Autonomic Nervous System Pharmacology

Adrenergic Pharmacology
Synthesis of Norepinephrine
NE is synthesized from tyrosine, which is actively transported into the varicosity of the postganglionic sympathetic nerve ending (Fig. 14–9). Tyrosine is synthesized from phenylalanine. One would therefore expect that in phenylketonuric patients, who lack phenylalanine hydroxylase, there would be a significant defect in the ANS. However, tyrosine is available from the diet as well as from phenylalanine, and no autonomic defect exists in phenylketonuric patients. In hypertensive rats, tyrosine may increase central adrenergic transmission, decreasing peripheral sympathetic outflow. [48] In hypotensive (hemorrhaged) rats, tyrosine may increase peripheral synthesis and release of catecholamines. Precursors are taken up in greater amounts in shock and may have beneficial effects on the efforts of the sympathetic nervous system to maintain perfusion pressure.

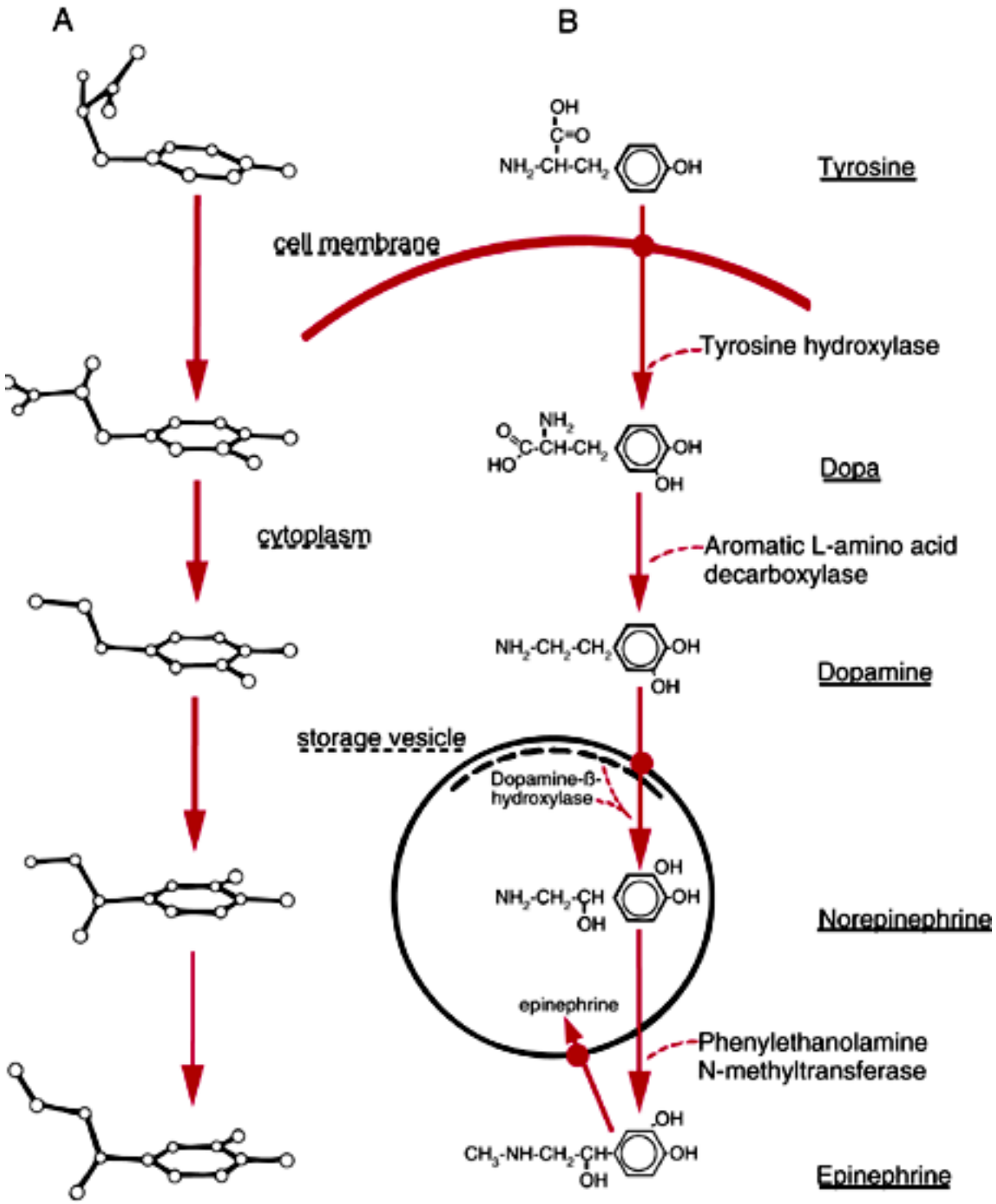

FIGURE 14–9 Biosynthesis of norepinephrine and epinephrine in sympathetic nerve terminal (and adrenal medulla). (A) Perspective view of molecules. (B) Enzymatic processes. (Modified from Tollenaerè,[455] as modified by Vanhoutte[456])

A series of steps results in the conversion of tyrosine to NE and (in the adrenal medulla) EPI. The first of these steps involves tyrosine hydroxylase (TH). *This cytoplasmic enzyme is the rate-controlling step for NE biosynthesis*. High levels of NE inhibit TH, and low levels stimulate the enzyme. Evidence indicates that during sympathetic nervous system stimulation, an increased supply of tyrosine also increases synthesis of NE. TH activity is modified by phosphorylation. TH depends on both a pteridine cofactor and the presence of molecular oxygen. Molecular oxygen, when in reduced quantity, may significantly reduce NE synthesis and may account for changes in wakefulness. Whereas acute control of TH occurs by altering enzyme activity, chronic stress can elevate TH levels by stimulating *synthesis* of new enzyme. Tyrosine is converted by the enzyme TH to dehydroxyphenylalanine (DOPA), which, in turn, is decarboxylated to dopamine by aromatic amino acid decarboxylase (DOPA decarboxylase), a relatively promiscuous enzyme in its substrate specificity. In Parkinson disease, central dopaminergic function is impaired. Administration of DOPA attempts to improve dopaminergic function in the brain, because DOPA, but not dopamine, crosses the blood-brain barrier. Dopamine can and does act as a neurotransmitter in some cells, but in most adrenergic neurons dopamine is catabolized quickly by the enzyme monoamine oxidase (MAO), found particularly in mitochondria. Subsequently, dopamine is β-hydroxylated within the vesicles to NE by the enzyme dopamine β-hydroxylase (DBH).

In the adrenal medulla and to a limited extent in discrete regions of the brain, there is an additional enzyme, phenylethanolamine *N*-methyl transferase (PNMT), which methylates about 85 percent of the NE in the adrenal medulla to EPI. Glucocorticoids from the adrenal cortex pass through the adrenal medulla and can activate the system, so that stress-induced steroid release can cause increased EPI production. This local circulation amplifies the effects of glucocorticoid release. [49]

Storage of Norepinephrine

NE is stored within large, dense-core vesicles. Electron microscopy demonstrates that the dense cores in these vesicles are not due to NE but perhaps to other binding proteins also contained in the vesicle. The vesicles also contain calcium and a variety of peptides and ATP. Depending on the nature and frequency of physiologic stimuli, the ATP can be selectively released to cause an immediate postsynaptic effect via purinoreceptors. Synaptic vesicles are heterogeneous and exist within functionally defined compartments. There appears to be an actively recycling population of synaptic vesicles and a reserve population of vesicles that is mobilized only on extensive stimulation. *Newly synthesized or taken up transmitters are preferentially incorporated into the actively recycling vesicles and thus are preferentially released on stimulation*. Therefore, drugs that mimic the neurotransmitter and are taken up presynaptically may be disproportionally represented in release. Functionally, NE is stored in compartments, of which 10 percent is readily releasable. *In general, 1 percent of stored NE is released with each depolarization, implying a significant functional reserve*. On stimulation, the contents of the vesicle are released into the synaptic cleft. Approximately 10 percent of stored NE is resistant to depletion, such as occurs with reserpine.

Synaptic vesicles have two fundamentally different functions: they take up and store neurotransmitters, and they both fuse with and bud from the presynaptic plasma terminal membrane. The proteins of synaptic vesicles can be divided into two functionally discrete classes. The first class consists of transport proteins providing the channels and pumps

needed for the uptake and storage of neurotransmitters. The second class consists of proteins involved in the directed movement and docking reactions of the synaptic vesicle membrane.

Release of Norepinephrine

There are two fundamentally different processes by which the contents of the vesicle enter the synaptic cleft. The first of these occurs by leakage from the vesicles into the presynaptic cytoplasm and subsequent release. This mechanism, known as *indirect release,* occurs with drugs such as ephedrine or bretylium, which displace NE from the vesicles. Drugs that inhibit vesicular uptake, such as reserpine, also facilitate indirect release. Although it is easy to underestimate vesicular leakage, NE leakage from storage vesicles into the axoplasm actually exceeds leakage into the synaptic cleft by 100-fold and presynaptic reuptake by 10-fold, explaining the initial hypertension seen with drugs such as reserpine. [50]

The physiologic mechanism of release is known as exocytosis, in which the vesicle responds to the entry of calcium by initiating a process of vesicle docking, fusion, and endocytosis (the process by which vesicular membrane and proteins are recaptured) (Fig. 14–10). [47] Proof of the physiologic relevance of exocytosis in adrenergic release resides in numerous studies that demonstrate that the vesicular contents (DBH and NE) are present in the identical ratio in the stimulated superfusate as in the intact isolated vesicle preparations. Thus, the entire contents of the vesicle are liberated on nerve stimulation. Angiotensin II, prostacyclin, and histamine may potentiate release, whereas ACh and prosta-glandin E inhibit release. Because of its generalized importance in neurotransmitter release, the process of exocytosis has been extensively investigated in the past decade.

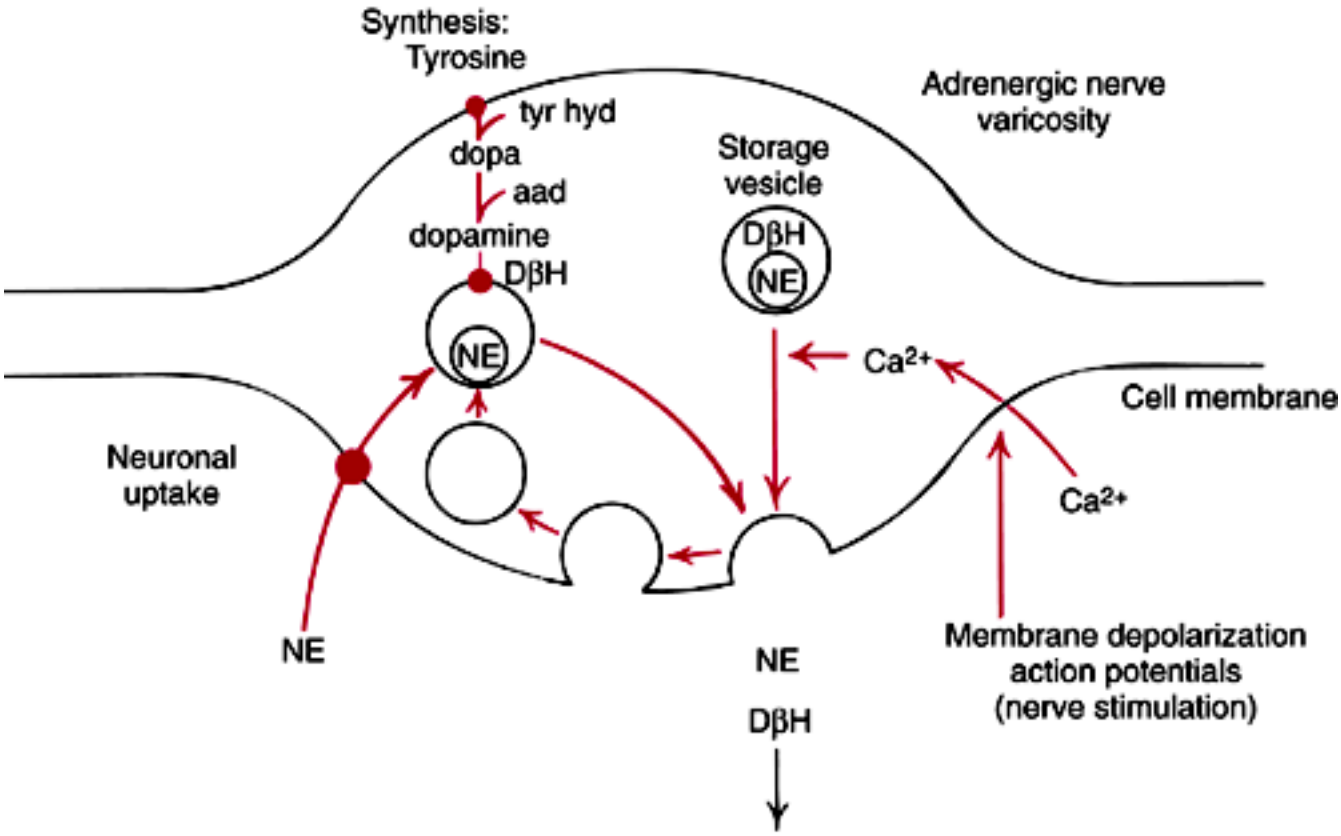

FIGURE 14–10 Release and reuptake of norepinephrine at sympathetic nerve terminals. aad, aromatic L-amino decarboxylase; DβH, dopamine β-hydroxylase; dopa, L-dihydroxyphenylalanine; NE, norepinephrine; tyr hyd, tyrosine hydroxylase; solid circle, active carrier. (Modified from Vanhoutte,[456] as modified by Shepherd and Vanhoutte[47])

n this model, the vesicle merges with the cell membrane, a process dependent on microfilaments and influenced by calcium. A widely accepted view of the role of synaptic vesicles in transmitter release is as follows: when an action potential reaches a nerve terminal, the presynaptic plasma membrane depolarizes, and the voltage-gated calcium channels open at the active zone. Although only small amounts of calcium are required to initiate the process, the concentration of calcium in the specialized zones of active release, nanodomains, is very high. This concept of calcium nanodo-mains is postulated to represent the biologic explanation underlying augmentation and post-tetanic potentiation [51] in that the gradual diffusion of these high calcium levels from the nanodomains recruits new vesicles for release on subsequent stimulations (Ch. 20). The dynamics of calcium levels in causing this phenomenon now appears well accepted. [52] The ensuing rise in intracellular calcium triggers exocytosis of synaptic vesicles, resulting in the release of neurotransmitters. [53] The synaptic vesicle membranes are reclaimed from the plasma membrane by endocytosis, and the vesicles eventually refill with

neurotransmitters. A more detailed examination of this process can be seen in Figure 14–11. [54]

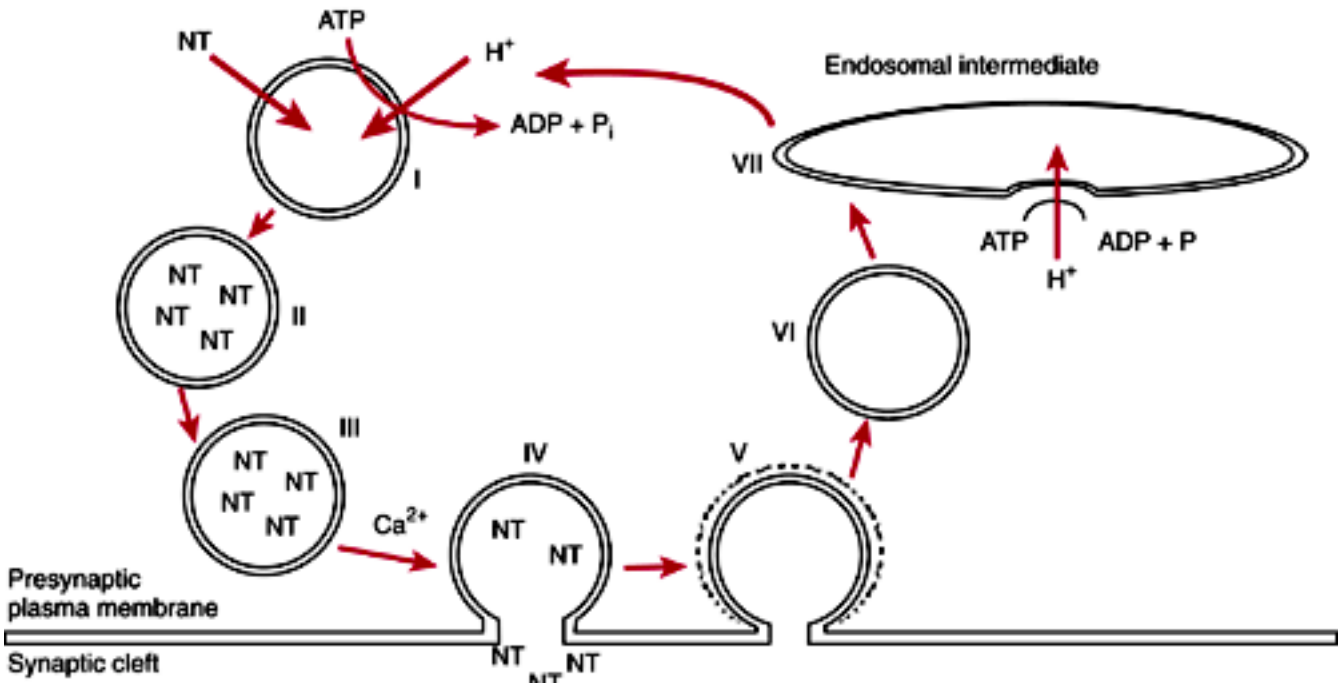

FIGURE 14–11 Pathway of synaptic vesicle movement in the nerve terminal. Synaptic vesicles accumulate neurotransmitters (NT) by active transport (stage I) and then move to the plasma membrane (stage II), where they become docked at the active zone (stage III). Calcium (Ca^{2+}) influx after membrane depolarization triggers synaptic vesicle exocytosis and release of neurotransmitters (stage IV), after which the empty synaptic vesicles are endocytosed by clathrin-coated pits (stage V) and are recycled (stage VI) via an endosomal intermediate (stage VII). Stages V and VII have not been definitely proved, but they are probable on the basis of morphologic observations. (Modified from Südhof and Jahn[54])

Various specific soluble and membrane-bound proteins have been identified that participate in docking, fusion, and endocytosis. There is increasing evidence that synaptotagmin serves as the intermediate between calcium entry and docking, because it binds calcium. [55] Microinjection of this protein participates in the step between docking and fusion, [56] and transgenic mice deficient in this protein exhibit attenuated neurotransmitter release. [57] Anatomic and molecular studies reveal vesicles that are predocked adjacent to the presynaptic membrane and permit rapid response. [54, 58, 59] The short latency between presynaptic excitation and vesicle release [60] has important functional implications, particularly in facilitating rapid transmission in the sympathetic nervous system.

The process by which docking and fusion occurs is incompletely understood, but it is thought to include two soluble proteins, *N*-ethylmaleimide-sensitive factor (NSF) and

soluble NSF attachment protein (SNAP). These membrane proteins bind to cell membrane-bound SNAP receptors (SNARE), of which synaptobrevin, syntaxin, and 25-kd synaptasome-associated proteins (SNAP-25) have been identified. Syntaxin may serve to couple calcium channels and vesicle proteins. [61] It is now believed that the initial events involve activation of vesicles by the NSF-SNAP-SNARE complex, which synaptotagmin activates as soon as calcium entry reaches a critical level. [62] Evidence for the biologic relevance of these proteins derives from observations that tetanus toxin and botulinus toxin block vesicular release by binding to the docking and fusion proteins, [63] whereas microinjection of SNAP into neurons enhances exocytosis. [55, 64] Synaptic vesicles also contain guanosine triphosphate (GTP) binding proteins, which also participate in docking and fusion. [65] Recent evidence based on the uptake of fluorescent membrane dye and measurement of capacitance in nerve terminals demonstrates that the entire process of exocytosis, endocytosis, and vesicular reconstitution occurs in seconds. [66, 67, 68, 69]

The intimate chemistry of vesicular release is not a random event, but a highly differentiated process. The fact that exocytosis is so highly conserved from species to species indicates the biologic importance of this process. However, exocytosis is distinct from the generalized secretory process. First, exocytosis is a local pathway of the nerve terminal that is *independent* of organelles such as the Golgi complex, whereas regulated secretion, particularly of peptide hormones, typically requires repackaging of secretory vesicles via the Golgi complex. Second, exocytosis is far faster than secretion. Release of neurotransmitter from a single nerve terminal can occur 50 times a second, requiring a coordinated and tightly linked regulation of underlying biochemical processes.
Although chromaffin cells in the adrenal medulla synthesize both EPI and NE, the two compounds are actually stored in and secreted from distinct chromaffin cell subtypes. Pharmacologic differences between cells containing NE and EPI have been described, and data suggest that there may be a preferential release from one or another form of chromaffin cell contingent on the nature of the stimulus. [70] Nicotinic agonists or depolarizing agents may cause the preferential release of NE, whereas histamine elicits predominantly EPI release. [71, 72, 73] Protein kinase C plays an important role in regulating catecholamine secretion from NE-containing chromaffin cells. [74]

Inactivation

Most of the NE released is rapidly removed from the synaptic cleft by either an amine uptake mechanism (uptake 1) or uptake by nonneuronal tissue (uptake 2). If a transmitter is to exert fine control over an effector system, as when NE controls blood pressure via the baroreceptor reflex, its half-life in the biophase (i.e., the extracellular space in close proximity of the receptor) must be very short. The uptake-1 mechanism represents the first and most important step in the inactivation of released NE. The majority of released NE is transported into the storage vesicle for reuse. This neurotransmitter uptake into synaptic vesicles is driven by an electrochemical proton gradient across the synaptic vesicle membrane. The vacuolar proton pump is a large, hetero-oligomeric complex, containing eight to nine different subunits. Following reuptake, the small amounts of NE not taken up into the vesicle are deaminated by MAO. There are several organ-specific forms of this enzyme.
In 1991, isolation and cloning of the human NE transporter were reported. [75] The cDNA sequence predicts a protein of molecular weight (MW) 69 kd with 12 to 13 highly

hydrophobic regions compatible with membrane-spanning domains. The pharmacologic characteristics of this binding protein identify it as the cocaine binding site (K_i = 140 nm), although tricyclic antidepressants (desipramine and nortriptyline) were also potent antagonists.

Uptake of NE into the nerve varicosity and its return to the storage vesicle, albeit efficient, is not specific for the neurotransmitter. Some compounds structurally similar to NE may enter the nerve by the same mechanism and may result in depletion of the neurotransmitter. These false transmitters can be of great clinical importance. Moreover, some drugs that block reuptake either into the vesicle or into the synaptic ending itself may cause an enhanced response to catecholamines, that is, more NE is available to receptors. These drugs include cocaine and tricyclic antidepressants (Table 14–5).

TABLE 14–5. Comparison of Direct- and Indirect-Acting Sympathomimetics

	RESPONSE OF EFFECTOR ORGAN TO	
PRETREATMENT	**DIRECT SYMPATHOMIMETIC (E.G., EPINEPHRINE) ACTS AT RECEPTOR**	**INDIRECT SYMPATHOMIMETIC (E.G., TYRAMINE) CAUSES NE RELEASE AFTER ITS UPTAKE BY UPTAKE 1**
Denervation	Increased	Reduced
Loss of uptake-1 sites		
Receptor upregulation		
Reserpine	Slightly increased	Reduced
Blocks vesicular uptake		
Depletes NE		
May cause upregulation		
Cocaine	Increased	Reduced
Blocks uptake 1		
Depletes NE		

NE, norepinephrine.

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Modified from Moore K: Drugs affecting the sympathetic nervous system. In Wingard L, Brody T, Larner J, et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby-Year Book, 1991, p 114.		

Activity of the uptake-1 system varies greatly among different tissues. *Peripheral blood vessels, because of anatomic barriers, have almost no reuptake of NE, but they have the highest rate of synthesis in the body, whereas the highest rate of reuptake is found in the heart*. Thus, those drugs or disease states that alter biosynthesis or storage (e.g., α-methyldopa decreases storage) would be expected to have a more profound effect on blood pressure, whereas those that affect reuptake (e.g., cocaine) would be expected to affect cardiac rate and rhythm.

Typically, the lungs remove 25 percent of the NE that passes through their circulation, whereas EPI and dopamine pass through unchanged. Pulmonary uptake of NE appears to be a sodium-dependent, facilitated-transport process occurring in the endothelial cells of pre- and postcapillary vessels and pulmonary veins. There is no significant uptake by nerve endings. Pulmonary hypertension causes the diminution of NE uptake, presumably because of concomitant thickening of the pulmonary vasculature. [76] Diminished uptake is seen in patients with either primary or secondary pulmonary hypertension with elevated pulmonary vascular resistance. Although the functional significance of the endothelial uptake mechanism of the pulmonary vasculature is unknown, this occurs for other powerful vasoactive compounds, suggesting that the pulmonary endothelium functions to protect the left heart. Defects in the ANS are common in patients with congestive heart failure (CHF). The reuptake of NE is decreased, both at rest and during sympathetic activation, even more than with aging. Sustained sympathoexcitation results in increased neuronal release of NE. The spillover of cardiac NE is increased, predominantly attributable to increased rates of sympathetic nerve firing, rather than faulty neuronal reuptake of NE. [77] Cardiac NE spillover rates differ widely, even among patients with end-stage heart failure awaiting cardiac transplantation. [77] Studies of patients with CHF demonstrate that the heart is depleted of catecholamines. [78] Decreased vesicular leakage of NE in the failing heart because of depleted cardiac NE stores limits the increase in cardiac NE turnover that results from increased NE release. Because their ability to augment catecholamine release further is markedly impaired, patients with CHF compensate for decreases in systemic vascular resistance by further activation of the reninangiotensin system. Decreased clearance of catecholamines also occurs, and indeed

some studies suggest that plasma catecholamine levels may provide a better guide to prognosis than traditional cardiovascular indices. [79, 80] Together, these events result in increased adrenergic drive, desensitization of β-receptors, and depletion of NE stores, which contribute to insufficient inotropic function. [81, 82]

Metabolism

During storage and reuptake, a small amount of NE escapes uptake into the nerve ending and enters the circulation, where it is metabolized by MAO and/or catechol- *O*-methyl transferase (COMT). This metabolism occurs in the blood, liver, and kidney [83](Fig. 14–12).

EPI, which is released by the adrenal medulla, is inactivated by the same enzymes. The final metabolic product of these inactivations is vanillylmandelic acid (VMA). The two catabolic enzymes and the vigorous uptake system account for an efficient clearance of catecholamines. *Because of this rapid clearance, the half-life of NE (and in fact most biogenic amines) in plasma is very short, less than 1 minute*. This short half-life necessitates administration of these agents by infusion. Another consequence of their short half-life is that measuring metabolic products, rather than catecholamines themselves, may be a more ideal measure of catecholamine production. For example, screening for an NE-producing pheochromocytoma is frequently done by measuring urine metanephrine and VMA. Only a small percentage of NE appears in the urine for assay.

Inhibition of MAO would be expected to have a great impact on the sympathetic function of a patient. MAO inhibitors (MAOI) are generally well tolerated, but the stability of the patient belies the fact that amine handling is fundamentally changed. Clinically important life-threatening drug interactions have been noted and are discussed in the section *Drugs and the Autonomic Nervous System*.

Other compounds can be metabolized by catabolic enzymes to produce "false transmitters." Although it is not used therapeutically, tyramine is the prototypic drug studied. Tyramine is present in many foods, particularly aged cheese and wines, or it can be synthesized from tyrosine. Tyrosine is decarboxylated in the liver and gut. Tyramine enters the sympathetic nerve terminal via the uptake-1 mechanism, displacing NE from the vesicles into the cytoplasm. This released NE leaks out from the cytoplasm and is responsible for the sympathomimetic effect of tyramine. However, a secondary effect can occur. In the vesicle, tyramine is converted by DBH into octopamine, which is eventually released as a false transmitter in place of NE, but without the expected effects, because it has only 10 percent of the potency of NE. [84] It is probably also clinically important to note that sodium plays a key role in the transport of NE into the cell. [85]

Adrenergic Receptors

Ahlquist originally identified α- and β-receptors by their differing response to pharmacologic agents. Initially, α-adrenergic receptors were distinguished from β-adrenergic receptors by their greater response to EPI and NE than to isoproterenol. The development of α- and β-antagonists further supported the existence of separate α-receptors. The advent of radioligand binding techniques signaled an era of pharmacology in which subtypes of receptors could be more readily assessed.

Although it has long been traditional to classify adrenergic receptors as either α- or β-, and more recently as α_1, α_2, β_1, or β_2 based on available drugs, the advent of molecular

biology has suggested a more rational classification into three major subtypes and nine sub-subtypes [86](Fig. 14–13). Justification for such a scheme is derived from pharmacologic analyses of drug affinity patterns (see later), functional differences in signal transduction mechanisms, and primary structural differences in the receptors. Although such a classification is consistent with the available scientific evidence, the drugs currently available for clinical use may still be classified in the more traditional pattern. (Table 14–6) describes the distribution, response, typical agonists, and antagonists of the α_1 -, α_2 -, β_1 -, and β_2 -receptors.

TABLE 14–6. Distribution of α- and β-Receptors

RECEPTOR	DISTRIBUTION	RESPONSE	AGONIST	ANTAGONIST
α_1	Smooth muscle	Constriction	Methoxamine	Prazosin
			Phenylephrine	
α_2	Presynaptic	Inhibit norepinephrine release	Clonidine	Yohimbine
			Dexmedetomidine	
β_1	Heart	Inotropy	Dobutamine	Metoprolol
		Chronotropy		
β_2	Smooth muscle	Dilation	Terbutaline	
		Relaxation		

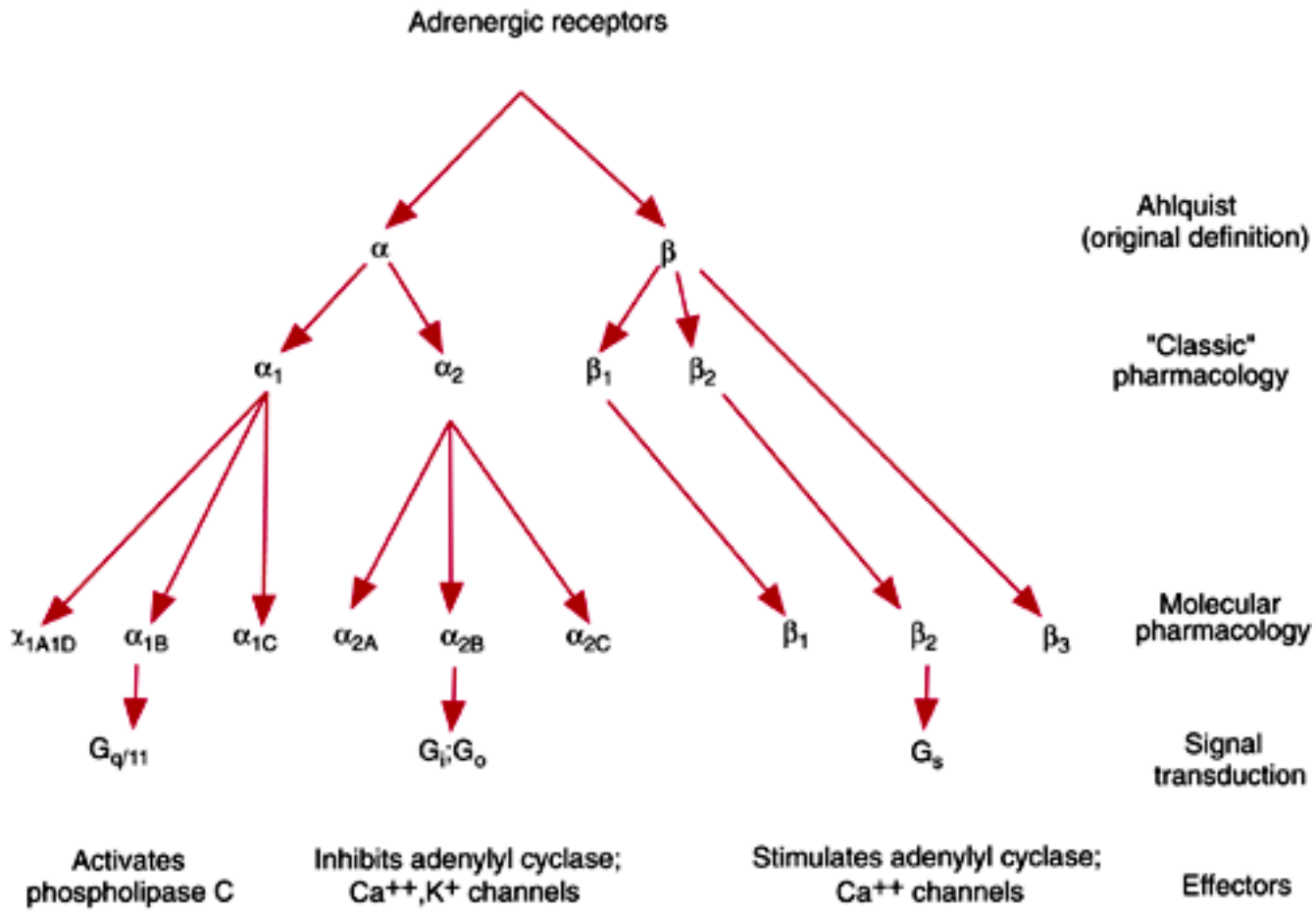


FIGURE 14–13 Classification of adrenergic receptors.

α-Receptors

Whereas α_1 - and α_2 -receptors are traditionally differentiated based on pharmacologic characteristics, radioligand binding affinities have more recently been examined. At the α_1 -receptor prazosin is more potent than yohimbine, whereas the reverse is true at α_2 -receptors. Functional and binding assays and molecular biologic approaches have unequivocally confirmed the classification of α-adrenoceptors into subtypes. [87] Within α_1 -adrenergic receptors, $\alpha_{1A/D}$ -, α_{1B} - and α_{1C} -receptors have been characterized. Several α_2 -isoreceptors (α_{2A}, α_{2B}, and α_{2C}) have been described. α_2 -Receptors can be expressed presynaptically or even in nonneuronal tissue. α_2 -Receptors are found in the peripheral nervous system and the CNS and in a variety of organs, including platelets, liver, pancreas, kidney, and the eye, where specific physiologic functions have been identified. [88] More recently, the predominant α_2 -receptor of the human spinal cord was identified as the α_{2A} -subtype. [86] It appears that mammalian genomes contain two sets of at least three unique genes encoding the α-adrenoceptors. The genes encoding α_2 -receptors have been localized in chromosomes 2, 4, and 10.

There is more than theoretic relevance in subclassification of receptors. For example, the α-adrenergic receptors in the prostate gland are predominantly α_{1A} . Thus, therapy with selective α_{1A} -antagonists for benign prostatic hypertrophy may avoid some of the postural hypotension and other deleterious effects that occur with less specific α-antagonists Localization of β_3 -receptors to fat cells suggests a new therapy for obesity. Polymorphism of this β-receptor subtype is associated with obesity and the potential for the development of diabetes. [89, 90, 91] There are also examples of point mutations in genes encoding β_2 -receptors that are correlated with decreased downregulation of β-receptors and nocturnal asthma. [92, 93]

Amino acid sequence comparisons indicate that α- receptors are members of the seven transmembrane segment gene superfamily utilizing G protein for signal transduction. A core of 175 amino acids constitutes the seven transmembrane regions that are highly conserved among different family members. [94] The plethora of receptor subtypes remains incompletely explained, although the observation that different signal transduction mechanisms are used suggests finer control and physiologic significance. It may be important that there is considerable variability in α-adrenergic receptor subtypes among species. [95]

Receptors can be presynaptic as well as postsynaptic. Presynaptic receptors may act as either heteroreceptors or autoreceptors. An *autoreceptor* is a presynaptic receptor that reacts with the neurotransmitter released from its own nerve terminal, providing feedback regulation. A *heteroreceptor* is a presynaptic receptor that responds to substances other than the neurotransmitter released from that specific nerve terminal.

Although several presynaptic receptors have been identified, the α_2 -receptor may be of the greatest clinical import. Presynaptic α_2 -receptors regulate the release of NE and ATP through a negative feedback mechanism. [96] Thus, activation of presynaptic α_2 -receptors by NE inhibits subsequent NE release in response to nerve stimulation. Clonidine is a prototype α_2 -agonist. In the human brain, ligand studies reveal a high density of α_2 -receptors, particularly in cerebral cortex and medulla. [97] This latter distribution may account for the bradycardiac and hypotensive responses to α_2 -agonist drugs. Whereas presynaptic α_2 -receptors and cholinergic receptors inhibit release, presynaptic β-receptors stimulate release of NE.

β-Receptors

The structure of the β-adrenergic receptor was among the first to be ascertained and is well characterized. Like the α-receptor, the β-receptor is one of the superfamily of proteins that have seven helices woven through the cellular membrane. These transmembrane domains are labeled M_1 through M_7 ; antagonists have specific binding sites, whereas agonists are more diffusely attached to hydrophobic membrane-spanning domains (Fig. 14–14). The extracellular portion of the receptor ends in an amino group. A carboxyl group occupies the intracellular terminus, and it is here that phosphorylation occurs. At these cytoplasmic domains, interaction with G proteins and kinases, including β-adrenergic receptor kinase, occurs (see later). Interestingly, the β- receptor has mechanistic and structural similarities with muscarinic, but not nicotinic, receptors, primarily in the transmembrane sections. Both muscarinic and β-receptors are coupled to adenylate cyclase through G proteins, and both can initiate the opening of ion channels.

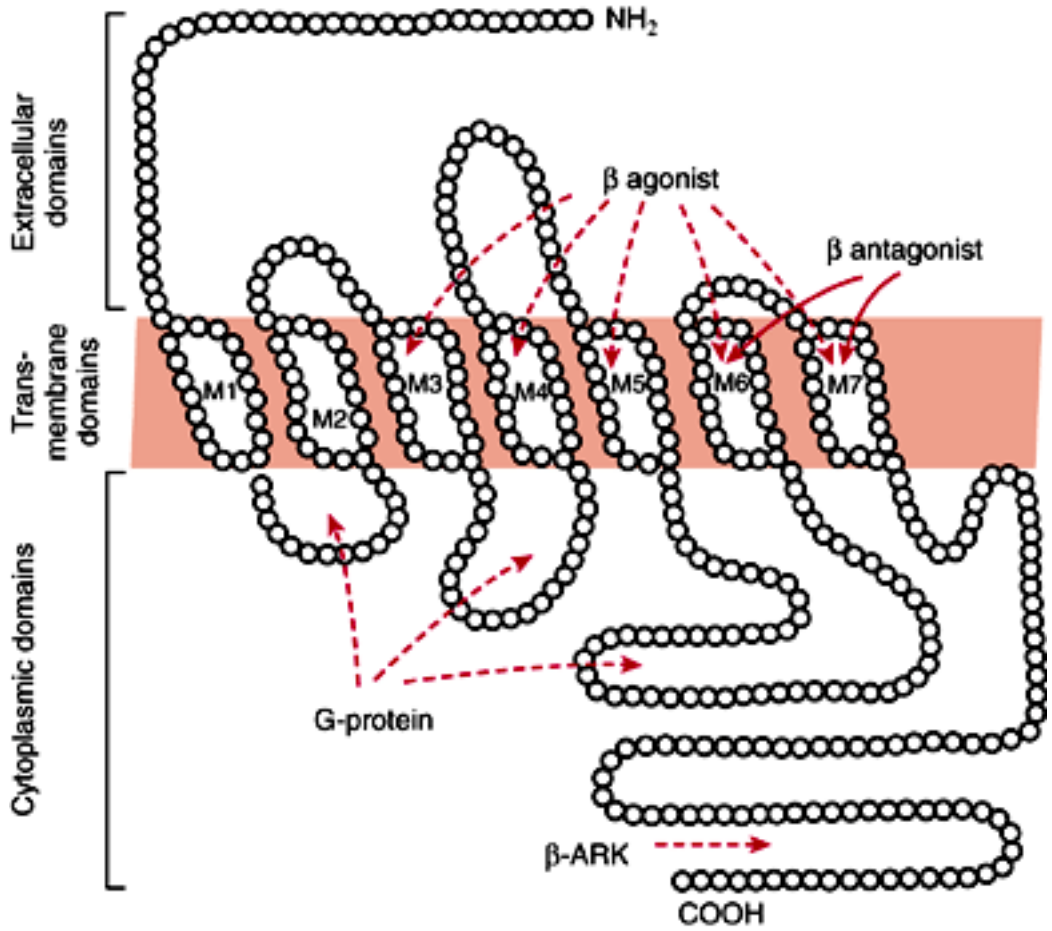


FIGURE 14–14 Molecular structure of the β-adrenergic receptor. Note the three domains. The transmembrane domains act as a ligand-binding pocket. Cytoplasmic domains can interact with G proteins and kinases, such as β-adrenergic receptor kinase (β-ARK). The latter can phosphorylate and desensitize the receptor. (Modified from Opie[98])

β-receptors have been further divided into β_1 -, β_2 -, and β_3 -subtypes, all of which increase cyclic adenosine monophosphate (cAMP) through adenylate cyclase and the mediation of G proteins. [99] Traditionally, the β_1 -receptors were thought isolated to cardiac tissue, and β_2 -receptors were believed to be restricted to vascular and bronchial smooth muscle. Although this model of distribution is still useful because it reflects the primary clinical effects of pharmacologic manipulation of the β_1 - and β_2 -receptor subtypes, the role of β_2 -receptors in cardiac function is more important than indicated by this model. The β_2 -receptor population in human cardiac tissue is sizable, accounting for 15 percent of the β-receptors in the ventricles and 30 to 40 percent in the atria. [100] These β_2 -receptors may play an important role in compensation for disease, helping to maintain response to catecholamine stimulation as β_1 -receptors are downregulated during chronic

catecholamine stimulation and CHF. [101] The β_2 -population is almost unaffected in end-stage congestive cardiomyopathy. [102] In addition to positive inotropic effects, β_2 -receptors in the human atria participate in the regulation of heart rate. The generation of cAMP in the human heart appears to be mediated primarily by β_2 -receptors, although this may be an artifact related to lability of β_1 -receptors. [102] Thus, β_2 -agonism may have significant effects on cardiac contractility and rate. [101]

Dopamine Receptors

Dopamine not only exists as an intermediate in NE biosynthesis, but also exerts α- or β-effects (depending on the dose administered). Further, Goldberg and Rajfer [103] demonstrated physiologically distinct dopamine-1 (DA_1)- and dopamine-2 (DA_2)-receptors, the most important of the five dopamine receptors cloned to date (Fig. 14–15). DA_1 -receptors are postsynaptic and act on renal, mesenteric, splenic, and coronary vascular smooth muscle to mediate vasodilatation through stimulated adenylate cyclase and increased cAMP production. The vasodilatory effect tends to be strongest in the renal arteries. It is for this action, particularly the redistribution of renal blood flow, that dopamine is most frequently used. Additional renal DA_1 -receptors located in the tubules modulate natriuresis through the sodium-potassium ATPase pump and the sodium-hydrogen exchanger. [103, 104, 105, 106] The DA_2 -receptors are presynaptic; their action may be to inhibit NE and perhaps ACh release. There are also central DA_2 -receptors that may mediate nausea and vomiting. The antiemetic activity of droperidol is thought to be related to its DA_2 activity.

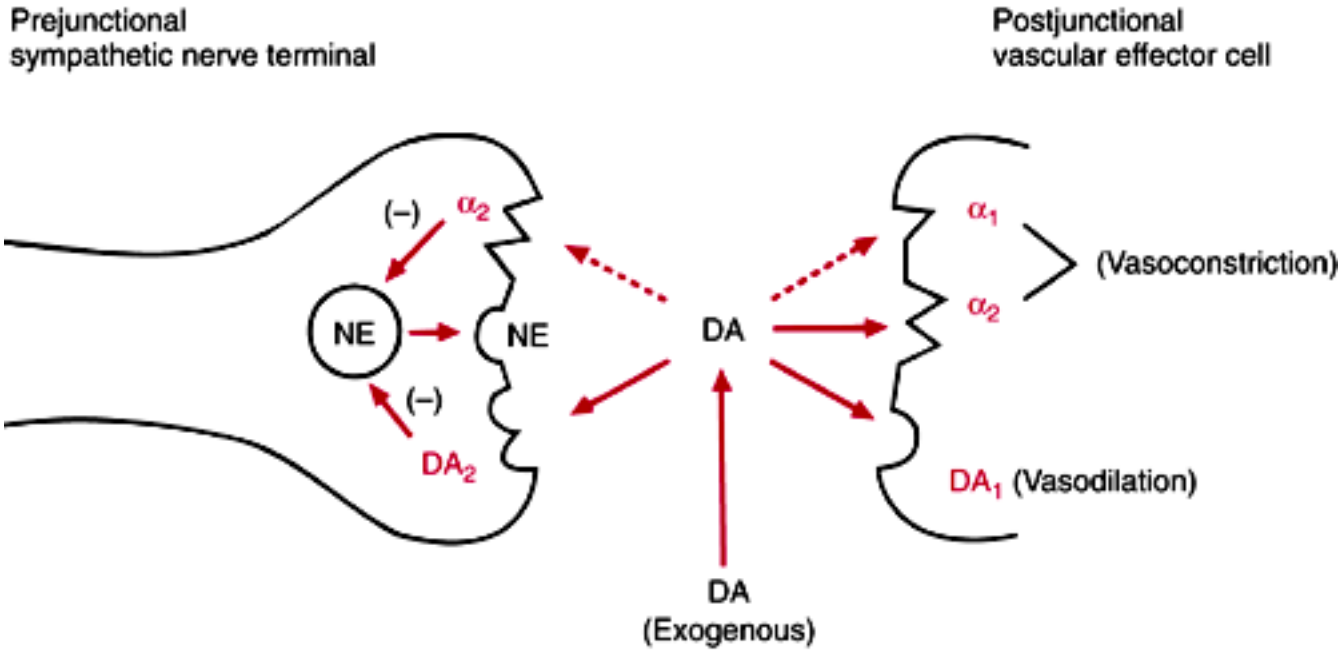


FIGURE 14–15 Location of dopamine-1-(DA_1) receptors, α_1- and α_2-adrenoceptors on postganglionic vascular effector cells, and DA_2-receptors and α_2-adrenoceptors on the prejunctional sympathetic nerve terminal. When dopamine is administered, activation of DA_1-receptors causes vasodilation, whereas activation of DA_2-receptors causes inhibition (–) of norepinephrine (NE) release from storage granules. A larger dose of dopamine activates α_1- and α_2-adrenoceptors on the postjunctional effector cells to cause

vasoconstriction and on α_2-adrenoceptors on the prejunctional sympathetic terminal to inhibit release of NE. NE released from the prejunctional sympathetic terminal also acts on α_1- and α_2-adrenoceptors. (Modified from Goldberg and Rajfer[103])

G Proteins

After adrenergic receptor stimulation, the extracellular signal is transformed into an intracellular signal by a process known as *signal transduction* in which α_1 - and β-receptors are coupled to G proteins. When activated, the G proteins can modulate either the synthesis or the availability of intracellular second messengers (Fig. 14–16). The activated second messenger diffuses through the cytoplasm and stimulates an enzymatic cascade. The sequence first messenger → receptor → G protein → effector → second messenger → enzymatic cascade is found in a wide variety of cells; the specific entities that fulfill the separate roles vary from cell to cell. [107] G proteins located on the inner surface of the cell membrane can also directly modify the activity of transmembrane ion channels.

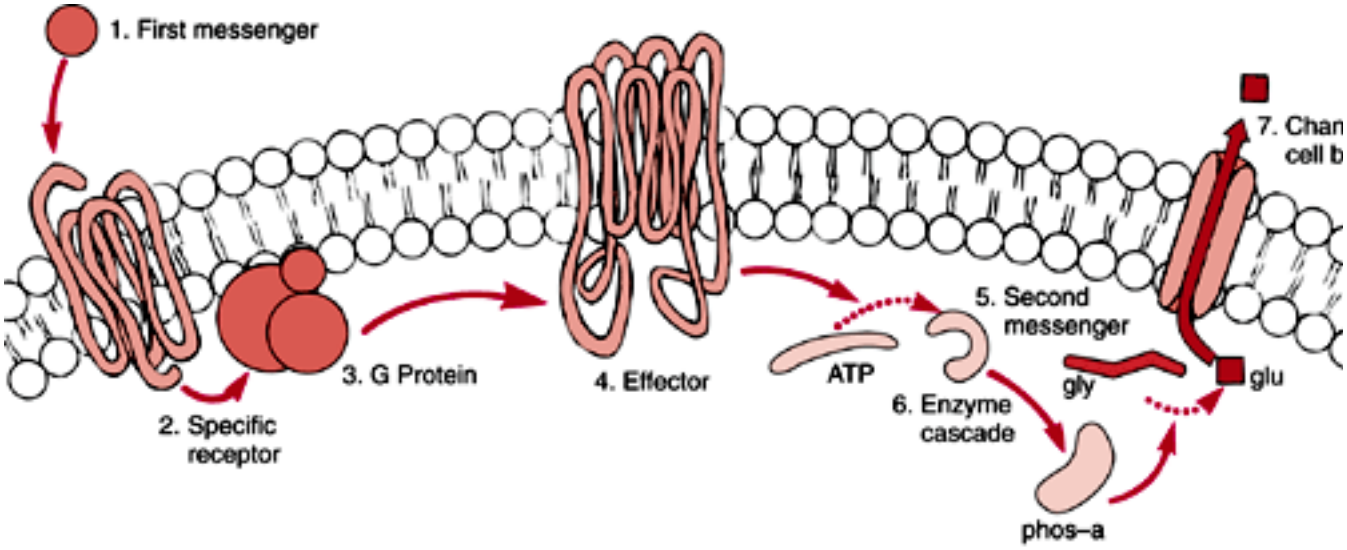


FIGURE 14–16 Epinephrine-stimulated glycogenolysis in a liver cell demonstrates the role of G proteins in cellular function. The first messenger (epinephrine) binds to its specific receptor, stimulating the G protein (in this case Gs) to activate the effector, adenylyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), the second messenger, which then triggers a cascade of enzymatic reactions that stimulates the enzyme phosphorylase (phos-a) to convert glycogen into glucose, which the cell finally extrudes. (Modified from Linder and Gilman[107])

The structure of G proteins has been the subject of intense scrutiny. Three types of subunits (α, β, and γ) have been described. The α-subunit is most variable and determines the activity of the protein—whether it is stimulatory (G_s), inhibitory (G_i), G_o or the recently-described $G_{q/11}$. [108, 109] The α-subunit may split off and behave independently, whereas the β- and γ-subunits remain together. Although 20 α-subunits, 5 β-subunits, and 6 γ-subunits have been cloned, the constellation of G proteins used by any individual receptor is more limited. Each class of adrenergic receptor couples to a different major subfamily of G proteins, which are, in turn, linked to different effectors. The major subtypes of α_1 -, α_2 - and β-receptors are linked to G_q, G_i, and G_s, respectively, which, in turn, are linked to phospholipase C activation (α_1), adenylyl cyclase inhibition (α_2), or adenylyl cyclase stimulation (β) (see Fig. 14–13). The pertussis-resistant G_q protein was identified in 1991 [109] and subsequently was observed to mediate α_1 -adrenergic receptor signal transduction by activation of phospholipase C and generation of inositol triphosphate (ITP) and diacylglycerol (DAG). [110] The physiologic relevance of the subunits is all the more important when one recognizes that the pharmacologic tools for dissecting signal transduction are all associated with diseases that have been scourges of humankind *(Bordetella pertussis, Vibrio cholerae,* and *Clostridium botulinum).*

In its resting state, the G protein is bound to guanosine diphosphate (GDP) and is not in contact with the receptor. When the receptor is activated by the first messenger, it stimulates the G protein to release GDP and bind GTP to its α-subunit, activating itself. The bound GTP signals the G protein to split into two parts consisting of the α-GTP structure and the β-γ–subunit. The released α-subunit binds to the effector and activates it, then converts its attached GTP to GDP thus returning itself to the resting state. The α-subunit joins with the β-γ–unit, and once again the reconstructed G protein waits at the inner membrane.

β-Receptor stimulation activates G proteins, enhancing adenylate cyclase activity and cAMP formation. The briefest encounter of plasma membrane β-adrenergic receptors with EPI or NE results in profound increases (up to 400-fold higher than the basal level within minutes) in the intracellular levels of cAMP. Increased cAMP synthesis, in turn, activates protein kinases, which phosphorylate target proteins. This phosphorylation elicits various cellular responses that complete the path between receptor and effect. Stimulation of α_2 -receptors results in G_i inhibition of the adenylate cyclase. There is a relative abundance of G proteins, resulting in amplification of receptor agonism at the signal transduction step. The number of G protein molecules greatly exceeds the number of β-adrenergic receptors and adenylate cyclase molecules. Thus, it is the receptor concentration and ultimately adenylate cyclase activity that limit the response to catecholamines, perhaps providing an explanation for the efficacy of phosphodiesterase inhibitors. [111, 112]

Other transduction pathways are known. The α_{1B} - receptor acts through G proteins, but it activates phospholipase C in the inner cell membrane, which then increases hydrolysis of the diphosphate form of phosphoinosotol (PIP_2) to the triphosphate and diacyglycerol. These two compounds then mobilize intracellular calcium stores from the sarcoplasmic reticulum and probably the subsarcolemma, resulting in a marked increase in intracellular

calcium ion concentration. Ultimately, the calcium ions bind to calmodulin. This calcium-sensitive intracellular protein then activates a myosin light-chain kinase that phosphorylates the myosin light chain and facilitates the interaction between actin and myosin, resulting in the contraction of the smooth muscle. In other cells, calmodulin stimulates other kinases, resulting in effector activity.

Myocardial cells respond to receptor stimulation differently depending on the identity of the first messenger. Two opposing effects, inhibition or stimulation of contractility, are produced by the sequence of receptor → G protein → effector → enzymatic cascade, but the identity of the chemicals in the sequence differs. [113] NE causes myocardial cells to contract with more vigor when the α-subunit of the stimulatory protein (G_s) activates adenylate cyclase. The α-subunits of this protein cause potassium channels to open and permit efflux of potassium ion. The force of contraction is diminished when ACh acts as a first messenger, stimulating its receptor to activate the inhibitory protein G_i or G_o. Clinically important second-to-second changes in heart rate can be explained by the simultaneous activation of G_s and G_o. The current caused by G_o is larger than that of G_s, which explains the clinical impression that vagal inhibition of heart rate is augmented in the presence of sympathetic stimulation, such as may occur in unpremedicated patients. [113]

Interaction of anesthetics with G proteins has been suggested as a mechanism for the negative inotropic effects of halothane and other volatile anesthetics. Although halothane attenuates neurotransmitter release from peripheral sympathetic neurons, [114, 115, 116, 117] other important postsynaptic effects may be involved in its negative inotropic action. [118, 119, 120, 121, 122]

Although an effect on cAMP formation would be a plausible explanation for halothane's negative inotropic effects, studies suggest that this effect is unrelated to adenylate cyclase. [123] Halothane blocks slow calcium channels in the heart, [124, 125] alters calcium fluxes in sarcoplasmic reticulum, [126, 127] and inhibits cAMP-dependent protein kinase. [119] Thus, at this time it appears that the negative inotropic effect of inhalational anesthetics occurs at several sites.

Upregulation and Downregulation

β *-Adrenergic receptors are not fixed, but they change significantly in dynamic response to the amount of NE present in the synaptic cleft or in plasma*. For β-adrenergic receptors, this response is fast: within 30 minutes of denervation or adrenergic blockade, there is an increased number of receptors. This upregulation may explain why sudden discontinuation of β-adrenergic receptor blocking drugs causes rebound tachycardia and increases the incidence of myocardial infarction and ischemia. Many chronic phenomena, such as varicose veins [128] or aging, can decrease adrenergic receptor number or responsiveness systemically.

Clinically, and at the cellular level, responses to many hormones and neurotransmitters wane rapidly despite continuous exposure to adrenergic agonists. [129] This phenomenon, termed *desensitization,* has been particularly well studied for the stimulation of cAMP levels by plasma membrane β-adrenergic receptors. [94] Mechanisms postulated for desensitization include uncoupling (phosphorylation), sequestration, and downregulation. The molecular mechanisms underlying *rapid* β-adrenergic receptor desensitization do not appear to require internalization of the receptors, but rather an alteration in the

functioning of β-receptors themselves that uncouples the receptors from the stimulatory G_s protein. Agonist-induced desensitization involves phosphorylation of G protein–coupled receptors by two classes of serine-threonine kinases. One of these initiates receptor-specific or homologous desensitization. The other works through second messenger–dependent kinases, thus mediating a general cellular hyporesponsiveness, termed *heterologous desensitization*. Ultimately, an inhibitory arrestin protein binds to the phosphorylated receptor, causing desensitization by blocking signal transduction. Because GPK only phosphorylate receptors in the activated state, there has been an attempt to utilize transient beta blockade in states of receptor desensitization such as CHF or cardiopulmonary bypass in order to achieve a "a receptor holiday." [11, 95, 130]

Regeneration of a functional β-adrenergic receptor is contingent on sequestration of the receptor, with dephosphorylation and presumed recycling. There has been some evidence that the arrestins contribute to desensitization not only by uncoupling signal transduction, but also by contributing to the process of receptor internalization. [131, 132] Rapid changes in receptor populations can occur with such sequestration, which does not require protein synthesis. Downregulation may be distinguished from these rapid mechanisms because it occurs after hours of exposure to an agonist (e.g., as in chronic stress or CHF), and receptors are actually destroyed. New receptors must be synthesized before a return to a baseline state is possible.

Chronic CHF is one of the most important and best studied pathophysiologic situations in which tolerance or downregulation occurs. Initially, it was noted that the density of cardiac β-receptors was markedly decreased in patients with terminal heart failure in response to the elevated plasma catecholamine levels. This finding explained why administration of exogenous β-agonists was relatively ineffectual in this syndrome. Subsequently, with the demonstration that β_1 - and β_2 -receptors coexisted in human ventricles, Bristow and coworkers, [134] using radioligand techniques, documented that β_1 -receptor density was decreased without change in the density of β_2 -receptors in human ventricles affected by CHF. Consequently, β_2 -agonism accounted for 60 percent of the total inotropic response stimulated by isoproterenol in the failing heart, as contrasted with 40 percent in the nonfailing heart. [134]

Another disease in which adrenergic receptor function is altered is hyperthyroidism. The activity of the thyroid gland influences the receptor density, with hyperthyroidism increasing density and hypothyroidism decreasing density. There is some evidence that corticosteroids decrease receptor density. [24] Consequently, the reaction of the body to well-characterized sympathetic agonists may be considerably different, depending on the pathologic and environmental circumstances. [135] However, the structural similarity of thyroid hormone and tyrosine suggests that false transmitters may play a role. [136]

Cholinergic Pharmacology

Acetylcholine Synthesis

Many of our presumptions about cholinergic pharmacology are drawn from what is known about the neuromuscular junction, where detailed electrophysiologic information on cholinergic transmission is readily available. ACh is synthesized intraneurally from acetyl coenzyme A (CoA) and choline via the enzyme choline acetyl transferase in the

synaptosomal mitochondria (Fig. 14–17). [137] Despite the presence of this enzyme, it should be noted that choline itself is not made in the brain, but it appears to be transported. Sources of choline include dietary phospholipids, hepatic synthesis of phosphatidylcholine from dietary precursors such as ethanolamines, and choline released by hydrolysis of ACh. Most choline originates in the liver. Choline is transported as the phospholipid and is taken up by a high-affinity transport system. This system appears to be largely responsible for determining ACh levels, although there is some evidence that precursor availability may limit cholinergic activity. The level of circulating choline can affect the release of ACh when rapid firing is taking place at cholinergic motor neurons. In one interesting experiment, plasma choline levels were measured in marathon runners before and immediately after a race; running a marathon decreased choline levels to well below those usually seen in fasting individuals, potentially lowering performance ability by possibly decreasing ACh release at the neuromuscular junction or cholinergic sites. [138] Choline analogues are being developed to enhance neuromuscular performance and to treat Alzheimer disease.

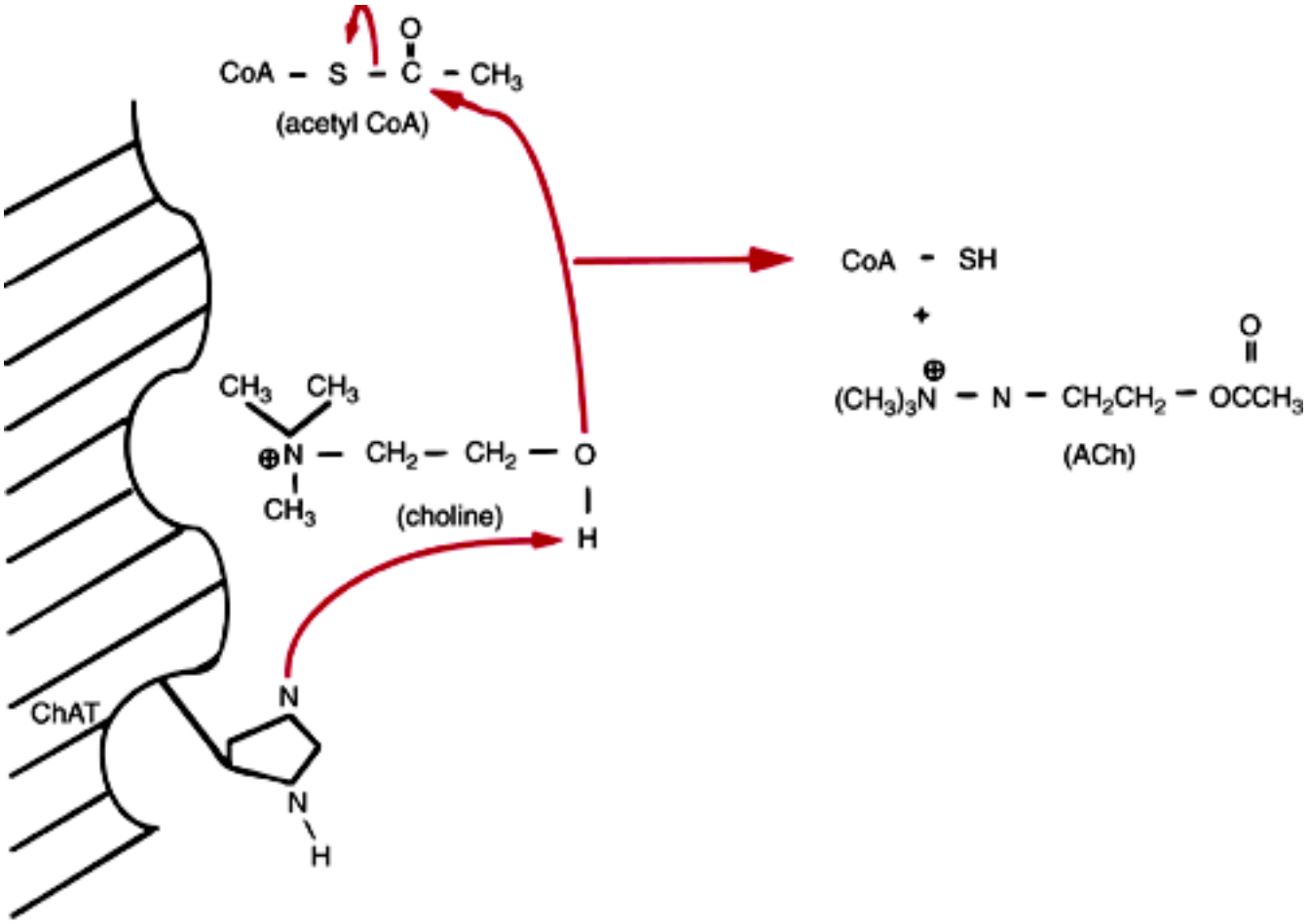


FIGURE 14–17 Synthesis of acetylcholine (ACh). Choline and acetyl coenzyme A (CoA) bind to the surface of choline acetyltransferase (ChAT). An imidazole on ChAT promotes proton removal and generates a more nucleophilic choline, thereby facilitating condensation with the acetyl group of acetyl CoA. The products of the reaction are CoA and ACh, which are rapidly packaged in vesicles for immediate release on proper

stimulation. ChAT also catalyzes the reverse reaction between ACh and CoASH, although at a much slower rate than the forward reaction. (Modified from Doukas[137])

Storage and Release

The neuromuscular junction includes the nerve ending, the muscle, and the synaptic cleft, which is a space between the nerve and the muscle. On the nerve or presynaptic side, the nerve ending contains many synaptic vesicles (quanta) that contain ACh. On the muscle membrane, there are many infoldings of the postjunctional membrane. Studies have demonstrated that there are presynaptic release sites located opposite the junctional folds at the shoulders of the junctional folds. Vesicles containing ACh move toward these specific release sites and then fuse with the presynaptic membrane and open, spilling their contents across the synaptic cleft onto the receptors on the postsynaptic membrane (Fig. 14–18). [139]

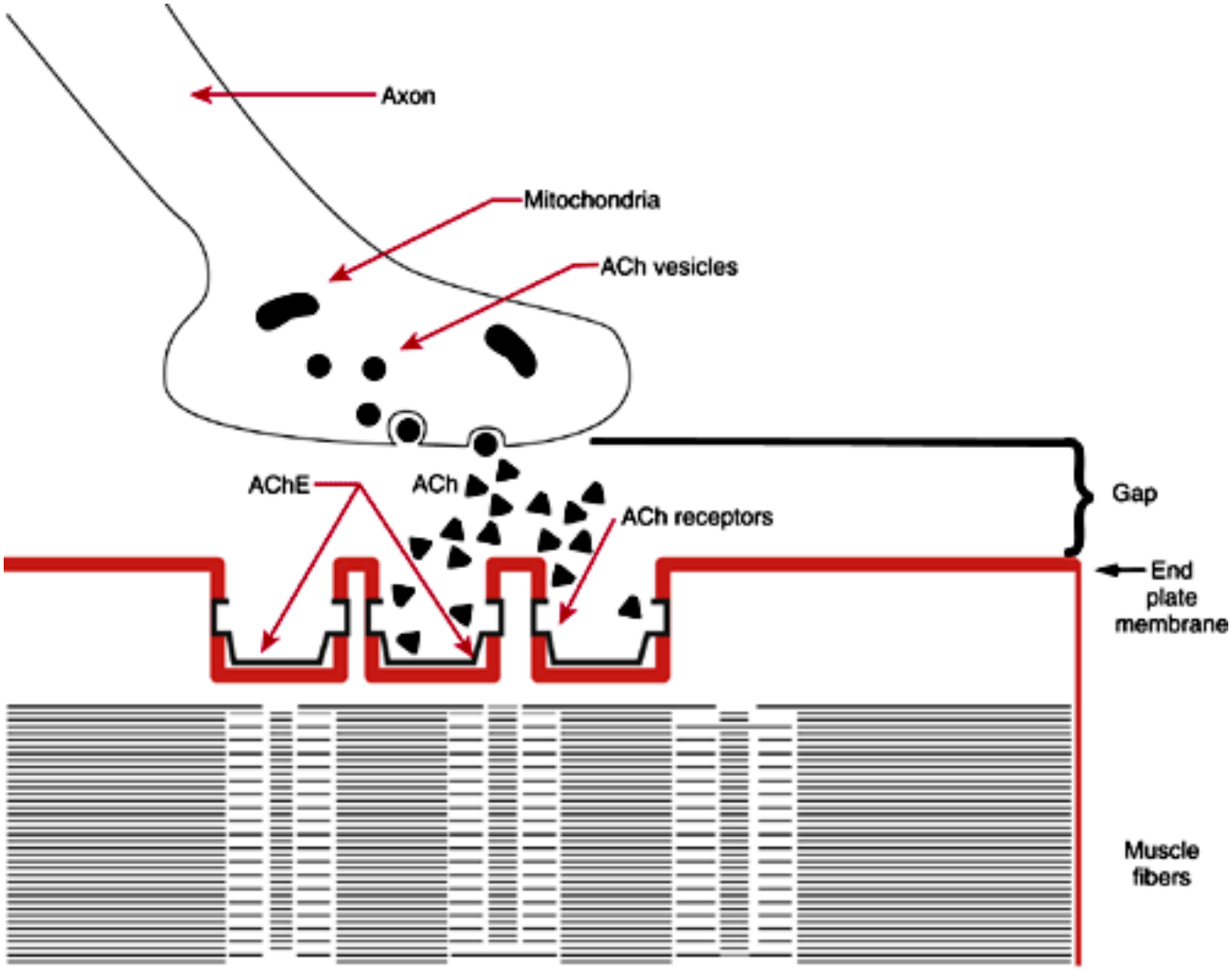


FIGURE 14–18 Acetylcholine (ACh) release, diffusion across the synaptic cleft, binding to receptors on end-plate membrane, and hydrolysis by acetylcholine esterase (AChE) in the absence of blocking drugs. (From Stiller[139])

ACh is stored in vesicles approximately 300 μm in diameter each containing 10,000 molecules of ACh. Central cholinergic transmission is different from the neuromuscular model in that few vesicles are present in the presynaptic terminal. These vesicles are "clear" on electron microscopy.

The spontaneous release of the ACh in one vesicle causes a miniature end-plate potential of 0.5 millivolts (mV) and 2,000 channels open in the membrane of a muscle cell, permitting sodium influx and potassium efflux. Twelve thousand ions enter the postsynaptic cell each millisecond each channel is open.

When a nerve impulse arrives at the presynaptic nerve terminal, it causes an influx of calcium ions across the membrane. This induces 100 to 300 synaptic vesicles to fuse with the presynaptic membrane at specific release sites at the active zone, resulting in the liberation of ACh from vesicles into the synaptic cleft.

Although the original hypothesis proposed by Katz of calcium as the exocytotic trigger has stood the test of time, *calcium entrance is necessary but not sufficient:* the presynaptic terminal must also be depolarized. Within 0.3 ms after the vesicle release occurs, the ACh in each vesicle causes 2,000 channels in the postsynaptic muscle cell membrane to open, with sodium entering the cell and potassium leaving. This ion flow gives rise to an electrical current and changes the normal resting potential of –90 mV. This nerve impulseinduced brief depolarization of 100 to 300 vesicles is known as an end-plate potential (EPP) but it is also a synaptic potential or an excitatory postsynaptic potential (EPSP), terms used to describe synaptic transmission in general. The EPP (50–100 mV) triggers a muscle action potential.

Normally, in the absence of a nerve impulse, there is a series of miniature end-plate potentials (MEPP) resulting from the spontaneous release of one quantum of ACh (10,000 molecules, or the contents of one vesicle). Each channel that is opened results in a depolarization of 0.00022 mV. The MEPP involves 1,500 ion channels being opened and causes a deflection of 0.5 mV. The EPP, which is summated, involves 500,000 ion channels opening and represents a depolarization of 50 to 100 mV.

Inactivation

ACh is an ester that hydrolyzes spontaneously in alkaline solutions into acetate and choline, neither of which has significant pharmacologic action. *In vivo,* the rate of hydrolysis is increased enormously by enzymatic catalysis. (Web sites: www.uoguelph.ca/GTI/urbanpst/cholin t.htm and www.biology.bnl.gov/disk$3/giles/che.html). The two most important enzymes are acetylcholinesterase and butyrylcholinesterase.

Sometimes called "tissue esterase" or "true esterase," *acetylcholinesterase* is a membrane-bound enzyme that is present in all cholinergic synapses, where it functions to destroy the neurotransmitter released from the nerve endings. Acetylcholinesterase is one of the most efficient of enzymes and destroys ACh, terminating transmission within

milliseconds after its release. The enzyme also is present in tissues that are not innervated, such as erythrocytes. Its function in these tissues is not known.
Butyrylcholinesterase, sometimes called "plasma esterase" or "pseudocholinesterase," is a soluble enzyme that is made primarily in the liver and circulates in the blood. Its function in normal situations is not known; individuals who are genetically incapable of making the enzyme are normal in all other regards.
Of these two enzymes, acetylcholinesterase is the more important in terms of the function of ACh. Not only is it present in all cholinergic synapses, where it destroys neurally released ACh, but also it is the more efficient of the two enzymes. The substrate turnover is 2,500 molecules per second, and one catalytic event lasts 40 μs. Butyrylcholinesterase is important for the destruction of some cholinergic drugs, many of which are not destroyed by acetylcholinesterase.
Both forms of cholinesterase have been cloned. It is of more than passing interest that the first example of gene amplification in humans occurred in this enzyme system. The offspring of Israeli farmers exposed to insecticide expressed abnormal cholinesterase. [140, 141]

Traditionally, the catalytic part of the enzyme has been thought to contain two areas: an anionic site (which carries a strong negative charge) and an esteratic site (which contains electrophilic amino acids). It has been believed that, during its hydrolysis, ACh is attracted to the enzyme because the negative charge of the anionic site attracts the positive charge in the quaternary nitrogen of ACh. The ester group of ACh aligns with the esteratic site of the enzyme. An electrophilic attack on the molecule occurs, and the acetate link is transferred from the choline to an amino acid in the enzyme. The choline drifts away, leaving a covalently bound, acetylated enzyme. The acetate link is subsequently attacked and broken by a hydroxyl group from water. The acetate drifts away, and the regenerated enzyme is ready to interact with another molecule of ACh.
However, the atomic structure of acetylcholinesterase has been found to be different from what had been previously thought, and our understanding of the binding of ACh to its hydrolytic enzyme has altered. [142] The new model predicts that the quaternary ammonium binds to some of the 14 aromatic amino acids lining a deep gorge in the enzyme.
Inhibition of acetylcholinesterase prevents the destruction of ACh in cholinergic synapses and so can activate all cholinergic systems simultaneously. In addition to their therapeutic use, cholinesterase inhibitors are the active ingredients in insecticides and many nerve gases.

Cholinergic Receptors

Traditionally, cholinergic receptors have been organized into two major subdivisions, nicotinic and muscarinic, that predict most clinical effects. Muscarinic receptors are mostly present in peripheral visceral organs, whereas nicotinic receptors are present on parasympathetic and sympathetic ganglia and on the neuromuscular junctions of skeletal muscle.
Although these two structurally and functionally distinct classes of receptors have significantly different responses to ACh, ACh itself exhibits no specificity. However, specific antagonists can exploit the difference between the muscarinic and nicotinic receptors. As a result, structure-activity relationships have emerged. All cholinergic agonists appear to need a quaternary ammonium group as well as an atom capable of

forming a hydrogen bond through an unshared pair of electrons. The distance between the two may determine whether the agonism is nicotinic or muscarinic. With muscarinic agonists, the distance appears to be about 4.4 Å, whereas for nicotinic agonists, the distance is 5.9 Å.

The nicotinic receptors on ganglia and motor end plates differ, and they are blocked by different drugs. *d*- Tubocurarine predominantly blocks the neuromuscular junction, whereas hexamethonium acts to block the ganglionic receptors. Methonium compounds were developed to explore the structure-activity relationships of the curare alkaloids. The most potent depolarizing neuromuscular blocking structure contained ten carbon atoms (decamethonium); in contrast, the structure containing six carbon atoms, hexamethonium, was an active ganglionic blocking agent but had little effect at the neuromuscular junction.

ACh receptors on the neuromuscular junctions of mature mammals belong to the superfamily of receptor-gated ion channels, which includes glutamate and glycine. The nicotinic receptors are pentameric membrane proteins, which form nonselective cation channels. There are two α-units, each 40 kd, and one each of the β-, ε-, and δ-units (Fig. 14–19). Although different subunits may be expressed developmentally, the α-subunits represent the binding sites for ACh or nicotinic antagonists. At birth, a γ-subunit occupies the position that will be taken by the ε-subunit within the first 2 weeks of life. This change in subunits converts the receptor from one with a low conductance and a relatively long duration of opening to a receptor with a high conductance but a brief duration of opening. [143] There are therefore important functional differences in ACh receptors during development, but the important drug-binding subunits remain constant.

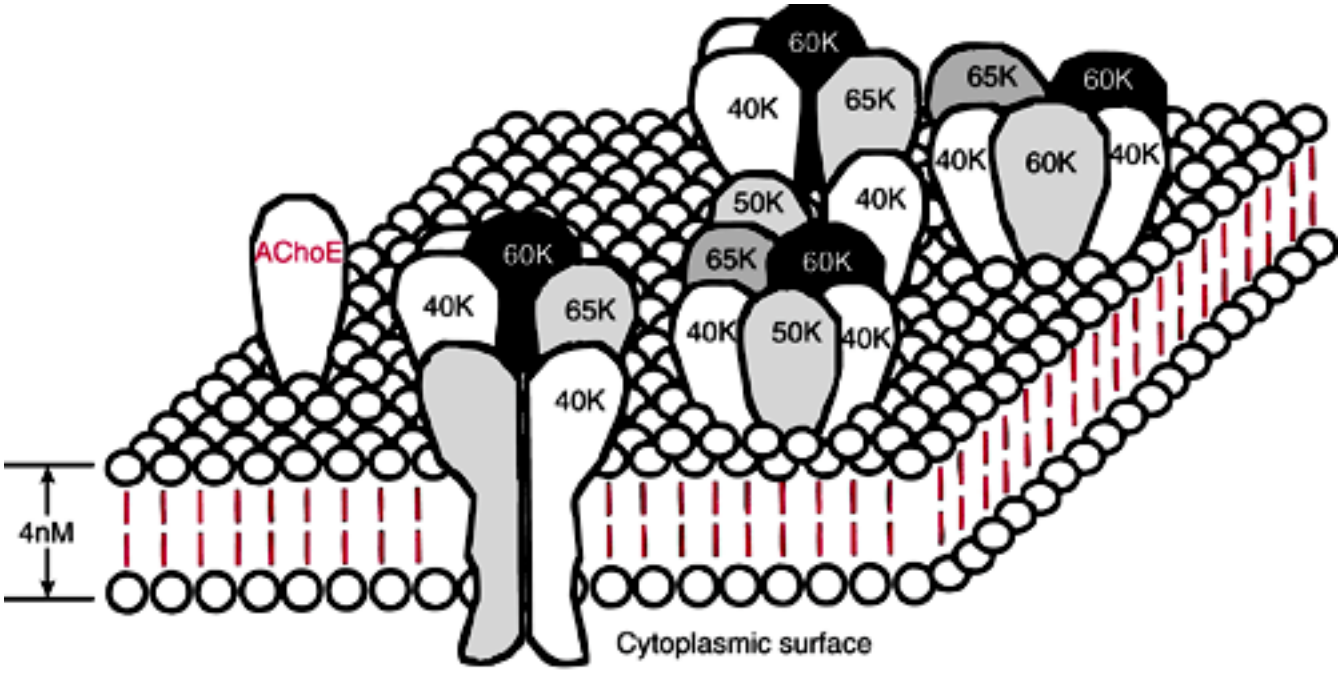


FIGURE 14–19 Sketch of postjunctional nicotinic acetylcholine receptors with an acetylcholinesterase (AChoE) molecule nearby. (Modified from Standaert[457])

These five subunits surround each ion channel through which sodium or calcium may enter the cell or potassium may exit. Each ion has its own separate channel, a unique characteristic of the neuromuscular junction. In order for the channel to open, ACh must occupy a receptor site on each of the two α-subunits. When ACh occupies both α-subunits, the channel opens; if only one site is occupied and the other is empty, the channel remains closed and there is no flow of ions and no change in electrical potential. In addition, if one site is occupied by ACh and the other site is occupied by an antagonist such as *d*-tubocurarine, the channel remains closed. If both sites are occupied by *d*-tubocurarine, the channel also remains closed. The ion channel response to ACh is instantaneous and usually lasts only a few milliseconds because ACh is rapidly destroyed by acetylcholinesterase in the synapse. This time course lends a rapidity and flexibility of response of motor end plates to neural stimulation that contributes profoundly not only to the viability of an organism, but also to its ability to control its own movements precisely and subsequently its environment.

In addition to binding of the α-subunit binding site by competing, non-ACh structures, there are two types of channel block (open and closed). With open-channel block, a drug enters a channel opened by ACh but cannot travel all the way through the channel. Thus, it impedes ionic flow and so prevents depolarization. Because only an open channel may be entered, the intensity of this block depends on how often the channels are open and how active the system is; thus, it is "use dependent." Open-channel block is driven by the electrical potential difference across the membrane and the charge inherent in the molecular structure. In addition, drugs penetrating an open channel may temporarily bind at some point on the wall of the channel. The duration of effect, therefore, is partially dependent on the identity of molecule. Closed-channel blockade is harder to study and is less well understood. In this case, a drug may react with the mouth of a closed channel and prevent ion flow. Channel opening is not required, and blockade is, therefore, not use dependent. Because block does not occur at the ACh receptor site, closed-channel block is not due to a competitive antagonism of ACh. Therefore, the classic agents that inhibit cholinesterase may not be completely effective.

In adult skeletal muscle and postganglionic cells, cholinoceptors and their associated ion channels are present only in the immediate synaptic area and are absent from the rest of the cell membrane. The high density (10,000 molecules/μm^{-2}) of nicotinic acetylcholine receptors at the motor end plate is central to accomplishing successful neuromuscular transmission. Studies have demonstrated that agrin, a nerve-derived extracellular basal lamina protein, provides the signal that directs formation of presynaptic terminals [144, 145] and results in a 1,000-fold increase in nicotinic receptors in the motor end plate within hours of the presynaptic terminals reaching the myoctye. A series of ACh receptor (AChR)–associated proteins has been identified, but the precise way in which these extracellular [146] (agrin, laminin, and dystroglycan) and intracellular (utrophin and syntrophin) membrane-associated proteins maintain the necessary AChR clustering and integrity of motor end plate and bind to the cytoskeleton is unclear. Only the synaptic area is depolarized by ACh. This depolarization usually leads to the generation of action potentials that spread along the whole membrane of the cell and cause muscles to contract or neurons to transmit. However, if ACh action is prolonged, such as by inhibition of

acetylcholinesterase, or if a longacting cholinomimetic drug is administered, the initial activation is quickly followed by blockade of transmission. This biphasic effect occurs because sodium channels in the membrane around the synapse, which are unaffected by ACh, accommodate to the continued depolarization of the synaptic membrane. They become inactivated and will not open again until the synaptic potential disappears. Propagated action potentials cannot be generated without sodium flow across the membrane, and so the message sent across the synapse is blocked from propagating through the postsynaptic cell.

Compared with adrenergic receptors, the cholinergic receptors turn over slowly. When a nerve to a muscle is transected, it takes 1 to 3 days to increase the number of cholinergic receptors. In the diaphragm, the number may increase 8 fold. These new receptors will no longer be confined to the motor end plate; that change has important clinical ramifications, especially in burn-induced denervation.

In contrast to the ion-gated nicotinic receptors, muscarinic receptors belong to the superfamily of G protein–coupled receptors. As noted earlier, it is of some interest that muscarinic receptors have a greater homology to α- and β-adrenergic receptors than to nicotinic receptors. Like the other members of the family of receptors with seven helices (α_2, β_1, β_2, serotonin, rhodopsin, and opsin), muscarinic receptors utilize G proteins for signal transduction. Five muscarinic receptors (M_1 –M_5) exist with the primary structural variability residing in a huge cytoplasmic loop between the fifth and sixth membrane-spanning domains. Although molecular studies have described five forms, of which four are defined pharmacologically (M_1, M_2, M_3, and M_4), selective muscarinic drugs are not available. The M_2 cholinergic postjunctional receptor predominates in visceral organs. M_2 and M_3 receptors have been identified in the airway smooth muscle of many species. *In vitro* studies reveal that the M_3 receptor mediates the contractile and secretory response. However, the excess of M_2 receptors could explain the relative ineffectiveness of β-adrenergic agonists in reversing cholinergic bronchoconstriction. [147]

The muscarinic receptors have diverse signal transduction mechanisms. The odd-numbered receptors (M_1, M_3, and M_5) work predominantly through the hydrolysis of polyphosphoinositide, whereas the even-numbered receptors work primarily through G_i proteins to regulate adenylate cyclase. [148]

When the M_3 muscarinic receptor is activated, G_q activates phospholipase C, which catalyzes the hydrolysis of phosphatidylinositol biphosphate into diacylglycerol and inositol triphosphate. Receptors in the muscarinic series are coupled to second messenger systems, such as cyclic nucleotides or phosphoinositides. These, in turn, are coupled to ion channels. In other cases, the influx of a cation is the trigger for cellular response. In some cases, however, an influx of calcium ions is initiated, and these ions act as messengers that react with and open other ion channels. The nature of the response is determined by the specific cation. If calcium or sodium is permitted to flow, then the membrane depolarizes; if only potassium is permitted to flow, then the membrane hyperpolarizes. In addition to affecting ion channels, the messenger calcium can stimulate various intracellular proteins to alter cell activity. In cardiac atria, activation of muscarinic receptors leads to the efflux of potassium and hyperpolarization of the cell membrane. This efflux slows conduction and slows or stops pacemakers. In glands, an influx of calcium and/or sodium activates intracellular events and causes the cells to

secrete. Similarly, the influx of these ions into smooth muscle cells causes them to contract.

Muscarinic receptors are found on both central and peripheral neurons; a single neuron may have muscarinic receptors with excitatory as well as inhibitory effects. Prejunctional autoreceptors are perhaps not as well studied in the parasympathetic nervous system as in the sympathetic nervous system. Exogenous α_2 -agonists may act on prejunctional cholinergic receptors to decrease ACh release. As in the sympathetic system, presynaptic inhibition is of clinical relevance. Presynaptic muscarinic receptors may inhibit the release of ACh from postganglionic parasympathetic neurons, whereas prejunctional nicotinic receptors may act to increase the release of ACh.

Because of the complex coupling, the response of the muscarinic system is sluggish; no response is seen for seconds to minutes after the application of ACh. Similarly, the effect long outlives the presence of the agonist. Even though the transmitter is destroyed rapidly, the train of events it initiated causes the cellular response to continue for many minutes. Desensitization of muscarinic receptors occurs via agonist-dependent phosphorylation in a mechanism similar to that described earlier for β-adrenergic receptors.

Ganglionic Pharmacology

Ganglia subserve far more complex functions than that of a simple connection between the nerve process of one cell and the cell body of its next connection. Integrative and processing functions may contribute to the subtlety of response and organization of the ANS. The electrophysiology of ganglionic stimulation is complex, with at least four different types of responses to electrical stimulation (Table 14–7). [149, 150]

TABLE 14–7. Fast and Slow Responses of Postganglionic Neurons in Sympathetic Ganglia

OTENTIAL	DURATION	MEDIATOR	RECEPTOR
	30 ms	Acetylcholine	Nicotinic cholinergic
	2 s	Dopamine	D_2
	30 s	Acetylcholine	M_1-cholinergic
PSP	4 min	GnRH	GnRH

ıe receptor inhibiting adenylate cyclase via inhibitory G protein; EPSP, excitatory postsynaptic potential; GnRH, gonadc ɔrmone; IPSP, inhibitory postsynaptic potential.

ıg[149]

The central event at the ganglion is the EPSP, which occurs when ACh interacts with a nicotinic receptor to cause a rapid depolarization of the postsynaptic membrane. This

depolarization primarily results from the influx of sodium ions through the nicotinic receptor channel, and it is sensitive to nondepolarizing nicotinic blocking drugs such as hexa-methonium. The other changes in electrical potential are related to secondary or subsidiary pathways that serve to augment or suppress; these pathways are insensitive to classic nicotinic antagonists.

The secondary pathways are indicated by the following changes in potential elicited by electrical stimulation of the ganglia:

1. A slow EPSP.
2. A late slow EPSP.
3. An inhibitory postsynaptic potential (IPSP).

The slow EPSP is slower in onset than the EPSP and lasts 30 to 60 seconds, because of a decrease in potassium ion conductance. The interaction of ACh with nicotinic receptors leads to closing of a potassium channel (m-channel). The slow EPSP is associated with the reduction or suppression of a potassium current through this channel. This wave is initiated by muscarinic receptor agonists and can be blocked by atropine and the selective M_1 muscarinic antagonists.

Like the slow EPSP, the late slow EPSP is due to a decrease in potassium ion conductance. It lasts for several minutes after being initiated by peptides in specialized ganglia. Peptides have special properties as neurotransmitters, showing prolonged stability and thus extending their influence to other postsynaptic sites, not just those in the immediate vicinity of the nerve ending. Depolarization of the membrane activates the potassium channel; the conductance of potassium ion has been labeled the "M current" and appears to act to regulate the cell's response to repetitive fast depolarizations.

The IPSP is inhibitory because the membrane is hyperpolarized and therefore is more resistant to depolarization. The slow IPSP seems to be mediated by the activation of an interneuron interposed between the preganglionic fiber and the ganglionic cell. The preganglionic nerve ending releases ACh, which stimulates the catecholamine-containing interneurons to release dopamine and NE. Catecholamine released by the interneuron then causes hyperpolarization of the ganglion cell membrane, or an IPSP. M_2 -receptors appear to be involved, as are SIF cells (*s*mall, *i*ntensely *f*luorescent cells). IPSP and catecholamine-induced hyperpolarization are both blocked by adrenergic blocking drugs. IPSP is not affected by classic nicotinic blocking agents, but is frequently sensitive to block by atropine.

The impact of the secondary pathways on the initial EPSP and the identity of the involved neurotransmitter varies among ganglia and differs between the parasympathetic and sympathetic ganglia. Many peptides have been identified in the ganglia and shown to be released on stimulation of preganglionic nerves, including gonadotropin-releasing hormone (GnRH), substance P, angiotensin, VIP, NPY, and the enkephalins. As mentioned, the peptides seem to be primarily associated with the late slow EPSP and inhibition of the M current. In addition, 5-HT and γ-aminobutyric acid (GABA) appear to modify ganglionic transmission.

Autonomic ganglia may be stimulated by two groups of drugs, the nicotinic and muscarinic agonists. Nicotinic agonists cause the rapid onset of excitatory effects, mimic the initial EPSP, and are blocked by classic nondepolarizing ganglionic blocking drugs. Muscarinic agonists cause the delayed onset of these excitatory effects, are blocked by atropine, and mimic the slow EPSP.

Blockade of ganglionic transmission results primarily from action at the nicotinic receptor to stop or inhibit transmission. There are two groups of drugs that block ganglionic transmission. The first group is classically represented by nicotine and initially stimulates the receptor, then blocks it. This action is similar to the action of persistent depolarization. The second group causes no prior stimulation of the ganglia or change in ganglionic potentials and includes the drugs hexamethonium, trimethaphan, and mecamylamine. Trimethaphan appears to act by competing with ACh at the cholinergic receptor sites on the ganglia; hexamethonium blocks the channel when it is open. Either mechanism blocks the initial EPSP and ganglionic transmission.

Muscarinic antagonists or α-agonists are incapable of completely blocking transmission, but they may act to inhibit normal modulation of the nerve impulse. β-Adrenergic stimulation appears to facilitate both nicotinic and muscarinic transmission, whereas α-adrenergic stimulation inhibits this transmission. 5-HT is mostly facilitative, but it can be inhibitory in certain areas. Dopamine may also be inhibitory through stimulation of the IPSP. It should be remembered that the adrenal medulla is a specialized ganglionic synapse and is therefore under influences similar to those arising on the autonomic ganglia.

DRUGS AND THE AUTONOMIC NERVOUS SYSTEM

The structure and function of the sympathetic and parasympathetic systems are discussed in the preceding sections. Pharmacologic manipulation of autonomic function is the basis of therapy in many acute and chronic illnesses. The complex pharmacology allows many points for intervention, including enhancement or inhibition of synthesis, storage, or receptor-mediated activity (Table 14–8). [149] In the following section, specific autonomic drugs of interest to anesthesiologists and the mechanisms by which they work are discussed.

javascript:parent.ShowTable('../tables/02014t08.htm')

TABLE 14–8. Some Drugs and Toxins That Affect Autonomic Activity[a]

SITE OF ACTION	COMPOUNDS THAT AUGMENT AUTONOMIC ACTIVITY	COMPOUNDS THAT DEPRESS AUTONOMIC ACTIVITY
Sympathetic and parasympathetic ganglia		
Stimulate postganglionic neurons		
Block conduction		
	Nicotine	
	Hexamethonium (C-6)	
Inhibit AChE		
		Mecamylamine (Inversine)
		Physostigmine (Eserine)
		Trimethaphan (Arfonad)
		Neostigmine (Prostigmin)
	High concentrations of ACh	
		Parathion
Anticholinesterase drugs		
Endings of postganglionic noradrenergic neurons		
Release NE		

Block NE synthesis
Tyramine
Metyrosine (Demser)
Ephedrine
Interfere with NE storage
Amphetamine
Reserpine
Guanethidine (Ismelin)
Prevent NE release
Bretylium (Bretylol)
Guanethidine (Ismelin)
Form false transmitters
Methyldopa (Aldomet)
α-Receptors
Stimulate α_1-receptors
Block α-receptors
Methoxamine (Vasoxyl)
Phenoxybenzamine (Dibenzyline)
Phenylephrine (Neo-Synephrine)
Phentolamine (Regitine)
Stimulate α_2-receptors
Prazosin (Minipres) (blocks α_1)
Clonidine[b] (Catapres)
Yohimbine (blocks α_2)
B-Receptors
Stimulate β-receptors
Block β-receptors
Isoproterenol (Isuprel)
Propranolol (Inderal) and others (block β_1 and β_2)
Dobutamine (Dobutrex)
Atenolol (Tenormin) and others (block β_1)
ACh, acetylcholine; NE, norepinephrine; AChE, acetylcholinesterase.

[a]Only the principal actions are listed. Note that guanethidine is believed to have two principal actions.

[b]Clonidine stimulates α_2-receptors in the periphery, but along with other α_2-agonists that cross the blood-brain barrier, it also stimulates α_2-receptors in the brain that decrease sympathetic output. Therefore, the overall effect is decreased sympathetic discharge.

Modified from Ganong[149]

Drugs Affecting Adrenergic Transmission

Endogenous Catecholamines

The endogenous sympathetic transmitters NE, EPI, and dopamine are catecholamines and are an important subclass of the sympathomimetic drugs (Fig. 14–20). The parent compound of this sympathomimetic group is β-phenylethylamine, the structure of which includes a benzene ring and ethylamine side chain. Substitution of hydroxyl groups at the 3 and 4 positions of the benzene ring converts benzene to catechol, and thus these compounds are known as *catecholamines*. Although synthetic, isoproterenol and dobutamine are also catecholamines. Noncatecholamine drugs may also act as sympathomimetics and have a similar structure.

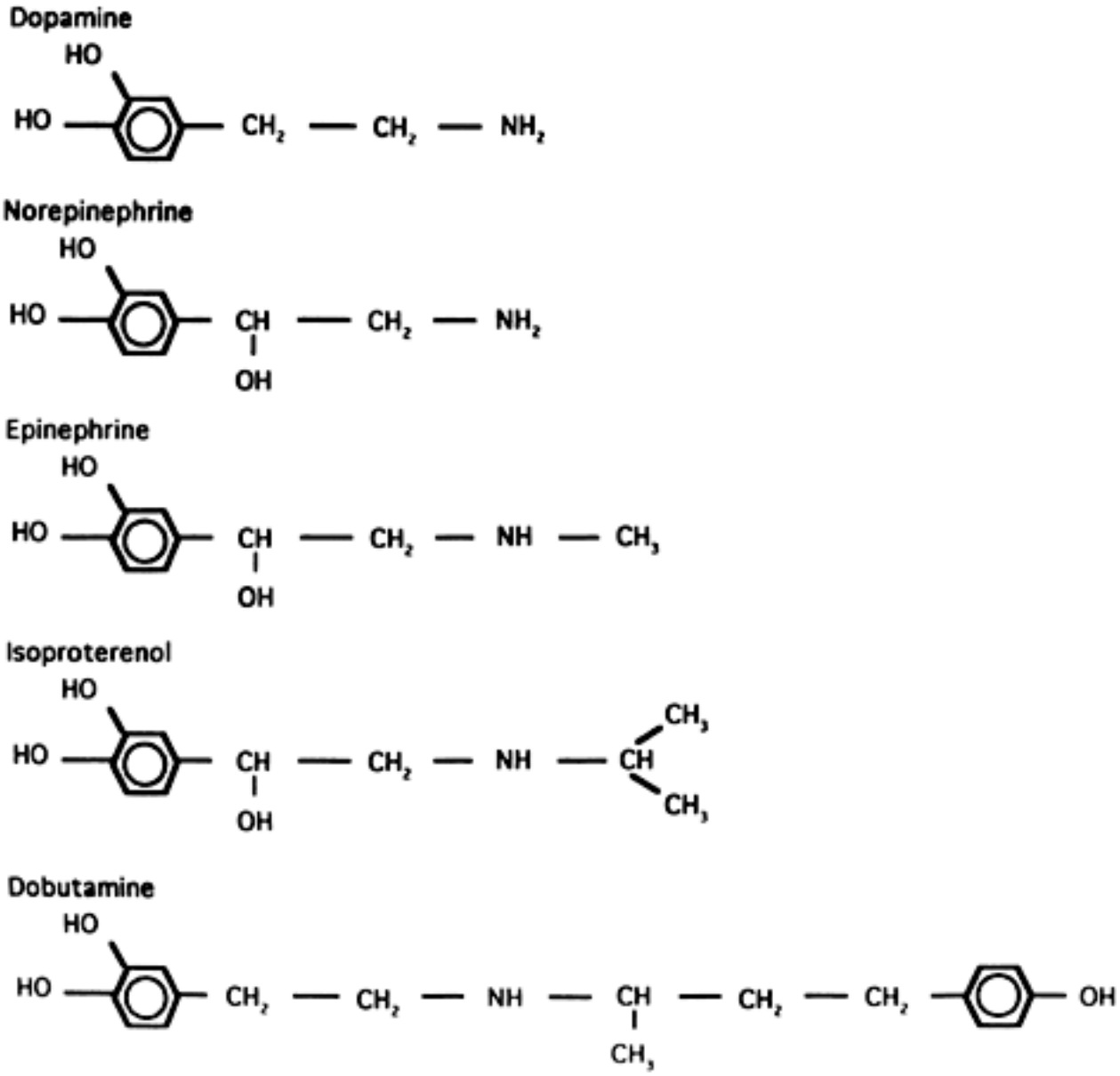


FIGURE 14–20 Catecholamine structures. A benzene ring with two adjacent hydroxyl groups forms the catechol nucleus.

The catecholamines are primarily metabolized by catechol-*O*-methyl transferase (COMT). The loss of either hydroxyl group enhances oral effectiveness and duration of action because the drug is no longer metabolized by COMT. Noncatecholamines are primarily metabolized by MAO. The noncatecholamines that have a substituted α-carbon have a longer duration of action because they are not metabolized by either COMT or MAO. [151]

Epinephrine

EPI is used IV in life-threatening circumstances, including the treatment of cardiac arrest, circulatory collapse, and anaphylaxis, but it is also commonly used locally to limit the spread of local anesthetics or to reduce blood loss. The systemic effects of EPI are variable and are related to blood levels. Therefore, the choice of dosing and the route of administration are determined by the indication for use and its urgency.

EPI activates all adrenergic receptors: α_1, α_2, β_1, β_2, and β_3 . Potential therapeutic effects of EPI include positive intropy, chronotropy, and enhanced conduction in the heart (β_1); smooth muscle relaxation in the vasculature and bronchial tree (β_2); and vasoconstriction (α_1). As a result of this vasoconstriction, aortic diastolic pressure is increased, promoting coronary flow during cardiac arrest, which may be the single most important determinant of survival. [152] Endocrine and metabolic effects of EPI include increased levels of glucose, lactate, and free fatty acids (see Table 14–1).

TABLE 14–1. Responses Elicited in Effector Organs by Stimulation of Sympathetic and Parasympathetic Nerves

EFFECTOR ORGAN	ADRENERGIC RESPONSE	RECEPTOR INVOLVED	CHOLINERGIC RESPONSE	DOMINANT RESPONSE (A OR C)
Heart				
Rate of contraction	Increase	β_1	Decrease	C
Force of contraction	Increase	β_1	Decrease	C
Blood vessels				
Arteries (most)	Vasoconstriction	α_1		A
Skeletal muscle	Vasodilation	β_2		A
Veins	Vasoconstriction	α_2		A
Bronchial tree	Bronchodilation	β_2	Bronchoconstriction	C
Splenic capsule	Contraction	α_1		A
Uterus	Contraction	α_1	Variable	A
Vas deferens	Contraction	α_1		A
Prostatic capsule	Contraction	α_1		A
Gastrointestinal tract	Relaxation	α_2	Contraction	C
Eye				
Radial muscle, iris	Contraction (mydriasis)	α_1		A
Circular muscle, iris			Contraction (miosis)	C
Ciliary muscle	Relaxation	β	Contraction (accommodation)	C
Kidney	Renin secretion	β_1		A
Urinary bladder				
Detrusor	Relaxation	β	Contraction	C

Trigone and sphincter
Contractionα_1RelaxationA, C UreterContractionα_1RelaxationA Insulin release from pancreasDecreaseα_2A Fat cellsLipolysisβ_1A Liver glycogenolysisIncreaseα_1A Hair follicles, smooth muscleContraction (piloerection)α_1A Nasal secretionIncreaseC Salivary glandsIncrease secretionα_1Increase secretionC Sweat glandsIncrease secretionα_1Increase secretionC A, adrenergic; C, cholinergic.

From Ruffolo[21]

EPI may be given IV as a bolus or by infusion. Usual bolus doses for pressure support begin at 2 to 8 μg IV; 0.02 mg/kg or approximately 1.0 mg is given for cardiovascular collapse, asystole, ventricular fibrillation, and electromechanical dissociation or anaphylactic shock. This higher dose range is recommended in these critical situations in order to maintain myocardial and cerebral perfusion through peripheral vasoconstriction. High-dose EPI (0.1–0.2 mg/kg) has been studied in resuscitation from cardiac arrest, but it does not appear to improve rates of survival in adults. High-dose EPI may be given in adults if usual doses fail to generate a response. [153] In pediatric patients, outcome from asystole and pulseless cardiac arrest is abysmal, and current recommendation is that high-dose EPI (0.1 mg/kg) be administered within 3 to 5 minutes after the initial dose (0.01 mg/kg) and repeated every 3 to 5 minutes throughout resuscitative attempts. [154] Doses as large as 0.2 mg/kg may be effective. [155] Endotracheal or intraosseous administration is an option in urgent situations such as cardiac arrest while IV access is obtained. Endotracheal doses should be at least tripled and diluted in 10 mL of normal saline in adult patients. [156] In pediatric patients, ten times the IV dose may be needed. [154] When continued cardiovascular support is required, infusion rates can be adjusted to elicit specific receptor stimulation. EPI should not be administered in alkaline solutions, because it is rapidly degraded to its biologically inactive metabolite, adrenochrome. If adrenochrome is present, the vial will have a pink hue and should be discarded. [151]
It should be remembered that patients vary tremendously in their response to these agents, and given rates of infusion cannot guarantee the expected serum levels in all patients; therefore, the "pressors" should be carefully titrated, and appropriate measures to monitor renal, cerebral, and myocardial perfusion are more critical than adherence to a rigid dosing scheme (Table 14–9). A rate of 1 to 2 μg/min, though rarely used, should predominantly activate β_2-receptors with resulting vascular and bronchial smooth muscle relaxation. A rate of 2 to 10 μg/min (25–120 ng/kg/min) will, in addition, increase heart rate, contractility, and conduction through the AV node and decrease the refractory period. Doses in excess of 10 μg/min (100 ng/kg/min) cause marked α-stimulation with resultant generalized vasoconstriction. EPI is a potent renal vasoconstrictor acting directly by α-receptor stimulation and indirectly by stimulation of renin release. It is frequently used in combination with "renal dose" dopamine in an attempt to avoid renal ischemia. Although low-dose EPI increases heart rate by direct β_1-stimulation, reflex bradycardia is seen with higher doses, because of marked elevation of blood pressure through peripheral vasoconstriction.

TABLE 14–9. Dose-Dependent Actions of Inotropes and Chronotropes

DRUG[a] (PROPRIETARY NAME) RECEPTORS USUAL INFUSION RATE Epinephrine (Adrenalin) β_2 1–2 μg/min $\beta_1 + \beta_2$ 2–10 μg/min α_1 ≥10 μg/min[b] (bolus: 2–10 μg; 0.5–1.0 mg[c]) Norepinephrine (Levophed) $\alpha_1, \beta_1, >>\beta_2$ 4–12 μg/min[b] Dopamine (Intropin) Dopaminergic 0–3 μg/kg/min β 3–10 μg/kg/min α >10 μg/kg/min[b] Dobutamine (Dobutrex) $\beta_1 >> \beta_2$, α 2.5–10 μg/kg/min[b] Isoproterenol (Isuprel) $\beta_1 > \beta_2$ 0.5–10 μg/min Amrinone (Inocor) Increase cyclic adenosine monophosphate through phosphodiesterase inhibition 0.75 mg/kg/load over 2–3 min 5–10 μg/kg/min infusion [a]All agents have elimination half-lives of a few minutes, except amrinone ($t_{½}$, 3.6 h; 5.8 h in congestive heart failure).

In the past, inhaled EPI was used in a 1 percent (1 g:100 mL) solution to treat bronchospasm, but it has been largely supplanted by β_2-specific agonists. Racemic EPI (a mixture of the levo- and dextrorotary isomers) acts to constrict edematous mucosa and is used in the treatment of severe croup [157] and of postextubation and traumatic airway edema. A 2.25 percent solution (microNefrin/Vaponefrin) is diluted with water or saline in a 1:8 ratio and is nebulized. Treatments may be given as frequently as every 2 hours, with effects lasting 30 to 60 minutes; the patient should remain under observation for at least 2 hours, because initial improvement may be followed by rebound swelling up to 2 hours after administration. [151] Although it is common clinical practice to utilize the racemic form of EPI for these clinical applications, data show that (levo)-EPI is 15 to 30 times more potent than the mixture [158, 159] and is equally effective and less expensive in treating these clinical complications. [160]

Bronchospasm may also be treated by subcutaneous (SQ) administration of EPI in doses of 300 μg every 20 minutes up to three doses. In addition to its direct bronchodilatory effects, EPI may decrease antigen-induced release of endogenous bronchospastic substances from mast cells and is particularly useful in anaphylactic reactions. [161]

Relative contraindications include advanced age, significant tachycardia, hypertension, and coronary occlusive disease. Absorption of SQ EPI is extremely slow because of intense local vasoconstriction, and the effect of a very large SQ dose of 0.5 to 1.5 mg is roughly equivalent to an IV infusion of 10 to 30 μg/min. [151] IV injection of EPI in a dose appropriate for SQ administration can result in life-threatening ventricular arrhythmias, hypertension, and cerebral hemorrhage. Sus-Phrine, a sustained-release form of EPI, may be used in children by SQ injection but should never be given IV.

EPI is often applied locally to mucosal surfaces to decrease bleeding in the operative site. It is mixed with local anesthetics for infiltration into tissues or intrathecal injection. The α-mediated vasoconstriction decreases bleeding in the area and slows vascular uptake of local anesthetic, prolonging both the duration of effect and decreasing the peak serum level of the local anesthetic. Although clinicians express concern over the systemic effects of such injections, several studies have shown that, barring intravascular injection, resultant elevations in plasma levels due to vascular uptake are relatively modest and are substantially less than levels seen in psychologic stress. [28, 162]

Drug interactions with EPI are often predictable. Cocaine and other uptake inhibitors enhance the effect and duration of exogenous EPI. Preexisting alpha$_1$-blockade can cause the paradoxic phenomenon of “EPI reversal” as the β_2-vasodilating effects are unmasked.

Patients receiving nonselective beta blockers may demonstrate unopposed α-responses. Cardioselective ($beta_1$) blockade does not have this effect. [163]

Halothane is known to sensitize the heart to catecholamines, and the potential for troublesome arrhythmias under light inhalational anesthesia has long been appreciated by clinicians. EPI decreases the refractory period, rendering the heart more susceptible to arrhythmias. In adults, the EPI ED_{50} (dose required to produce three premature ventricular contractions in 50 percent of patients) at 1.25 minimum alveolar concentration (MAC) was 2.1 μg/kg for halothane, 6.7 μg/kg for isoflurane, and 10.9 μg/kg for enflurane. [164] Children appear to tolerate higher doses than do adults. It has been suggested that children receiving a halothane anesthetic can receive a maximum of 10 to 15 μg/kg SQ of EPI every 10 minutes. [157] Hypocapnia potentiates this drug interaction.

Norepinephrine

NE differs structurally from EPI only in its lack of a methyl group. Like EPI, NE acts at both α- and β-receptors, but it is usually used for its potent α-agonism. It is frequently the pressor of last resort in supporting the systemic vascular resistance. Because of its short half-life of 2.5 minutes, a continuous infusion is preferred. Whereas less than 2 μg/min (30 ng/kg/min) may uncover β_1-stimulation effects, the usual infusion rates of greater than 3 μg/min (50 ng/kg/min) elicit peripheral vasoconstriction from α-stimulation. [165]

The peripheral vasoconstriction increases blood pressure and may cause reflex bradycardia. Venous return is increased by the powerful venoconstriction. Cardiac output is frequently unchanged or decreased; oxygen consumption is markedly increased. Pulmonary vascular resistance may be increased, and NE should be used with caution in patients with pulmonary hypertension. [166]

Like EPI, NE is a potent constrictor of the renal and mesenteric vascular beds and can cause renal failure, mesenteric infarction, and peripheral hypoperfusion. The decrease in hepatic flow is of clinical relevance because plasma levels of hepatically metabolized drugs (such as lidocaine) are markedly increased. [167] To ameliorate the renal effects, low-dose dopamine infusion may be added to NE. [168] Extravasation can cause tissue necrosis and may be treated with local infiltration of phentolamine. Prolonged infusion has caused gangrene of the digits. The potential for profound vasoconstriction makes careful patient selection and close monitoring mandatory.

Dopamine

Dopamine acts at α-, β-, and dopaminergic receptors; it also acts to release NE and therefore has mixed direct and indirect effects. Although dopamine is a precursor of NE, its most important effect may be to cause peripheral vasodilation. Improvement of blood flow through the renal and mesenteric beds in shock-like states is expected through its action at dopamine receptors on the postjunctional membrane. It is rapidly metabolized by MAO and COMT, and so has a short half-life of about 1 minute. Therefore, like other endogenous catecholamines, it is given as a continuous IV infusion and without a loading dose. At low doses (0.5–2.0 μg/kg/min), DA_1-receptors are stimulated, and renal and mesenteric vascular beds dilate. [169] In addition to an improvement in renal blood flow, glomerular filtration rate and sodium excretion increase. With an infusion rate of 2 to 10 μg/kg/min, β_1-receptor stimulation is seen, with resultant increases in cardiac contractility and output. Rates higher than 5 μg/kg/min stimulate release of endogenous NE, which

contributes to cardiac stimulation. At higher doses, (10–20 μg/kg/min), both α- and β_1-receptors are stimulated, the alpha-vasoconstrictive effect predominates, and the benefit to renal perfusion may be lost. [170] Patients' responses to dopamine are extremely variable, and dosages must be individualized. Appropriate monitoring to ensure organ and peripheral perfusion is critical. The dose should be significantly decreased in patients treated previously with an MAOI or tricyclic antidepressant.

Dopamine is frequently the initial agent used in the treatment of shock, particularly in vasodilated states such as sepsis; as discussed earlier, it is frequently used to protect the kidney and also to aid in diuresis. It is particularly useful for this purpose in severe CHF. [171] Infusion in combination with dobutamine for the therapy of cardiogenic shock may be more effective than either agent given alone. [172]

Dopexamine hydrochloride (Dopacard), an inotropic vasodilator, is a synthetic parenteral dopamine analogue that may be of use in CHF. Intrinsic activity of dopexamine relative to dopamine is approximately 60 times more potent at β_2-adrenoreceptors and one-third at DA_1-receptors and one-seventh at DA_2-receptors. [173, 174] Unlike dopamine, it shows no α- and negligible β_1-adrenergic effects and is therefore devoid of any vasoconstrictive activity. [173, 175] Dopexamine has a reported half-life of 3 to 7 minutes in healthy patients and approximately 11 minutes in patients with low cardiac output. [176] β_2-Agonism produces systemic vasodilatation and indirect inotropic activity (via inhibition of neuronal uptake of NE). [173, 175, 177, 178, 179] The stimulation of dopaminergic receptors produces selective vasodilatation of renal and splanchnic vessels and increased glomerular filtration rate, diuresis, and natriuresis. [175, 180, 181, 182, 183]

The use of dopexamine seems preferable when vascular resistance is high. Within the dose range of 1 to 6 μg/kg/min, the combined inotropic, vasodilative, diuretic, and natriuretic effects have shown benefit in the management of CHF, [184, 185, 186, 187] but they have had an indeterminant outcome in the treatment of septic shock. [186, 188, 189, 190, 191, 192] Use of this agent has been limited by dose-dependent tachycardia, mainly at doses higher than 4 μg/kg/min. [193, 194] The effects of dopexamine on intestinal mucosal and hepatic perfusion remain controversial. [195, 196, 197, 198, 199, 200] In general, systemic vasodilatation appears more pronounced with dopexamine, and positive inotropic effects appear more marked with dopamine [201] and dobutamine. [202]

Fenoldopam is a selective DA_1-agonist and potent vasodilator (6–9 times as potent as dopamine) that enhances natriuresis, diuresis, and renal blood flow. [203, 204, 205, 206, 207] Because of its poor bioavailability and varied results in clinical trials, fenoldopam is no longer being investigated as a candidate for therapy of chronic hypertension or CHF. Instead, IV fenoldopam, given by infusion at rates of 0.1 to 0.8 μg/kg/min with incremental titration at 0.1 μg/kg/min, has recently been approved to treat severe hypertension. It is an alternative to sodium nitroprusside, with potentially fewer side effects (no thiocyanate toxicity, rebound effect, or "coronary steal") and improved renal function. Its peak effects occur within 15 minutes. [208, 209]

Noncatecholamine Sympathomimetic Amines

Whereas the β-agonist isoproterenol and the α-agonists phenylephrine and methoxamine act predominantly at only one type of receptor, most of the sympathomimetic drugs act at both α- and β-receptors. Most noncatecholamine sympathomimetic amines act at α- and

β-receptors because they have two mechanisms of action: directly at a receptor and indirectly by releasing endogenous NE.

Mephentermine (Wyamine), ephedrine, and metaraminol (Aramine) are mixed-acting drugs. Ephedrine increases blood pressure and has a positive inotropic effect. Because it does not have detrimental effects on uterine blood flow, ephedrine is widely used as a pressor in the hypotensive parturient patient. [210] Because of its β_1-stimulating effects, ephedrine is helpful in treating moderate hypotension, particularly if accompanied by bradycardia. It also has some direct β_2-stimulating effects and has been used orally as a bronchodilator. The usual dose is 2.5 to 25 mg IV, or 25 to 50 mg intramuscularly (IM). Mephentermine is similar to ephedrine in its effects, whereas metaraminol has relatively stronger direct α_1-stimulating effects and may be associated with reflex bradycardia. Tachyphylaxis to the indirect effect may develop through depletion of NE stores. Although all sympathomimetic amines are capable of producing tolerance or tachyphylaxis, the mechanism has been best studied with metaraminol. Metaraminol is taken up into the sympathetic nerve ending, displacing NE and producing the sympathomimetic effect. However, after a period of time, the drug acts as a false transmitter, and subsequent sympathetic nerve stimulation results in much less effect. Consequently, the drug probably should not be used widely when other, more effective drugs are available. Indirect action is attenuated in the presence of long-term reserpine or cocaine use, but these drugs may still be efficacious, although at higher doses. Although indirect-acting agents are widely used as a first-line therapy for intraoperative hypotension, epidemiologic studies of adverse reactions under anesthesia suggest that dependence on these agents in life-threatening events may contribute to morbidity. [211]

α - Agonists

Phenylephrine and methoxamine are selective α_1-agonists. These drugs are commonly used when peripheral vasoconstriction is needed, sometimes when cardiac output is adequate, as in the hypotension that may accompany spinal anesthesia, and at other times in patients with coronary artery disease or aortic stenosis to increase coronary perfusion pressure without chronotropic side effects. Phenyl-ephrine (Neo-Synephrine) has a rapid onset and a relatively short duration of action (5–10 min) when given intravenously. It may be given by bolus doses of 40 to 100 μg or by infusion at a starting rate of 10 to 20 μg/min. Higher doses of up to 1 mg may be used to slow supraventricular tachycardia through reflex action. Phenylephrine is also used as a mydriatic and nasal decongestant. In anesthetic practice, it is applied topically either alone or mixed with local anesthetic gel to prepare the nose for intubation. It is also added to local anesthetic to prolong subarachnoid block. In contrast, methoxamine (Vasoxyl) is a much longer-acting drug (30–60 min). [212] At high doses, the drug possesses some membrane-stabilizing properties and even β-adrenergic blocking properties.

The α_2-agonists are assuming greater importance as anesthetic adjuvants and analgesics. Their primary effect is sympatholytic. They reduce peripheral NE release by stimulation of prejunctional inhibitory α_2-adrenoreceptors, and they inhibit central neural transmission in the dorsal horn, by both presynaptic and postsynaptic mechanisms, and directly in spinal preganglionic sympathetic neurons. Although traditionally they have primarily been used as antihypertensive drugs, new roles based on sedative, anxiolytic, and analgesic properties are being developed.

Clonidine, the prototypic drug of this class (Table 14–10), is a selective partial agonist for α_2-adrenoreceptors, with a ratio of approximately 200:1 (α_2 :α_1). The antihypertensive effects are due to central and peripheral attenuation of sympathetic outflow and central activation of nonadrenergic imidazoline-preferring receptors. [164, 253, 254, 255] The decrease in central sympathetic outflow reduces activity in peripheral sympathetic neurons without affecting baroreceptor reflexes. [256] Arterial blood pressure is thereby decreased without the accompanying orthostatic hypotension seen with many antihypertensive drugs. [257] Because clonidine is lipid soluble, it is able to penetrate the blood-brain barrier to reach the hypothalamus and medulla, and thus, unlike α-methyldopa, it does not require transformation into another substance. [258] Clonidine withdrawal may precipitate hypertensive crises, and clonidine should be continued throughout the perioperative period (perhaps by patch) or at the least replaced by close monitoring of blood pressure and ready ability to treat hypertension. The administration of nonselective beta blockers during clonidine withdrawal could worsen hypertension by leaving α_1-receptor– mediated vasoconstriction unopposed. Labetalol has been used to treat this withdrawal syndrome.

TABLE 14–10. Clonidine Dosing

ROUTE	BOLUS	CONTINUOUS INFUSION	REFERENCES
Oral	150 μg, 4–5 μg/kg	—	
Intramuscular	2 μg/kg	—	[218]
Intravenous	150 μg, 4–8 μg/kg	2 μg/kg/h	
Epidural	150–450 μg	12.5–70 μg/h	6–8 μg/kg 1–2 μg/kg/h
Intrathecal	30–225 μg	8–400 μg/d	

Although the use of α_2-agonists as the sole anesthetic agents has not been demonstrated in humans, these drugs can reduce the anesthetic requirement and may provide a more stable cardiovascular course, presumably because of the sympatholytic effect of the drug and the need for lower doses of cardioactive anesthetic. [213, 214, 259] Clonidine reduced halothane MAC by up to 50 percent in a dosedependent fashion, [260] limited by α_1-adrenoreceptor activation at higher concentrations, whereas dexmedetomidine, the prototype of novel superselective α_2-agonists (α_1 :α_2 of 10:1), decreased halothane MAC by more than 95 percent in animals. [260, 261, 262] Data suggest that oral, IV, epidural, and intrathecal administration of clonidine potentiates the anesthetic action of other agents, either volatile or injectable, and reduces both general and regional anesthetic requirements with correspondingly fewer side effects, [213, 214, 215, 222, 223, 224, 225, 238, 239, 240, 241, 242, 243, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272] although it has not been shown to reduce perioperative ischemia. [273] Clonidine also attenuates the rise in intraocular pressure associated with laryngoscopy and endotracheal intubation. [274, 275, 276]

α_2 - Agonists provide effective analgesia for acute and chronic pain, particularly as adjuncts to local anesthestics and opioids. The addition of clonidine results both in increased duration of analgesia and reduced doses of each component. [218, 219, 220, 222, 224, 225, 226, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288] Epidural clonidine is indicated for the treatment of intractable pain, which is the basis for the approval of parenteral clonidine in the United States as an orphan drug. [289] Patients with intractable pain, unresponsive to maximal doses of oral or epidural opioids, benefit from oral, patch, IM, and neuraxial administration of clonidine, [228, 229, 230, 231, 232] as do patients with reflex sympathetic dystrophy [294] and neuropathic pain. [229, 291] The intrinsic analgesic effects of α_2-agonists

have been demonstrated with large doses of clonidine alone, administered either intrathecally (as much as 450 mg) or epidurally (1–2 μg/kg/h) to control intraoperative and postoperative pain. Clonidine decreases postoperative oxygen consumption and adrenergic stress response. [292, 293] Although there are dose-dependent side effects such as hypotension and sedation and idiosyncratic side effects with clonidine such as bradycardia, it does not induce profound respiratory depression and only mildly potentiates opiate-induced respiratory depression. [216, 295, 298]

Aside from its role as an anesthetic adjuvant and antihypertensive agent, clonidine has been used to treat panic disorder; [296] symptoms of opiate, benzodiazepine, and ethanol withdrawal; [297, 298] cigarette craving after heavy smoking cessation; [299, 300, 301] and as an antiemetic in cancer chemotherapeutic regiment. Its use in diabetic diarrheas is based on the presence of α_2-receptors on gut epithelial cells. Normally, stimulation of ileal mucosal α_2-receptors by EPI promotes sodium chloride absorption and inhibits bicarbonate secretion. In diabetes, in which intractable diarrhea can be a major problem, there is a depletion of mucosal NE stores and a denervation hypersensitivity, resulting in increased numbers of postsynaptic α_2-receptors. Clonidine may increase blood glucose concentrations by inhibiting insulin release. [302] Further, unlike spinal opioids, clonidine does not cause urinary retention and may actually hasten time to first micturition after spinal anesthesia. [244, 245, 246, 302]

β - Agonists

Nonselective: Dobutamine

Although at clinical doses it can act at β_2- and α_1-receptors, this synthetic analogue of dopamine has predominantly β_1-effects. Compared with isoproterenol, it is reported to have more inotropy than chronotropy, but it increases conduction velocity through nodal tissue to the same extent. [303] It exerts less β_2-effect than does isoproterenol and less α_1-effect than NE. Unlike dopamine, it does not directly release endogenous NE, nor does it act at dopaminergic receptors.

Dobutamine is particularly useful in CHF and MI complicated by a low-output state, although in cases of severe hypotension it may not be effective because of a lack of a significant α_1-pressor effect. Although dobutamine increases cardiac contractility in the failing heart, its ability to lower filling pressures contrasts with the effects of dopamine and NE. It is relatively safe to use in myocardial ischemia without increasing the size of the infarct or causing arrhythmias. [304] Tachycardia does not usually occur with doses less than 20 μg/kg/min, but in especially severe CHF, significant tachycardia may occur and is the primary side effect. Because dobutamine directly stimulates β_1-receptors, it does not rely on NE stores and may still be effective in catecholamine-depleted states such as chronic CHF. However, in severe chronic CHF, the downregulation of β-adrenergic receptors may hamper its effectiveness.

The β_2-vasodilating effects of dobutamine are almost exactly offset by its α_1-constricting effects, which experimentally can be revealed by administering a nonselective beta blocking drug. [305] Its modest ability to dilate the peripheral vasculature is probably more closely connected with its ability to relieve the high-adrenergic state of decompensated CHF than to a specific β_2-mediated vasodilative effect. [306] Clinical situations that call for distinct afterload reduction may be better served by an agent such as nitroprusside.

Prolonged treatment with dobutamine causes downregulation of β-receptors; tolerance to its hemodynamic effects is significant after 3 days and may be temporarily offset by increasing the rate of infusion. [307] Intermittent infusions of dobutamine have been used in the long-term treatment of heart failure and have been shown to cause some persistent improvement in exercise tolerance, [308] but they do not improve survival. [309]

Nonselective: Isoproterenol

Isoproterenol (Isuprel) provides relatively pure nonselective β-stimulation with no significant effect at α-receptors. Its β_1-stimulation is significantly stronger than β_2, but it still causes more β_2-activity than does dobutamine. Since the development of other inotropes, its popularity has declined because of its side effects of tachycardia and arrhythmias. These side effects have limited its use in myocardial ischemia or when ventricular irritability is a concern. Isoproterenol has been used in aerosol form to treat bronchospasm, but it has been replaced by β_2-selective drugs with their lower risk of cardiac side effects. Its lack of α-agonist properties renders it ineffective to raise perfusion pressure in shock. In the past, isoproterenol was used in bradycardia or heart block resistant to atropine, but it is no longer part of the American Heart Association Advanced Cardiac Life Support protocol. Infusion rates start at 0.5 to 5 μg/min for adults. It is metabolized primarily by COMT. It is not taken up into adrenergic nerve endings, so its duration of action is slightly longer than that of the natural catecholamines.

Selective β_2-Agonists

As mentioned earlier, isoproterenol was used in the treatment of bronchospasm for its β_2-stimulating properties, but unpleasant and dangerous β_1-mediated side effects limited its use. The development of β_2-selective agents has made β-stimulants a cornerstone of the treatment of bronchospasm. However, it should be noted that this β_2-selectivity is only relative, and it may be lost at higher doses; in addition, β_2-receptors in the SA node may cause tachycardia when stimulated. The structures of these drugs have also been modified to slow their metabolism, thus prolonging therapeutic benefit and enabling oral administration. In particular, the addition of bulky structures on the catecholamine amino group increases β_2-selectivity, decreases affinity for α-receptors, and protects against metabolism by COMT. These agents are preferentially given by inhalation aerosol both for reasons of rapid onset and to minimize systemic drug levels and side effects by reducing drug levels. However, a well-documented increase in the annual number of deaths from asthma has been described, and it has been suggested that this increase may be related to β_2-agonist use, [310, 311, 312] in part because of the severity of illness and patient factors. A susceptibility to arrhythmia caused by these agents either by direct cardiac stimulation or by β_2-induced hypokalemia is one suggested mechanism, although it has been hypothesized that the long-term use of these drugs may increase airway hyperreactivity. Nonetheless, the safe use of these drugs in many thousands of patients is well documented. Commonly used drugs include metaproterenol (Alupent, Metaprel), terbutaline (Brethine, Bricanyl), and albuterol (Proventil, Ventolin). Metaproterenol is probably less β_2-selective than albuterol or terbutaline. Terbutaline is the only β_2-selective agent that can be given SQ and therefore may have particular use in status asthmaticus; the normal SQ dose is 0.25 mg, which may be repeated after 15 to 30 minutes.

β_2 - Agonists are also used to treat premature labor. [313] Ritodrine (Yutopar) has been marketed for this purpose. β_1-side effects are common, particularly when the drugs are used IV. The other β_2-selective drugs have also been used as tocolytics, and all have been associated with significant β_1-side effects as well as the occasional incidence of pulmonary edema. [314] Their use for this purpose has recently been questioned. [315]

α - Receptor Antagonists

α_1-Antagonists have long been utilized clinically as antihypertensives, but they have become less popular over the years. Alpha$_1$-blockade vasodilates by blocking the effect of endogenous catecholamines on arterial and venous constriction. The effects are potentiated when standing or in the presence of hypovolemia. Reflex tachycardia and fluid retention can ensue. α_2-Antagonists may act presynaptically to release NE.

Phenoxybenzamine (Dibenzyline) is a prototype α_1-antagonist, although it irreversibly binds to both α_1- and α_2-receptors. New receptors must be synthesized before complete offset of its effects occurs. Its half-life after oral administration is unknown, but that after an IV dose is about 24 hours. Effects include a decrease in peripheral resistance and an increase in cardiac output; blood flow to skin and viscera is increased. As would be expected, its primary side effect is orthostatic hypotension; nasal stuffiness may occur. In addition to receptor blockade, phenoxybenzamine inhibits neuronal and extraneuronal uptake of the catecholamines. Phenoxybenzamine is used to treat pheochromocytoma through relatively long-term preoperative treatment ("chemical sympathectomy") that aids in blood pressure control, but also permits correction of a contracted plasma volume and protects against catecholamine-induced cardiac damage, yielding a smoother perioperative course. Total daily dose is 40 to 360 mg in two or three divided doses.

When exogenous sympathomimetics are administered after α_1-receptor blockade, their vasoconstrictive effects are inhibited. The effect of phenylephrine is completely blocked, whereas that of NE is limited to its β_1-effect of cardiac stimulation. There is potential "EPI reversal" caused by unopposed β_2-agonism, seen as severe hypotension and tachycardia. Despite its irreversible binding to the receptor, the recommended treatment for overdosage of phenoxybenzamine is NE infusion, because some receptors would still be free of the drug. [316]

Phentolamine (Regitine) is a shorter-acting agent that blocks both α_1- and α_2-receptors. Historically of use in pulmonary hypertension, it has been largely supplanted by nitroglycerin and nitroprusside. It is used to treat hypertension associated with clonidine withdrawal or with tyramine ingestion during MAOI therapy, but few real data have been collected on its efficacy and safety for these indications. The dose is 1 to 5 mg IM or slowly IV. Its plasma half-life is 19 minutes after IV administration. Phentolamine has also been infiltrated into affected tissues after extravasation of agents such as NE in an attempt to relax vasoconstriction: 5 to 10 mg is diluted in 10 mL of saline. Adverse effects of phentolamine include hypotension and gastrointestinal distress; reflex tachycardia and arrhythmias may be seen, at least partly resulting from action at α_2-receptors. Coronary artery disease and peptic ulcer disease are relative contraindications. As in phenoxybenzamine overdosage, severe hypotension may require treatment with NE rather than EPI. Tolazoline (Priscoline) is a related drug used in persistent pulmonary hypertension of the newborn. [316]

Prazosin (Minipress) is a potent selective α_1-adrenergic blocker often used as a prototypic antagonist in pharmacologic experiments. It antagonizes the vasoconstrictor effects of NE and EPI, causing a fall in peripheral vascular resistance and venous return to the heart. Although there is usually no increase in heart rate, orthostatic hypotension is a major problem. Unlike other antihypertensive drugs, prazosin improves lipid profiles, lowering lower-density lipid levels while raising the level of high-density lipids. It is primarily used to treat hypertension. It has also been used in CHF, but unlike the angiotensin-converting enzyme inhibitors (ACEI), prazosin does not prolong life. It is extensively hepatically metabolized. Supplied as 1-, 2-, and 5-mg tablets, its starting dose is usually 0.5 to 1 mg, given at bedtime only because of the orthostatic hypotension, and eventually it is given twice daily. [316]

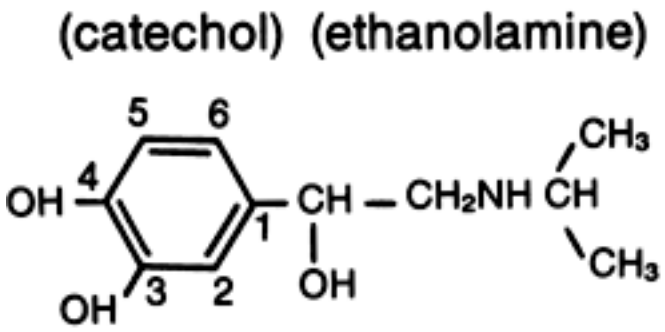
α_2-Antagonists, such as yohimbine, increase sympathetic outflow by enhancing release of NE. Although these drugs have proven to be of little clinical utility in anesthesia, they are used in urology.

β - Receptor Antagonists

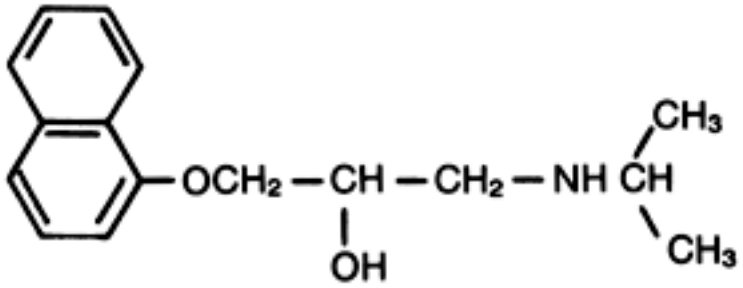
Pharmacology

β-Adrenergic receptor antagonists ("beta blockers") are among the most commonly prescribed drugs and are frequently taken by patients presenting for surgery. Current indications for the use of β-blockade include ischemic heart disease, postinfarction management, arrhythmias, hypertrophic cardiomyopathy, hypertension, and prophylaxis of migraine headache. Initial concern that patients treated with beta blockers would be hemodynamically unstable under anesthesia has proven to be largely unjustified. In addition, these drugs are an important part of the armamentarium of the anesthesiologist in the ongoing attempt to limit stress responses perioperatively and to protect the cardiovascular system.

There is a confusing spectrum of beta blockers currently available to the clinician. The most important properties to consider in choosing a beta blocker for long-term use are cardioselectivity, intrinsic sympathomimetic activity, and lipid solubility. [317, 318] In anesthetic practice, cardioselectivity, duration of action, and a formulation suitable for IV use are crucial factors to consider (Table 14–11). The β-antagonists all resemble isoproterenol in structure and bind competitively to the β-receptor, blocking access by more potent β-agonists (Fig. 14–21). [316] Competitive inhibition at the β-receptor can be overcome by increasing the available concentration of β-agonist. In fact, the potency of a beta blocker is often determined by its ability to inhibit induction of tachycardia by isoproterenol. Propranolol is assigned a potency of 1, and the other drugs are evaluated in relation to it.



Isoproterenol



Propranolol

FIGURE 14–21 Structures of isoproterenol and propranolol. (From Tollenaerè[455])

Nonselective beta blockers act at both the β_1- and β_2- receptors. The nonselective beta blockers include propranolol, nadolol, pindolol, sotalol, oxprenolol, penbutolol, and timolol. [306, 318] Cardioselective beta blockers have a stronger affinity for β_1- than for β_2-adrenergic receptors, and therefore the predominant effects are cardiac. Velocity of AV conduction, heart rate, and cardiac contractility are decreased, as well as the release of renin by the juxtaglomerular apparatus and lipolysis at the adipocytes. At higher doses, the relative selectivity for β_1-adrenergic receptors is lost, and β_2-receptors are also blocked, [319] with potential bronchoconstriction, peripheral vasoconstriction, and decreased glyco-genolysis. Cardioselective agents include atenolol, betaxolol, bevantolol, esmolol, and metoprolol. [306, 318] These drugs may be preferable in patients with obstructive pulmonary disease, peripheral vascular disease, Raynaud phenomenon, and diabetes mellitus. However, because the selectivity is only relative and may be lost at conventional clinical doses, extreme care must be used in administering a beta blocker in the presence of pulmonary disease, because death may result. Some β-antagonists also have vasodilatory effects, making them particularly useful in the treatment of

hypertension. [306] Labetalol vasodilates by blocking α_1-receptors, as well as by direct β_2-agonism.

As mentioned, some beta blockers exert a partial agonist effect at the receptor while blocking access by more potent agonists and thus possess intrinsic sympathomimetic activity (ISA). Agents with ISA include acebutolol, carteolol, celiprolol, dilevalol, oxprenolol, penbutolol, and pindolol. [318] Of these, acebutolol and pindolol are more often used in the United States, but neither is commonly used in anesthetic practice. These agents lower blood pressure with less decrease in *resting* heart rate and left ventricular function. When sympathetic activity is high, such as during exercise, these drugs behave more like conventional beta blockers. The partial β_2-agonism of pindolol induces bronchodilation. [320] ISA may therefore be useful if beta blockade is required in a patient with bradycardia, peripheral vascular disease, or very mild hyperreactive airway disease. Beta blockers with ISA appear not to have the adverse effects on triglyceride and high-density lipoprotein levels seen after use of the other agents, although the clinical significance of this finding is unclear. [321] Agents with ISA may not be as effective in controlling symptoms in severe angina or in reducing mortality after MI. [322] ISA may protect against beta blocker withdrawal syndrome. [323]

The degree of lipid solubility greatly affects absorption and metabolism. Propranolol, metoprolol, and pindolol are the most lipid-soluble agents, are readily absorbed from the gastrointestinal tract, and are metabolized in the liver, undergoing extensive first-pass metabolism. Thus, propranolol and metoprolol are given IV in a much lower dose than that used orally because up to 70 percent of the orally administered drug is removed on the first pass of portal blood through the liver. [317] In addition, altered hepatic function may have a profound effect on plasma levels. The oral or IV dose of these agents required to reach a clinical end point varies greatly between patients. Because of a relatively short half-life, lipid-soluble agents are usually given at least twice a day. [318] The extremely short half-life of esmolol, however, is due to its metabolism by esterases. The non–lipid-soluble, or hydrophilic, drugs are atenolol, sotalol, and nadolol. They are not as readily absorbed from the gastrointestinal tract, not as extensively metabolized, and are excreted unchanged by the kidneys. Because of a relatively long half-life, daily dosing may be adequate. There is less interpatient variability in plasma drug level and clinical effect because of the lack of hepatic metabolism and first-pass effect. [318] The lipid-insoluble drugs are slower to cross the blood-brain barrier and so may be chosen in an attempt to avoid the CNS side effects associated with beta blocker therapy (depression, sleep disturbances, nightmares, and fatigue). However, the relationship between lipid solubility and the occurrence of these symptoms is not consistent. [324, 325]

Propranolol and acebutolol possess membrane stabilizing activity (MSA), also referred to as the quinidine-like or local anesthetic effect. This reduces the rate of rise of the cardiac action potential. However, MSA is seen only at very high concentrations (ten times that required for blockade of beta receptors) [326] and is probably of little clinical consequence. Overdose with agents with MSA is associated with a higher incidence of fatality. [327]

Indications for Use

Myocardial Ischemia

Propranolol was initially introduced for treatment of myocardial ischemia three decades ago, and beta blocking drugs remain an important part of drug therapy for myocardial ischemia. This class of drugs reduces oxygen demand by decreasing heart rate and

cardiac contractility. Both cardio-selective and nonselective beta blockers are effective: atenolol, metoprolol, nadolol, and propranolol have been approved in the United States for the treatment of angina; metoprolol and atenolol are the only beta blockers approved for IV use in acute MI. [318] Although initially there was concern that β_2-receptor blockade could worsen ischemia through unopposed alpha-mediated vasoconstriction, this phenomenon is rarely seen even in patients with variant angina. In usual clinical practice, the dose is increased until the heart rate is 60 to 80 beats/min at rest, and there is no tachycardia with exercise. Although in theory a nonselective antagonist may seem a better choice in acute MI, because the blockade of β_2-receptors may protect against stressinduced potassium shifts and hypokalemia-associated arrhythmias, cardioselective and nonselective drugs appear equally useful. [306] Agents with ISA are not as beneficial in this situation. [306] β-antagonists are used both acutely in MI and on a long-term basis in postinfarction patients to reduce reinfarction and mortality. [328, 329, 330, 331] Early administration of IV beta blocking agents to patients receiving thrombolytic therapy appears to lower the incidence of ischemia and reinfarction [332] and may reduce the incidence of serious ventricular arrhythmias.[333] The long-term use of beta blockers (timolol, propranolol, metoprolol, and atenolol) has been shown unequivocally to decrease mortality after MI.

Hypertension

Although beta blockers are now recognized by the Joint National Council of the USA Guidelines as one of the two preferred first-line therapies for hypertension (the other being diuretics), [334] the mechanisms by which β-antagonists treat hypertension are incompletely understood. The blood pressure reduction is specific to hypertensive patients because long-term treatment of normotensive individuals does not lower blood pressure. Reduced cardiac output and renin release have been suggested as mechanisms. In hypertensive patients, β-antagonists without ISA may cause a 15 to 20 percent reduction in cardiac output and a 60 percent reduction in renin release. However, pindolol, which has ISA and minimal effect on renin, is successful in treating hypertension. [335] In addition, maximum renin suppression precedes significant changes in arterial blood pressure. [336] Generally, beta blockade initially increases peripheral vascular resistance, then over time lowers it. [337] The decrease in cardiac output and eventual lowering of peripheral resistance may account for much of the antihypertensive efficacy of these drugs. However, this too is an incomplete explanation because labetalol is an effective antihypertensive despite its lack of effect on cardiac output. A primary CNS effect is not likely to be a major mechanism because of the similarity of antihypertensive efficacy of lipophilic and hydrophilic compounds. Generally, beta blockade is ineffective as monotherapy in African-American patients more than 60 years of age.

Cardiac Arrhythmias

Beta blockers are also widely used in the therapy of tachyarrhythmias as class II agents (Ch.32). Two possible mechanisms of action are blockade of catecholamine effects and MSA, although the latter is most likely not clinically significant, because antiarrhythmic effects are present in agents without MSA. [338] β-Antagonists slow the rate of depolarization of the sinus node and any ectopic pacemakers, slow conduction through atrial tissue and the AV node, and increase the refractory period of the AV node. These drugs can convert atrial arrhythmias to sinus rhythm, [339] but beta blockade is primarily used to slow the ventricular response. Reentrant tachyarrhythmias and those associated

with Wolff-Parkinson-White syndrome, mitral valve prolapse, and prolonged QT interval may also respond to these drugs. [326] Care should be exercised if AV block is present, as in digitalis toxicity, although these drugs are useful in the treatment of digitalis-associated tachyarrhythmias. [326] Sotalol, a beta blocker with added class III activity, is effective against ventricular tachyarrhythmias. A trial comparing racemic sotalol to *d*-sotalol in post-MI patients to protect against ventricular fibrillation showed an *increased* mortality with *d*-sotalol. [340] This finding suggests that β-antagonists may perform differently as racemates than as optically pure agents.

Tachycardia

β-Antagonists are frequently used as adjuvants to moderate the reflex tachycardia associated with vasodilators. This tachycardia can limit the effectiveness of blood pressure control or may cause myocardial ischemia. It is particularly crucial that appropriate beta blockade be administered during vasodilator therapy of aortic dissection because, in addition to potentiating blood pressure reduction, beta blockade reduces the velocity of left ventricular ejection (dp/dt) to attenuate the shearing force associated with tachycardia. [341] Nitroprusside used without concomitant beta blockade may propagate the dissection. Labetalol has been particularly useful in this situation. [342]

Perioperative Use

The safety of continuing beta blockade perioperatively is well established, and initial concerns regarding interaction with general anesthesia have not been confirmed. [343] In addition, attempts to discontinue beta blockers increase the risk of rebound tachycardia and myocardial ischemia in patients with coronary disease. These drugs should be given up to the time of surgery, and IV forms in appropriate dosages should be used whenever gastrointestinal absorption may be in question. As noted earlier, doses for IV administration vary less among patients because of the absence of first-pass hepatic effects. If beta blockers have been omitted from the preoperative regimen, esmolol or labetalol may be used acutely to blunt tachycardia and hypertension. Both cardio-selective and nonselective beta blockers appear effective in blocking chronotropic effects of endotracheal intubation and surgical stress. [344]

Thyrotoxicosis

Cardiac complications are a primary cause of morbidity in thyrotoxicosis. Beta blockade can suppress the tachycardia and rhythm disturbances, although very large doses may be required. β-Antagonists also may be combined with digitalis for their synergistic effect on AV node conduction. Care should be exercised in the presence of CHF, but if the cause is tachyarrhythmia and ventricular function is adequate, beta blockers with or without digitalis may be helpful. Propranolol has been shown to inhibit conversion of thyroxine to the active form, triiodothyronine, in the periphery. [345]

Miscellaneous Conditions

Timolol (Timoptic) and betaxolol (Betoptic) are beta blocking drugs used topically in the eye to treat glaucoma through their reduction of the production of aqueous humor. Even topical use of these agents has been associated with significant systemic effects of beta blockade. Beta blockers are used in idiopathic hypertrophic subaortic stenosis in order to reduce the obstruction to left ventricular outflow and in the medical management of acute dissecting aortic aneurysm. The drugs are also effective in prophylaxis, but not therapy, of migraine headaches and in controlling acute panic symptoms and essential tremor.

Adverse Effects

The adverse effects of most concern are those involving cardiopulmonary function. Severe noncardiopulmonary reactions such as cutaneous reactions or anaphylaxis are extremely rare. Life-threatening bradycardia, even asystole, may occur; decreased contractility may precipitate CHF in vulnerable individuals. Beta$_2$ blockade in patients with bronchospastic lung disease may be fatal. CNS effects, although an appropriate consideration in long-term therapy, are not a concern in the usual anesthetic use of these agents. Diabetes mellitus is a relative contraindication to the long-term use of β-antagonists, because hypoglycemia in the face of sympathetic blockade is not accompanied by warning signs such as tachycardia and tremor, and compensatory glycogenolysis is blunted. However, most non–insulindependent diabetic patients can tolerate these drugs, although beta blockade may rarely cause insulin resistance. In addition to the potential worsening of peripheral perfusion by beta$_2$ blockade in patients with peripheral vascular disease, Raynaud phenomenon may be triggered in susceptible patients. Sudden withdrawal of beta blockers may cause myocardial ischemia and possibly infarction, although this is less of a problem with beta blockers with ISA such as pindolol. [323, 346, 347] Although β-antagonists may reduce renal blood flow and glomerular filtration rate, these agents can be used in renal failure. In this case, the doses of lipidinsoluble drugs should be reduced. Use in pheochromocytoma should be avoided unless α-receptors have previously been blocked, to avoid worsening of hypertension. Hypertensive responses to nonselective agents may occur in cases of high sympathetic stimulation. [348]

Important drug interactions may occur. [316, 318] Verapamil has rate and contractility effects that are additive with those of the beta blockers, [349, 350] and care should be used in combining these agents, especially when using the IV forms in acute situations such as supraventricular tachycardia. The combination of digoxin and beta blockers can have powerful effects on heart rate and conduction and should be used with special care. Pharmacokinetic interactions are of note and are predictable from the degree of lipid solubility of the drug. Cimetidine and hydralazine may reduce hepatic perfusion, thereby increasing plasma levels and half-lives of the lipid-soluble β-antagonists. Barbiturates, phenytoin, rifampin, and smoking may induce hepatic enzymes, thus enhancing metabolism. Propranolol may reduce hepatic clearance of lidocaine, increasing the risk of toxicity.

Overdose of beta blocking drugs may be treated with atropine, but isoproterenol, dobutamine, and/or glucagon infusions may be required, as well as cardiac pacing, to ensure an adequate rate of contraction.

Specific Drugs

The drugs propranolol, metoprolol, labetalol, and esmolol are particularly useful in anesthetic practice because they are widely available in IV formulation and have wellcharacterized effects. They are discussed in further detail in the following sections. If the drug the patient has taken on a long-term basis is propranolol, metoprolol, or labetalol, then that drug may be continued in IV form, if the clinical situation is relatively stable. In deciding which intravenous beta blocker to substitute in a patient taking a beta blocker on a long-term basis, the need for cardioselectivity is a primary consideration. Cardioselectivity is provided by metoprolol or esmolol. If the long-term agent has ISA, oxprenolol and acebutolol have IV forms, but they are not readily available. In many

situations, esmolol may be substituted and titrated to effect, with the expectation that, if it is not well tolerated, its effects will fade relatively rapidly.

Propranolol

Propranolol (Inderal, Ipran) is the prototypic beta blocker, and its actions and its use are well characterized. [338] It is a nonselective beta blocking drug with MSA but no ISA. [318] It readily penetrates the CNS. Because of its high lipid solubility, it is extensively metabolized in the liver, but to an extent that varies greatly from patient to patient. Therefore, its effective dose is extremely variable: 10 mg to as much as 1 g may be given orally each day. Clearance of the drug can be affected by liver disease or altered hepatic blood flow. Renal impairment does not require adjustment of dosing. Despite its half-life of 4 hours, its antihypertensive effect is long-lived enough to permit dosing once or twice a day. [338, 351] Inderal LA is a sustained-release formulation given once a day. [316]

Propranolol is available in IV form; although initially used as either bolus or infusion, the latter use has been largely supplanted by esmolol. For bolus administration, doses of 0.1 mg/kg may be given, although most practitioners initiate therapy with much smaller doses, typically 0.25 to 0.5 mg, and titrate to effect. Interestingly, propranolol shifts the oxyhemoglobin dissociation curve to the right, perhaps accounting for its efficacy in vasospastic disorders. [352, 353, 354]

Metoprolol

Metoprolol (Lopressor) is approved for the treatment of angina pectoris and is the only IV beta blocker formally approved by the U.S. Food and Drug Administration for treatment of acute myocardial infarction. Lacking either ISA or MSA, it is cardioselective. Because it is metabolized in the liver by the monooxygenase system, doses need not be adjusted in the presence of renal failure. [318] The usual oral dose is 100 to 200 mg per day, once or twice a day for hypertension and twice a day for angina pectoris. It may be administered IV in doses of 2.5 to 5 mg every 2 to 5 minutes up to about 15 mg, titrating to control of heart rate and acceptable blood pressure.

Labetalol

Labetalol (Trandate, Normodyne) is representative of a class of drugs that act as competitive antagonists at both α_1- and β-adrenergic receptors. Labetalol consists of four isomers that block the α_1-, β_1-, and β_2-receptors, inhibit neuronal uptake of NE (uptake 1), act as a partial agonist at β_2-receptors, and possibly have some direct dilating abilities. [316] The potency of the mixture for beta blockade is 5- to 10-fold that for alpha blockade. [355] The usual oral dose of labetalol is 200 to 400 mg twice a day, although much larger doses have been used. It is hepatically metabolized, and therefore clearance is affected by hepatic perfusion. The dose need not be adjusted for renal dysfunction. [318] Labetalol may be given IV every 5 minutes in 5- to 10-mg doses or up to a 2-mg/min infusion. It significantly blunts cardiovascular responses to tracheal intubation. [356] It can be effective in treatment of aortic dissection, [342] hypertensive emergencies, [357, 358] and postoperative cardiac surgical patients, [359] particularly because its vasodilatation is not accompanied by tachycardia. It may be used in pregnancy to treat hypertension, both on a long-term basis and in more urgent situations. [360] Uterine blood flow is not affected even with significant reduction of blood pressure. [361] Carvedilol, a mixed α- and β-antagonist, has been introduced as therapy for mild to moderate hypertension, [362, 363, 364, 365, 366, 367, 368, 369, 370] for management of stable or unstable angina, and after acute MI. [371, 372, 373, 374, 375] Clinical trials of carvedilol use in the treatment of controlled CHF (New York Heart Association

class II–IV) suggest a significant reduction in the risk of mortality, [376, 377, 378, 379] especially for patients with diabetes. [380]

Esmolol

Because of its hydrolysis by esterases, esmolol (Brevibloc) has a uniquely short half-life of 9 to 10 minutes, which makes it particularly useful in anesthetic practice. It is administered when beta blockade of short duration is desired or in critically ill patients for whom adverse effects of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug. Peak effects of a loading dose are seen within 5 to 10 minutes and diminish rapidly (within 20–30 min). It is cardioselective. It may be given as a bolus of 0.5 mg/kg to blunt cardiovascular responses to tracheal intubation. If used as an infusion for the treatment of supraventricular tachycardia, 500 μg/kg is given over 1 minute, followed by an infusion of 50 μg/kg/min for 4 minutes. If the rate is not controlled, a repeat loading dose followed by a 4-minute infusion of 100 μg/kg/min is given, and this sequence is repeated, increasing the infusion in 50-μg/kg/min increments, up to 200 or 300 μg/kg/min if needed. It should be remembered that the clinical effect may persist for 20 to 30 minutes after discontinuation of the infusion. Compared with verapamil, esmolol may be more likely to convert atrial fibrillation to sinus rhythm. [339] Esmolol is safe and effective in treatment of intraoperative and postoperative hypertension and tachycardia. [381, 382, 383] If continuous use is required, it may be reasonably replaced by a longer-lasting cardioselective drug such as IV metoprolol. It has been used safely even in patients with compromised left ventricular function. [384, 385]

Drugs that Inhibit Synthesis, Storage or Release of Norepinephrine

Some early antihypertensive drugs acted by replacing NE in the nerve ending with a much less potent false transmitter. α-Methyldopa (Aldomet) is such a drug and was, in fact, the most popular nondiuretic antihypertensive used prior to the development of beta blockers. [317] Like DOPA, α- methyldopa enters the biosynthetic pathway for NE (see Fig. 14–9). It is then decarboxylated to α-methyl-NE. Initially, this chemical was thought to act as a false transmitter, but it was found to be almost as potent as NE. In the CNS, α-methyldopa may be further metabolized to α-methylepinephrine, [386] and it acts at α_2-receptors to decrease sympathetic outflow, [387] thus reducing blood pressure. Because of its sedating qualities, fluid retention, postural hypotension, and occasional reports of hepatic necrosis, α-methyldopa is now used much less often. [317]

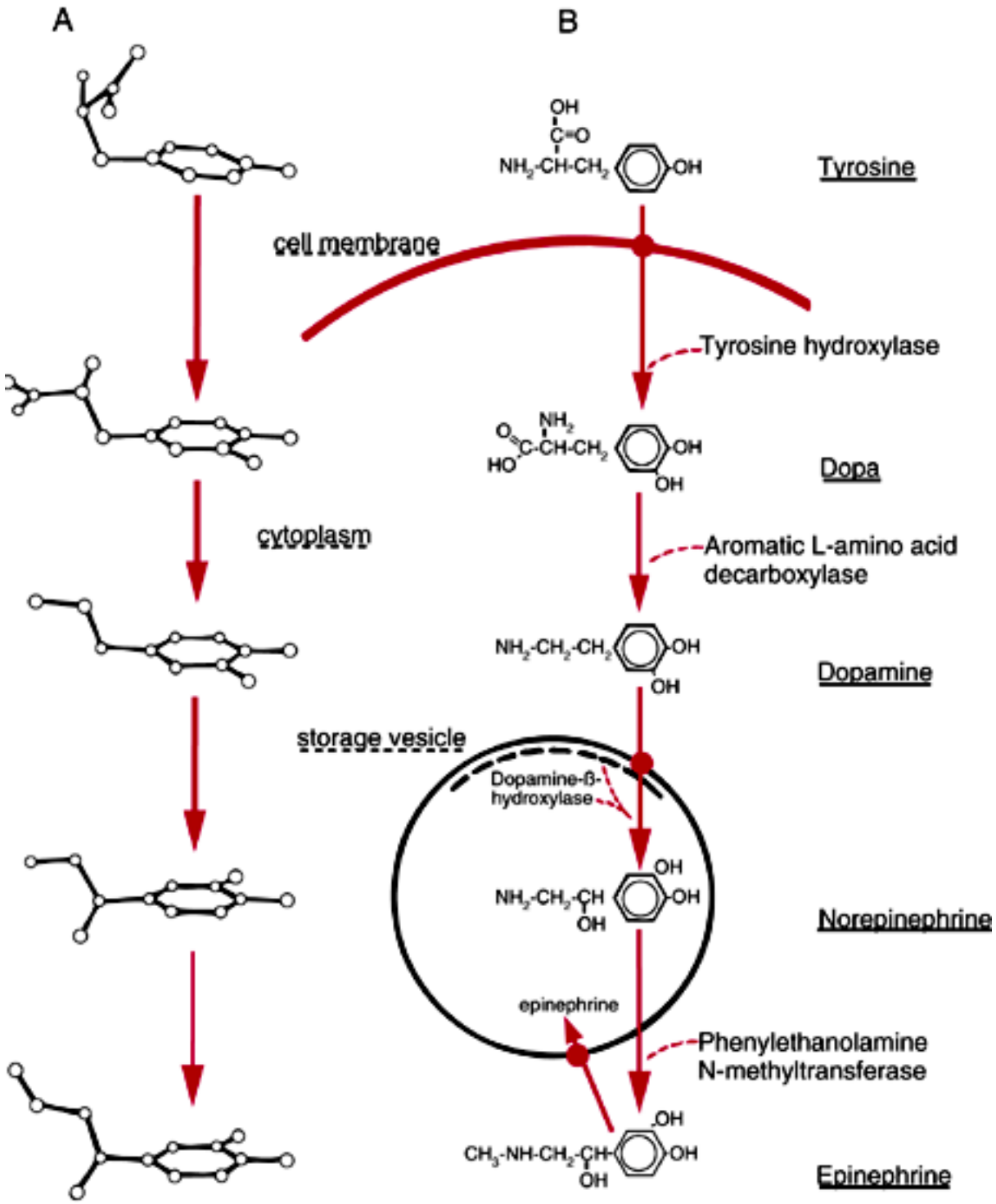


FIGURE 14–9 Biosynthesis of norepinephrine and epinephrine in sympathetic nerve terminal (and adrenal medulla). (A) Perspective view of molecules. (B) Enzymatic processes. (Modified from Tollenaerè,[455] as modified by Vanhoutte[456])

Methylparatyrosine (metyrosine, Demser) is a potent inhibitor of tyrosine hydroxylase, which catalyzes the formation of DOPA from tyrosine (see Fig. 14–9). Because this is the rate-limiting step in the biosynthesis of NE, the drug significantly decreases levels of endogenous catecholamines and is useful in treating inoperable or malignant pheochromocytomas. [388]

Reserpine affects the uptake of NE not at the neuronal membrane but at the vesicular membrane, thereby inhibiting transport and storage of NE and dopamine. Eventually, NE stores are depleted, and postsynaptic receptors increase in number, which may increase the effects of EPI in patients who have been given reserpine (see Table 14–5). In these patients who require a sympathomimetic drug, direct-acting agents may be more useful, whereas mixed-acting drugs would only be efficacious at higher doses, if at all. Although the agent has central effects that lead to side effects such as sedation and depression, its peripheral effects are responsible for its utility as an antihypertensive drug.

TABLE 14–5. Comparison of Direct- and Indirect-Acting Sympathomimetics

RESPONSE OF EFFECTOR ORGAN TO PRETREATMENT	DIRECT SYMPATHOMIMETIC (E.G., EPINEPHRINE) ACTS AT RECEPTOR	INDIRECT SYMPATHOMIMETIC (E.G., TYRAMINE) CAUSES NE RELEASE AFTER ITS UPTAKE BY UPTAKE 1
Denervation	Increased	Reduced
Loss of uptake-1 sites Receptor upregulation		
Reserpine	Slightly increased	Reduced
Blocks vesicular uptake Depletes NE May cause upregulation		
Cocaine	Increased	Reduced
Blocks uptake 1 Depletes NE		

NE, norepinephrine.

Modified from Moore K: Drugs affecting the sympathetic nervous system. In Wingard L, Brody T, Larner J, et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby-Year Book, 1991, p 114.

Guanethidine (Ismelin) is taken up into adrenergic nerve endings by the uptake-1 mechanism and depletes NE stores, after initially blocking release of NE. It is used in therapy of hypertension, usually after trial of many other drugs. Its inability to cross the blood-brain barrier accounts for its lack of sedative effect. Guanadrel (Hylorel) is similar to guanethidine, but it has a shorter onset and duration of action.

Bretylium is a class III antiarrhythmic used parenterally to treat life-threatening ventricular tachyarrhythmias. Like guanethidine, it is taken up into adrenergic nerve terminals, but its mechanism of action is otherwise quite different. Bretylium initially causes NE release, then subsequently blocks that release by decreasing sympathetic nerve excitability. Unlike guanethidine, bretylium does not deplete NE stores. [389] The initial

catecholamine release may worsen some arrhythmias, such as those associated with digitalis toxicity and myocardial ischemia. [326]

MAO and COMT are enzymes important in degradation of the catecholamines. MAOI bind irreversibly to the enzyme and cause increased amine concentration within the presynaptic terminal. This increase is associated with antihypertensive, antidepressant, and antinarcoleptic effects. [390] MAOI are thought to exert their antihypertensive effect through a false transmitter mechanism. Tyramine is usually oxidatively deaminated in the gut by MAO. With administration of an MAOI, tyramine levels rise. When tyramine is taken up into the sympathetic nerve terminal via uptake 1, it enters the varicosities and is transformed by DBH into octopamine. On its subsequent release in place of NE, octopamine is only weakly reactive at sympathetic receptors, resulting in a lowering of blood pressure. The MAOI are no longer used as antihypertensives because many other drugs with better risk-benefit ratios have been developed.

MAOI are now primarily used in psychiatric practice. The use of MAOI as antidepressants is based on the theory that depression is due to decreased amine in the synapses of the CNS. Inhibition of MAO thus makes more amine available for release. MAOI currently available for treatment of depression include isocarboxazid (Marplan), phenelzine sulfate (Nardil), and tranylcypromine sulfate (Parnate).

There are at least two forms of this enzyme, based on substrate specificity. MAO-A acts on 5-HT, NE, and dopamine, whereas MAO-B is specific for tyramine. A specific MAO-B inhibitor, selegiline hydrochloride (deprenyl), has been developed for the treatment of Parkinson disease, in hopes that by blocking central dopamine breakdown, more dopamine will be preserved in the affected areas. [391]

Drug and food reactions have been of great concern in patients taking MAOI. Ingestion of tyramine-containing foods such as red wine and aged cheese must be avoided by patients taking these drugs. Consumption delivers a huge amount of tyramine to the adrenergic nerve terminal, with a subsequent massive release of NE. This is manifest clinically as a hypertensive crisis with potential for MI, cerebral hemorrhage, and death. Any intake of biogenic amine precursors would be expected to increase catecholamine levels greatly, as seen with the concurrent administration of levodopa with MAOI. The effects of sympathomimetic amines, particularly the indirect-acting drugs, are enhanced. [390] Of commonly used drugs, narcotics, in particular meperidine, have been associated with hyperpyrexic coma and death in patients treated with MAOI. Depressant effects of agents such as sedatives, alcohol, and general anesthetics are enhanced in these patients. Interaction between MAOI and tricyclic antidepressants can be disastrous. [390] Anesthetic interactions with deprenyl have not been reported, but experience with this drug is currently limited. [391] Great concern has been expressed that patients receiving long-term therapy with MAOI risk life-threatening drug interactions during anesthesia. Emergency surgery in patients given MAOI can be punctuated by marked hemodynamic instability. Severe reactions to narcotics and indirect-acting sympathomimetics, as well as altered metabolism of endogenous and exogenous catecholamines, make these patients potentially difficult to manage. Because of the possibly dangerous interactions of many drugs with MAOI, controversy exists over the best way to anesthetize these patients. [392, 393] It has been suggested that the level of concern expressed over the years may be excessive. Although prudence and custom dictate discontinuation of MAOI well in advance of elective procedures (2 weeks), there appear to be rational anesthetic choices

based on pharmacology and risk-benefit considerations in patients in whom surgery cannot be delayed.

Drugs Affecting the Renin-Angiotensin System

The renin-angiotensin system is important in maintaining blood pressure and fluid balance (see Fig. 14–7). The major end product of the system, angiotensin II, is a potent vasoconstrictor that stimulates the release of aldosterone from the adrenal cortex. Aldosterone causes salt and water retention by the kidney. The mechanism by which angiotensin II is produced is as follows. The juxtaglomerular cells of the renal cortex secrete the proteolytic enzyme called renin, which cleaves angiotensinogen, a protein produced in the liver, producing the decapeptide angiotensin I. Angiotensin I is converted almost immediately to angiotensin II by ACE. This converting enzyme is located predominantly in the endothelial tissue of the lung. In addition to its direct vasoconstrictive activity, angiotensin II enhances the prejunctional release of NE from the adrenergic nerve ending and increases efferent sympathetic nerve activity. Angiotensin II also affects sodium and water homeostasis by directly decreasing tubular reabsorption of sodium, increasing ADH and adrenocorticotropic hormone secretion, and stimulating the secretion of aldosterone. ACE is also a kinase that degrades the vasodilator bradykinin. Therefore, ACE inhibition blocks angiotensin II formation and delays bradykinin breakdown along with effects on associated prostaglandins. [394]

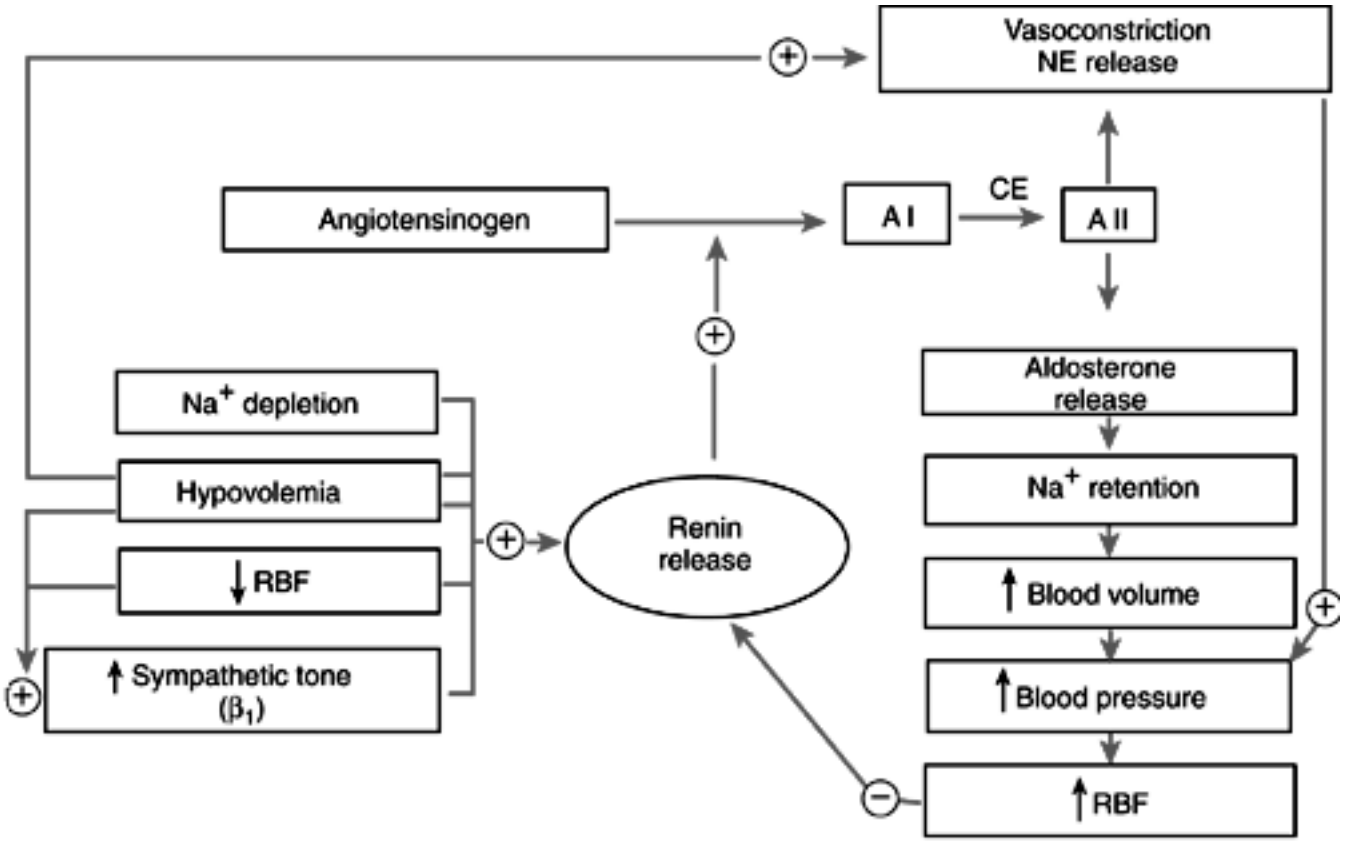


FIGURE 14–7 The interactions of the renin-angiotensin-aldosterone and sympathetic nervous systems in maintaining blood pressure and volume. +, stimulating effects; –,

inhibiting effects; RBF, renal blood flow; NE, norepinephrine; AI, angiotensin I; AII, angiotensin II; CE, converting enzyme.

A few patients with hypertensive vascular disease have high circulating plasma renin levels, but many more, 70 percent of patients, respond to the antihypertensive effects of ACEI, and there is no dramatic difference in hypertensive response among patients with low or high renin levels. [317] The ACEI have proven to be useful in the treatment of hypertension and CHF and have decreased mortality after MI [395](Table 14–12). Captopril (Capoten), was the first active oral agent available, followed by enalapril (Vasotec) and lisinopril (Prinivil, Zestril). Four new ACEI have been marketed: benazepril (Lotensin), fosinopril (Monopril), quinapril (Accupril), and ramipril (Altace). The ACEI affect the renin-angiotensin aldosterone system by inhibiting ACE activity. [394, 396, 397] Enalapril is the only ACEI available in a parenteral dosage at this time. Lisinopril offers once-a-day dosing.

TABLE 14–12. Comparative Pharmacokinetics of Angiotensin-Converting Enzyme Inhibitors

	BENAZEPRIL	CAPTOPRIL	ENALAPRIL	FOSINOPRIL	LISINOPRIL	QUINAPRIL	RAMIPRIL
Prodrug	Yes	No	Yes	Yes	No	Yes	Yes
Lipid solubility	No data	Not very lipophilic	Lipophilic	Very lipophilic	Very lipophilic	No data	Somewhat lipophilic
Absorption	37%	75%	60% (53–73%)	36%	25% (6–60%)	60%	50–60%
Serum $t_{½}$ (h)	Benazeprilat 10–12	<2	Enalapril 1.3, enalapril at 11	Fosinoprilat 12	12	Quinapril 0.8, quinapril at 2	Ramipril 1–2, ramipril at 13/17
Serum protein binding	>95%	25–30%	<50%	>95%	0	0.97	Ramipril 73%, ramipril at 56%

TABLE 14–12. Comparative Pharmacokinetics of Angiotensin-Converting Enzyme Inhibitors							
	BENAZEPRIL	**CAPTOPRIL**	**ENALAPRIL**	**FOSINOPRIL**	**LISINOPRIL**	**QUINAPRIL**	**RAMIPRIL**
Elimination	Primarily renal, some biliary	Metabolized to disulfide, then renal	Renal	Renal 50%, hepatic 50%	Renal	Renal 61%, hepatic 37%	Renal
Onset of hypotensive action (h)	1	0.25	1	1	1	1	1–2
Peak hypotensive effects (h)	2–4	1–1.5	4–6	2–6	6	2	3–6
Duration of hypotensive effects (h)	>20 mg/day, 24	Dose-related	24 (18–30)	24	24 (18–30)	24	≥24 (24–60)
Dosage	20–80 mg daily, dosed 1–2 × day, maximum 80 mg daily	25–150 mg/dose, dosed 2–3 × day, maximum 450 mg daily	5–40 mg daily, dosed 1–2 × day, maximum 40 mg daily	10–40 mg daily, dosed 1–2 × day, maximum 80 mg daily	10–40 mg daily, dosed 1–2 × day, maximum 80 mg daily	10–80 mg daily, dosed 1–2 × day, maximum 80 mg daily	2.5–20 mg daily, dosed 1–2 × day, maximum 20 mg daily

Although all the ACEI are approved for the treatment of hypertension, only captopril and enalapril are approved for the treatment of CHF. Both these agents have been shown to decrease morbidity and mortality in patients with CHF. Captopril is associated with more frequent adverse effects than enalapril, may have a few more drug interactions, and has a two- to three-times daily dosing regimen as compared with enalapril, which has a once-daily to twice-daily dosing regimen.

Some adverse effects observed with ACEI are common to the entire class, such as cough, angioedema, acute renal failure, and hyperkalemia. Angioedema has occurred, especially after the first dose, affecting the face, extremities, lips, mucous membranes, tongue, glottis, or larynx. [394, 398, 399] Some occurrences may be fatal. [394, 398, 400] This common side effect has led to the approval of the angiotensin II receptor antagonist, losartan. Rash and taste disturbance occur more frequently with captopril than with the other ACEI. Renal function impairment has occurred with ACEI, but it is usually reversible after withdrawal of the drug. Renal function should be monitored. [398, 399] Because hyperkalemia may result from inhibition of aldosterone secretion, it is recommended that serum potassium levels be monitored. [394, 397, 398, 399] ACEI have demonstrated fetal morbidity and mortality in humans. It is advised not to use these agents at all during the second or third trimester of pregnancy. [400]

Cholinergic Drugs

Overview of Mechanisms of Action

The cholinergic drugs act by mimicking, amplifying, or inhibiting the effects of ACh. Cholinergic drugs do not behave exactly as does ACh: their drug action is more specific, affecting fewer sites than ACh, and their duration of action is generally longer than that of ACh.

Unlike adrenergic pharmacology, in which the clinician can select from a wide choice of drugs, there is a relative paucity of drugs that influence parasympathetic function. In general, drugs that affect the parasympathetic system act in one of four ways:

1. As an agonist, stimulating cholinergic receptors.
2. As an antagonist, blocking or inhibiting the actions mediated by the cholinergic receptor.
3. Blocking or stimulating receptors on autonomic ganglia.
4. Inhibiting the metabolism of ACh, thus increasing and prolonging the effect of ACh.

There are currently no effective clinically used drugs that act through mechanisms affecting synthesis of ACh (e.g., by inhibiting choline acetyltransferase) or by causing indirect release of ACh (as tyramine, ephedrine, and amphetamine may release NE). Hemicholinium does interfere with choline uptake and could deplete ACh stores, but it is not used clinically. Adenosine may inhibit the release of ACh by decreasing the affinity of binding sites for calcium ions; aminoglycoside antibiotics may compete with calcium for membrane calcium channels, as does magnesium ion. Exocytotic release of ACh is inhibited by botulinum toxin; this toxin is sometimes given by local injection to treat strabismus and blepharospasm. In a full-blown botulism poisoning syndrome, fatalities may result from muscle weakness and respiratory failure.

Agonists

Cholinergic agonists have limited therapeutic use because of their detrimental effects. ACh, as a result of its diffuse, nonselective actions and rapid hydrolysis by both acetylcholinesterase and butyrylcholinesterase, has had almost no therapeutic use other than as an intraocular medication for transient constriction of the pupil during ophthalmic surgery.

Cholinergic agonists in clinical use have been derived from ACh, but they resist hydrolysis by cholinesterase, permitting a useful duration of action. The different systemic effects of the cholinergic agonists are more quantitative than qualitative, but some limited organ selectivity is useful therapeutically, as is seen with the synthetic choline esters bethanechol and carbachol. Methacholine and bethanechol are primarily muscarinic agonists; carbachol has significant nicotinic and muscarinic effects. The simple maneuver of adding a methyl group to the β-position of the choline in ACh produces methacholine, which is almost purely muscarinic and is almost totally resistant to hydrolysis by either of the cholinesterases. An IV infusion of methacholine causes hypotension and bradycardia; a small SQ dose causes a more transient hypotension with a reflex increase in heart rate. The sole current use of methacholine (Provocholine) is as a provocative agent in diagnosing hyperreactive airways, making positive use of the deleterious bronchoconstrictive effect of muscarinic agonists. It is administered only by inhalation; serious side effects including gastrointestinal symptoms, chest pain, hypotension, loss of consciousness, and complete heart block have occurred when the drug is given orally or parenterally. Excessive bronchoconstrictive response should be treated by an inhaled β-agonist; coexisting beta blockade is considered a contraindication to the use of methacholine.

The carbamate derivative of methacholine, bethanecol (Urecholine), is occasionally used postoperatively to reinstitute peristaltic activity in the gut or to force the extrusion of urine from an atonic bladder. It is administered SQ or orally to avoid effects in other organ systems.

Carbachol is used topically or intraocularly to constrict the pupil, for long-term treatment of wide-angle glaucoma. When used topically, it is often better tolerated than the ophthalmic anticholinesterase agents, and it may be effective in patients resistant to pilocarpine and physostigmine. The rapid pupillary constriction is due to the combination of ganglionic block and muscarinic effects. Another natural alkaloid, pilocarpine, was used to treat glaucoma until the advent of more modern drugs.

Muscarinic Antagonists

Muscarinic antagonists are the active ingredients in some common plants used since antiquity for both medicinal and poisonous effects. It has been suggested that atropine poisoning figures in the American classic, *The Scarlet Letter*.[401] Despite their age, muscarinic antagonists still represent important drugs in anesthesia and critical care (Fig. 14–22).

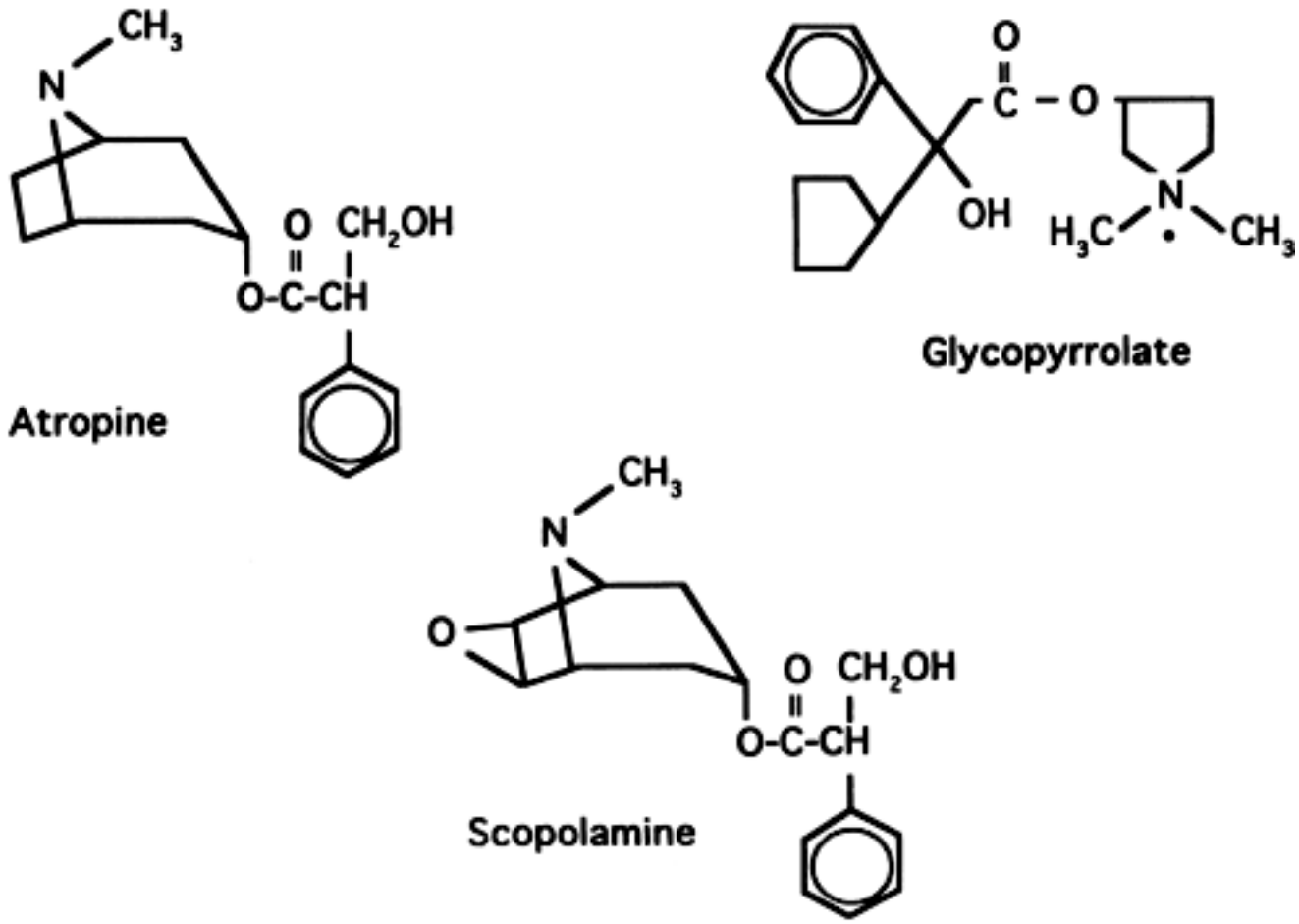


FIGURE 14–22 Structural formulas of the clinically useful antimuscarinic drugs.

Muscarinic antagonists compete with neurally released ACh for access to muscarinic cholinoceptors and block its effects. They also antagonize the actions of muscarinic agonists at noninnervated, muscarinic cholinoceptors. Presynaptic muscarinic receptors on the adrenergic nerve terminal may inhibit NE release. Hence, muscarinic antagonists may enhance sympathetic activity. With the exception of quaternary ammonium compounds that do not readily cross the blood-brain barrier and so have few CNS actions, there is no significant specificity of action among these drugs; they block all muscarinic effects with equal efficacy, although some quantitative differences in effect may be seen (Table 14–13). Research has revealed several subtypes of muscarinic receptors, and agonists and antagonists have been synthesized that bind preferentially to one or another. None of these selective agents is yet available commercially, but this is a rapidly developing area of research, and there will soon be drugs that selectively act on one site or another, such as the heart, bronchial system, smooth muscle, gastric mucosa, or some particular area of the CNS.

TABLE 14–13. Muscarinic Anticholinergic Drugs

Historically, these drugs were used in peptic ulcer disease, various forms of "spastic bowel syndrome," upper respiratory illness, and asthma. However, with the availability of the specific histamine (H_2) drug cimetidine for peptic ulcer disease and inhaled β-agonists and steroids for asthma, these uses have markedly decreased. Historically, atropine was one of the important drugs used to treat bronchospasm, but it was displaced with the introduction of β_2 -agonist drugs that did not cause drying of secretions or diminished ciliary motility. Topical use of atropine analogues in ophthalmologic practice to dilate the pupil is still common.

The addition of a muscarinic anticholinergic drug to anesthetic premedication to decrease secretions and to prevent harmful vagal reflexes was mandatory in the era of ether anesthesia, but it is no longer necessary with modern inhalational agents. Scopolamine combined with an opiate, usually morphine, is still used by cardiac anesthesiologists to sedate a patient while minimizing cardiorespiratory effects. Routine preoperative use of these drugs as antisialogogues continues in some pediatric and otorhinolaryngologic cases.

Atropine is a tertiary structure that easily crosses the blood-brain barrier (see Fig. 14–22). CNS effects have been seen with the relatively large doses (1–2 mg) given to block the muscarinic side effects of the anticholinesterase drugs used for reversal or neuromuscular blockade reversal (Ch. 12). In contrast, one of the synthetic antimuscarinic drugs, glycopyrrolate (Robinul), does not cross the blood-brain barrier and has gained popularity for this use. In addition, glycopyrrolate has a longer duration of action than does atropine. Scopolamine, which resembles the others of this class in peripheral actions, has pronounced CNS effects. It is the active ingredient in most over-the-counter preparations sold as soporifics, and it is effective in preventing motion sickness. The patch preparation of scopolamine can be used prophylactically for motion sickness and postoperative nausea and vomiting, but like oral and parenteral forms, it may be associated with eye, bladder, skin and psychologic side effects. [402, 403]

The development of ipratropium (Atrovent) reestablished antimuscarinic drugs as an important therapeutic approach in asthma and bronchospastic disorders. [404] Although ipratropium is structurally similar to atropine and has essentially the same effects when administered parenterally, an important difference is that ipratropium is a quarternary ammonium compound. Thus, it is very poorly absorbed when delivered via inhalation and essentially has few extrapulmonary effects even when given in extremely large doses by this route. Ninety percent of inhaled drug is swallowed, but only 1 percent of the total dose is absorbed systemically.

When administered to normal volunteers, ipratropium provides almost complete protection against bronchospasm induced by a variety of provocative agents. However, in asthmatic patients, results are more variable. The bronchospastic effects of some agents, such as methacholine or sulfur dioxide, are completely blocked, whereas there is little effect on leukotriene-induced bronchoconstriction. Further, there is considerable variability among patients. The onset of bronchodilation is slow, and the maximal effect is less than that seen with β-agonists. Unlike atropine, ipratropium has no negative effect on ciliary clearance. In general, more therapeutic effect from antimuscarinics, including ipra-tropium, is seen in patients with chronic obstructive pulmonary disease than in asthmatic patients. [404, 405] Ipra-tropium is supplied as a metered-dose inhaler supplying 18

μg per puff. Dosage is two puffs orally four times a day. Maximum bronchodilation occurs in 30 to 90 minutes, but the duration may be 4 hours. [405]

The toxic effects of the muscarinic antagonists are due to the blockade of muscarinic cholinoceptors in the periphery and the CNS. The peripheral effects (e.g., dry mouth) may be irritating, but not life-threatening, in healthy adults. However, children are more dependent than adults on sweating for thermoregulation and easily become dangerously hyperthermic. Moreover, older individuals may not be able to tolerate the cardiac, ocular, or urinary effects of muscarinic blockade.

The CNS effects are the usual cause of death or injury. Increasing doses of atropine or scopolamine cause greater distortions of mentation, progressing from thought disorders to hallucinations, delusions, delirium, and severe psychoses. These effects are reversible, but the mental dysfunction can persist for weeks. Left alone, the intoxicated individual will die of starvation, dehydration, and/or trauma. However, recovery will be complete if the individual receives appropriate supportive and protective care until the drug is eliminated. Volunteers have received more than 500 mg of atropine, more than 1,000 times the usual dose, and, although they have been disabled for weeks, they have recovered fully.

Small doses of atropine (0.05 mg) can evoke bradycardia, a finding that has led some clinicians to increase the dose in children. It was thought that a CNS effect of atropine could be responsible, but the time course, as well as the fact that it occurred in vagotomized animals, cast doubt on this mechanism. Whether this paradoxic bradycardia is a central or peripheral effect, or both, and the role of muscarinic subtypes, are still subjects of debate. [406]

Atropine and scopolamine toxicity have been treated for decades by the use of the naturally occurring alkaloid physostigmine (Antilirium), which is an anticholinesterase that penetrates the blood-brain barrier. [407] Consequently, the use of this drug in doses of 1 to 2 mg IV to treat the postoperative CNS effects of IV atropine or scopalamine has been successful. Physostigmine may also reverse the CNS effects of other compounds with anticholinergic activity, including the tricyclic antidepressants, several major tranquilizers, and antihistamine drugs. [408] Physostigmine may antagonize the sedative effects of the benzodiazepines as well, but the specific benzodiazepine antagonist, flumazenil (Romazicon), will undoubtedly supplant physostigmine for this use. [409, 410]

Physostigmine must be administered with care because of its potentially lethal nicotinic effects, which are not prevented by the muscarinic antagonists, and because its half-life rarely matches that of the intoxicant.

Cholinesterase Inhibitors

Anticholinesterase drugs provide the most commonly used means of producing sustained systemic cholinergic agonism. These drugs are used to reverse neuromuscular blockade, to treat myasthenia gravis, and to treat certain tachyarrhythmias.

The first anticholinesterase agent available was physostigmine (see earlier). There are currently three chemical classes of compounds used as cholinesterase inhibitors: carbamates, organophosphates, and quaternary ammonium alcohols. Neostigmine was first used as a gastrointestinal tract stimulant and later as a treatment for myasthenia gravis.

Physostigmine, neostigmine, and pyridostigmine are carbamates, whereas edrophonium is a quaternary ammonium alcohol. The cholinesterase enzyme is inhibited so long as the

esteratic site is bound to an acetate, carbamate, or phosphate. Carbamate and phosphate bonds are much more resistant to attack by hydroxyl groups than are acetate bonds. The acetylated form lasts for only microseconds, whereas the carbamylated form lasts for 15 to 20 minutes. Organophosphates include diisopropylfluorophosphate, parathion, malathion, soman, sarin, VX, and a variety of other compounds used as insecticides. Although the toxicity of the organophosphate insecticides is primarily related to their anticholinesterase activity, the mechanism of this effect is different from the clinically used anticholinesterase drugs. The organophosphates produce an irreversible enzyme inhibition and have CNS effects as well. [411] Consequently, treatment of organophosphate insecticide poisoning relies on chemical compounds capable of displacing the insecticides from the enzyme and therefore of reactivating the cholinesterase activity. The best-documented of these chemicals is pralidoxime (2-PAM). Physostigmine and most of the organophosphates are not quaternary ammonium compounds and have major effects on cholinergic functions in the CNS.

Edrophonium is unique in that it lacks an acetate, carbamate, or a phosphate group. It acts because the positive charge of the nitrogen is attracted strongly by the anionic site and physically blocks the esteratic site. Thus, the edrophonium molecule is postulated to be held in place only by an ionic bond. The duration of inhibition provided by each molecule is short (e.g. milliseconds), but because they are not changed in the reaction, the molecules can hop onto and off the enzyme repeatedly and consequently render the enzyme unavailable to ACh.

Aside from reversal of neuromuscular blockade, there are few other therapeutic uses of these compounds. Because these compounds can increase the effect and duration of neurally released ACh, they are useful in situations in which such release is deficient, such as myasthenia gravis. Further, anticholinesterase drugs are occasionally used to stimulate intestinal function and topically in the eye as a miotic. An irreversible organophosphate anticholinesterase that is used clinically is echothiophate iodide (Phospholine), which is available as topical drops for the treatment of glaucoma. Its major advantage over other topical agents is its prolonged duration of action. Because this chemical also inactivates plasma cholinesterase, it may prolong the action of succinylcholine. Although prudence dictates discontinuation of echothiophate for 1 week prior to surgery, there are numerous case reports of successful anesthesia performed under emergency conditions.

Ganglionic Drugs

Agonists

The agonists are essential for analyzing the mechanism of ganglionic function, but they have no therapeutic use. Nicotine is the classic ganglionic agonist, and its effects have been well described. [412]

Parasympathetic drugs stimulate ganglia, but this action is usually masked by the other parasympathomimetic effects. Experimentally, relatively large doses of ACh administered IV after blockade of muscarinic receptors by atropine causes ganglionic stimulation and release of EPI by the adrenal medulla. [412]

Antagonists

The ganglionic antagonists were the first effective therapy for the management of hypertension and were used extensively during the 1950s and 1960s. However, because

of interference with transmission through both sympathetic and parasympathetic ganglia, antihypertensive action was accompanied by numerous undesirable side effects. Hexamethonium is the prototypic drug of this class, and it has minimal neuromuscular and muscarinic activity. Paton [413] provided a vivid description of the clinical effects of chronic ganglionic blockade with his "hexamethonium man." The systemic effects of ganglionic blockade are determined by the "resting tone" of a specific body system prior to the application of ganglionic blockade (see Table 14–2).

TABLE 14–2. Usual Sympathetic or Parasympathetic Dominance at Specific Effector Sites

SITE	PREDOMINANT TONE
Ciliary muscle	Parasympathetic
Iris	Parasympathetic
Sinoatrial node	Parasympathetic
Arterioles	Sympathetic
Veins	Sympathetic
Gastrointestinal tract	Parasympathetic
Uterus	Parasympathetic
Urinary bladder	Parasympathetic
Salivary glands	Parasympathetic
Sweat glands	Sympathetic (cholinergic)

Although not as reliable or as potent as nitroprusside, trimethaphan has a quick onset and short duration of action that makes it useful in situations in which moment-to-moment control of blood pressure is critical, while avoiding some of the toxicity and side effects associated with agents such as nitroprusside and beta blockers. Because it does not increase cerebral blood flow, it may be used in hypertensive encephalopathy without worsening cerebral edema and also in intracranial hem-orrhage associated with hypertension. In acute aortic dissection, trimethaphan may lower blood pressure without causing significant tachycardia, avoiding the increase in shearing forces (dp/dt) seen with increased heart rate. [341]

Trimethaphan may be used for controlled hypotension under certain circumstances, as an alternative to or in combination with nitroprusside. The two agents combined may avoid the sympathoadrenal stimulation and rebound hypertension seen with nitroprusside alone.

The dosages are also decreased with the use of combination therapy, thus avoiding cyanide toxicity in patients who have renal insufficiency or who require large cumulative doses of trimethaphan. Side effects and rapidly developing tolerance limit its use. Other noncardiovascular side effects related to effects of ganglionic blockade include blurred vision, persistent pupillary dilatation (which may interfere with neurologic evaluation), and gastrointestinal and urinary atony. Orthostatic hypotension occurs, but it may not be a serious concern in these usually critically ill patients. Histamine release also occurs at clinically relevant concentrations.

AUTONOMIC DYSFUNCTION

Plasma Catecholamines

Accurate and sensitive techniques for measuring plasma catecholamines have existed for three decades, but interpretation of the data they yield has been controversial. Plasma EPI and NE levels are typically in the 100 to 400 pg/mL normal range, but they can easily increase 6-fold or more in stress.

Plasma concentrations of EPI reflect adrenal medullary activity, [414] if not overall sympathetic activity, and are labile. The uncontrolled stress experienced by experimental subjects has clouded the meaning of measured levels. Significant isolated adrenal medullary secretion can occur in certain stressful situations, such as public speaking. [28] Moreover, venous samples may reflect the EPI kinetics in the organ being sampled rather than in the whole body, and arterial samples may be more reliable. [415]

The significance of plasma NE concentration is even more controversial. Although the adrenal medulla secretes some NE, plasma NE levels generally reflect spillover from sympathetic stimulation because most of the plasma NE released at the nerve ending is taken up again by the nerve terminal. Although reuptake may be tissue-specific and markedly influenced by alterations in physiology or diseases, this spillover in humans is 10 to 20 percent of the NE synthesis rate at baseline and may be greatly enhanced in periods of sympathetic activation. [416] The most compelling argument for use of plasma NE as a marker for sympathetic activity comes from animal studies in which plasma NE levels directly mirrored nerve stimulation. [417] Many important studies have correlated elevations in plasma catecholamines with acute and chronic stress and have led to the concept of stress-free anesthesia. The landmark study showing a striking relationship between mortality in CHF and plasma NE levels resulted in attempts to utilize β-adrenergic antagonists in the treatment of ventricular dysfunction. [79, 418, 419]

The development of experimental radiotracer techniques to assess the *in vivo* kinetics of catecholamines has provided additional information that is of clinical importance, particularly in relation to regional kinetics. For example, studies relying only on arterial and venous catecholamines suggested that the hepatomesenteric bed contributed significantly to the total body clearance of catecholamines but only minimally (<8%) to the spillover. However, more recent studies of regional NE kinetics demonstrate that the gut release of NE (≤25% of the total body) is largely obscured by efficient extraction (>80%) in the liver. Similarly, selective elevations in NE release from the heart, which may be associated with ischemia, the early onset of CHF, and tachyarrhythmias may not be apparent in measuring arterial or venous levels. [420] The observations involving regional spillover have led to the realization that although stress may activate a generalized sympathetic response, there may be different patterns contingent on the

stimulus. Thus, it is possible that the lack of association of plasma NE levels in the presence of clinically significant sympathetic activation may be a function of the measurement technique or the particular stressor. Although there are increasing data that many anesthetic techniques, including inhalational, opiate, and regional, can attenuate the stress response, the question whether this represents a benefit or liability in patient care remains a matter of controversy. [421, 422] Until recently, there were few data to suggest that the attenuation of the stress response altered outcome, with the exception of prolonged postoperative epidural anesthesia or special surgical situations. However, results of several studies in infants and adults undergoing heart surgery suggest that the use of high-dose opiates or other strategies to diminish perioperative stress may improve outcome. [423, 424, 425, 426] Since the last edition of this book, several studies have reported that the ability of neur-axial analgesia to attenuate the sustained increase in perioperative catecholamines usually associated with general anesthesia leads to decreased ischemic and thrombotic complications. [427, 428, 429, 430]

It is our belief that, given the effects of age, posture, and hydration, small changes in plasma catecholamines levels correlate poorly with hemodynamic changes and merit cautious interpretation, whereas significant increases (>1,000 pg) in levels are good markers of sympathetic nervous system activation.

Clinical Syndromes

Diabetes Mellitus

Diabetes mellitus is the most common cause of autonomic neuropathy. Early small-fiber damage is revealed by loss or impairment of vagally controlled normal heart rate variability, decreased peripheral sympathetic tone with subsequent increase in blood flow, and diminished sweating. The diabetic neuropathic foot demonstrates early loss of pain and temperature sense before loss of touch or vibration. With sympathetic denervation, sympathetic nerves normally found supplying small arterioles are either entirely absent or are abnormally distant from their effector sites. The neuropathic foot may show increased blood flow with arteriovenous shunting, whereas peripheral arteries are dilated and stiff; despite the total increase in flow, capillaries may be "missed," with distal ischemia the result. The arterial walls may be stiff from calcification in the media; interestingly, calcification has been reported after surgical sympathectomy.

Mechanisms maintaining normal standing blood pressure are altered, and normal precapillary vasoconstriction in the foot on standing may be diminished. When healthy people stand, roughly 700 mL of the blood volume may pool in the legs and splanchnic circulation, with an associated 20 percent decrease in cardiac output. In healthy individuals, baroreceptors in the carotid sinus and aortic arch detect the decrease and mediate sympathetic impulses to the heart and blood vessels. The sympathetic denervation associated with diabetes may cause loss of the normal compensatory vasoconstriction in the peripheral and gut tissues, and this may be potentiated also by a failure of appropriate acceleration of heart rate and reduced cardiac output. Diabetic patients with orthostatic hypotension usually have lower NE levels.

Most clinicians recognize that diabetic patients with autonomic neuropathy may be at additional risk in general anesthesia. The increased cardiovascular casualty is shown in a number of case reports and at least one prospective study. [431] Gastroparesis is most

probably due to vagal degeneration and is of clinical relevance, because awake or rapidsequence intubation may be required.

Autonomic Changes with Aging

Although numerous studies have examined the effects of maturation and aging on vascular reactivity, the human paradigm is one of exaggerated changes in blood pressure.[432] Aging is associated with alterations in vascular reactivity manifest clinically as exaggerated changes in blood pressure, namely, hypertension and orthostatic hypotension. Orthostatic hypotension is quite common (≈20%) in the elderly and may result largely from diminished baroreceptor responsiveness. Heart rate response to changes in blood pressure, Valsalva maneuver, and the respiratory cycle are blunted with aging.[433, 434, 435, 436, 437]

Resting and exercise-induced NE levels increase with age in healthy subjects (by ≈13% per decade),[438] in part owing to decreased clearance.[438, 439] Previously a matter of controversy, it now appears that besides the well-documented reduction in vagal function associated with aging,[440, 441] the primary autonomic defect in aging is an impairment in NE reuptake, perhaps as a function of decreased nerve density. Although there is no apparent age-dependent decrement in nerve firing rates from sympathetic efferents in skeletal muscle,[442] kinetic studies reveal selective and dramatic increases in cardiac NE spillover attributable to decreased reuptake in elderly patients subjected to mental stress or exercise.[416] The augmented synaptic concentration of NE in the setting of age-related reduction in vagal function can precipitate clinical complications (arrhythmogenesis and sudden cardiac death) in patients with cardiac disease. However, end-organ responsiveness is blunted by compensatory downregulation of the β_1 -adrenoreceptors (decreased receptor density and affinity) and uncoupling of β_2 -adrenoreceptors (via decreased G_s activity).[443, 444, 445] Despite increased cardiac spillover cardiac oxygen consumption was not altered.[446]

Attenuation of presynaptic α_2 -adrenoreceptor–mediated inhibition of neuronal NE release[447, 448, 449] also accounts for increased NE levels observed with age. Reduced postsynaptic α_2 -adrenoreceptor activity decreases contractile responses and further attenuates vasoconstrictor tone. In a seemingly vicious cycle, the increase in circulating NE levels are associated with downregulation of platelet α_2 -adrenoreceptor density and responsiveness.[450] The loss of adrenergic control via the reduction of α_2 - and β-receptor–mediated responses with age causes a loss in the efficacy of the sympathetic system to control cardiovascular responsiveness with advancing age, implying a relationship with or an explanation of the increased incidence of cardiovascular disorders, such as CHF, in the elderly.

Autonomic Changes in Spinal Cord Transection

The most drastic of all alterations in the ANS an anesthesiologist may encounter is complete spinal cord transection. Spinal cord transection not only may affect motor and sensory function, but also may exhibit profound alterations and autonomic activity that can alter anesthetic care. As is obvious from the anatomy of the sympathetic and parasympathetic outflow, spinal cord injuries or transection can cause varying degrees of autonomic dysfunction, depending on the site, extent, and timing of the lesion.

In patients with cervical spinal cord transection, both sympathetic and parasympathetic outflows are detached from central control mechanisms. Thus, in addition to expected motor and sensory changes, there are profound abnormalities altering the cardiovascular,

thermoregulatory, gastrointestinal, and urinary systems. The autonomic consequences of transection are not always apparent because the distal portion of the spinal cord may retain some function, resulting in unanticipated autonomic abnormalities.

There are fundamental differences between the acute and chronic effects of spinal cord transection. Initially, a transient state of decreased excitability occurs. This phenomenon, known as "spinal shock," usually occurs immediately after the lesion and may last from days to weeks. In these patients, the periphery is generally atonic, and the peripheral blood vessels are largely dilated. Investigators have suggested that methylprednisolone may be of some use in treating this phase of spinal shock. [451] In patients with high thoracic lesions who have sustained recent injury, the basal supine blood pressure is usually low and is accompanied by plasma catecholamine levels that are approximately 35 percent of normal. [452] Patients with recent low spinal injuries may exhibit compensatory tachycardia from intact parts of the ANS.

In contrast, patients with high spinal lesions may fail to respond to hypovolemia with an increased heart rate and may actually exhibit bradycardia. The only intact efferent component of baroreflex pathways in quadriplegic patients is the vagus. Bradycardia occurs not only with changes in position, but also with Valsalva maneuvers or increased intrathoracic pressure. [453]

One aspect of care that is frequently overlooked is the effect of tracheal suctioning on patients with high spinal transection. Given that many of these patients are dependent on artificial respiration because of their respiratory muscle paralysis, there may be unopposed vagal stimuli contributing to profound bradycardia in these patients. This vagal response is particularly accentuated during hypoxemia.

Because the sympathetic nervous system may be dysfunctional in these patients, there is a compensatory enhancement of the renin-angiotensin-aldosterone system for the maintenance of blood pressure. Therefore, patients who have spinal cord transection may be exquisitely sensitive to ACEI, even with modest changes in intravascular volume or posture. It should be emphasized that the release of renin may be independent of sympathetic stimulation and may be due to renal baroreceptor stimulation that accompanies the fall in renal perfusion pressure.

Although pressure stimuli above the lesion do not usually cause a change in blood pressure, the phenomenon of *autonomic dysreflexia* can occur when stimulation occurs below the lesion. Thus, bladder or bowel distention can elicit the so-called "mass reflex." This autonomic reflex includes a dramatic rise in blood pressure, a marked reduction in flow to the periphery, and flushing and sweating in areas above the lesion. The patient's heart rate may fall as a reflex. Surprisingly, evidence from microneurography studies indicates that there is only a modest rise in sympathetic nerve activity during activation of the mass reflex, [454] and plasma levels increase only modestly. Thus, speculation has arisen that the exaggerated blood pressure response may be due to supersensitivity of adrenoreceptors. As would be anticipated, there is an increase in sensitivity to exogenously administered pressors in quadriplegic patients. [452] It is interesting to note, however, that quadriplegic patients may exhibit a 5- to 10-fold increase in blood pressure in response to the exogenous administration of angiotensin as well as to catecholamines. It is thus possible that impairment of descending inhibitory reflex pathways that are activated during hypertension may contribute to the supersensitivity. This hypothesis is supported by the finding that lesions below T5 only infrequently exhibit the increased

sensitivity. Further, there is apparently a normal level of adrenoreceptors even in patients with chronic quadriplegia.

The management of autonomic dysreflexia is of clinical importance. Although the anesthesiologist may be tempted to utilize minimal anesthesia in a patient without sensory or motor function, significant visceral reflexes can be evoked. For these reasons, one may utilize spinal anesthesia, general anesthesia, or a vasodilator such as nitroprusside or nitroglycerin to attenuate this reflex even if pain is not appreciated. There has been some enthusiasm for using clonidine prophylactically to diminish this response.

An additional problem arising from the autonomic denervation occurring with spinal cord transection involves thermogenesis. Hypothermia may occur readily in such patients resulting from cutaneous vasodilatation and the inability to shiver. Similarly, hyperthermia can occur because the normal sweating mechanism can be impaired. It is therefore important to monitor temperature assiduously in these patients during the course of anesthesia.