Chapter 13

AUTONOMIC NERVOUS SYSTEM PHARMACOLOGY

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The autonomic nervous system (ANS) maintains homeostasis by integrating signals from peripheral and central sensors to modulate organ perfusion and function. Autonomic "tone" maintains cardiac muscle, visceral organs, and vascular smooth muscle in a state of intermediate function. From this state, rapid increases or decreases in autonomic outflow can adjust blood flow and organ activity in response to the environment. The rapidity of the ANS response is impressive considering that neurotransmitters must be released from terminals, cross a synaptic cleft to an effector site, bind to a receptor, and initiate an intracellular event. For example, in just a few seconds, ANS activation can double heart rate (HR) and arterial blood pressure (BP). In a nearly similar time frame it can cause sweating, nausea, loss of bladder control, and fainting. The sympathetic nervous system (SNS) has been called the "fight-or-flight" response system and is activated under stress. In contrast, the parasympathetic nervous system is responsible for "rest and digest." The anatomy and physiology of the ANS are discussed in Chapter 12.

In the perioperative and intensive care settings, multiple factors disrupt the typically tight ANS control of organ and vascular homeostasis. Thus pharmacologic activation or inhibition of the ANS is commonplace in these settings. For example, both general and regional anesthesia have powerful influences on normal ANS function. When an inhaled anesthetic acts to directly relax vascular smooth muscle and lower BP, the ANS reacts to counteract hypotension via baroreflex adjustments of ANS activity. However, a second effect of volatile anesthetics is to impair baroreflex function. The net effect of these influences requires treatment of unwanted hypotension with sympathomimetic or vagolytic drugs. Laryngoscopy and tracheal intubation or surgical incision powerfully activate the SNS; adrenergic receptor blocking drugs are used to dampen these responses.

HISTORICAL PERSPECTIVE

The sympathomimetic properties of the Ma-huang plant were appreciated in China as early as 3000 BC. Ma-huang was used as a diaphoretic, circulatory stimulant, antipyretic, and sedative for cough.[1] Ephedrine, the main alkaloid of Ma-huang, was isolated in 1886.[2] Over the next 25 years, adrenal extracts were described and analyzed, and the term *sympathomimetic* was coined. Adrenergic receptors were

identified and subdivided into two primary types (α and β) according to their responses to epinephrine and norepinephrine.[3] The β-receptors were further divided into β1-, β2-, and β3-receptors based on their actions at receptors and sensitivities to inhibitors.[4-6] The α-receptors were similarly subdivided into α1- and α2-receptors, but have been further subdivided into $\alpha1_a$-, $\alpha1_b$-, $\alpha1_d$-, $\alpha2_a$-, $\alpha2_b$-, and $\alpha2_c$-receptors based on their pharmacology and associated second messenger systems.[7,8]

The history of parasympatholytic drugs dates back to ancient times when Mandragora, the mandrake plant, was used for wounds and sleeplessness. Henbane, which contains atropine, was used in ancient Egyptian times as a mydriatic. In the Middle Ages, henbane extract was used to enhance the inebriating qualities of beer and by "witches" to produce flushed skin and vivid hallucinations.

Muscarine, the first parasympathomimetic drug, derives from the fungus *Amanita muscaria* and was described in 1869. It was found to bind receptors that would be called *muscarinic* and had the same effect on the heart as did stimulation of the vagus nerve. Originally discovered by Loewi, the "heart inhibiting" substance that decreased HR and contractility was acetylcholine.[9] Muscarinic receptors are activated by acetylcholine and are thus called *cholinergic*.

STRUCTURE AND MECHANISM OF ADRENERGIC RECEPTORS

The basic catecholamine structure is an aromatic phenylethylamine with two hydroxyl groups. The name *catecholamine* derives from the molecule 3,4-dihydroxylphenyl, known as *catechol*. Epinephrine and norepinephrine have a chiral center at the hydroxyl group on the β-carbon, where the L-isomer is active, while dopamine has no chiral center (Figure 13-1). Intravenous formulations of epinephrine and norepinephrine consist of the L-isomer; a racemic formulation of epinephrine is available for inhalation.

Epinephrine and norepinephrine are predominantly charged molecules at physiologic pH due to their amine moiety and are unable to cross lipid cellular membranes on their own (although they can cross via transporters). Their actions are mediated following signal transduction by transmembrane receptors that initiate intracellular signaling events. Adrenergic receptors are coupled to guanine nucleotide binding proteins (G proteins) that couple the receptor to an effector system (see Chapter 1). Adrenergic G protein-coupled receptors (GPCRs) are classified according to their actions on adenylyl cyclase and their sensitivity to pertussis toxin. The structure of the β-adrenergic receptor is consistent with most GPCRs, with seven transmembrane segments.[10] The signaling cascade of β1- and β2-adrenergic receptors begins with ligand binding to the amino terminus of the receptor on the extracellular surface, then proceeds to the intracellular carboxyl terminal loop of the receptor coupling to G_s-proteins, which stimulate adenylyl cyclase to convert adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (AMP). The resulting phosphorylation by cyclic AMP-dependent protein kinase produces cellular responses.[11,12] The atomic resolution structure of the β2-receptor bond to G_s has recently been determined and shows the involvement of the amino- and carboxy-terminal alpha helices of G_s as the main interaction between the two proteins. The activated receptor demonstrates outward movement of the sixth transmembrane segment and the presence of a second intracellular loop between the β2-adrenergic receptor-G_s complex. The receptor is stabilized extracellularly by fusion of the amino-terminus to T4 lysozyme, and intracellularly by numerous interactions with G_s. The Gβ and Gγ subunits of G_s do not directly interact with the β2-adrenergic receptor.[13]

The α2-receptors are coupled to G_i-proteins to inhibit adenylyl cyclase. The α1-receptors are coupled to G_q-proteins activating phospholipase C that hydrolyzes phosphatidylinositol diphosphates (PIP_2) to the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 activates Ca^{2+} release from intracellular stores via IP_3 receptors, while DAG activates lipid mediated signaling pathways including members of the protein kinase C family.[14]

Dopamine receptors also are GPCRs and are classified as D1-type (D1 and D5) and D2-type (D2, D3, and D4) receptors.[15] These receptors are located throughout the central nervous system (CNS), on SNS postganglionic nerve terminals, on afferent and efferent arterioles of the nephron, and in the adrenal glands. D1-like receptors stimulate adenylyl cyclase via G_s, and D2-like receptors inhibit adenylyl cyclase via G_i. D1-receptors are postsynaptic and stimulation mimics β2 effects, leading to regional vascular dilation. D2-like receptors occur at presynaptic and postsynaptic sites. Presynaptic D2-like receptor activation inhibits norepinephrine release from sympathetic terminals, an effect similar to the presynaptic effects of acetylcholine and α2-agonists. Postsynaptic sites mimic α1 and α2 vasoconstriction on blood vessels, but this action is relatively weak.

The α1-adrenoceptors are activated by the selective α1-receptor agonists phenylephrine and methoxamine, and inhibition by low concentrations of the antagonist prazosin. The α1-receptors are widely distributed, and when stimulated mediate primarily arterial and venous vascular constriction (Table 13-1). The α2-adrenoceptors are activated by the selective α2-receptor agonists clonidine and dexmedetomidine and are blocked by the antagonist yohimbine; they exist as three subtypes: $\alpha2_a$, $\alpha2_b$, and $\alpha2_c$.[16] The α2-receptors are located presynaptically on sympathetic neurons where they inhibit the release of norepinephrine. Postsynaptic α2-receptors are located on blood vessels and in tissues including liver, pancreas, platelets, kidney, adipose tissue, and the eye (Figure 13-2). Within the CNS, receptors in the locus ceruleus likely account for the sedative properties of α2-agonists, and in the medullary dorsal horn area for the reduction in sympathetic outflow.[17] The α2-receptors are also in the vagus nerve, intermediolateral cell column, and the substantia gelatinosa. The dorsal horn of the spinal cord contains $\alpha2_a$-adrenoceptors co-localized with opioid receptors that modulate afferent pain signals.

Both β1- and β2-adrenergic receptors are characterized by their stimulation by epinephrine and norepinephrine and are heavily expressed in myocardial tissue including atria, ventricular papillary muscle, sinoatrial and atrioventricular nodes, left and right bundles, and Purkinje fibers. They have inotropic (increased contractility), chronotropic (increased HR), and dromotropic (increased conduction velocity) effects (Figure 13-3). Activation of β1-receptors increases renin and aqueous humor production. The β2-receptors are the major

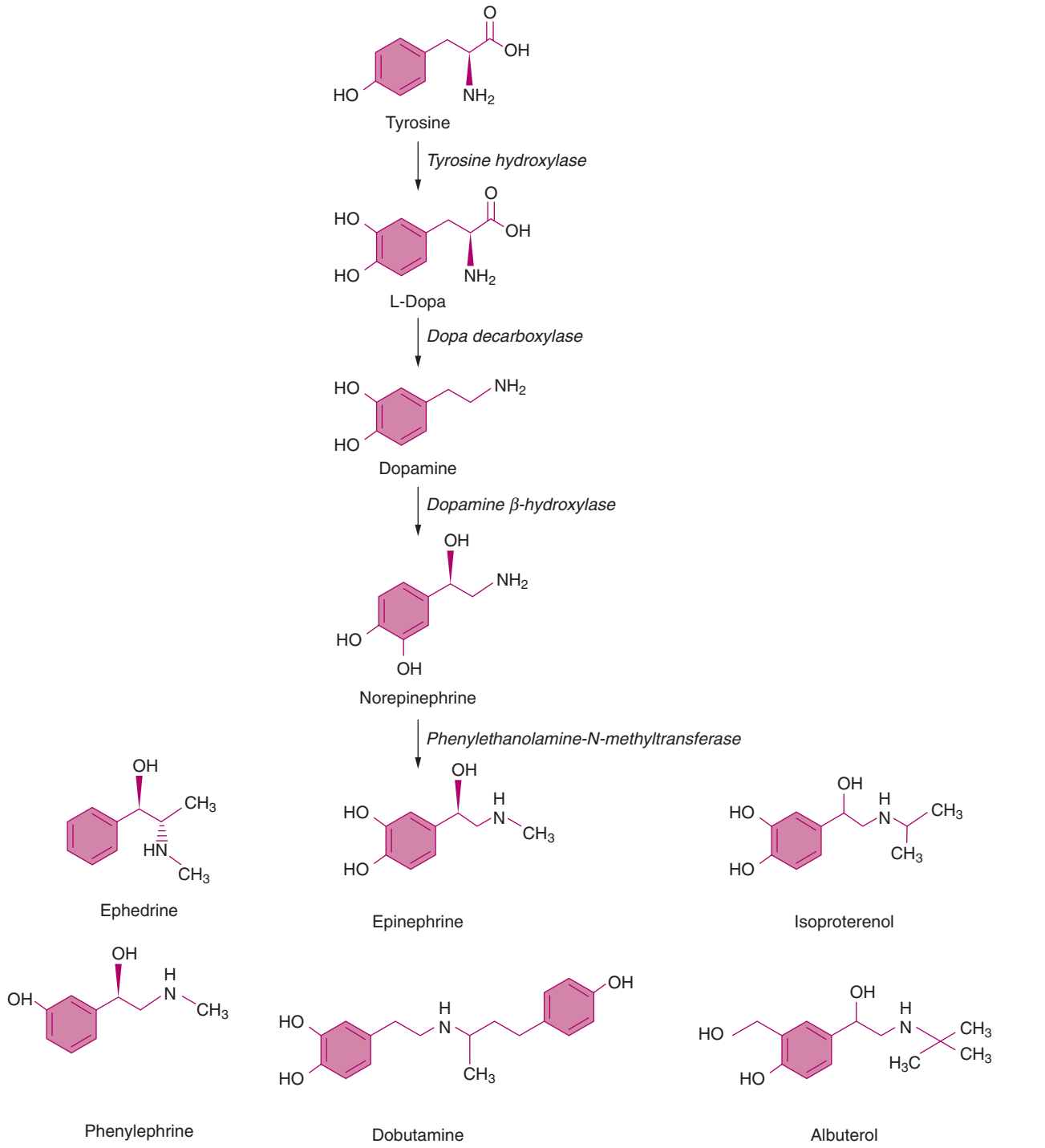


Figure 13-1 Biosynthesis and structures of the catecholamines, and their structures compared to common adrenergic drugs. Stereochemical structure is indicated as shown; Isoproterenol, dobutamine and albuterol are racemates.

β-receptors in arterioles and the only β-receptors in the vena cava, aorta, and pulmonary artery.[18] Activation of β2-receptors leads to uterine relaxation and relaxation of vascular smooth muscle including splanchnic, muscular, and renal vasculature, resulting in a reduction in diastolic pressure and systemic vascular resistance. β2-receptor activation also reduces plasma K^+ concentration by promoting uptake into skeletal muscle and reducing aldosterone secretion leading to renal losses of K^+ (see Figure 13-3). The β3-receptors are expressed in visceral adipocytes, gallbladder, and colon. Their activation mediates lipolytic and thermogenesis in brown and white adipose tissue.[19]

ENDOGENOUS CATECHOLAMINES

The biosynthesis of the naturally occurring catecholamines (epinephrine, norepinephrine, and dopamine) begins with the

conversion of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) (see Figure 13-1). The rate-limiting step in catecholamine synthesis is conversion of tyrosine to DOPA by the enzyme tyrosine hydroxylase.

Epinephrine

Epinephrine, also known as adrenaline, is an endogenous monoamine with broad clinical applications. Epinephrine is present in chromaffin cells in the adrenal medulla, where it is synthesized, stored, and released upon sympathetic stimulation. On average, 80% of the secreted catecholamine in the adrenal medulla is epinephrine and 20% is norepinephrine. The normal resting rate of secretion by the adrenal medulla is about 0.2 μg/kg/min of epinephrine and about 0.05 μg/kg/min of norepinephrine. These rates are sufficient to support arterial BP fully if the SNS is denervated. The effects of secreted epinephrine and norepinephrine on organ function lasts 5 to 10 times longer than the effect from a burst of sympathetic stimulation to an organ or vascular bed, in part due to their slow removal from the bloodstream. Because epinephrine has a large β-receptor effect, cardiac function (i.e., HR and contractility) increases far more than for norepinephrine (Table 13-2). The β-receptor effect also constricts precapillary blood vessels and large veins. Epinephrine has a weaker effect on blood vessels in skeletal muscle than norepinephrine due to the greater affinity of epinephrine for β2- than α1-receptors. Epinephrine, due to its greater β-effects, can increase metabolic rate twice normal, and can increase glycogenolysis in liver and muscle, thereby raising blood glucose levels.

Infusions of epinephrine have dose-dependent actions at α- and β-receptors. Low doses (2-10 μg/min) predominantly stimulate β1- and β2-receptors (see Table 13-2). β1-receptor stimulation results in increased HR, cardiac output, contractility, and conduction. Activation of β2-adrenoceptors causes relaxation of bronchial smooth muscle, increased liver glycogenolysis, and vasodilatation in many regional vascular tissues. Blood vessel dilation leads to decreased diastolic BP from redistribution of blood flow to low-resistance circulations. At higher doses of epinephrine (>10 μg/min), α-receptors are activated, leading to vasoconstriction of the skin, mucosa, and renal vascular beds, which promotes blood flow redistribution away from these circulations. Further stimulation of α-receptors decreases skeletal muscle and splanchnic blood flow and inhibits insulin secretion.

Table 13-1. Relative Adrenergic Drug Effects on Peripheral Resistance and Capacitance Vessels*

	Vasoconstriction	
	α1 ARTERIAL	**α1 VENOUS**
Norepinephrine	+++++	+++++
Phenylephrine	++++	+++++
Epinephrine	0/++++†	0/++++†
Dopamine	0/++++‡	+++
Methoxamine, metaraminol	+++++	++++
Ephedrine	++	+++
Dobutamine	+/0	?
Isoproterenol	0	0

*Drugs are listed in descending order of potency within each vascular region.
†Dose-dependent; β effects of epinephrine predominate at low doses.
‡Dose-dependent; dopamine and β effects predominate at low doses.

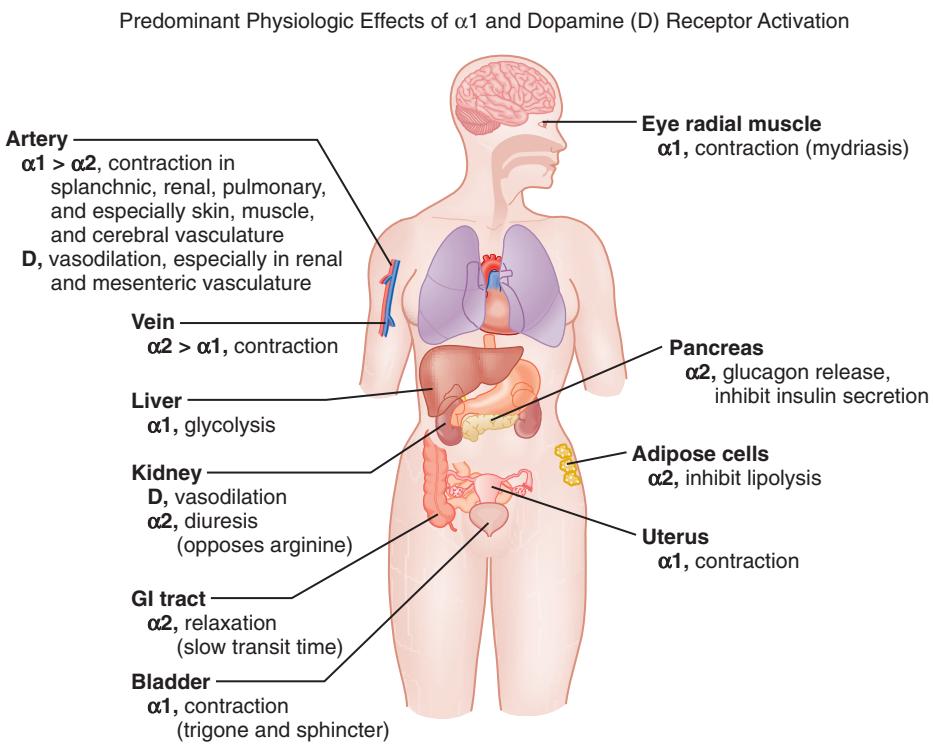


Figure 13-2 Predominant physiologic effects of α1-adrenergic and dopamine (D) receptors.

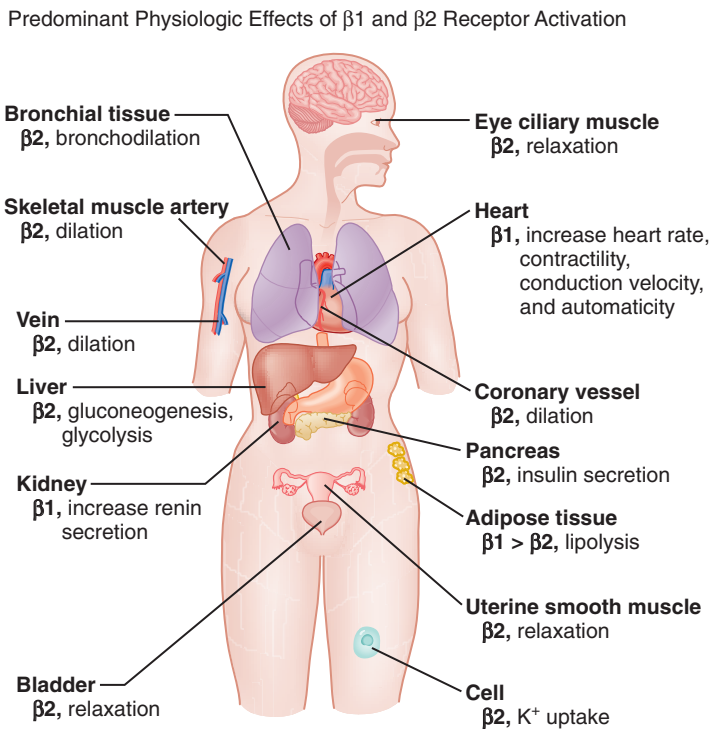


Figure 13-3 Predominant physiologic effects of β_1- and β_2-adrenergic receptor activation.

Epinephrine has broad clinical effects and thus its use has diminished as more selective synthetic adrenergic agonists have become available. However, epinephrine is still commonly added to local anesthetics to prolong their duration of action. Epinephrine is also indicated in anaphylactic shock, localized bleeding, bronchospasm, and stridor related to laryngotracheal edema. Subcutaneous doses of 0.2 to 0.5 mg can be used in early anaphylaxis to stabilize mast cells and reduce degranulation. Epinephrine also stimulates cellular K^+ uptake via β2-receptors and for short periods can be used to treat life-threatening hyperkalemia.

Norepinephrine

Norepinephrine is the principal endogenous mediator of SNS activity secreted from postganglionic terminals to act on adrenergic effector organs. Intravenous administration (4-12 μg/min) results in dose-dependent hemodynamic effects on α1- and β-adrenoceptors (see Table 13-2). Compared with the effects of epinephrine, norepinephrine has a greater effect at α1-receptors and no effect on β2-receptors, thereby creating greater arterial and venous vascular constriction than epinephrine (see Table 13-1). In lower doses, β1 actions predominate, and BP increases due to augmented cardiac output. Larger doses of norepinephrine stimulate the α1-receptors and result in arterial and venous smooth muscle contraction in hepatic, skeletal muscle, splanchnic, and renal vascular systems. At these larger doses, HR and cardiac output can decrease via baroreflex mechanisms.

Intravenous administration of norepinephrine is most often used therapeutically for treatment of profound vasodilation, as in septic shock unresponsive to fluid administration. It will increase BP, left ventricular stroke work index, cardiac output, and urine output. When given to patients already exhibiting marked vasoconstriction, further increases in vascular resistance can lead to compromised limb and organ blood flow, resulting in ischemia. Norepinephrine can produce arrhythmias, but it is less arrhythmogenic than epinephrine. Its effect on pulmonary α1-receptors combined with its increase in venous return can result in pulmonary hypertension and right heart failure. To minimize this effect during open heart surgery, it can be given directly into the left atrium along with a selective pulmonary vasodilator such as prostaglandin E_1.

Dopamine

Dopamine is an endogenous catecholamine that is also involved in central and peripheral neural transmission. Dopamine is synthesized from tyrosine and is the immediate precursor to norepinephrine (see Figure 13-1). Parenteral administration of dopamine does not cross into the CNS; therapy of Parkinson's disease requires use of the precursor L-DOPA that can cross the blood-brain barrier. Dopamine is commonly used for hemodynamic support and maintenance of adequate perfusion during shock. For these hemodynamic effects it must be given via continuous infusion because of rapid metabolism. At low infusion rates (1-3 μg/kg/min), vasodilation of coronary, renal, and mesenteric vasculature occurs and renal blood flow, glomerular filtration, and Na^+ excretion increase due to D1-like receptor agonism (see Figure 13-2). Although this "renal dose" of dopamine was purported to improve kidney function in patients at risk for acute renal failure, metaanalysis has failed to show improvement in renal dysfunction or mortality.[20] At doses of 3 to 10 μg/kg/min, β1-receptor stimulation leads to positive inotropic and chronotropic effects, and at higher doses (>10 μg/kg), α1-receptor activation

Table 13-2. Relative Potency of Common, Naturally Occurring, and Synthetic Adrenergic Agonists

	Receptors						
SYMPATHOMIMETICS	**α1**	**α2**	**β1**	**β2**	**D1**	**D2**	**DOSE DEPENDENCE***
Phenylephrine	+++++	?	±	0	0		++
Norepinephrine	+++++	+++++	+++	0	0		+++
Epinephrine	++++	+++	++++	++	0		++++
Ephedrine	++	?	++++	++	0		++
Dopamine	+ to +++++	?	++++	++	+++	?	+++++
Dobutamine†	0 to +	?	++++	++	0		++
Isoproterenol	0	0	+++++	+++++	0		0
Dexmedetomidine	+	+++++	0	0	0		
Clonidine	++	+++++	0	0	0		
Fenoldopam	0	0	0	0	+++++		

†Dobutamine is a racemic mixture; (–)dobutamine is a potent α_1-agonist, and (+)dobutamine is a potent α_1-antagonist, reducing its net vascoconstrictor effect.
*(α, β, or D).

causes peripheral vasoconstriction and can reduce renal blood flow.

Metabolism of Catecholamines

The catecholamines are metabolized by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). COMT is an intracellular enzyme located in postsynaptic neurons. MAO is concentrated in the mitochondria of nerve terminals, resulting in a constant turnover of norepinephrine even in the resting nerve terminal. Metabolites can be detected in urine as metanephrines or vanillylmandelic acid. Urine collections and analysis can be useful to follow progress in treatment of pheochromocytoma. There are two primary termination routes for norepinephrine released from nerve terminals: simple diffusion (and metabolism in plasma, kidney, or liver) and reuptake into noradrenergic nerve terminals (which can be blocked by cocaine and most tricyclic antidepressants). Synthetic sympathomimetic drugs that mimic endogenous catecholamines can have longer durations of action due to resistance to metabolism by MAO or COMT.

Synthetic Catecholamine-Like Drugs

Synthetic catecholamines, which are also included as sympathomimetic drugs, are a mainstay of critical care and perioperative medicine for support of the circulation. Depending on their selectivity and potency for different subtypes of α-, β-, and dopamine-receptors, their route of administration, their lipid solubility, and their metabolism, sympathomimetic drugs can be used to achieve a variety of clinical effects. Certain drugs also have indirect sympathomimetic action; these include ephedrine, tyramine, and the amphetamines. They cause release of norepinephrine from its storage vesicles in the sympathetic nerve endings, thereby increasing synaptic concentration and postsynaptic effects.

D1-Receptor Agonists

Fenoldopam is a synthetic, selective D1-agonist without significant D2-, α-adrenergic, or β2-adrenergic effects (see Table 13-2 and Figure 13-2).[21] It is 10-fold more potent than dopamine. The principal use of fenoldopam is to manage hypertension in doses of 0.1 to 0.8 μg/kg/min, with upward titration in 0.1-μg/kg/min steps as needed. A low-dose infusion of fenoldopam (~0.1-0.2 μg/kg/min) produces renal vasodilation and increases renal blood flow, glomerular filtration rate, and Na^+ excretion without changes in systemic BP. A renal protective effect has been observed in aortic and cardiac surgery involving cardiopulmonary bypass.[22,23] When compared with dopamine in acute early renal dysfunction, fenoldopam is more effective at reversing renal hypoperfusion.[24] A metaanalysis indicated that fenoldopam reduces both the need for renal replacement therapy and in-hospital death in cardiovascular surgery.[25]

α1-Receptor Agonists

Agonists of α1-adrenoceptors exert vasoconstrictor actions on arteries and veins, leading to BP increase and redistribution of blood flow (see Figure 13-2).[26] In healthy individuals, cardiac output is maintained because of increased preload. HR typically slows via the baroreflex response to increased BP. Myocardial blood flow and oxygen delivery can be improved due to the longer diastolic filling time from the lower HR, and from improved diastolic coronary blood flow because of the increased aortic BP. In patients with impaired ventricular function, increases in afterload can impair myocardial function. Topical use of α1-agonists can be used for vasoconstriction (e.g., on nasal mucosa).

PHENYLEPHRINE

The effects of phenylephrine were described in the 1930s, and it was first used to maintain BP during spinal anesthesia.[27] It is a nearly pure α1 selective agonist, only affecting β-receptors at very high doses (see Table 13-2). It has similar potency to norepinephrine for α1-receptors but has a longer duration of action. Phenylephrine produces greater venoconstriction than arterial vasoconstriction and therefore increases venous return and stroke volume. Cardiac output typically does not change due to baroreflex slowing of HR. Phenylephrine can be useful as a bolus or continuous infusion for treatment of hypotension, and can be used to reverse unwanted right-to-left shunt in tetralogy of Fallot. Newer evidence suggests that phenylephrine is not detrimental to fetal oxygen delivery in pregnant patients who are hypotensive after neuraxial blockade. However, although not harmful, it still might be inferior to ephedrine in maintaining placental blood flow during cesarean delivery.[28,29] A 0.25%, 0.5%, or 1% phenylephrine solution can be used topically as a nasal decongestant; 2.5% or

10% phenylephrine solutions are used to produce mydriasis when administered into the eye. Both these routes can raise BP. Rarely, more serious side effects such as pulmonary edema and adverse cardiac events result. Thus α1-adrenergic antagonists, such as phentolamine or tolazoline, or direct vasodilating drugs, such as hydralazine or nicardipine, should be available. β-blockers are contraindicated to treat a hypertensive crisis from phenylephrine (such as an accidental overdose). β-blockers in this situation can reduce myocardial contractility and produce acute pulmonary edema in the face of high afterload.[30]

METHOXAMINE

First described in 1948 and used to maintain BP during spinal anesthesia, methoxamine has a longer duration of action, more arterial vasoconstriction, and less venoconstriction compared with phenylephrine.[31] It is not typically used to support BP acutely since it can increase afterload and has a long half-life. Doses of 1 to 5 mg every 15 minutes are typical. Untoward hypertension can occur following its use to treat regional anesthetic-induced hypotension because sympathetic tone returns as the spinal anesthetic recovers before the action of methoxamine dissipates.

MIDODRINE

Midodrine is an orally absorbed α1-agonist with a half-life of about 3 hours and duration of action of 4 to 6 hours. It is used to treat dialysis-related hypotension or autonomic failure resulting in postural hypotension, but hypertension is a possible effect while supine.

α2-Receptor Agonists

Agonists of α2-receptors such as clonidine were originally used as antihypertensive agents because of their central effect to decrease sympathetic outflow from the CNS and to reduce presynaptic norepinephrine release. The $\alpha 2_a$-receptor mediates sedation and hypnosis, sympatholysis, neuroprotection, diuresis and inhibition of insulin and growth hormone secretion.[32-34] Rapid intravenous administration of α2-agonists such as dexmedetomidine can transiently increase BP through vasoconstriction at postsynaptic $\alpha 2_b$-receptors on arteries and veins. This receptor subtype might also account for their antishivering effect. Postsynaptic α2-receptors exist in a number of other tissues and organs including liver, pancreas, platelets, kidney, fat, and eye (see Figure 13-2).

Within the CNS, a large density of α2-receptors is located in the medullary dorsal motor complex and in the locus ceruleus. The locus ceruleus is an important modulator of wakefulness and the major site of the sedative/hypnotic actions of the α2-agonists. Among the many desirable properties of α2-agonists that promote their use in the perioperative period are anxiolysis, sedation, reductions in minimal alveolar concentration (MAC) of volatile anesthetics, reduced chest wall rigidity from opioids, reduction in intraoperative BP variability from intubation, extubation and surgical stress response, and reductions in postanesthetic shivering.[35] A metaanalysis found that α2-receptor agonists reduce perioperative cardiac mortality and ischemia, a benefit likely attributable to reduced sympathetic outflow and reduced shivering.[36] Side effects include sedation, dry mouth, and bradycardia via reduced sympathetic "tone," and a slight vagomimetic effect. It is likely that some of the effects from α2-receptor agonists are from actions at nonadrenergic imidazoline receptors.

Table 13-3. Classification of α-Receptors and the Relative α1/α2 Selectivity

	Order of Selectivity AGONISTS	ANTAGONISTS
α1 ↕ α2	Methoxamine Phenylephrine Norepinephrine Epinephrine Dopamine Clonidine (220:1) Dexmedetomidine (1620:1)	Prazosin Phenoxybenzamine Phentolamine Tolazoline Yohimbine

CLONIDINE

Clonidine, first synthesized in the 1960s, has an onset time after oral administration of 30 to 60 minutes, with a half-life of 6 to 24 hours. The α2: α1-receptor affinity is ~220 : 1 (Table 13-3). It is available in 100-, 250-, and 300-μg tablets for oral administration, a transdermal patch releasing 150 to 200 μg over 24 hours, and an injectable solution of 150 μg/mL. Oral dosing is typically every 8 hours. Clonidine should not be withheld prior to surgery because acute withdrawal can result in rebound hypertension.[37] Neuraxial administration can be used to lessen the requirement for opioids when treating acute and chronic pain. Epidural clonidine is indicated for treatment of severe cancer pain (0.5 μg/kg/hr). When given in this manner, bradycardia and sedation can occur but respiratory drive is maintained. Clonidine also is beneficial in the treatment of opioid withdrawal in an intensive care unit (ICU) setting.[38]

DEXMEDETOMIDINE

Dexmedetomidine is highly selective for α2-adrenoceptors (see Table 13-3), with an α2:α1-receptor affinity of 1620 : 1. Intravenous administration in the ICU setting is useful for continuous sedation and analgesia while sparing respiratory drive. Sedation is described as "arousable sedation" much like natural sleep, consistent with effects on central sleep mechanisms. Patients receiving dexmedetomidine for postsurgical pain have slower early postoperative HRs and require 50% less morphine in the PACU.[39] In a prospective randomized study, dexmedetomidine initiated at the end of coronary artery bypass surgery and continued into the ICU resulted in reduced use of analgesics, β-blockers, diuretics, antiemetics, and epinephrine, and achieved adequate sedation compared to propofol sedation.[40] In the ICU setting following cardiac surgery, the combination of opioid/dexmedetomidine sedation resulted in less delirium compared to opioid/benzodiazepine sedation.[41,42] Recommended dosage is a 1 μg/kg load given over 10 to 20 minutes followed with a 0.2 to 0.7 μg/kg/hr infusion. Hypotension and bradycardia are common side effects and bradyarrhythmias and sinus arrest are rare but potential serious adverse events. Newer applications for dexmedetomidine include pediatric sedation for hospital procedures, treatment of emergence agitation, and sedation in the ICU setting. Additionally, the FDA approved the use of dexmedetomidine for MAC sedation in 2010.[43]

β1-Receptor Agonists

ISOPROTERENOL

Isoproterenol, the isopropyl derivative of norepinephrine, was the first synthetic β-receptor agonist in clinical use. It is given parenterally due to its short duration of action (less than 1 hour).[44] It has almost purely β-receptor activity, with minimal α-receptor affinity. It is nonselective for β1- and β2-receptors (see Table 13-2). Isoproterenol produces positive chronotropic and inotropic cardiac effects via β1-adrenoceptor stimulation, and bronchodilation and vasodilatation in vascular smooth muscle through β2-activation. Large doses cause tachycardia and decrease diastolic BP, which reduces coronary blood flow and thus can compromise myocardium at risk or worsen dysrhythmias. Dobutamine is a common substitute for isoproterenol due to lesser effects on HR and myocardial oxygen demand. The emergence of phosphodiesterase inhibitors to improve myocardial performance has also reduced the need for isoproterenol as an inotropic agent.[45] The β2 response from isoproterenol can be used for bronchodilation, although other β2 drugs are more typically used. Isoproterenol has been used to manage heart failure secondary to bradycardia, cor pulmonale, pulmonary hypertension, as a chemical "pacer" in third-degree heart block, and in torsades de pointes ventricular tachycardia.

DOBUTAMINE

Dobutamine is a synthetic catecholamine obtained by substitution of a bulky aromatic group on the side chain of dopamine. Dobutamine is a racemic mixture of the (+) and (–) isomers. The (–) isomer acts on α1-adrenergic receptors and increases vascular resistance, and the (+) isomer is a potent β1-adrenergic receptor agonist and a potent α1-adrenergic receptor antagonist that blocks the effects of (–) dobutamine (see Table 13-2). Compared to dopamine, dobutamine has less notable venoconstriction and is less likely to increase HR and more likely to decrease pulmonary vascular resistance. The most prominent effects with increasing infusion rates of dobutamine (2-20 μg/kg/min IV) are a progressive increase in cardiac output, decrease in left ventricular filling pressure, minimal increase in HR until higher doses, and decreases or no change in systematic vascular resistance. However, when given to β-blocked patients, systemic vascular resistance can increase, leading to increases in BP from the unmasked α1-effect. Dobutamine has minimal β2-effects. Thus it often improves cardiac output without major adverse effects on the myocardial oxygen supply/demand ratio because afterload is maintained, thereby improving coronary blood flow.[46] It enhances automaticity of the sinus and atrioventricular nodes and facilitates intraventricular conduction. It does not affect dopamine receptors. Dobutamine is prepared in 5% dextrose in water because it is inactivated in alkaline solutions. Tachyphylaxis can occur with infusions longer than 72 hours. Dobutamine is often used for nonexercise cardiac stress testing and for the treatment of acute heart failure, especially in patients being weaned from cardiopulmonary bypass.

Selective β2-Receptor Agonists

Selective β2-receptor agonists are indicated in the treatment of acute asthma and chronic obstructive pulmonary disease (COPD). These agents work by reducing bronchial airway resistance via smooth muscle relaxation. By changing the catechol ring (3,4-dihydroxylphenyl) to a resorcinol ring (3,5-dihydroxylphenyl), there is improved bioavailability due to reduced action of COMT. Further substitutions on the amino group increase β-receptor activity, reduce α-receptor activity, and increase the duration of action by decreasing metabolism by MAO.

Metaproterenol (orciprenaline), albuterol, salmeterol, and isoetharine (isoetarine) are inhaled, thereby reducing their systemic side effects. These reach therapeutic concentrations in the bronchi with minimal activation of cardiac and peripheral β2-receptors. In addition to bronchodilation, therapeutic effects include suppression of release of leukotrienes and histamine from mast cells and decreased microvascular permeability. However, at higher concentrations all currently used β2-selective agonists also stimulate β1-receptors, which increases the risk for arrhythmias (predominantly atrial fibrillation). Other potential adverse effects, particularly when given orally or parenterally, are skeletal muscle tremor, tachycardia, mismatching of pulmonary ventilation and perfusion, and pulmonary edema. Long-term use can lead to tolerance, bronchial hyperreactivity, and hyperglycemia in diabetic patients.

TERBUTALINE AND RITODRINE

Terbutaline can be administered orally, subcutaneously, or by inhalation. It is rapidly effective by the latter two routes and its effects persist for 36 hours, in part due to its structure with a resorcinol ring preventing COMT action. A subcutaneous dose of 0.25 mg can be useful to treat status asthmaticus. Terbutaline is used primarily long term for obstructive pulmonary disease, and acutely for status asthmaticus, bronchospasm, and acute anaphylactic shock, where it does not have the cardiac stimulating effects of epinephrine.

Terbutaline and ritodrine are also tocolytic drugs used to manage premature labor contractions through relaxation of the myometrium via their β2 effect. Ritodrine is usually started intravenously and is continued orally if tocolysis is achieved. It is metabolized in the liver to inactive conjugates, and about half the drug is excreted unchanged in the urine. Albuterol is similar to terbutaline, although it cannot be given subcutaneously. Continuous use of β-agonists has been associated with hypokalemia as well as tachyphylaxis. The mechanism of hypokalemia involves insulin mediated increase in uptake of extracellular K^+ or increased Na^+/K^+ ATPase activity.[47] Angina, cardiac arrhythmias, hyperglycemia, hypokalemia, and pulmonary edema with normal pulmonary capillary wedge pressures have been attributed to terbutaline and ritodrine therapy.[48]

INDIRECT-ACTING SYMPATHOMIMETICS

Some of the synthetic catecholamine-like drugs have an indirect sympathomimetic action. These drugs include ephedrine, tyramine, and the amphetamines. Because their effects are to cause release of norepinephrine from synaptic vesicles in sympathetic nerve endings, care must be taken when they are administered to patients taking tricyclic antidepressants (TCA) or monoamine oxidase inhibitors (MAOIs).[49] The TCAs inhibit catecholamine reuptake and the MAOIs inhibit

catecholamine breakdown. MAOIs in combination with serotonin reuptake inhibitors can also lead to neuromuscular and autonomic hyperactivity and altered mental status (serotonin syndrome).[50]

Ephedrine

Ephedrine is one of the most commonly used noncatecholamine sympathomimetic drugs in the perioperative period. Ephedrine is a natural product of the ephedra plant *(Ephedra sinica)*, and is a mixed-acting, noncatecholamine sympathomimetic with both direct and indirect stimulating effects on α- and β-adrenergic receptors. It acts indirectly by competing with norepinephrine for local reuptake into synaptic vesicles, resulting in elevated concentrations of norepinephrine at receptor sites. Intravenous effects resemble those of epinephrine, albeit with a less potent but longer lasting effect. It causes increases in HR, cardiac output, and BP that last 10 to 15 minutes. Tachyphylaxis due to catecholamine depletion can occur with repeat doses.

Ephedrine relaxes bronchial smooth muscle, increases trigone and sphincter muscle tone in the urinary bladder, and has a stimulatory effect on the CNS that increases MAC (minimum alveolar concentration). Uterine and placental artery blood flow are not adversely affected when ephedrine is used to sustain BP during spinal anesthesia for cesarean section, and umbilical artery vascular resistance remains unchanged. This is due to an often unappreciated, pronounced effect of ephedrine to cause venoconstriction, thereby improving preload, cardiac output, and uterine blood flow.

Amphetamine and Other Central Nervous System Stimulants

Amphetamine and methamphetamine are powerful stimulants of the CNS, in addition to having peripheral α and β actions common to indirect acting sympathomimetics. They cause release and inhibit reuptake of stimulatory neurotransmitters in the cortex, motor nuclei, and reticular activating system. Acute effects include wakefulness, alertness, mood elevation, decreased sense of fatigue, and increased initiative, self-confidence, euphoria, and elation. Peripheral indirect activity leads to acute increases in BP with reflex bradycardia; large doses can cause arrhythmias. Chronic use leads to a decrease in BP because the metabolites are false neurotransmitters. Even though therapeutic use has declined, their respective methylenedioxy derivatives (MDA and MDMA) remain popular illicit recreational drugs. Treatment of acute intoxication consists of acidification of urine to enhance elimination, administration of sedatives, and control of cardiovascular side effects. Dantrolene is indicated to prevent hyperthermia.

Methylphenidate (Ritalin, Methylin) is structurally related to amphetamine, but has milder CNS-stimulating activity and less effect on motor function. It is used to treat narcolepsy and attention deficit/hyperactivity disorder. Side effects of insomnia, anorexia, weight loss, suppression of growth, and abdominal pain have been described in children. Overdose causes symptoms similar to those of overdose with amphetamine, including restlessness, agitation, irritability progressing to confusion, aggressive behavior, delirium, and paranoid delusions.

False Transmitters and Monoamine Oxidase Inhibition

MAOIs are powerful drugs used to treat depression and Parkinson's disease. They include phenelzine, iproclozide, isocarboxazid, tranylcypromine, selegiline, rasagiline, and moclobemide. MAO catalyzes the oxidation of monoamines such as norepinephrine, serotonin (MAO-A), phenylethylamine (MAO-B), and dopamine (MAO-A,B). Dietary amines (e.g., tyramine derived from fermentation processes in cheese, wine, and beer) can cause a hypertensive reaction in patients taking MAOIs. In the presence of MAOIs, tyramine displaces norepinephrine from synaptic vesicles leading to profound hypertension. When an indirect acting sympathomimetic drug such as ephedrine is administered, an exaggerated BP increase can occur, especially in the first weeks of therapy with an MAOI. With long-term use, there is downregulation of adrenergic receptors, and tricyclic antidepressants and selective serotonin reuptake inhibitors are usually continued through the perioperative period given their rapid excretion and long latency period for effectiveness.[51] MAOIs require discontinuation before surgery to allow restoration of enzyme activity. Irreversible MAOIs should be discontinued two weeks before surgery or switched to a reversible MAOI (moclobemide), which needs to be stopped only 24 hours before surgery.[52] Because dopamine is a substrate for MAO, it should be administered at much lower doses in patients taking an MAOI or TCA. Use of meperidine with an MAOI can lead to hypertension, convulsions, and coma. Because of their risk for lethal dietary and drug interactions, MAOIs are generally used only when patients are unresponsive to first-line antidepressants.

Ergot Alkaloids

Poisoning caused by the fungus *Claviceps purpurea* on wheat or rye in the Middle Ages was associated with mental disturbances and severe, painful peripheral vasoconstriction frequently leading to gangrene of the extremities. Often termed *St. Anthony's fire*, this effect is from ergot alkaloids that stimulate contraction of a variety of smooth muscles, both directly and indirectly via adrenergic and serotonergic receptors. Contraction of vascular smooth muscle leads to coronary, cerebral, and peripheral vasoconstriction. In clinical practice, the ergot alkaloids are taken orally and are slowly absorbed from the gut with bioavailability of approximately 10%; they are hepatically metabolized and eliminated primarily in the bile. The oral dose of ergotamine to treat an acute migraine is 2 mg, followed by a 1-mg dose every half hour to a maximum of 6 mg. The intramuscular dose is 0.5 mg, repeated every half hour to a maximum of 3 mg. Intramuscular administration of ergonovine is used to enhance postpartum uterine contractions. The usual dose of 0.2 mg can be continued up to a week postpartum as an oral preparation. Ergot alkaloids are contraindicated in patients with sickle cell disease, peripheral and coronary artery disease, thyrotoxicosis, and porphyria.

Other Sympathomimetic Drugs

Pseudoephedrine and phenylpropanolamine are commonly used as oral preparations to treat nasal congestion via vasoconstriction. These sympathomimetic drugs are similar to

ephedrine in releasing norepinephrine and epinephrine, but have fewer CNS effects. Several drugs are used primarily as vasoconstrictors via α1-receptor agonism for local application to the nasal mucous membranes or to the conjunctiva, including propylhexedrine, tetrahydrozoline, oxymetazoline, naphazoline, and xylometazoline. Their systemic absorption is minimal when compared with topical phenylephrine solutions. Cocaine is another sympathomimetic still used clinically for its analgesic and vasoconstrictive properties. Intranasal cocaine with a topical local anesthetic has been shown to provide adequate pain control during repair of nasal fractures.[53] However, given the potential for abuse and toxicity, the aforementioned topical drugs have largely replaced the use of cocaine-containing topical solutions for vasoconstriction.

Vasopressin

Vasopressin, commonly known as arginine vasopressin (AVP), is an endogenous hormone that regulates urine volume and plasma osmolality. Although not a sympathomimetic, it, too, is used as a potent vasoconstrictor that preserves splanchnic perfusion.[54,55] It acts on V2-receptors on the collecting ducts to promote water reabsorption and concentration of urine. Higher concentrations of AVP, which result from a baroreflex response to hypotension, act on $V1_a$-receptors located on vascular smooth muscle to promote vasoconstriction via a phosphoinositol pathway. Vasopressin is available in an aqueous solution of 20 units/mL. A dose of 40 units is recommended as an alternative to a first or second dose of epinephrine during resuscitation from cardiac arrest, and can be useful in smaller doses to treat refractory intraoperative hypotension in patients on angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. Doses of 1 to 8 units are typical. Vasopressin also has been cited as a useful pharmacologic aid in hemorrhagic shock due to its augmentation of the neuroendocrine stress response and can reverse severe hypotension, restore cardiovascular function, and decrease catecholamine requirements.[56-59] Furthermore, it has demonstrated these effects in hypotension that had been resistant to fluids and exogenous catecholamines.[59]

ADRENERGIC BLOCKING DRUGS

Sympatholytic drugs oppose the effects transmitted by postganglionic fibers of the SNS. Most drugs of this class act postsynaptically to compete reversibly with agonists for α- and β-adrenergic receptors. Adrenergic activity can be disrupted at several points in the stimulatory process, as follows:

1. Blockade of α-receptors, resulting primarily in dilation of vascular tissue; examples are phenoxybenzamine and phentolamine.
2. Blockade of β-receptors, the major pharmacologic target being the heart and vascular smooth muscle. Propranolol blocks β1- and β2-receptors; atenolol and metoprolol block mainly β1-receptors.
3. Blockade of sympathetic activity by drugs that block transmission of nerve impulses through autonomic ganglia at nicotinic receptors; hexamethonium blocks both sympathetic and parasympathetic transmission through the ganglia.
4. Inhibition of synthesis and storage of norepinephrine in sympathetic nerve endings; examples are reserpine and α-methyldopa.
5. Blockade of release of norepinephrine from sympathetic endings; an example is guanethidine.

α-Antagonists

The "α-blockers" play an important role in regulating the activity of the SNS both peripherally and centrally. Blockade of α2-adrenergic receptors with selective antagonists such as yohimbine can potentiate release of norepinephrine to activate both α1- and α2-receptors. Antagonists of α1-adrenergic receptors such as prazosin also stimulate release of norepinephrine, but the α1-receptor effect is blocked.

PHENOXYBENZAMINE

Phenoxybenzamine is an irreversible, noncompetitive blocker of α-adrenergic receptors (see Table 13-3). It forms a covalent link with the α-receptor such that recovery of receptor function requires synthesis of new receptor molecules with a half-life of 18 to 24 hours. The consequent reduction in peripheral vascular tone leads to orthostatic hypotension and is accompanied by baroreflex-mediated sympathetic activation resulting in increases in HR and cardiac output. Phenoxybenzamine also improves cardiac output by other mechanisms. It blocks presynaptic inhibitory α2-receptors in the heart and decreases elimination of myocardial norepinephrine by inhibition of reuptake. Overdoses are treated with norepinephrine when unopposed β1-receptor effects are present. Epinephrine is not recommended for this purpose in that its β2 effects lead to further hypotension. Oral doses of phenoxybenzamine are used to manage pheochromocytoma or urinary retention caused by neurogenic bladder or benign prostatic hypertrophy. For adults, initial dosing is 10 to 20 mg bid for pheochromocytoma and 10 to 20 mg per day for relief of obstruction in neurogenic bladder.

PHENTOLAMINE AND TOLAZOLINE

Phentolamine and tolazoline are competitive, nonselective α-receptor antagonists (see Table 13-3). Although these drugs have cardiovascular effects similar to those of phenoxybenzamine, α-blockade is short-lived and the effects are reversible with α-receptor agonists. Phentolamine and tolazoline can be used to treat hypertensive crisis due to ingestion of tyramine-containing substances in patients taking MAOIs, or due to clonidine withdrawal. Phentolamine can be given as a 5- to 15-mg intravenous bolus and has an onset in 12 minutes and duration of 10 to 30 minutes. Tolazoline has a plasma half-life of 313 hours and is excreted mainly unchanged by the kidney. The recommended dose for treatment of neonatal persistent pulmonary hypertension is a 0.5 to 2 mg/kg loading dose administered over 10 minutes followed by 0.5 to 2 mg/kg per hour. Their use to treat pulmonary hypertension has fallen out of favor with the advent of newer agents (see Chapter 23). Phentolamine can be infiltrated into tissues to reduce the vasoconstriction from accidental extravasation of norepinephrine.

PRAZOSIN

Prazosin is the prototype of a family of α-adrenergic drugs that contain a piperazinyl quinazole nucleus. Prazosin has a

very high affinity for most subtypes of α1-receptors (see Table 13-3). Its $\alpha 1_B$-receptor antagonism results in dilation of arteries and veins with a decrease in peripheral vascular resistance and venous return and cardiac filling. The unexpectedly blunted reflex HR response to the hypotensive effect of prazosin might be due to a CNS effect to suppress sympathetic outflow. Prazosin is given orally (15 mg); the starting dose to treat hypertension is usually 0.5 mg at bedtime. The effects of a single dose last about 10 hours.

DOXAZOSIN, TERAZOSIN, TAMSULOSIN

Doxazosin has hemodynamic effects similar to prazosin, but its duration is about three times longer. Terazosin is less potent than prazosin but has higher bioavailability so its effects last longer. Selectivity of $\alpha 1_A$-subtype over $\alpha 1_B$-subtype receptors for relaxation of bladder neck, prostate capsule, and prostatic urethra make doxazosin and tamsulosin useful for treating benign prostatic hypertrophy with little effect on BP.

β-Antagonists

The β-adrenergic receptor blockers have a range of lipid solubilities that influence their absorption and distribution (Table 13-4). The prototype drug propranolol, developed in the early 1960s, has high lipid solubility and attains high brain concentrations. The lipid-insoluble β-blockers such as atenolol are less well absorbed orally, have fewer CNS side effects, and are excreted primarily via the kidneys (with prolonged excretion in renal failure). β2-blockade can cause bronchospasm and peripheral vasoconstriction; this can be problematic in patients with chronic obstructive pulmonary disease and peripheral vascular disease.

Modifications of the molecular structure of β-blockers can lead to a range of desired pharmacodynamic effects, including enhanced selectivity for β1-receptors, partial agonist activity at β2-receptors (known as intrinsic sympathomimetic activity, ISA), α1-receptor antagonism, and/or quinidine-like membrane stabilizing activity. ISA from drugs such as pindolol leads to less reduction of HR, cardiac output, and peripheral blood flow and reduced risk of bronchoconstriction. Most β-adrenergic antagonists do not block α-adrenergic receptors. Two exceptions are labetalol and carvedilol, which have both nonselective β-receptor antagonist and α-receptor antagonist activity. Blockade of stimulatory presynaptic β2-receptors reduces release of norepinephrine and contributes to the hypotensive effect of β-receptor antagonists.

The β-receptor antagonists have a number of predictable side effects. They can lead to profound bradycardia, asystole and heart failure. They inhibit gluconeogenesis; in diabetics receiving β-blockers, the common signs of hypoglycemia such as tremors and tachycardia can be masked. Hypoglycemia-induced perspiration, mediated by cholinergic mechanisms, can remain the only warning sign in these patients. Blockade of peripheral β2-receptors can precipitate Raynaud's vascular spasm in susceptible patients. The use of β-blockers to attenuate adrenergic crisis can worsen hypertension (from β2-receptor blockade) if α-receptor blockade is not adequate due to unopposed α effects. Combination of β-blockers with non-dihydropyridine calcium channel blockers can significantly reduce cardiac conduction, and when also combined with H_2-receptor blockers, severe negative inotropism can result.

Even though myocardial depression from volatile or intravenous anesthetics is additive with that of pure β-blockers, perioperative use of β-blockers reduces morbidity and mortality in patients with documented coronary artery disease and in patients at high risk for coronary artery disease.[60-65] However, there has been some controversy regarding β-blockade with metoprolol in particular. The POISE trial showed that while those starting metoprolol in the perioperative period experienced fewer myocardial infarctions, this group also had more deaths and nonfatal cerebrovascular accidents. A metaanalysis has shown significant heterogeneity across studies, suggesting that the benefits and risks of initiating a perioperative β-blockade should be carefully weighed for each patient.[65] Clinically, both partial and pure antagonists are used in the treatment of hypertension and tachyarrhythmias, and both decrease mortality after myocardial infarction. Sudden withdrawal of β-receptor blockers can lead to rebound adrenergic effects, including tachycardia, hypertension, arrhythmias, myocardial ischemia, and infarction. The enhanced adrenergic state occurs 2 to 6 days after withdrawal.[66] This has led to the current recommendation to continue β-blockers in the perioperative period to avoid withdrawal.[51]

Table 13-4. β-Adrenergic Blocking Drugs

DRUG	RECEPTOR SELECTIVITY	ISA	PLASMA HALF-LIFE (HR)	ORAL AVAILABILITY (%)	LIPID SOLUBILITY	ELIMINATION	ORAL DOSE	IV DOSE
Propranolol	β1β2	0	3-4	36	+++	Hepatic	40-320 mg	0.5-1 mg to max 3 mg
Metoprolol	β1	0	3-4	38	+	Hepatic	100-400 mg	5 mg q 2 min to 15 mg total
Atenolol	β1	0	6-9	57	0	Renal	50-100 mg	2.5 mg over 2.5 min q 5 min to 10 mg or 0.15 $mg \cdot kg^{-1}$ over 20 min
Esmolol	β1	0	9 min	–	?	RBC esterase	NA	50-100 mg bolus, 0.05-0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ infusion
Timolol	β1β2	0	4-5	50	+	Hepatic > renal	15-45 mg; 60 mg max	Ophthalmic prep for glaucoma, 0.25-0.5 $mg \cdot mL^{-1}$
Carvedilol	α1β1β2		2-8			Hepatic	12.5-50 mg	NA
Labetalol	α1β1β2		~6			Hepatic	400-1200 mg	5-20 mg IV q 5-10 min to max 300 mg; start infusion at 2 $mg \cdot min^{-1}$

ISA, Intrinsic sympathomimetic activity; *NA*, not applicable; *RBC*, red blood cells.

ESMOLOL

Esmolol is a selective β1-adrenoceptor antagonist with a rapid onset of 90 seconds. Due to rapid hydrolysis by red blood cell esterase, it has a short duration of action with a half-life of only 9 to 10 minutes (see Table 13-4). Esmolol is not metabolized by plasma cholinesterase. The brevity of esmolol makes it useful as a bolus of 10 to 100 mg to reduce cardiac effects from transient β-adrenergic stimulation in the perioperative period and as an infusion in critically ill patients where it can be withdrawn quickly if adverse cardiac effects (congestive heart failure, bradycardia, hypotension) occur. As an infusion, a loading dose of 500 μg/kg followed by a 50 to 300 μg/kg/min infusion results in steady-state concentrations in 5 minutes.[67,68] β1-selectivity allows esmolol to be used safely in patients with bronchospastic and vascular disease.

LABETALOL

Labetalol is a mixture of four stereoisomers that block α1-, β1-, and β2-receptors, and is therefore considered a mixed antagonist (see Table 13-4). It is considered a peripheral vasodilator that does not cause reflex tachycardia.[69] It has an α:β antagonistic potency ratio of 1:7 when given intravenously and a ratio of 1:3 after oral administration. It is lipid soluble and has substantial first pass hepatic metabolism. The peak hypotensive effect from intravenous labetalol occurs within 5 to 15 minutes and the duration of action is 4 to 6 hours. It can be used to treat hypertension in pregnancy. Despite bradycardia from labetalol, the decreased afterload helps maintain cardiac output. It may be given in 5- to 10-mg bolus doses at 5-minute intervals to control a hypertensive crisis. Uterine blood flow is not affected, due in part to preserved cardiac output.

METOPROLOL AND ATENOLOL

Metoprolol is cardioselective with a ratio of 30:1 in affinity for β1- and β2-receptors (see Table 13-4). It is lipid soluble and has a high first pass hepatic metabolism resulting in the need for high oral doses (100-200 mg/day) compared to intravenous doses of 2.5 to 5 mg, titrated to effect. It is roughly half as potent as propranolol, and maximum β1-blockade effect is achieved at 0.2 mg/kg. Atenolol is also β1 selective, is lipophilic, and has an elimination half-life of 6 hours. Even so, the effect of an oral dose of 25 to 100 mg lasts 24 hours. In a recent study, perioperative blockade with atenolol resulted in a reduced short- and long-term mortality in high-risk patients having noncardiac surgery compared with metoprolol.[70] The differences might be explained by the longer metabolic half-life of atenolol and a higher chance of missing a dose and/or experiencing a "withdrawal" sympathetic response from a missed dose of metoprolol.

INHIBITION OF SYNTHESIS, STORAGE, AND RELEASE OF NOREPINEPHRINE

α-Methyldopa is one of a group of antihypertensive drugs called *false neurotransmitters* that replace norepinephrine in the synaptic vesicles located in postganglionic nerve endings of the SNS. It is metabolized to α-methyldopamine and then to α-methylnorepinephrine, which are less potent at adrenergic receptors than dopamine and norepinephrine, thus accounting for some of their antihypertensive effects. Central effects of the metabolites result from action on α2-receptors to decrease sympathetic outflow and to reduce anesthetic requirements by 20% to 40%. *Reserpine* prevents uptake of norepinephrine into vesicles, thereby inhibiting storage of dopamine and norepinephrine. *Guanethidine* acts by reducing norepinephrine release from sympathetic terminals and by depleting norepinephrine storage. It does not have sedating effects since it does not cross the blood-brain barrier. Side effects from the false transmitters include orthostatic hypotension, drowsiness, diarrhea, bradycardia, hepatitis, and autoimmune hemolytic anemia. Thus their use as antihypertensive drugs has fallen out of favor.

PARASYMPATHETIC PHARMACOLOGY

Cholinergic Receptors

The neurotransmitter acetylcholine (ACh) acts at distinct receptor types: nicotinic and muscarinic. The naturally occurring substances, muscarine and nicotine, were originally used to define and name the two receptor families. They have distinctly different tissue locations (see Chapter 12). Muscarinic receptors are G protein-coupled receptors with a typical seven-transmembrane configuration. There are five subtypes, M1-M5. The odd numbered subtypes are defined by *Pertussis* toxin insensitivity, coupling to G_q/G_{11} protein and stimulating phospholipase C to alter one or more ion channels. This effect generally leads to depolarization or increased excitability.[71,72] The even numbered subtypes M2 and M4 are *Pertussis* toxin sensitive, are coupled to the G_i/G_0 protein, and inhibit adenylyl cyclase to initiate a presynaptic inhibitory effect. Muscarinic subtypes M1 and M4 are found primarily in brain, M3 and M4 are found in lung, gastrointestinal tract, and glandular tissue, and M2-receptors are located in cardiac tissue. Muscarinic receptor activation by ACh at the postsynaptic junction in heart and smooth muscle leads to bradycardia, salivation, bronchoconstriction, miosis, and increased gastrointestinal motility and secretion (Table 13-5). In

Table 13-5. Antimuscarinic Drugs

DRUG	IV	IM	CNS†	GI TONE	GASTRIC ACID	AIRWAY SECRETIONS*	HEART RATE
Atropine	15-30 min	2-4 hr	++	--	-	--	+++††
Scopolamine	30-60 min	4-6 hr	+++†	-	-	----	–0††
Glycopyrrolate	2-4 hr	6-8 hr	0	---	---	---	+0

CNS, Central nervous system; *IV*, intravenous; *IM*, intramuscular; *GI*, gastrointestinal.
*Secretions may be reduced by inspissation.
†CNS effect often manifest as sedation before stimulation.
††May decelerate initially.

addition, "adrenergic" muscarinic receptors are located on presynaptic sympathetic terminals in the cardiovascular and coronary systems, and their activation reduces norepinephrine release. In brain, release of ACh is subject to substantial ongoing autoinhibition as a result of coactivation of presynaptic muscarinic receptors on cholinergic terminals.

Nicotinic receptors activate postganglionic junctions of both the sympathetic and parasympathetic nervous systems (see Chapter 12). Nicotinic receptors are also located at the neuromuscular junction (see Chapter 18). Nicotinic cholinergic receptors are heteropentameric ligand-gated ion channels that allow depolarizing inward flow of monovalent cations.[73] The nicotinic receptor agonists consist primarily of the depolarizing neuromuscular-blocking drugs (e.g., succinylcholine [suxamethonium], hexamethonium) and can simultaneously stimulate autonomic ganglia. The neuromuscular blocking drugs are considered in Chapter 19.

Muscarinic Receptor Agonists

Muscarinic agonists are divided into two general groups:

1. The choline esters (acetylcholine [ACh], methacholine, carbachol, bethanechol) and alkaloids (pilocarpine, muscarine, arecoline) that act directly on muscarinic receptors
2. Acetylcholinesterase inhibitors or anticholinesterases (physostigmine, neostigmine, pyridostigmine, edrophonium, echothiophate) that act indirectly by inhibiting ACh hydrolysis

The anticholinesterase drugs are frequently employed to reverse the action of nondepolarizing neuromuscular blocking drugs (see Chapter 19), to improve neuromuscular function in myasthenia gravis, and for colonic pseudo-obstruction. Newer drugs have been designed to improve cognitive function in Alzheimer's disease.

Due to rapid hydrolysis, direct-acting agonists such as ACh have few clinical applications, with the exception of topical application to produce miosis. Longer activity of the direct acting agonists can be achieved by methylation of the choline moiety as noted with the synthetic drug methacholine. This modification prevents significant nicotinic receptor effects and slows acetylcholinesterase metabolism (Table 13-6). Carbachol and bethanechol are long-acting synthetic parasympathetic agonists; the carbamic-linked ester moiety significantly reduces metabolism. Carbachol has significant nicotinic activity at autonomic ganglia. Bethanechol is similar to methacholine and is highly specific for muscarinic receptors. It is used orally or parenterally, has only minimal cardiac negative chronotropic and inotropic effects, and is useful therapy for postoperative urinary retention and neurogenic bladder from spinal cord injury.

Pilocarpine is a tertiary amine alkaloid with actions similar to methacholine (see Table 13-6). Clinical use includes treatment for xerostomia and glaucoma, where it is employed as a topical drug to produce miosis and reduce intraocular pressure. Pilocarpine has minimal nicotinic effects unless given systemically, in which case hypertension and tachycardia can result.

Echothiophate, a long-acting irreversible anticholinesterase, is instilled into the eye to reduce resistance to aqueous humor outflow and lower intraocular pressure. Echothiophate is absorbed into the circulation and, therefore, can prolong the duration of succinylcholine because of a reduction in cholinesterase levels. The action of ester-based local anesthetics can also be lengthened in patients receiving echothiophate through slower metabolism of the local anesthetic. Enzyme activity might not return to normal for 4 to 6 weeks after discontinuation of long-term therapy.

Muscarinic Receptor Antagonists

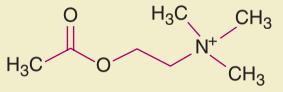
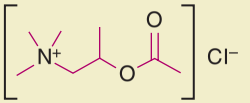
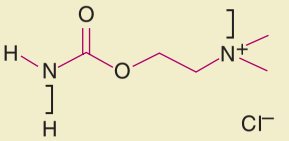
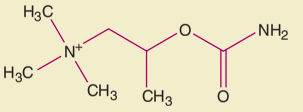
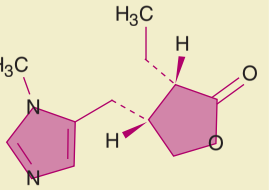
Anticholinergic drugs (atropine, scopolamine, glycopyrrolate) competitively inhibit the action of ACh by reversibly binding at muscarinic receptors. Nicotinic ACh receptors are not affected by doses usually employed. The naturally occurring anticholinergic drugs atropine and scopolamine are tertiary amines derived from the belladonna plant. Low doses of atropine and scopolamine (up to 2 μg/kg) have effects within the CNS to augment vagal outflow, which can result in bradycardia.[74]

At usual clinical doses (0.5-1 mg), atropine acts at peripheral muscarinic receptors to block the action of ACh, thereby increasing HR, producing mydriasis (pupil dilation) and cycloplegia (paralysis of accommodation), and inhibiting salivary, bronchial, pancreatic, and gastrointestinal secretions (see Table 13-5). It reduces gastric secretion of acid, mucin and proteolytic enzymes, slows gastric emptying, reduces lower esophageal tone and slows gastric motility. Atropine reduces the activity of sweat glands and thus evaporative heat loss, even in small doses. It relaxes bronchial smooth muscle, reduces airway resistance, inhibits mucociliary clearance in the airways, and thickens bronchial secretions.[75] Atropine and scopolamine are tertiary amines that cross the blood-brain barrier and the placenta. There is no harmful effect on the fetus. Their central effects might account for their antiemetic properties and control of nausea triggered by the vestibular apparatus.[76] Scopolamine skin patches are used to control motion sickness and postoperative nausea and vomiting (see Chapter 29). Atropine can block presynaptic muscarinic receptors on adrenergic terminals leading to a sympathomimetic effect. These drugs should be used with caution in patients with cardiac tachyarrhythmias or severe coronary artery disease, and are contraindicated in narrow angle glaucoma because they can increase intraocular pressure. They are considered safe when given parenterally to patients with the more common open angle glaucoma.

Scopolamine in the usual clinical doses of 0.3 to 0.6 mg displays stronger antisialagogue and ocular activity, but is less likely than glycopyrrolate or atropine to increase HR (see Table 13-5).[77] Scopolamine crosses the blood-brain barrier more effectively than atropine and is commonly associated with amnesia, drowsiness, fatigue, and non-REM sleep. One limitation imposed by the central actions of higher doses of scopolamine (and atropine) is an infrequent side effect termed the *central anticholinergic syndrome*. The origin of the syndrome is due to blockade of the abundant muscarinic ACh receptors in the CNS, which leads to agitation, disorientation, delirium, hallucinations, and restlessness. It can manifest as somnolence and should be considered in the differential diagnosis of delayed awakening from anesthesia. Physostigmine is a tertiary amine anticholinesterase that crosses into the CNS and can be administered in intravenous doses of 15 to 60 mg/kg for the treatment of central anticholinergic syndrome.

Glycopyrrolate is a synthetic quaternary amine that does not cross into the CNS and does not produce the CNS side

Table 13-6. Comparative Muscarinic Actions of Systemic Direct Cholinomimetic Agents

	ACETYLCHOLINE	METHACHOLINE	CARBAMYLCHOLINE	BETHANECHOL	PILOCARPINE
					
Esterase hydrolysis	+++	+	0	0	0
Eye (topical)					
Iris	++	++	+++	+++	+++
Ciliary	++	++	+++	+++	++
Heart					
Rate	−−−	−−−	−	−	?
Contractility	−	−	−	−	
Conduction	−−−	−−−	−	−	
Smooth muscle					
Vascular	−−−	−−−	−	−	−−
Bronchial	++	++	+	+	++
GI motility	++	++	+++	+++	++
GI sphincters	−−−	−	−−−	−−−	++
Biliary	++	++	+++	+++	++
Bladder					
Detrusor	++	++	+++	+++	++
Sphincter	−−−	−	−−−	−−−	++
Exocrine glands					
Respiratory	+++	++	+++	++	++++
Salivary	++	++	++	++	+++++
Pharyngeal	++	++	++	++	++++
Lacrimal	++	++	++	++	++++
Sweat	++	++	++	++	+++++
GI acid, secretions	++	++	++	++	++++
Nicotinic actions	+++	+	+++	−	+++

GI, Gastrointestinal; *+*, stimulation; *−*, inhibition.

effects noted with atropine and scopolamine (see Table 13-5). It is more potent and longer acting at peripheral muscarinic receptors than atropine. It is used clinically as an antisialagogue to treat bradycardia and to inhibit cardiac muscarinic receptor side effects when anticholinesterase agents are employed to reverse the effects of muscle relaxants. The antisialagogue dose of 0.004 mg/kg can last up to 8 hours. Similar to atropine, low doses can cause initial bradycardia.

Inhalation of anticholinergics is the most effective route of administration when bronchodilation without systemic side effects is desired. Ipratropium, a derivative of methylatropine, is an inhaled anticholinergic that inhibits muscarinic receptor subtypes with a peak effect of 30 to 60 minutes and a duration of action of 3 to 6 hours.[78] Low doses of ipratropium decrease airway size via preferential blockade of neuronal M2-muscarinic receptors. However, following large ipratropium doses, bronchodilation results from blockade of M3-muscarinic receptors on airway smooth muscle. Ipratropium, unlike atropine, does not affect mucociliary clearance of respiratory secretions. In chronic obstructive pulmonary disease, ipratropium is beneficial in improving pulmonary function, and tachyphylaxis with long-term use has not been demonstrated.[79] In acute asthma exacerbations, ipratropium can provide additional benefit when used with inhaled β2-agonists.

KEY POINTS

- The naturally occurring catecholamines epinephrine, norepinephrine, and dopamine are derived from the amino acid L-tyrosine. Their sites of action are on adrenergic and dopaminergic receptors.
- Adrenergic receptors have been subdivided based on their effector responses. β1-receptors are localized in cardiac tissue and mediate increases in HR, contractility, and conduction velocity whereas β2-receptors are found on arterioles, vena cava, pulmonary artery, aorta, and uterine smooth muscle; both types mediate smooth muscle relaxation. The α1-receptors mediate arterial and venous smooth muscle contraction. The α2-receptors also mediate vascular constriction but have additional actions in the CNS to reduce sympathetic outflow and pain perception and to produce sedation.
- Dopamine is an endogenous catecholamine involved in neural transmission. Parenteral administration can be used for hemodynamic support and, depending on the infusion rate, activates D1-receptors to dilate renal and coronary vessels and β1-receptors to cause chronotropic and inotropic effects, or, at high doses, activates α1-receptors to mediate vasoconstriction. Fenoldopam is a synthetic selective D1-agonist used to treat hypertension or to improve renal function via selective vasodilation.
- Dexmedetomidine is a highly selective α2-agonist used for sedation. It produces an "arousable" sedation much like natural sleep and is associated with less delirium compared to benzodiazepine sedation.
- Dobutamine is a racemic synthetic catecholamine. The (−) isomer acts on α1-receptors to increase vascular resistance and the (+) isomer acts on β1-receptors to increase contractility while antagonizing the increase in vascular resistance. It increases cardiac output, decreases pulmonary vascular resistance and is unlikely to increase HR.
- Selective β2-agonists are indicated for the treatment of acute asthma and chronic obstructive pulmonary disease by reducing smooth muscle tone and bronchial airway resistance. They are most commonly given via inhalation, with longer duration of action due to structural changes that reduce metabolism.
- Ephedrine is a noncatecholamine sympathomimetic drug with both direct and indirect actions on α- and β-adrenergic receptors.
- Vasopressin is an endogenous hormone that acts on V1- and V2-receptors to promote water reabsorption and to preserve coronary, cerebral, and pulmonary blood flow while constricting splanchnic vessels during severe hypotension and shock.
- β-adrenergic receptor blockers have a number of predictable effects to slow HR and inhibit gluconeogenesis. Their effects to reduce myocardial oxygen demand and myocardial infarction can be overshadowed in select circumstances by their association with a higher risk of stroke and death.
- Muscarinic receptor antagonists inhibit the action of acetylcholine at muscarinic receptors to increase HR and pupil dilation, and reduce production of secretions.

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