

# Drugs Acting on the Autonomic Nervous System

## I. THE PERIPHERAL EFFERENT NERVOUS SYSTEM

**A. The autonomic nervous system (ANS)** controls **involuntary activity** (Fig. 2-1, Table 2-1).

**1. Parasympathetic nervous system (PNS)**

- a. Long preganglionic axons originate from neurons in the cranial and sacral areas of the spinal cord and, with few exceptions, synapse on neurons in ganglia located close to or within the innervated organ.
- b. Short postganglionic axons innervate cardiac muscle, bronchial smooth muscle, and exocrine glands.
- c. Parasympathetic innervation predominates over sympathetic innervation of salivary glands, lacrimal glands, and erectile tissue.

**2. Sympathetic nervous system (SNS)**

- a. Short preganglionic axons originate from neurons in the thoracic and lumbar areas of the spinal cord and synapse on neurons in ganglia located outside of, but close to, the spinal cord. The adrenal medulla, anatomically considered a modified ganglion, is innervated by sympathetic preganglionic axons.
- b. Long postganglionic axons innervate many of the same tissues and organs as the PNS.
- c. Innervation of **thermoregulatory sweat glands** is anatomically sympathetic, but the postganglionic nerve fibers are cholinergic and release acetylcholine as the neurotransmitter

**3. Enteric nervous system (ENS)**

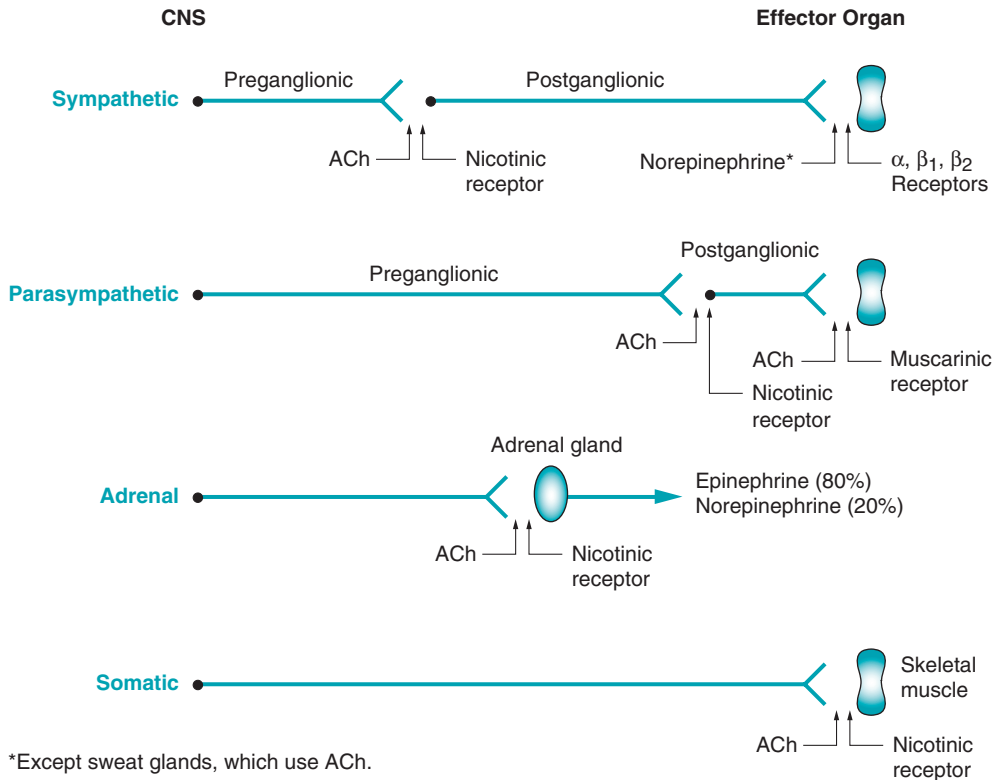
- a. Considered a third branch of the ANS
- b. Highly organized, semiautonomous, neural complex localized in the **GI system**
- c. Receives preganglionic axons from the PNS and postganglionic axons from the SNS
- d. Nerve terminals contain peptides and purines as neurotransmitters.

**B. The somatic nervous system** (Fig. 2-1) controls **voluntary activity**. This system contains long axons that originate in the spinal cord and directly innervate skeletal striated muscle.

**C. Neurotransmitters of the autonomic and somatic nervous systems** (Fig. 2-1)

**1. Acetylcholine (ACh)**

- a. ACh is released by exocytosis from nerve terminals.
- b. ACh is the neurotransmitter across synapses at the ganglia of the SNS and PNS and across synapses in tissues innervated by the PNS and the somatic nervous system.
- c. ACh is synthesized in nerve terminals by the cytoplasmic enzyme choline acetyltransferase (ChAT), which catalyzes the transfer of an acetate group from acetyl coenzyme A (acetyl CoA) to choline that has been transported into “cholinergic” neurons by a sodium-dependent membrane carrier. Synthesized ACh is transported from cytoplasm to vesicle-associated transporters (VAT).
- d. ACh is stored in nerve terminal vesicles that, through calcium-dependent exocytosis, are released by nerve action potentials. On release, a step blocked by **botulinum toxin**, ACh is



**FIGURE 2-1.** Organization of the autonomic nervous system.

rapidly hydrolyzed and inactivated by tissue acetylcholinesterase (AChE) and also by non-specific butyrylcholinesterase (pseudocholinesterase) to choline and acetate.

**e.** ACh is not administered parenterally for therapeutic purposes because it is hydrolyzed nearly instantly by butyrylcholinesterase.

**2. Norepinephrine and epinephrine** are **catecholamines**, possessing a catechol nucleus and an ethylamine side chain.

**a.** Storage and release

**(1)** Norepinephrine is stored in vesicles that, through a calcium-dependent process, release their contents by exocytosis from nerve terminals at postganglionic nerve endings of the SNS (except at thermoregulatory sweat glands, where ACh is the neurotransmitter).

**(2)** Norepinephrine release can be blocked by such drugs as **bretelium** and **guanethidine**.

**(3)** Norepinephrine also exists in a nonvesicular cytoplasmic pool that is released by indirectly acting sympathomimetic amines (e.g., **tyramine**, **amphetamine**, **ephedrine**) by a process that is not calcium dependent.

**(4)** Norepinephrine and some epinephrine are released from adrenergic nerve endings in the brain. In the periphery, epinephrine, along with some norepinephrine, is the major catecholamine released from adrenal medullary chromaffin cells into the general circulation, where they function as hormones.

**b.** Biosynthesis of catecholamines (Fig. 2-2)

**(1)** In prejunctional nerve endings, tyrosine is hydroxylated by tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, to form dihydroxyphenylalanine (dopa); dopa is then decarboxylated by dopa decarboxylase to form dopamine.

**(2)** Dopamine is transported into vesicles, a step blocked by **reserpine**, where it is hydroxylated on the side chain by dopamine  $\beta$ -hydroxylase to form norepinephrine.

**(3)** In certain areas of the brain and in the adrenal medulla, norepinephrine is methylated on the amine group of the side chain by phenylethanolamine-*N*-methyltransferase (PNMT) to form epinephrine.

**table 2-1** Actions of the Autonomic Nervous System on Selected Effector Organs

Effector	Action of Sympathetic (Thoracolumbar) Division	Action of Parasympathetic (Craniosacral) Division
Eye (pupil)	Dilation (ex)	Constriction (ex)
Heart		
Rate	Acceleration (ex)	Slowing (in)
Contractility	Increased (ex)	Decreased (in)
Arterioles		
Skin and most others	Constriction (ex)	—
Skeletal muscle	Dilation (ex)	—
Glands		
Salivary	Viscid secretion (ex)	Watery secretion (ex)
Lacrimal	—	Secretion (ex)
Sweat	Secretion (ex)	—
Bronchial muscle	Relaxation (in)	Contraction (ex)
GI tract		
Muscle wall	Relaxation (in)	Contraction (ex)
Sphincters	Contraction (ex)	Relaxation (in)
Urinary bladder		
Fundus	Relaxation (in)	Contraction (ex)
Trigone; sphincter	Contraction (ex)	Relaxation (in)
Penis	Ejaculation (ex)	Erection (in)
Uterus	Relaxation (in)	—
Metabolism		
Liver	Gluconeogenesis (ex)	—
	Glycogenolysis (ex)	—
Kidney	Renin secretion(ex)	—
Fat Cells	Lipolysis (ex)	—

ex, excitatory; in, inhibitory; —, no functionally important innervation.

### c. Termination

- (1) The action of **norepinephrine** is terminated primarily by **active transport** from the cytoplasm into the nerve terminal (**uptake 1**), a process that is inhibited by **cocaine** and tricyclic antidepressant agents such as **imipramine**. **Norepinephrine** is then transported by a second carrier system into storage vesicles, as is **dopamine** and **serotonin**, a process also blocked by **reserpine**.
- (2) Another active transport system (**uptake 2**) is located on glia and smooth muscle cells.
- (3) There is also some simple **diffusion** away from the synapse.
- (4) **Norepinephrine** and **epinephrine** also are oxidatively deaminated by **mitochondrial monoamine oxidase (MAO)** in nerve terminals and effector cells, notably in the liver and intestine. **Isoforms** of MAO (A and B) have been identified. Dopamine is metabolized primarily by MAO-B.
- (5) Nerve cells and effector cells contain **catechol-O-methyltransferase (COMT)**, which metabolizes catecholamines. Metabolites, including **3-methoxy-4-hydroxymandelic acid (VMA)**, provide a measure of catecholamine turnover in the body.

## D. Receptors of the nervous system

### 1. Cholinergic receptors

#### a. Nicotinic receptors: Cholinergic receptors that are activated by the alkaloid nicotine (Fig. 2-1)

- (1) Nicotinic receptors are localized at myoneural junctions of somatic nerves and skeletal muscle ( $N_M$ ), autonomic ganglia ( $N_G$ ), including the adrenal medulla, and certain areas in the brain.
- (2) Nicotinic receptors consist of a pentamer of **four protein subunits** in skeletal muscle (e.g.,  $\alpha$  (2),  $\beta$ ,  $\gamma$ ,  $\delta$ ) and two protein subunits in neurons ( $\alpha$  and  $\beta$ ) that form **ligand-gated** (i.e., regulated) ion channel pores in the cell membranes (see Fig. 1-1A).

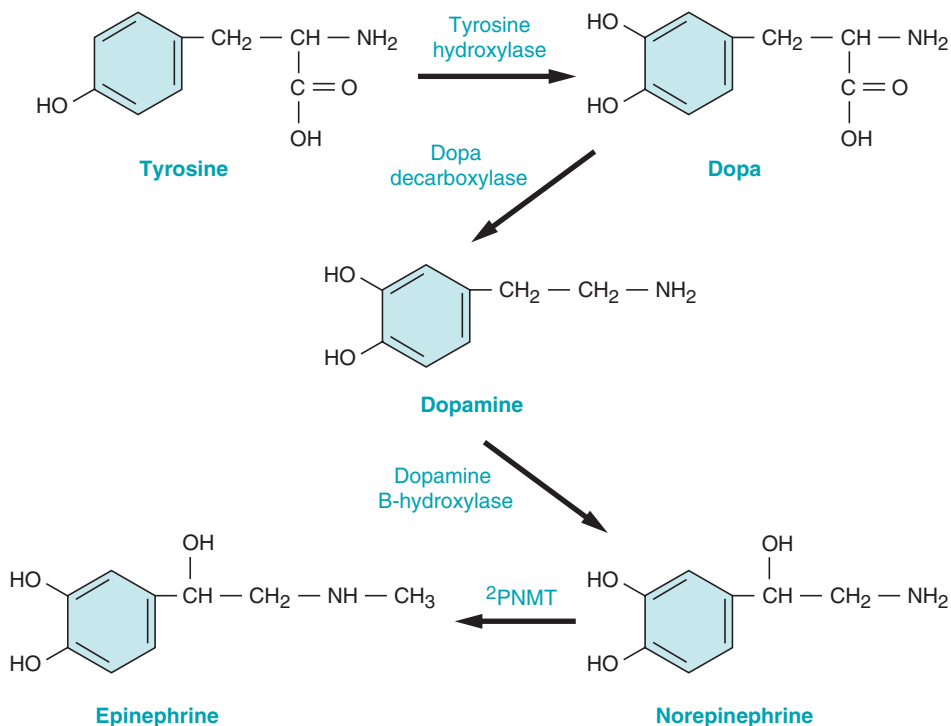


FIGURE 2-2. Biosynthesis of catecholamines.

(3) In skeletal muscle, **ACh interacts with nicotinic receptors** (one molecule of ACh per  $\alpha$  subunit) **to open channels that permit passage of ions, mostly  $\text{Na}^+$** . The  $\text{Na}^+$  current produces membrane depolarization and a propagated action potential through the transverse tubules of skeletal muscle, resulting in the release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum and, through a further series of chemical and mechanical events, **muscle contraction**. Hydrolysis of ACh by AChE results in muscle cell repolarization.

(a) The continued presence of a nicotine agonist, like **succinylcholine**, at nicotinic receptors, or excessive cholinergic stimulation, can lead to a “**depolarizing blockade**” (phase I block), in which normal depolarization is followed by persistent depolarization. During phase I block, skeletal muscle is unresponsive to either neuronal stimulation or direct stimulation.

(b) The selective nicotinic receptor antagonists **tubocurarine** and **trimethaphan** can block the effect of ACh at skeletal muscle and autonomic ganglia, respectively.

**b. Muscarinic receptors:** Cholinoceptors that are activated by the alkaloid muscarine (Fig. 2-1)

(1) Muscarinic receptors are localized on numerous autonomic effector cells, including cardiac atrial muscle and cells of the sinoatrial (SA) and atrioventricular (AV) nodes, smooth muscle, exocrine glands, and vascular endothelium (mostly arterioles), although the latter does not receive parasympathetic innervation, as well as certain areas in the brain.

(2) Muscarinic receptors consist of at least three **functional receptor subtypes ( $M_1$ – $M_3$ )**. Muscarinic  $M_1$ -receptors are found in sympathetic postganglionic neurons and in CNS neurons;  $M_2$ -receptors are found in cardiac and smooth muscle; and  $M_3$ -receptors are found in glandular cells (e.g., gastric parietal cells), and the vascular endothelium and vascular smooth muscle.  $M_2$ - and  $M_3$ -receptors predominate in the urinary bladder. All three subtypes are found in the CNS.

(3) ACh interacts with  **$M_1$  and  $M_3$  muscarinic cholinoceptors** to increase **phosphatidylinositol (PI) turnover** and  **$\text{Ca}^{2+}$  mobilization** (see Fig. 1-1D).

- (a) By activation of **G protein** ( $G_q$ ), the interaction of ACh with  $M_1$  and  $M_3$  muscarinic cholinergic receptors stimulates **polyphosphatidylinositol phosphodiesterase (phospholipase C)**, which hydrolyzes PI to **inositol trisphosphate ( $IP_3$ )** and **diacylglycerol (DAG)**.
  - (b)  **$IP_3$  mobilizes intracellular  $Ca^{2+}$**  from the endoplasmic and sarcoplasmic reticula, and activates  $Ca^{2+}$ -regulated enzymes and cell processes.
  - (c) **Diacylglycerol activates protein kinase C**, which results in phosphorylation of cellular enzymes and other protein substrates and the **influx of extracellular calcium** that results in activation of contractile elements in smooth muscle.
- (4) ACh also interacts with  **$M_2$  muscarinic cholinergic receptors** to **activate G proteins ( $G_i$ )**, which leads to **inhibition of adenylyl cyclase** activity with decreased levels of cyclic AMP and to **increased  $K^+$  conductance** with effector cell hyperpolarization.
- (5) Cholinergic agonists act on  **$M_3$  muscarinic receptors** of **endothelial cells** to promote the release of **nitric oxide (NO)**, which diffuses to the **vascular smooth muscle** to activate guanylyl cyclase and increase cyclic GMP (cGMP) and to produce **relaxation**.

## 2. Adrenoceptors (Fig. 2-1)

### a. $\alpha$ -Adrenoceptors

- (1)  $\alpha$ -Adrenoceptors are classified into two major receptor subgroups (there are subtypes of each group).  **$\alpha_1$ -Receptors** are located in **postjunctional** effector cells, notably vascular smooth muscle, where responses are mainly excitatory;  **$\alpha_2$ -receptors** are located primarily in **prejunctional** adrenergic nerve terminals, and also in fat cells and in beta cells of the pancreas.
- (2)  $\alpha$ -Adrenoceptors mediate vasoconstriction ( $\alpha_1$ ), GI relaxation ( $\alpha_1$ ), mydriasis ( $\alpha_1$ ), prejunctional inhibition of release of norepinephrine and other neurotransmitters ( $\alpha_2$ ), inhibition of insulin release ( $\alpha_2$ ), and inhibition of lipolysis ( $\alpha_2$ ).
- (3)  $\alpha$ -Adrenoceptors are distinguished from  $\beta$ -adrenoceptors by their interaction (in descending order of potency), with the adrenergic agonists **epinephrine = norepinephrine**  $\gg$  **isoproterenol**, and by their interaction with relatively selective antagonists such as **phentolamine**.
- (4)  **$\alpha_1$ -Receptors**, like muscarinic  $M_1$  and  $M_3$  cholinergic receptors, **activate guanine nucleotide-binding proteins ( $G_q$ )** in many cells, which results in activation of **phospholipase C** and stimulation of phosphoinositide (PI) hydrolysis that leads to increased formation of **inositol trisphosphate ( $IP_3$ )** and mobilization of intracellular stores of  $Ca^{2+}$  and to increased **diacylglycerol (DAG)** and activation of protein kinase C.
- (5)  **$\alpha_2$ -Receptors**, like muscarinic  $M_2$ -cholinergic receptors, **activate inhibitory guanine nucleotide-binding proteins ( $G_i$ )**, **inhibit adenylyl cyclase** activity, and decrease intracellular cyclic AMP (cAMP) levels and the activity of cAMP-dependent protein kinases (see Fig. 1-1C).

### b. $\beta$ -Adrenoceptors (Fig. 2-1)

- (1)  $\beta$ -Adrenoceptors, located mostly in postjunctional effector cells, are classified into two major receptor subtypes,  $\beta_1$ -receptors (primarily excitatory) and  $\beta_2$ -receptors (primarily inhibitory).
  - (a)  **$\beta_1$ -Receptor subtype**
    - (i)  $\beta_1$ -Receptors mediate increased contractility and conduction velocity, and renin secretion in the kidney ( $\beta_3$ -receptors mediate activation of fat cell lipolysis).
    - (ii) The  $\beta_1$ -receptor subtype is defined by its interaction (in descending order of potency) with the adrenergic agonists **isoproterenol**  $>$  **epinephrine = norepinephrine** and by its interaction with relatively selective antagonists such as **atenolol**.
  - (b)  **$\beta_2$ -Receptor subtype**
    - (i)  $\beta_2$ -Receptors mediate vasodilation and intestinal, bronchial, and uterine smooth muscle relaxation.
    - (ii) The  $\beta_2$ -receptor subtype is defined by its interaction (in descending order of potency) with the adrenergic agonists **isoproterenol = epinephrine**  $\gg$  **norepinephrine**.
- (2)  **$\beta$ -Receptor activation**
  - (a)  $\beta$ -Receptors activate **guanine nucleotide-binding proteins ( $G_s$ )**; see Fig. 1-1B).

- (b) Activation **stimulates adenylate cyclase** activity and increases intracellular cAMP levels and the activity of cAMP-dependent protein kinases. Adrenoceptor-mediated changes in the activity of protein kinases (and also levels of intracellular  $\text{Ca}^{2+}$ ) bring about changes in the activity of specific enzymes and structural and regulatory proteins, resulting in modification of cell and organ activity.

## II. PARASYMPATHOMIMETIC DRUGS

### A. Direct-acting muscarinic cholinergic agonists

#### 1. Action and chemical structure

- a. Direct-acting parasympathomimetic drugs act at muscarinic cholinergic receptors to mimic many of the physiologic effects that result from stimulation of the parasympathetic division of the autonomic nervous system (see Fig. 2-1).
- b. **Bethanechol** (Urecholine) and **carbachol** are choline esters with a quaternary ammonium group that are structurally similar to acetylcholine but more resistant to hydrolysis by acetylcholinesterase. The  $\beta$ -methyl group of bethanechol substantially reduces its activity at nicotinic receptors.
- c. **Pilocarpine** is a tertiary amine alkaloid.

#### 2. Pharmacologic effects (Tables 2-2 and 2-3)

##### a. Eye

- (1) Direct-acting muscarinic cholinergic agonists contract the circular smooth muscle fibers of the ciliary muscle and iris to produce, respectively, a spasm of accommodation and an increased outflow of aqueous humor into the canal of Schlemm, resulting in a **reduction in intraocular pressure**.
- (2) These drugs contract the smooth muscle of the iris sphincter to cause **miosis**.

##### b. Cardiovascular system

- (1) Direct-acting muscarinic cholinergic agonists produce a **negative chronotropic effect** (reduced SA node activity).
- (2) These drugs **decrease conduction velocity** through the AV node.
- (3) These drugs have no effect on force of contraction because there are no muscarinic receptors on, or parasympathetic innervation of, ventricles.
- (4) Direct-acting muscarinic cholinergic agonists produce **vasodilation** that results primarily from their action on endothelial cells to promote the release of **nitric oxide (NO)**, which diffuses to the vascular smooth muscle and produces relaxation. Vascular smooth muscle has muscarinic receptors but no parasympathetic innervation. The resulting

table 2-2 Actions of Direct-Acting Cholinergic Agonists

Effector	Effects of Muscarinic Agonists
Heart (rate, conduction velocity) <sup>a</sup>	Decrease
Arterioles (tone)	Decrease
Blood pressure	Decrease
Pupil size	Decrease
Salivation	Increase
Lacrimation	Increase
Bronchial tone	Increase
Intestine (motility)	Increase
GI secretions	Increase
Urinary bladder	
Body (tone)	Increase
Sphincter	Decrease

<sup>a</sup>Responses (e.g., heart rate) may be affected by reflexes.

**table 2-3** Effects of Muscarinic Cholinoceptor and Adrenoceptor Agonists on Smooth Muscles of the Eye

Type of Drug	Muscle	Effect	Result
Muscarinic agonist	Iris circular (constrictor)	Contraction	Miosis
	Ciliary circular	Contraction	Accommodation
Muscarinic antagonist	Iris circular (constrictor)	Relaxation	Mydriasis
	Ciliary circular	Relaxation	Cycloplegia
$\alpha$ -Adrenergic agonist	Iris radial (dilator)	Contraction	Mydriasis
	Ciliary circular	None	None

decrease in blood pressure can result in a reflex increase in heart rate. (Intravenous infusion of low doses of ACh causes a reflex sympathetic-stimulated increase in heart rate; higher doses directly inhibit heart rate.)

**c. GI tract**

(1) Direct-acting muscarinic cholinoceptor agonists increase smooth muscle contractions and tone, with increased **peristaltic activity and motility**.

(2) These drugs increase salivation and acid secretion.

**d. Urinary tract**

(1) Direct-acting muscarinic cholinoceptor agonists **increase contraction of the ureter and bladder smooth muscle**.

(2) These drugs increase **sphincter relaxation**.

**e. Respiratory system** effects of direct-acting muscarinic cholinoceptor agonists include **bronchoconstriction** with increased resistance and increased bronchial secretions.

**f. Other effects**

(1) These drugs increase the secretion of tears from lacrimal glands and increase sweat gland secretion.

(2) These drugs produce tremor and ataxia.

**3. Specific drugs and their therapeutic uses.** These drugs are used primarily for diseases of the eye, GI tract, urinary tract, the neuromuscular junction, and the heart (Table 2-4).

**a. Bethanechol (Urecholine)**

(1) Bethanechol is used to stimulate smooth muscle motor activity of the urinary tract to **prevent urine retention**.

(2) It is used occasionally to stimulate GI smooth muscle motor activity for **postoperative abdominal distention** and for **gastric atony** following bilateral vagotomy (in the absence of obstruction).

(3) Bethanechol is administered PO or SC, not by IV or IM route, because parenteral administration may cause cardiac arrest.

(4) This drug has low lipid solubility and is poorly absorbed from the GI tract. When given orally, GI effects predominate, and there are relatively minor cardiovascular effects.

(5) Bethanechol has limited distribution to the CNS.

(6) It is resistant to hydrolysis by AChE and plasma cholinesterase and thus has a longer duration of action than ACh (2–3 hours).

**table 2-4** Selected Therapeutic Uses of Selected Direct-Acting Cholinoceptor Agonists

Agent	Conditions/Disorders
Bethanechol	Prevents urine retention; postoperative abdominal distension; gastric atony
Methacholine	Diagnostic for bronchial hypersensitivity
Pilocarpine	Open-angle glaucoma; acute narrow-angle glaucoma; Sjögren syndrome



- b. **Methacholine** (Mecholyl) is occasionally used to **diagnose bronchial hypersensitivity**. Patients with no clinically apparent asthma are more sensitive to methacholine-induced bronchoconstriction than normal patients.
- c. **Pilocarpine**
  - (1) Pilocarpine is occasionally used topically for **open-angle glaucoma**, either as eyedrops or as a sustained-release ocular insert (Ocusert).  $\beta$ -Adrenergic receptor antagonists such as **timolol** and **betaxolol** and prostaglandin analogues such as **latanoprost** are the drugs of choice to treat open-angle glaucoma. Other drug classes used include  $\alpha$ -adrenergic receptor agonists such as **epinephrine** and diuretics such as **acetazolamide**.
  - (2) When used before surgery to treat **acute narrow-angle glaucoma** (a medical emergency), pilocarpine is often given in combination with an indirectly acting muscarinic agonist such as **physostigmine**.
  - (3) Pilocarpine and **cevimeline** (Evoxac), a newer muscarinic receptor agonist, increase salivary secretion. They are used to treat **Sjögren syndrome**.
  - (4) Pilocarpine is a tertiary amine that is well absorbed from the GI tract and enters the CNS.
- d. **Carbachol** is rarely used except if pilocarpine is ineffective as a treatment for open-angle glaucoma.
- e. **Cevimeline** (Evoxac) is used to treat **Sjögren syndrome**–associated dry mouth.
- f. **Varenicline** (Chantix), a direct-acting nicotinic receptor agonist, is approved for use in smoking cessation (Chapter 5 X D 2).

#### 4. **Adverse effects and contraindications**

- a. The **adverse effects** associated with direct-acting muscarinic cholinergic agonists are extensions of their pharmacologic activity. The most serious include **nausea, vomiting, sweating, salivation, bronchoconstriction, decreased blood pressure, and diarrhea**, all of which can be blocked or reversed by atropine. Systemic effects are minimal for drugs applied topically to the eye.
- b. These drugs are contraindicated in the presence of **peptic ulcer** (because they increase acid secretion), **asthma, cardiac disease, and Parkinson disease**. They are not recommended in hyperthyroidism because they predispose to arrhythmia; they are also not recommended when there is mechanical obstruction of the GI or urinary tract.

## B. Indirect-acting parasymphomimetic agents

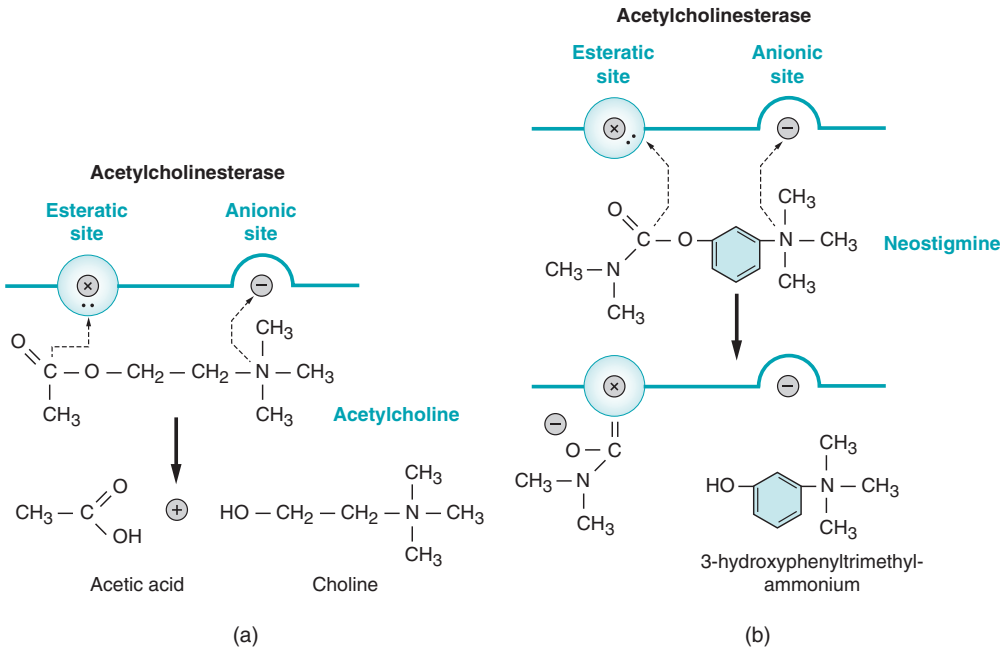
### 1. **Chemical structure**

- a. **Edrophonium** is an alcohol with a quaternary ammonium group.
- b. **Neostigmine** and **physostigmine** are examples of carbamic acid esters of alcohols (carbamates) with either quaternary or tertiary ammonium groups.
- c. **Echothiophate** and **isofluorophate** are examples of organic derivatives of phosphoric acid.

### 2. **Mechanism of action** (Fig. 2-3A and B)

- a. Indirect-acting parasymphomimetic agents **inhibit AChE** and **increase ACh levels** at both muscarinic and nicotinic cholinergic receptors to mimic many of the physiologic effects that result from increased ACh in the synaptic junction and stimulation of cholinergic receptors of the parasymphomimetic division of the ANS.
- b. **ACh interacts with AChE at two sites**: The  $N^+$  of choline (ionic bond) binds to the **anionic site**, and the acetyl ester binds to the **esteratic site** (serine residue). As ACh is hydrolyzed, the serine-OH side chain is acetylated and free choline is released. Acetyl-serine is hydrolyzed to serine and acetate. The half-life ( $t_{1/2}$ ) of acetylserine hydrolysis is 100–150 microseconds.
- c. **Edrophonium** (Tensilon) acts at the same sites of AChE to competitively inhibit ACh hydrolysis by the following processes:
  - (1)  $N^+$  of edrophonium binds the anionic site.
  - (2) Phenolic hydroxyl of edrophonium interacts with histidine imidazolium  $N^+$  of the esteratic site.
  - (3) Edrophonium has a short duration of action (5–15 min).
- d. **Neostigmine** (Prostigmin), **physostigmine** (Eserine, Antilirium), and **demecarium** (Humorsol), like ACh, interact with AChE and undergo a two-step hydrolysis. However, the serine





**FIGURE 2-3. A.** Hydrolysis of acetylcholine by acetylcholinesterase. **B.** Interaction of neostigmine with acetylcholinesterase.

residue of the enzyme is covalently carbamylated rather than acetylated. Hydrolysis of the carbamylserine residue is much slower than that of acetylserine (30 min–6 h).

(1) Neostigmine, physostigmine, and demecarium also have direct agonist action at skeletal muscle nicotinic cholinergic receptors.

(2) These drugs differ in absorption as follows:

(a) Because of its quaternary ammonium structure, **neostigmine is poorly absorbed** from the GI tract and has negligible distribution into the CNS.

(b) **Physostigmine is well absorbed** after oral administration, and it enters the CNS.

**e. Echothiophate** (Phospholine) and **isofluorophate** (Floropyryl), irreversible and toxic organophosphate cholinesterase inhibitors, result in **phosphorylation of AChE** rather than acetylation. With time, the strength of the bond increases (“aging”), and AChE becomes irreversibly inhibited. The enzyme can be reactivated within the first 30 minutes by **pralidoxime**. Hydrolysis of the covalent alkylphosphoryl-serine bond takes days.

(1) **Echothiophate** is poorly absorbed from the GI tract and has negligible distribution into the CNS.

(2) **Isofluorophate** is highly lipid soluble and is well absorbed across all membranes, including skin.

**f. Pralidoxime** (Protopam)

(1) Pralidoxime is an **AChE reactivator** that must be administered IV within minutes of exposure to an AChE inhibitor because it is effective only prior to “aging.”

(2) Pralidoxime acts as an **antidote for organophosphorus insecticide and nerve gas poisoning**. It binds the anionic site and undergoes a nucleophilic reaction with P=O group of alkylphosphorylated serine to cause hydrolysis of the phosphoserine bond that is at least  $10^6$  times faster than that occurring in water.

(3) This drug is most effective at the neuromuscular junction. It is ineffective in the CNS and against carbamylated AChE.

(4) Pralidoxime produces few adverse effects in normal doses.

### 3. **Pharmacologic effects** (Table 2-2)

**a.** With the major exception of arteriole tone and blood pressure, where their effects are less pronounced, the pharmacologic effects of indirect-acting parasympathomimetic agents are similar to those of direct-acting muscarinic cholinergic receptor agonists.

- b. By increasing ACh at the neuromuscular junction, these drugs increase the contraction strength of skeletal muscle. The effect is more pronounced if muscle contraction is already weak, as occurs in **myasthenia gravis**.

#### 4. Therapeutic uses

##### a. Glaucoma

(1) **Physostigmine** is often used concurrently with **pilocarpine** for maximum effect in the treatment of **acute angle-closure glaucoma**, a medical emergency.

(2) **Physostigmine, demecarium, echothiophate**, and other cholinesterase inhibitors have been largely replaced for the treatment of chronic **open-angle glaucoma** by topical  $\beta$ -adrenergic receptor antagonists such as **timolol** and **betaxolol**, and by prostaglandin analogues such as **latanoprost**. They are used when other drugs are ineffective. Prolonged use may increase the possibility of cataracts.

b. **GI and urinary tract atony** can be treated with **neostigmine**, which is used much like bethanechol.

##### c. Myasthenia gravis

(1) Myasthenia gravis is an **autoimmune disease** in which antibodies complex with nicotinic receptors at the neuromuscular junction to cause skeletal muscle weakness and fatigue. **Neostigmine**, or the related AChE inhibitors **pyridostigmine** (Mestinon, Regonol) or **amibenonium** (Myltelase), is used to increase ACh levels at the neuromuscular junction to activate fully the remaining receptors.

(2) Myasthenia gravis can be diagnosed using the **Tensilon test**, which can also assess the adequacy of treatment with AChE inhibitors. Small doses of **edrophonium** improve muscle strength in untreated patients with myasthenia or in treated patients in whom AChE inhibition is inadequate. If there is no effect, or if muscle weakness increases, the dose of the AChE inhibitor is too high (excessive ACh stimulation at the neuromuscular junction results in a depolarizing blockade).

(3) **Atropine** can be used to control excessive muscarinic stimulation by AChE inhibitors.

(4) Tolerance may develop to long-term use of the AChE inhibitors.

d. **Alzheimer disease: Donepezil** (Aricept), **galantamine** (Reminyl), **rivastigmine** (Exelon), and **tacrine** (Cognex) are AChE inhibitors used to ameliorate the cognitive deficit associated with Alzheimer disease (see Chapter 5 VI E).

e. **Neostigmine** or **edrophonium** can be used following surgery to **reverse neuromuscular blockade** and paralysis resulting from adjunct use of nondepolarizing agents.

f. **Atropine** and **scopolamine poisoning** can be treated with **physostigmine**, which reverses the central and (to some extent) the peripheral effects of competitive muscarinic antagonists.

#### 5. Adverse effects and toxicity

a. The adverse effects associated with indirect-acting sympathomimetic agents are an extension of pharmacologic activity and arise from **excessive cholinergic stimulation**.

b. Adverse effects include muscarinic effects similar to those of direct-acting cholinergic drugs and nicotinic effects such as **muscle weakness, cramps and fasciculations, excessive bronchial secretions, convulsions, coma, cardiovascular collapse, and respiratory failure**.

c. Many lipid-soluble organophosphates are used as insecticides (e.g., malathion) or nerve gases (e.g., sarin) and may be absorbed in sufficient quantities from the skin or lungs to cause cholinergic intoxication. Treatment includes the following steps:

(1) Maintain respiration and decontaminate to prevent further absorption.

(2) Administer **atropine** parenterally to inhibit muscarinic effects.

(3) Administer **pralidoxime** within minutes of exposure.

## III. MUSCARINIC-RECEPTOR ANTAGONISTS

### A. Mechanism and chemical structure (Table 2-5)

1. Muscarinic-receptor antagonists are competitive antagonists of ACh at all muscarinic cholinergic receptors.

table 2-5 Properties of Some Cholinoceptor Blocking Agents

Agent	Action	Receptors		Comments
		Muscarinic	Nicotinic	
Atropine	Competitive antagonist	+		Prototype muscarinic cholinergic blocking agent
Scopolamine	Competitive antagonist	+		Actions similar to those of atropine
Propranolol	Competitive antagonist	+		Peripheral-acting cholinergic blocking agent
Trimethaphan	Competitive, nondepolarizing antagonist		+	Peripheral-acting ganglionic blocking agent
Cisatracurium	Competitive, nondepolarizing antagonist at motor endplate		+	Neuromuscular junction blocking agent
Succinylcholine	Depolarizing agonist at motor endplate		+	Neuromuscular junction blocking agent

- Muscarinic-receptor antagonists are either tertiary amine alkaloids (e.g., **atropine**, **scopolamine**, **tropicamide**) or quaternary amines (e.g., **propranolol** [**Pro-Banthine**], **ipratropium** [**Atrovent**]).
- Tertiary amines** are often used for their effects on the **CNS**. **Quaternary amines**, which have minimal CNS actions, are often used for their effects on **peripheral systems**.

## B. Pharmacologic effects

### 1. Eye (Table 2-3)

- Muscarinic-receptor antagonists produce **cycloplegia** by blocking parasympathetic tone, leading to paralysis of the ciliary muscle and loss of accommodation.
- These drugs produce **mydriasis** by blocking parasympathetic tone to the iris circular (constrictor) muscle. Unopposed sympathetic stimulation of the radial muscle results in dilation of the pupil.

### 2. Cardiovascular system

- Muscarinic-receptor antagonists **increase heart rate** due to cholinergic blockade at the SA node.
- These drugs dilate blood vessels in facial blush area (atropine flush), which is not related to the antagonist action.

### 3. GI tract

- Muscarinic-receptor antagonists **decrease salivation**.
- These drugs **reduce peristalsis**, resulting in prolonged gastric emptying and intestinal transit.
- They also reduce gastric acid secretion.

### 4. Other effects

- Muscarinic-receptor antagonists produce some **bronchodilation** and decrease mucus secretion.
- These drugs relax the ureters and bladder in the urinary tract and constrict the urinary sphincter.
- Tertiary amines can produce restlessness, headache, excitement, hallucinations, and delirium.
- These drugs produce **anhidrosis** and dry skin because of the inhibition of sympathetic cholinergic innervation of the sweat glands.

## C. Pharmacologic properties

- Unlike quaternary ammonium drugs (10%–30% absorption), most tertiary muscarinic-receptor antagonists are well absorbed across the GI tract or mucosal surfaces and distribute throughout the body, including the brain.
- Atropine** and **scopolamine** have relatively long durations of action.

Table 2-6 Selected Therapeutic Use of Muscarinic Cholinoceptor Antagonists

Organ/System	Therapeutic Use
Eye	Refractive measurement; ophthalmologic examination, uveitis and iritis
Heart	Acute myocardial infarction
Bladder	Urinary urgency
Lung	Surgical anesthesia to suppress secretions
CNS	Motion sickness (scopolamine); Parkinson disease
Multiple organs/systems	Cholinergic poisoning

#### D. Therapeutic uses (Table 2-6)

##### 1. Eye

- Shorter-acting muscarinic-receptor antagonists (e.g., **homatropine**, **cyclopentolate** [Cyclogyl], **tropicamide**) are administered topically as eyedrops or as ointments for **refractive measurements** and for **ophthalmoscopic examination** of the retina and other structures of the eye ( $\alpha$ -adrenoceptor agonists, such as **phenylephrine**, are used for simple funduscopic examination without cycloplegia).
- Longer-acting muscarinic-receptor antagonists (such as **homatropine**) are generally preferred as adjuncts to **phenylephrine** to prevent synechia formation in **anterior uveitis and iritis**.

2. **Cardiovascular system** uses are limited and include the administration of these drugs as a treatment for **acute myocardial infarction** with accompanying bradycardia and hypotension or arrhythmias (e.g., **atropine**).

3. **Urinary tract** uses of **atropine** and other muscarinic-receptor antagonists include the administration of these drugs for symptomatic treatment of **urinary urgency** in inflammatory bladder disorder. **Oxybutynin** (Ditropan), a selective muscarinic  $M_2$ -receptor antagonist, **tolterodine** (Detrol), a selective muscarinic  $M_3$ -receptor antagonist, and **tropium** (Spas Max), are additional agents in this class used to treat certain urinary disorders.

##### 4. Central nervous system

- Antimuscarinic drugs, **benztropine**, **biperiden**, **trihexyphenidyl**, and others, are used as adjunct to levodopa therapy for some patients with **Parkinson disease** (see Chapter 5).
- Scopolamine** (used orally, intravenously, or transdermally) prevents motion sickness by blocking muscarinic receptors in the vestibular system and in the CNS (see Chapter 8).

##### 5. Respiratory system

- Atropine** and **scopolamine** can be used to suppress bronchiolar secretions during **surgical and spinal anesthesia** and to prevent the muscarinic effects of AChE inhibitors used to reverse muscle paralysis at the end of surgery. **Scopolamine** also has additional amnestic and sedative properties.
- Ipratropium** is used as an inhalant to treat reactive airway disease such as asthma and chronic obstructive pulmonary disease (COPD).

6. **Other uses:** Tertiary agents such as **atropine** are used to block peripheral and CNS effects due to cholinergic excess, especially those caused by poisoning with AChE inhibitor-containing insecticides and muscarine-containing mushrooms.

#### E. Adverse effects and contraindications

- The adverse effects** of muscarinic-receptor antagonists are extensions of pharmacologic activity and include **mydriasis**, **cycloplegia**, **dry eyes**, **tachycardia**, **dry mouth**, **elevated temperature**, **dry skin**, **urine retention**, **agitation**, **hallucinations**, and **delirium** (“hot as a hare, dry as a bone, red as a beet, blind as a bat, mad as a hatter”). **Physostigmine** administration for treatment of tertiary amine overdose is not recommended. Rather, treatment is symptomatic. **Neostigmine** is used to treat poisoning with quaternary muscarinic-receptor antagonists.
- Contraindications (relative)** are **glaucoma**, particularly angle-closure glaucoma, **GI and urinary tract obstruction** (e.g., prostatic hypertrophy), and **gastric ulcer**.

3. **Drug interactions** of muscarinic-receptor antagonists include the production of additive effects when administered with other drugs with muscarinic-receptor antagonist activity (certain antidepressants, antipsychotics, and antihistamines).

## IV. GANGLION-BLOCKING DRUGS

### A. Mechanism and therapeutic uses (see Table 2-5)

#### 1. Ganglion-blocking drugs

- Trimethaphan** (Arfonad) and **mecamylamine** (Inversine) inhibit the effect of ACh at nicotinic receptors by acting competitively (**nondepolarizing blockade**) at both sympathetic and parasympathetic autonomic ganglia.
- Because of a lack of selectivity and numerous adverse effects, they are **used rarely in the clinical setting** (hypertensive emergencies).

## V. SKELETAL MUSCLE RELAXANTS

### A. Classification and structure

#### 1. Neuromuscular junction-blocking drugs (see Table 2-5)

- Classified as either **nondepolarizing** or **depolarizing** types, neuromuscular junction-blocking drugs cause neuromuscular paralysis. They are structurally similar to ACh.
- These drugs contain one or two **quarternary nitrogens** that limits their entry into the CNS.
- Nondepolarizing neuromuscular junction-blocking drugs, the prototype is **tubocurarine**, are arranged in a bulky, rigid conformation.
- Depolarizing neuromuscular junction-blocking drugs have a linear structure. **Succinylcholine**, the only one used clinically, is composed of two ACh molecules linked end to end.

2. **Spasmolytic drugs** act to reduce abnormal muscle tone without paralysis. These drugs increase or mimic the activity of  **$\gamma$ -aminobutyric acid (GABA)** in the spinal cord and brain or interfere with the release of calcium in skeletal muscle.

### B. Nondepolarizing agents

#### 1. Mechanism

- Nondepolarizing agents **competitively inhibit the effect of ACh** at the postjunctional membrane nicotinic receptor of the neuromuscular junction. There is some prejunctional inhibition of ACh release.
- These agents prevent depolarization of the muscle and propagation of the action potential.

#### 2. Pharmacologic properties

- Nondepolarizing agents are administered parenterally and are generally used for long-term motor paralysis. Paralysis and muscle relaxation occur within 2–5 minutes.
- Nondepolarizing agents have durations of action that range from 20–90 minutes, which can be extended by supplemental fractional dosing and is increased by larger initial doses (although this also increases the likelihood of adverse effects).
- Most nondepolarizing agents are metabolized by the liver or are excreted unchanged. The duration of action may be prolonged by hepatic or renal disease.
- Intermediate-acting steroid muscle relaxing agents (e.g., **rocuronium** [Zemuron], **vecuronium** [Norcuron]) are more commonly used than long-acting agents.

#### 3. Specific drugs (Table 2-7)

- Tubocurarine** (prototype), an isoquinoline derivative, is seldom used clinically at this time.
- Metocurine** (Metubine) is a derivative of tubocurarine. It has the same properties, but with less histamine release and thus less hypotension and bronchoconstriction. Metocurine has a long duration of action (>40 min).

table 2-7 Properties of Some Skeletal Muscle Relaxants

Nondepolarizing Agent	Duration of Action	Ganglion Blockade	Histamine Release	Cardiac Muscarinic Receptors	Comments
Tubocurarine <sup>a</sup>	Long	+	++	—	Prototype
Metocurine <sup>a</sup>	Long	+	+	—	Less hypotension and bronchoconstriction than tubocurarine
Atracurium <sup>a</sup>	Intermediate	—	+	—	Inactivated spontaneously in plasma; laudanosine, a breakdown product, may cause seizures.
Cisatracurium <sup>a</sup>	Intermediate	—	—	—	Less laudanosine formed than atracurium.
Mivacurium <sup>a</sup>	Short	—	++	—	Hydrolyzed by plasma cholinesterase.
Pancuronium <sup>b</sup>	Long	—	—	++	Increased heart rate
Vecuronium <sup>b</sup>	Intermediate	—	—	—	Metabolized by liver
<b>Depolarizing Agent</b>					
Succinylcholine	Very short	++	+	++	Hydrolyzed by cholinesterase; malignant hyperthermia is a rare, potentially fatal complication

<sup>a</sup>Isoquinoline derivative.<sup>b</sup>Steroid derivative.**c. Atracurium (Tracrium)**

(1) Atracurium causes some histamine release. It is **inactivated spontaneously in plasma** by nonenzymatic hydrolysis that is delayed by acidosis. Its duration of action is reduced by hyperventilation-induced respiratory alkalosis. **Laudanosine**, a breakdown product of atracurium, may accumulate to cause **seizures**.

(2) **Cisatracurium** (Nimbex) is a stereoisomer of atracurium that releases less histamine and forms less laudanosine. It has **replaced atracurium** use in clinical practice.

**d.** Other available isoquinoline derivatives similar to atracurium include short-acting (10–20 min) **mivacurium** (Mivacron), which is rapidly hydrolyzed by plasma cholinesterase (pseudocholinesterase), has a short duration of action, and produces moderate histamine release at high doses, and **doxacurium** (Nuromax), which is stable in plasma, has a long duration of action (90–120 min), is excreted unchanged, and is devoid of vagolytic activity.

**e. Pancuronium (Pavulon)**

(1) Pancuronium has a steroid nucleus with two attached quaternary amine groups.

(2) This drug has a long duration of action (120–180 min).

(3) Pancuronium produces **no histamine release or ganglia blockade**.

(4) Pancuronium causes a moderate **tachycardia**, primarily due to cardiac muscarinic receptor blockade.

(5) This drug is excreted by the kidney with only minimal hepatic metabolism.

**f. Vecuronium (Norcuron)**

(1) Vecuronium is a steroid derivative that has an intermediate duration of action (30–40 min).

(2) Vecuronium has **little vagolytic, histaminic, or ganglion-blocking activity**.

(3) This drug is primarily metabolized by the liver.

**g. Rocuronium** (Zemuron) is a derivative of vecuronium with an intermediate duration of action (30–40 min) that undergoes primarily hepatic clearance (75%–90%).

**h. Pipecuronium** (Arduan) has a long duration of action (80–100 min) and undergoes both renal (60%) and hepatic clearance.

**4. Therapeutic uses**

**a.** Nondepolarizing agents are used during surgery as adjuncts to general anesthetics to induce muscle paralysis and muscle relaxation. The order of muscle paralysis is small, rapidly contracting muscles (e.g., extrinsic muscles of the eye) before slower contracting muscle groups (e.g., face and extremities), followed by intercostal muscles, and then the

diaphragm. Recovery of muscle function is in reverse order, and respiration often must be assisted.

- b. These agents are also used for muscle paralysis in patients when it is critical to control ventilation, and they are used to control muscle contractions during **electroconvulsive therapy**.
5. **Reversal of nondepolarizing drug blockade:** AChE inhibitors, such as **neostigmine**, are administered for pharmacologic antagonism to reverse residual postsurgical muscarinic receptor blockade and avoid inadvertent hypoxia or apnea.
6. **Adverse effects and contraindications** (Table 2-7)
  - a. Cardiovascular system
    - (1) Nondepolarizing agents that are **isoquinoline derivatives** may produce **hypotension** due to histamine release and ganglionic-blocking activity.
    - (2) Nondepolarizing agents that are **steroid derivatives** may produce **tachycardia** due to vagolytic activity, leading to potential arrhythmias. These drugs should be used cautiously in patients with cardiovascular disease.
  - b. Respiratory system: Some nondepolarizing agents that are **isoquinoline derivatives** can produce **bronchospasm** in sensitive individuals due to histamine release. Agents that release histamine are contraindicated for asthmatic patients and patients with a history of anaphylactic reactions.
7. **Drug interactions**
  - a. **General inhalation anesthetics**, particularly **isoflurane**, increase the neuromuscular blocking action of nondepolarizing agents. The dose of the neuromuscular junction-blocking drug may have to be reduced.
  - b. **Aminoglycoside antibiotics**, among others, inhibit prejunctional ACh release and potentiate the effect of nondepolarizing and depolarizing neuromuscular junction-blocking drugs.

**C. Depolarizing agents** (Table 2-7) include **succinylcholine** (Anectine), the only depolarizing drug of clinical importance.

#### 1. Mechanism of action

- a. Succinylcholine is a **nicotinic receptor agonist** that acts at the motor endplate of the neuromuscular junction to produce **persistent stimulation and depolarization of the muscle**, thus preventing stimulation of contraction by ACh.
- b. After a single IV injection and depolarization of the muscle, there are initial muscle contractions or **fasciculations** (in the first 30–60 s) that may be masked by general anesthetics. Because succinylcholine is metabolized more slowly than ACh at the neuromuscular junction, the muscle cells remain depolarized (**depolarizing or phase I block**) and unresponsive to further stimulation, resulting in a **flaccid paralysis** (5–10 min).
- c. With continuous long-term exposure (45–60 min), the muscle cells repolarize. However, they cannot depolarize again while succinylcholine is present and, therefore, remain unresponsive to ACh (**desensitizing or phase II block**).
- d. AChE inhibition will enhance the initial phase I block by succinylcholine, but can reverse phase II block.

#### 2. Pharmacologic properties

- a. Succinylcholine has a rapid onset and short duration of action. Action is rapidly terminated (5–10 min) by **hydrolysis by plasma and liver cholinesterase**.
- b. Reduced plasma cholinesterase synthesis in end-stage hepatic disease or reduced activity following the use of irreversible AChE inhibitors may increase the duration of action.

3. **Therapeutic uses** of succinylcholine include the administration of the drug to induce brief **paralysis in short surgical procedures** such as tracheal intubation or in electroconvulsive shock therapy.

#### 4. Adverse effects

- a. **Postoperative muscle pain** at higher doses
- b. **Hyperkalemia**
  - (1) Hyperkalemia results from loss of tissue potassium during depolarization.
  - (2) Risk of hyperkalemia is enhanced in patients with burns, muscle trauma, or spinal cord transections.
  - (3) Hyperkalemia can be life-threatening, leading to **cardiac arrest** and circulatory collapse.



**c. Malignant hyperthermia**

- (1) Malignant hyperthermia is a rare but often fatal complication in susceptible patients that results from a rapid increase in muscle metabolism. About 50% of patients are genetically predisposed, with mutations in the skeletal muscle  $\text{Ca}^{2+}$ -release channel of the sarcoplasmic reticulum (ryanodine receptor, RYR1).
  - (2) Malignant hyperthermia is most likely to occur when succinylcholine is used with the general anesthetic **halothane**.
  - (3) It is characterized by tachycardia and, among other manifestations, intense **muscle spasm** that results in a rapid and profound **hyperthermia**.
  - (4) Drug treatment is with **dantrolene** (see following).
- d. Prolonged paralysis** may result in apnea (lasting 1–4 h) in a small percentage of patients (1/10,000) with **genetically atypical or low levels of plasma cholinesterase**. Mechanical ventilation is necessary.
- e. Bradycardia** from direct stimulation of muscarinic cholinergic stimulation is prevented by atropine
- f. Increased intraocular pressure** may result from extraocular muscle contractions; use of succinylcholine may be contraindicated for penetrating eye injuries.
- g.** Succinylcholine produces increased intragastric pressure, which may result in fasciculations of abdominal muscles and a danger of aspiration.

**D. Spasmolytic drugs**

1. **These muscle relaxants reduce increased muscle tone** associated with a variety of nervous system disorders (e.g., **cerebral palsy, multiple sclerosis, spinal cord injury, and stroke**) that result in loss of supraspinal control and hyperexcitability of  $\alpha$ - and  $\gamma$ -motoneurons in the spinal cord, causing abnormal skeletal muscle, bowel, and bladder function.
2. **Selected drugs**
  - a. **Dantrolene** (Dantrium)
    - (1) Dantrolene acts directly on muscle to reduce skeletal muscle contractions.
    - (2) Dantrolene is also used to treat **malignant hyperthermia**.
    - (3) This drug interferes with  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum; benefit may not be apparent for a week or more.
    - (4) The major adverse effects of dantrolene are **muscle weakness**, which may limit therapy, and sedation. Long-term use can result in hepatotoxicity that may be fatal. Hepatic function should be monitored during treatment.
  - b. **Baclofen** (Lioresal)
    - (1) Baclofen is an analogue of GABA. It is a  $\text{GABA}_B$ -receptor agonist that hyperpolarizes neurons to inhibit synaptic transmission in the spinal cord.
    - (2) Adverse effects include some drowsiness and an increased frequency of seizures in epileptic patients.
  - c. **Benzodiazepines** (see Chapter 5)
    - (1) Benzodiazepines such as **diazepam** act on the spinal cord and CNS to facilitate GABA activity.
    - (2) The major adverse effect is **sedation**.
3. **Botulinum toxin (Botox)**
  - a. Botulinum toxin acts by **inhibiting the release of ACh from motor nerve terminals**.
  - b. **Botulinum toxin** is used to treat local muscle spasms associated with **cervical dystonia** and blepharospasm- and strabismus-associated dystonia. It is also used for cosmetic reduction of **facial wrinkles**.

**VI. SYMPATHOMIMETIC DRUGS****A. Action and chemical structure**

1. These drugs act either **directly** or **indirectly** to **activate** postjunctional and prejunctional **adrenoceptors** to **mimic** the effects of **endogenous catecholamines** such as norepinephrine and

epinephrine. Their actions can generally be predicted from the type and location of the receptors with which they interact and whether or not they cross the blood–brain barrier to enter the CNS.

2. Indirectly acting agents either act within nerve endings to **increase the release of stored catecholamines** or at the prejunctional membrane to **block the reuptake of catecholamines** that have been released from nerve endings.
3. Sympathomimetic agents are usually derived from the parent compound  $\beta$ -phenylethylamine. Chemical modifications of the side chain or the catechol nucleus can markedly alter their relative selectivity and intrinsic activity at  $\alpha$ - and  $\beta$ -receptors, their disposition, and their metabolism.

## B. Pharmacologic effects (Table 2-8)

### 1. Cardiovascular system

- a.  **$\beta_1$ -Receptor agonists** increase the rate (chronotropic effect) and force (inotropic effect) of myocardial contraction and increase the conduction velocity through the AV node, with a decrease in the refractory period.
- b.  **$\beta_2$ -Receptor agonists** cause relaxation of vascular smooth muscle that may invoke a reflex increase in heart rate.
- c.  **$\alpha_1$ -Receptor agonists** constrict smooth muscle of resistance blood vessels (e.g., in the skin and splanchnic beds), causing increased peripheral resistance and venous return. In normotensive patients (less effect in those with hypotension), the increased blood pressure may invoke a reflex baroreceptor vagal discharge and a slowing of the heart, with or without an accompanying change in cardiac output.
- d.  **$\alpha_2$ -Receptor agonists** reduce blood pressure by a prejunctional action on neurons in the CNS to inhibit sympathetic outflow.

### 2. Eye (see Table 2-3)

- a.  **$\alpha$ -Receptor agonists** contract the radial muscle of the iris and dilate the pupil (mydriasis). These drugs also increase outflow of aqueous humor from the eye.
- b.  **$\beta$ -Receptor antagonists** decrease the production of aqueous humor.

3. **Respiratory system effects** include  **$\beta_2$ -receptor agonist**-induced relaxation of bronchial smooth muscle and decreased airway resistance.

table 2-8 Direct Effects of Adrenoceptor Agonists

Effector	$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$
Heart				
Rate			Increase	
Force			Increase	
Arterioles (most)	Constrict			Dilate
Blood pressure	Increase			Decrease
Intestine				
Wall	Relax	Relax		Relax
Sphincters	Contract			
Salivation				
Volume	Increase			
Amylase			Increase	
Pupil	Dilate			
Bronchial smooth muscle				Relax
Urinary bladder				
Body	Constrict			Relax
Sphincter	Constrict			
Release of NE from nerves		Decrease		

#### 4. GI tract

- a.  **$\alpha$ -Receptor and  $\beta$ -receptor** agonists relax GI smooth muscle.  $\alpha$ -Receptor agonists reduce the release of ACh and other transmitters from intramural nerves by a prejunctional action;  $\beta$ -receptors are located directly on smooth muscle.
- b.  **$\alpha_1$ -Receptor agonists** contract GI sphincters.

#### 5. Metabolic and endocrine effects

- a.  **$\beta$ -Receptor agonists** increase liver and skeletal muscle glycogenolysis and increase lipolysis in fat cells ( $\beta_3$ ).
- b.  **$\beta$ -Receptor agonists** increase, and  **$\alpha_2$ -receptor agonists** decrease, insulin secretion.

- 6. **Genitourinary tract effects** include  **$\beta_2$ -receptor agonist**-induced relaxation of uterine smooth muscle and the bladder wall.  **$\alpha$ -Receptor agonists** constrict the bladder wall ( $\alpha_1$ ).

**C. Specific sympathomimetic drugs** are selected for use depending on the duration of action, route of administration, and also the specific effect on a particular tissue, which in turn depends on the tissue population of adrenoceptor subtypes.

#### 1. Epinephrine and norepinephrine

- a. Epinephrine and norepinephrine are poorly absorbed from the GI tract and do not enter the CNS to any appreciable extent. Absorption of epinephrine from subcutaneous sites is slow because of local vasoconstriction. Although rarely used, nebulized and inhaled solutions and topical preparations of epinephrine are available. Epinephrine and norepinephrine are most often **administered IV** (with caution to avoid cardiac arrhythmias or local tissue necrosis).
- b. These drugs are metabolized extensively by enzymes in the liver. **COMT** methylates the *meta*-hydroxyl group of the catechol, and **MAO** removes the amine group of the side chain. Metabolites are excreted by the kidney.
- c. Epinephrine and norepinephrine actions at neuroeffector junctions are terminated primarily by **simple diffusion** away from the receptor site and by **active uptake** into sympathetic nerve terminals and subsequent active transport into storage vesicles. Actions are also partially terminated at neuroeffector junctions by metabolism by extraneuronal COMT and intraneuronal MAO.

##### (1) Epinephrine

- (a) Epinephrine activates  $\beta_1$ -,  $\beta_2$ -, and  $\alpha$ -adrenoceptors.
- (b) Epinephrine administration in humans **increases systolic pressure** as a result of positive inotropic and chronotropic effects on the heart ( $\beta_1$ -receptor activation) and generally results in **decreased total peripheral resistance** and **decreased diastolic pressure due to vasodilation** in the vascular bed of skeletal muscle ( $\beta_2$ -receptor activation) that overcomes the vasoconstriction produced in most other vascular beds, including the kidney ( $\alpha$ -receptor activation). The mean arterial pressure may increase slightly, decrease, or remain unchanged, depending on the balance of effects on systolic and diastolic pressure.
- (c) At high doses, epinephrine causes vasoconstriction in the vascular bed of skeletal muscle ( $\alpha$ -receptor activation).
- (d) Epinephrine **increases coronary blood flow** as a result of increased cardiac workload; it may precipitate **angina** in patients with coronary insufficiency.
- (e) Epinephrine **increases the drainage of aqueous humor** ( $\alpha$ -receptor activation) and reduces pressure in **open-angle glaucoma**. It **dilates the pupil** (mydriasis) by contraction of the radial muscle of the eye ( $\alpha$ -receptor activation).
- (f) Epinephrine **relaxes bronchial smooth muscle** ( $\beta_2$ -receptor activation).

##### (2) Norepinephrine

- (a) Norepinephrine **activates  $\beta_1$ -receptors** (it is equipotent to epinephrine) and  **$\alpha$ -receptors** (it is slightly less potent than epinephrine). It has little activity at  $\beta_2$ -receptors.
- (b) Norepinephrine **increases total peripheral resistance** and **diastolic blood pressure** to a greater extent than epinephrine because of its vasoconstrictor activity and lack of effect on  $\beta_2$ -receptors in the skeletal muscle vascular bed.
- (c) Norepinephrine increases systolic blood pressure and mean arterial pressure.

(d) It has a direct stimulant effect on heart rate, but this is overcome by reflex baroreceptor-mediated vagal bradycardia.

(e) Norepinephrine is rarely used therapeutically.

## 2. Dopamine (Intropin)

- Dopamine activates peripheral  $\beta_1$ -adrenoceptors to increase heart rate and contractility.
- Dopamine **activates** prejunctional and postjunctional dopamine **D<sub>1</sub>-receptors** in the renal, coronary, and splanchnic vessels to reduce arterial resistance and increase blood flow. Prejunctionally, dopamine inhibits norepinephrine release.
- At **low doses**, dopamine has a positive inotropic effect and increases systolic pressure, with little effect on diastolic pressure or mean blood pressure.
- At **higher doses**, dopamine activates  $\alpha$ -receptors and causes vasoconstriction, with a reflex decrease in heart rate.

## 3. $\beta$ -Adrenoceptor agonists

### a. Dobutamine

(1) Dobutamine is a **synthetic catecholamine** that is related to **dopamine**.

(2) Dobutamine has a relatively selective effect on  **$\beta_1$ -receptors** and no effect on dopamine receptors.

(3) This drug increases cardiac output with limited vasodilating activity and reflex tachycardia.

(4) Dobutamine is administered by **IV infusion** because of its short half-life ( $t_{1/2} = 2$  min).

### b. Terbutaline (Brethine, Bricanyl), albuterol (Proventil, Ventolin), metaproterenol (Alupent), pirbuterol (Maxair), levalbuterol (Xopenex), bitolterol (Tornalate), salmeterol (Serevent), and formoterol (Foradil)

(1) These drugs are more **selective  $\beta_2$ -receptor agonists** that **relax bronchial smooth muscle** with fewer cardiac effects and longer duration of action than epinephrine.

(2) Selectivity is lost at high concentrations.

### c. Isoproterenol (Isuprel)

(1) Isoproterenol **activates  $\beta$ -receptors** with little activity on  $\alpha$ -receptors.

(2) Isoproterenol **dilates bronchial smooth muscle**.

(3) This drug **increases heart rate and contractility** and causes **vasodilation** in skeletal muscle vascular beds with decreased total peripheral resistance and decreased diastolic blood pressure.

(4) It is infrequently used because of the availability of selective  $\beta_2$ -adrenoceptor agonists.

## 4. $\alpha$ -Adrenoceptor agonists

### a. Phenylephrine, methoxamine (Vasoxyl), and metaraminol (Aramine)

(1) These drugs produce effects primarily by **direct  $\alpha_1$ -receptor stimulation** that results in vasoconstriction, increased total peripheral resistance, and increased systolic and diastolic pressure. **Metaraminol** also has **indirect activity**; it is taken up and released at sympathetic nerve endings, where it acts as a false neurotransmitter. It also releases epinephrine.

(2) Because they are not metabolized by COMT, these drugs are less potent but have longer durations of action than catecholamines.

### b. Xylometazoline (Otrivin) and oxymetazoline (Afrin)

(1) These drugs have selective action at  $\alpha$ -receptors.

(2) At **high doses**, these drugs may cause **clonidine-like effects** because of their action in the CNS.

### c. Clonidine (Catapres), methyldopa (Aldomet), guanabenz (Wytensin), and guanfacine (Tenex)

(1) These antihypertensive agents directly or indirectly activate prejunctional and, probably, postjunctional  **$\alpha_2$ -receptors** in the **vasomotor center** of the medulla to **reduce sympathetic tone**.

(2) These drugs reduce **blood pressure**, with a decrease in total peripheral resistance and minimal long-term effects on cardiac output and heart rate.

(3) **Methyldopa** is a **prodrug** that is metabolized to the active agent  **$\alpha$ -methylnorepinephrine** (and  $\alpha$ -methyldopamine) in nerve endings. It **lowers blood pressure by reducing peripheral vascular resistance**. At higher, nontherapeutic doses, it activates peripheral  $\alpha$ -receptors to cause vasoconstriction.

## 5. Other adrenoceptor agonists

### a. Ephedrine and mephenteramine

- (1) These drugs act indirectly to release norepinephrine from nerve terminals and have some direct action on adrenoceptors.
- (2) Ephedrine and mephenteramine have effects similar to those of **epinephrine**, but they are less potent; they have a longer duration of action because they are resistant to metabolism by COMT and MAO.
- (3) These drugs are effective orally and, unlike catecholamines, penetrate the brain and can produce CNS stimulation.
- (4) **Ephedrine** is found in the herbal medication **ma huang**.
- (5) **Pseudoephedrine** (Sudafed) is an isomer of ephedrine.
- (6) After continued use, **tachyphylaxis** may develop due to their peripheral effects.

### b. Amphetamine, dextroamphetamine (Dexedrine), methamphetamine (Desoxyn), phendimetrazine (Preludin), modafinil (Provigil), methylphenidate (Ritalin), and hydroxyamphetamine (Paredrine) (see Chapter 5)

- (1) These drugs produce effects similar to those of **ephedrine**, with indirect and some direct activity.
- (2) **Dextroamphetamine** has more CNS-stimulatory activity than the *levo* isomer, which has more cardiovascular activity.
- (3) These drugs are well absorbed and, except for **hydroxyamphetamine**, enter the CNS readily and have marked stimulant activity.

## D. Therapeutic uses (Table 2-9)

### 1. Cardiovascular system

- a. **Phenylephrine, methoxamine, norepinephrine**, and other direct-acting  $\alpha$ -receptor sympathomimetic drugs are used for **short-term hypotensive emergencies** when there is inadequate perfusion of the heart and brain such as during severe hemorrhage.
- b. **Ephedrine and midodrine** (Pro-Amatine), prodrug that are hydrolyzed to the  $\alpha_1$ -adrenoceptor agonist **desglymidodrine**, to treat **chronic orthostatic hypotension**.
- c. **The use of sympathomimetic agents in most forms of shock is controversial and should be avoided. Further vasoconstriction may be harmful.**
  - (1) Low-to-moderate doses of **dobutamine** or **dopamine** may be useful in cases of **cardiogenic or septic shock** because they increase cardiac output with minimal vasoconstrictive effect on the peripheral vasculature.
  - (2) **Epinephrine** is used to reverse hypotension and angioedema associated with **anaphylactic shock**.
- d. **Dobutamine** is used to treat **congestive heart failure**.
- e. **Methyldopa** is used to treat **hypertension**.
- f. **Fenoldopam** (Corlopan) is a selective dopamine **D<sub>1</sub>-receptor agonist** used to treat severe hypertension.

table 2-9 Selected Therapeutic Uses of Adrenoceptor Agonists

Clinical Condition/Application	Agonist	Receptor
Hypotensive emergency	Phenylephrine; methoxamine; norepinephrine	$\alpha_1$
Orthostatic hypotension	Ephedrine; midodrine	$\alpha_1$
Anaphylactic shock	Epinephrine	$\alpha$ and $\beta$
Heart block, cardiac arrest	Isoproterenol; epinephrine	$\beta_1$
Congestive heart failure	Dobutamine	$\beta_1$
Infiltration nerve block	Epinephrine	$\alpha_1$
Hay fever and rhinitis	Phenylephrine; OTC <sup>a</sup>	$\alpha_1$
Asthma	Metaproterenol; terbutaline; albuterol	$\beta_2$

<sup>a</sup>Over-the-counter preparations.

- g. **Isoproterenol** and **epinephrine** have been used for temporary emergency treatment of **cardiac arrest** and **heart block** because they increase ventricular automaticity and rate and increase AV conduction.
- h. **Epinephrine** is commonly used in combination with local anesthetics (1:200,000) during infiltration block to reduce blood flow.  $\alpha$ -Receptor agonist activity causes local vasoconstriction, which **prolongs local anesthetic action** and allows the use of lower doses with reduced chance of toxicity. **Phenylephrine** and **norepinephrine** have also been used.
- i. **Epinephrine** is used during **spinal anesthesia** to maintain blood pressure, as is **phenylephrine**, and topically to reduce superficial bleeding.

## 2. Respiratory system

- a. **Phenylephrine** and other short- and longer acting  $\alpha$ -adrenoceptor agonists, including **oxymetazoline**, **xylometazoline**, **tetrahydrozoline** (Tyzine), ephedrine, and pseudoephedrine, are used for symptomatic relief of **hay fever and rhinitis** of the common cold. Long-term use may result in ischemia and rebound hyperemia, with development of chronic rhinitis and congestion.
- b. **Metaproterenol**, **terbutaline**, **albuterol**, **bitolterol**, and other  $\beta_2$ -adrenoceptor agonists are preferred for treating **asthma**. **Epinephrine** is also used for management of acute **bronchospasm**.
- c. **Epinephrine** is administered IM to treat bronchospasm, congestion, angioedema, and cardiovascular collapse of **anaphylaxis**.

## 3. Eye

- a. **Phenylephrine** facilitates **examination of the retina** because of its mydriatic effect. It is also used for minor allergic hyperemia of the conjunctiva.
- b.  $\alpha_2$ -Receptor agonists (**apraclonidine** [Lopidine] and **brimonidine** [Alphagan]) that lower intraocular pressure by increasing aqueous outflow (**epinephrine** and **dipivefrin** [Propine] are rarely used) have been largely **supplanted by  $\beta$ -adrenoceptor blockers and prostaglandin analogues** for treatment of **chronic open-angle glaucoma**.

## 4. CNS

- a. **Amphetamine** and related analogues (e.g., **modafinil**) are used to treat **narcolepsy** (controversial) because of their arousal effects and their ability to increase the attention span; as occasional adjunct therapy for obesity because of their anorexiatic effects; and to treat **attention-deficit hyperactivity disorder** in children (e.g., **methylphenidate**).
- b. **Hydroxyamphetamine** and **phenylephrine** are used for the **diagnosis of Horner syndrome**.
- c. **Dexmedetomidine** (Precedex), a novel selective  $\alpha_2$ -adrenoceptor agonist that acts centrally, is used intravenously as a **sedative** in patients hospitalized in intensive care settings.

- 5. **Other uses** include **ritodrine** and **terbutaline** to **suppress premature labor** by relaxing the uterus, although the efficacy of these drugs is controversial.

## E. Adverse effects and toxicity

1. The adverse effects of sympathomimetic drugs are generally extensions of their pharmacologic activity.
2. Overdose with **epinephrine** or **norepinephrine** or other pressor agents may result in **severe hypertension**, with possible **cerebral hemorrhage**, **pulmonary edema**, and **cardiac arrhythmia**. Milder effects include headache, dizziness, and tremor. Increased cardiac workload may result in angina or myocardial infarction in patients with coronary insufficiency.
3. Phenylephrine should not be used to treat closed-angle glaucoma before iridectomy as it may cause **increased intraocular pressure**.
4. Sudden discontinuation of an  $\alpha_2$ -adrenoceptor agonist may cause **withdrawal symptoms** that include headache, tachycardia, and a rebound rise in blood pressure.
5. Drug abuse may occur with amphetamine and amphetamine-like drugs.
6. Drug interactions
  - a. **Tricyclic antidepressants** block catecholamine reuptake and may potentiate the effects of norepinephrine and epinephrine.
  - b. Some **halogenated anesthetic agents** and **digitalis** may sensitize the heart to  $\beta$ -receptor stimulants, resulting in ventricular arrhythmias.

## VII. ADRENERGIC RECEPTOR ANTAGONISTS

These drugs interact with either  $\alpha$ - or  $\beta$ -adrenoceptors to prevent or reverse the actions of endogenously released norepinephrine or epinephrine or exogenously administered sympathomimetic agents.

### A. $\alpha$ -Adrenoceptor antagonists

#### 1. Pharmacologic effects

- The pharmacologic effects of  $\alpha$ -adrenoceptor antagonists are predominantly cardiovascular and include **lowered peripheral vascular resistance and blood pressure**. These agents prevent pressor effects of  $\alpha$ -receptor agonists.
- $\alpha$ -Adrenoceptor antagonists convert the pressor action of sympathomimetic agents with both  $\alpha$ - and  $\beta$ -adrenoceptor agonist activity to a depressor response; this is referred to as **epinephrine reversal**.

#### 2. Specific drugs (Table 2-10)

- Phentolamine** (Regitine) is an intravenously administered, short-acting competitive antagonist at both  $\alpha_1$ - and  $\alpha_2$ -receptors. It reduces peripheral resistance and decreases blood pressure. **Tolazoline** (Priscoline), a drug similar to phentolamine, is rarely used.

table 2-10 Therapeutic Uses of Selected Adrenoceptor Antagonists

Drug	Receptor	Features	Major Uses
<b>Phentolamine</b> <sup>a</sup>	$\alpha_1$ and $\alpha_2$	Short duration of action (1–2 h)	Hypertension of pheochromocytoma
<b>Phenoxybenzamine</b> <sup>a</sup>		Long duration of action (15–50 h)	Hypertension of pheochromocytoma
<b>Prazosin</b> <sup>a</sup>	$\alpha_1$	Minimal reflex tachycardia	Mild-to-moderate hypertension (often with a diuretic or a $\beta$ -adrenoceptor antagonist); severe congestive heart failure (with a cardiac glycoside and a diuretic)
Terazosin			Mild-to-moderate hypertension
Doxazosin			Mild-to-moderate hypertension
<b>Propranolol</b> <sup>a</sup>	$\beta_1$ and $\beta_2$	Local anesthetic activity	Hypertension; angina; pheochromocytoma, cardiac arrhythmias; migraine headache; hypertrophic subaortic stenosis
Timolol			Hypertension; glaucoma
Metipranolol			Glaucoma
Levobunolol			Glaucoma
Nadolol		Long duration of action (15–25 h)	Hypertension; angina
Pindolol		Partial $\beta_2$ -receptor agonist activity <sup>b</sup>	Hypertension; angina
Penbutolol		Partial $\beta_2$ -receptor agonist activity <sup>b</sup> ; mild-to-moderate hypertension	Hypertension; angina
Carteolol		Partial $\beta_2$ -receptor agonist activity <sup>b</sup> ; excreted unchanged	Hypertension; angina; glaucoma
<b>Metoprolol</b> <sup>a</sup>	$\beta_1 > \beta_2$	Patient bioavailability is variable; extended release form available	Hypertension; angina
Atenolol		Eliminated by the kidney	Hypertension; angina
Esmolol		Ultrashort acting (10 min)	Supraventricular tachycardia
Betaxolol		Long duration of action (15–25 h)	Glaucoma; hypertension
Acebutolol		Partial agonist <sup>b</sup>	Hypertension; ventricular arrhythmias
<b>Labetalol</b> <sup>a</sup>	$\beta_1$ , $\beta_2$ , and $\alpha_1$	Partial agonist <sup>b</sup> ; rapid blood pressure reduction; local anesthetic activity	Mild-to-severe hypertension; hypertensive emergencies

<sup>a</sup>Drugs listed in **boldface type** are considered prototype drugs.

<sup>b</sup>Lower blood pressure without significant reduction in cardiac output or resting heart rate; also do not elevate triglyceride levels or decrease high-density lipoprotein cholesterol.



- b. Prazosin** (Minipress)
- (1) Prazosin is the prototype of competitive antagonists selective for  $\alpha_1$ -receptors. Others include **terazosin** (Hytrin), **doxazosin** (Cardura), **tamsulosin** (Flomax), and **alfuzosin** (Uroxatral).
  - (2) Prazosin reduces peripheral resistance and blood pressure.
  - (3) This drug is administered orally. Prazosin has a **slow onset** (2–4 h) and a **long duration of action** (10 h) and is extensively metabolized by the liver (50% during first pass).
- c. Labetalol** (Normodyne and Trandate)
- (1) Labetalol is a **competitive antagonist** (partial agonist) that is relatively selective for  $\alpha_1$ -receptors and also blocks  $\beta$ -receptors.
  - (2) Labetalol reduces heart rate and myocardial contractility, decreases total peripheral resistance, and lowers blood pressure.
  - (3) This drug is administered **orally** or **intravenously** and undergoes extensive first-pass metabolism.
- d. Phenoxybenzamine** (Dibenzyline)
- (1) Phenoxybenzamine is a noncompetitive, irreversible  $\alpha_1$ -receptor antagonist.
  - (2) Phenoxybenzamine binds covalently, resulting in a long-lasting (15–50 h) blockade.
- 3. Therapeutic uses** (Table 2-10)
- a. Overview**
- (1)  $\alpha_1$ -Adrenoceptor antagonists are used most often to treat hypertension and urinary obstruction of benign prostatic hypertrophy.
  - (2)  $\alpha_2$ -Adrenoceptor antagonists have no important therapeutic uses.
- b. Pheochromocytoma**
- (1) Pheochromocytoma is a **tumor** of the **adrenal medulla** that secretes excessive amounts of catecholamines. Symptoms include hypertension, tachycardia, and arrhythmias.
  - (2) **Phentolamine** and **phenoxybenzamine** are used to treat the tumor in the preoperative stage; they also are used for long-term management of inoperable tumors.
  - (3)  $\beta$ -Receptor antagonists are often used to prevent the cardiac effects of excessive catecholamines after an  $\alpha$ -receptor blockade is established.
- c. Adrenoceptor antagonists, particularly labetalol, are occasionally used to reverse hypertensive crisis** due to sudden increase in  $\alpha$ -receptor stimulation (e.g., with a pheochromocytoma or with an overdose of a sympathomimetic agonist).
- d. Prazosin and labetalol are used to treat essential hypertension.**
- e.  $\alpha_1$ -Adrenoceptor antagonists, such as prazosin, terazosin, doxazosin, and alfuzosin, are used to treat urinary obstruction of benign prostatic hypertrophy (BPH). Tamsulosin may have greater efficacy due to its selective action at  $\alpha_{1A}$ -receptors.**
- f. Other uses of  $\alpha$ -adrenoceptor antagonists (e.g., phentolamine) include reversible peripheral vasospasm like Raynaud syndrome, and erectile dysfunction (in combination with papaverine).**
- 4. Adverse effects**
- a. Adverse effects of phentolamine** include postural hypotension, reflex tachycardia, arrhythmia, angina, and diarrhea. This drug should be used cautiously in patients with a peptic ulcer or with coronary artery disease.
- b. Prazosin, terazosin, and doxazosin** produce postural hypotension and bradycardia on initial administration; these drugs produce no significant tachycardia.
- c. Adverse effects of labetalol** include postural hypotension and GI disturbances. Bradycardia occurs with overdose. Labetalol produces fewer adverse effects on the bronchi and cardiovascular system than selective  $\beta$ -receptor antagonists.

## B. $\beta$ -Adrenoreceptor antagonists

### 1. Pharmacologic effects

#### a. Cardiovascular system

- (1)  $\beta$ -Adrenoreceptor antagonists **lower blood pressure**, possibly because of their combined effects on the heart, the renin–angiotensin system, and the CNS.
- (2) These drugs **reduce** sympathetic-stimulated increases in **heart rate** and **contractility** and **cardiac output**.
- (3)  $\beta$ -Adrenoreceptor antagonists **lengthen AV conduction time and refractoriness and suppress automaticity**.

- (4) Initially, they may increase peripheral resistance. However, long-term administration results in decreased peripheral resistance in patients with hypertension.
- (5)  $\beta$ -Adrenoreceptor antagonists reduce renin release.

#### b. Respiratory system

- (1)  $\beta$ -Adrenoreceptor antagonists **increase airway resistance** as a result of  $\beta_2$ -receptor blockade.
- (2) This respiratory effect is more pronounced in asthmatics because of unopposed, compensatory, reflex sympathomimetic  $\alpha$ -receptor activity resulting from decreased cardiac output.

#### c. Eye

- (1)  $\beta$ -Adrenoreceptor antagonists decrease the production of aqueous humor, resulting in **reduced intraocular pressure**.

#### d. Other activities

- (1)  $\beta$ -Adrenoreceptor antagonists **inhibit lipolysis** ( $\beta_3$ ).
- (2) These drugs **inhibit glycogenolysis** ( $\beta_2$ ) in the liver (they may impede recovery from the hypoglycemic effect of insulin).
- (3) These drugs decrease high-density lipoprotein (HDL) levels.
- (4) Some  $\beta$ -adrenoceptor antagonists have local anesthetic action, including **propranolol** and **labetalol**.

### 2. Specific drugs (Table 2-10)

#### a. Overview

- (1) **Propranolol** is the **prototype**  $\beta$ -adrenoreceptor antagonist.
- (2) These drugs have an **antihypertensive effect** that is slow to develop (the mechanism is unclear).
- (3)  $\beta$ -Adrenoreceptor antagonists are absorbed well after oral administration. Including **propranolol**, many have **low bioavailability** (<50%) because of extensive first-pass metabolism; marked interpatient variability is seen, particularly with **metoprolol**.
- (4) With the exceptions of **esmolol** (10 min) and **nadolol** and **betaxolol** (15–25 h), most have a  $t_{1/2}$  of 3–12 hours.

#### b. Propranolol (Inderal)

- (1) Propranolol is a competitive antagonist at  $\beta_1$ - and  $\beta_2$ -receptors.
- (2) Propranolol is used in **long-term treatment of hypertension**, but it is not useful for hypertensive crisis.
- (3) This drug is used to treat **supraventricular and ventricular arrhythmias** and is administered IV for the emergency treatment of arrhythmias.
- (4) Propranolol is 90% bound to plasma proteins.
- (5) This drug is cleared by hepatic metabolism and, therefore, has prolonged action in the presence of liver disease.
- (6) Propranolol is also available in sustained-release preparation.

#### c. Metoprolol (Lopressor), betaxolol (Betoptic), bisoprolol (Zebeta), atenolol (Tenormin), acebutolol (Sectral), and esmolol (Brevibloc)

- (1) These drugs are somewhat selective  **$\beta_1$ -receptor antagonists** that may offer some advantage over nonselective  $\beta$ -adrenoceptor antagonists to treat cardiovascular disease in asthmatic patients, although cautious use is still warranted.
- (2) **Atenolol** is **eliminated** primarily by the **kidney** and undergoes little hepatic metabolism; it has little local anesthetic activity; it enters the CNS poorly.
- (3) **Acebutolol** has partial agonist activity.
- (4) **Betaxolol** is used topically for chronic **open-angle glaucoma**.
- (5) **Esmolol** is **ultrashort acting** ( $t_{1/2} = 10$  min) because of extensive plasma hydrolysis by esterases; it is administered by **IV infusion**.
- (6) **Metoprolol** is also available in sustained-release preparation.

#### d. Labetalol (Normodyne and Trandate), Carvedilol (Coreg)

- (1) Labetalol is a partial agonist that blocks  $\beta$ -receptors and  $\alpha_1$ -receptors (3:1 to 7:1 ratio). Carvedilol also has mixed activity but is equiactive at  $\beta$ -receptors and  $\alpha_1$ -receptors.
- (2) Labetalol reduces heart rate and myocardial contractility, decreases total peripheral resistance, and lowers blood pressure.
- (3) This drug is administered PO or IV and undergoes extensive first-pass metabolism.

- e. **Timolol** (Blocadren), **levobunolol** (Betagan), **nadolol** (Corgard), and **sotalol** (Betapace)
- (1) These drugs are **nonselective  $\beta$ -receptor antagonists**.
  - (2) **Timolol and levobunolol** have excellent **ocular effects** when applied **topically for glaucoma**. Like propranolol, these drugs have no local anesthetic activity. **Metipranolol** (OptiPranolol) is also used to treat glaucoma.
  - (3) **Sotalol** additionally prolongs the cardiac action potential and is used to treat **arrhythmias**.
- f. **Pindolol** (Visken), **carteolol** (Cartrol), and **penbutolol** (Levatol) are nonselective antagonists with partial  $\beta_2$ -receptor agonist activity.
- (1) **Carteolol** is used topically to treat **open-angle glaucoma**. It is **excreted unchanged**.
3. **Therapeutic uses** (see Table 2-10)
- a. **Cardiovascular system** (see also Chapter 4)
- (1)  $\beta$ -Adrenoreceptor antagonists are used to treat **hypertension**, often in combination with a diuretic or vasodilator.
  - (2) These drugs reduce incidence of **myocardial infarction**.
  - (3) These drugs provide prophylaxis for **supraventricular and ventricular arrhythmias**.
  - (4)  $\beta$ -Adrenoreceptor antagonists provide prophylaxis for **angina pectoris**. Long-term use of **timolol, propranolol, and metoprolol** may prolong survival after myocardial infarction.
  - (5) **Propranolol** relieves angina, palpitations, dyspnea, and syncope in **obstructive cardiomyopathy**. This effect is thought to be related to the slowing of ventricular ejection and decreased resistance to outflow.
- b. **Eye**
- (1) Topical application of **timolol, betaxolol, levobunolol, and carteolol** reduces intraocular pressure in **glaucoma**.
  - (2) Sufficient **timolol** can be absorbed after topical application to increase airway resistance and decrease heart rate and contractility.
- c. **Other uses**
- (1) **Propranolol** is used to control clinical symptoms of sympathetic overactivity in **hyperthyroidism** by an unknown mechanism, perhaps by inhibiting conversion of thyroxine to triiodothyronine.
  - (2) **Propranolol** and others may be beneficial in the prophylaxis of **migraine headache** by an unknown mechanism.
  - (3) **Propranolol** relieves acute **anxiety** and panic symptoms by inhibiting overactivity of the SNS.
4. **Adverse effects and contraindications**
- a. **All agents**
- (1)  $\beta$ -Adrenoreceptor antagonists should be administered with extreme caution in patients with preexisting compromised cardiac function because they can precipitate **heart failure** or heart block.
  - (2) These drugs may augment insulin action in diabetics and **mask tachycardia** associated with hypoglycemia.
  - (3)  $\beta$ -Adrenoreceptor antagonists may **mask** the signs of developing **hyperthyroidism**.
  - (4) After abrupt withdrawal, adrenoceptor “supersensitivity” and increased risk of **angina** and **arrhythmias** may occur. **Tapered withdrawal** is recommended.
- b. **Nonselective adrenoceptor antagonists**
- (1) These drugs may cause **bronchoconstriction**, and thus they are contraindicated for asthmatics. Patients with chronic obstructive lung disease are particularly susceptible.
  - (2) These drugs should be used cautiously in patients with **peripheral vascular disease**.
  - (3)  $\beta_1$ -Selective antagonists should also be used cautiously to treat asthmatics and patients with peripheral vascular disease because they have some  $\beta_2$ -receptor antagonist activity.
- c. **Propranolol**, and other  $\beta$ -receptor blockers, cause **sedation, sleep disturbances, and depression**.

## DRUG SUMMARY TABLE

**Direct-Acting Cholinoceptor Agonists**

Acetylcholine (Miochol-E)  
Bethanechol (Urecholine)  
Carbachol (generic)  
Cevimeline (Evoxac)  
Methacholine (Mecholyl)  
Pilocarpine (generic)  
Varenicline (Chantix)

**Indirect-Acting Cholinoceptor Agonists**

Ambenonium (Mytelase)  
Demecarium (Humorsol)  
Donepezil (Aricept)  
Echothiophate (Phospholine)  
Edrophonium (Tensilon)  
Galantamine (Reminyl)  
Neostigmine (Prostigmin)  
Physostigmine (Eserine, Antilirium)  
Pyridostigmine (Mestinon, Regonol)  
Rivastigmine (Exelon)  
Tacrine (Cognex)

**Cholinesterase Regenerator**

Pralidoxime (Protopam)

**Muscarinic Cholinoceptor Antagonists**

Atropine (generic)  
Clidinium (Quarzan)  
Cyclopentolate (Cyclogyl)  
Darifenacin (Enablex)  
Dicyclomine (Bentyl)  
Flavoxate (Uripas)  
Glycopyrrolate (Robinul)  
Homatropine (generic)  
Ipratropium (Atrovent)  
Mepenzolate (Cantil)  
Methantheline (Banthine)  
Oxybutynin (Ditropan)  
Propantheline (Pro-Banthine)  
Scopolamine (generic)  
Solifenacin (Vesicare)  
Tiotropium (Spiriva)  
Tolterodine (Detrol)  
Tridihexethyl (Pathilon)  
Tropicamide (generic)  
Trospium (Spasmex)

**Ganglion Blocking Drugs**

Mecamylamine (Inversine)  
Trimethaphan (Arfonad)

**Skeletal Muscle Relaxants****Neuromuscular Blocking Drugs**

Atracurium (generic)  
Cisatracurium (Nimbex)  
Doxacurium (Nuromax)  
Metocurium (Metubine)  
Mivacurium (Mivacron)  
Pancuronium (Pavulon)  
Pipocurium (Arduan)  
Rocuronium (Zemuron)  
Succinylcholine (Anectine)  
Tubocurarine (generic)  
Vecuronium (Norcuron)  
**Spasmolytic Drugs**  
Baclofen (Lioresal)  
Botulinum toxin-type A (Botox)  
Botulinum toxin-type B (Myobloc)  
Dantrolene (Dantrium)

**Sympathomimetic Drugs**

Albuterol (Proventil, Ventolin)  
Amphetamine (generic)  
Apraclonidine (Lopidine)  
Bitolterol (Tornalate)  
Brimonidine (Alphagan)  
Clonidine (Catapres)  
Dexmedetomidine (Precedex)  
Dextroamphetamine (Dexedrine)  
Dipivefrin (Propine)  
Dobutamine (Dobutrex)  
Dopamine (Intropin)  
Ephedrine (generic)  
Epinephrine (generic)  
Fenoldopam (Corlopan)  
Formoterol (Foradil)  
Guanabenz (Wytensin)  
Guanfacine (Tenex)  
Hydroxyamphetamine (Paredrine)  
Isoproterenol (Isuprel)  
Levalbuterol (Xopenex)  
Mephenteramine (Wyamine)  
Metaproterenol (Alupent)  
Metaraminol (Aramine)  
Methamphetamine (Desoxyyn)

Methoxamine (Vasoxyl)  
Methyldopa (Aldomet)  
Methylphenidate (Ritalin)  
Midodrine (ProAmatine)  
Modafinil (Provigil)  
Naphazoline (Privine)  
Norepinephrine (generic)  
Oxymetazoline (Afrin, Visine)  
Phenylephrine (Neo-Synephrine)  
Pirbuterol (Maxair)  
Pseudoephedrine (Sudafed)  
Salmeterol (Serevent)  
Terbutaline (Brethine, Bricanyl)  
Tetrahydrozoline (Tyzine)  
Xylometazoline (Otrivin)

**Adrenergic Receptor Antagonists****Alpha-Receptor Blockers**

Alfuzosin (Uroxatral)  
Doxazosin (Cardura)  
Phenoxybenzamine (Dibenzyline)  
Phentolamine (Regitine)  
Prazosin (Minipress)  
Tamsulosin (Flomax)  
Terazosin (Hytrin)  
Tolazoline (Priscoline)

**Beta-Receptor Blockers**

Acebutolol (Sectral)  
Atenolol (Tenormin)  
Betaxolol (Betoptic)  
Bisoprolol (Zebeta)  
Carteolol (Cartrol)  
Carvedilol (Coreg)  
Esmolol (Brevibloc)  
Labetalol (Normodyne, Trandate)  
Levobunolol (Betagan)  
Metipranolol (OptiPranolol)  
Metoprolol (Lopressor)  
Nadolol (Corgard)  
Penbutolol (Levatol)  
Pindolol (Visken)  
Propranolol (generic)  
Sotalol (Betapace)  
Timolol (Blocadren)

# Review Test for Chapter 2

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

- Botulinum toxin causes paralysis by
  - Inhibiting choline acetyltransferase
  - Blocking transport of choline into neurons
  - Blocking release of acetylcholine from storage vesicles
  - Inhibiting acetylcholinesterase
  - Blocking the synapse at ganglia
- Which of the following neurotransmitters interacts with guanethidine?
  - Acetylcholine
  - Epinephrine
  - Dopamine
  - Norepinephrine
  - Serotonin
- What is the mechanism of action of cocaine?
  - Propagation of action of norepinephrine by inhibiting its active transport from the synapse
  - Oxidative deamination of norepinephrine in nerve terminals and the effector cells
  - Inhibition of metabolism of norepinephrine in nerve terminals
  - Potential of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of norepinephrine
  - Promotion of release of norepinephrine from adrenergic nerve endings
- What intracellular effect does albuterol, a  $\beta_2$ -agonist, produce?
  - Allows passage of sodium through a ligand-gated ion channel
  - Activates  $G_s$ -protein, resulting in stimulation of adenylyl cyclase
  - Activates  $G_q$ -protein, resulting in increase of phosphatidylinositol and calcium mobilization
  - Activates  $G_i$ -protein, resulting in inhibition of adenylyl cyclase
  - Binds to  $\mu$ -receptors in the specific areas of the brain
- What class of medications does bethanechol belong to?
  - Nicotinic blockers
  - $\alpha$ -Agonists
  - $\beta_1$ -Blockers
  - $\beta_2$ -Blockers
  - Muscarinic agonists
- A 38-year-old farmer is brought to the ER by his wife with symptoms of sudden difficulty breathing, sweatiness, and anxiety. He was spraying insecticide when this happened. It has been 25 minutes since the symptoms started. The patient is emergently intubated and given atropine and another medication that acts to reactivate acetylcholinesterase. What medication is it?
  - Physostigmine
  - Propranolol
  - Pralidoxime
  - Phenylephrine
  - Pancuronium
- Oxybutynin works by
  - Inhibiting acetylcholinesterase at muscarinic and nicotinic receptors
  - Causing a neuromuscular blockade
  - Antagonizing  $\alpha_1$ -adrenoceptors
  - Binding to muscarinic receptors
  - Activating  $\beta_2$ -adrenoceptors
- A 78-year-old man with Parkinson disease experiences worsening of his symptoms. He is already taking levodopa. Since the disease is characterized by degeneration of dopaminergic neurons, leading to the lack of inhibition of cholinergic neurons, the addition of which medication is likely to help alleviate the patient's symptoms?
  - Benztrapine
  - Reserpine
  - Doxazocin
  - Timolol
  - Tubocurarine

9. A 66-year-old woman with a long history of heavy smoking presents to her doctor with complaints of shortness of breath and chronic coughing that has been present for about 2 years and has been worsening in frequency. The doctor decides to prescribe a bronchodilator agent that has minimal cardiac side effects, since the patient also has an extensive cardiac history. Which medication did the doctor likely prescribe?
- (A) Albuterol
  - (B) Prazosin
  - (C) Atenolol
  - (D) Ipratropium
  - (E) Pseudoephedrine
10. From the list below, choose the depolarizing neuromuscular blocker most likely to be used in “rapid sequence intubation,” a procedure that is done when the stomach contents have a high risk of refluxing and causing aspiration.
- (A) Baclofen
  - (B) Succinylcholine
  - (C) Neostigmine
  - (D) Homatropine
  - (E) Pralidoxime
11. Ephedra (ephedrine) causes increased blood pressure by
- (A) Indirect action on cholinergic receptors
  - (B) Blockade of adrenergic receptors
  - (C) Stimulation of release of epinephrine
  - (D) Inhibition of reuptake of catecholamines
  - (E) Direct action on dopamine receptors
12. A 34-year-old carpenter presents to the ER after an accident in which he inadvertently chopped off the tip his index finger. He is taken to the OR for reattachment of the digit, and after sedation, a local anesthetic is administered around the site of the injury. The local anesthetic used in the procedure did not contain any epinephrine, as it usually does for most surgical procedures. The reason for this is
- (A) Epinephrine causes increased blood loss during delicate surgery
  - (B) Epinephrine causes swelling of the tissues, making surgery more challenging
  - (C) Epinephrine is contraindicated in emergency surgery
  - (D) Epinephrine causes vasoconstriction, which can lead to vascular ischemia in digits
  - (E) Epinephrine can cause hypotension when administered with sedative agents
13. A 7-year-old boy is brought in by his parents for complaints of hyperactivity at school. He is also inattentive and impulsive at home. After a detailed interview, the physician decides to give the boy amphetamine-containing medication for presumed attention hyperactivity disorder. Amphetamine
- (A) Inhibits epinephrine reuptake
  - (B) Indirectly acts on norepinephrine receptors
  - (C) Blocks effects of norepinephrine
  - (D) Directly acts on cholinoreceptors
  - (E) Inhibits serotonin reuptake
14. Which of the following medications is used to prevent premature labor?
- (A) Tamsulosin
  - (B) Cevimeline
  - (C) Atracurium
  - (D) Tolterodine
  - (E) Terbutaline
15. What significant side effect of terazosin should the doctor warn a 69-year-old patient about?
- (A) Bronchospasm
  - (B) Postural hypotension
  - (C) Heart failure
  - (D) Sedation
  - (E) Drug abuse
16. A floor nurse pages you about a patient who is having chest pain. You order an electrocardiogram and rush to see the patient. He describes the pain as tight pressure and is demonstrably sweating and gasping for air. The ECG comes back with acute ST-segment elevations in inferior leads, and you diagnose a myocardial infarction. You start giving the patient oxygen and give him sublingual nitroglycerin and morphine for pain. You also give him another medication, which you have read may prolong his survival in this dire situation. What class of medication is it?
- (A)  $\beta$ -Blocker
  - (B)  $\alpha$ -Agonist
  - (C) Muscarinic agonist
  - (D) Neuromuscular blocker
  - (E) Dopamine agonist
17. A 35-year-old woman presents to your office for a regular check-up. Her only complaint is recurrent migraine headaches, which have increased in frequency over the years. On examination, her blood pressure is elevated at



150/70. You decide to start her on antihypertensive therapy that is also used for prophylaxis of migraines. Which medication is it?

- (A) Clonidine
- (B) Prazosin
- (C) Hydrochlorothiazide
- (D) Propranolol
- (E) Verapamil

18. In contrast to propranolol, metoprolol

- (A) Is used for the management of hypertension
- (B) Has greater selectivity for  $\beta_2$ -adrenoceptors
- (C) May be beneficial for the acute treatment of migraine headache
- (D) Is less likely to precipitate bronchoconstriction in patients with asthma

19. Intravenous administration of epinephrine to a patient results in a severe decrease in diastolic pressure and an increase in cardiac output. Which of the following drugs might the patient have previously taken that could account for this unexpected effect?

- (A) Propranolol
- (B) Atropine
- (C) Phenylephrine
- (D) Prazosin

20. Which of the following drugs is used to diagnose myasthenia gravis?

- (A) Atropine
- (B) Neostigmine
- (C) Bethanechol
- (D) Edrophonium
- (E) Pralidoxime

21. Pilocarpine reduces intraocular pressure in patients with glaucoma because it

- (A) Activates nicotinic cholinergic receptors
- (B) Blocks muscarinic cholinergic receptors
- (C) Selectively inhibits peripheral activity of sympathetic ganglia
- (D) Inhibits acetylcholinesterase

22. Prolonged apnea may occur following administration of succinylcholine to a patient with a hereditary deficiency of which of the following enzymes?

- (A) Glucose-6-phosphate dehydrogenase
- (B) Plasma cholinesterase
- (C) Monoamine oxidase
- (D) Cytochrome P450<sub>3A</sub>
- (E) Acetylcholinesterase

23. Dantrolene is the drug of choice to treat malignant hyperthermia caused by succinylcholine because dantrolene

- (A) Blocks  $Ca^{2+}$  release from sarcoplasmic reticulum
- (B) Induces contraction of skeletal muscle
- (C) Increases the rate of succinylcholine metabolism
- (D) Inhibits succinylcholine binding to nicotinic receptors
- (E) Acts centrally to reduce fever

24. A drug that acts at prejunctional  $\alpha_2$ -adrenoceptors and is used to treat hypertension is

- (A) Clonidine
- (B) Methoxamine
- (C) Metaproterenol
- (D) Dobutamine
- (E) Dopamine

25. Drug X causes an increase in blood pressure and a decrease in heart rate when administered to a patient intravenously. If an antagonist at ganglionic nicotinic receptors is administered first, drug X causes an increase in blood pressure and an increase in heart rate. Drug X most likely is

- (A) Propranolol
- (B) Norepinephrine
- (C) Isoproterenol
- (D) Terbutaline
- (E) Curare

26. Poisoning with an insecticide containing an acetylcholinesterase inhibitor is best managed by administration of which one of the following agents?

- (A) Physostigmine
- (B) Bethanechol
- (C) Propranolol
- (D) Pilocarpine
- (E) Atropine

27. Receptor actions of acetylcholine are mimicked by nicotine at which one of the following sites?

- (A) Adrenal medullary chromaffin cells
- (B) Urinary bladder smooth muscle cells
- (C) Iris circular (constrictor) muscle
- (D) Heart sinoatrial pacemaker cells

28. Muscarinic cholinergic agonists may cause vasodilation through the release of endothelial



- (A) Histamine
  - (B) Norepinephrine
  - (C) Acetylcholine
  - (D) Nitric oxide
29. Emergency treatment of acute heart failure is best managed with which of the following drugs?
- (A) Metaproterenol
  - (B) Phenylephrine
  - (C) Dobutamine
  - (D) Norepinephrine
  - (E) Isoproterenol
30. Which one of the following agents, when applied topically to the eye, would cause both mydriasis and cycloplegia?
- (A) Phenylephrine
  - (B) Carbachol
  - (C) Prazosin
  - (D) Atropine
31. Neostigmine would be expected to reverse which one of the following conditions?
- (A) Paralysis of skeletal muscle induced by a competitive, nondepolarizing muscle relaxant
  - (B) Paralysis of skeletal muscle induced by a depolarizing muscle relaxant
  - (C) Cardiac slowing induced by stimulation of the vagus nerve
  - (D) Miosis induced by bright light
32. The direct cardiac effects of dobutamine would be blocked by which one of the following agents?
- (A) Prazosin
  - (B) Metoprolol
  - (C) Clonidine
  - (D) Isoproterenol
33. Topical application of timolol to the eye would be expected to induce which of the following?
- (A) Miosis
  - (B) Mydriasis
  - (C) Decreased formation of aqueous humor
  - (D) Increased outflow of aqueous humor
34. Phenylephrine is used to treat patients with nasal mucosa stuffiness because it causes vasoconstriction by
- (A) Blocking nicotinic cholinergic receptors
  - (B) Blocking  $\beta$ -adrenoceptors
  - (C) Stimulating  $\alpha$ -adrenoceptors
  - (D) Stimulating muscarinic cholinergic receptors

# Answers and Explanations

- 1. The answer is C.** Botulinum toxin blocks calcium-dependent exocytosis of acetylcholine from storage vesicles, producing paralysis. Common sources of botulinum toxin include canned home goods and, in cases of infant botulism, honey. The condition is life threatening, and urgent care is necessary. Choline acetyltransferase is an enzyme catalyzing synthesis of acetylcholine from an acetate and choline. Sodium-dependent transport of choline can be blocked by hemicholinium. Enzyme acetylcholinesterase is responsible for catalyzing hydrolysis of acetylcholine. Acetylcholine synapses at the ganglia of many neurons and tissues, and this step is not blocked by botulinum toxin.
- 2. The answer is D.** Guanethidine blocks the release of norepinephrine from storage vesicles into the nerve terminals. Acetylcholine release can be blocked by botulinum toxin. Epinephrine, dopamine, and serotonin release can be blocked by other agents (beyond the scope of this chapter), but not by guanethidine.
- 3. The answer is A.** Cocaine is a potent inhibitor of norepinephrine uptake, a process that normally terminates norepinephrine's action. Oxidative deamination of norepinephrine in nerve terminals and the effector cells describes the action of monoamine oxidase, which is targeted by certain antidepressant medications. Inhibition of metabolism of norepinephrine in nerve terminals describes catechol-*O*-methyltransferase, which is found in nerve and other effector cells. Potentiation of tyrosine dehydroxylase would, in fact, cause excessive amounts of norepinephrine to accumulate; however, this enzyme is not affected by cocaine. Norepinephrine release can be blocked, not promoted, by agents such as bretylium and guanethidine.
- 4. The answer is B.**  $\beta_2$ -agonists, like albuterol, activate  $G_s$ -protein, which results in stimulation of adenylyl cyclase, with subsequent increase in intracellular cAMP. Passage of sodium via ligand-gated ion channel is manifested by nicotinic acetylcholine receptors. Activation of  $G_q$ -protein resulting in increase of phosphatidylinositol and calcium mobilization refers to the mechanism of action of muscarinic receptors type  $M_1$  and  $M_3$ , as well as  $\alpha_1$ -adrenoceptors. Activation of  $G_q$ -protein resulting in increase of phosphatidylinositol and calcium mobilization refers to mechanism of action of  $M_2$ -cholinoceptors and  $\alpha_2$ -adrenoceptors. Finally, binding to  $\mu$ -receptors in the specific areas of the brain describes the action of opioid agents.
- 5. The answer is E.** Bethanechol is a type of muscarinic receptor agonist that is used clinically to ameliorate urinary retention. Nicotinic blockers such as trimethaphan are rarely used in clinical practice because of the lack of selectivity.  $\alpha$ -Agonists such as epinephrine can be used in management of acute bronchospasm (anaphylaxis).  $\beta_1$ -Blockers do not have direct effects on bronchial smooth muscle.  $\beta_2$ -Agonists such as albuterol are used for treatment of asthma.
- 6. The answer is C.** Acetylcholinesterase reactivator pralidoxime has to be given within 30 minutes of exposure to insecticide because of the effects of "aging" (i.e., strengthening of the alkylphosphoryl-serine bond formed between AChE and organophosphate). Physostigmine is a cholinesterase inhibitor that is occasionally used in atropine or scopolamine poisoning. Propranolol is a  $\beta$ -blocker used for hypertension as well as other indications. Phenylephrine is an  $\alpha$ -agonist used for hypotensive emergencies. Pancuronium is a nondepolarizing inhibitor of acetylcholine that is used for muscle paralysis.
- 7. The answer is D.** Oxybutynin acts by binding to muscarinic receptors located on the detrusor muscle of the bladder, suppressing involuntary contraction of the muscle. Acetylcholinesterase inhibitors such as edrophonium are used for myasthenia gravis. Neuromuscular blockers such as succinylcholine are used for anesthesia.  $\alpha_1$ -Antagonists such as terazosin are used for benign prostatic hypertrophy.  $\beta_2$ -Agonists such as terbutaline can be used to suppress premature labor.

8. **The answer is A.** Benztropine, an antimuscarinic agent, is used as an adjunct for treatment of Parkinson disease. Reserpine is a norepinephrine uptake inhibitor occasionally used for treatment of hypertension. Doxazosin, an  $\alpha$ -blocker, is used for benign prostatic hyperplasia. Timolol is a  $\beta$ -blocker used for glaucoma. Tubocurarine is a neuromuscular blocker used in anesthesia.
9. **The answer is D.** Ipratropium bromide is used extensively for chronic obstructive pulmonary disease (COPD), which is the most likely diagnosis in this case. It acts by antagonizing muscarinic receptors in bronchial smooth muscle, thereby causing bronchodilation. Albuterol is also used for treatment of COPD; however, it can cause adverse cardiac effects such as tachycardia and is not recommended in this case. Prazosin is an  $\alpha$ -blocker used for benign prostatic hypertrophy (BPH). Atenolol is a  $\beta$ -blocker used for hypertension. Pseudoephedrine is an  $\alpha$ -agonist used for nasal congestion.
10. **The answer is B.** Succinylcholine is a depolarizing neuromuscular blocker that is used in rapid-sequence intubation, as well as other procedures. It quickly relaxes all muscles in the body, allowing a prompt intubation to prevent the reflux of gastric contents into the trachea. Baclofen is a centrally acting skeletal muscle relaxant used for spasticity. Neostigmine is an indirect-acting cholinergic agent used for treatment of myasthenia gravis and reversal of neuromuscular blockade. Homatropine is an antimuscarinic agent used for induction of mydriasis for ophthalmologic examinations. Pralidoxime is an acetylcholinesterase reactivator used for organophosphate poisoning.
11. **The answer is C.** Ephedrine acts indirectly to release norepinephrine from nerve terminals, causing effects similar to those of catecholamines, including elevated blood pressure. This potentially dangerous agent has been removed from the OTC market because of an increasing number of deaths being reported as caused by this agent. An example of an indirect-acting cholinergic agonist is edrophonium, which is used for diagnosis of myasthenia gravis. Some adrenoceptor blockers, such as atenolol, are used for treatment of hypertension. Catecholamine reuptake inhibition is a property of some antidepressant medications. Dopamine receptor agonists are used in treatment of Parkinson disease.
12. **The answer is D.** Epinephrine is contraindicated as an anesthetic adjuvant for surgeries involving most facial structures, digits, and the penis, because of the risk of vascular compromise. This agent causes decreased blood loss for most other surgeries because of vasoconstriction. Although local anesthetic agents such as Marcaine or Xylocaine can cause mild local tissue swelling, epinephrine does not; either way, it is not a contraindication for hand surgery. Epinephrine causes elevated blood pressure when administered systemically; however, it has no systemic side effects when administered locally.
13. **The answer is B.** Amphetamine and similar compounds are stimulants used for treatment of attention-deficit/hyperactivity disorder (ADHD) in which they are thought to act centrally to increase attention span. Currently there is no medication on the U.S. market that inhibits reuptake of epinephrine. Blocking of the effects of norepinephrine will not alleviate symptoms of ADHD. Direct-acting cholinergic agonists are not used in treatment of ADHD. Serotonin reuptake inhibitors are used for depression and some other conditions.
14. **The answer is E.** Terbutaline, a  $\beta_2$ -agonist, is used to suppress premature labor because of its ability to stop uterine contractions. Tamsulosin, an  $\alpha_1$ -blocker, is used for benign prostatic hypertrophy. Cevimeline, a cholinergic agonist, is used for Sjögren syndrome. Atracurium a non-depolarizing muscular blocker, is used for anesthesia. Tolterodine, a muscarinic blocker, is used for urinary incontinence.
15. **The answer is B.**  $\alpha_1$ -Adrenoceptor agonists such as terazosin may cause significant postural hypotension, and should be prescribed carefully in the elderly population. Bronchospasm is a possible side effect of  $\beta$ -blockers.  $\beta$ -Blockers can also produce heart failure in some patients. Sedation is common with the use of some agents such as propranolol. Drug abuse can be observed in patients using centrally acting adrenoceptor agonists such as amphetamine.

16. **The answer is A.**  $\beta$ -Blockers such as atenolol are now part of management of acute myocardial infarction, along with oxygen, nitroglycerin, and morphine. They reduce sympathetic activity and heart contractility, thereby reducing the oxygen demand.  $\alpha$ -Agonists such as phenylephrine are used in management of hypotension due to shock. Muscarinic agonists such as pilocarpine can be used in management of glaucoma. Neuromuscular blockers such as atracurium are used in anesthesia. Dopamine agonists are used in management of Parkinson disease.
17. **The answer is D.** The  $\beta$ -blocker propranolol is a good choice for an antihypertensive medication; however, it is also successfully used for other indications, such as prophylaxis of migraine headaches, situational anxiety, and hyperthyroidism-induced palpitations. The other choices are all acceptable antihypertensive medications, but from this list, only propranolol is used for migraine prophylaxis.
18. **The answer is D.** Metoprolol is more selective at  $\beta_1$ -adrenoceptors, which are more abundant in the heart than in the lungs. Like propranolol, it may be beneficial in the prophylaxis of migraine.
19. **The answer is D.** Prazosin is the only drug listed that blocks postjunctional  $\alpha_1$ -adrenoceptors and inhibits epinephrine-mediated vasoconstriction.
20. **The answer is D.** Edrophonium, which will increase muscle strength in untreated myasthenic patients, is the preferred acetylcholinesterase inhibitor (Tensilon test) because it has a short duration of action.
21. **The answer is B.** Pilocarpine is a muscarinic cholinergic agonist.
22. **The answer is B.** Plasma cholinesterase is responsible for the rapid inactivation of succinylcholine.
23. **The answer is A.** In patients with malignant hyperthermia, a rare hereditary disorder, an impaired sarcoplasmic reticulum is unable to sequester calcium. The sudden release of calcium results in extensive muscle contraction that can be reduced with dantrolene.
24. **The answer is A.** Clonidine acts at prejunctional  $\alpha_2$ -adrenoceptors and is used to treat hypertension. Methoxamine is a non-selective  $\alpha$ -adrenoceptor agonist. Metaproterenol is a selective  $\beta_2$ -adrenoceptor agonist. Dobutamine is a relatively selective  $\beta_1$ -adrenoceptor agonist. Dopamine activates both pre-junctional and postjunctional dopamine receptors and also  $\beta_1$ -adrenoceptor.
25. **The answer is B.** In the absence of a nicotinic receptor antagonist, norepinephrine may result in a reflex baroreceptor-mediated increase in vagal activity. The presence of such an agent unmasks the direct stimulant effect of norepinephrine on heart rate.
26. **The answer is E.** Atropine blocks the effects of increased acetylcholine resulting from cholinesterase inhibition. Physostigmine indirectly activates cholinergic receptors; bethanechol and pilocarpine directly activate cholinergic receptors. Propranolol is a  $\beta$ -adrenoceptor antagonist.
27. **The answer is A.** Nicotinic cholinergic receptors are found in adrenal medullary chromaffin cells. At the other sites, acetylcholine activates muscarinic cholinergic receptors.
28. **The answer is D.** The release of nitric oxide activates guanylate cyclase, increasing guanosine 3',5'-monophosphate (cyclic GMP) and sequestering calcium. This leads to a relaxation of vascular smooth muscle.
29. **The answer is C.** Dobutamine, a relatively selective  $\beta_1$ -adrenoceptor agonist, increases cardiac output and lowers peripheral resistance. Metaproterenol has a relatively more selective action on the respiratory system than the cardiovascular system. Phenylephrine and norepinephrine increase peripheral resistance. Isoproterenol increases heart rate.
30. **The answer is D.** Atropine produces both mydriasis and cycloplegia (the inability to accommodate for near vision). Phenylephrine causes mydriasis without cycloplegia. Carbachol causes pupillary constriction. Prazosin is an  $\alpha$ -adrenoceptor antagonist.

31. **The answer is A.** Acetylcholine accumulation due to neostigmine inhibition of cholinesterase will reverse the action of the competitive neuromuscular blocking agents.
32. **The answer is B.** The  $\beta_1$ -adrenoceptor antagonist metoprolol blocks the  $\beta_1$ -adrenoceptor activity of dobutamine.
33. **The answer is C.**  $\beta$ -Adrenoceptor blocking agents such as timolol reduce aqueous humor formation.
34. **The answer is C.** Phenylephrine activates  $\alpha$ -adrenoceptors, producing vasoconstriction.