmission
(see Chapter 27: Skeletal Muscle Relaxants). To reverse the muscarinic effects, a tertiary (not
quaternary) amine drug must be used (preferably atropine), since the central nervous system effects
as well as the peripheral effects of the organophosphate inhibitors must be treated. Large doses of
atropine may be needed to combat 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
repeated many times, since the acute effects of the anticholinesterase agent may last for 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.

Cholinesterase Regenerator Compounds

A second class of compounds, 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), and others.

The oxime group (=NOH) has a very high affinity for the phosphorus atom, and these drugs are able to hydrolyze the phosphorylated enzyme if the complex has not "aged" (see Chapter 7: Cholinceptor-Activating & Cholinesterase-Inhibiting Drugs). 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. Because of its positive charge, it does not enter the central nervous system and is ineffective in reversing the central effects of organophosphate poisoning. Diacetylmonoxime, on the other hand, does cross the blood-brain barrier and, in experimental animals, can regenerate some of the central nervous system 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 59: Management of the Poisoned Patient.

A third approach to protection against excessive AChE inhibition lies in pretreatment with reversible inhibitors of the enzyme to prevent binding of the irreversible organophosphate inhibitor. This prophylaxis can be achieved with pyridostigmine or physostigmine but is reserved for situations in which possibly lethal poisoning is anticipated, eg, chemical warfare. 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 15–30 minutes following ingestion of the mushrooms. It is often characterized entirely by signs of muscarinic excess: nausea, vomiting, diarrhea, vasodilation, reflex tachycardia (occasionally bradycardia), sweating, salivation, and sometimes bronchoconstriction. Although Amanita muscaria contains muscarine (the alkaloid was named after the mushroom), numerous other alkaloids, including antimuscarinic agents, are found in this fungus. In fact, ingestion of A muscaria may produce signs of atropine poisoning, not muscarine.
excess. Other mushrooms, especially those of the *Inocybe* genus, cause rapid-onset poisoning of the muscarinic excess type. Parenteral atropine, 1–2 mg, is effective treatment in such intoxications.

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 59: Management of the Poisoned Patient).

Other Applications

Hyperhidrosis 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 being 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 a 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 59: Management of the Poisoned Patient). In the past, physostigmine or another cholinesterase inhibitor was recommended, but most poison control experts now consider physostigmine more dangerous and no more effective in most patients than symptomatic management. 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 the quaternary antimuscarinic drugs is associated with all of the peripheral signs of parasympathetic blockade but few or none of the central nervous system 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.

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 63: Drugs Used in the Treatment of Gastrointestinal Diseases).

Basic & Clinical Pharmacology of the Ganglion-Blocking Drugs

These agents block the action of acetylcholine and similar agonists at the 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 cholinceptor. The ganglion-blocking drugs are still important and useful in pharmacologic and physiologic research because of their ability to block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have been abandoned for clinical use.

Chemistry & Pharmacokinetics

All ganglion-blocking drugs of interest are synthetic amines. The first to be recognized as having this action was tetraethylammonium (TEA). Because of the very short duration of action of TEA, hexamethonium ("C6") was developed and was soon introduced into clinical medicine as the first effective drug 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 an effective neuromuscular depolarizing blocking agent.

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

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

**Pharmacodynamics**

**Mechanism of Action**

Ganglionic nicotinic receptors, like those of the skeletal muscle neuromuscular junction, are subject to both depolarizing and nondepolarizing blockade (see Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs and Chapter 27: Skeletal Muscle Relaxants). Nicotine itself, carbamoylcholine, and even acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.

The drugs presently used as ganglion blockers are classified as nondepolarizing competitive antagonists. However, evidence suggests that hexamethonium actually produces most of its blockade by occupying sites in or on the ion channel that is controlled by the acetylcholine receptor, not by occupying the cholinoceptor itself. In contrast, trimethaphan appears to block the nicotinic receptor, not the channel. Blockade can be at least partially overcome by increasing the concentration of normal agonists, eg, acetylcholine.

**Organ System Effects**

**Central Nervous System**
The quaternary amine agents and trimethaphan lack central effects because they do not cross the blood-brain barrier. Mecamylamine, however, readily enters the central nervous system. Sedation, tremor, choreiform movements, and mental aberrations have all been reported as effects of the latter drug.

Eye

Because the ciliary muscle receives innervation primarily from the parasympathetic nervous system, the ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation. 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). Because parasympathetic tone is usually dominant in this tissue, ganglionic blockade usually causes moderate dilation of the pupil.

Cardiovascular System

The blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a very important decrease in arteriolar and venomotor tone. The blood pressure may drop 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.

Gastrointestinal Tract

Secretion is reduced, although not enough to effectively treat peptic disease. Motility is profoundly inhibited, and constipation may be marked.

Other Systems

Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function. Ganglionic blockade therefore 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 blocked 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.

Response to Autonomic Drugs

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

Clinical Applications & Toxicity
Because of the availability of more selective autonomic blocking agents, the applications of the ganglion blockers have almost disappeared. Mecamylamine is being studied for possible use in reducing nicotine craving in patients attempting to quit smoking and for some other central indications. Trimethaphan is occasionally used in the treatment of hypertensive emergencies and dissecting aortic aneurysm, to produce controlled hypotension, which can be of value in neurosurgery to reduce bleeding in the operative field, and in 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.

Preparations Available

Antimuscarinic Anticholinergic Drugs*

**Atropine** (generic)
Oral: 0.4 mg tablets
Parenteral: 0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1 mg/mL for injection
Ophthalmic (generic, Isopto Atropine): 0.5, 1, 2% drops; 1% ointments

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

**Clidinium** (Quarzan)
Oral: 2.5, 5 mg capsules

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

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

**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)

Ophthalmic: 2, 5% drops

**/-Hyoscyamine** (Anaspaz, Cystospaz-M, Levsinex)

Oral: 0.125, 0.15 mg tablets; 0.375 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

Solution for nebulizer: 0.02%

Nasal spray: 0.03, 0.06%

**Mepenzolate** (Cantil)

Oral: 25 mg tablets

**Methantheline** (Banthine)

Oral: 50 mg tablets

**Methscopolamine** (Pamine)

Oral: 2.5 mg tablets

**Oxybutynin** (generic, Ditropan)

Oral: 5 mg tablets; 5, 10, 15 mg extended-release tablets; 5 mg/5 mL syrup

**Propantheline** (generic, Pro-Banthine)

Oral: 7.5, 15 mg tablets

**Scopolamine** (generic)

Oral: 0.4 mg tablets

Parenteral: 0.3, 0.4, 0.65, 0.86, 1 mg/mL for injection

Ophthalmic (Isopto Hyoscine): 0.25% solution

Transdermal (Transderm Scop): 1.5 mg (delivers 0.5 mg) patch

**Tolterodine** (Detrol)
Chapter 9. Adrenoceptor-Activating & Other Sympathomimetic Drugs

Adrenoceptor-Activating & Other Sympathomimetic Drugs: Introduction

The sympathetic nervous system is an important regulator of the activities of organs such as the heart and peripheral vasculature, especially in responses to stress (see Chapter 6: Introduction to Autonomic Pharmacology). The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals that serve to activate the adrenoceptors on postsynaptic sites. 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. Drugs that mimic the actions of epinephrine or nor-epinephrine—sympathomimetic drugs—would be expected to have a wide range of effects. An understanding of the pharmacology of these agents is thus a logical extension of what we know about the physiologic role of the catecholamines.

The Mode & Spectrum of Action of Sympathomimetic Drugs
Like the cholinomimetic drugs, the sympathomimetics can be grouped by mode of action and by the spectrum of receptors that they activate. Some of these drugs (e.g., norepinephrine, epinephrine) act by a *direct* mode, i.e., they directly interact with and activate adrenoceptors. Others act *indirectly*; their actions are dependent on the release of endogenous catecholamines. These indirect agents may have either of two different mechanisms: (1) displacement of stored catecholamines from the adrenergic nerve ending (e.g., amphetamine and tyramine) or (2) inhibition of reuptake of catecholamines already released (e.g., cocaine and tricyclic antidepressants). Some drugs have both direct and indirect actions. Both types of sympathomimetics, direct and indirect, ultimately cause activation of adrenoceptors, leading to some or all of the characteristic effects of catecholamines. The selectivity of different sympathomimetics for various types of adrenoceptors is discussed below.
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>$\alpha_{1B}$</td>
<td>CEC (irreversible)</td>
<td>C8</td>
</tr>
<tr>
<td>$\alpha_{1D}$</td>
<td>WB4101</td>
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<tr>
<td>$\alpha_2$ type</td>
<td>Rauwolscine, yohimbine</td>
<td>C20</td>
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<tr>
<td>$\alpha_{2A}$</td>
<td>Clonidine, BHT920, Oxymetazoline</td>
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</tr>
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<td>C2</td>
</tr>
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<td>C4</td>
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<td>C10</td>
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<td>C10</td>
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<tr>
<td>$\beta_2$</td>
<td>Procaterol, terbutaline</td>
<td>C5</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>BRL37344</td>
<td>C8</td>
</tr>
<tr>
<td>Dopamine type</td>
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<td>$D_1$</td>
<td>Fenoldopam</td>
<td>C5</td>
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<td>$D_2$</td>
<td>Bromocriptine</td>
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<td>Clozapine</td>
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<tr>
<td>$D_5$</td>
<td></td>
<td>C4</td>
</tr>
</tbody>
</table>

Key: BRL37344 = Sodium-4-(2-[2-hydroxy-{3-chlorophenyl} ethylamino]propyl)phenoxyacetate
BHT920 = 6-Allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine
CEC = Chloroethylclonidine
DAG = Diacylglycerol
IP₃ = Inositol trisphosphate
WB4101 = N-[2-(2,6-dimethoxyphenoxy)ethyl]-2,3-dihydro-1,4-benzodioxan-2-methanamine

Alpha Adrenoceptors

Following the demonstration of the α subtypes, it was found that there are two major groups of α receptors: α₁ and α₂. These receptors were originally identified with antagonist drugs that distinguished between α₁ and α₂ receptors. For example, α₁ adrenoceptors were identified in a variety of tissues by measuring the binding of radiolabeled antagonist compounds that are considered to have a high affinity for these receptors, e.g., dihydroergocryptine (α₁ and α₂), prazosin (α₁), and yohimbine (α₂). These radioligands were used to measure the number of receptors in tissues and to determine the affinity (by displacement of the radiolabeled ligand) of other drugs that interact with the receptors.

The concept of subtypes within the α₁ group emerged out of pharmacologic experiments that demonstrated complex shapes of agonist dose-response curves of smooth muscle contraction as well as differences in antagonist affinities in inhibiting contractile responses in various tissues. These experiments demonstrated the existence of two subtypes of α₁ receptor that could be distinguished on the basis of their reversible affinities for a variety of drugs and experimental compounds. A third α₁ receptor subtype was subsequently identified by molecular cloning techniques. These α₁ receptors are termed α₁A, α₁B, and α₁D receptors. There is evidence that the α₁A receptor has splice variants. A major current area of investigation is determining the importance of each of these various subtypes in mediating α₁ receptor responses in a variety of organs.

The hypothesis that there are subtypes of α₂ receptors emerged from pharmacologic experiments and molecular cloning. It is now known that there are three subtypes of α₂ receptors, termed α₂A, α₂B, and α₂C, that are products of distinct genes.

Dopamine Receptors

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 Chapter 21: Introduction to the Pharmacology of CNS Drugs and Chapter 29: Antipsychotic Agents & Lithium) and in the splanchnic and renal vasculature. There is now considerable evidence for the existence of at least five subtypes of dopamine receptors. Pharmacologically distinct dopamine receptor subtypes, termed D₁ and D₂, have been known for some time. Molecular cloning has identified several distinct genes encoding each of these subtypes. Further complexity occurs because of the presence of introns within the coding region of the D₂-like receptor genes, which allows for alternative splicing of the exons in this major subtype. There is extensive polymorphic variation in the D₁ human receptor gene. The terminology of the various subtypes is D₁, D₂, D₃, D₄, and D₅. They comprise two D₁-like receptors (D₁ and D₅) and three D₂-like (D₂, D₃, and D₄). These subtypes may have importance for understanding the efficacy and adverse effects of novel antipsychotic drugs (see Chapter 29: Antipsychotic Agents & Lithium).

Receptor Selectivity
Examples of clinically useful sympathomimetic agonists that are relatively selective for $\alpha_1$, $\alpha_2$, and $\beta$-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. For example, norepinephrine preferentially activates $\beta_1$ receptors as compared with $\beta_2$ receptors. However, selectivity is not usually absolute (nearly absolute selectivity has been termed "specificity"), and at higher concentrations related classes of receptor may also interact with the drug. As a result, the "numeric" subclassification of adrenoceptors is clinically important mainly for drugs that have relatively marked selectivity. Given interpatient variations in drug kinetics and dynamics, the extent of a drug’s selectivity should be kept in mind if this property is viewed as clinically important in the treatment of an individual patient.

Table 9–2. Relative Selectivity of Adrenoceptor Agonists.

<table>
<thead>
<tr>
<th>Relative Receptor Affinities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha agonists</strong></td>
</tr>
<tr>
<td>Phenylephrine, methoxamine</td>
</tr>
<tr>
<td>Clonidine, methylnorepinephrine</td>
</tr>
<tr>
<td><strong>Mixed alpha and beta agonists</strong></td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td><strong>Beta agonists</strong></td>
</tr>
<tr>
<td>Dobutamine$^1$</td>
</tr>
<tr>
<td>Isoproterenol</td>
</tr>
<tr>
<td>Terbutaline, metaproterenol, albuterol, ritodrine</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Fenoldopam</td>
</tr>
</tbody>
</table>

$^1$ See text.

The exact number of adrenoceptor subtypes that are actually expressed in human tissues is uncertain, but expression of subtypes has been demonstrated in tissues where the physiologic or
tissue. For example, determining which blood vessels express which subtypes of \( \alpha_1 \) and \( \alpha_2 \) receptors could lead to design of drugs having selectivity for certain vascular beds such as the splanchnic or coronary vessels. Similarly, there has been extensive investigation into the \( \alpha_1 \) receptor subtypes mediating pharmacologic responses in the human prostate.

Molecular Mechanisms of Sympathomimetic Action

The effects of catecholamines are mediated by cell surface receptors. As described in Chapter 2: Drug Receptors & Pharmacodynamics, these 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 \( \alpha \), \( \beta \), and \( \gamma \) subunits. G proteins are classified on the basis of their distinctive \( \alpha \) subunits. G proteins of particular importance for adrenoceptor function include \( G_s \), the stimulatory G protein of adenylyl cyclase; \( G_i \), the inhibitory G protein of adenylyl cyclase; and \( G_q \), the protein coupling \( \alpha \) receptors to phospholipase C. The activation of G protein-coupled receptors by catecholamines promotes the dissociation of GDP from the \( \alpha \) subunit of the appropriate G protein. GTP then binds to this G protein, and the \( \alpha \) subunit dissociates from the \( \beta-\gamma \) unit. The activated GTP-bound \( \alpha \) subunit then regulates the activity of its effector. Effectors of adrenoceptor-activated \( \alpha \) subunits include adenylyl cyclase, cGMP phosphodiesterase, phospholipase C, and ion channels. The \( \alpha \) subunit is inactivated by hydrolysis of the bound GTP to GDP and P\(_i\), and the subsequent reassociation of the \( \alpha \) subunit with the \( \beta-\gamma \) subunit. The \( \beta-\gamma \) subunits have additional independent effects, acting on a variety of effectors such as ion channels and enzymes.

Receptor Types

Alpha Receptors

\( \alpha_1 \) receptors stimulate polyphosphoinositide hydrolysis, leading to the formation of inositol 1,4,5-trisphosphate (IP\(_3\)) and diacylglycerol (DAG) (Figure 9–1). G proteins in the \( G_q \) family couple \( \alpha_1 \) receptors to phospholipase C. 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. Inositol 1,4,5-trisphosphate is sequentially dephosphorylated, which ultimately leads to the formation of free inositol. DAG activates protein kinase C that modulates activity of many signaling pathways. In addition, \( \alpha_1 \) receptors activate signal transduction pathways that were originally described for peptide growth factor receptors which activate tyrosine kinases. For example, \( \alpha_1 \) 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 \( \alpha_1 \) receptor-mediated stimulation of cell growth and proliferation through the regulation of gene expression. The physiologic significance of this "cross talk" between major signaling pathways remains to be determined.

Figure 9–1.
Activation of α₁ responses. Stimulation of α₁ receptors by catecholamines leads to the activation of a Gq coupling protein. The α₁ subunit of this G protein activates the effector, phospholipase C, which leads to the release of IP₃ (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol) from phosphatidylinositol 4,5-bisphosphate (PtdIns 4,5-P₂). IP₃ stimulates the release of sequestered stores of calcium, leading to an increased concentration of cytoplasmic Ca²⁺. Ca²⁺ may then activate Ca²⁺-dependent protein kinases, which in turn phosphorylate their substrates. DAG activates protein kinase C. See text for additional effects of α₁ receptor activation.

Alpha₂ receptors inhibit adenylyl cyclase activity and cause intracellular cAMP levels to decrease. In addition to this well-documented effect, activation of α₂ receptors utilize additional signaling pathways, including regulation of ion channel activities and the activities of important enzymes involved in signal transduction. Alpha₂-receptor-mediated inhibition of adenylyl cyclase activity is transduced by the inhibitory regulatory protein, Gᵢ, which couples α₂ receptors to the inhibition of adenylyl cyclase (Figure 9–2). How the activation of Gᵢ leads to the inhibition of adenylyl cyclase is unclear, but it is likely that both α and the βγ subunits of Gᵢ contribute to this response. In addition, some of the effects of α₂ adrenoceptors are independent of their ability to inhibit adenylyl cyclase; for example, α₂-receptor agonists cause platelet aggregation and a decrease in platelet cAMP levels, but it is not clear that aggregation is the result of the decrease in cAMP or other mechanisms involving Gᵢ-regulated effectors.

Figure 9–2.
Activation and inhibition of adenylyl cyclase by agonists that bind to catecholamine receptors. Binding to \( \beta \)-adrenoceptors stimulates adenylyl cyclase by activating the stimulatory G protein, \( G_s \), which leads to the dissociation of its subunit charged with GTP. This subunit directly activates adenylyl cyclase, resulting in an increased rate of synthesis of cAMP. Alpha2 adrenoceptor ligands inhibit adenylyl cyclase by causing dissociation of the inhibitory G protein, \( G_i \), into its subunits; i.e., an \( a \) subunit charged with GTP and a \( \beta \)-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 \( \beta \) and \( \alpha_2 \) adrenoceptors.

Beta Receptors

The mechanism of action of \( \beta \) agonists has been studied in considerable detail. Activation of all three receptor subtypes (\( \beta_1 \), \( \beta_2 \), and \( \beta_3 \)) results in activation of adenylyl cyclase and increased conversion of ATP to cAMP (Figure 9–2). Activation of the cyclase enzyme is mediated by the stimulatory coupling protein \( G_s \). cAMP is the major second messenger of \( \beta \)-receptor activation. For example, in the liver of many species, \( \beta \)-receptor activation increases cAMP synthesis, which leads to a cascade of events culminating in the activation of glycogen phosphorylase. In the heart, \( \beta \)-receptor activation 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. While the mechanism 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_{i}-mediated enhancement independently of changes in cAMP concentration. Under certain circumstances, B_{2} receptors may couple to G_{i} proteins. These receptors have been demonstrated to activate additional kinases, such as MAP kinases, by forming multi-subunit complexes, found within cells, containing multiple signaling molecules. In addition, recent evidence suggests that formation of dimers of B receptors themselves (both homodimers and heterodimers of B_{1} and B_{2} receptors) is importantly involved in their signaling mechanisms.

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 where dopamine is a vasodilator. D_{2} receptors have been found to inhibit adenylyl cyclase activity, open potassium channels, and decrease calcium influx.

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. 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. 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. Operating at transcriptional, translational, and protein levels, some mechanisms function relatively slowly—over the course of hours or days. 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 a drug. Heterologous desensitization refers to loss of responsiveness of some cell surface receptors that have not been directly activated by the drug 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 at least seven members. Specific adrenoreceptors are substrates for these kinases only when they are bound to an agonist. This mechanism is an example of homologous desensitization since it specifically involves only agonist-occupied receptors.

Phosphorylation of these receptors enhances their affinity for B-arrestins; upon binding of a B-arrestin molecule, the capacity of the receptor to activate G proteins is blunted, presumably due to steric hindrance (see Figure 2–12). Arrestins constitute another large family of widely expressed
proteins. Receptor phosphorylation followed by β-arrestin binding has been linked to subsequent endocytosis of the receptor. This response may be facilitated by the capacity of β-arrestins to bind to the structural protein clathrin. 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 example, for the β2 receptor, phosphorylation occurs on serine residues both in the third cytoplasmic loop and carboxyl terminal tail of the receptor. Similarly, activation of protein kinase C by Gq-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 α1, α2, 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. There is evidence that some of these polymorphisms may change the susceptibility to diseases such as heart failure, alter the propensity of a receptor to desensitize, and alter therapeutic responses to drugs in diseases such as asthma.

Chemistry & Pharmacokinetics of Sympathomimetic Drugs

Phenylethylamine may be considered the parent compound from which sympathomimetic drugs are derived (Figure 9–3). This compound consists of a benzene ring with an ethylamine side chain. Substitutions may be made (1) on the terminal amino group, (2) on the benzene ring, and (3) on the α or β carbons. 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 as well as to influence the intrinsic ability to activate the receptors. In addition, chemical structure determines the pharmacokinetic properties of these molecules. Sympathomimetic drugs may activate both α and β receptors; however, the relative α-receptor versus β-receptor activity spans the range from almost pure α activity (methoxamine) to almost pure β activity (isoproterenol).

Figure 9–3.
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 β2 receptors. Beta activity is further enhanced with isopropyl substitution at the amino nitrogen (isoproterenol). Beta2-selective agonists generally require a large amino substituent group. The larger the substituent on the amino group, the lower the activity at α receptors; eg, isoproterenol is very weak at α receptors.

Substitution on the Benzene Ring

Maximal α and β activity are found with catecholamines (drugs having –OH groups at the 3 and 4 positions). The absence of one or the other of these groups, particularly the hydroxyl at C3, without other substitutions on the ring may dramatically reduce the potency of the drugs. For example, phenylephrine (Figure 9–4) is much less potent than epinephrine; indeed, α-receptor affinity is decreased about 100-fold and β activity is almost negligible except at very high concentrations. However, catecholamines are subject to inactivation by catechol-O-methyltransferase (COMT), an enzyme found in gut and liver (see Chapter 6: Introduction to Autonomic Pharmacology). Therefore, 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 9–4) are orally active, have a prolonged duration of action, and produce central nervous system effects not typically observed with the catecholamines.

Figure 9–4.
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 noncatecholamines. Ephedrine and amphetamine are examples of α-substituted compounds (Figure 9–4). 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. Therefore, a portion of their activity is dependent upon the presence of normal norepinephrine stores in the body; they are indirectly acting sympathomimetics.

Substitution on the Beta Carbon

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

Organ System Effects of Sympathomimetic Drugs

General outlines of the cellular actions of sympathomimetics are presented in Tables 6–3 and 9–3. The net effect of a given drug in the intact organism depends on its relative receptor affinity (α or β), intrinsic activity, and the compensatory reflexes evoked by its direct actions.

Table 9–3. Distribution of Adrenoceptor Subtypes.

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Most vascular smooth muscle (innervated)</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increases force of contraction</td>
</tr>
<tr>
<td>α₂</td>
<td>Postsynaptic CNS adrenoceptors</td>
<td>Probably multiple</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Platelets</td>
<td>Aggregation</td>
<td></td>
</tr>
<tr>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibition of transmitter release</td>
<td></td>
</tr>
<tr>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
<td></td>
</tr>
<tr>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β₁</th>
<th>Heart</th>
<th>Increases force and rate of contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂</td>
<td>Respiratory, uterine, and vascular smooth muscle</td>
<td>Promotes smooth muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td>Promotes potassium uptake</td>
</tr>
<tr>
<td></td>
<td>Human liver</td>
<td>Activates glycogenolysis</td>
</tr>
<tr>
<td>β₃</td>
<td>Fat cells</td>
<td>Activates lipolysis</td>
</tr>
<tr>
<td>D₁</td>
<td>Smooth muscle</td>
<td>Dilates renal blood vessels</td>
</tr>
<tr>
<td>D₂</td>
<td>Nerve endings</td>
<td>Modulates transmitter release</td>
</tr>
</tbody>
</table>

Cardiovascular System

Blood Vessels

Vascular smooth muscle tone is regulated by adrenoceptors; consequently, catecholamines are important in controlling peripheral vascular resistance and venous capacitance. Alpha receptors increase arterial resistance, whereas β₂ receptors promote smooth muscle relaxation. There are major differences in receptor types in the various vascular beds (Table 9–4). The skin vessels have predominantly α receptors and constrict in the presence of 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. Consequently, the overall effects of a sympathomimetic drug on blood vessels depend on the relative activities of that drug at α and β receptors and the anatomic sites of the vessels affected. In addition, D₁ receptors promote vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels. Activation of the D₁ receptors in the renal vasculature may play a major role in the natriuresis induced by pharmacologic administration of dopamine.

Heart

Direct effects on the heart are determined largely by β₁ receptors, although β₂ and to a lesser extent α receptors are also involved. Beta-receptor activation results in increased calcium influx in cardiac cells. This has both electrical (Figure 9–5) 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, and the refractory period is decreased. Intrinsic contractility is increased, 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.

**Figure 9–5.**

Effect of epinephrine on the transmembrane potential of a pacemaker cell in the frog heart. The arrowed trace was recorded after the addition of epinephrine. Note the increased slope of diastolic depolarization and decreased interval between action potentials. This pacemaker acceleration is typical of β₁-stimulant drugs. (Modified and reproduced, with permission, from Brown H, Giles W, Noble S: Membrane currents underlying rhythmic activity in frog sinus venosus. In: The Sinus Node: Structure, Function, and Clinical Relevance. Bonke FIM [editor]. Martinus Nijhoff, 1978.)

**Blood Pressure**

The effects of sympathomimetic drugs on blood pressure can be explained on the basis of their effects on the heart, the peripheral vascular resistance, and the venous return (see Figure 6–7 and Table 9–4). 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. 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. While these are the expected effects of pure α-agonists in normal subjects, their use in hypotensive patients usually does not lead to brisk reflex responses because in this situation blood pressure is returning to normal, not exceeding normal.

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

The blood pressure response to a pure \( \beta \)-adrenoceptor agonist is quite different. Stimulation of \( \beta \) receptors in the heart increases cardiac output. A relatively pure \( \beta \) agonist such as isoproterenol also decreases peripheral resistance by activating \( \beta_2 \) receptors, leading to vasodilation in certain vascular beds (Table 9–4). The net effect is to maintain or slightly increase systolic pressure while permitting a fall in diastolic pressure owing to enhanced diastolic runoff (Figure 9–6). The actions of drugs with both \( \alpha \) and \( \beta \) effects (eg, epinephrine and norepinephrine) are discussed below.

<table>
<thead>
<tr>
<th>Vascular resistance (tone)</th>
<th>Phenylephrine</th>
<th>Epinephrine</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous, mucous membranes (( \alpha ))</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Skeletal muscle (( \beta_2, \alpha ))</td>
<td>↑</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renal (( \alpha, \beta ))</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Splanchnic (( \alpha ))</td>
<td>++</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Table 24.1: Cardiovascular and Hemodynamic Effects of Adrenoceptor Stimulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Increase</th>
<th>Increase or Decrease</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total peripheral resistance</td>
<td>↑↑↑</td>
<td>or ↑²</td>
<td>↓</td>
</tr>
<tr>
<td>Venous tone (α, β)</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractility (β₁)</td>
<td>0 or ↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Heart rate (predominantly β₁)</td>
<td>↓(vagal reflex)</td>
<td>↑ or ↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0, ↓, ↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
<td>++</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Diastolic</td>
<td>↑↑</td>
<td>↓ or ↑²</td>
<td>↓↓</td>
</tr>
<tr>
<td>Systolic</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0 or ↓</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0</td>
<td>↑↑</td>
<td>↑++</td>
</tr>
</tbody>
</table>

¹ = increase; ↓ = decrease; 0 = no change.
² Small doses decrease, large doses increase.

Eye

The radial pupillary dilator muscle of the iris contains α receptors; activation by drugs such as phenylephrine causes mydriasis (Figure 6–9). Alpha and β stimulants also have important effects on intraocular pressure. Present evidence suggests that agonists increase the outflow of aqueous humor from the eye, while antagonists decrease the production of aqueous humor. These effects are important in the treatment of glaucoma (see Chapter 10: Adrenoceptor Antagonist Drugs), a leading cause of blindness. Beta stimulants relax the ciliary muscle to a minor degree, causing an insignificant decrease in accommodation. In addition, adrenergic drugs may directly protect neuronal cells in the retina.

Respiratory Tract

Bronchial smooth muscle contains β₂ receptors that cause relaxation. Activation of these receptors results in bronchodilation (see Chapter 20: Drugs Used in Asthma and Table 9–3). The blood vessels of the upper respiratory tract mucosa contain α receptors; the decongestant action of adrenoceptor stimulants is clinically useful (see Clinical Pharmacology).

Gastrointestinal Tract

Relaxation of gastrointestinal smooth muscle can be brought about by both α and β-stimulant agents. Beta receptors appear to be located directly on the smooth muscle cells and mediate relaxation via hyperpolarization and decreased spike activity in these cells. Alpha stimulants, especially α₂-selective agonists, decrease muscle activity indirectly by presynaptically reducing the release of acetylcholine and possibly other stimulants within the enteric nervous system (see...
Chapter 6: Introduction to Autonomic Pharmacology. The α-receptor-mediated response is probably of greater pharmacologic significance than the β-stimulant response. Alpha2 receptors may also decrease salt and water flux into the lumen of the intestine.

Genitourinary Tract

The human uterus contains α and β2 receptors. The fact that the β receptors mediate relaxation may be clinically useful in pregnancy (see Clinical Pharmacology). The bladder base, urethral sphincter, and prostate contain α receptors that mediate contraction and therefore promote urinary continence. The specific subtype of α1 receptor involved in mediating constriction of the bladder base and prostate is uncertain, but α1A receptors probably play an important role. The β2 receptors of the bladder wall mediate relaxation. Ejaculation depends upon normal α receptor (and possibly purinergic receptor) activation in the ductus deferens, seminal vesicles, and prostate. 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.

Exocrine Glands

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, though 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 eccrine sweat glands usually associated with psychologic stress. (The diffusely distributed thermoregulatory eccrine sweat glands are regulated by sympathetic cholinergic postganglionic nerves that activate muscarinic cholinoceptors; see Chapter 6: Introduction to Autonomic Pharmacology.)

Metabolic Effects

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. Beta3 adrenoceptors play a role in mediating this response. There is considerable interest in developing β3 receptor-selective agonists, which could be useful in some metabolic disorders. Human lipocytes also contain α2 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 α1 receptors may also play a role. Catecholamines in high concentration may also cause metabolic acidosis. Activation of β2 adrenoceptors by endogenous epinephrine or by sympathomimetic drugs promotes the uptake of potassium into cells, leading to a fall in extracellular potassium. This may lead to 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. Beta receptors and α2 receptors that are expressed in pancreatic islets tend to increase and decrease, respectively, insulin secretion, although the major regulator of insulin release is the plasma concentration of glucose.

Effects on Endocrine Function & Leukocytosis
Catecholamines are important endogenous regulators of hormone secretion from a number of glands. As mentioned above, insulin secretion is stimulated by \( \beta \) receptors and inhibited by \( \alpha_2 \) receptors. Similarly, renin secretion is stimulated by \( \beta_1 \) and inhibited by \( \alpha_2 \) receptors; indeed, \( \beta \)-receptor antagonist drugs may lower plasma renin and blood pressure in patients with hypertension at least in part by this mechanism. 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 white blood cells sequestered away from the general circulation.

Effects on the Central Nervous System

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 central nervous system effects are noted only at the highest rates of infusion. These effects have been described as ranging from "nervousness" to "a feeling of impending disaster," sensations that are undesirable. Furthermore, peripheral effects of \( \beta \) 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 central nervous system 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 \( \alpha \)- or \( \beta \)-mediated actions and may represent enhancement of dopamine-mediated processes or other effects of these drugs in the central nervous system.

Specific Sympathomimetic Drugs

Catecholamines

Epinephrine (adrenaline) is 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 \( \beta_1 \) receptors) and the vasoconstriction induced in many vascular beds (\( \alpha \) receptors). Epinephrine also activates \( \beta_2 \) 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 these \( \beta_2 \) receptors in skeletal muscle contributes to increased blood flow during exercise. Under physiologic conditions, ephinephrine functions largely as a hormone; after release from the adrenal medulla into the blood, it acts on distant cells.

Norepinephrine (levarterenol, noradrenaline) and epinephrine have similar effects on \( \beta_1 \) receptors in the heart and similar potency at \( \alpha \) receptors. Norepinephrine has relatively little effect on \( \beta_2 \) receptors. Consequently, norepinephrine increases peripheral resistance and both diastolic and systolic blood pressure. Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained (Table 9–4).

Isoproterenol (isoprenaline) is a very potent \( \beta \)-receptor agonist and has little effect on \( \alpha \) receptors. The drug has positive chronotropic and inotropic actions; because isoproterenol activates \( \beta \) 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).

**Dopamine**, the immediate metabolic precursor of norepinephrine, activates D₁ receptors in several vascular beds, which leads to vasodilation. The effect this has on renal blood flow may be of clinical value, though this is uncertain. The activation of presynaptic D₂ receptors, which suppress norepinephrine release, contributes to these effects to an unknown extent. In addition, dopamine activates β₁ 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.

**Fenoldopam** is a D₁ receptor agonist that selectively leads to peripheral vasodilation in some vascular beds. The primary indication for fenoldopam is as an intravenously administered drug for the treatment of severe hypertension (Chapter 11: Antihypertensive Agents). Continuous infusions of the drug have prompt effects on blood pressure.

**Dopamine agonists** with central actions are of considerable value for the treatment of Parkinson's disease and prolactinemia. These agents are discussed in Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders and Chapter 37: Hypothalamic & Pituitary Hormones.

**Dobutamine** is a relatively β₁-selective synthetic catecholamine. As discussed below, dobutamine also activates α₁ receptors.

**Other Sympathomimetics**

These agents are of interest because of pharmacokinetic features (oral activity, distribution to the central nervous system) or because of relative selectivity for specific receptor subclasses.

**Phenylephrine** was previously described as an example of a relatively pure α₁ agonist (Table 9–2). It acts directly on the receptors. Because it is not a catechol derivative (Figure 9–4), it is not inactivated by COMT and has a much 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).

**Methoxamine** acts pharmacologically like phenylephrine, since it is predominantly a direct-acting α₁-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.

**Midodrine** is a prodrug that is enzymatically hydrolyzed to desglymidodrine, an α₁ receptor-selective agonist. The peak concentration of desglymidodrine is achieved about 1 hour after midodrine is administered. The primary indication for midodrine is the treatment of postural hypotension, typically due to impaired autonomic nervous system function. While 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.

**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 in Ma-huang, a popular herbal medication (see Chapter 65: Botanicals ("Herbal Medications") & Nutritional Supplements). Ma-huang contains multiple ephedrine-like alkaloids in
addition to ephedrine. Because ephedrine is a noncatechol phenylisopropylamine (Figure 9–4), it has high bioavailability and a relatively long duration of action—hours rather than minutes. As is the case 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 in spite of 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, is available over the counter as a component of many decongestant mixtures.

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 (Chapter 11: Antihypertensive Agents). (As noted in Table 9–1, oxymetazoline has significant affinity for α2A receptors.)

Amphetamine is a phenylisopropylamine (Figure 9–4) that is important chiefly because of its use and misuse as a central nervous system stimulant (see Chapter 32: Drugs of Abuse). Its pharmacokinetics are similar to those of ephedrine; however, amphetamine very readily enters the central nervous system, where it has marked stimulant effects on mood and alertness and a depressant effect on appetite. Its peripheral actions are mediated primarily through the release of catecholamines. Methamphetamine (N-methylamphetamine) is very similar to amphetamine with an even higher ratio of central to peripheral actions. Phenmetrazine (see Figure 32–1) is a variant phenylisopropylamine with amphetamine-like effects. It has been promoted as an anorexiant and is also a popular drug of abuse. Methylphenidate and pemoline are amphetamine variants whose major pharmacologic effects and abuse potential are similar to those of amphetamine. These two drugs appear to have efficacy in some children with attention deficit hyperactivity disorder (see Clinical Pharmacology). Pemoline must be used with great caution because of an association with life-threatening hepatic failure. Modafinil is a new drug with both similarities to and differences from amphetamine. It has significant effects on central α1B receptors but in addition appears to affect GABAergic, glutaminergic, and serotonergic synapses (see Clinical Pharmacology).

Phenylpropanolamine (PPA) is a sympathomimetic drug that for many years was used as an over-the-counter agent in numerous weight reduction and cold medications. It has been withdrawn from over-the-counter use in the USA because of concerns regarding an association with hemorrhagic stroke.

Receptor-Selective Sympathomimetic Drugs

Alpha2-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: Antihypertensive Agents. Dexmedetomidine is a centrally acting α2-selective agonist that is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

Beta-selective agonists are very important because of the separation of β1 and β2 effects that has been achieved (Table 9–2). Although this separation is incomplete, it is sufficient to reduce adverse effects in several clinical applications.
Beta₁-selective agents include dobutamine and a partial agonist, prenalterol (Figure 9–7). Because they are less effective in activating vasodilator β₂ receptors, they may increase cardiac output with less reflex tachycardia than occurs with nonselective β agonists such as isoproterenol. Dobutamine consists of two isomers, administered as a racemic mixture. The (+) isomer is a potent β₁ agonist and an α₁ receptor antagonist. The (–) isomer is a potent α₁ agonist, capable of causing significant vasoconstriction when given alone. This action tends to reduce vasodilation and may also contribute to the positive inotropic action caused by the isomer with predominantly β-receptor activity. A major limitation with these drugs—as with other direct-acting sympathomimetic agents—is that tolerance to their effects may develop with prolonged use and the likelihood that chronic cardiac stimulation in patients with heart failure may worsen long-term outcome.

Figure 9–7.

Examples of β₁- and β₂-selective agonists.

Beta₂-selective agents have achieved an important place in the treatment of asthma and are discussed in Chapter 20: Drugs Used in Asthma. An additional application is to achieve uterine relaxation in premature labor (ritodrine; see below). Some examples of β₂-selective drugs currently in use are shown in Figures 9–7 and 20–4; many more are available or under investigation.

Special Sympathomimetics

Cocaine is a local anesthetic with a peripheral sympathomimetic action that results from inhibition of transmitter reuptake at noradrenergic synapses (see Chapter 6: Introduction to Autonomic Pharmacology). It readily enters the central nervous system and produces an amphetamine-like effect that is shorter lasting and more intense. 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 it can be smoked, "snorted" into the nose, or injected for rapid onset of
effect have made it a heavily abused drug (see Chapter 32: Drugs of Abuse). Interestingly, dopamine-transporter knockout mice still self-administer cocaine, suggesting that cocaine may have additional pharmacologic targets.

**Tyramine** (see Figure 6–5) is a normal by-product of tyrosine metabolism in the body and is also found in high concentrations in fermented foods such as cheese (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, its 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 on account 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 Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders and Chapter 30: Antidepressant Agents).

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

Note: In a patient taking an irreversible 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.
Clinical Pharmacology of Sympathomimetic Drugs

The rationale for the use of sympathomimetic drugs in therapy rests on a knowledge of the physiologic effects of catecholamines on tissues. Selection of a particular sympathomimetic drug from the host of compounds available depends upon such factors as whether activation of α₁, α₂, or β₂ receptors is desired; the duration of action desired; and the preferred route of administration. Sympathomimetic drugs are very potent and can have profound effects on a variety of organ systems, particularly the heart and peripheral circulation. Therefore, great caution is indicated when these agents are used parenterally. In most cases, rather than using fixed doses of the drugs, careful monitoring of pharmacologic response is required to determine the appropriate dosage, especially if the drug is being infused. Generally, it is desirable to use the minimum dose required to achieve the desired response. The adverse effects of these drugs are generally understandable in terms of their known physiologic effects.

Cardiovascular Applications

Conditions in Which Blood Flow or Pressure Is to Be Enhanced

Hypotension may occur in a variety of settings such as decreased blood volume, cardiac arrhythmias, neurologic disease, adverse reactions to 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 (see Toxicity of Sympathomimetic Drugs, below). Sympathomimetic drugs may be used in a hypotensive emergency to preserve cerebral and coronary blood flow. Such situations might arise in severe hemorrhage, spinal cord injury, or overdoses of antihypertensive or central nervous system depressant medications. The treatment is usually of short duration while the appropriate intravenous fluid or blood is being administered. Direct-acting αagonists such as norepinephrine, phenylephrine, or methoxamine have been utilized in this setting if vasoconstriction is desired. For the treatment of chronic orthostatic hypotension, oral ephedrine has been the traditional therapy. Midodrine, an orally active αagonist, may be the preferred sympathomimetic in this application if further studies confirm its long-term safety and efficacy.

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. While sympathomimetic drugs have been used in the treatment of virtually all forms of shock, their efficacy is unclear. In most forms of shock, vasoconstriction mediated by the sympathetic nervous system is already intense. Indeed, efforts aimed at reducing rather than increasing peripheral resistance may be more fruitful if cerebral, coronary, and renal perfusion are improved. A decision to use vasoconstrictors or vasodilators is best made on the basis of information about the underlying cause, which may require invasive monitoring.
Cardiogenic shock, 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 have a role in this situation. 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: Drugs Used in Heart Failure and Table 13–6 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 great to use vasoconstrictors to maintain adequate blood pressure. While coronary perfusion may be improved, 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.

Conditions in Which Blood Flow Is to Be Reduced

Reduction of 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, \( \alpha \)-receptor activation is desired, and the choice of agent depends upon 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 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 \( \alpha \)-agonists have also been used. Systemic effects on the heart and peripheral vasculature may occur even with local drug administration.

Mucous membrane decongestants are \( \alpha \)-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 \( \alpha_1 \) 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 \( \alpha_2 \) receptors. For example, 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. All of these mucous membrane decongestants are available as over-the-counter products.

Cardiac Applications
Catecholamines such as isoproterenol and epinephrine have been utilized 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.

**Heart failure** may respond to the positive inotropic effects of drugs such as dobutamine. These applications are discussed in Chapter 13: Drugs Used in Heart Failure. The development of tolerance or desensitization is a major limitation to the use of catecholamines in heart failure.

Pulmonary Applications

One of the most important uses of sympathomimetic drugs is in the therapy of bronchial asthma. This use is discussed in Chapter 20: Drugs Used in Asthma. Nonselective drugs (epinephrine), β-selective agents (isoproterenol), and β₂-selective agents (metaproterenol, terbutaline, albuterol) are all available for this indication. Sympathomimetics other than the β₂-selective drugs are now rarely used because they are likely to have more adverse effects than the selective drugs.

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 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) may be unpredictable in hypotensive patients. In some patients with impaired cardiovascular function, very cautious intravenous injection of epinephrine may be required. Epinephrine is the agent of choice because of extensive experimental and clinical experience with the drug in anaphylaxis and because epinephrine activates α, β₁, and β₂ receptors, all of which may be important in reversing the pathophysiologic processes underlying anaphylaxis. Glucocorticoids and antihistamines (both H₁ and H₂ receptor antagonists) may be useful as secondary therapy in anaphylaxis; however, epinephrine is the initial treatment.

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 An Application of Basic Pharmacology to a Clinical Problem.)

Glaucoma responds to a variety of sympathomimetic and sympathoplegic drugs. (See box in Chapter 10: Adrenoceptor Antagonist Drugs: The Treatment of Glaucoma.) Epinephrine and its prodrug dipivefrin are now rarely used, but β-blocking agents are among the most important therapies. Apraclonidine and brimonidine are α₂-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, β₂-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 β₂-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.

**Central Nervous System Applications**

As noted above, the amphetamines have a mood-elevating (euphoriant) effect; this effect is the basis for the widespread abuse of this drug and some of its analogs (see Chapter 32: Drugs of Abuse). 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 EEG. 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, 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 CNS-active sympathomimetics is in the attention-deficit hyperactivity disorder (ADHD) of children, a poorly defined and overdiagnosed 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 or to clonidine. Extended-release formulations of methylphenidate may simplify dosing regimens and increase adherence to therapy, especially in school-age children. Evidence from several clinical trials suggests that modafinil may also be useful in ADHD.

**Additional Therapeutic Uses**

While the primary use of the α₂ agonist clonidine is in the treatment of hypertension (Chapter 11: Antihypertensive Agents), the drug has been found to have efficacy in the treatment of diarrhea in diabetics with autonomic neuropathy, perhaps due to its ability to enhance salt and water absorption from the intestines. 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 indicated for sedation under intensive care circumstances.

**Toxicity of Sympathomimetic Drugs**

The adverse effects of adrenoceptor agonists are primarily extensions of their pharmacologic effects in the cardiovascular and central nervous systems.

Adverse cardiovascular effects seen with intravenously infused pressor agents include marked elevations in blood pressure that cause increased cardiac work, which may precipitate cardiac ischemia and failure. Systemically administered β receptor-stimulant drugs may cause sinus
tachycardia and may even provoke serious ventricular arrhythmias. Sympathomimetic drugs may lead to myocardial damage, particularly after prolonged infusion. Special caution is indicated in elderly patients or those with hypertension or coronary artery disease. To avoid excessive pharmacologic responses, it is essential to monitor the blood pressure when administering sympathomimetic drugs parenterally.

If an adverse sympathomimetic effect requires urgent reversal, a specific adrenoceptor antagonist can be used (see Chapter 10: Adrenoceptor Antagonist Drugs).

Central nervous system toxicity is rarely observed with catecholamines or drugs such as phenylephrine. In moderate doses, amphetamines commonly cause restlessness, tremor, insomnia, and anxiety; in high doses, a paranoid state may be induced. Cocaine may precipitate convulsions, cerebral hemorrhage, arrhythmias, or myocardial infarction. Therapy is discussed in Chapter 59: Management of the Poisoned Patient.

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 side affected. 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.

An understanding of the effects of denervation on neurotransmitter metabolism permits the clinician to use drugs to localize the lesion. In most situations, a localized lesion in a nerve will cause 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 will leave 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 will dilate 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, will show a normal response to both drugs, since the postganglionic fibers and their catecholamine stores remain intact in this situation.
Amphetamine, racemic mixture (generic)
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)
Topical: 0.5, 1% solutions

Brimonidine (Alphagan)
Topical: 0.15, 0.2% solution

Dexmedetomidine (Precedex)
Parenteral: 100 μg/mL

Dexmethylphenidate (Focalin)
Oral: 2.5, 5, 10 mg tablets

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

Dipivefrin (generic, Propine)
Topical: 0.1% ophthalmic solution

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

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

Ephedrine (generic)
Oral: 25 mg capsules
Parenteral: 50 mg/mL for injection
Nasal: 0.25% spray

**Epinephrine**(generic, Adrenalin Chloride, others)
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): 1:2000 (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): 0.16, 0.2 mg/spray
Solution for aerosol: 1:100

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

**Hydroxyamphetamine** (Paredrine)
Ophthalmic: 1% drops

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

**Mephentermine** (Wyamine Sulfate)
Parenteral: 15, 30 mg/mL for injection

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

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

**Methoxamine** (Vasoxyl)
Parenteral: 20 mg/mL for injection

**Methylphenidate**(generic, Ritalin, Ritalin-SR)
Oral: 5, 10, 20 mg tablets
Oral sustained-release: 10, 18, 20, 27, 36, 54 mg tablets; 20, 30, 40 mg capsules
**Midodrine** (ProAmatine)
Oral: 2.5, 5 mg tablets

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

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

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

**Oxymetazoline** (generic, Afrin, Neo-Synephrine 12 Hour, others)
Nasal: 0.025, 0.05% sprays
Ophthalmic: 0.025% drops

**Pemoline** (generic, Cylert)
Oral: 18.75, 37.5, 75 mg tablets; 37.5 mg chewable tablets

**Phendimetrazine** (generic)
Oral: 35 mg tablets, capsules; 105 mg sustained-release capsules

**Phenylephrine** (generic, Neo-Synephrine)
Oral: 10 mg chewable tablets
Parenteral: 10 mg/mL for injection
Nasal: 0.125, 0.16, 0.25, 0.5, 1% drops and spray; 0.5% jelly

**Pseudoephedrine** (generic, Sudafed, others)
Oral: 30, 60 mg tablets; 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, Tyzine)
Nasal: 0.05, 0.1% drops
Ophthalmic: 0.05% drops

**Xylometazoline** (generic, Otrivin, Neo-Synephrine Long-Acting, Chlorohist LA)

Nasal: 0.05 drops, 0.1% drops and spray

1 \(\alpha_2\)-Agonists used in hypertension are listed in Chapter 11: Antihypertensive Agents. \(\beta_2\)-Agonists used in asthma are listed in Chapter 20: Drugs Used in Asthma.

**Chapter 10. Adrenoceptor Antagonist Drugs**

Adrenoceptor Antagonist Drugs: Introduction

Since catecholamines play a role in a variety of physiologic and pathophysiologic responses, drugs that block adrenoceptors have important effects, some of which are of great clinical value. These effects vary dramatically according to the drug’s selectivity for \(\alpha\) and \(\beta\) receptors. The classification of adrenoceptors into \(\alpha_1\), \(\alpha_2\), and \(\beta\) subtypes and the effects of activating these receptors are discussed in Chapters 6 and 9. Blockade of peripheral dopamine receptors is of no recognized 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 either \(\alpha_1\), \(\alpha_2\), or \(\beta\) receptors outside the central nervous system and prevent their activation by catecholamines and related agonists.

For pharmacologic research, \(\alpha_1\)- and \(\alpha_2\)-adrenoceptor antagonist drugs have been very useful in the experimental exploration of autonomic nervous system function. In clinical therapeutics, nonselective \(\alpha\) antagonists have been used in the treatment of pheochromocytoma (tumors that secrete catecholamines), and \(\alpha_1\)-selective antagonists are used in primary hypertension and benign prostatic hyperplasia. Beta-receptor antagonist drugs have been found 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, and other conditions.

**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; irreversible drugs do not. Phentolamine (Figure 10–1) and tolazoline are examples of reversible antagonists. Prazosin (and analogs) and labetalol—drugs used primarily for their antihypertensive effects—as well as several ergot
derivatives (see Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids) are also reversible α-adrenoceptor antagonists. Phenoxybenzamine, an agent related to the nitrogen mustards, 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.

Figure 10–1.

[Structures of several α-receptor-blocking drugs are shown, including Tamsulosin, Phenolamine, Phenoxybenzamine, and Prazosin.]

Structure of several α-receptor-blocking drugs.

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.)

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 or of binding to its receptor, the less time it takes for the effects of the drug to dissipate. However, 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 α₁ adrenoceptor drug effect may be particularly important in patients having a sudden cardiovascular event or who become candidates for urgent surgery.

**Pharmacologic Effects**

**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 β₂ effects (eg, epinephrine), selective α₁ 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 same tissue may lead to opposite responses. Alpha-receptor antagonists may cause postural hypotension and reflex tachycardia. Postural hypotension is due to antagonism of sympathetic nervous system stimulation of α₁ receptors in venous smooth muscle; contraction of veins is an
important component of the capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery. Constriction of arterioles in the legs may also contribute to the postural response. Tachycardia may be more marked with agents that block α₂-presynaptic receptors in the heart (Table 10–1), since the augmented release of norepinephrine will further stimulate β receptors in the heart.

**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.)

**Other Effects**

Minor effects that signal the blockade of α-receptors in other tissues include miosis and nasal stuffiness. Alpha₁-receptor blockade of the base of the bladder and the prostate is associated with decreased resistance to the flow of urine. Individual agents may have other important effects in addition to α-receptor antagonism (see below).

**Specific Agents**

**Phentolamine**, an imidazoline derivative, is a potent competitive antagonist at both α₁ and α₂ receptors (Table 10–1). Phentolamine causes a reduction in peripheral resistance through blockade
of $\alpha_1$ receptors and possibly $\alpha_2$ receptors on vascular smooth muscle. The cardiac stimulation induced by phentolamine is due to sympathetic stimulation of the heart resulting from baroreflex mechanisms. Furthermore, since phentolamine potently blocks $\alpha_2$ receptors, antagonism of presynaptic $\alpha_2$ receptors may lead to enhanced release of norepinephrine from sympathetic nerves. Enhanced norepinephrine release may contribute to cardiac stimulation via unblocked $\beta$ adrenoceptors, especially after intravenous injection. In addition to being an $\alpha_1$- and $\alpha_2$-receptor antagonist, phentolamine also inhibits responses to serotonin and may be an agonist at muscarinic and H₁ and H₂ histamine receptors. Consequently, phentolamine has multiple potential actions, though it is not clear which if any of these are clinically significant.

### Table 10–1. Relative Selectivity of Antagonists for Adrenoceptors.

<table>
<thead>
<tr>
<th>Receptor Affinity</th>
<th>α-Antagonists</th>
<th>Mixed antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1 &gt;&gt;&gt;&gt; \alpha_2$</td>
<td>Prazosin, terazosin, doxazosin</td>
<td>Labetalol, carvedilol</td>
</tr>
<tr>
<td>$\alpha_1 &gt; \alpha_2$</td>
<td>Phenoxybenzamine</td>
<td>$\beta_1 = \beta_2, \alpha_1 &gt; \alpha_2$</td>
</tr>
<tr>
<td>$\alpha_1 = \alpha_2$</td>
<td>Phentolamine</td>
<td>$\beta_1 = \beta_2$</td>
</tr>
<tr>
<td>$\alpha_2 &gt;&gt;&gt;&gt; \alpha_1$</td>
<td>Rauwolscine, yohimbine, tolazoline</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
</tr>
<tr>
<td>$\beta_1 &lt;&lt;&lt; \beta_2$</td>
<td>Metoprolol, acebutolol, alpenolol, atenolol, betaxolol, celiprolol, esmolol</td>
<td>$\beta_1 &lt;&lt;&lt; \beta_2$</td>
</tr>
<tr>
<td>$\beta_1 = \beta_2$</td>
<td>Propranolol, carteolol, penbutolol, pindolol, timolol</td>
<td>$\beta_1 = \beta_2$</td>
</tr>
<tr>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>Butoxamine</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
</tr>
</tbody>
</table>

Phentolamine has limited absorption after oral administration. Its pharmacokinetic properties are not well known; it may reach peak concentrations within an hour after oral administration and has a half-life of about 5–7 hours. The principal adverse effects are related to cardiac stimulation, which may cause severe tachycardia, arrhythmias, and myocardial ischemia, especially after intravenous administration. With oral administration, adverse effects include tachycardia, nasal congestion, and headache.

Phentolamine has been used in the treatment of pheochromocytoma—especially intraoperatively—as well as for male erectile dysfunction by injection intracavernosally and when taken orally (see below).
**Tolazoline** is similar to phentolamine. Tolazoline has very limited clinical application in the treatment of pulmonary hypertension in newborn infants with respiratory distress syndrome. Its efficacy in this condition is doubtful, and the drug is rarely used.

**Ergot derivatives**—eg, ergotamine, dihydroergotamine—cause reversible \( \alpha \)-receptor blockade. However, most of the clinically significant effects of these drugs are the result of other actions; eg, ergotamine probably acts at serotonin receptors in the treatment of migraine (Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids).

**Phenoxybenzamine** binds covalently to \( \alpha \) receptors, causing irreversible blockade of long duration (14–48 hours or longer). It is somewhat selective for \( \alpha_1 \) 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 \( \alpha \) receptors (see Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids).

The pharmacologic actions of phenoxybenzamine are primarily related to antagonism of \( \alpha \)-receptor-mediated events. Most importantly, phenoxybenzamine attenuates 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 \( \alpha_2 \) 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 low doses of 10–20 mg/d and progressively increasing the dose until the desired effect is achieved. Less than 100 mg/d is usually sufficient to achieve adequate \( \alpha \)-receptor blockade. The major use of phenoxybenzamine is in the treatment of pheochromocytoma (see below).

Many of the adverse effects of phenoxybenzamine derive from its \( \alpha \)-receptor-blocking action; the most important are postural 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. Since phenoxybenzamine is an alkylating agent, it may have other adverse effects that have not yet been characterized. Phenoxybenzamine causes tumors in animals, but the clinical implications of this observation are unknown.

**Prazosin** is a piperazinyl quinazoline effective in the management of hypertension (see Chapter 11: Antihypertensive Agents). It is highly selective for \( \alpha_1 \) receptors, having relatively low affinity for \( \alpha_2 \) receptors (typically 1000-fold less potent). This may partially explain the relative absence of tachycardia seen with prazosin as compared to what is reported with phentolamine and phenoxybenzamine. Prazosin leads to relaxation of both arterial and venous smooth muscle due to blockade of \( \alpha_1 \) 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 \( \alpha_1 \)-selective antagonist that is effective in hypertension (Chapter 11: Antihypertensive Agents); it has also been 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 \( \alpha_1 \) antagonist with a structure quite different from that of most other \( \alpha_1 \)-receptor blockers. It has high bioavailability and a long half-life of 9–15 hours. It is metabolized extensively in the liver. Tamsulosin has higher affinity for \( \alpha_{1A} \) and \( \alpha_{1D} \) receptors than for the \( \alpha_{1B} \) subtype. The drug's efficacy in BPH suggests that the \( \alpha_{1A} \) subtype may be the most important \( \alpha \) subtype mediating prostate smooth muscle contraction. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle, compared with other \( \alpha_1 \)-selective antagonists, which have equal or greater effects in vascular smooth muscle. This finding suggests that \( \alpha_{1A} \) receptors are less important in mediating contraction in human arteries and veins. Furthermore, compared with other antagonists, tamsulosin has less effect on standing blood pressure in patients. Nonetheless, caution is appropriate in using any \( \alpha \)-antagonist in patients with diminished sympathetic nervous system function.

Other Alpha-Adrenoceptor Antagonists

Alfuzosin is an \( \alpha_1 \)-selective quinazoline derivative that has also been shown to be efficacious in BPH. It has a bioavailability of about 60%, is extensively metabolized, and has an elimination half-life of about 5 hours. This drug is not currently available in the USA. Indoramin is another \( \alpha_1 \)-selective antagonist that also has efficacy as an antihypertensive. Urapidil is an \( \alpha_1 \) antagonist (its primary effect) that also has weak \( \alpha_2 \)-agonist and 5-HT\(_{1A} \)-agonist actions and weak antagonist action at \( \beta_1 \) receptors. It is used in Europe as an antihypertensive agent and for benign prostatic hyperplasia. Labetalol has both \( \alpha_1 \)-selective and \( \beta \)-antagonistic effects; it is discussed below. Neuroleptic drugs such as chlorpromazine and haloperidol are potent dopamine receptor antagonists but may also be antagonists at \( \alpha \)-receptors. Their antagonism of \( \alpha \)-receptors probably contributes to some of their adverse effects, particularly hypotension. Similarly, the antidepressant trazodone has the capacity to block \( \alpha \)-receptors.

Yohimbine, an indole alkaloid, is an \( \alpha_2 \)-selective antagonist. It has no established clinical role. Theoretically, it could be useful in autonomic insufficiency by promoting neurotransmitter release through blockade of presynaptic \( \alpha_2 \) receptors. It has been suggested that yohimbine improves male sexual function; however, evidence for this effect in humans is limited. Yohimbine can abruptly reverse the antihypertensive effects of an \( \alpha_2 \)-adrenoceptor agonist such as clonidine—a potentially serious adverse drug interaction.

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Clinical Pharmacology of the Alpha-Receptor-Blocking Drugs

Pheochromocytoma

The major clinical use of both phenoxybenzamine and phentolamine is in the management of pheochromocytoma. Pheochromocytoma is a tumor usually found in the adrenal medulla that releases a mixture of epinephrine and norepinephrine. Patients have many symptoms and signs of catecholamine excess, including intermittent or sustained hypertension, headaches, palpitations, and increased sweating.
The diagnosis of pheochromocytoma is usually made on the basis of chemical assay of circulating catecholamines and urinary excretion of catecholamine metabolites, especially 3-hydroxy-4-methoxymandelic acid, metanephrine, and normetanephrine. Measurement of plasma metanephrines has shown promise as an effective diagnostic tool. A variety of diagnostic techniques are available to localize a pheochromocytoma diagnosed biochemically, including CT and MRI scans as well as scanning with various radioisotopes.

Infusion of phentolamine was advocated in the past as a diagnostic test when pheochromocytoma was suspected, since patients with this tumor often manifest a greater drop in blood pressure in response to α-blocking drugs than do patients with primary hypertension. Provocative testing by infusion of histamine was occasionally used because this vasodilator drug may elicit a marked reflex rise in pressure in patients with pheochromocytoma. These tests are obsolete because measurement of circulating catecholamines and urinary catecholamines and their metabolites is a safer and far more reliable diagnostic approach.

Unavoidable release of stored catecholamines sometimes occurs during operative manipulation of pheochromocytoma; the resulting hypertension may be controlled with phentolamine or nitroprusside. Nitroprusside has many advantages, particularly since 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 will help control hypertension and will tend 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 10–20 mg/d may 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 may 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 α₁-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 employed prior to establishing effective α-receptor blockade, since unopposed β-receptor blockade could theoretically cause blood pressure elevation from increased vasoconstriction.

Figure 10–4.
Effects of phenoxybenzamine (Dibenzyline) on blood pressure in a patient with pheochromocytoma. Dosage of the drug was begun in the third week as shown by the shaded bar. Supine systolic and diastolic pressures are indicated by the circles, the standing pressures by triangles and the hatched area. Note that the $\alpha$-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 long-standing pheochromocytoma-induced hypertension. (Redrawn and reproduced, with permission, from Engelman E, Sjoerdsma A: Chronic medical therapy for pheochromocytoma. Ann Intern Med 1961;61:229.)

Pheochromocytoma is rarely treated with metyrosine ($\alpha$-methyltyrosine), the $\alpha$-methyl analog of tyrosine. This agent is a competitive inhibitor of tyrosine hydroxylase and, in oral doses of 1–4 g/d, interferes with synthesis of dopamine (see Figure 6–5), thereby decreasing the amounts of norepinephrine and epinephrine secreted by the tumor. Metyrosine, while not an $\alpha$-adrenoceptor antagonist, may act additively with phenoxybenzamine and a $\beta$-adrenoceptor antagonist in the treatment of pheochromocytoma. Metyrosine is especially useful in symptomatic patients with inoperable or metastatic pheochromocytoma.

Hypertensive Emergencies

The $\alpha$-adrenoceptor antagonist drugs have limited application in the management of hypertensive emergencies, although labetalol has been used in this setting. In theory, $\alpha$-adrenoceptor antagonists
are most useful when increased blood pressure reflects excess circulating concentrations of agonists. In this circumstance, which may result from pheochromocytoma, overdosage of sympathomimetic drugs, or clonidine withdrawal, phentolamine can be used to control high blood pressure. However, other drugs are generally preferable (see Chapter 11: Antihypertensive Agents), since considerable experience is necessary to use phentolamine safely in these settings and few physicians have such experience.

Chronic Hypertension

Members of the prazosin family of α1-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension. They are generally well tolerated by most patients. However, their efficacy in preventing heart failure when used as monotherapy for hypertension has been questioned. Their major adverse effect is postural hypotension, which may be severe after the first dose but is otherwise uncommon (see Chapter 11: Antihypertensive Agents). Nonselective α antagonists are not used in primary systemic hypertension. Prazosin and related drugs may also be associated with feelings of dizziness. This symptom may not be due to a fall in blood pressure, but postural changes in blood pressure should be checked routinely in any patient being treated for hypertension.

Interestingly, 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 HDL, which could be a favorable alteration. The mechanism for this effect is not known.

Peripheral Vascular Disease

Although α-receptor-blocking drugs have been tried in the treatment of peripheral vascular occlusive disease, there is no evidence that the effects are significant when morphologic changes 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 phentolamine, prazosin, or phenoxybenzamine, although calcium channel blockers may be preferable for many patients.

Local Vasoconstrictor Excess

Phentolamine has been used to reverse the intense local vasoconstriction caused by inadvertent infiltration of agonists (e.g., norepinephrine) into subcutaneous tissue during intended intravenous administration. The antagonist is administered by local infiltration into the ischemic tissue.

Urinary Obstruction

Benign prostatic hyperplasia is a prevalent disorder in elderly men. A variety of surgical treatments are effective in relieving the urinary symptoms of BPH; however, drug therapy is efficacious in many patients. Alpha-receptor blockade was first found to be helpful in BPH using phenoxybenzamine in selected patients who were poor operative risks. 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 α1-receptor antagonists may have additional effects on cells in the prostate that help improve symptoms.

A number of well-controlled studies have demonstrated reproducible efficacy of several α1-receptor antagonists in patients with BPH—lasting for several years in many cases. Prazosin, doxazocin, and terazosin are efficacious. These drugs are particularly useful in patients who also have hypertension.
Considerable interest has focused on which $\alpha_1$-receptor subtype is most important for smooth muscle contraction in the prostate: *subtype-selective* $\alpha_1A$-receptor antagonists might lead to improved efficacy and safety in treating this disease. As indicated above, tamsulosin is also efficacious in BPH and has little if any effect on blood pressure. This drug may be preferred in patients who have experienced postural hypotension with other $\alpha_1$-receptor antagonists. Some evidence suggests that the efficacy of $\alpha_1$-receptor antagonists exceeds that of finasteride, the 5$\alpha$-reductase inhibitor (see Chapter 40: The Gonadal Hormones & Inhibitors).

**Erectile Dysfunction**

A combination of the $\alpha$-adrenoceptor antagonist phentolamine with the nonspecific vasodilator papaverine, when injected directly into the penis, may cause erections in men with sexual dysfunction. Fibrotic reactions may occur, especially with long-term administration. Systemic absorption may lead to orthostatic hypotension; priapism may require direct treatment with an $\alpha$-adrenoceptor agonist such as phenylephrine. Orally administered phentolamine is being investigated in patients with erectile dysfunction (and in women with disorders of arousal.) Alternative therapies include prostaglandins (see Chapter 18: The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds), sildenafil, a cGMP phosphodiesterase inhibitor (see Chapter 12: Vasodilators & the Treatment of Angina Pectoris), and apomorphine.

**Applications of Alpha2 Antagonists**

Alpha2 antagonists have relatively little clinical usefulness. There has been experimental interest in the development of highly selective antagonists for use in Raynaud's phenomenon to inhibit smooth muscle contraction and in the treatment of type 2 diabetes ($\alpha_2$ receptors inhibit insulin secretion) and psychiatric depression. It is not known to what extent the recognition of multiple subtypes of $\alpha_2$ receptors will lead to development of clinically useful subtype-selective new drugs.

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**Basic Pharmacology of the Beta-Receptor-Antagonist Drugs**

Drugs in this category share the common feature of antagonizing the effects of catecholamines at $\beta$ adrenoceptors. Beta-blocking drugs occupy $\beta$receptors and competitively reduce receptor occupancy by catecholamines and other $\beta$agonists. (A few members of this group, used only for experimental purposes, bind irreversibly to $\beta$receptors.) Most $\beta$-blocking drugs in clinical use are pure antagonists; ie, the occupancy of a $\beta$ receptor by such a drug causes no activation of the receptor. However, some are partial agonists; ie, they cause partial activation of the receptor, albeit less than that caused by the full agonists epinephrine and isoproterenol. As described in Chapter 2: Drug Receptors & Pharmacodynamics, partial agonists inhibit the activation of $\beta$ receptors in the presence of high catecholamine concentrations but moderately activate the receptors in the absence of endogenous agonists. Another major difference among the many $\beta$-receptor-blocking drugs concerns their relative affinities for $\beta_1$ and $\beta_2$ receptors (Table 10–1). Some of these antagonists have a higher affinity for $\beta_1$ than for $\beta_2$ receptors, and this selectivity may have important clinical implications. Since none of the clinically available $\beta$ receptor antagonists are absolutely specific for $\beta_1$ receptors, the selectivity is dose-related, ie, it tends to diminish at higher drug concentrations. Other major differences among $\beta$ antagonists relate to their pharmacokinetic characteristics and local anesthetic membrane-stabilizing effects.

Chemically, the $\beta$-receptor-antagonist drugs (Figure 10–5) resemble isoproterenol (see Figure 9–3),...
a potent β-receptor agonist.

Figure 10–5.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Propranolol" /></td>
<td>Propranolol</td>
</tr>
<tr>
<td><img src="image" alt="Metoprolol" /></td>
<td>Metoprolol</td>
</tr>
<tr>
<td><img src="image" alt="Nadolol" /></td>
<td>Nadolol</td>
</tr>
<tr>
<td><img src="image" alt="Timolol" /></td>
<td>Timolol</td>
</tr>
<tr>
<td><img src="image" alt="Pindolol" /></td>
<td>Pindolol</td>
</tr>
<tr>
<td><img src="image" alt="Atenolol" /></td>
<td>Atenolol</td>
</tr>
<tr>
<td><img src="image" alt="Acebutolol" /></td>
<td>Acebutolol</td>
</tr>
<tr>
<td><img src="image" alt="Labetalol" /></td>
<td>Labetalol</td>
</tr>
</tbody>
</table>

Structures of some β-receptor antagonists.

Pharmacokinetic Properties of the Beta-Receptor Antagonists

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.

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. Bioavailability is limited to varying degrees for most β-antagonists with the exception of betaxolol, penbutolol, pindolol, and sotalol.

Table 10–2. Properties of Several Beta-Receptor-Blocking Drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>B₁</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Atenolol</td>
<td>B₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
<td>40</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>B₁</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14–22 hours</td>
<td>90</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>B₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9–12 hours</td>
<td>80</td>
</tr>
<tr>
<td>Carteolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
</tr>
<tr>
<td>Carvedilol¹</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No data</td>
<td>6–8 hours</td>
<td>25–35</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>B₁</td>
<td>Yes²</td>
<td>No</td>
<td>No data</td>
<td>4–5 hours</td>
<td>70</td>
</tr>
<tr>
<td>Esmolol</td>
<td>B₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>–0</td>
</tr>
<tr>
<td>Labetalol¹</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>B₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14–24 hours</td>
<td>33</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
<td>90</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3.5–6 hours</td>
<td>30³</td>
</tr>
</tbody>
</table>
Sotalol | None | No | No | Low | 12 hours | 90
---|---|---|---|---|---|---
Timolol | None | No | No | Moderate | 4–5 hours | 50

1Carvedilol and labetalol also cause $\alpha_1$ adrenoceptor blockade.

2Partial agonist effects at $\beta_2$ receptors.

3Bioavailability is dose-dependent.

### Distribution and Clearance

The $\beta$ 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 $\beta$ 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 (Chapter 4: Drug Biotransformation). 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 $\beta$ 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 often 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 occupancy and blockade of $\beta$ receptors. However, some actions may be due to other effects, including partial agonist activity at $\beta$ receptors and local anesthetic action, which differ among the $\beta$-blockers (Table 10–2).

### Effects on the Cardiovascular System

Beta-blocking drugs given chronically lower blood pressure in patients with hypertension. The mechanisms involved may include effects on the heart and blood vessels, suppression of the renin-angiotensin system, and perhaps effects in the central nervous system or elsewhere. Beta-adrenoceptor-blocking drugs are of major clinical importance in the treatment of hypertension (see Chapter 11: Antihypertensive Agents). In contrast, conventional doses of these drugs do not usually cause hypotension in healthy individuals with normal blood pressure.

Beta-receptor antagonists have prominent effects on the heart (Figure 10–6). The negative inotropic and chronotropic effects are predictable from 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. These effects may be clinically valuable in some patients but are potentially hazardous in others. In the vascular system, $\beta$-receptor blockade opposes $\beta_2$-mediated vasodilation. This may acutely lead to a rise in peripheral resistance from unopposed $\alpha$-receptor-mediated effects as the sympathetic nervous system discharges in response to lowered blood pressure due to the fall in cardiac output. Beta-blocking drugs antagonize the release of renin
caused by the sympathetic nervous system. As noted in Chapter 11: Antihypertensive Agents, the relation between the effects on renin release and those on blood pressure is unclear. In any event, while 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. How this adjustment occurs is not yet clear.

Figure 10–6.

The effect in an anesthetized dog of the injection of epinephrine before and after propranolol. In the presence of a $\beta$-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 $\beta$ sympathetic blockade. Am J Cardiol 1966;18:312.)

Effects on the Respiratory Tract

Blockade of the $\beta_2$ 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 or atenolol may have some advantage over nonselective $\beta$ antagonists when blockade of $\beta_1$ receptors in the heart is desired and $\beta_2$-receptor blockade is undesirable. However, no currently available $\beta_1$-selective antagonist is sufficiently specific to completely avoid interactions with $\beta_2$ adrenoceptors. Consequently, these drugs should generally be avoided in patients with asthma. On the other hand, some patients with chronic obstructive pulmonary disease (COPD) may tolerate these drugs quite well.

Effects on the Eye

Several $\beta$-blocking agents reduce intraocular pressure, especially in glaucomatous eyes. The mechanism usually reported is decreased aqueous humor production. (See Clinical Pharmacology and The Treatment of Glaucoma.)
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 \( \beta_2 \)-receptor blockade. However, glucagon is the primary hormone employed to combat hypoglycemia. It is unclear to what extent \( \beta \) 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 \( \beta \)-adrenoceptor antagonists has been associated with increased plasma concentrations of VLDL and decreased concentrations of HDL cholesterol. Both of these changes are potentially unfavorable in terms of risk of cardiovascular disease. Although 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 \( \beta \)-blockers, though they are perhaps less likely to occur with \( \beta \)-blockers possessing intrinsic sympathomimetic activity (partial agonists). The mechanisms by which \( \beta \)-receptor antagonists cause these changes are not understood, though changes in sensitivity to insulin action may contribute.

Effects Not Related to Beta-Blockade

Partial \( \beta \)-agonist activity was significant in the first \( \beta \)-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 \( \beta \)-adrenoceptor drugs, but only if they are strongly indicated for a particular clinical indication.

Local anesthetic action, also known as "membrane-stabilizing" action, is a prominent effect of several \( \beta \)-blockers (Table 10–2). This action is the result of typical local anesthetic blockade of sodium channels 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. These drugs are not used topically on the eye, where local anesthesia of the cornea would be highly undesirable. Sotalol is a nonselective \( \beta \)-receptor antagonist that lacks local anesthetic action but has marked class III antiarrhythmic effects, reflecting potassium channel blockade (see Chapter 14: Agents Used in Cardiac Arrhythmias).

Specific Agents

(See Table 10–2.)

**Propranolol** is the prototypical \( \beta \)-blocking drug. It has low and dose-dependent bioavailability, the result of extensive first-pass metabolism in the liver. 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 (see Table 10–2) are members of the β₁-selective group. These agents may be safer in patients who experience bronchoconstriction in response to propranolol. Since their β₁ 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 chronic obstructive lung disease the benefits may exceed the risks, eg, in patients with myocardial infarction. Beta₁-selective antagonists may be preferable in patients with diabetes or peripheral vascular disease when therapy with a β-blocker is required since β₂ receptors are probably important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

**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. **Levocabunonol** (nonselective) and **betaxolol** (β₁-selective) are 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.

* Not available in the USA.

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 β₁-selective antagonist with a modest capacity to activate β₂ receptors.

* Not available in the USA.

There is limited evidence suggesting that celiprolol may have less adverse bronchoconstrictor effects in asthma and may even promote bronchodilation. Acebutolol is also a β₁-selective antagonist.

**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 inactive, (S,R)- 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 α₁-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 α₁-adrenergic receptors.

* Not available in the USA.

Carvedilol antagonizes the actions of catecholamines more potently at β-receptors than at α-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 cytochrome P450 2D6 activity and by drugs that inhibit this enzyme's activity (such as quinidine and fluoxetine), 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: Drugs Used in Heart Failure).

**Esmolol** is an ultra-short–acting \( \beta \)-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 \( \beta \) 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 is potentially safer to use than longer-acting antagonists in critically ill patients who require a \( \beta \)-adrenoceptor antagonist. Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients.

**Butoxamine** is selective for \( \beta \)-receptors. Selective \( \beta \)-blocking drugs have not been actively sought because there is no obvious clinical application for them and none are available for clinical use.

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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 (or 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 (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 closed-angle glaucoma fall into two classes: reduction of aqueous humor secretion and enhancement of aqueous outflow. Five general groups of drugs—cholinomimetics, \( \alpha \)-agonists, \( \beta \)-blockers, prostaglandin \( \mathrm{F}_{2 \alpha} \) 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 \( \beta \)-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 \( \beta \)-blockers, in patients with asthma or cardiac pacemaker or conduction pathway disease). Other drugs that have been reported to reduce intraocular pressure include prostaglandin \( \mathrm{E}_2 \) 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.
Table 10–3. Drugs Used in Open-Angle Glaucoma.

<table>
<thead>
<tr>
<th></th>
<th>Mechanism</th>
<th>Methods of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinomimetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocarpine, carbachol, physostigmine, echothiophate, demecarium</td>
<td>Ciliary muscle contraction, opening of trabecular meshwork; increased outflow</td>
<td>Topical drops or gel; plastic film slow-release insert</td>
</tr>
<tr>
<td><strong>Alpha agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unselective</td>
<td>Increased outflow</td>
<td>Topical drops</td>
</tr>
<tr>
<td>Epinephrine, dipivefrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha2-selective</td>
<td>Decreased aqueous secretion</td>
<td></td>
</tr>
<tr>
<td>Apraclonidine</td>
<td></td>
<td>Topical, postlaser only</td>
</tr>
<tr>
<td>Brimonidine</td>
<td></td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol, betaxolol, carteolol, levobunolol, metipranolol</td>
<td>Decreased aqueous secretion from the ciliary epithelium</td>
<td>Topical drops</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorzolamide, brinzolamide</td>
<td>Decreased secretion due to lack of HCO₃⁻</td>
<td>Topical</td>
</tr>
<tr>
<td>Acetazolamide, dichlorphenamidine, methazolamide</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Prostaglandins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost, unoprostone</td>
<td>Increased outflow</td>
<td>Topical</td>
</tr>
</tbody>
</table>

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Clinical Pharmacology of the Beta-Receptor-Blocking Drugs

Hypertension

The β-adrenoceptor-blocking drugs have proved to be effective and well tolerated in hypertension. While many hypertensive patients will 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 detail in Chapter 11: Antihypertensive Agents. There is some evidence that drugs in this class may be less effective in blacks and the elderly. 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: Vasodilators & the Treatment of Angina Pectoris). 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. Importantly, surveys in many populations have indicated that the β-receptor antagonists are underused, leading to unnecessary morbidity and mortality. Studies in experimental animals suggest that use of β-receptor antagonists during the acute phase of a myocardial infarction may limit infarct size. However, this use is still controversial.

Cardiac Arrhythmias

Beta antagonists are effective in the treatment of both supraventricular and ventricular arrhythmias (see Chapter 14: Agents Used in Cardiac Arrhythmias). It has been suggested that the improved

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, black) or 40 mg of oxprenolol (color), 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.)
survival following myocardial infarction in patients using β-antagonists (Figure 10–8; see above) 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 additional antiarrhythmic effects involving ion channel blockade in addition to its β-blocking action; these are discussed in Chapter 14: Agents Used in Cardiac Arrhythmias.

![Figure 10–8.](image)

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 line) or timolol (color). (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.)

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. Clinical trials have demonstrated that at least three β-antagonists—metoprolol, bisoprolol, and carvedilol—are effective in treating chronic heart failure in selected patients. While administration of these drugs may acutely worsen congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life. While mechanisms are uncertain, there appear to be beneficial effects on myocardial remodeling and in decreasing the risk of sudden death (see Chapter 13: Drugs Used in Heart Failure).

Glaucoma

See 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 newer β-receptor antagonists approved for the treatment of glaucoma. Betaxolol has the potential advantage of being β₁-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: Thyroid & Antithyroid Drugs). The β-antagonists have salutary effects in this condition. These beneficial effects presumably relate to blockade of adrenoreceptors 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

Several studies show a beneficial effect of propranolol in reducing 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: Pharmacologic Management of Parkinsonism & Other Movement Disorders). 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 isosorbid mononitrate appears to be more efficacious than sclerotherapy in preventing re-bleeding in patients who have previously bled from esophageal varices.
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, it 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 hyperthyroidism 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 to pure antagonists.

Clinical Toxicity of the Beta-Receptor Antagonist Drugs

A variety of minor toxic effects have been reported for propranolol. Rash, fever, and other manifestations of drug allergy are rare. Central nervous system effects include sedation, sleep disturbances, and depression. Rarely, psychotic reactions may occur. Discontinuing the use of β-blockers in any patient who develops a 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. Beta2-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 life-saving possibilities 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 β1-selective drugs may have less effect on airways than nonselective β antagonists, they must be used very cautiously, if at all, in patients with reactive airways. While β1-selective antagonists are generally well tolerated in patients with mild to moderate peripheral vascular disease, 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 using β-receptor antagonists 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.

Some hazards are associated with abruptly discontinuing β-antagonist therapy after chronic use. Evidence suggests that patients with ischemic heart disease may be at increased risk if β-blockade is suddenly interrupted. The mechanism of this effect is uncertain but 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 in diabetics that are exacerbated by β-blocking agents 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. Beta₁-selective antagonists offer some advantage in these patients, since the rate of recovery from hypoglycemia may be faster compared with 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.

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**Preparations Available**

**Alpha Blockers**

**Doxazosin** (generic, Cardura)

Oral: 1, 2, 4, 8 mg tablets

**Phenoxybenzamine** (Dibenzyline)

Oral: 10 mg capsules

**Phentolamine** (generic, Regitine)

Parenteral: 5 mg/vial for injection

**Prazosin** (generic, Minipress)

Oral: 1, 2, 5 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: 10, 20 mg tablets (Kerlone)
Ophthalmic: 0.25%, 0.5% drops (generic, Betoptic)

Bisoprolol (Zebeta)
Oral: 5, 10 mg tablets

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

Carvedilol (Coreg)
Oral: 3.125, 6.25, 12.5, 25 mg tablets

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

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

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

Synthesis Inhibitor

**Metyrosine** (Demser)
Oral: 250 mg capsules
Antihypertensive Agents: Introduction

Hypertension is the most common cardiovascular disease. Thus, the third National Health and Nutrition Examination Survey (NHANES III), conducted from 1992 to 1994, found that 27% of the USA adult population had hypertension. The prevalence varies with age, race, education, and many other variables. Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, cardiac failure, and stroke. Effective pharmacologic lowering of blood pressure has been shown to prevent damage to blood vessels and to substantially reduce morbidity and mortality rates. Many effective drugs are available. Knowledge of their antihypertensive mechanisms and sites of action allows accurate prediction of efficacy and toxicity. As a result, rational use of these agents, alone or in combination, can lower blood pressure with minimal risk of serious toxicity in most patients.

Hypertension & Regulation of Blood Pressure

Diagnosis

The diagnosis of hypertension is based on repeated, reproducible measurements of elevated blood pressure. The diagnosis serves primarily as a prediction of consequences for the patient; it seldom includes a statement about the cause of hypertension.

Epidemiologic studies indicate that the risks of damage to kidney, heart, and brain are directly related to the extent of blood pressure elevation. Even mild hypertension (blood pressure ≥ 140/90 mm Hg) in young or middle-aged adults increases the risk of eventual end organ damage. The risks—and therefore the urgency of instituting therapy—increase in proportion to the magnitude of blood pressure elevation. The risk of end organ damage at any level of blood pressure or age is greater in black people and relatively less in premenopausal women than in men. Other positive risk factors include smoking, hyperlipidemia, diabetes, manifestations of end organ damage at the time of diagnosis, and a family history of cardiovascular disease.

It should be noted that the diagnosis of hypertension depends on measurement of blood pressure and not on symptoms reported by the patient. In fact, hypertension is usually asymptomatic until overt end organ damage is imminent or has already occurred.

Etiology of Hypertension

A specific cause of hypertension can be established in only 10–15% of patients. It is important to consider specific causes in each case, however, because some of them are amenable to definitive surgical treatment: renal artery constriction, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism.

Patients in whom no specific cause of hypertension can be found are said to have essential hypertension.*

* The adjective originally was intended to convey the now abandoned idea that blood pressure elevation was essential for adequate perfusion of diseased tissues.