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CHAPTER 57

Sympathomimetic Drugs

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The next five chapters treat specifically of autonomic drugs, and several other chapters (eg, Chapters 53, 55, 71, and 74) include descriptions of or references to a number of autonomic drugs. Consequently, it will be helpful to review briefly the autonomic nervous system and the classification of drugs that act on or simulate components of that system.

Autonomic Nervous System and Autonomic Drugs

The *autonomic (involuntary) nervous system* generally is defined as that system of motor (efferent) nerves which contains cell bodies and corresponding synapses (ie, ganglia) outside of the cerebrospinal axis. The definition includes the sensory (afferent) nerves that subserve functions mediated by the autonomic motor nerves, although a given sensory nerve also may subserve somatic motor functions. This system modulates or controls the activities of smooth (involuntary) muscles of the body, including those that control the caliber of blood vessels, the heart muscle and the digestive, salivary, sweat and some endocrine glands. Unconsciously (without conscious control), it tends to maintain a constant state (homeostasis) of the vital functions of the body, constantly adjusting one or more factors to attempt to maintain equilibrium or restore an equilibrium upset by external or internal influences; cerebral blood flow, body temperature, visual accommodation, blood sugar and body fluid composition, for example, are kept remarkably constant by means of servoadjustments mediated through the autonomic nerves. However, it should be noted that the *somatic* (voluntary) *nervous system* also unconsciously subserves vital functions such as respiration, posture, swallowing, motor reflexes, body temperature and many less vital but important unconscious modulations of skeletal muscle tone; however, the degree of conscious modulation of this control is much greater than in the autonomic nervous system. These involuntary somatic motor functions are coordinated with autonomic functions.

There are two main motor divisions to the autonomic nervous systems—the *sympathetic* (thoracolumbar) and the *parasympathetic* (craniosacral) divisions. Most organs or systems (effectors) receive innervation from both these divisions; generally, but not invariably, the two divisions qualitatively are opposed in their actions on a given effector. An abridged list of responses is presented in Table 1.

The opposition of the two divisions of the autonomic nervous system reflects the fact that the chemical substances (mediator, transmitter or neurohumor) liberated by the postganglionic nerve terminals are not the same for the two divisions. Parasympathetic postganglionic nerves liberate acetylcholine and, hence, are called *cholinergic* nerves. Most sympathetic postganglionic nerves liberate norepinephine; however, sympathetic postganglionic fibers to the sweat glands and a few fibers to the vascular beds of the mouth, face and skeletal muscles liberate acetylcholine (ie, are cholinergic). The adrenal medulla, which is innervated by sympathetic preganglionic nerves, liberates mostly epinephrine, also known as adrenaline; since adrenaline originally was thought to be the sympathetic transmitter, norepinephrine-releasing nerves are termed *adrenergic.*

At the ganglia, preganglionic nerves of either division liberate acetylcholine (ie, are cholinergic), but the character of the acetylcholine ganglionic receptors is different from those in the neuroeffectors, so that the two types of receptors are not blocked by the same drugs. Somatic motor nerves also liberate acetylcholine (ie, are cholinergic) and are similar to autonomic preganglionic nerves in this regard.

Autonomic drugs are classified according to their relation to the chemical mediator that they either mimic or block. Thus, a drug is cholinergic if it either mimics or blocks stimulation by cholinergic nerves. The terms *cholinomimetic* and *adrenomimetic* have been advanced for the appropriate mimetic agents. There also prevails an older terminology. Hence, adrenomimetics are usually called *sympathomimetics* (this chapter) and cholinomimetics are often called *parasympathomimetics* (Chapter 58); the term parasympathomimetic applies to those drugs that act upon the cholinergic neuroeffectors (ie, are muscarinic), not the ganglionic synapses. Agents that block the receptors are called *blocking agents,* according to the nature of the chemical transmitter with which they compete. Thus, there are *adrenergic blocking agents* (Chapter 59) and *antimuscarinic agents* (Chapter 60), the latter term again restricted to those drugs that block acetylcholine at the neuroeffector receptors. Those agents that block acetylcholine at the ganglionic synapses are simply called *ganglionic blocking agents* (Chapter 55); their somatic motor counterparts (generally loosely included among the autonomic drugs) are called *neuromuscular blocking agents (curarimimetics)* (Chapter 61). The suffix *lytic* sometimes is used in lieu of the word *blocking*; thus, a sympatholytic agent is an adrenergic blocking agent. Also, agents, such as the anticholinesterases, which enhance autonomic transmission by preserving the transmitter from enzymatic destruction, are endowed with no definitive designation; the *anticholinesterases* (Chapter 58) are classified awkwardly as cholinomimetics or parasympathomimetics.

An autonomic mediator not only is liberated at different sites and exerts different effects but also may act on different receptors. The actions of acetylcholine on the exocrine glands, smooth muscle and heart differ from those on autonomic ganglia and the voluntary neuromuscular junction. The former (and not the latter) effects are blocked by atropine, whereas the latter (and not the former) are blocked by tubocurarine. Since muscarine exerts the former actions (and not the latter), the corresponding receptors are called *muscarinic;* since nicotine exerts the latter reactions (and not the former), the corresponding receptors are called *nicotinic.* Three main types of muscarinic receptors are important: M_1-receptors predominate in the CNS and on gastric parietal cells where stimulation increases gastric secretion; M_2-receptors predominate in the heart and M_3-receptors are found in secretory glands and most smooth muscle.

In the adrenergic system there are also two main types of receptors: α and β. There are two types of α- adrenoreceptors: α_1 and α_2. The α_1-adrenoreceptors subserve smooth muscular stimulant functions, adrenergic sweating and adrenergic salivation. The α_2-adrenoreceptors serve to inhibit the presynaptic release of norepinephrine and other mediators and the postsynaptic activation of adenyl cyclase

Table 1—Response of Human Effector Organs to Autonomic Nerve Impulses

Effector system	Sympathetic nerve impulses	Parasympathetic nerve impulses
Systemic blood vessels	Constrict Dilate[a]	Innervate few systemic vessels, but dilate
Pulmonary blood vessels	Constrict	Dilate
Coronary blood vessels	Dilate	Dilate
Bronchioles	Dilate[b]	Constrict
Stomach motility and tone	Decrease	Increase
Gastric secretion	Little effect	Increase
Intestinal motility and tone	Decrease	Increase
Urinary bladder sphincter	Constrict	Dilate
Heart	Increase rate and strength	Decrease rate and strength, block
Pupil of eye	Dilate	Constrict
Salivary glands	Stimulate to viscid saliva	Stimulate to watery saliva
Sweat glands	Stimulate	Not innervated[c]
Lacrimal glands	Not innervated	Stimulate

[a] Constriction is produced in most vascular beds by stimulation of α-receptors. Dilation is produced primarily in skeletal muscle and the liver by stimulation of β-receptors.

[b] Adrenergic nerves do not innervate directly bronchiolar smooth muscle but instead act on cholinergic nerve terminals to decrease the release of acetylcholine.

[c] Most sweat glands *anatomically* are *sympathetic* but *functionally* are *muscarinic*.

(and hence inhibit postsynaptic responses). The β-adrenoreceptors are subdivided into β_1- and β_2-adrenoreceptors, and perhaps more. They are characterized and defined by differences in responsiveness to sympathomimetics and blocking drugs. β_1-Adrenoreceptors effect cardiac stimulation and lipolysis; β_2-adrenoreceptors subserve adrenergic smooth muscle relaxation (eg, vasodilatation, bronchodilatation and intestinal and uterine relaxation) and glycolysis. Both α-adrenoreceptors are blocked by phenoxybenzamine. α_1-Adrenoreceptors are blocked selectively by prazosin and α_2-receptors by yohimbine and rauwolscine. β-Adrenoreceptors are blocked by propranolol. β-Adrenoreceptors are blocked somewhat selectively by metoprolol and β_2-receptors somewhat selectively by butoxamine. Dopamine excites dopamine receptors that are found in kidney and mesenteric blood vessels and are blocked by haloperidol; this receptor does not appear to be activated by other adrenergic stimulants.

Sympathomimetics

The abbreviated list of functions affected by sympathetic nerves, shown in Table 1, indicates the potential complexity of the pharmacology of the sympathomimetics. It is, in fact, considerably more complex than might be surmised from the table, not only because of the several different receptors with different functions and structure-activity requirements, but also because some sympathomimetics do not even act directly upon these receptors; these act indirectly by releasing norepinephrine from adrenergic nerve terminals. Furthermore, some sympathomimetics can pass through the blood-brain barrier into the central nervous system, where they may elicit a variety of effects. Consequently, it is not possible to describe the actions, uses, adverse effects, etc of a prototype sympathomimetic that will apply to all sympathomimetics. The text below discusses prototypic actions rather than prototypic drugs, in order to explain the varied behavior among the sympathomimetics. The dependent uses, adverse effects and precautions are discussed in relation to the actions, in order that the pharmacodynamic bases of these may be comprehended better.

Peripheral Actions and Uses

Not all sympathomimetics are capable of activating all adrenergic and dopaminergic receptors; even among those which are, there is marked variation in the relative intensities of activation of the several receptor types. Thus dopamine stimulates dopaminergic receptors strongly, β_1-adrenoreceptors moderately, α-adrenoreceptors weakly and β_2-adrenoreceptors negligibly. The predominant sympathetic neurotransmitter, norepinephrine, stimulates α_1- and β_1-adrenoreceptors strongly, α_2-adrenoreceptors moderately, β_2-adrenoreceptors weakly and dopaminergic receptors negligibly. Epinephrine stimulates all of the α_1-, α_2-, β_1- and β_2-adrenoreceptors strongly and dopaminergic receptors negligibly. Obviously, then, the pharmacodynamic profiles of these three natural sympathomimetics differ considerably from one another. Several sympathomimetics act selectively on a single type of receptor.

α-Adrenoreceptor Agonists—α-Agonists cause arteriolar and venous constriction and, hence, have an action to increase blood pressure. This vasopressor action is used to *support blood pressure* in hypotensive states, such as in *orthostatic hypotension, carotid sinus syndrome, shock* and during *spinal anesthesia*. In the treatment of *hypovolemic shock*, the constriction of the capacitance vessels (ie, large veins) increases the venous return to the heart and, hence, the cardiac output, but once the blood volume is repleted, α-agonists may not be necessary. In fact, the use of α-agonists in any kind of shock (except anaphylaxis) is usually counterproductive, because there is already ischemia of certain critical organs like the kidney and bowel, and vasoconstriction exacerbates the ischemia in these two organs and contributes to irreversible damage and life-threatening complications.

The systemic vasoconstrictor effects also are employed in the management of a variety of serious allergic conditions, such as *giant urticaria, serum sickness, drug reactions, angioneurotic edema* and *anaphylaxis*. For these uses, epinephrine is the drug of choice. Also, the vasopressor effects of selective α-agonists (ie, devoid of significant β-activity) are sometimes used to elicit compensatory vagal reflexes, which slow the heart and depress atrioventricular conduction and, hence, terminate *paroxysmal supraventricular (atrial)* or *nodal tachycardia*.

The α-agonists are applied topically to induce local vasoconstriction in the nasopharyngeal, scleroconjunctival and otic blood vessels in *vasomotor rhinitis, acute rhinitis, acute coryza, nasopharyngitis, acute sinusitis, eustachian salpingitis, conjunctivitis, scleritis, hay fever, otitis media, barotitis media*, etc. This use to suppress hyperemia and the related edema is called *decongestion*. Conjunctival and scleral decongestion may relieve irritative *blepharospasm*. α-Agonists that are capable of penetrating the cornea may be used to relieve *uveal congestion*. α-Agonists also are applied topically as *styptics* to arrest superficial hemorrhage. Lastly, they may be *combined with local anesthetics*; vasoconstriction keeps the local anesthetic at the injection site for a longer time.

Topically administered α-agonists are used to stimulate the radial smooth muscle of the iris and, hence, cause *mydriasis* for ophthalmologic examination or to break *posterior synechiae* in uveitis. Their effects on the ciliary body are slight, and they do not cause significant cycloplegia or increase intraocular pressure, even in susceptible persons. However, their mydriatic effects are additive with those of antimuscarinic drugs, with which they are sometimes combined, to produce maximum mydriasis for optimal examination of the eyegrounds. In *open-angle glaucoma*, intraocular vasoconstriction causes an increase in the outflow of aqueous humor and, hence, in the intraocular pressure; they are sometimes used in combination with carbonic anhydrase inhibitors in this use.

β_1-Adrenoreceptor Agonists—The β_1-agonists increase n-

They also induce lipolysis and, thus, increase the concentration of plasma free fatty acids. These effects are achieved, in part, through the activation of adenylyl cyclase and the synthesis of 3′,5′-cyclic adenosine monophosphate (cAMP). In the heart, especially, β_1-agonists also increase calcium influx and storage, in part the result of mediation by cAMP.

Use is made of the cardiostimulatory effects of β_1-agonists. They may be administered by intracardiac injection to restore the *heart beat* in *cardiac arrest* and *heart block with syncopal seizures* (as in Adams-Stokes syndrome) and by intravenous injection to sustain restored rhythm or to prevent a recurrence of arrests; however, β_1-agonists are not the treatment of choice, and physical and electrical measures take precedence. More often, β_1-agonists are used for their positive inotropic actions in the treatment of *acute heart failure* and in *cardiogenic* or other types of *shock*, in which contractility often is diminished. However, they are less than ideal in the treatment of shock, not only because they favor arrhythmias, which are an especial threat in cardiogenic shock, but also because they promote a metabolic acidosis through the lipolytic action.

β_2-Adrenoreceptor Agonists—The β_2-agonists relax smooth muscle and induce hepatic and muscle glycogenolysis, by activating the adenylyl cyclase system and increasing the intracellular levels of cAMP. Thus, they dilate the bronchioles, arterioles in vascular beds which are invested with β_2-receptors (such as in skeletal muscle, splanchnic and coronary but not renal or cutaneous beds) and veins, and they relax the uterus and intestines. The glycogenolytic effects in liver and muscle, respectively, result in hyperglycemia and hyperlactic acidemia. The hyperglycemic actions are sometimes used to treat *insulin overdosage*. At present, there are no "pure" β_2-agonists without some degree of β_1-agonist activity.

Most β_2-agonists are used as bronchodilators in the treatment of *bronchial asthma*, *emphysema*, *bronchitis* and *bronchiectasis*, often in combination with theophylline. They also increase ciliary activity and liquefy tenacious mucus and, so, have a mild expectorant action. These effects are usually beneficial, but they may cause mucus plugs. Tachyphylaxis to the bronchodilator effects sometimes occurs, especially if they are used continuously or in excess of recommended dosage or frequency.

Selective β_2-agonists, when administered by inhalation, may dilate bronchioles with a minimum of hypotensive side effects. However, some degree of cardiostimulation can occur with current drugs. Muscle tremor, by an action on the skeletal muscle spindles, also commonly occurs.

Certain β-agonists may be used as vasodilators in the treatment of peripheral vascular diseases. There are two preconditions for efficacy: (1) the disease process must predominantly have a vasospastic and not obliterative component and (2) the vessels involved must have an effective population of β_2-receptors. Efficacy, thus, is limited essentially to selected cases of *intermittent claudication* and *thrombophlebitis*. Some of the presumed selective β_2-agonists for peripheral vascular disease relax vascular smooth muscle partly by a direct smooth muscle depressant mechanism.

β_2-Agonists may be used to relax the uterus and delay delivery in *premature labor*. Although they do depress the premature contractions for a time, they seldom avoid subsequent premature delivery.

Dopaminergic Agonists—Dopamine is the only marketed sympathomimetic with significant dopaminergic actions in the periphery. In the periphery, dopamine receptors are prominent in the splanchnic and renal vascular beds, where they mediate vasodilatation. Dilatation in these beds is important in the treatment of *shock* and *acute heart failure*, since these beds often are constricted critically in these conditions. Dopamine is used in the management of these disorders.

Combined Agonist Activity—Most sympathomimetics act upon two or more receptor types, and the net effects are the algebraic sum of the α-, β_1- and β_2-activities. In describing the properties of a sympathomimetic, it is necessary to indicate the relative agonist activities in order to understand the overall effects.

Central Nervous System Actions and Uses

The actions of sympathomimetics in the central nervous system are exceedingly complex. Noradrenergic and dopaminergic nerves are disseminated widely throughout the central nervous system, and dopaminergic nerves are crucial to some brain functions. A limited number of epinephrine (adrenaline) nerves also are found in several areas. Not only are there α-, β-adrenergic and dopamine receptors at the synapses; but the actions subserved may be either excitatory or inhibitory at a specific structure, which structure may, in turn, have facilitatory or inhibitory influences on other structures. Furthermore, some sympathomimetics appear to activate serotoninergic and possibly histaminergic receptors in the central nervous system. Also, some centrally acting sympathomimetics appear to act as agonists at some loci and transmitter-releasing agents at other loci. One drug, thus, may display simultaneously a number of activities.

The most prominent central nervous system effects of centrally acting sympathomimetics are various manifestations of stimulation, which may give rise to nervousness, sleeplessness, hyperactivity, irritability and increased respiration. In some users they may induce anxiety and in others a kind of euphoria that gives the user a feeling of accomplishment, expectation and affectations for which some sympathomimetics may be abused widely. They allay the perception but not the reality of fatigue, and users often drive themselves to physical and emotional exhaustion (the "crash"). Large doses can cause hallucinations, and long, continued use may result in paranoia and other dangerous behavior, as well as exhaustion. Some tolerance to the euphoric and certain other central nervous system actions occurs.

The effects to promote wakefulness are used in the treatment of *narcolepsy*. They seldom are used any longer to treat central nervous system depression from overdoses of drugs, although the antagonism of respiratory depression is sometimes dramatic.

The centrally acting sympathomimetics may be beneficial in certain disorders of movement. In *parkinsonism* they often diminish rigidity, relieve oculogyric crises and improve sleep. They also may provide relief in *spasmodic torticollis*. They also have a beneficial effect on mood in depressive states, but they have been superseded by other drugs. In the *attention deficit hyperkinetic disorder* (ADHD) they have a paradoxical calming effect, but this use is controversial because of perceptions of overuse.

A very widely used and greatly abused effect is that of the *suppression of appetite* (anorexiant, anorectic or anorexigenic effect). The drugs may induce temporary weight loss in *exogenous obesity*. However, the weight loss is usually the least in those who need it most and seldom exceeds 10 lb, the effectiveness usually lasts but a few weeks (ie, tolerance develops) and there is danger of abuse; abuse potential varies among the sundry anorexiant drugs. At best, anorexiant drugs should be used only in a training program to condition the patient to new eating habits. Even so, the patient usually resumes hyperphagic behavior eventually and may even show a rebound-like gain in weight.

Centrally acting sympathomimetics may exert autonomic actions by acting both in the periphery and upon the various autonomic nervous centers in the brain. Stimulants used for their pressor effects usually act in the periphery, but central sympathoadrenal stimulation may augment such effects and may be an important factor in the cardiovascular effects of intoxication. Some centrally acting sympathomimetics are used to *support blood pressure* in the *carotid sinus syndrome* or *orthostatic hypotension*; the oral efficacy and convenient duration of action offer advantages that partially offset disadv
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