The adrenomimetic drugs mimic the effects of adrenergic sympathetic nerve stimulation on sympathetic effectors; these drugs are also referred to as sympathomimetic agents. The adrenergic transmitter norepinephrine and the adrenal medullary hormone epinephrine also are included under this broad heading. The adrenomimetic drugs are an important group of therapeutic agents that can be used to maintain blood pressure or to relieve a life-threatening attack of acute bronchial asthma. They are also present in many over-the-counter cold preparations because they constrict mucosal blood vessels and thus relieve nasal congestion.

CHEMISTRY

The adrenomimetic drugs can be divided into two major groups on the basis of their chemical structure: the catecholamines and the noncatecholamines. The catecholamines include norepinephrine, epinephrine, and dopamine, all of which are naturally occurring, and several synthetic substances, the most important of which is isoproterenol (isopropyl norepinephrine). The skeletal structure of the catecholamines is shown in Figure 10.1.

The L-isomers are the naturally occurring forms of epinephrine and norepinephrine and possess considerably greater pharmacological effects than do the D-isomers. Throughout most of the world, epinephrine and norepinephrine are known as adrenaline and noradrenaline, respectively.

Noncatecholamine adrenomimetic drugs differ from the basic catecholamine structure primarily by having substitutions on their benzene ring.

MECHANISM OF ACTION

Many adrenomimetic drugs produce responses by interacting with the adrenoceptors on sympathetic effector cells. An examination of Table 9.1 reveals that sympathetic effectors have activity at $\alpha_2$, $\alpha_2$, $\beta_1$, or $\beta_2$ adrenoceptors or in some cases, combinations of these adrenoceptors. Adrenomimetic drugs vary in their affinities for each subgroup of adrenoceptors. Some, like epinephrine, have a high affinity for all of the adrenocep-
Adrenomimetic Drugs can be divided into two major groups on the basis of their mechanism of action. Norepinephrine, epinephrine, and some closely related adrenomimetics produce responses in effector cells by directly stimulating α- or β-adrenoceptors and are referred to as directly acting adrenomimetic drugs.

Many other adrenomimetic drugs, such as amphetamine, do not themselves interact with adrenoceptors, yet they produce sympathetic effects by releasing norepinephrine from neuronal storage sites (vesicles). The norepinephrine that is released by these compounds interacts with the receptors on the effector cells. These adrenomimetics are called indirectly acting adrenomimetic drugs. The effects elicited by indirectly acting drugs resemble those produced by norepinephrine.

An important characteristic of indirectly acting adrenomimetic drugs is that repeated injections or prolonged infusion can lead to tachyphylaxis (gradually diminished responses to repeated administration). This is a result of a gradually diminishing availability of releasable norepinephrine stores on repeated drug administration. The time frame of the tachyphylaxis will vary with individual agents.

The actions of many indirectly acting adrenomimetic drugs are reduced or abolished by the prior administration of either cocaine or tricyclic antidepressant drugs (e.g., imipramine). These compounds can block the adrenergic neuronal transport system and thereby prevent the indirectly acting drug from being taken up into the nerve and reaching the norepinephrine storage vesicles. Lipophilic drugs (e.g., amphetamine), however, can enter nerves by diffusion and do not need membrane transport systems.

 Destruction or surgical interruption of the adrenergic nerves leading to an effector tissue renders indirectly acting adrenomimetic drugs ineffective because neuronal norepinephrine is no longer available for release since the nerves have degenerated. Also, patients being treated for hypertension with reserpine or guanethidine, which deplete the norepinephrine stores in adrenergic neurons (see Chapter 20), respond poorly to administration of indirectly acting adrenomimetic drugs.

Some adrenomimetic drugs act both directly and indirectly; that is, they release some norepinephrine from storage sites and also directly activate tissue receptors. Such drugs are called mixed-action adrenomimetics. However, most therapeutically important adrenomimetic drugs in humans act either directly or indirectly.
The structure of a particular adrenomimetic drug will influence its susceptibility to metabolism by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). The actions of COMT are specific for the catechol structure. If either the meta or para hydroxyl group is absent, COMT will not metabolize the drug. The presence of a substitution, such as a methyl group, on the α-carbon of the side chain reduces the affinity of the adrenomimetic drug for MAO. Also, drugs with a large substitution on the terminal nitrogen will not be degraded by MAO. A noncatecholamine that has a methyl group attached to its α-carbon will not be metabolized by either enzyme and will have a greatly prolonged duration of action (e.g., amphetamine).

The Role of Second Messengers in Receptor-mediated Responses

The adrenomimetic drugs, including the naturally occurring catecholamines, initiate their responses by combining with α-, β-, or dopamine adrenoceptors. This interaction triggers a series of biochemical events starting within the effector cell membrane that eventually culminates in the production of a physiological response, for example contraction, secretion, relaxation, or altered metabolism. The total process of converting the action of an external signal (e.g., norepinephrine interacting with its receptor) to a physiological response (e.g., vascular smooth muscle contraction) is called signal transduction.

Following the binding of the agonist (the first messenger) to its appropriate receptor on the external surface of the effector cell, a second messenger is generated (or synthesized) and participates in a particular series of biochemical reactions that ultimately result in the generation of a specific physiological response by that cell (Figs. 10.2 and 10.3). For both α- and β-adrenoceptors, the signal transduction process seems to involve the participation of G proteins (see Chapter 2).

The specific second-messenger pathways constitute a highly versatile signaling system that can modify (stimulate or inhibit) numerous cellular processes including secretion, contraction and relaxation, metabolism, neuronal excitability, cell growth, and apoptosis. The second messengers that participate in signal transduction include cyclic adenosine monophosphate (cAMP), diacylglycerol, and inositol triphosphate. Once liberated within the cell, second messengers will activate specific

**FIGURE 10.2**
The role of cyclic 3′,5′-adenosine monophosphate (cAMP) as a second messenger in the actions of catecholamines acting on β-receptors. ATP, adenosine triphosphate.
The role of diacylglycerol (DAG) and inositol triphosphate (Ins 1,4,5 P3) as second messengers linked to agonist-receptor (α₁-adrenoceptor) interactions. PtdIns 4,5 P2 is a phosphatidylinositol precursor in cell membranes that is hydrolyzed following receptor activation to form the two second messengers, Ins 1,4,5 P3 and DAG. Once liberated within the cell, these second messengers activate separate but interacting pathways. Ins 1,4,5 P3 releases Ca²⁺ stored in cells and can be phosphorylated to form a tetraphosphate (Ins 1,3,4,5 P4), which can open Ca²⁺ channels in the membrane. DAG triggers protein phosphorylation through the activation of protein kinase C. Ca²⁺-induced activation of the enzyme calmodulin also phosphorylates protein. Adenylyl cyclase traverses the membrane. Cyclic AMP-dependent protein kinase can phosphorylate and inactivate the β-adrenoceptors. This kinase may have a role in homologous desensitization of G protein–coupled β-adrenoceptors. β-Receptor stimulation can (1) activate Ca²⁺ channels through an action of Gs proteins without the participation of cAMP and (2) affect other ion channels through phosphorylation via kinases. (Modified from Berridge MJ. Inositol triphosphate and diacylglycerol: Two interacting second messengers. ISI Atlas of Science: Pharmacology, 1:91, 1987.)
signal pathways. For example, inositol triphosphate functions by mobilizing calcium from intracellular stores or opening channels; the calcium can be used to initiate vascular smooth muscle contraction, probably through a protein phosphorylation pathway (Fig. 10.3). Diacylglycerol is known to stimulate an enzyme, protein kinase C, that phosphorylates specific intracellular proteins, some of which regulate ionic mechanisms such as the Na+/H+ exchanger and potassium channels.

The basic features of the signaling system found in different cells are remarkably similar. It appears that protein phosphorylation is a final common pathway in the molecular mechanisms through which neurotransmitters, hormones, and the nerve impulse produce many of their biological effects in target cells.

**PHARMACODYNAMIC ACTIONS OF NOREPINEPHRINE, EPINEPHRINE, AND ISOPROTERENOL**

**Vascular Effects**

The cardiovascular effects of norepinephrine, epinephrine, and isoproterenol are shown in Table 10.1. Differences in the action of these three catecholamines on various vascular beds are due both to the different affinities possessed by the catecholamines for α- and β-adrenoceptors and to differences in the relative distribution of the receptors in a particular vascular bed. The hemodynamic responses of the major vascular beds to these amines are shown in Table 10.2.

The blood vessels of the skin and mucous membranes predominantly contain α-adrenoceptors. Both epinephrine and norepinephrine produce a powerful constriction in these tissues, substantially reducing blood flow through them. Isoproterenol, which is almost a pure β-adrenoceptor agonist, has little effect on the vasculature of the skin and mucous membranes. The blood vessels in visceral organs, including the kidneys, contain predominantly α-adrenoceptors, although some β2-adrenoceptors are also present. Consequently, epinephrine and norepinephrine cause vasoconstriction and reduced blood flow through the kidneys and other visceral organs. Isoproterenol produces either no effect or weak vasodilation.

The blood vessels in skeletal muscle contain both α- and β2-adrenoceptors. Norepinephrine constricts these blood vessels and reduces blood flow through an interaction with α-adrenoceptors. Isoproterenol dilates the vessels in skeletal muscle and consequently increases blood flow through the tissue by interaction with the β2-adrenoceptors. Epinephrine has a more complex ac-

---

**Table 10.1** Cardiovascular Effects of Catecholamines in Humans (in therapeutic doses of 0.1-0.4 μg/kg/min IV or 0.5–1.0 mg SC)

<table>
<thead>
<tr>
<th>Cardiovascular function</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>++</td>
<td>+++</td>
<td>0+</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>++0–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>– –</td>
<td>+++</td>
<td>– –</td>
</tr>
<tr>
<td>Heart rate (chronotropic effect)</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Stroke output (inotropic effect)</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>+ + +</td>
<td>– 0</td>
<td>+ + +</td>
</tr>
</tbody>
</table>

Key: 0 = no effect; + = increased; – = decreased. The number of symbols indicates the approximate magnitude of the response.

---

**Table 10.2** Response of the Major Vascular Beds to Usual Doses of the Catecholamines

<table>
<thead>
<tr>
<th>Vascular bed</th>
<th>Receptor type*</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous blood vessels</td>
<td>α</td>
<td>Constriction</td>
<td>Constriction</td>
<td>None</td>
</tr>
<tr>
<td>Visceral blood vessels</td>
<td>α</td>
<td>Constriction</td>
<td>Constriction</td>
<td>None (weak dilation)</td>
</tr>
<tr>
<td>Renal blood vessels</td>
<td>α</td>
<td>Constriction</td>
<td>Constriction</td>
<td>None (weak dilation)</td>
</tr>
<tr>
<td>Coronary blood vessels</td>
<td>α, β</td>
<td>Dilation</td>
<td>Dilation</td>
<td>Dilation</td>
</tr>
<tr>
<td>Skeletal muscle blood vessels</td>
<td>α, β2</td>
<td>Constriction/dilation</td>
<td>Dilation/dilation</td>
<td>Dilation</td>
</tr>
<tr>
<td>Pial blood vessels</td>
<td>α, β1</td>
<td>Constriction/dilation</td>
<td>Dilation/dilation</td>
<td>Dilation</td>
</tr>
</tbody>
</table>

*While virtually all blood vessels have α1-receptors, some also have α2-receptors. Stimulation of either subtype generally results in vasoconstriction.
tion on these blood vessels because of its high affinity for both α- and β₁-adrenoceptors. Whether epinephrine produces vasodilation or vasoconstriction in skeletal muscle depends on the dose administered. Low doses of epinephrine will dilate the blood vessels; larger doses will constrict them.

Although several factors can influence the flow of blood through the coronary vessels, the most important of these is the local production of vasodilator metabolites that results from stimulation-induced increased work by the heart. α-Adrenoceptors and β₁-adrenoceptors in the coronary vascular beds do not play a major role in determining the vasodilator effects of the administration of epinephrine or norepinephrine.

**Effects on the Intact Cardiovascular System**

An increase in sympathetic neuronal activity causes an increase in heart rate (positive chronotropic effect, or tachycardia) and an increase in cardiac contractile force (positive inotropic effect) such that the stroke output is increased. Cardiac output, which is a function of rate and stroke output, is thus increased. A physiological increase in sympathetic tone is almost always accompanied by a diminution of parasympathetic vagal tone; this allows full expression of the effects of increased sympathetic tone on the activity of the heart.

An increase in sympathetic tone constricts blood vessels in most vascular beds and therefore causes a net increase in total peripheral resistance. Increased sympathetic tone increases neural release of norepinephrine and its interaction both with β₁-adrenoceptors on cardiac cells and with α₁-adrenoceptors on vascular smooth muscle cells. As a consequence, the systolic and diastolic blood pressures are elevated. It follows that the mean arterial blood pressure must also be increased.

**Norepinephrine**

Norepinephrine, administered to a normotensive adult either subcutaneously or by slow intravenous injection, constricts most blood vessels. Venules as well as arterioles are constricted. As a consequence, there is a net increase in the total peripheral resistance.

The effects of norepinephrine on cardiac function are complex because of the dynamic interaction of the direct effects of norepinephrine on the heart and the initiation of powerful cardiac reflexes. The baroreceptor reflexes are discussed in detail in Chapter 9.

Important considerations are as follows: (1) **The direct effect of norepinephrine on the heart is stimulatory.** (2) **The reflex initiated is inhibitory,** that is, opposite to the direct effect. (3) The reflex varies with the level of sympathetic and parasympathetic activity just before the initiation of the reflex. (4) The distribution of sympathetic and parasympathetic nerves is not uniform in the heart.

The net effect of norepinephrine administration on heart rate and ventricular contractile force therefore varies with the dose of norepinephrine, the physical activity of the subject, any prior cardiovascular and baroreceptor pathology, and the presence of other drugs that may alter reflexes.

In a normal resting subject who is receiving no drugs, there is a moderate parasympathetic tone to the heart, and sympathetic activity is relatively low. The ventricular muscle receives little, if any, parasympathetic innervation. As the blood pressure rises in response to norepinephrine, the baroreceptor reflex is activated, parasympathetic impulses (which are inhibitory) to the heart increase in frequency, and what little sympathetic outflow there is may be reduced. Heart rate is slowed so much that the direct effect of norepinephrine to increase the rate is masked and there is a net decrease in rate. Under the conditions described, however, the impact of the reflex on the ventricles is very slight because there is no parasympathetic innervation and the preexisting level of sympathetic activity is already low. A further decrease in sympathetic activity therefore would have little further effect on contractility in this subject. Thus, a decrease in heart rate and an increase in stroke volume will occur, and cardiac output will change very little.

The reflex nature of the bradycardia induced by parenterally administered norepinephrine can readily be demonstrated by administration of atropine, a cholinergic antagonist. Atropine abolishes the compensatory vagal reflexes. Under conditions of vagal blockade, the direct cardiac stimulatory effects of norepinephrine are unmasked. There is marked tachycardia, an increase in stroke volume, and as a consequence, a marked increase in cardiac output (Fig. 10.4).

**Epinephrine**

A small dose of epinephrine causes a fall in mean and diastolic pressure with little or no effect on systolic pressure. This is due to the net decrease in total peripheral resistance that results from the predominance of vasodilation in the skeletal muscle vascular bed. The intravenous infusion or subcutaneous administration of epinephrine in the range of doses used in humans generally increases the systolic pressure, but the diastolic pressure is decreased. Therefore, the mean pressure may decrease, remain unchanged, or increase slightly, depending on the balance between the rise in systolic and fall in diastolic blood pressures (Fig. 10.4).

The cardiac effects of epinephrine are due to its action on β₁-adrenoceptors in the heart. The rate and contractile force of the heart are increased; consequently, cardiac output is markedly increased. Because total peripheral resistance is decreased, the increase in cardiac output is largely responsible for the increase in systolic pressure. Since epinephrine causes little change in the
mean arterial blood pressure, reflex slowing of the heart is usually not seen in humans.

**Isoproterenol**

Slow intravenous infusion of therapeutic doses of isoproterenol in humans produces a marked decrease in total peripheral resistance, owing to the predominance of vasodilation in skeletal muscle vascular beds. As a consequence, diastolic and mean blood pressures fall (Fig. 10.4). The depressor action of isoproterenol is more pronounced than that of epinephrine because isoproterenol causes no vasoconstriction, whereas epinephrine does in some vascular beds. Systolic blood pressure may remain unchanged or may increase. When an increase in systolic blood pressure is seen, it is due to the marked increase in cardiac output produced by isoproterenol.

Isoproterenol usually increases the heart rate and stroke volume more than does epinephrine. This is partly due to its ability to decrease mean blood pressure, which then reflexively diminishes vagal activity, and partly to its action on the heart.

**Effects on Vascular Smooth Muscle**

Postjunctional α₁-adrenoceptors are always found in veins, arteries, and arterioles. Activation of these receptors results in the entry of extracellular calcium through receptor-operated channels and in the release of intracellularly stored calcium; this is brought about through the participation of the inositol triphosphate second-messenger system. This system plays an important role in the regulation of blood pressure and vascular tone.

Vascular endothelium also plays an important role in maintaining vascular tone. The endothelium can modulate both vasodilation and vasoconstriction through its ability to locally synthesize and release vasodilators such as nitric oxide, endothelium-derived hyperpolarizing factor, and PGI₂, and vasoconstrictors such as endothelin, which in turn directly affect vascular smooth muscle activity. Stimulation of α₂-adrenoceptors located on the endothelial cells in certain vascular beds (such as the coronary artery) results in the release of nitric oxide and vasodilation.

In any blood vessel, the final integrated response to either neuronally released norepinephrine or to circulating epinephrine probably depends on the relative participation of at least four populations of α-adrenoceptors: postjunctional α₁- and α₂-adrenoceptors mediate constriction of vascular smooth muscle, while prejunctional and endothelial α₂-adrenoceptors mediate vasodilation. An understanding of the vessel vascular response to adrenomimetic drugs also must include the effects of drugs on adventitial innervation, smooth muscle, and other vascular factors that may be present.

**Effects on Nonvascular Smooth Muscle**

In general, the responses to administered catecholamines are similar to those seen after sympathetic nerve stimulation and depend on the type of adrenoceptor in the muscle.
Bronchial smooth muscle is relaxed by epinephrine and isoproterenol through their interaction with β₂-adrenoceptors. Epinephrine and isoproterenol are potent bronchodilators, while norepinephrine has a relatively weak action in this regard (see Chapter 39).

Smooth muscle of the gastrointestinal tract is generally relaxed by catecholamines, but this may depend on the existing state of muscle tone. Usually motility of the gut is reduced by catecholamines while the gastrointestinal sphincters are contracted. Catecholamines appear to produce relaxation of the gut through an action on α₂-adrenoceptors on ganglionic cells. Activation of these receptors reduces acetylcholine release from cholinergic neurons. Catecholamines also may produce gastrointestinal relaxation through an action on β₂-adrenoceptors on smooth muscle cells. Contraction of the sphincters occurs through an action on α₁-adrenoceptors. These effects are quite transient in humans and therefore have no therapeutic value.

The radial (dilator) muscle of the iris contains α-adrenoceptors. Epinephrine and norepinephrine cause dilation of the pupil (mydriasis) by contracting the dilator muscle.

Uterine muscle contains both α- and β-adrenoceptors, which mediate contraction and relaxation, respectively. The response of the human uterus to catecholamines is variable and depends on the endocrine balance of the individual at the time of amine administration (see Chapter 62). During the last stage of pregnancy and during parturition, epinephrine inhibits the uterine muscle, as does isoproterenol; norepinephrine contracts the uterus.

The detrusor muscle (which contains β₁-adrenoceptors) in the body of the urinary bladder is relaxed by epinephrine and isoproterenol. On the other hand, the trigone and sphincter (which contain α₁-receptors) are contracted by norepinephrine and epinephrine; this action inhibits the voiding of urine.

Central Nervous System Effects

Epinephrine, in therapeutic doses, mildly stimulates the CNS. The most noticeable features of this stimulation are apprehension, restlessness, and increased respiration. In therapeutic doses both isoproterenol and norepinephrine also have minor CNS stimulant properties. Since these compounds do not easily cross the blood-brain barrier, the mechanism of their stimulatory effects is not clear. It is likely that the stimulating effects are primarily, if not entirely, due to actions in the periphery that alter the neural input to the CNS.

Metabolic Effects

The catecholamines, primarily epinephrine and isoproterenol, exert a number of important effects on metabolic processes. Most of these are mediated through an interaction with β-adrenoceptors. Norepinephrine is usually effective only in large doses. Epinephrine and isoproterenol in therapeutic doses increase oxygen consumption by 20 to 30%. Endogenous epinephrine secreted by the adrenal medulla in response to stress such as exercise increases blood levels of glucose, lactic acid, and free fatty acids.

Epinephrine, the most potent stimulant of hepatic glycogenolysis, gives rise to glucose, which readily enters the circulation; isoproterenol produces relatively weak hyperglycemia. Administration of both α- and β-adrenoceptor blocking agents is necessary for complete antagonism of glycogenolysis in this tissue.

Isoproterenol is the most potent stimulant of skeletal muscle glycogenolysis, followed by epinephrine and norepinephrine. β₂-Adrenoceptors mediate muscle glycogenolysis. Stimulation of skeletal muscle glycogenolysis will raise blood lactic acid levels rather than blood glucose levels because skeletal muscle lacks the enzyme glucose-6-phosphatase, which catalyzes the conversion of glucose-6-phosphate to glucose.

The release of free fatty acids from adipose tissue (lipolysis) is mediated through β₁-adrenoceptors. Isoproterenol is the most potent agonist, followed by epinephrine and norepinephrine.

Potassium Homeostasis

The catecholamines can play an important role in the short-term regulation of plasma potassium levels. Stimulation of hepatic α-adrenoceptors will result in the release of potassium from the liver. In contrast, stimulation of β₂-adrenoceptors, particularly in skeletal muscle, will lead to the uptake of potassium into this tissue. The β₂-adrenoceptors are linked to the enzyme Na⁺, K⁺ adenosine triphosphatase (ATPase). Excessive stimulation of these β₂-adrenoceptors may produce hypokalemia, which in turn can be a cause of cardiac arrhythmias.

PHARMACOLOGICAL ACTIONS OF DOPAMINE

Dopamine is a naturally occurring catecholamine; it is the immediate biochemical precursor of the norepinephrine found in adrenergic neurons and the adrenal medulla. It is also a neurotransmitter in the CNS, where it is released from dopaminergic neurons to act on specific dopamine receptors (see Chapter 31).

Dopamine is a unique adrenomimetic drug in that it exerts its cardiovascular actions by (1) releasing norepinephrine from adrenergic neurons, (2) interacting with α- and β₁-adrenoceptors, and (3) interacting with specific dopamine receptors.
The cardiovascular response to dopamine in humans depends on the concentration infused. Low rates of dopamine infusion can produce vasodilation in the renal, mesenteric, coronary, and intercerebral vascular beds with little effect on other blood vessels or on the heart. The vasodilation produced by dopamine is not antagonized by the β-adrenoceptor blocking agent propranolol but is antagonized by haloperidol and other dopamine receptor-blocking agents.

Dopamine can exert pronounced cardiovascular and renal effects through the activation of both D₁ and D₂-receptor subtypes. Stimulation of the D₁-receptor, which is present on blood vessels and certain other peripheral sites, will result in vasodilatation, natriuresis, and diuresis. D₂-receptors are found on ganglia, on sympathetic nerve terminals, on the adrenal cortex, and within the cardiovascular centers of the CNS; their activation produces hypotension, bradycardia, and regional vasodilatation (e.g., renal vasodilation). The kidney appears to be a particularly rich source for endogenous dopamine in the periphery.

The infusion of moderately higher concentrations of dopamine increases the rate and contractile force of the heart and augments the cardiac output. This action is mediated by β₁-adrenoceptors and norepinephrine release and is antagonized by propranolol. In contrast to isoproterenol, which has a marked effect on both the rate and the contractile force of the heart, dopamine has a greater effect on the force than on cardiac rate. The advantage of this greater inotropic than chronotropic effect of dopamine is that it produces a smaller increase in oxygen demand by the heart than does isoproterenol. Systolic blood pressure is increased by dopamine, whereas diastolic pressure is usually not changed significantly. Total peripheral resistance is decreased because of the vasodilator effect of dopamine (Fig. 10.4).

At still higher concentrations, dopamine causes α-adrenoceptor-mediated vasoconstriction in most vascular beds and stimulates the heart. Total peripheral resistance may be increased. If the concentration of dopamine reaching the tissue is high enough, vasoconstriction of the renal and mesenteric beds also occurs. The vasoconstrictive action of dopamine is antagonized by α-adrenoceptor blocking agents such as phentolamine.

**CLINICAL USES OF CATECHOLAMINES**

The clinical uses of catecholamines are based on their actions on bronchial smooth muscle, blood vessels, and the heart. Epinephrine is also useful for the treatment of allergic reactions that are due to liberation of histamine in the body, because it produces certain physiological effects opposite to those produced by histamine. It is the primary treatment for anaphylactic shock and is useful in the therapy of urticaria, angioneurotic edema, and serum sickness.

Epinephrine also has been used to lower intraocular pressure in open-angle glaucoma. Its use promotes an increase in the outflow of aqueous humor. Because epinephrine administration will decrease the filtration angle formed by the cornea and the iris, its use is contraindicated in angle-closure glaucoma; under these conditions the outflow of aqueous humor via the filtration angle and into the venous system is hindered, and intraocular pressure may rise abruptly.

The vasoconstrictor actions of epinephrine and norepinephrine have been used to prolong the action of local anesthetics by reducing local blood flow in the region of the injection. Epinephrine has been used as a topical hemostatic agent for the control of local hemorrhage. Norepinephrine is infused intravenously to combat systemic hypotension during spinal anesthesia or other hypotensive conditions in which peripheral resistance is low, but it is not used to combat the hypotension due to most types of shock. In shock, marked sympathetic activity is already present, and perfusion of organs, such as the kidneys, may be jeopardized by norepinephrine administration.

Dopamine is used in the treatment of shock owing to inadequate cardiac output (cardiogenic shock), which may be due to myocardial infarction or congestive heart failure. It is also used in the treatment of septic shock, since renal circulation is frequently compromised in this condition. An advantage of using dopamine in the treatment of shock is that its inotropic action increases cardiac output while dilating renal blood vessels and thereby increasing renal blood flow.

**Adverse Effects**

Because they increase the force of the heartbeat, all three catecholamines may produce an excessively rapid heart rate. Palpitations produced by epinephrine and isoproterenol are accompanied by tachycardia, whereas those produced by norepinephrine usually are accompanied by bradycardia owing to reflex slowing of the heart. Headache and tremor are also common. Epinephrine is especially likely to produce anxiety, fear, and nervousness.

The greatest hazards of accidental overdosage with epinephrine and norepinephrine are cardiac arrhythmias, excessive hypertension, and acute pulmonary edema. Large doses of isoproterenol can produce such excessive cardiac stimulation, combined with a decrease in diastolic blood pressure, that coronary insufficiency may result. It also may cause arrhythmias and ventricular fibrillation. Tissue sloughing and necrosis due to severe local ischemia may follow extravasation of norepinephrine at its injection site.
OTHER ADRENOMIMETIC AGENTS

A number of adrenomimetic amines are not catecholamines. Some of these are directly acting amines that must interact with adrenoceptors to produce a response in effector tissues. Some directly acting compounds, such as phenylephrine and methoxamine, activate \( \alpha \)-adrenoceptors almost exclusively, whereas others, like albuterol and terbutaline, are nearly pure \( \beta \)-adrenoceptor agonists. Drugs that exert their pharmacological actions by releasing norepinephrine from its neuronal stores (indirectly acting) produce effects that are similar to those of norepinephrine. They tend to exert strong \( \alpha \)-adrenoceptor activity, but \( \beta \)-adrenoceptor activity typical of norepinephrine, such as myocardial stimulation, also occurs.

Some of the indirectly acting adrenomimetic amines are used primarily for their vasoconstrictive properties. They are applied locally to the nasal mucosa or to the eye. Other amines are used as bronchodilators, while still others are used exclusively for their ability to stimulate the CNS. Many noncatecholamine adrenomimetic amines resist enzymatic destruction, have prolonged actions, and are orally effective. The indirectly acting drugs are effective only when given in large doses, and they often produce tachyphylaxis.

**Directly Acting Adrenomimetic Drugs**

**Phenylephrine, Metaraminol, and Methoxamine**

These drugs are directly acting adrenomimetic amines that exert their effects primarily through an action on \( \alpha \)-adrenoceptors. Consequently, these agents have little or no direct action on the heart. All three drugs increase both systolic and diastolic blood pressures through their vasoconstrictor action. The pressor response is accompanied by reflex bradycardia, no change in the contractile force of the heart, and little change in cardiac output. They do not precipitate cardiac arrhythmias and do not stimulate the CNS.

Phenylephrine is not a substrate for COMT, while metaraminol and methoxamine are not metabolized by either COMT or MAO. Consequently, their duration of action is considerably longer than that of norepinephrine. Following intravenous injection, pressor responses to phenylephrine may persist for 20 minutes, while pressor responses to metaraminol and methoxamine may last for more than 60 minutes.

The clinical uses of these drugs are associated with their potent vasoconstrictor action. They are used to restore or maintain blood pressure during spinal anesthesia and certain other hypotensive states. The reflex bradycardia induced by their rapid intravenous injection has been used to terminate attacks of paroxysmal atrial tachycardia. Phenylephrine is commonly used as a nasal decongestant, although occasional nasal mucosal damage has occurred from injudicious use of the nasal spray. It is also employed in ophthalmology as a mydriatic agent. Phenylephrine, however, should not be given to patients with closed-angle glaucoma before iridectomy, since further increases in intraocular pressure may result. In dentistry, phenylephrine is used to prolong the effectiveness of a local anesthetic.

**Dobutamine**

Dobutamine (Dobutrex), in contrast to dopamine, does not produce a significant proportion of its cardiac effects through the release of norepinephrine from adrenergic nerves; dobutamine acts directly on \( \beta \)-adrenoceptors in the heart. Dobutamine exerts a greater effect on the contractile force of the heart relative to its effect on the heart rate than does dopamine. Dobutamine increases the oxygen demands on the heart to a lesser extent than does dopamine. Like dopamine, although at higher doses, it produces vasodilation of renal and mesenteric blood vessels. Dobutamine may be more useful than dopamine in the treatment of cardiogenic shock.

**Terbutaline and Albuterol**

Terbutaline and albuterol are relatively selective \( \beta_2 \)-adrenoceptor agonists. Both have a longer duration of action than isoproterenol because they are not metabolized by COMT. Like isoproterenol, they are not metabolized by MAO and are not transported into adrenergic neurons. Terbutaline and albuterol are effectively administered either orally or subcutaneously. Because of their selectivity for \( \beta_2 \)-adrenoceptors, they produce less cardiac stimulation than does isoproterenol but are not completely without effects on the heart.

Therapeutically, terbutaline and albuterol are used to treat bronchial asthma and bronchospasm associated with bronchitis and emphysema (see Chapter 39).

Side effects include nervousness, tremor, tachycardia, palpitations, headache, nausea, vomiting, and sweating. The frequency of appearance of these adverse effects is minimized, however, when the drugs are given by inhalation.

**Indirectly Acting Adrenomimetic Drugs**

**Ephedrine**

Ephedrine is a naturally occurring alkaloid that can cross the blood-brain barrier and thus exert a strong CNS-stimulating effect in addition to its peripheral actions. The latter effects are primarily due to its indirect actions and depend largely on the release of norepinephrine. However, ephedrine may cause some direct receptor stimulation, particularly in its bronchodilating effects. Because it resists metabolism by both COMT and MAO, its duration of action is longer than that of norepinephrine. As is the case with all indirectly acting adrenomimetic amines,
ephedrine is much less potent than norepinephrine; in addition, tachyphylaxis develops to its peripheral actions. Unlike epinephrine or norepinephrine, however, ephedrine is effective when administered orally.

**Pharmacological Actions**

Ephedrine increases systolic and diastolic blood pressure; heart rate is generally not increased. Contractile force of the heart and cardiac output are both increased. Ephedrine produces bronchial smooth muscle relaxation of prolonged duration when administered orally. Aside from pupillary dilation, ephedrine has little effect on the eye.

**Clinical Uses**

Ephedrine is useful in relieving bronchoconstriction and mucosal congestion associated with bronchial asthma, asthmatic bronchitis, chronic bronchitis, and bronchial spasms. It is often used prophylactically to prevent asthmatic attacks and is used as a nasal decongestant, as a mydriatic, and in certain allergic disorders. Although its bronchodilator action is weaker than that of isoproterenol, its oral effectiveness and prolonged duration of action make it valuable in the treatment of these conditions. Because of their oral effectiveness and greater bronchiolar selectivity, terbutaline and albuterol are replacing ephedrine for bronchodilation.

**Adverse Effects**

Symptoms of overdose are related primarily to cardiac and CNS effects. Tachycardia, premature systoles, insomnia, nervousness, nausea, vomiting, and emotional disturbances may develop. Ephedrine should not be used in patients with cardiac disease, hypertension, or hyperthyroidism.

**Amphetamine**

Amphetamine is an indirectly acting adrenomimetic amine that depends for its action on the release of norepinephrine from noradrenergic nerves. Its pharmacological effects are similar to those of ephedrine; however, its CNS stimulant activity is somewhat greater. Both systolic and diastolic blood pressures are increased by oral dosing with amphetamine. The heart rate is frequently slowed reflexively. Cardiac output may remain unchanged in the low- and moderate-dose range.

The therapeutic uses of amphetamine are based on its ability to stimulate the CNS. The D-isomer (dextroamphetamine) is three to four times as potent as the L-isomer in producing CNS effects. It has been used in the treatment of obesity because of its anorexic effect, although tolerance to this effect develops rapidly. It prevents or overcomes fatigue and has been used as a CNS stimulant. Amphetamine is no longer recommended for these uses because of its potential for abuse. Amphetamine is useful in certain cases of narcolepsy or minimal brain dysfunction.

Further discussion of amphetamine can be found in Chapters 29 and 35.

---

**Study Questions**

1. Selective β₂-agonists, such as terbutaline
   - (A) Have shorter durations of action than catecholamines when taken orally
   - (B) Have stronger cardiac stimulant effects than epinephrine
   - (C) Can be taken orally because these agents are not degraded by COMT
   - (D) Are definitely no better than methylxanthines for asthmatic patients who are hypertensive.

2. Which drug does not induce mydriasis?
   - (A) Phenylephrine
   - (B) Cocaine
   - (C) Phentolamine
   - (D) Norepinephrine
   - (E) Ephedrine

3. Epinephrine given in small therapeutic doses
   - (A) Increases systolic blood pressure through β₂-receptor stimulation in the left ventricle
   - (B) Decreases heart rate reflexively.
   - (C) Decreases peripheral resistance through stimulation of β₁-receptors on the vascular smooth muscle cells.
   - (D) Decreases peripheral resistance through β₂-adrenoceptor stimulation predominantly in skeletal muscle vascular beds.

4. The pressor response to amphetamine is
   - (A) Decreased in the presence of a monoamine oxidase (MAO) inhibitor.
   - (B) Potentiated by a reuptake inhibitor, such as cocaine
   - (C) Associated with marked tolerance (tachyphylaxis)
   - (D) Potentiated by pretreatment with reserpine

5. When phenylephrine is administered by slow infusion of the therapeutic dose, which is the most likely effect illustrated in the following table: increase (↑); decrease (↓); no change (0)?
ANSWERS

1. C. Structural modification by placing the hydroxy groups at positions 3 and 5 of the phenyl ring has resulted in compounds that are not substrates for COMT, resulting in lower rates of metabolism and enhanced oral bioavailability compared to catecholamines.

2. C. α-Adrenoceptors mediate contraction of the radial muscle of the iris. The shortening of the radial muscle cells opens the pupil. Phentolamine blocks α-adrenoceptors, allowing parasympathetic nerves innervating the sphincter muscle to take over. This leads to a less opposed contraction of the sphincter muscle induced by transmitter acetylcholine and a constriction of the pupil or miosis.

3. D. A small dose of epinephrine (0.1 μg/kg) given by intravenous route may cause the blood pressure to fall, decreasing peripheral resistance. The depressor effect of small doses is due to greater sensitivity to epinephrine of vasodilator β2-adrenoceptors than of constrictor α-adrenoceptors and a dominant action on β2-adrenoceptors of vessels in skeletal muscle. Consequently, diastolic blood pressure usually falls. The mean blood pressure in general, however, is not greatly elevated. The compensatory baroreceptor reflexes do not appreciably antagonize the direct cardiac actions.

4. C. Amphetamine is an indirectly acting adrenomimetic amine that depends on the release of norepinephrine from noradrenergic nerves for its action. Thus, its effect depends on neuronal uptake (blocked by cocaine) to displace norepinephrine from the vesicles and the availability of norepinephrine (depleted by reserpine). The substitution on the α-carbon atom blocks oxidation by monoamine oxidase. With no substitution on its benzene ring, amphetamine resists metabolism by COMT.

5. B. Phenylephrine is an α1-selective agonist. It causes an increase in peripheral vascular resistance. The major cardiovascular response to this drug is a rise in blood pressure associated with reflex bradycardia. The slowing of the heart rate is blocked by atropine.

SUPPLEMENTAL READING


Case Study  Help for the Heart

T. L. is a highly successful scientist who spends long hours in the laboratory and is constantly in demand as a speaker and reviewer for scientific papers and grants. He has a family history of cardiovascular disease, having lost both his father and grandfather before either reached age 60. He has recently noticed decreased energy, especially during exercise, and had symptoms (difficulty in breathing, chest pain) that took him to the emergency department. The examining physician thought the best treatment would be short-term therapy with a directly acting inotropic agent, especially one that would not markedly increase an already elevated heart rate. Based on a knowledge of the distribution of cardiovascular autonomic receptors, which of the following agents—epinephrine, norepinephrine, amphetamine, or dobutamine—would be a logical choice to use in this initial short-term treatment?

**Answer:** Dobutamine injection would provide particular benefit in meeting the therapeutic needs of this patient. Dobutamine augments ventricular contractility and thus enhances cardiac output, especially stroke volume, in patients with depressed cardiac function. It does this by stimulating β-adrenoceptors in the heart while producing relatively little increase in chronotropic activity or any significant elevation in systemic blood pressure since it lacks α-adrenoceptor stimulating effects. Thus, in contrast to a nonselective β-adrenoceptor stimulant such as isoproterenol, which increases cardiac output primarily by increasing heart rate, dobutamine’s actions increase cardiac output without being accompanied by either a marked increase in heart rate or a significant increase in systemic vascular resistance.