Adrenergic Agonists

6

I. OVERVIEW

The adrenergic drugs affect receptors that are stimulated by *norepinephrine* or *epinephrine*. Some adrenergic drugs act directly on the adrenergic receptor (adrenoceptor) by activating it and are said to be sympathomimetic. Others, which will be dealt with in Chapter 7, block the action of the neurotransmitters at the receptors, while still other drugs affect adrenergic function by interrupting the release of *norepinephrine* from adrenergic neurons. This chapter describes agents that either directly or indirectly stimulate the adrenoceptor (Figure 6.1).

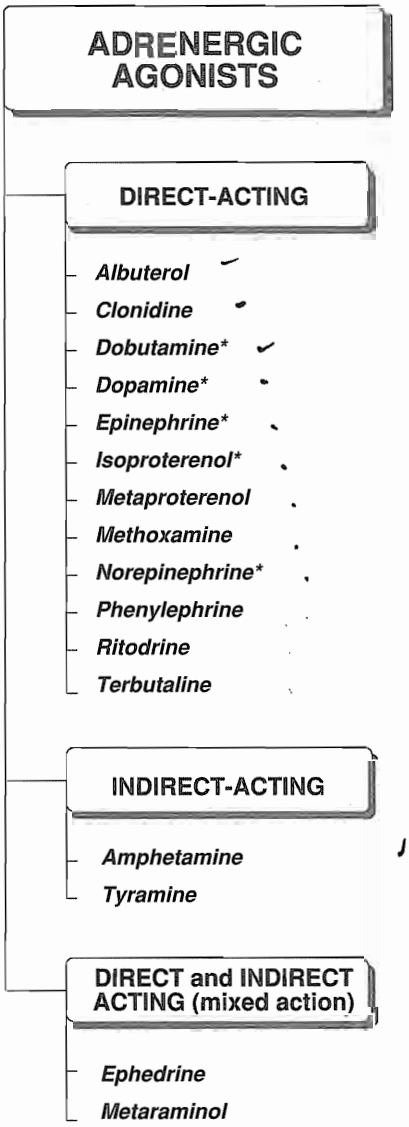


Figure 6.1
Summary of adrenergic agonists. Agents marked with an asterisk (*) are catecholamines.

II. THE ADRENERGIC NEURON

Adrenergic neurons release *norepinephrine* as the neurotransmitter. These neurons are found in the central nervous system (CNS), and also in the sympathetic nervous system where they serve as links between ganglia and the effector organs. The adrenergic neurons and receptors located either presynaptically on the neuron or post-synaptically on the effector organ are the sites of action of the adrenergic drugs (Figure 6.2).

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons (p. 37), except that *norepinephrine* is the neurotransmitter instead of acetylcholine. Neurotransmission takes place at numerous beadlike enlargements called varicosities; the process involves five steps: the synthesis, storage, release, and receptor binding of the *norepinephrine*, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a Na^+-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase[1]. This is the rate-limiting step in the formation of *norepinephrine*. DOPA is decarboxylated to form *dopamine*.

[1]See p. 70 for Infolink references to other books in this series.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers , Philadelphia, PA © 1997.

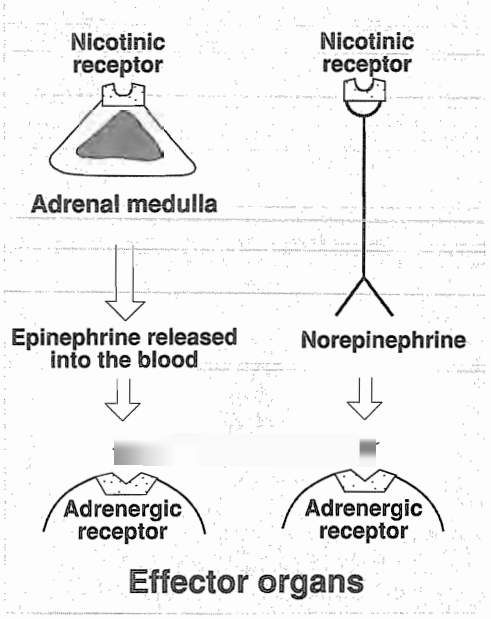


Figure 6.2
Sites of actions of adrenergic agonists.

2. **Storage of norepinephrine in vesicles:** *Dopamine* is transported into synaptic vesicles by an amine transporter system that is also involved in the re-uptake of preformed *norepinephrine*. This carrier system is blocked by *reserpine* (see p. 78). *Dopamine* is hydroxylated to form *norepinephrine* by the enzyme, *dopamine* β-hydroxylase. Synaptic vesicles contain dopamine or *norepinephrine* plus adenosine triphosphate and the β-hydroxylase. Not all of the *norepinephrine* is packaged in vesicles; some exists in a cytoplasmic pool that can be displaced. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*; both are stored in chromaffin cells. On stimulation, the adrenal medulla releases about 85% *epinephrine* and 15% *norepinephrine*.

3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes vesicles inside the neuron to fuse with the cell membrane and expel their contents into the synapse. This release is blocked by drugs such as *guanethidine* (see p. 78).

4. **Binding by receptor:** *Norepinephrine* released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending (see Figure 6.3). The recognition of *norepinephrine* by the membrane receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphoinositide cycle, described on p. 33, to transmit the signal into an effect.

5. **Removal of norepinephrine:** *Norepinephrine* may (1) diffuse out of the synaptic space and enter the general circulation, (2) be metabolized to O-methylated derivatives by post-synaptic cell membrane-associated catechol O-methyltransferase (COMT) in the synaptic space, or (3) be recaptured by an uptake system that pulls the *norepinephrine* back into the neuron. The uptake by the neuronal membrane involves a sodium-potassium activated ATPase that can be inhibited by tricyclic antidepressants such as *imipramine* (see p. 119), or by *cocaine* (see Figure 6.3).

6. **Potential fates of recaptured norepinephrine:** Once *norepinephrine* reenters the cytoplasm of the adrenergic neuron it may be taken up into adrenergic vesicles via the amine transporter system and be sequestered for release by another action potential or persist in a protected pool. Alternatively, *norepinephrine* can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. The inactive products of *norepinephrine* metabolism are excreted in the urine as vanillylmandelic acid (VMA), metanephrine and normetanephrine.

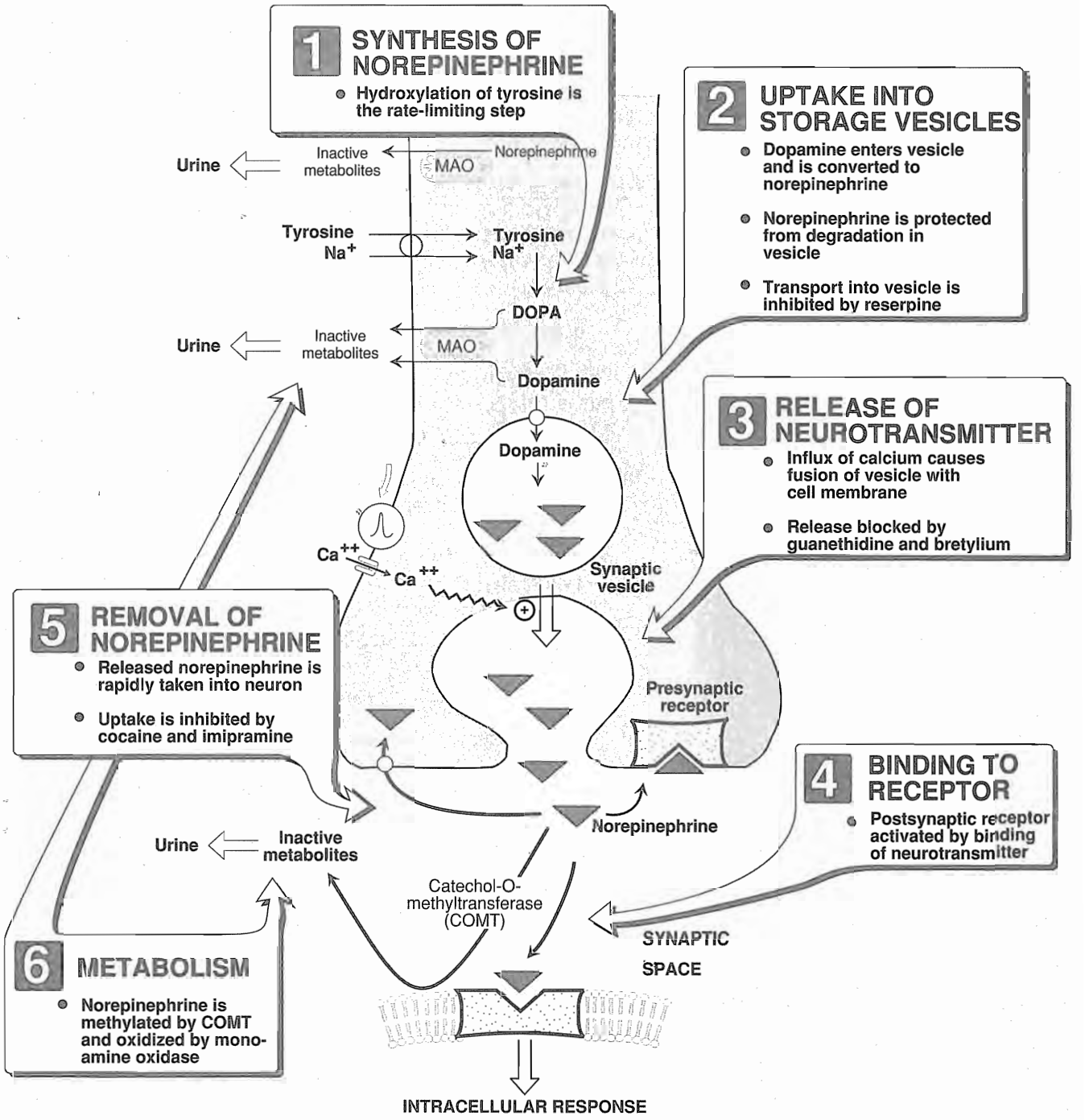


Figure 6.3
Synthesis and release of norepinephrine from the adrenergic neuron.

B. Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two families of receptors, designated "α" and "β", were initially identified on the

basis of their responses to the adrenergic agonists, *epinephrine*, *norepinephrine*, and *isoproterenol*. The use of specific blocking drugs and the cloning of genes have revealed the molecular identities of a number of subtypes. These proteins belong to a multigene family. Alterations in the primary structure of the receptors influence their affinity for various agents.

1. α_1 and α_2 receptors: The α adrenoceptors show a weak response to the synthetic agonist, *isoproterenol*, but are responsive to the naturally occurring catecholamines, *epinephrine*, and *norepinephrine* (Figure 6.4). For α receptors the rank order of potency is:

epinephrine ≥ *norepinephrine* >> *isoproterenol*

The α adrenoceptors are subdivided into two groups, α_1 and α_2, based on their affinities for α agonists and blocking drugs. For example, the α_1 receptors have a higher affinity for *phenylephrine* (see p. 66) than do the α_2 receptors. Conversely, the drug *clonidine* (see p. 67) selectively binds to α_2 receptors, and has less effect on α_1 receptors.

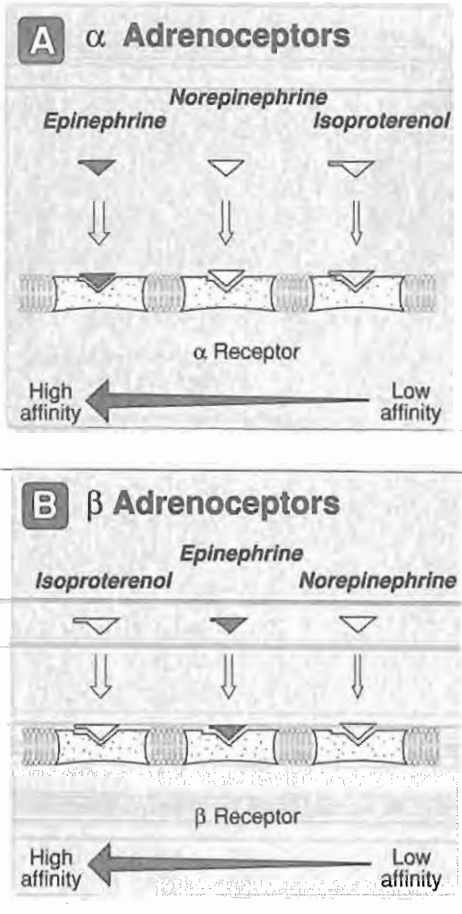


Figure 6.4
Types of adrenergic receptors.

a. α_1 receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α_1 receptors initiates a series of reactions through a G-protein activation of phospholipase C, resulting in the generation of IP_3 from phosphatidylinositol, causing the release of Ca^{++} from the endoplasmic reticulum into the cytosol[2] (Figure 6.5).

b. α_2 receptors: These receptors, located primarily on presynaptic nerve endings and on other cells, such as the β cell of the pancreas, control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released *norepinephrine* traverses the synaptic cleft and interacts with the α_1 receptor. A portion of the released *norepinephrine* "circles back" and reacts with the α_2 receptor on the neuronal membrane (see Figure 6.5). The stimulation of the α_2 receptor causes feedback inhibition of the ongoing release of *norepinephrine* from the stimulated adrenergic neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuromediator output when there is high sympathetic activity. In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and a fall in the levels of intracellular cAMP.

2. β receptors: β receptors exhibit a set of responses different from those of the α receptors. These are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and *norepinephrine* (see Figure 6.4). For β receptors, the rank order of potency is:

isoproterenol > *epinephrine* > *norepinephrine*

[2]See p. 70 for Infolink references to other books in this series.

The β adrenoceptors can be subdivided into two major groups, β_1 and β_2, based on their affinities for adrenergic agonists and antagonists although several others have been identified by gene cloning. β_1 Receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine*. Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating *epinephrine* released by the adrenal medulla. Binding of a neurotransmitter at the β_1 or β_2 receptor results in activation of adenylyl cyclase and therefore increased concentrations of cAMP within the cell.

3. **Distribution of receptors:** Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor. For example, tissues such as the vasculature to skeletal muscle have both α_1 and β_2 receptors, but the β_2 receptors predominate. Other tissues may have one type of receptor exclusively, with practically no significant numbers of other types of adrenergic receptors. For example, the heart contains predominantly β_1 receptors.

4. **Characteristic responses mediated by adrenoceptors:** It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, since many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of α_1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Conversely, stimulation of β_1 receptors characteristically causes cardiac stimulation, while β_2 produces vasodilation (in skeletal vascular beds), and bronchiolar relaxation.

5. **Desensitization of receptors:** Prolonged exposure to the catecholamines reduces the responsivity of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: (1) sequestration of the receptors so that they are unavailable for interaction with the ligand; (2) down-regulation, that is, a disappearance of the receptor either by destruction or decreased synthesis; and (3) inability to couple to G-protein because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase A or β adrenergic receptor kinase (βARK).

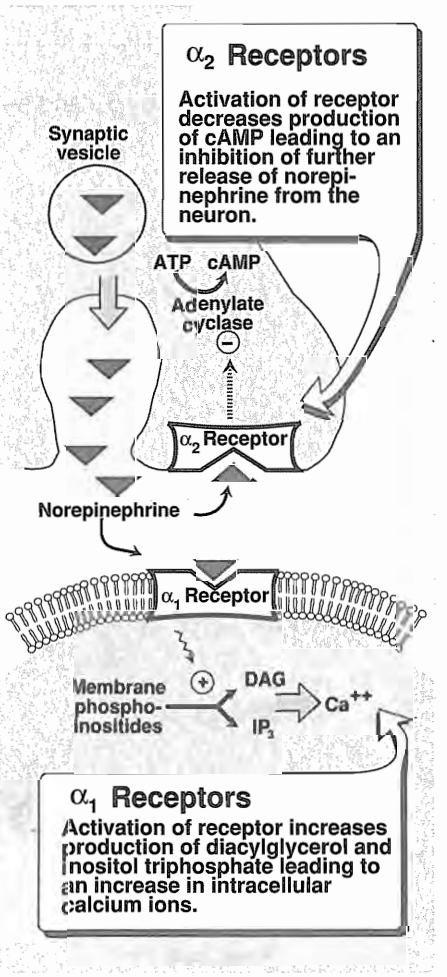


Figure 6.5
Second messengers mediate the effects of α receptors. DAG = diacylglcerol; IP_3 = inositol triphosphate.

III. CHARACTERISTICS OF ADRENERGIC AGONISTS

Most of the adrenergic drugs are derivatives of β-phenylethylamine (Figure 6.7). Substitutions on the benzene ring or on the ethylamine side chains produce a great variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are the number and location of OH substitutions on the benzene ring and the nature of the substituent on the amino nitrogen.

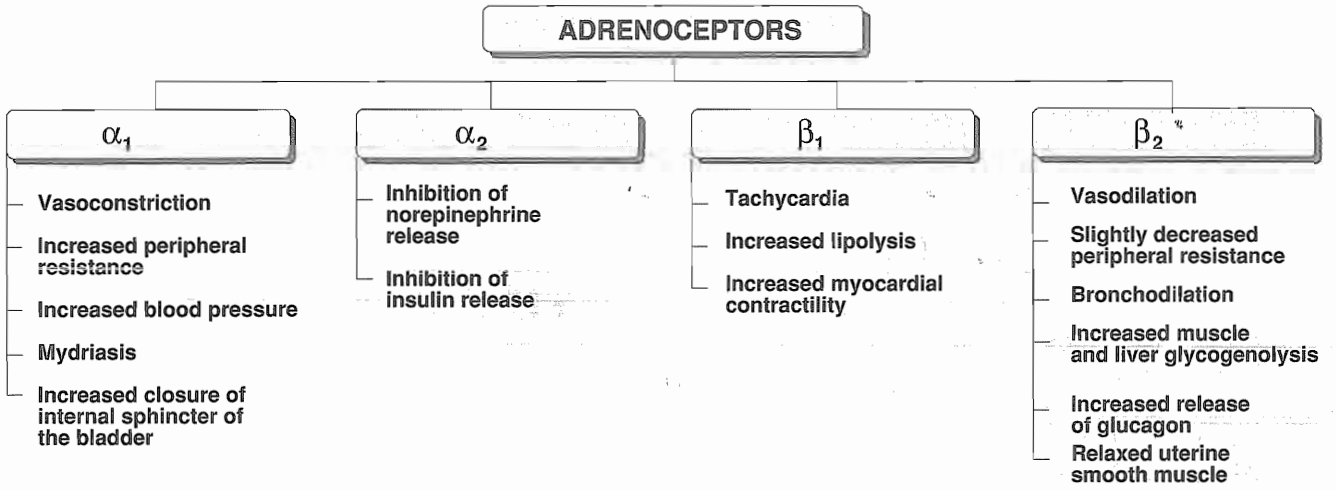


Figure 6.6
Major effects mediated by α– and β–adrenoceptors.

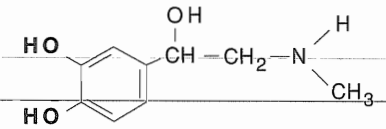
A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as, *epinephrine*, *norepinephrine*, *isoproterenol*, and *dopamine*) are called catecholamines. [Note: 1,2-dihydroxybenzene is catechol, Figure 6.7.] These compounds share the following properties:

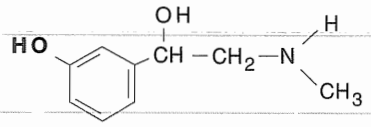
1. **High potency:** Drugs that are catechol derivatives (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in activating α or β receptors.

2. **Rapid inactivation:** Not only are the catecholamines metabolized by COMT postsynaptically and by MAO intraneuronally, but they are also metabolized in other tissues. For example, COMT is in the gut wall and MAO is in the liver and gut wall. Thus catecholamines have only a brief period of action when given parenterally, and are ineffective when administered orally because of inactivation.

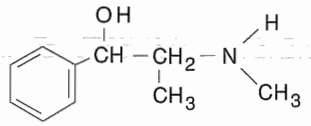
3. **Poor penetration into the CNS:** Catecholamines are polar and therefore do not readily penetrate into the CNS. Nevertheless, most of these drugs have some clinical effects (anxiety, tremor, headaches) that are attributable to action on the CNS.



Epinephrine



Phenylephrine



Ephedrine

B. Non-catecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, since they are not inactivated by COMT. These include *phenylephrine*, *ephedrine*, and *amphetamine*. *Phenylephrine*, an analog of *epinephrine*, has only a single OH at position 3 on the benzene ring, whereas *ephedrine* lacks hydroxyls on the ring but has a methyl substitution at the α-carbon. These are poor substrates for MAO and thus show a prolonged duration of action, since MAO is an important route of detoxification. Increased lipid solubility of many of the non-catecholamines permits greater access to the CNS. These compounds may act indirectly by causing the release of stored catecholamines.

C. Substitution on amine nitrogen

The nature and bulk of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist. For example, *epinephrine* with a $-CH_3$ substituent on the amine nitrogen is more potent at β receptors than *norepinephrine*, which has an unsubstituted amine. Similarly, *isoproterenol* with an isopropyl substituent $-CH(CH_3)_2$ on the amine nitrogen (see Figure 6.7), is a strong β agonist with little α activity (see Figure 6.4).

D. Mechanism of action of adrenergic agonists

1. **Direct-acting agonists:** These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone *epinephrine* from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, and *phenylephrine*.

2. **Indirect-acting agonists:** These agents, which include *amphetamine* and *tyramine*, are taken up into the presynaptic neuron and cause the release of *norepinephrine* from the cytoplasmic pools or vesicles of the adrenergic neuron (see Figure 6.8). As with neuronal stimulation, the *norepinephrine* then traverses the synapse and binds to the α or β receptors.

3. **Mixed-action agonists:** Some agonists, such as *ephedrine* and *metaraminol*, have the capacity both to directly stimulate adrenoceptors and to release *norepinephrine* from the adrenergic neuron (see Figure 6.8).

IV. DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors without interacting with the presynaptic neuron. The activated receptor initiates synthesis of second messengers and subsequent intracellular signals. As a group these agents are widely used clinically.

A. Epinephrine

Epinephrine [ep ee NEF rin] is one of five catecholamines—*epinephrine*, *norepinephrine*, *dopamine*, *dobutamine*, and *isoproterenol*—commonly used in therapy. The first three catecholamines occur naturally, the latter two are synthetic compounds (see Figure 6.7). *Epinephrine* is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of *norepinephrine*, into the blood stream. *Epinephrine* interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstrictor) are strongest.

first β → α

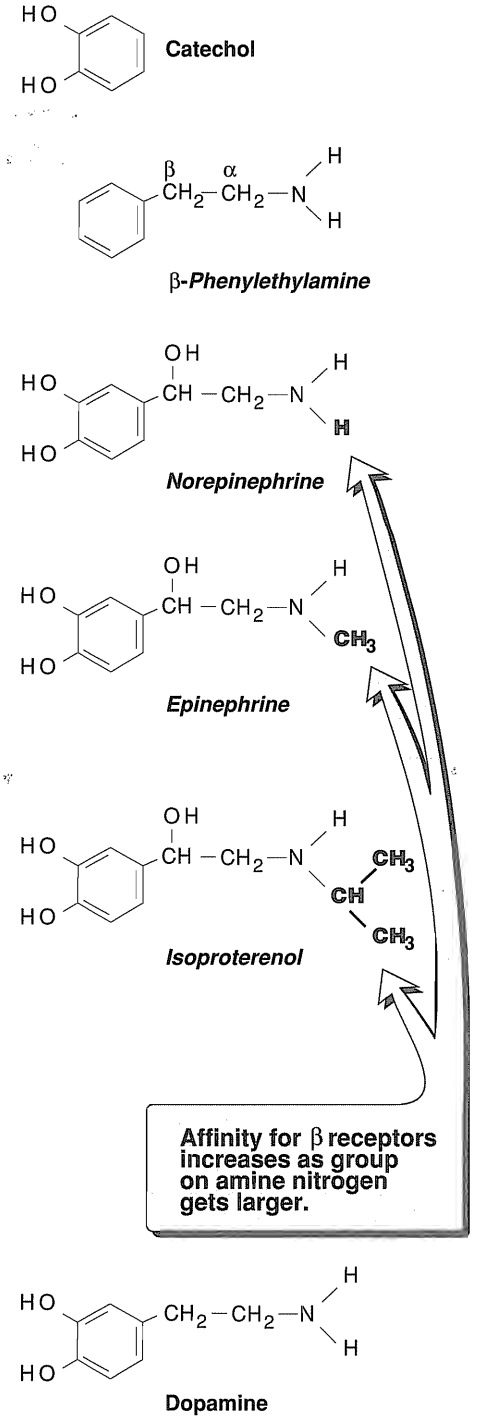


Figure 6.7
Structures of several important adrenergic agonists.

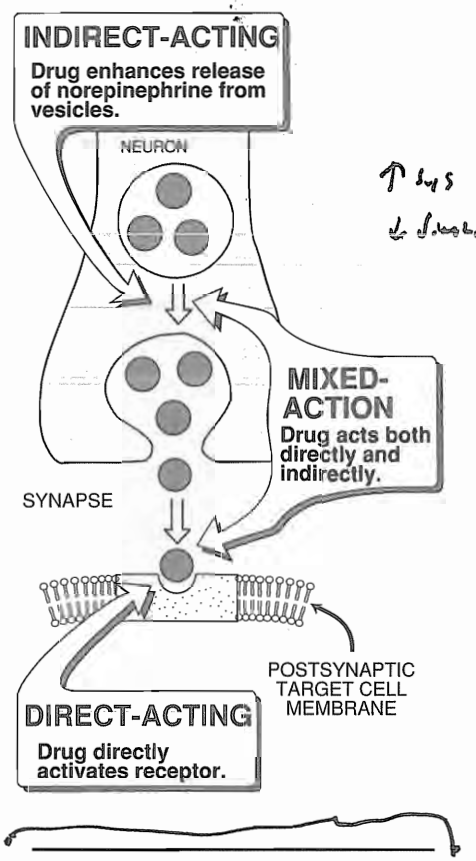


Figure 6.8
Sites of action of direct-, indirect- and mixed-acting adrenergic agonists.

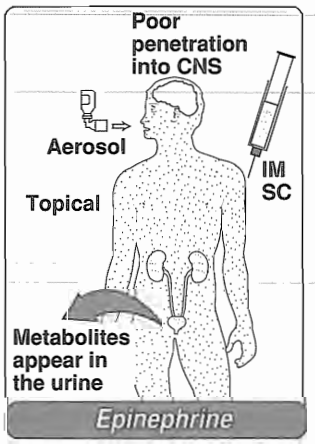
1. Actions:

a. Cardiovascular: The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotropic: β_1 action) and increases its rate of contraction (positive chronotropic: β_1 action). Cardiac output therefore increases. With these effects comes increased oxygen demands on the myocardium. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera (α effects) and dilates vessels going to the liver and skeletal muscle (β_2 effects). Renal blood flow is decreased. The cumulative effect, therefore, is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure (Figure 6.9) that can result in a reflex slowing of the heart.

b. Respiratory: *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). This action relieves all known allergic- or histamine-induced bronchoconstriction. In the case of anaphylactic shock, this can be life-saving. In individuals suffering from an acute asthmatic attack, *epinephrine* rapidly relieves the dyspnea (labored breathing) and increases the tidal volume (volume of gases inspired and expired).

c. Hyperglycemia: *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in liver (β_2 effect), increased release of glucagon (β_2 effect), and a decreased release of insulin (α_2 effect). These effects are mediated via the cyclic AMP mechanism.

d. Lipolysis: *Epinephrine* initiates lipolysis through its agonist activity on the β_1 receptors of adipose tissue, which upon stimulation, activate adenylyl cyclase to increase cyclic AMP levels. Cyclic AMP stimulates a hormone-sensitive lipase, which hydrolyzes triacylglycerols to free fatty acids and glycerol.[3]



2. Biotransformations: *Epinephrine*, like the other catecholamines, is metabolized by two enzymatic pathways: COMT, which has S-adenosylmethionine as a cofactor, and MAO (see Figure 6.3). The final metabolites found in the urine are metanephrine and vanillylmandelic acid. [Note: Urine also contains normetanephrine, a product of *norepinephrine* metabolism.]

3. Therapeutic uses

a. Bronchospasm: *Epinephrine* is the primary drug used in the emergency treatment of any condition of the respiratory tract where the presence of bronchoconstriction has resulted in diminished respiratory exchange. Thus, in treatment of acute asthma and anaphylactic shock, *epinephrine* is the drug of choice; within a few minutes after subcutaneous administration, greatly improved respiratory exchange is observed. Administration may be repeated after a few hours. However, selective β_2 agonists, such as *terbutaline*, are presently favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effect.

[3]See p. 70 for Infolink references to other books in this series.

b. Glaucoma: In ophthalmology, a 2% *epinephrine* solution may be used topically to reduce intraocular pressure in open-angle glaucoma. It reduces the production of aqueous humor by vasoconstriction of the ciliary body blood vessels.

c. Anaphylactic shock: *Epinephrine* is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.

d. In anesthetics: Local anesthetic solutions usually contain 1:100,000 parts *epinephrine* (p. 118). The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection, thereby allowing the local anesthetic to persist at the site before being absorbed into the circulation and metabolized. Very weak solutions of *epinephrine* (1:100,000) can also be used topically to vasoconstrict mucous membranes to control oozing of capillary blood.

4. Pharmacokinetics: *Epinephrine* has a rapid onset but brief duration of action. In emergency situations *epinephrine* is given intravenously for the most rapid onset of action; it may also be given subcutaneously, by endotracheal tube, by inhalation, or topically to the eye. Oral administration is ineffective, since *epinephrine* and the other catecholamines are inactivated by intestinal enzymes. Only metabolites are excreted in the urine.

5. Adverse effects:

a. CNS disturbances: *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor.

b. Hemorrhage: The drug may induce cerebral hemorrhage as a result of a marked elevation of blood pressure.

c. Cardiac arrhythmias: *Epinephrine* can trigger cardiac arrhythmias, particularly if the patient is receiving *digitalis* (see p. 157).

d. Pulmonary edema: *Epinephrine* can induce pulmonary edema.

6. Interactions

a. Hyperthyroidism: *Epinephrine* may have enhanced cardiovascular actions in patients with hyperthyroidism. If *epinephrine* is required in such an individual, the dose must be reduced. The mechanism appears to involve increased production of adrenergic receptors on the vasculature of the hyperthyroid individual leading to a hypersensitive response.

b. Cocaine: In the presence of *cocaine*, *epinephrine* produces exaggerated cardiovascular actions. This is due to the ability of *cocaine* to prevent re-uptake of catecholamines into the adrenergic neuron; thus, like *norepinephrine*, *epinephrine* remains at the receptor site for longer periods of time (see Figure 6.3).

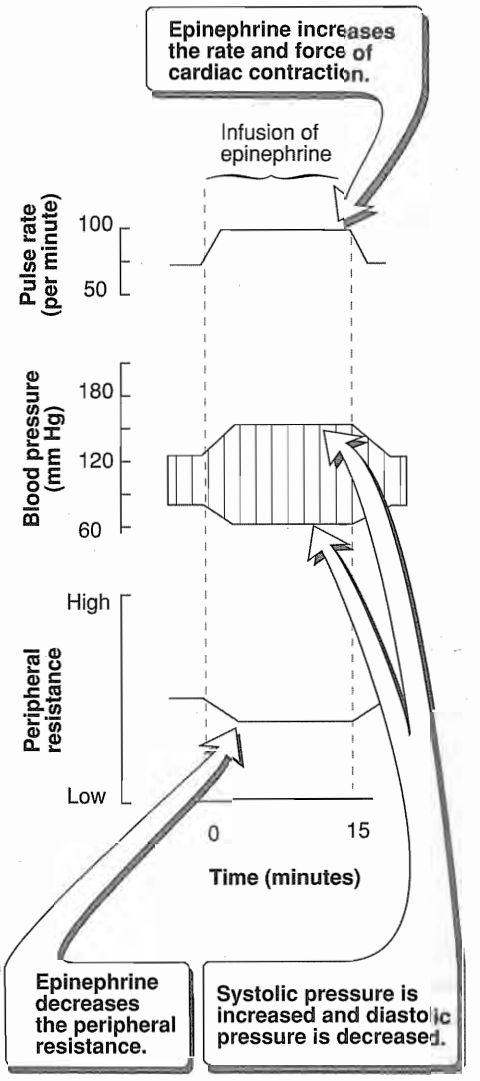


Figure 6.9
Cardiovascular effects of intravenous infusion of low doses of epinephrine.

B. Norepinephrine

Since *norepinephrine* [nor ep ee NEF rin] is the neuromediator of adrenergic nerves, it should theoretically stimulate all types of adrenergic receptors. In practice, when the drug is given in therapeutic doses to humans, the α-adrenergic receptor is most affected.

1. Cardiovascular Actions

a. Vasoconstriction: *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (an α_1-receptor effect). Both systolic and diastolic blood pressures increase (Figure 6.10).

b. Baroreceptor reflex: In isolated cardiac tissue *norepinephrine* stimulates cardiac contractility; however, in vivo, little if any cardiac stimulation is noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This bradycardia is sufficient to counteract the local actions of *norepinephrine* on the heart although the reflex compensation does not affect the positive inotropic effects of the drug (Figure 6.10).

c. Effect of atropine pretreatment: If *atropine* (which blocks the transmission of vagal effects, see p. 45) is given before *norepinephrine*, then *norepinephrine* stimulation of the heart is evident as tachycardia.

2. Therapeutic uses: *Norepinephrine* is used to treat shock because it increases vascular resistance and, therefore, increases blood pressure; however, *dopamine* (see p. 65) is better, because it does not reduce blood flow to the kidney as does *norepinephrine*. Other actions of *norepinephrine* are not considered clinically significant. It is never used for asthma. [Note: When *norepinephrine* is used as a drug, it is sometimes called *levarterenol* [leev are TER a nole].]

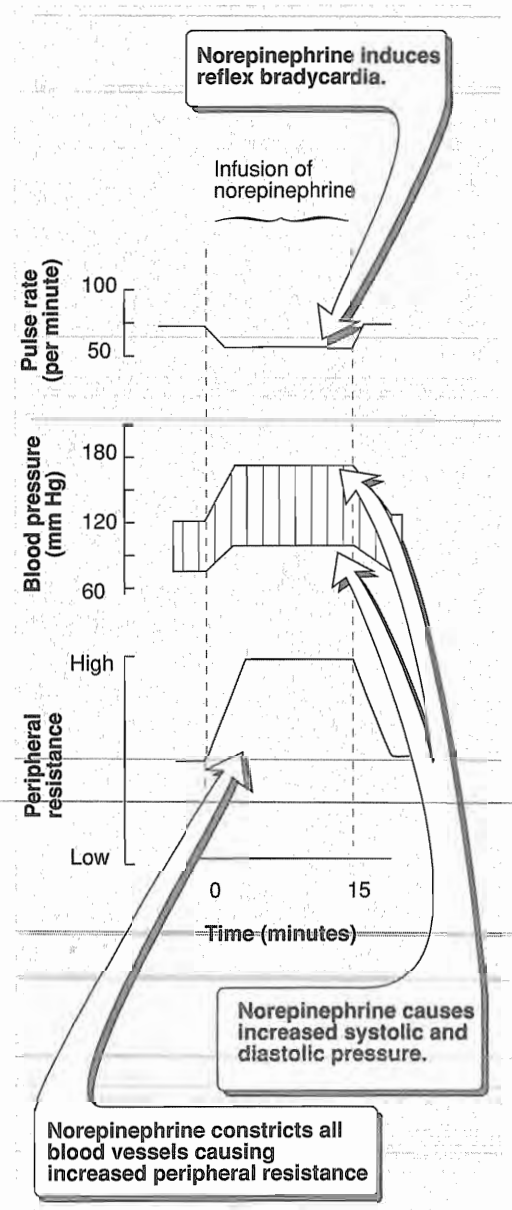


Figure 6.10
Cardiovascular effects of intravenous infusion of norepinephrine.

C. Isoproterenol

Isoproterenol [eye soe proe TER a nole] is a direct-acting synthetic catecholamine that predominantly stimulates both β_1 and β_2 adrenergic receptors. Its non-selectivity is one of its drawbacks. Its action on α receptors is insignificant. Its chemical structure is given in Figure 6.7.

1. Actions

a. Cardiovascular: *Isoproterenol* produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output (Figure 6.11). It is as active as *epinephrine* in this action and is therefore useful in the treatment of atrioventricular block or cardiac arrest. *Isoproterenol* also dilates the arterioles of skeletal muscle (β_2), resulting in a decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure (Figure 6.11).

b. Pulmonary: A profound and rapid bronchodilation is produced by the drug (β_2 action, Figure 6.12). *Isoproterenol* is as active as *epinephrine* and rapidly alleviates an acute attack of asthma, when taken by inhalation (which is the recommended route). This action lasts about one hour and may be repeated by subsequent doses.

c. Other effects: Other actions on β receptors, such as increases in blood sugar and increased lipolysis can be demonstrated, but are not clinically significant.

2. Therapeutic uses: *Isoproterenol* is now rarely used as a bronchodilator in asthma. It can be employed to stimulate the heart in emergency situations.

3. Pharmacokinetics: *Isoproterenol* can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as an inhaled aerosol. It is a marginal substrate for COMT and is stable to MAO action.

4. Adverse effects: *Isoproterenol's* adverse effects are similar to those of *epinephrine*.

D. Dopamine

Dopamine [DOE pa meen], the immediate metabolic precursor of *norepinephrine*, occurs naturally in the CNS in the basal ganglia where it functions as a neurotransmitter as well as in the adrenal medulla. *Dopamine* can activate α- and β-adrenergic receptors. For example, at higher doses it can cause vasoconstriction by activating α receptors, whereas at lower doses, it stimulates β_1 cardiac receptors. In addition, D_1 and D_2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilatation. D_2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with *norepinephrine* release.

1. Actions

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β_1 receptors of the heart, having both inotropic and chronotropic effects (Figure 6.12). At very high doses, *dopamine* activates α receptors on the vasculature, resulting in vasoconstriction.

b. Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thus increasing blood flow to the kidneys and other viscera (see Figure 6.12). These receptors are not affected by α- or β-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function. [Note: Similar *dopamine* receptors are found in the autonomic ganglia and in the CNS.]

2. Therapeutic uses

a. Shock: *Dopamine* is the drug of choice for shock and is given by continuous infusion. It raises the blood pressure by stimulating

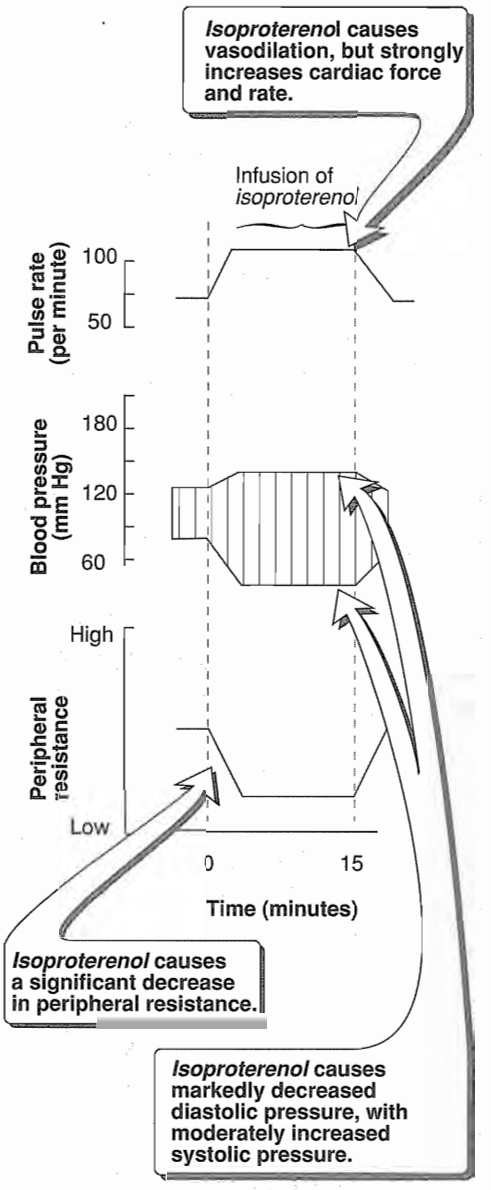


Figure 6.11
Cardiovascular effects of intravenous infusion of *isoproterenol*.

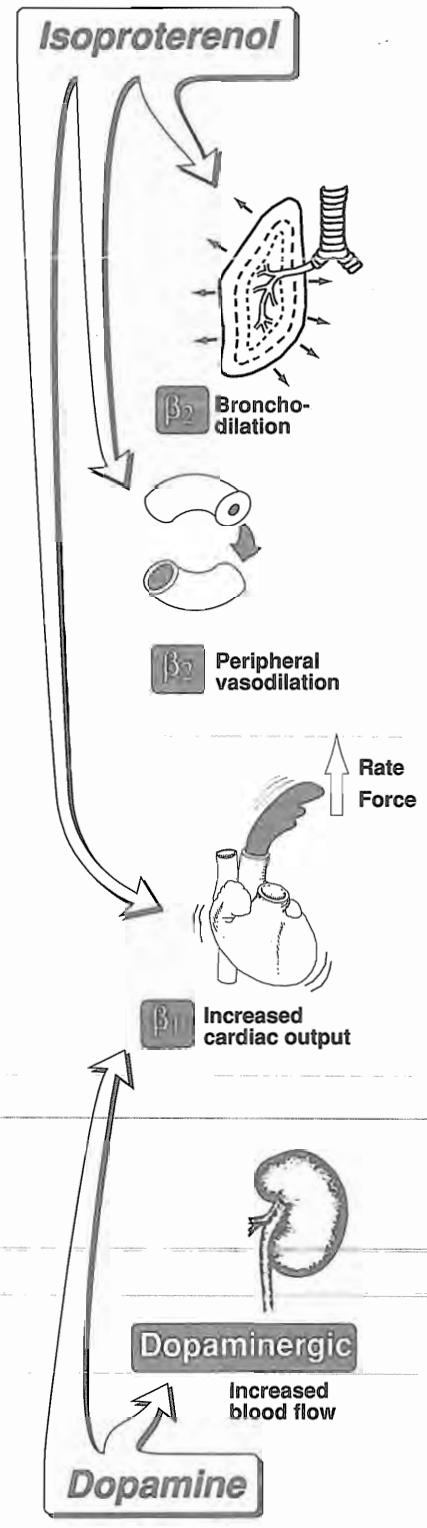


Figure 6.12
Clinically important actions of *isoproterenol* and *dopamine*.

the heart (β_1 action). In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. An increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis. In this regard, *dopamine* is far superior to *norepinephrine*, which diminishes the blood supply to the kidney and may cause kidney shutdown.

3. **Adverse effects:** An overdose of *dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized to homovanillic acid, and its adverse effects (nausea, hypertension, arrhythmias) are therefore short-lived.

E. Dobutamine — β_1

1. **Actions:** *Dobutamine* [doe BYOO ta meen] is a synthetic, direct-acting catecholamine that is a β_1-receptor agonist. It is available as a racemic mixture. One of the stereoisomers has a stimulatory activity. It increases cardiac rate and output with few vascular effects.

2. **Therapeutic uses:** *Dobutamine* is used to increase cardiac output in congestive heart failure (p. 161). The drug increases cardiac output with little change in the heart rate and does not significantly elevate oxygen demands of the myocardium—a major advantage over other sympathomimetic drugs.

3. **Adverse effects:** *Dobutamine* should be used with caution in atrial fibrillation, since the drug increases atrioventricular conduction. Other adverse effects are the same as those for *epinephrine*. Tolerance may develop on prolonged use.

F. Phenylephrine $\alpha_1 \rightarrow \alpha_2$

Phenylephrine [fen ill EF rin] is a direct-acting, synthetic adrenergic drug that binds primarily to α receptors and favors α_1 receptors over α_2 receptors. It is not a catechol derivative and therefore not a substrate for COMT. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. *Phenylephrine* acts as a nasal decongestant (p. 221), and produces prolonged vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the atrioventricular junction and atria). Large doses can cause hypertensive headache and cardiac irregularities.

G. Methoxamine

Methoxamine [meth OX a meen] is a direct-acting synthetic adrenergic drug that binds primarily to α receptors, with α_1 receptors favored over α_2 receptors. *Methoxamine* raises blood pressure by stimulating α_1 receptors in the arterioles, causing vasoconstriction. This causes an increase in total peripheral resistance. Because of its effects on the vagus, *methoxamine* is used clinically to relieve attacks of paroxysmal supraventricular tachycardia. It is also used to

overcome hypotension during surgery involving *halothane* anesthetics. In contrast to most other adrenergic drugs, *methoxamine* does not tend to trigger cardiac arrhythmias in the heart that is sensitized by these general anesthetics. Adverse effects include hypertensive headache and vomiting.

H. Clonidine

Clonidine [KLOE ni deen] is an α_2 agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS (see p. 189). It can be used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines. *Clonidine* acts centrally to produce inhibition of sympathetic vasomotor centers. Recently, an endogenous substance, agmantine, which appears to be the natural ligand at clonidine binding sites, has been identified.

I. Metaproterenol

Metaproterenol [met a proe TER a nole], although chemically similar to *isoproterenol*, is not a catecholamine and is resistant to methylation by COMT. It can be administered orally or by inhalation. The drug acts primarily at β_2 receptors, producing little effect on the heart. *Metaproterenol* produces dilation of the bronchioles and improves airway function. The drug is useful as a bronchodilator in the treatment of asthma and to reverse bronchospasm (Figure 6.13).

J. Terbutaline

Terbutaline [ter BYOO te leen] is a β_2 agonist with more selective properties than *metaproterenol* and a longer duration of action. *Terbutaline* can be administered either orally or subcutaneously. It is used as a bronchodilator and to reduce uterine contractions in premature labor.

K. Albuterol

Albuterol [al BYOO ter ole] is a selective β_2 agonist with properties similar to those of *terbutaline*. The drug is widely used as an inhalant to relieve bronchospasm.

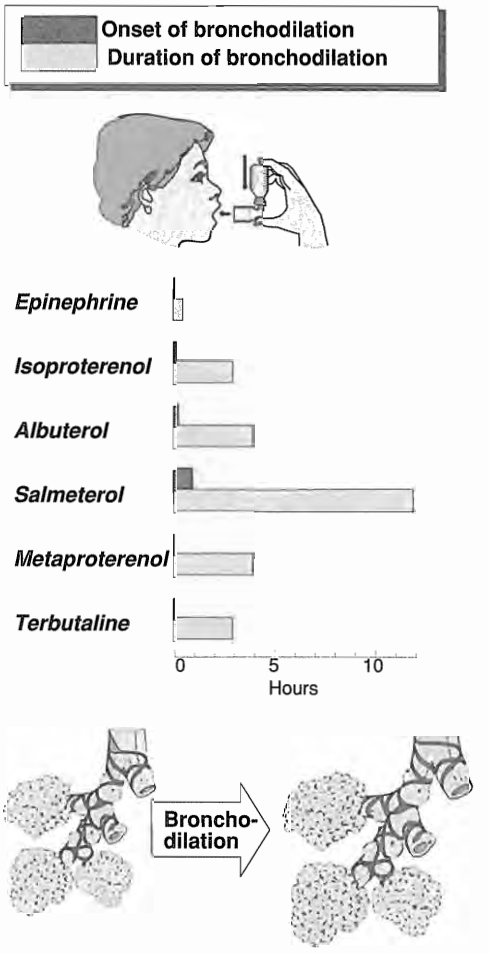


Figure 6.13
Onset and duration of bronchodilation effects of inhaled adrenergic agonists.

V. INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause *norepinephrine* release from presynaptic terminals (see Figure 6.8). They potentiate the effects of *norepinephrine* produced endogenously, but these agents do not directly affect postsynaptic receptors.

A. Amphetamine

Amphetamine's [am FET a meen] marked central stimulatory action is often mistaken by drug abusers as its only action. However, the drug can increase blood pressure significantly by α-agonist action on the vasculature as well as β- stimulatory effects on the heart. Its

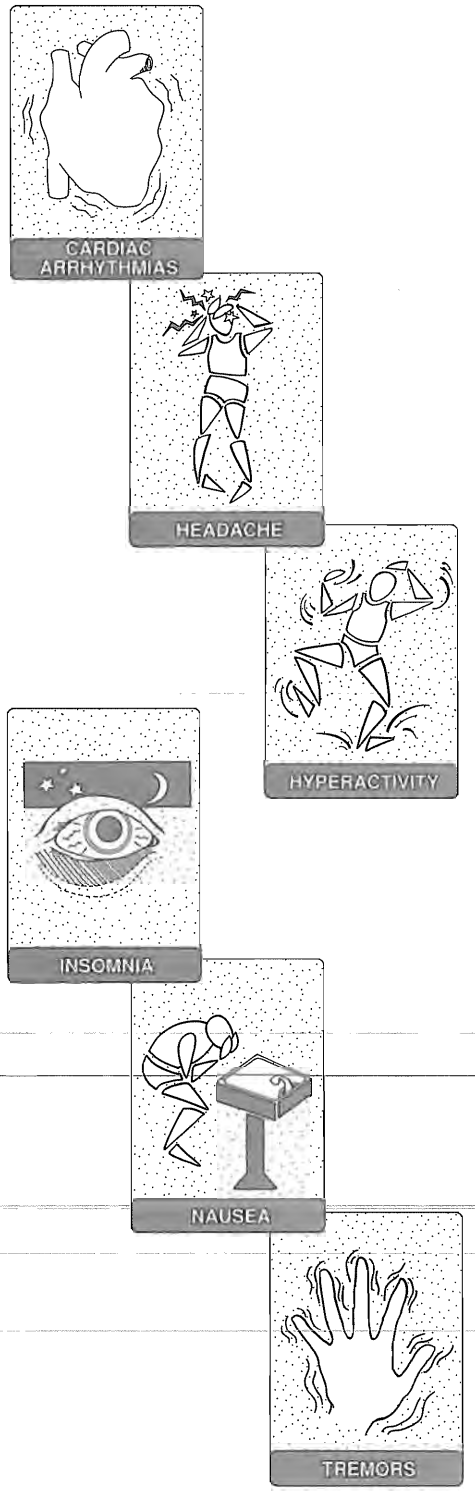


Figure 6.14
Some adverse effects observed with adrenergic agonists.

peripheral actions are mediated primarily through the cellular release of stored catecholamines; thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and uses of amphetamines are discussed under stimulants of the CNS (see p. 103).The CNS stimulant effects of *amphetamine* and its derivatives have led to their use in the therapy of depression, hyperactivity in children, narcolepsy, and appetite control. Its use in pregnancy should be avoided because of adverse effects on the development of the fetus.

B. Tyramine

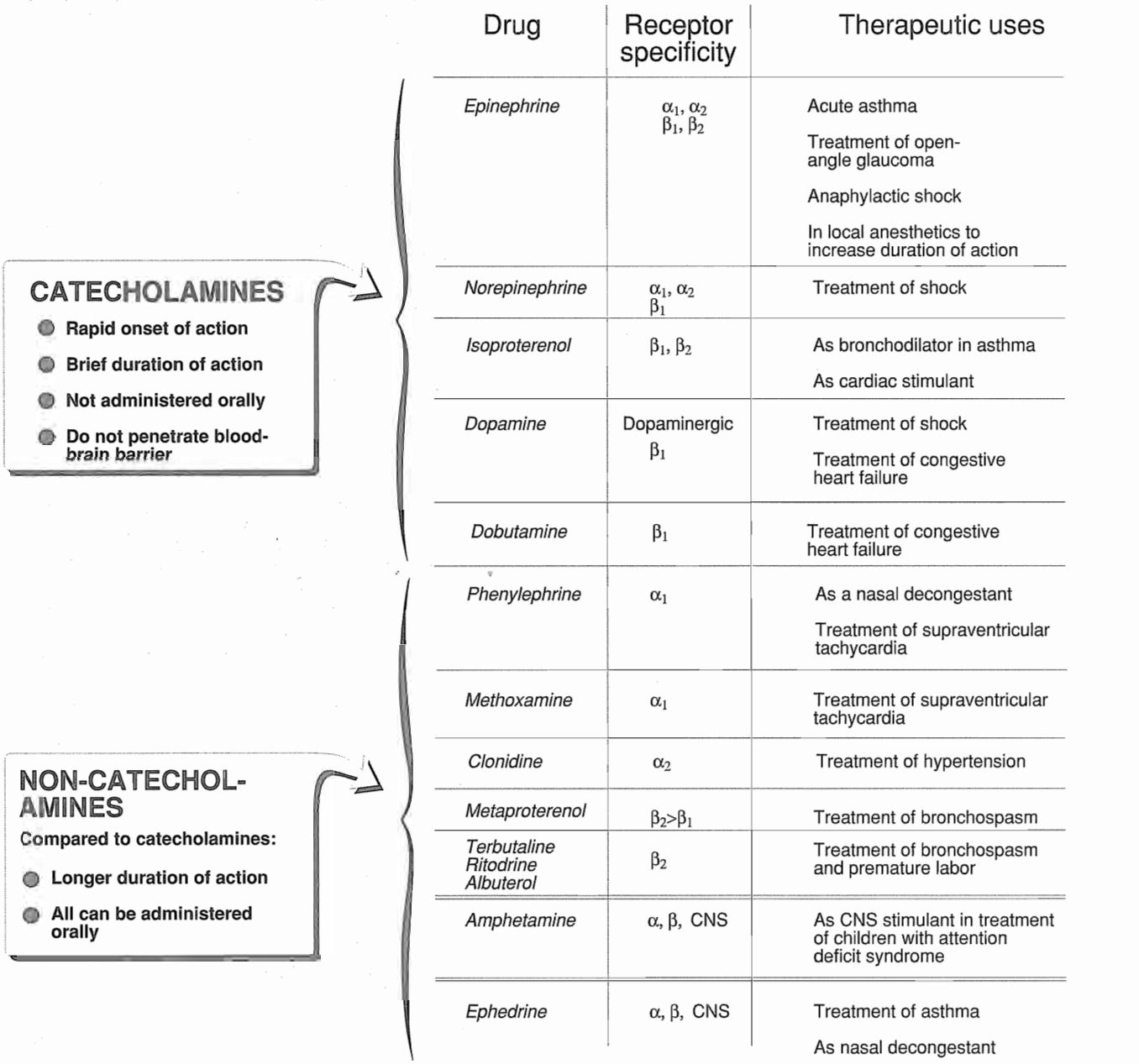
Tyramine [teye ra meen] is not a clinically useful drug, but it is found in fermented foods, such as ripe cheese and Chianti wine (see MAO inhibitors, p. 123). It is a normal by-product of tyrosine metabolism. Normally, it is oxidized by MAO, but if the patient is taking MAO inhibitors, it can precipitate serious vasopressor episodes. Like *amphetamine*, *tyramine* can enter the nerve terminal and displace stored *norepinephrine*. The released catecholamine acts on adrenoceptors.

VI. MIXED-ACTION ADRENERGIC AGONISTS

Mixed-action drugs induce the release of *norepinephrine* from presynaptic terminals and activate adrenergic receptors on the postsynaptic membrane (see Figure 6.8).

A. Ephedrine

Ephedrine [e FED rin], a plant alkaloid, is now made synthetically. The drug is a mixed-action adrenergic agent. It not only releases stored *norepinephrine* from nerve endings (Figure 6.8) but also directly stimulates both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent. *Ephedrine* is not a catechol and is a poor substrate for COMT and MAO; thus, the drug has a long duration of action. *Ephedrine* has excellent absorption orally and penetrates into the central nervous system. It is eliminated unchanged in the urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. *Ephedrine* produces bronchodilation, but it is less potent than *epinephrine* or *isoproterenol* in this regard and produces its action more slowly. It is therefore sometimes used prophylactically in chronic treatment of asthma to prevent attacks, rather than to treat the acute attack. *Ephedrine* enhances contractility and improves motor function in myasthenia gravis, particularly when used in conjunction with anticholinesterases (see p. 43). *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. *Ephedrine* has been used to treat asthma, as a nasal decongestant (due to its local vasoconstrictor action), and to raise blood pressure. [Note: the clinical use of *ephedrine* is declining due to the availability of better, more potent agents which cause fewer adverse effects.]



Drug	Receptor specificity	Therapeutic uses
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Treatment of open-angle glaucoma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As bronchodilator in asthma As cardiac stimulant
Dopamine	Dopaminergic β_1	Treatment of shock Treatment of congestive heart failure
Dobutamine	β_1	Treatment of congestive heart failure
Phenylephrine	α_1	As a nasal decongestant Treatment of supraventricular tachycardia
Methoxamine	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Metaproterenol	$\beta_2 > \beta_1$	Treatment of bronchospasm
Terbutaline *Ritodrine* *Albuterol*	β_2	Treatment of bronchospasm and premature labor
Amphetamine	α, β, CNS	As CNS stimulant in treatment of children with attention deficit syndrome
Ephedrine	α, β, CNS	Treatment of asthma As nasal decongestant

Figure 6.15
Summary of the adrenergic agonists.

B. Metaraminol

Metaraminol [met a RAM i nole] is a mixed-action adrenergic drug with actions similar to *norepinephrine*. This agent has been used in the treatment of shock (when an infusion of *norepinephrine* or *dopamine* is not possible) and to treat acute hypotension. It is given parenterally as a single injection. It enhances cardiac activity and produces mild vasoconstriction.

The important characteristics of the adrenergic agonists are summarized in Figures 6.14 and 6.15.

Choose the ONE best answer.

6.1 Diastolic pressure is increased after the administration of which one of the following drugs?

A. Norepinephrine
B. Epinephrine
C. Isoproterenol
D. Albuterol
E. Terbutaline

Correct answer = A. Norepinephrine produces intense vasoconstriction and thereby increases peripheral resistance, so that both systolic and diastolic blood pressures increase. Epinephrine increases cardiac output, constricts arterioles in the skin and viscera (α effects), and dilates vessels going to skeletal muscle (β_2 effects); the overall result is an increase in systolic pressure. Isoproterenol is a β-specific agonist that increases cardiac output and decreases peripheral resistance; this causes a slight increase in systolic blood pressure and a significant decrease in diastolic blood pressure. Albuterol and terbutaline are vasodilators that act primarily at β_2 receptors.

6.2 All of the following statements are true EXCEPT:

A. Among the physiologic responses caused by α-receptor stimulation are vasoconstriction, mydriasis, and decreased gastrointestinal motility.
B. Among the physiologic responses caused by β-receptor stimulation are vasodilation, cardiac stimulation, and bronchial relaxation.
C. Norepinephrine has a stronger affinity for α receptors compared to β receptors.
D. Administration of atropine prior to norepinephrine leads to an increase in heart rate after norepinephrine administration.
E. Dobutamine is a potent vasoconstrictor.

Correct choice = E. Dobutamine acts primarily at β_2 receptors and has little effect on vascular resistance.

6.3 Dopamine causes all but which one of the following actions?

A. Increases cardiac output
B. Dilates renal vasculature
C. Dilates bronchi
D. Increases blood pressure
E. Increases production of urine

Correct choice = C. Dopamine has little effect of the β_2 receptors of the lung.

6.4 All of the following statements concerning phenylephrine are true EXCEPT:

A. It is an α agonist that causes vasoconstriction.
B. It is a synthetic, direct-acting agonist.
C. It is used to prevent bronchospasm.
D. It causes mydriasis when introduced into the eye.
E. It is often found in over-the-counter nasal decongestants.

Correct choice = C. Phenylephrine is a synthetic, direct-acting α agonist. It does not affect alveolar smooth muscle, which contains primarily β_2 receptors.

6.5 A 58-year-old female has undergone surgery for a necrotic bowel. Despite having been treated with antibiotics, on postoperative day 5, she develops symptoms (fever, hypotension, tachycardia, declining urine output, and confusion) consistent with septic shock. To manage her care, what hemodynamic support would be helpful?

A. Fluid administration
B. Dopamine infusion
C. Antibiotic administration
D. Fluids and Dopamine

Correct answer = D. It is important to increase the cardiac output to improve oxygen delivery and thus minimize anaerobic metabolism and improve CNS and renal perfusion. Since this patient apparently does not have a heart condition, such as congestive heart failure, she could benefit from fluid therapy. An inotropic agent, such as dopamine, would lead to an increased cardiac output and dilation of the renal vasculature. [Note: At high doses, however, it may constrict the renal beds due to interaction on α receptors.] Antibiotic administration is also important but will not improve the patient's hemodynamics.

[1]See p. 267 in **Biochemistry** (2nd ed.) for a discussion of the synthesis DOPA from tyrosine.

[2]See p. 267 in **Biochemistry** (2nd ed.) for a discussion of the synthesis and actions of IP_3.

[3]See p. 267 in **Biochemistry** (2nd ed.) for a discussion of hormone-sensitive lipase.

Adrenergic Antagonists

7

I. OVERVIEW

The adrenergic antagonists (also called blockers) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinity for α or β receptors in the peripheral nervous system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system and will be considered in that section (see p. 127.] The receptor-blocking drugs discussed in this chapter are summarized in Figure 7.1.

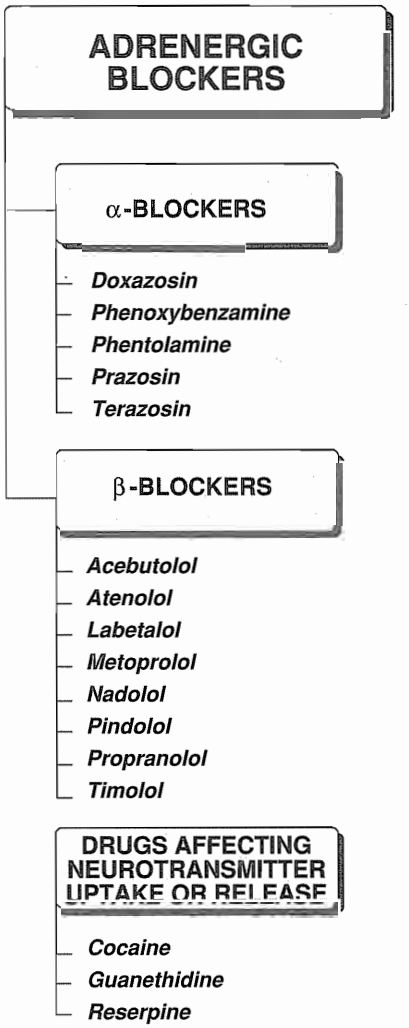


Figure 7.1
Summary of blocking agents and drugs affecting neurotransmitter uptake or release.

II. α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. Since normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. [Note: β receptors, including β_1 adrenoceptors on the heart, are not affected by α blockade.] *Phenoxybenzamine* and *phentolamine* have limited clinical applications.

A. Phenoxybenzamine

Phenoxybenzamine [fen ox ee BEN za meen], a drug related to the nitrogen mustards, is non-selective, linking covalently to both α_1-postsynaptic and α_2-presynaptic receptors (Figure 7.2). The block is irreversible and noncompetitive; the only mechanism the body has to overcome the block is to synthesize new adrenoceptors, which requires a day or more. Therefore, the actions of *phenoxybenzamine* last about 24 hours after a single administration. After the drug is injected, a delay of a few hours occurs before a blockade develops, since the molecule must undergo biotransformation to the active form.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

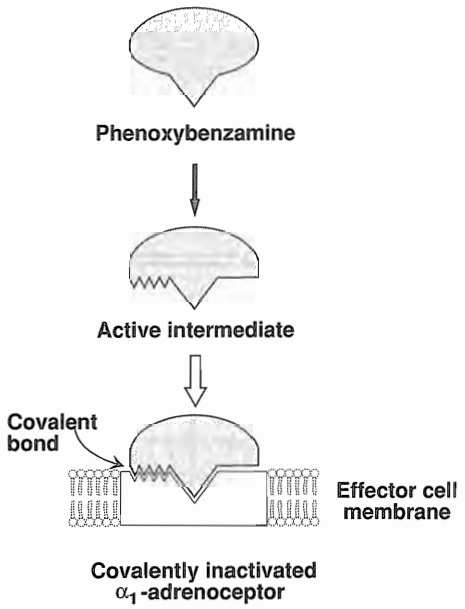


Figure 7.2
Covalent inactivation of α_1 adrenoceptor by phenoxybenzamine.

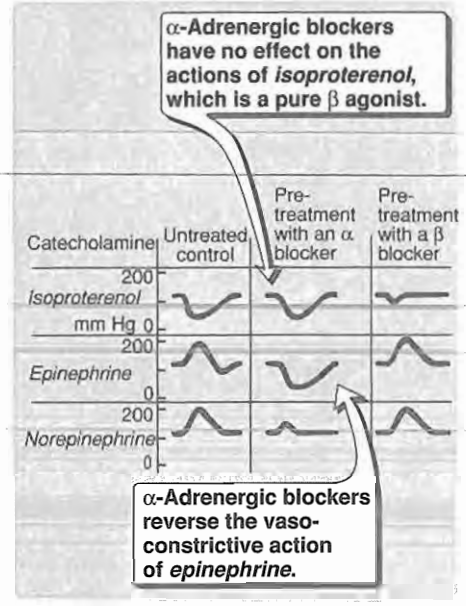


Figure 7.3
Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.

1. Actions:

a. Cardiovascular effects: By blocking α receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic α_2 receptors in the heart can contribute to an increased cardiac output. Thus the drug has been unsuccessful in maintaining lowered blood pressure in hypertension and has been discontinued for this purpose.

b. Epinephrine reversal: All α-adrenergic blockers reverse the α-agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of β-receptors is not blocked. Therefore, the systemic blood pressure decreases in response to *epinephrine* given in the presence of *phenoxybenzamine* (Figure 7.3). [Note: The actions of *norepinephrine* are not reversed but diminished, since *norepinephrine* lacks significant β-agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist (Figure 7.3).

2. Therapeutic uses: *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with *phenoxybenzamine* to preclude hypertensive crisis that can result from manipulation of the tissue. This drug also finds use in the chronic management of these tumors, particularly when the catecholamine-secreting cells are diffuse and therefore inoperable. *Phenoxybenzamine* or *phentolamine* are sometimes effective in treating Raynaud's disease. Autonomic hyperreflexia which predisposes paraplegics to strokes can be managed with *phenoxybenzamine*.

3. Adverse effects: *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, and nausea and vomiting. It can inhibit ejaculation. The drug also may induce tachycardia, mediated by the baroreceptor reflex and is contraindicated in patients with decreased coronary perfusion.

B. Phentolamine

In contrast to *phenoxybenzamine*, *phentolamine* [fen TOLE a meen] produces a competitive block of α_1 and α_2 receptors. The drug's action lasts for approximately 4 hours after a single administration. Like *phenoxybenzamine*, it produces postural hypotension and causes *epinephrine* reversal. *Phentolamine* had been used in the diagnosis of pheochromocytoma and in other clinical situations associated with excess release of catecholamines. *Phentolamine*-induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the α_2 receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain and is contraindicated in patients with decreased coronary perfusion.

C. Prazosin, terazosin and doxazosin

Prazosin [PRAY zoe sin], *terazosin* [ter AY zoe sin] and *doxazosin* [dox AY zoe sin] are selective competitive blockers of the α_1 receptor. In contrast to *phenoxybenzamine* and *phentolamine*, these drugs are useful in the treatment of hypertension. Metabolism leads to inactive products that are excreted in the urine, except for those of *doxazosin* which appear in the feces. *Doxazosin* is longest acting.

1. **Cardiovascular effects:** *Prazosin* and *terazosin* decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

2. **Therapeutic uses:** Individuals with elevated blood pressure who have been treated with *prazosin* or *terazosin* do not become tolerant to its action (see p. 189). However, the first dose of these drugs produces an exaggerated hypotensive response that can result in syncope (fainting). This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one third or one fourth of the normal dose, and by giving the drug at bed time. The α_1 antagonists have been used as an alternative to surgery in patients with symptomatic benign prostatic hypertrophy. Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. [Note: *Finasteride*, which inhibits dihydrotestosterone synthesis, has been approved for treatment of benign prostatic hypertrophy, but its effects are not evident for several weeks.]

3. **Adverse effects:** *Prazosin* and *terazosin* may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). An additive antihypertensive effect occurs when *prazosin* is given with either a diuretic or a β-blocker, thereby necessitating a reduction in its dose. Due to a tendency to retain sodium and fluid, *prazosin* is frequently used along with a diuretic. Male sexual function is not as severely affected by these drugs as it is by *phenoxybenzamine* and *phentolamine*. Figure 7.4 summarizes some adverse effects observed with α-blockers.

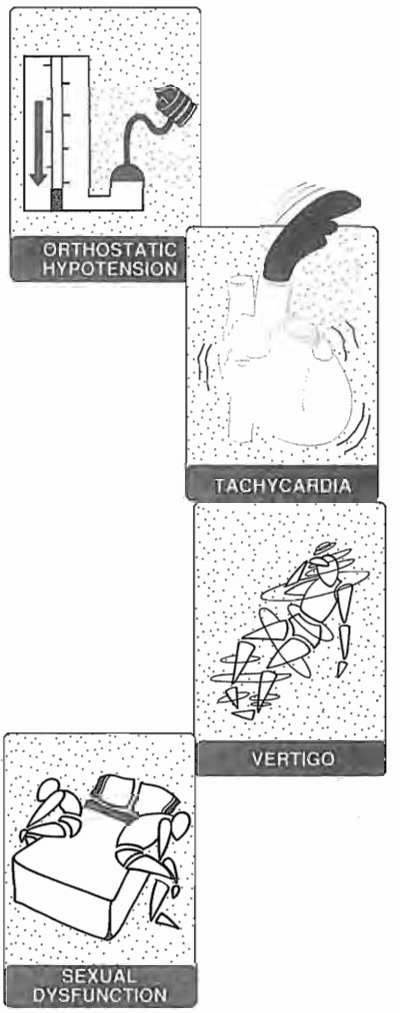


Figure 7.4
Some adverse effects common observed with α blockers.

III. β-ADRENERGIC BLOCKING AGENTS

All the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β_1 and β_2 receptors, whereas cardioselective β-antagonists primarily block β_1 receptors. These drugs also differ in intrinsic sympathomimetic activity, in central nervous system (CNS) effects, and in pharmacokinetics (Figure 7.5). Although all β-blockers lower blood pressure in hypertension, they do not induce postural hypotension because the α-adrenoceptors remain functional; therefore, normal sympathetic control of the vasculature is maintained. β-blockers are also effective in treating angina, cardiac arrhythmias,

myocardial infarction, and glaucoma, as well as serving in the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol", except for *labetalol*, which has a component of α_1-blocking actions.]

A. Propranolol: a nonselective β-antagonist

Propranolol [proe PRAN oh lole] is the prototype β-adrenergic antagonist and blocks both β_1 and β_2 receptors. Sustained release preparations for once-a-day dosing are available.

1. Actions

a. Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 7.6). It directly depresses sino-auricular and atrioventricular activity. The resulting bradycardia usually limits the dose of the drug. Cardiac output, work, and oxygen consumption are decreased by blockade of β_1 receptors; these effects are useful in the treatment of angina (see p. 176). The β-blockers are effective in attenuating supraventricular cardiac arrhythmias but are generally not effective against ventricular arrhythmias (except those induced by exercise).

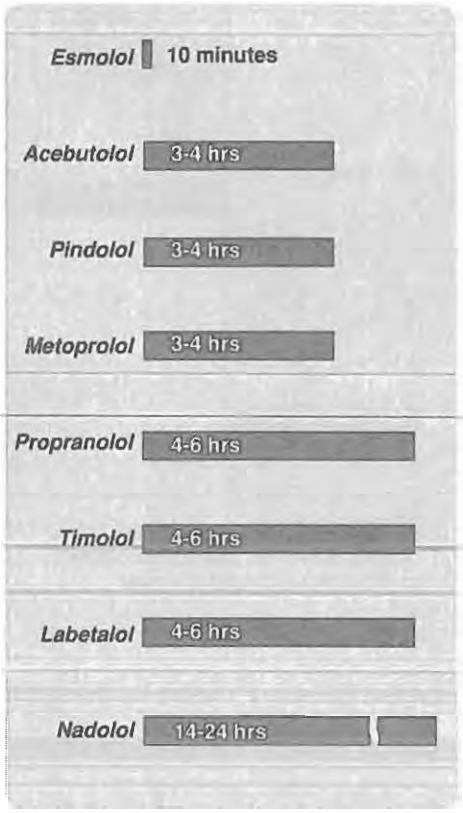


Figure 7.5
Elimination half-lives for some β blockers.

b. Peripheral vasoconstriction: Blockade of β receptors prevents β_2-mediated vasodilation (see Figure 7.6). The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction, which is reflected in reduced blood flow to the periphery. On balance, there is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, since the α_1-adrenergic receptors that control vascular resistance are unaffected.

c. Bronchoconstriction: Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (see Figure 7.6). This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease or asthma. β-Blockers are thus contraindicted in patients with asthma.

d. Increased Na^+ retention: Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume (see Figure 7.6). In some cases this compensatory response tends to elevate the blood pressure. For these patients, β-blockers are often combined with a diuretic to prevent Na^+ retention.

e. Disturbances in glucose metabolism: β blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if an *insulin*-dependent diabetic is to be given *propranolol*, very careful monitoring of blood glucose is essential, since pronounced hypoglycemia may occur after *insulin* injection. β-Blockers also attenuate the normal physiologic response to hypoglycemia.

f. Blocks action of isoproterenol: All β-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* on the cardiovascular system. Thus, in the presence of a β-blocker, *isoproterenol* does not produce either the typical reductions in mean arterial pressure and diastolic pressure, nor cardiac stimulation (see Figure 7.3). [Note: In the presence of a β-blocker, *epinephrine* no longer lowers diastolic blood pressure nor stimulates the heart, but its vasoconstrictive action (mediated by α-receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are primarily mediated by α receptors and are, therefore, unaffected.]

2. Therapeutic effects

a. Hypertension: *Propranolol* lowers blood pressure in hypertension by decreasing cardiac output (see p. 176).

b. Glaucoma: *Propranolol* and other β-blockers, particularly *timolol* (see p. 76), are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Many patients with glaucoma have been maintained with these drugs for years. They neither affect the ability of the eye to focus for near vision, nor change pupil size, as do the cholinergic drugs. However, in an acute attack of glaucoma, *pilocarpine* (see p. 41) is still the drug of choice.The β-blockers are only used to treat this disease chronically.

c. Migraine: *Propranolol* is also effective in reducing migraine episodes (see p. 427). The value of the β-blockers is in the treatment of chronic migraine in which the drug decreases the incidence and severity of the attacks. The mechanism may depend on the blockade of catecholamine-induced vasodilation in the brain vasculature. [Note: During an attack, the usual therapy with *sumatripan* (see p. 427) or other drugs is used.]

d. Hyperthyroidism: *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

e. Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and therefore is effective in reducing the chest pain on exertion that is common in angina (see p. 176). *Propranolol* is therefore useful in the chronic management of stable angina (not for acute treatment). Tolerance to moderate exercise is increased and this is noticeable by improvement in the electrocardiogram. However, treatment with *propranolol* does not allow strenuous physical exercise, such as tennis.

f. Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a

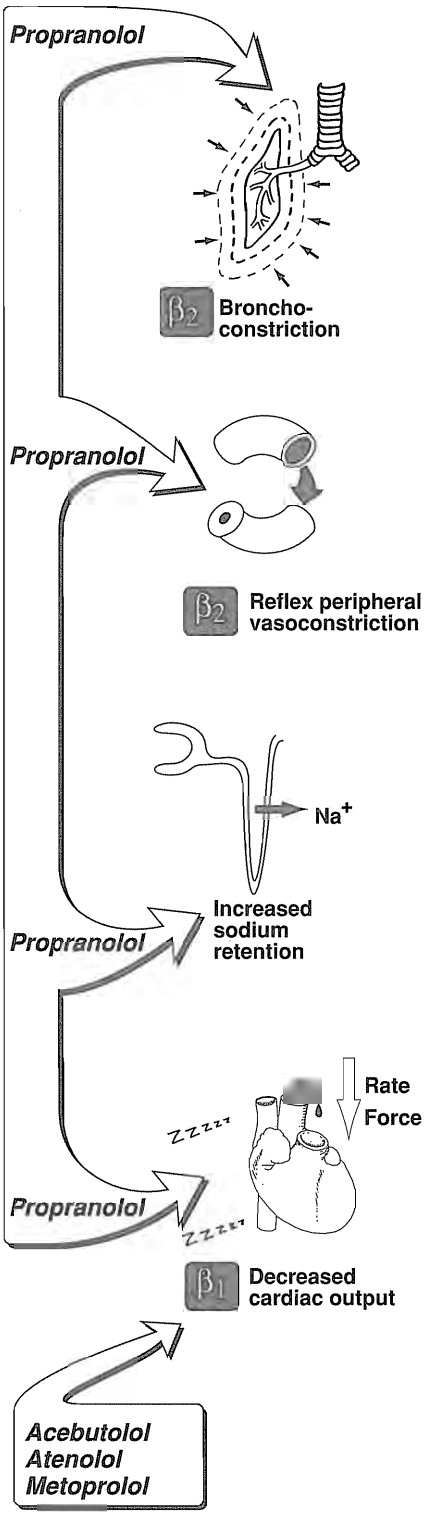


Figure 7.6
Actions of *propranolol* and other β_1 blockers.

myocardial infarction reduces infarct size and hastens recovery. The mechanism for these effects may be blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction (see p. 171).

3. Adverse effects:

a. Bronchoconstriction: *Propranolol* has a serious and potentially lethal side effect when administered to an asthmatic (Figure 7.7). An immediate contraction of the bronchiolar smooth muscle prevents air from entering the lungs. Deaths by asphyxiation have been reported for asthmatics who were inadvertently administered the drug. Therefore, *propranolol* must never be used in treating any individual with obstructive pulmonary disease.

Figure 7.7
Adverse effects commonly observed in individuals treated with *propranolol*.

b. Arrhythmias: Treatment with the β-blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually for 1 week. Long-term treatment with a β-antagonist leads to up-regulation of the β-receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

c. Sexual impairment: Since sexual function in the male occurs through α-adrenergic activation, β-blockers do not affect normal ejaculation nor the internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β-receptor blockade.

d. Disturbances in metabolism: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. [Note: Cardioselective β-blockers are preferred in treating *insulin*-dependent asthmatics. (see below).]

e. Drug interactions: Drugs that interfere with the metabolism of *propranolol*, such as *cimetidine* (see p. 236), *furosemide* (see p. 227), and *chlorpromazine* (see p. 127), may potentiate its antihypertensive effects. Conversely, those that stimulate its metabolism, such as barbiturates (see p. 94), *phenytoin* (see p. 146) and *rifampin* (see p. 333), can mitigate its effects.

B. Timolol and nadolol: nonselective β-antagonists

Timolol [TIM o lole] and *nadolol* [NAH doh lole] also block β_1 and β_2 adrenoceptors and are more potent than *propranolol*. *Nadolol* has a very long duration of action (see Figure 7.5). *Timolol* reduces the production of aqueous humor in the eye and is used topically in the treatment of chronic open-angle glaucoma, and occasionally for systemic treatment of hypertension.

C. Acebutolol, atenolol, metoprolol and esmolol: selective β1 antagonists

Drugs that preferentially block the β_1 receptors have been developed to eliminate the unwanted bronchoconstrictor effect (β_2) of *propranolol* seen among asthmatic patients. Cardioselective β-blockers, such as *acebutolol* [a se BYOO toe lole], *atenolol* [a TEN oh lole], and *metoprolol* [me TOE proe lole], antagonize β_1 receptors at doses 50 to 100 times less than those required to block β_2 receptors. This cardioselectivity is thus most pronounced at low doses and is lost at high drug doses. [Note: *Acebutolol* has some intrinsic agonist activity.]

1. **Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (see Figure 7.6). *Esmolol* [EZ moe lole] has a very short lifetime (see Figure 7.5) due to metabolism of an ester linkage. It is only given intravenously if required during surgery or diagnostic procedures (for example, cystoscopy). In contrast to *propranolol*, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthmatics treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised.

2. **Therapeutic use in hypertension:** The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function. Since these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities, a common side effect of β-blocker therapy, is less frequent. Cardioselective β-blockers are useful in diabetic hypertensive patients who are receiving *insulin* or oral hypoglycemic agents.

D. Pindolol and acebutolol: antagonists with partial agonist activity

1. **Actions:**

   a. **Cardiovascular:** *Acebutolol* and *pindolol* [PIN doe lole] are not pure blockers; instead they have the ability to weakly stimulate both β_1 and β_2 receptors (Figure 7.8) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β-receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, *epinephrine* and *norepinephrine*. The result of these opposing actions is a much diminished effect on cardiac rate and cardiac output, compared to β-blockers without ISA.

   b. **Decreased metabolic effects:** Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism seen with other β-blockers.

2. **Therapeutic use in hypertension:** β-blockers with ISA are effective in hypertensive patients with moderate bradycardia, since a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with *acebutolol* and *pindolol* than it is with *propranolol,* making them valuable in the treatment of diabetics.

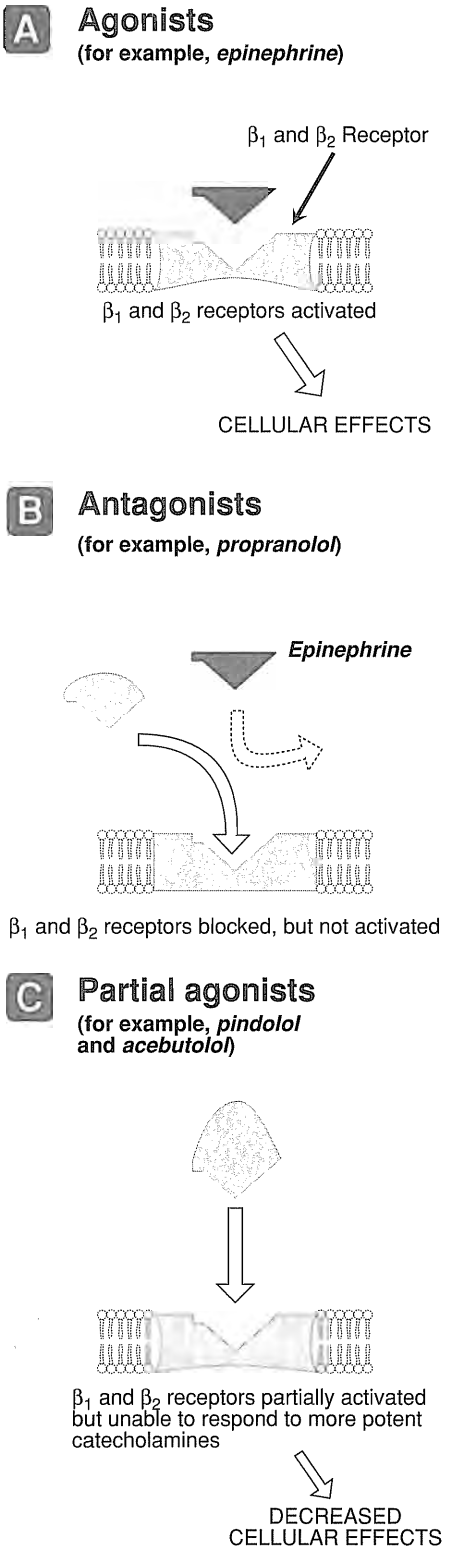


Figure 7.8
Comparison of agonists, antagonists, and partial agonists of β adrenoceptors.

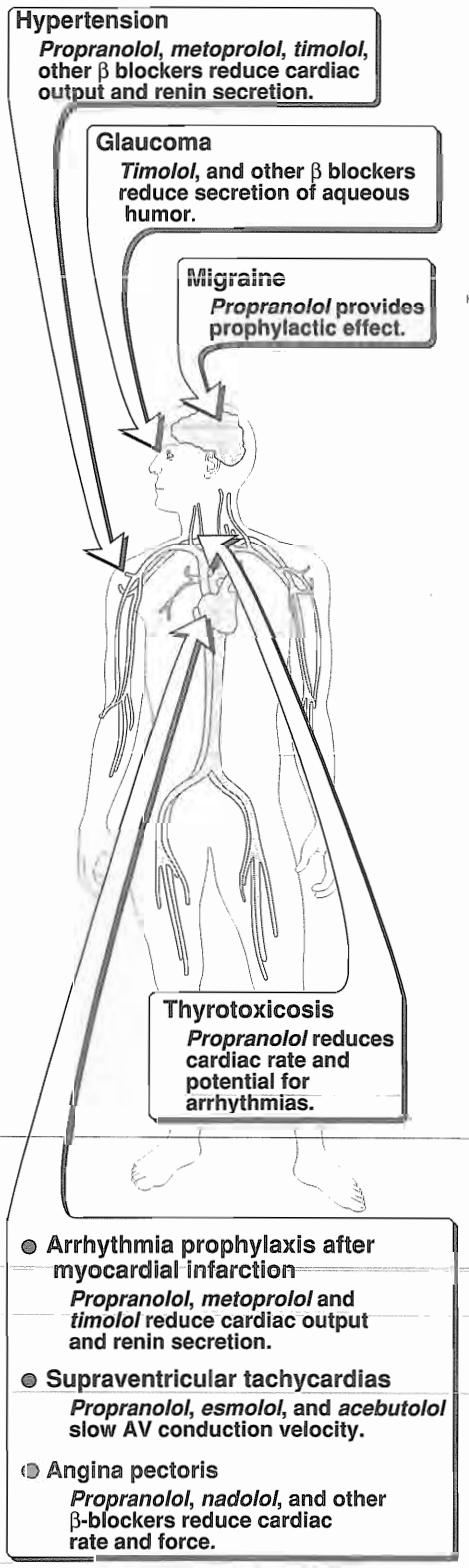


Figure 7.9
Some clinical applications of β-blockers.

E. Labetalol: an α and β-blocker

1. **Actions:** *Labetalol* [lay BET a lole] is a reversible β-blocker with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. *Labetalol* thus contrasts with the other β-blockers that produce peripheral vasoconstriction, and it is therefore useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. Labetalol does not alter serum lipid or blood glucose levels.

2. **Therapeutic use in hypertension:** *Labetalol* is useful for treating the elderly or black hypertensive patient in whom increased peripheral vascular resistance is undesirable. [Note: In general black hypertensive patients are not well controlled with β-blockers.] *Labetalol* may be employed as an alternative to *hydralazine* in the treatment of pregnancy-induced hypertension (PIH).

3. **Adverse affects:** Orthostatic hypotension and dizziness are associated with α_1 blockade. Figure 7.9 summarizes some of the indications for β-blockers.

IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

As was noted on p. 68, some agonists, such as *amphetamine* and *tyramine*, do not act directly on the adrenoceptor. Instead, they exert their effects indirectly on the adrenergic neuron by causing the release of neurotransmitter from storage vesicles. Similarly, some agents act on the adrenergic neuron, to either interfere in neurotransmitter release or alter the uptake of the neurotransmitter into the adrenergic nerve.

A. Reserpine

Reserpine [re SER peen], a plant alkaloid, blocks the Mg^{++}/adenosine triphosphate (ATP)-dependent transport of biogenic amines, *norepinephrine*, *dopamine* and *serotonin*, from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues (see p. 57). This causes an ultimate depletion of *norepinephrine* levels in the adrenergic neuron, since monoamine oxidase can degrade the *norepinephrine* in the cytoplasm. Sympathetic function, in general, is impaired because of decreased release of *norepinephrine*. Hypertensive patients taking the drug show a gradual decline in blood pressure with a concomitant slowing of the cardiac rate. The drug has a slow onset of action and a long duration of action. When one stops taking the drug, the actions persist for many days.

B. Guanethidine

Guanethidine [gwahn ETH i deen] inhibits the response of the adrenergic nerve to stimulation or to indirectly-acting sympathomimetic amines. *Guanethidine* acts by blocking the release of stored *norepinephrine*. This results in a gradual lowering of blood pressure in hypertensives, and a decrease in cardiac rate. [Note:

There is also an accentuation of parasympathetic tone of the gastrointestinal tract.] *Guanethidine* also displaces *norepinephrine* from storage vesicles (thus producing a transient increase in blood pressure). This leads to gradual depletion of *norepinephrine* in nerve endings except those in the CNS. *Guanethidine* is now rarely used in the treatment of hypertension. *Guanethidine* commonly causes orthostatic hypotension and interferes with male sexual function. Supersensitivity to norepinephrine due to depletion of the amine can result in hypertensive crises in patients with pheochromocytoma. Due to supersensitivity patients taking cold preparations containing *phenylpropanolamine* also may have an exaggerated hypertensive response.

C. Cocaine

Cocaine [koe KANE] is unique among local anesthetics in having the ability to block the Na^+-K^+-activated ATPase (required for cellular uptake of norepinephrine) across the cell membrane of the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine* as compared to one who is not. In addition, the duration of action of epinephrine and norepinephrine is increased. [Note: *Cocaine* as a CNS stimulant and drug of abuse is discussed on p. 101.]

Figure 7.10 summarizes the β-adrenergic antagonists.

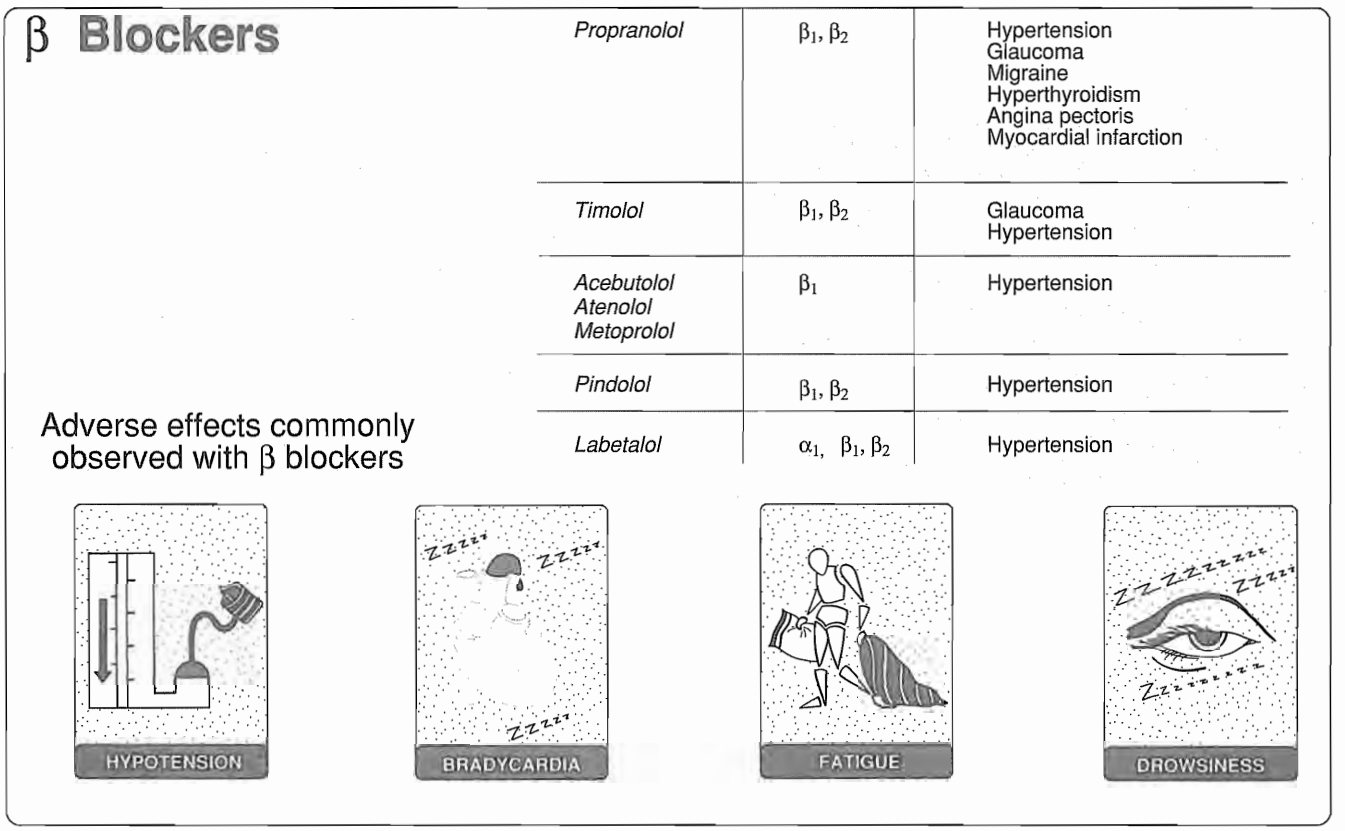


Figure 7.10
Summary of β- adrenergic antagonists.

Choose the ONE best answer.

7.1 Systolic pressure is decreased after the injection of which of following drugs?

A. Phenylephrine
B. Dopamine
C. Ephedrine
D. Reserpine
E. Norepinephrine

Correct answer = D. Reserpine blocks the uptake of norepinephrine into intracellular storage vesicles, resulting in depletion of norepinephrine and gradual decline in blood pressure. Phenylephrine is a pure vasoconstrictor and raises systolic and diastolic blood pressures. Dopamine raises systolic and diastolic blood pressures by stimulating the heart and (at high doses) causing vasoconstriction. Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. Norepinephrine has a pressor effect.

7.2 Which one of the following drugs is useful in treating tachycardia?

A. Phenoxybenzamine
B. Isoproterenol
C. Phentolamine
D. Propranolol
E. Prazosin

Correct answer = D. Propranolol is a nonspecific β blocker that interferes with β_1 receptors on the heart, causing bradycardia, that is, a slowing of the heart rate. Phenoxybenzamine blocks α receptors and prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. This leads to a decrease in blood pressure and peripheral resistance, which causes a reflex tachycardia. Isoproterenol is a potent β agonist that promotes tachycardia. Phentolamine is an α blocker that causes hypotension, which may set off reflex tachycardia. Prazosin is not indicated for tachycardia.

7.3 A 60-year-old asthmatic man comes in for a check-up and complains that he is having some difficulty in "starting to urinate". Physical examination indicates that the man has a blood pressure of 160/100 mm Hg and a slightly enlarged prostate. Which of the following medications would be useful in treating both of these conditions?

A. Doxazosin
B. Labetalol
C. Phentolamine
D. Propranolol
E. Isoproterenol

The correct answer = A. Doxazosin is an competitive blocker at the α_1 receptor and lowers blood pressure. In addition it blocks the α receptors in the smooth muscle of the bladder neck and prostate to improve urine flow. Labetalol and propranolol, while effective for treating the hypertension, are contraindicated in an asthmatic. They would not improve urine flow. Phentolamine has too many adverse effects to be used as an hypertensive agent. Isoproterenol is a β agonist and is not employed as an hypertensive nor would it affect urinary function.

UNIT III:
Drugs Affecting the Central Nervous System

Treatment of Parkinson's Disease

8

I. OVERVIEW OF CNS

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs. These concepts are useful in understanding the etiology of and the treatment strategies for Parkinson's disease—a disorder caused by the death of a group of brain cells whose actions are mediated by the neurotransmitter dopamine. Figure 8.1 shows the drugs used in the treatment of Parkinson's disease.

ANTIPARKINSON'S DRUGS

- ***Amantadine***
- **Antimuscarinic agents**
- ***Bromocriptine***
- ***Carbidopa***
- ***Deprenyl (Selegiline)***
- ***Levodopa***

Figure 8.1
Summary of agents used in the treatment of Parkinson's disease.

II. NEUROTRANSMISSION IN THE CNS

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system described in Chapter 3. For example, transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes (see p. 33). Several major differences exist between neurons in the peripheral autonomic nervous system and those of the CNS. The circuitry of the CNS is much more complex than the autonomic nervous

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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system, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral autonomic nervous system, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 10 (and perhaps as many as 50) different neurotransmitters. In contrast, the autonomic system uses only two primary neurotransmitters, acetylcholine and norepinephrine.

III. SYNAPTIC POTENTIALS

In the CNS, receptors at most synapses are coupled to ion channels, that is, binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.

A. Excitatory pathways

Neurotransmitters can be classified as excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: (1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as norepinephrine or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. (2) The influx of Na^+ causes a weak depolarization or excitatory postsynaptic potential (EPSP). (3) If the number of excitatory fibers stimulated increases, more excitatory neurotransmitter is released, finally causing the EPSP depolarization of the postsynaptic cell to pass a threshold, and an all-or-none action potential is generated. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] (See Figure 8.2 for an example of an excitatory pathway.)

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: (1) Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as, potassium and chloride ions. (2) The influx of chloride (Cl^-) and efflux of potassium (K^+) cause a weak hyperpolarization or inhibitory post-

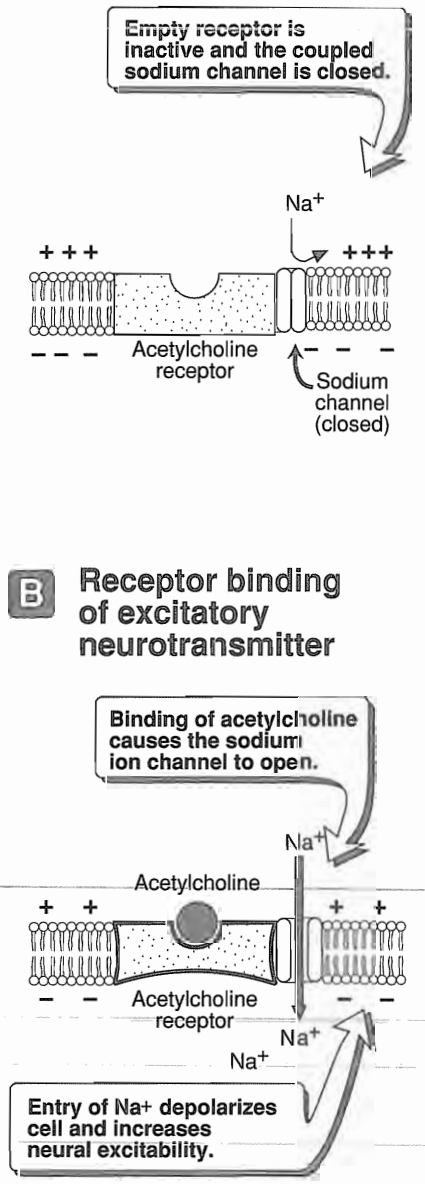


Figure 8.2
Binding of excitatory neurotransmitter, acetylcholine, causes depolarization of neuron.

synaptic potential (IPSP) that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. (See Figure 8.3 for an example of an inhibitory pathway.)

C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall resultant action is due to the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons whose axons may synapse with specific regions of the brain. Many neuronal tracts thus seem to be chemically coded, and this may offer greater opportunity for selective modulation of certain neuronal pathways.

IV. OVERVIEW OF PARKINSON'S DISEASE

Parkinsonism is a progressive neurologic disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities. Parkinson's disease is the fourth most common neurologic disorder among the elderly, affecting 500,000 people in the United States alone. Most cases involve people over the age of 65 among whom the incidence is about 1:100 individuals.

A. Etiology

The cause of Parkinson's disease is unknown for most patients. The disease is correlated with a reduction in the activity of inhibitory dopaminergic neurons in the substantia nigra and corpus striatum—parts of the brain's basal ganglia system that are responsible for motor control. Genetic factors do not play a dominant role in the etiology of Parkinson's disease, although they may exert some influence on an individual's susceptibility to the disease. It appears increasingly likely that an unidentified environmental factor may play a role in the loss of dopaminergic neurons.

1. **Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum (Figure 8.4). Each dopaminergic neuron makes thousands of synaptic contacts within the striatum and therefore modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically, rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

2. **Striatum:** Normally, the striatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia

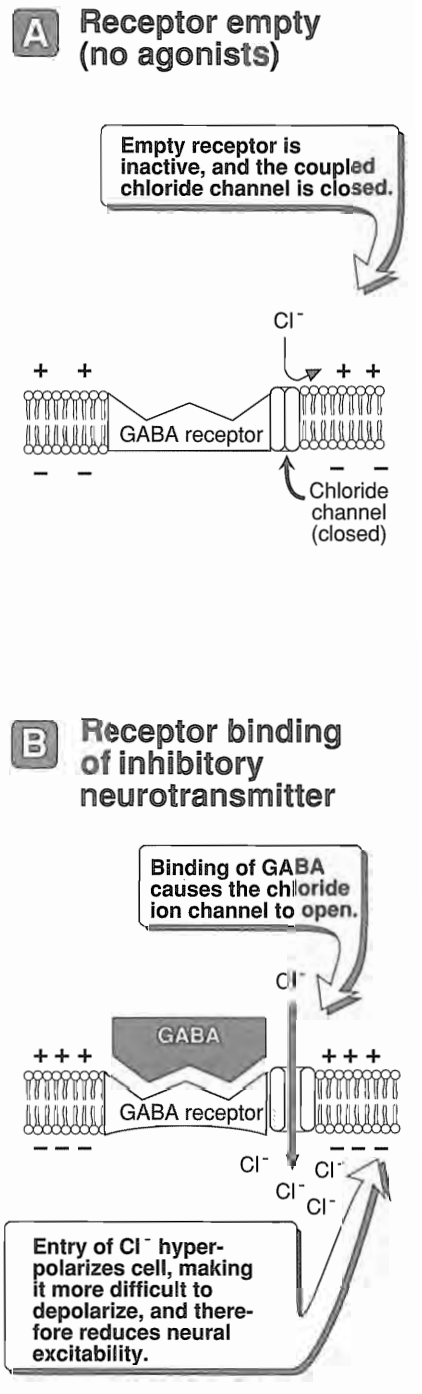


Figure 8.3
Binding of inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of neuron.

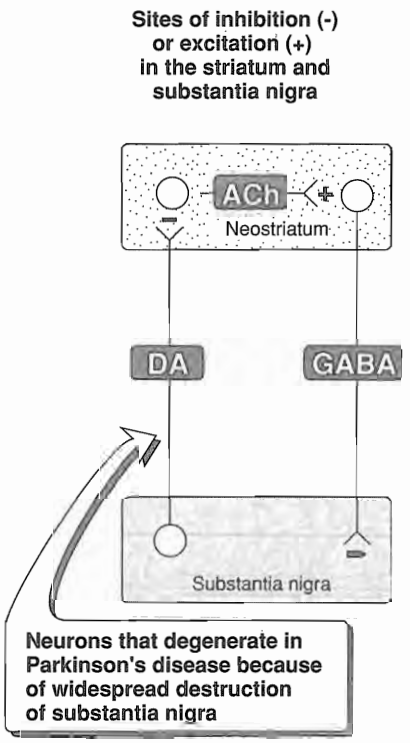


Figure 8.4
Location of dopaminergic neurons deficient in Parkinson's disease. DA=dopamine; GABA= γ-aminobutyric acid; ACh=Acetylcholine.

nigra send neurons back to the striatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas. Nerve fibers from the cerebral cortex and thalamus secrete acetylcholine in the neostriatum, causing excitatory effects that initiate and regulate gross intentional movements of the body. In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of neurons responsible for secreting dopamine in the neostriatum. Thus the normal modulating inhibitory influence of dopamine on the neostriatum is significantly diminished, resulting in the parkinsonian degeneration of the control of muscle movement (see Figure 8.4).

3. **Secondary parkinsonism:** Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as the phenothiazines and *haloperidol* (see p. 127), whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms. These drugs should not be used in parkinsonian patients.

B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (see Figure 8.4). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

V. DRUGS USED IN PARKINSON'S DISEASE

Currently available drugs offer temporary relief from the symptoms of the disorder, but do not arrest or reverse the neuronal degeneration caused by the disease.

A. Levodopa (L-dopa) and carbidopa

Levodopa is a metabolic precursor of dopamine. It restores dopamine levels in the extrapyramidal centers (substantia nigra) that atrophy in parkinsonism. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients the therapeutic response to *levodopa* is consistent and the patient rarely complains that the drug effects "wear off." Unfortunately, with time the number of neurons decreases and there are fewer cells capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic and lasts only while the drug is present in the body.

1. Mechanism of action

a. Levodopa: Since parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Dopamine itself does not cross the blood-brain barrier, but its immediate precursor *levodopa* [lee voe DOE pa] is readily transported into the CNS and is converted to dopamine in the brain (Figure 8.5). Large doses of *levodopa* are required because much of the drug is decarboxylated to dopamine in the periphery (Figure 8.5), resulting in peripheral side effects (nausea, vomiting, cardiac arrhythmias, hypotension).

b. Carbidopa: The effects of *levodopa* on the CNS can be greatly enhanced by coadministering *carbidopa* [kar bi DOE pa], a dopamine decarboxylase inhibitor that does not cross the blood-brain barrier. *Carbidopa* diminishes the metabolism of *levodopa* in the GI tract and peripheral tissues; thus, it increases the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by 4- to 5-fold and, consequently, decreases the severity of the side effects of peripherally formed dopamine.

2. Actions: *Levodopa* decreases the rigidity, tremors, and other symptoms of parkinsonism.

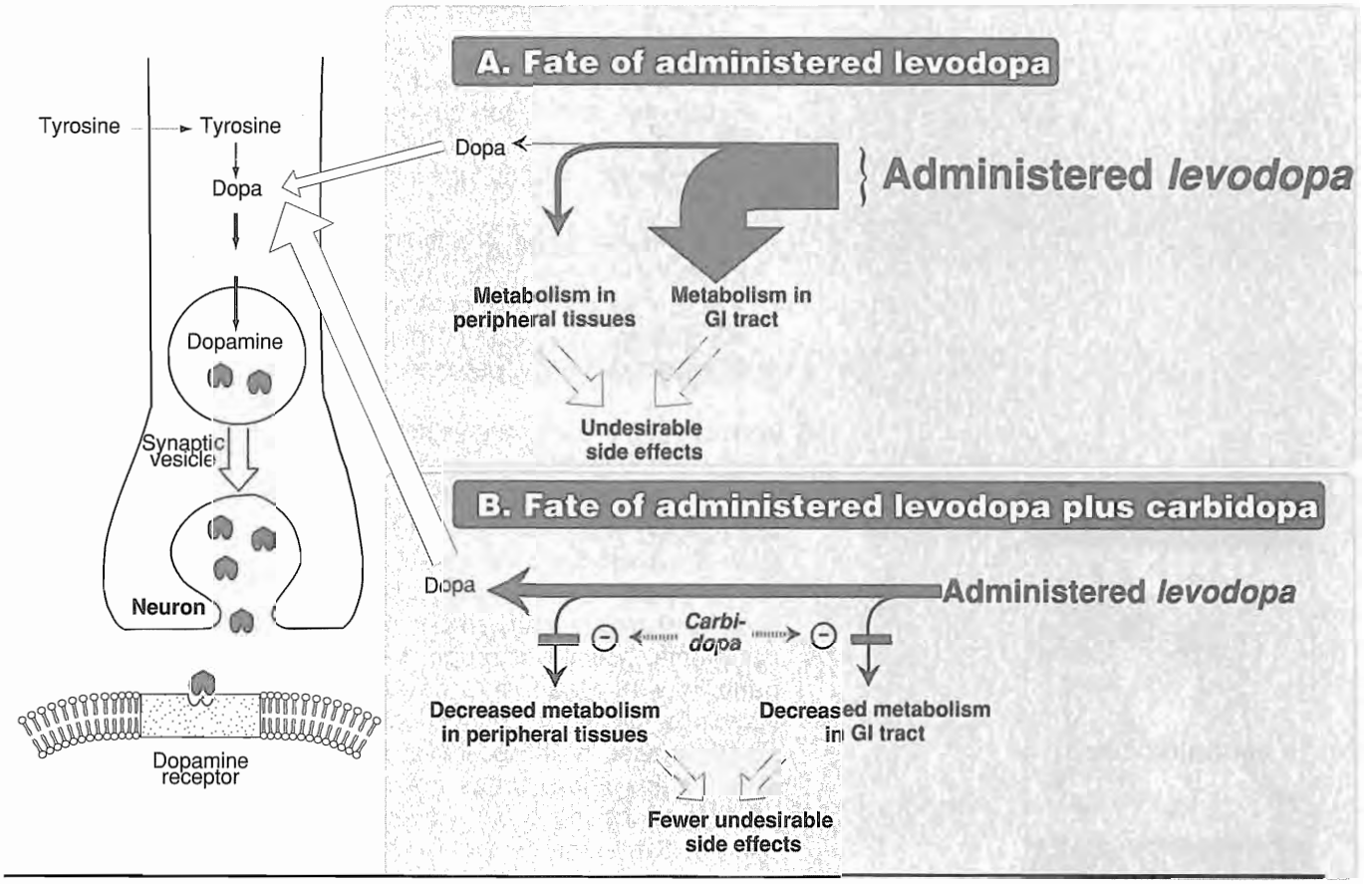


Figure 8.5
Synthesis of dopamine in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues.

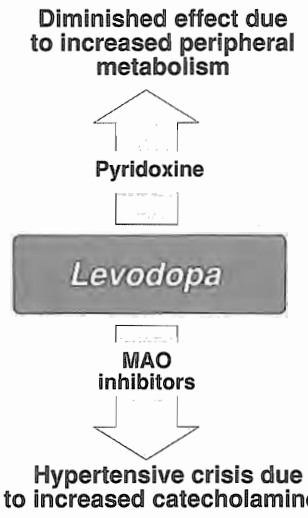


Figure 8.6
Some drug interactions observed with *levodopa*.

3. **Therapeutic uses:** *Levodopa* in combination with *carbidopa* is a potent and efficacious drug regimen currently available to treat Parkinson's disease. In approximately two thirds of patients with Parkinson's disease, *levodopa/carbidopa* treatment substantially reduces the severity of the disease for the first few years of treatment. Patients then typically experience a decline in response during the third to fifth year of therapy.

4. **Absorption and metabolism:** The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response ("on-off" phenomenon), which may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein content, interferes with the transport of *levodopa* into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with *levodopa* for absorption from the gut and for transport across the blood-brain barrier. Thus *levodopa* should be taken on an empty stomach, typically 45 minutes before a meal. Withdrawal from the drug must be gradual.

5. **Adverse effects**

   a. **Peripheral effects:** Anorexia, nausea, and vomiting occur because of stimulation of the emetic center. Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis, and in some individuals, blood dyscrasias and a positive reaction to the Coombs' test are seen. Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.

   b. **CNS effects:** Visual and auditory hallucinations and abnormal involuntary movements (dyskinesia) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia. *Levodopa* can also cause mood changes, depression, and anxiety.

6. **Interactions:** The vitamin pyridoxine (B_6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 8.6). Concomitant administration of *levodopa* and monoamine oxidase (MAO) inhibitors, such as *phenelzine* (see p. 124), can produce a hypertensive crisis caused by enhanced catecholamine production; therefore, caution is required when they are used simultaneously. In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central amines. In patients with glaucoma, the drug can cause an increase in intraocular pressure. Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias. Antipsychotic drugs are contraindicated in parkinsonian patients, since these block dopamine receptors and produce a parkinsonian syndrome themselves.

B. Bromocriptine

Bromocriptine [broh moh KRIP teen], an ergotamine (an alkaloid with vasoconstrictor action) derivative, is a dopamine receptor agonist. The drug produces little response in patients who do not react to *levodopa*, but it is often used with *levodopa* in patients responding to drug therapy. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists (Figure 8.7). The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, *bromocriptine* causes the mental condition to worsen. Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction. In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer.

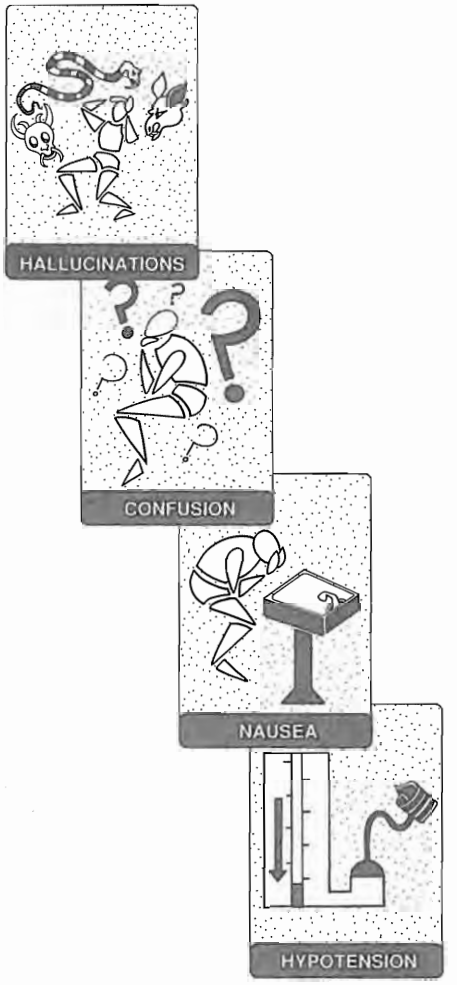


Figure 8.7
Some adverse effects of *bromocriptine*.

C. Amantadine

It was accidentally discovered that the antiviral drug, *amantadine* [a MAN ta deen], effective in the treatment of influenza (see p. 363), has antiparkinsonism action. It appears to enhance the synthesis, release, or re-uptake of dopamine from the surviving neurons. [Note: If dopamine release is already at a maximum, *amantadine* has no effect.] The drug may cause restlessness, agitation, confusion, and hallucinations, and at high doses it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa* and tolerance develops more readily, but it has fewer side effects. The drug has little effect on tremor but is more effective than the anticholinergics against rigidity and bradykinesia.

D. Deprenyl

Deprenyl [DE pren ill], also called *selegiline* [se LE ge leen] selectively inhibits monoamine oxidase B (which metabolizes dopamine), but does not inhibit monoamine oxidase A (which metabolizes norepinephrine and serotonin). By thus decreasing the metabolism of dopamine, *deprenyl* has been found to increase dopamine levels in the brain (Figure 8.8). Therefore, it enhances the actions of *levodopa*, and when these drugs are administered together, *deprenyl* substantially reduces the required dose of *levodopa*. Unlike nonselective MAO inhbitors, *deprenyl* at recommended doses has little potential for causing hypertensive crises. However, if *deprenyl* is administered at high doses, the selectivity of the drug is lost and the patient is at risk for severe hypertension. Recent data suggest that early use of *deprenyl* may actually prolong the period before severe symptoms set in by as much as 50%, possibly by reducing the formation of free radicals.

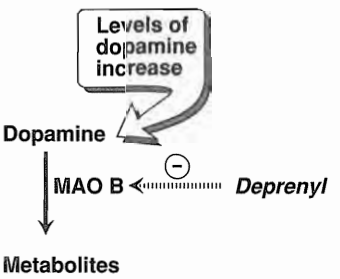


Figure 8.8
Action of *deprenyl* in dopamine metabolism.

E. Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism therapy. The

actions of *benztropine*, *trihexyphenidyl*, and *biperiden* are similar, although individual patients may respond more favorably to one drug. All these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristalsis and cannot be used in patients with glaucoma, prostatic hypertrophy, or pyloric stenosis. Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission (again, because of the creation of an imbalance in the dopamine/acetylcholine ratio). Adverse effects are similar to those caused by high doses of *atropine* (see p. 45), for example, pupillary dilation, confusion, hallucination, urinary retention, and dry mouth.

Study Questions

Choose the ONE best answer.

8.1 Which one of the following statements is correct?

A. Chlorpromazine is indicated in treating the nausea of levodopa treatment.
B. Vitamin B_6 increases the effectiveness of levodopa.
C. Administration of dopamine is an effective treatment of Parkinson's disease.
D. Levodopa-induced nausea is reduced by carbidopa.
E. Nonspecific MAO-inhibitors, such as phenelzine, are a useful adjunct to levodopa therapy.

Correct answer = D. Carbidopa inhibits the peripheral decarboxylation of levodopa, permitting lower dosage. Chlorpromazine blocks the dopamine receptor site in the brain and therefore blocks the beneficial effects of levodopa. Vitamin B_6 enhances the peripheral decarboxylation of levodopa. Dopamine does not itself cross the blood-brain barrier. Phenelzine inhibits the metabolism of norepinephrine and serotonin and may produce a hypertensive crisis.

8.2 Which one of the following statements is INCORRECT?

A. Parkinsonian patients are characterized by an increased ratio of dopaminergic/cholinergic activity in the neostriatum.
B. Overtreatment of Parkinson's disease can result in the symptoms of psychosis.
C. Diets rich in protein may decrease the effects of levodopa.
D. Dyskinesia is the most important side effect of levodopa.
E. Treatment with deprenyl can delay the onset of parkinsonian symptoms.

Correct choice = A. Parkinsonian patients show a deficiency of dopaminergic neurons, without a decrease in cholinergic actions. Elevated levels of dopamine can lead to behavorial disorders. Levodopa and large, neutral amino acids share a transport system that is needed to enter the brain; thus high protein diets may lead to elevated levels of circulating amino acids, resulting in a decrease in levodopa uptake. Dyskinesia is usually seen with longer-term therapy and is dose-related and reversible. The mechanism of action of deprenyl is not understood.

8.3 All of the following statements are correct EXCEPT:

A. Atropine blocks the cholinergic pathway in the neostriatum.
B. Deprenyl inhibits monoamine oxidase B and increases dopamine levels in the brain.
C. Bromocriptine directly activates dopaminergic receptors.
D. Amantadine inhibits the metabolism of levodopa.
E. Antimuscarinic agents are generally less efficacious then levodopa in the treatment of Parkinson's disease.

Correct choice = D. The mechanism of action in parkinsonism of amantadine is unclear. It does not affect the metabolism of levodopa. The other statements are true.

Anxiolytic and Hypnotic Drugs

9

I. OVERVIEW

Anxiety is an unpleasant state of tension, apprehension, or uneasiness—a fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances. The symptoms of severe anxiety are similar to those of fear (such as, tachycardia, sweating, trembling, palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytic or minor tranquilizers), and/or some form of psycho- or behavioral therapy. Since all of the antianxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. Figure 9.1 summarizes the anxiolytic and hypnotic agents.

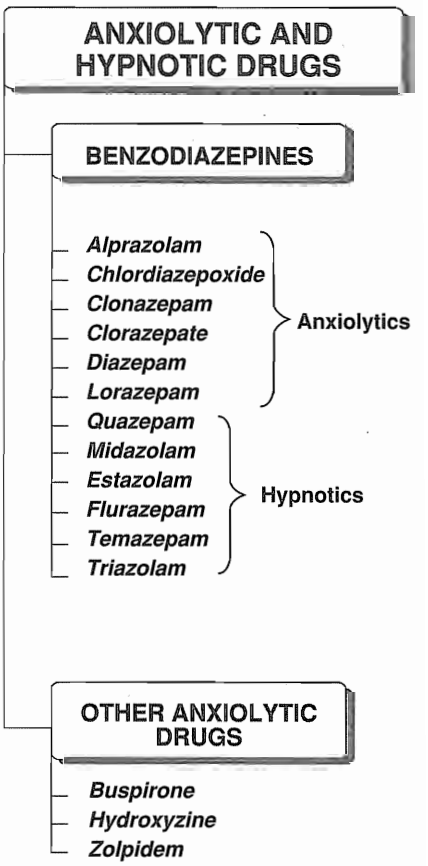


Figure 9.1
Summary of anxiolytic and hypnotic drugs.
(Figure continues on next page.)

II. BENZODIAZEPINES

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety, since the benzodiazepines are more effective and safer (Figure 9.2). Approximately 20 benzodiazepine derivatives are currently available.

A. Mode of action

Binding of γ-aminobutyric acid (GABA) to its receptor on the cell membrane triggers an opening of a chloride channel, which leads to an increase in chloride conductance (Figure 9.3). The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and thus inhibits the formation of action potentials (see p. 82). Benzodiazepines bind to specific, high affinity sites on the cell membrane, which are separate from but adjacent to the receptor for GABA. The benzodiazepine receptors are found only in the central nervous system (CNS), and their location parallels that of the GABA neurons. The binding of benzodiazepines enhances the affinity of GABA receptors for this neurotransmitter, resulting in a more frequent opening of adjacent chloride channels (see Figure 9.3). This in turn results in enhanced hyperpolarization and further inhibition of neuronal firing. [Note:

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

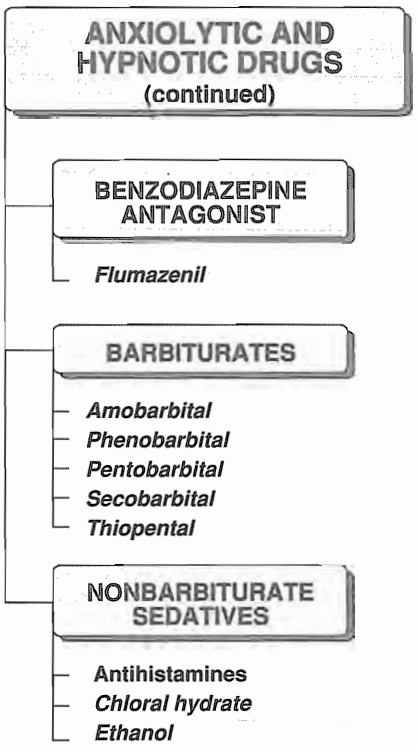


Figure 9.1 (continued)
Summary of anxiolytic and hypnotic drugs.

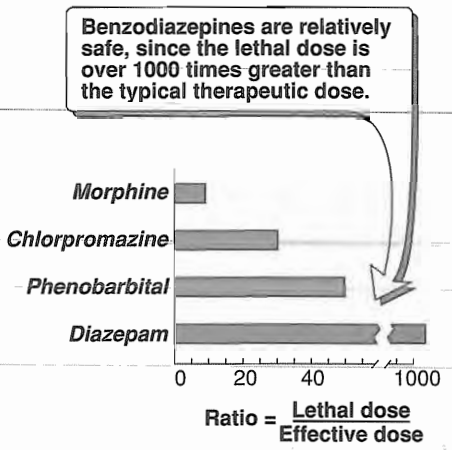


Figure 9.2
Ratio of lethal dose to effective dose for *morphine* (an opioid, Chapter 14), *chlorpromazine* (a neuroleptic, Chapter 13), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

Benzodiazepines and GABA mutually increase the affinity of their binding sites without actually changing the total number of sites.] The clinical effects of the various benzodiazepines correlate well with each drug's binding affinity for the GABA receptor-chloride ion channel complex.

B. Actions

The benzodiazepines have no antipsychotic activity, nor any analgesic action and do not affect the autonomic nervous system. All of the benzodiazepines exhibit the following actions to a greater or lesser extent:

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively inhibiting neuronal circuits in the limbic system of the brain.

2. **Sedative and hypnotic actions:** All of the benzodiazepines used to treat anxiety have some sedative properties. At higher doses, certain benzodiazepines produce hypnosis (artificially-produced sleep).

3. **Anticonvulsant:** Several of the benzodiazepines have anticonvulsant activity and are used to treat epilepsy and other seizure disorders.

4. **Muscle relaxant:** The benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord.

C. Therapeutic uses

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choice of drug.

1. **Anxiety disorders:** The benzodiazepines are useful in treating the anxiety that accompanies some forms of depression and schizophrenia. These drugs should not be used to alleviate the normal stress of everyday life, but should be reserved for continued severe anxiety, and then should only be used for short periods of time because of addiction potential. The longer acting agents such as *diazepam* [dye AZ e pam], are often preferred in those patients with anxiety that may require treatment for prolonged periods of time. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. For panic disorders, *alprazolam* [al PRAY zoe lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of sufferers.

2. **Muscular disorders:** *Diazepam* is useful in the treatment of skeletal muscle spasms such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

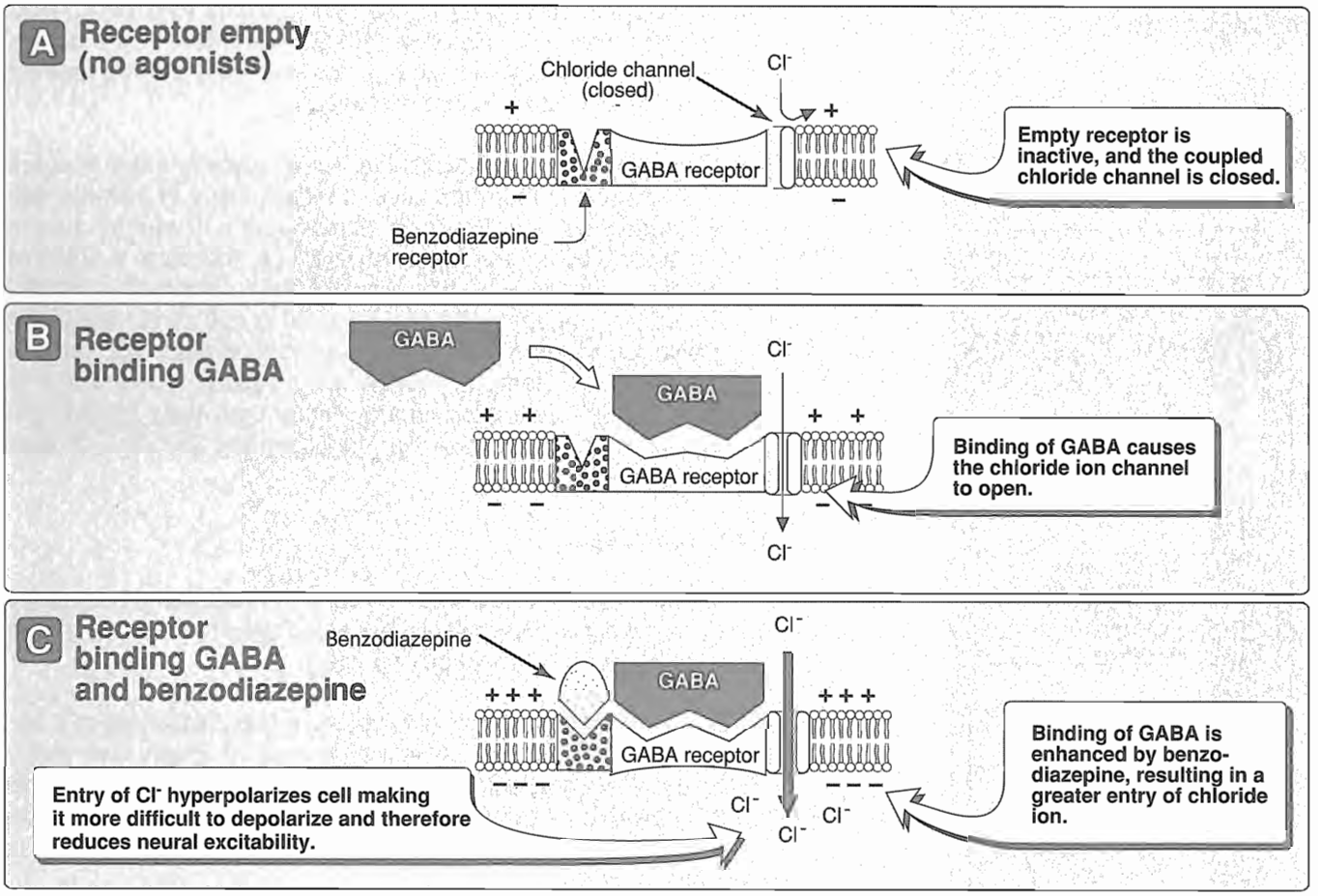


Figure 9.3
Schematic diagram of benzodiazepine-GABA-chloride ion channel complex. GABA= γ–aminobutyric acid.

3. **Seizures:** *Clonazepam* [kloe NA ze pam] is useful in the chronic treatment of epilepsy, whereas *diazepam* is the drug of choice in terminating grand mal epileptic seizures and status epilepticus (see p. 149). *Chlordiazepoxide* [klor di az e POX ide], *clorazepate* [klor AZ e pate], *diazepam*, and *oxazepam* [ox A ze pam] are useful in the acute treatment of alcohol withdrawal.

4. **Sleep disorders:** Not all of the benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. The three most commonly prescribed benzodiazepines for sleep disorders are long-acting *flurazepam* [flure AZ e pam], intermediate-acting *temazepam* [tem AZ e pam] and short-acting *triazolam* [trye AY zoe lam].

   a. **Flurazepam:** This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakenings, and increases the duration of sleep. *Flurazepam* has a long-acting effect (Figure 9.4) and causes little rebound insomnia. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. *Flurazepam* and its active metabolites have a half-life of appoximately 85 hours, which may result in daytime sedation and accumulation of the drug.

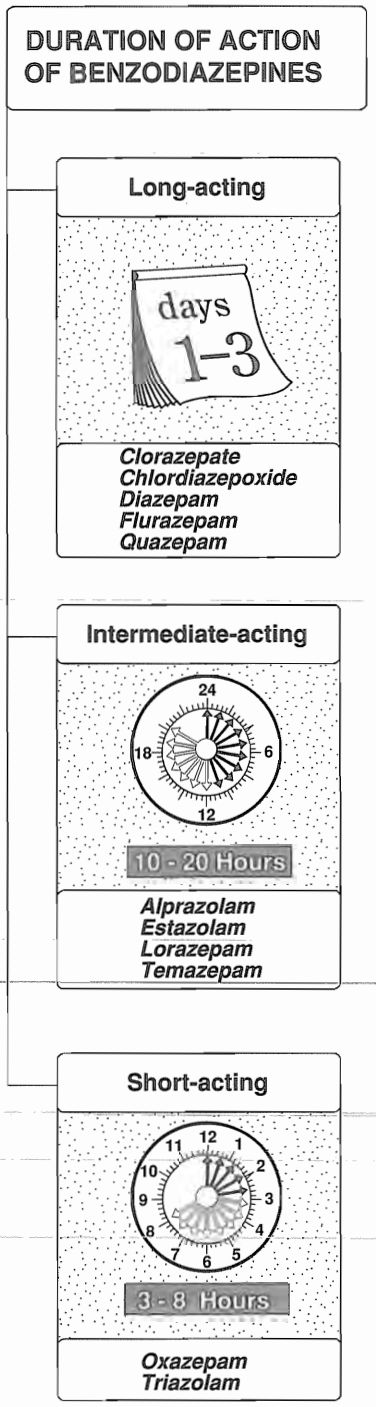


Figure 9.4
Comparison of the durations of action of the benzodiazepines.

b. Temazepam: This drug is useful in patients who experience frequent wakening. However, the peak sedative effect occurs two to three hours after an oral dose, and therefore it may be given several hours before bedtime.

c. Triazolam: This benzodiazepine has a relatively short duration of action and is therefore used to induce sleep in patients with recurring insomnia. Whereas *temazepam* is useful for insomnia caused by the inability to stay asleep, *triazolam* is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

D. Pharmacokinetics

1. **Absorption and distribution:** The benzodiazepines are lipophilic and are rapidly and completely absorbed after oral administration and are distributed throughout the body.

2. **Duration of actions:** The half-lives of the benzodiazepines are very important clinically, since the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate- and long-acting groups (see Figure 9.4). The longer acting agents form active metabolites with long half-lives.

3. **Fate:** Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by the hepatic microsomal metabolizing system (see p. 14) to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites.

E. Dependence

Psychological and physical dependence on benzodiazepines can develop if high doses of the drug are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, and tension. Because of the long half-lives of some of the benzodiazepines, withdrawal symptoms may not occur until a number of days after discontinuation of therapy. Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated, such as *flurazepam* (Figure 9.5).

F. Adverse effects

1. **Drowsiness and confusion:** These effects are the two most common side effects of the benzodiazepines. Ataxia occurs at high

doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased long-term recall and acquisition of new knowledge) can occur with use of benzodiazepines. *Triazolam*, the benzodiazepine with the most rapid elimination, often shows a rapid development of tolerance, early morning insomnia and daytime anxiety, along with amnesia and confusion.

2. **Precautions:** Use benzodiazepines cautiously in treating patients with liver disease. They potentiate alcohol and other CNS depressants. Benzodiazepines are, however, considerably less dangerous than other anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal, unless other central depressants, such as alcohol, are taken concurrently.

III. OTHER ANXIOLYTIC AND HYPNOTIC AGENTS

A. Zolpidem

Although the hypnotic *zolpidem* [ZOL pih dem] is not a benzodiazepine, it acts on a subset of the benzodiazepine receptor family. *Zolpidem* has no anticonvulsant or muscle relaxing properties. It shows no withdrawal effects, exhibits minimal rebound insomnia and little or no tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed from the gastrointestinal tract, and has a rapid onset of action and short elimination half-life (about 3 hours). Adverse effects of *zolpidem* include nightmares, agitation, headache, gastrointestinal upset, dizziness, and daytime drowsiness. Although *zolpidem* potentially has advantages over the benzodiazepines, clinical experience with the drug is still limited.

B. Buspirone

Buspirone [byoo SPYE rone] is useful in the treatment of generalized anxiety disorders and has an efficacy comparable to the benzodiazepines. The actions of *buspirone* appear to be mediated by serotonin (5-HT_{1A}) receptors, although other receptors could be involved, since *buspirone* displays some affinity for DA_2 dopamine receptors and 5-HT_2 serotonin receptors. The mode of action thus differs from that of the benzodiazepines. Further, *buspirone* lacks anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. The frequency of adverse effects is low, the most common effects being headaches, dizziness, nervousness, and lightheadness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. *Buspirone* has the disadvantage of a slow onset of action. Figure 9.6 compares some of the common adverse effects of *buspirone* and the benzodiazepine, *alprazolam*.

C. Hydroxyzine

Hydroxyzine [hye DROX i zeen] is an antihistamine with antiemetic activity. It has a low tendency for habituation; thus it is useful for patients with anxiety, who have a history of drug abuse. It is also often used for sedation prior to dental procedures or surgery.

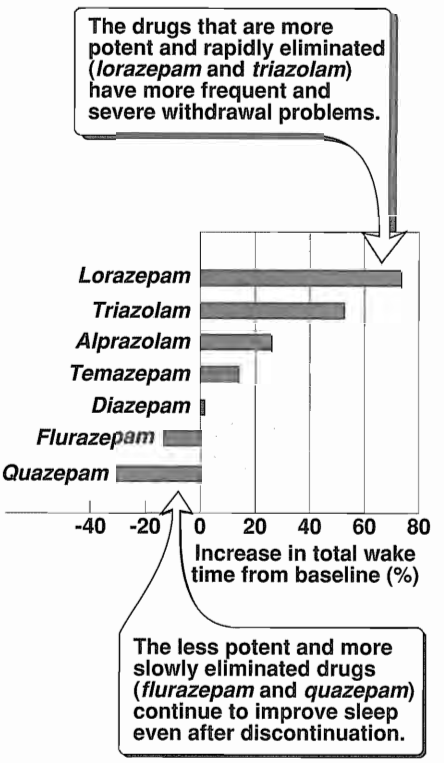


Figure 9.5
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

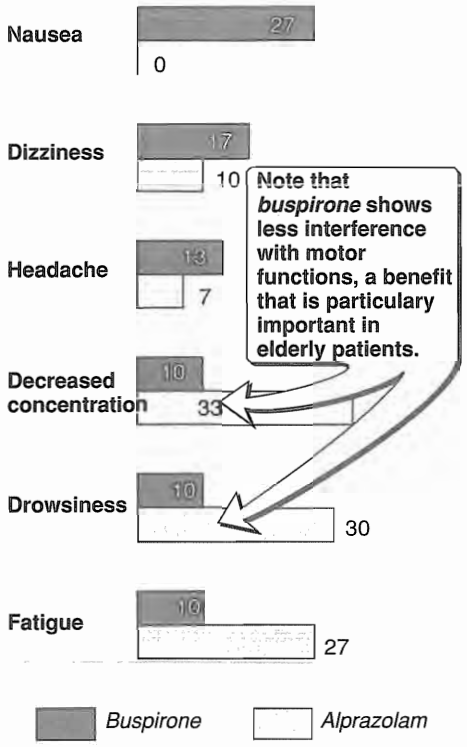


Figure 9.6
Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as percent of patients showing each symptom.

IV. BENZODIAZEPINE ANTAGONIST

Flumazenil [floo MAZ eh nill] is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available by IV administration only. Onset is rapid but duration is short, with a half-life of about one hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. Administration of *flumazenil* may precipitate withdrawal in dependent patients or may cause seizures if a benzodiazepine is used to control seizure activity. Dizziness, nausea, vomiting, and agitation are the most common side effects.

V. BARBITURATES

The barbiturates were formerly the mainstay of treatment used to sedate the patient or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, mainly because barbiturates induce tolerance, drug-metabolizing enzymes, physical dependence, and very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting *thiopental*, are still used to induce anesthesia (see p. 115).

A. Mode of action

Barbiturates are thought to interfere with sodium and potassium transport across cell membranes. This leads to inhibition of the mesencephalic reticular activating system. Polysynaptic transmission is inhibited in all areas of the CNS. Barbiturates also potentiate GABA action on chloride entry into the neuron, although they do not bind at the benzodiazepine receptor.

B. Actions

Barbiturates are classified according to their duration of action (Figure 9.7). For example, *thiopental* [thye oh PEN tal], which acts within seconds and has a duration of action of about 30 minutes, is used in the intravenous induction of anesthesia. By contrast, *phenobarbital* [fee noe BAR bi tal], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 148). *Pentobarbital* [pen toe BAR bi tal], *secobarbital* [see koe BAR bi tal] and *amobarbital* [am oh BAR bi tal] are short-acting barbiturates, which are effective as sedative and hypnotic (but not antianxiety) agents.

1. **Depression of CNS:** At low doses, the barbiturates produce sedation (calming effect, reducing excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and finally coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain.

2. **Respiratory depression:** Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death.

3. **Enzyme induction:** Barbiturates induce P-450 microsomal enzymes in the liver (see p. 14). Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on P-450 metabolism to reduce their concentration.

C. Therapeutic uses

1. **Anesthesia:** Selection of a barbiturate is strongly influenced by the desired duration of action. The ultra-short-acting barbiturates, such as *thiopental*, are used intravenously to induce anesthesia.

2. **Anticonvulsant:** *Phenobarbital* is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. *Phenobarbital* has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures. However, *phenobarbital* can depress cognitive performance in children, and the drug should be used cautiously. *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

3. **Anxiety:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. Most have been replaced by the benzodiazepines.

D. Pharmacokinetics

Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute in the body from the brain to the splanchnic areas, to skeletal muscle, and finally to adipose tissue. This movement is important in causing the short duration of action of *thiopental* and similar short-acting derivatives (see p. 115). Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.

E. Adverse effects

1. **CNS:** Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness.

2. **Drug hangover:** Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient awakes. This drug hangover leads to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

3. **Precautions:** As noted previously, barbiturates induce the P-450 system and therefore may decrease the effect of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin synthesis, and are contraindicated in patients with acute intermittent porphyria.

4. **Addiction:** Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

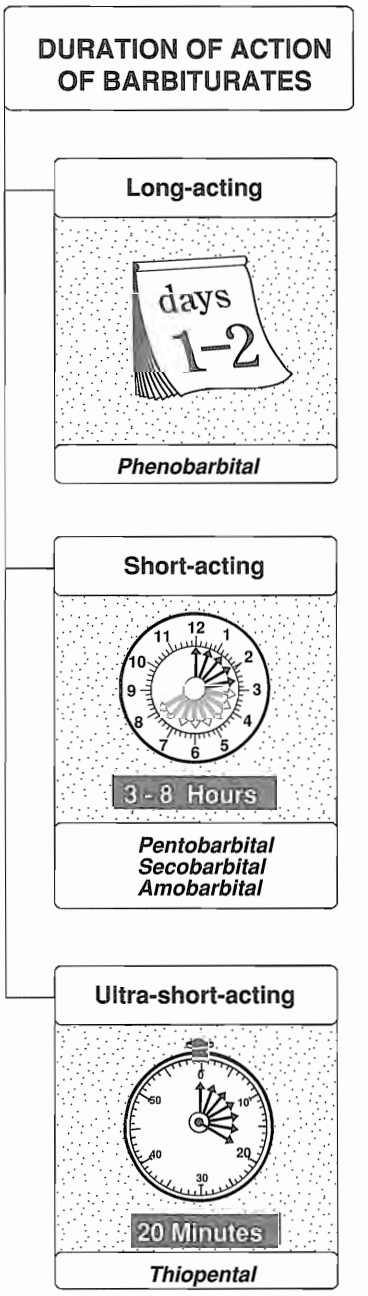
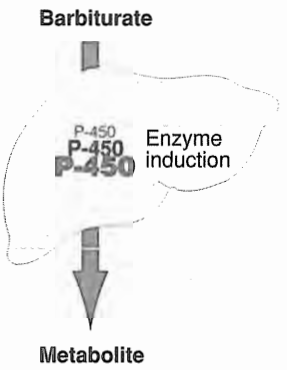


Figure 9.7
Barbiturates classified according to their duration of actions.



5. **Poisoning:** Barbiturate poisoning has been a leading cause of death among drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression, and results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of *phenobarbital* (see p. 24).

VI. NONBARBITURATE SEDATIVES

A. Chloral hydrate

Chloral hydrate [KLOR al HYE drate] is a trichlorinated derivative of acetaldehyde that is converted to trichloroethanol in the body. The drug is an effective sedative and hypnotic that induces sleep in about 30 minutes and lasts about 6 hours. *Chloral hydrate* is irritating to the gastrointestinal tract and causes epigastric distress. It also produces an unusual, unpleasant taste sensation.

B. Antihistamines

Nonprescription antihistamines with sedating properties, such as *diphenhydramine* and *doxylamine* (see p. 422), are effective in treating mild types of insomnia. However, these drugs are usually ineffective for all but the milder form of situational insomnia. Further, they have numerous undesirable side effects that make them less useful than the benzodiazepines. These sedative antihistamines are marketed in numerous over-the-counter products.

C. Ethanol

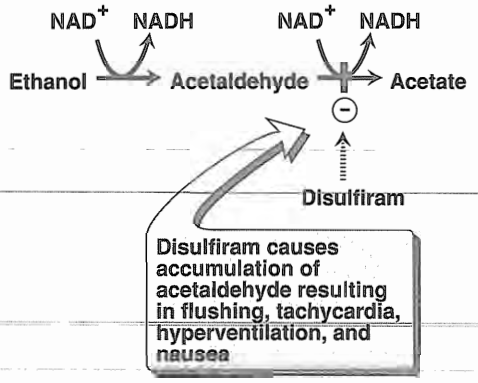


Figure 9.8
Metabolism of ethanol.

Ethanol (ethyl alcohol) has antianxiety and sedative effects, but its toxic potential outweighs its benefits. *Ethanol* [ETH an ol] is a CNS depressant, producing sedation and ultimately hypnosis with increasing dosage. *Ethanol* has a shallow dose-response curve; therefore, sedation occurs over a wide dosage range. Alcohol synergizes with many other sedative agents and can produce severe CNS depression with antihistamines or barbiturates.

1. **Disulfiram:** *Ethanol* is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase, and then to acetate by aldehyde dehydrogenase. *Disulfiram* [dye SUL fi ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase (Figure 9.8). This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea. *Disulfiram* has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of *disulfiram*-induced acetaldehyde accumulation.

Figure 9.9 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

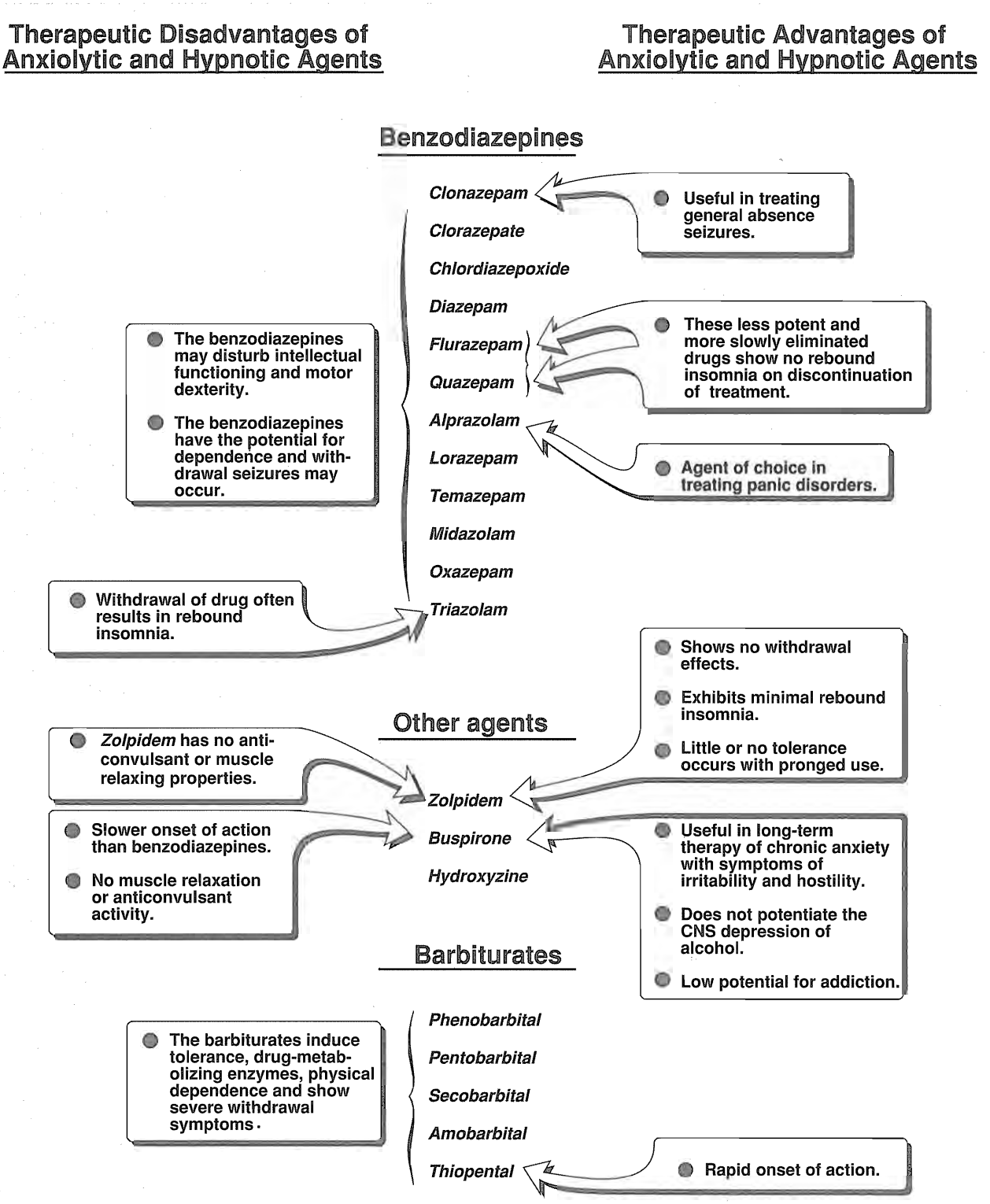


Figure 9.9
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents.

Choose the ONE best answer.

9.1 Which one of the following statements is CORRECT?

A. Benzodiazepines directly open chloride channels.
B. Benzodiazepines show analgesic actions.
C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.
D. All benzodiazepines have some sedative effects.
E. Benzodiazepines, like other CNS depressants, readily produce general anesthesia.

Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled "benzodiazepine hypnotics" in Figure 9.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of GABA to its receptor, which increases the permeability of chloride. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidpressants and the MAO-inhibitors, the benzodiazepines are effective within hours of administration. Benzodiazepines do not produce general anesthesia and are, therefore, relatively safe drugs with a high therapeutic index.

9.2 All of the following respond to treatment with benzodiazepines EXCEPT:

A. Tetanus.
B. Schizophrenia.
C. Epileptic seizure.
D. Insomnia.
E. Anxiety.

Correct choice = B. Benzodiazepines have no antipsychotic activity.

9.3 Which one of the following is a short-acting hypnotic?

A. Phenobarbital
B. Diazepam
C. Chlordiazepoxide
D. Thiopental
E. Flurazepam

Correct answer = D. Thiopental is an ultra-short-acting drug used as an adjuvant to anesthesia.

9.4 Which one of the following statements is CORRECT?

A. Phenobarbital shows analgesic properties.
B. Diazepam and phenobarbital induce the P-450 enzyme system.
C. Phenobarbital is useful in the treatment of acute intermittent porphyria.
D. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol.
E. Buspirone has actions similar to the benzodiazepines.

Correct answer = D. Barbiturates and ethanol are a potentially lethal combination. Phenobarbital is unable to alter the pain threshold. Only phenobarbital strongly induces the synthesis of the hepatic cytochrome P-450 drug metabolizing system. Phenobarbital is contraindicated in the treatment of acute intermittent porphyria. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.

9.5 A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. None
B. Lorazepam
C. Pentobarbital
D. Phenytoin

The correct answer = B. It is important to treat the seizures associated with alcohol withdrawal. Benzodiazepines, such as chlordiazepoxide, diazepam or or the shorter-acting lorazepam, are effective in controlling this problem. They are less sedating than pentobarbital or phenytoin.