Cardiovascular Pharmacology

Third Edition

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Editor

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To my parents, Frances and Mario Antonaccio,
My wife, Patty, and son, Nick,
For their love and support through the years

Preface

The evolution of cardiovascular medicine has been dramatic and rapid during the time span of the three editions of *Cardiovascular Pharmacology*. The fundamentals of this science have remained secure and the first chapter by Thomas Baum remains untouched—a fitting memorial to a superb pharmacologist, an inspiring teacher, and a close friend taken too soon from all of us.

The third edition contains several new chapters on new subjects or updated chapters on still important areas of research. New chapters include those on antihypertensive agents interacting with the sympathetic nervous system, vascular smooth muscle and vasodilators, modulation of neuroeffector transmission, and the pathophysiology and therapy of hyperlipidemia. Expanded and updated chapters deal with calcium antagonists, the renin-angiotensin system, ischemic heart disease, congestive heart failure, antiarrhythmic drugs, and thrombosis and antithrombotic agents.

The spirit of this book remains the same. It is a convenient single source of the elements of cardiovascular pharmacology, the important new research in this area, and the drugs that are contained within it. Although each chapter is an entity unto itself, there is also an interrelationship among them that weaves throughout the text and binds the chapters into a whole. The extensive use of figures and tables provides a concise summary of the information presented and will be particularly useful to teachers and students.

This book will be a useful adjunct in teaching cardiovascular pharmacology as well as serve as a source of information to professionals in pharmacology and other related areas of medicine.

Michael J. Antonaccio

Preface to Second Edition

The first edition of *Cardiovascular Pharmacology* sought to fill a need for a single text containing the basic elements of cardiovascular pharmacology useful to both graduate students and experienced investigators. The success of the first edition clearly demonstrated the existence of such a need, and the second edition is intended to build and expand upon the original publication.

Most of the original chapters have been retained and brought up to date. Others have been divided where appropriate so that topics that have grown in importance could be adequately covered. For instance, there are now entire chapters devoted to the topics of hypertensive vascular pathophysiology, antihypertensives, calcium antagonists, and the control of renin release. Recent findings in presynaptic modulation of neurotransmitter release are considered important enough to be treated independently. In 1977, this area of research was in its infancy.

This volume, like the first edition, will be of interest to both new and established investigators in cardiovascular pharmacology who wish to broaden their general knowledge, as well as to practicing and teaching clinicians.

Michael J. Antonaccio

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Contents

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Fundamental Principles Governing Regulation of Circulatory Function

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Editor's note. This chapter has been left intact from previous volumes. The primary reason for this is that the chapter still contains all the appropriate information necessary to provide the background required for a sound understanding of the more detailed chapters that follow. It is fitting that this chapter has remained as timely now as it was several years ago because it demonstrates sound thinking and vision on Dr. Baum's part. It gives me great sadness to inform you that Tom died suddenly and unexpectedly in 1983, but it is with tribute to and fond personal memories of him that his chapter remains as it was when he was living.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system plays a central role in the regulation of cardiovascular function. Although the system is not essential to life, it does enable organs to respond rapidly and efficiently to changing requirements. In its absence, overall adaptation to stressful situations may be severely compromised, although function at rest may remain within normal limits.

The system consists of two major divisions: the parasympathetic and the sympathetic (1,2). Autonomic outflow originates from "centers" (i.e., nuclei or more diffusely arranged groups of cells) in the midbrain and hypothalamus. These regions are closely interrelated and are further subject to excitatory and inhibitory input from afferents and from higher brain structures and the cerebellum. Preganglionic fibers emerge from the brainstem or cord and synapse or relay in ganglia (Fig. 1). These structures contain cell bodies of postganglionic fibers that innervate target organs. Activation of autonomic fibers results in the release of chemical substances (transmitters, mediators) from their terminals. The transmitter binds to a sensitive region (receptor) on the membrane of the target cell and initiates a complex series of events resulting in a response. Many organs (e.g., the viscera) are innervated by both divisions of the autonomic nervous system, which may exert opposing actions either directly or by modifying mediator release from opposing fibers. Other structures, such as most blood vessels, are predominantly supplied by fibers from only the sympathetic system. Some cells receive both sympathetic and parasympathetic innervation (e.g., in the sinoatrial node). Other organs, such as the iris, are also innervated by both systems, but sympathetic fibers supply the radial muscle and parasympathetic fibers the circular muscle. During the resting state, individual autonomic nerves may be quiescent or may fire at a relatively low rate. Activity of an organ may be initiated or enhanced by increasing the "tone" (i.e., firing rate) of the excita-

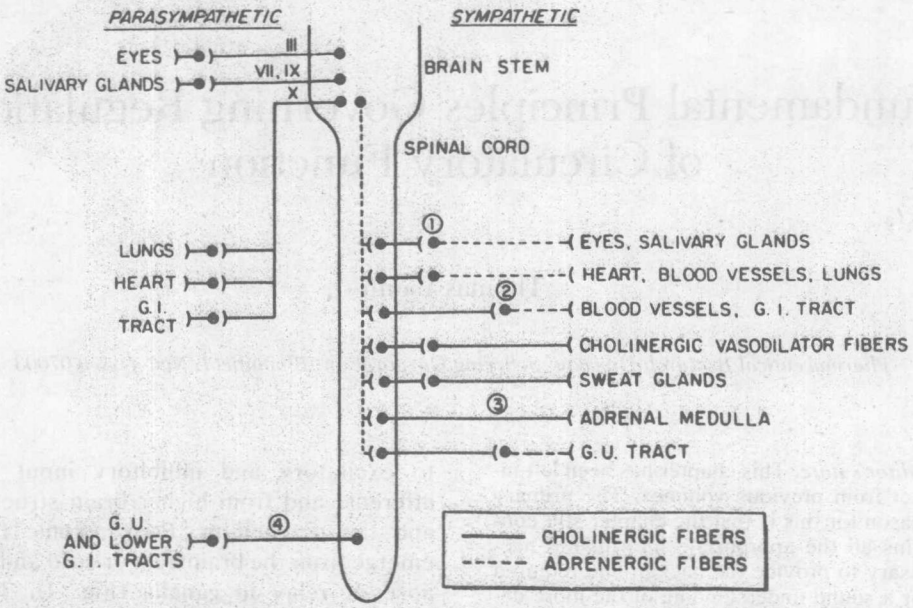

FIG. 1. Schematic representation of autonomic outflow. Various outflow patterns are illustrated in a highly schematic form. Roman numerals refer to cranial nerves. (1) Synapses in ganglia of the paravertebral sympathetic chain. (2) Synapses in more distal ganglia (e.g., celiac, superior and inferior mesenteric). (3) Preganglionic fibers in the splanchnic nerve. (4) Sacral parasympathetic outflow.

tory system and/or by reducing the activity of the inhibitory system. Cell bodies of afferent fibers lie in dorsal root ganglia or in the sensory ganglia of cranial nerves.

Parasympathetic Nervous System

Preganglionic fibers arise from the midbrain, medulla oblongata, and the sacral portion of the spinal cord (Fig. 1) (1). The third, seventh, ninth, and tenth cranial nerves contain fibers emanating from the brainstem. The sacral outflow forms the pelvic nerve and innervates the bladder, sexual organs, and terminal portions of the intestinal tract. Preganglionic parasympathetic fibers synapse in ganglia located in proximity to the target innervated. Consequently, postganglionic nerves are relatively short. On activation, both preganglionic and postganglionic fibers release acetylcholine (ACh) from their terminals.

Choline is transported into nerve terminals by an active process (2). Choline acetyltransferase catalyzes its synthesis into ACh, which is then stored in discrete vesicles within nerve endings. The enzyme is synthesized in the perikaryon and transported along the axon to the terminal by the microtubules. Small quantities of ACh ar continuously released. Nerve activation re sults in dramatic changes in the permeabil ity characteristics of the neuronal membrane, with consequent influx of ions (predominantly sodium and calcium) and depolarization (3). These events cause the migration of ACh-containing vesicles toward and fusion with the neurolemma, and extrusion of their contents (exocytosis). The released ACh combines with its receptors on target cells (*vide infra*). Acetylcholine esterase rapidly degrades free ACh. The enzyme is located on the postsynaptic membrane and, in some structures, also on the presynaptic side.

The cholinergic transmission process has a high degree of efficiency. Prolonged stimulation does not reduce tissue ACh content. The ACh release process is subject to modulation by numerous factors. It is highly dependent on calcium influx and can be inhibited by agents that depress nerve transmission (tetrodotoxin) or calcium entry. Several substances, including morphine, enkephalins, prostaglandins, botulism toxin, and adenosine triphosphate (ATP), diminish exocytotic release of ACh. Hemicholinium inhibits ACh synthesis by blocking its membrane transport system.

Sympathetic Nervous System

Anatomy

Descending tracts originating primarily from the medulla oblongata but also from the hypothalamus innervate, directly or via interneurons, cell bodies of preganglionic neurons located in the intermediolateral column of the thoracolumbar spinal cord (C-8 to L2–3). Preganglionic myelinated fibers emerge via the anterior roots and white rami and synapse in the paravertebral sympathetic chain or traverse the chain and relay in more peripheral ganglia (1,2). The former consists of 22 pairs of ganglia lying parallel to the vertebral column and extending from the superior cervical ganglion to the lumbar region. Individual segments carry descending and ascending efferent and afferent fibers. Gray rami convey postganglionic fibers from the chain to spinal nerves. Preganglionic fibers not synapsing in the paravertebral chain usually do so in more peripheral ganglia in the abdomen (i.e., celiac, superior and inferior mesenteric, and aorticorenal). Some fibers may synapse in even more distal ganglia lying in proximity to the organs innervated (e.g., genitourinary tract, rectum). Fibers to the adrenal medulla do not synapse on route. Most sympathetic postganglionic fibers release norepinephrine (NE, noradrenaline) at their endings and consequently are considered "adrenergic" or "noradrenergic" (4–7). These fibers form an extensive terminal plexus in the organ innervated. Varicosities appear periodically along the terminal network. Some sympathetic fibers liberate ACh (e.g., fibers to sweat glands and vasodilator fibers to skeletal muscle). Sympathetic cholinergic vasodilator pathways originate in the cortex and hypothalamus.

Adrenergic Synthesis, Storage, and Release Mechanisms

NE synthesis, storage, and release occur in the varicosities of the terminal fibers (2,5). These structures contain mitochondria as well as catecholamine-containing vesicles (Fig. 2). The vesicles are formed within the cell body and are transported peripherally.

Hydroxylation of tyrosine to form 3,4-dihydroxyphenylalanine (DOPA) initiates the enzymatic synthesis of NE and occurs in the axoplasm of the varicosity (2,5–9). The reaction is catalyzed by tyrosine hydroxylase utilizing a pteridine cofactor and constitutes the rate-limiting step. DOPA is decarboxylated to form dopamine, which is then transported into the vesicle, where β-hydroxylation to form NE occurs. Dopamine β-hydroxylase (DBH), a copper-containing enzyme, catalyzes the latter step. NE is stored within vesicles partially as a complex with ATP and the protein chromogranin, as well as in a more loosely bound form in both the vesicle and cytoplasm. Turnover studies have demonstrated that newly synthesized NE is incorporated into a more mobile pool and is preferentially released by nerve stimulation.

Uptake of catecholamines into vesicles is an active transport process requiring ATP and magnesium (10). NE can be highly concentrated within these structures and thereby protected from degradative enzymes. Several substances, including reser-

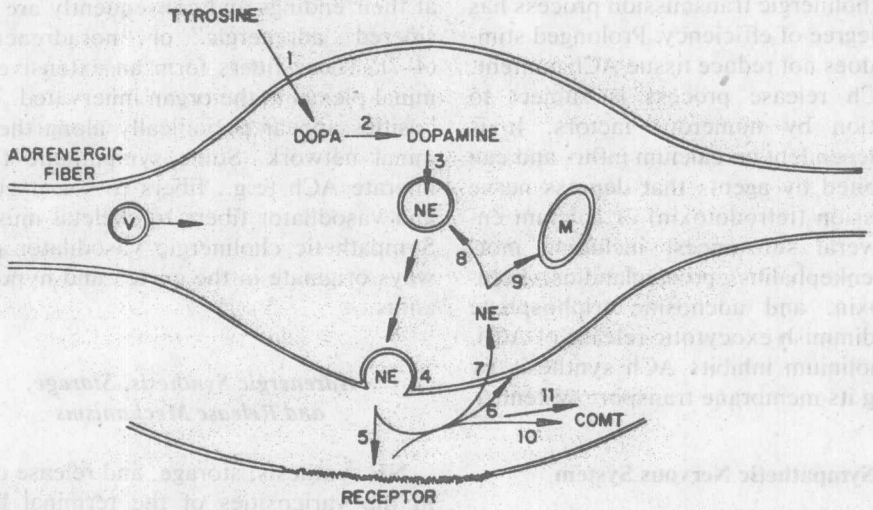

FIG. 2. Schematic representation of the adrenergic transmission process. The diagram illustrates a varicosity in a terminal sympathetic fiber and the effector cell. Tyrosine is transported across the axoplasmic membrane into the cytoplasm and hydroxylated to form DOPA by tyrosine hydroxylase (1). DOPA is then decarboxylated by DOPA decarboxylase to form dopamine (2). The latter is transported into the vesicles (V), where it is hydroxylated to form NE by dopamine β-hydroxylase (3). Vesicles are synthesized within the cell body and transported peripherally. NE is stored in vesicles partly in association with ATP and the protein chromogranin. An action potential results in the extrusion of the contents of the varicosity into the synaptic cleft (4). The released NE may then activate α- or β-adrenergic receptors on the effector cell (5). It also participates in a negative-feedback loop by activating α receptors on the presynaptic membrane, resulting in inhibition of the release process (6). NE is also returned to the fiber by the uptake-1 process (7). Free intracellular NE may then be transported into vesicles (8) or metabolized by mitochondria (M, 9). NE in the synaptic cleft is susceptible to metabolism by catecholamine-*o*-methyltransferase (COMT, 10), or it may diffuse away from the synaptic region (11).

pine, tetrabenazine, and prenylamine, inhibit the uptake mechanism into vesicles and consequently prevent storage of NE.

Conducted action potentials induce influx of sodium and calcium into adrenergic nerve endings. As in cholinergic terminals, calcium promotes the migration of vesicles toward the neurolemma, fusion of the vesicular membrane with the neurolemma, and extrusion of the vesicular contents (NE, ATP, DBH, and chromogranin) into the extracellular space (2,7). Autonomic fibers can release more than one type of transmitter (e.g., an amine and a peptide) (11).

Released NE can exert a negative feedback on its own liberation (7,12,13). Receptors (α_2) (*vide infra*) on the presynaptic membrane mediate this inhibition (Fig. 2). The process is probably physiologically relevant at low rates of sympathetic firing. However, contradictory views have been offered (14). A β-receptor-mediated facilitatory mechanism also exists on the presynaptic membrane (7,12). Its physiologic role remains uncertain, but it may be activated by circulating epinephrine. Angiotension II (AII) can also facilitate NE release (7,15). Several other substances, including ACh, dopamine, prostaglandins of the E series, 5-hydroxytryptamine (serotonin, 5HT), adenosine, and opiate peptides, attenuate NE release. Their contribution to the regulation of adrenergic transmission is even more speculative. In the heart, however, vagally released ACh can inhibit responses to sym-

pathetic stimulation, probably by a presynaptic mechanism (6,7), as well as by physiologic postsynaptic antagonism.

In contrast to the situation with action-potential-induced NE liberation, tyramine and similar substances release NE most probably by displacement from the cytoplasmic pool rather than by exocytosis (2,5). These agents do not simultaneously liberate DBH, ATP, and chromogranin along with NE. Further, the process does not depend on availability of extracellular calcium.

The adrenergic transmission mechanism is remarkably efficient. Prolonged physiologic or electrical activation of sympathetic nerves does not reduce tissue NE levels (9). Enhanced turnover, in conjunction with a highly effective reuptake process of released transmitter and accelerated synthesis, maintains tissue concentrations. Tyrosine hydroxylase is subject to feedback inhibition by free NE in the cytoplasm (9). Nerve activation accelerates synthesis partially by attenuating this feedback. More prolonged periods of enhanced sympathetic activity result in the synthesis of additional quantities of enzymes (9,17,18).

A major factor contributing to the overall efficiency of sympathetic transmission is a mechanism for the reuptake of released mediator. An active process in the axoplasmic membrane termed "uptake-1" transports NE from the extracellular space back into the nerve terminal (10). The carrier requires energy, is linked to Na-K ATPase, and exhibits stereospecificity. However, other phenolic phenethylamines in addition to NE (e.g., metaraminol, α-methyl NE, α-methylepinephrine, tyramine, and octopamine) are also transported across the nerve membrane, although at slower rates. Several classes of compounds inhibit uptake-1. These include phenethylamines lacking a phenolic hydroxyl group (e.g., amphetamine), as well as structurally diverse substances such as ouabain, cocaine, imipramine, and guanethidine. Inhibitors of the axoplasmic transport system also attenuate the actions of agents capable of gaining access to the interior of the nerve ending and subsequently causing the release of NE (i.e., indirectly acting sympathomimetic amines such as tyramine). 6-Hydroxydopamine is also a substrate for the membrane pump. After uptake, it causes the destruction of the adrenergic fiber.

In contrast to the normal state, continuous sympathetic activation rapidly leads to depletion of tissue stores of NE after blockade of the membrane pump. On the other hand, pump inactivation can lead to potentiation and prolongation of effects of sympathetic nerve stimulation and injected NE.

NE can also be taken up into extraneuronal sites in smooth muscle, heart, glandular tissue, and other organs ("uptake-2") (10). The capacity of this mechanism to store NE exceeds that of uptake-1; however, its affinity for NE and epinephrine is more limited. Consequently, uptake-1 predominates at relatively lower concentrations. Amines taken up by the second process are rapidly metabolized. Uptake-2 can be blocked by drugs such as phenoxybenzamine and metanephrine.

Several drugs inhibit action-potential-evoked release of NE. Both guanethidine and bretylium rapidly attenuate NE release, but probably by different mechanisms (19). In addition, guanethidine produces a long-lasting depletion of tissue stores of NE, probably by blocking both the axoplasmic and vesicular uptake mechanisms. The initial short-latency inhibitory action of guanethidine can be rapidly reversed by administration of substances that have an affinity for uptake-1, such as amphetamine (20). Displacement of guanethidine from its inhibitory site probably accounts for restoration of the transmission process. The efficacy of these release inhibitors varies with the frequency of nerve activation.

Certain substances can affect the transmission process by acting as "false transmitters." For example, α-methyldopa is incorporated into storage vesicles after

transformation into α-methylnorepinephrine, which in turn is released by physiologic impulses (19). Octopamine, formed by β-hydroxylation of tyramine, and, indeed, guanethidine, can be released in a similar fashion. The end-organ response to the false transmitter may be subnormal and may lead to reduced responsiveness, as in the case of octopamine.

Reduction or depletion of tissue stores of NE can alter organ responses to sympathetic nerve activation. Reserpine diminishes the NE content of nerve endings by inhibiting the vesicular membrane pump (10). NE not sequestered into vesicles is exposed to the action of degradative enzymes. However, total tissue NE content must be greatly reduced in order to depress transmission. For example, organ responses to nerve stimulation recover much more rapidly after reserpine than do tissue stores of NE.

As discussed earlier, reuptake of released NE is the major process for terminating the response to sympathetic nerve activation. NE is metabolized by two major pathways (7). Extracellular NE is subject to *o*-methylation by catechol-*o*-methyltransferase. Monoamine oxidase also deactivates NE rapidly; the enzyme resides primarily within mitochondria in nerve terminals and participates in the control of levels of free NE within nerve endings. NE may also diffuse from the synaptic site into the circulation.

Autonomic Ganglia

Activation of preganglionic fibers initiates a complex series of events in postganglionic neurons. An initial fast negative potential (excitatory postsynaptic potential, EPSP), a positive potential (inhibitory postsynaptic potential, IPSP), a late negative potential, and a late-late negative potential can be recorded from autonomic ganglia (21–23). ACh, the primary excitatory transmitter in ganglia, induces the initial fast EPSP and the late EPSP by activating nicotinic and muscarinic receptors, respectively (*vide infra*). The nature of the IPSP remains uncertain; it may be generated either monosynaptically by ACh or by ACh-induced release of dopamine or NE from interneurons (22,23). Exogenous dopamine and NE can hyperpolarize postganglionic membranes under appropriate circumstances. Preganglionic stimulation can elevate cyclic adenosine 3′,5′-monophosphate (cAMP) levels in ganglia. The late-late EPSP may be mediated by a peptide (22).

Adrenal Medulla

Synthetic processes in the adrenal medulla follow the scheme outlined earlier for catecholamines. Final methylation of NE to epinephrine by phenylethanolamine-*N*-methyltransferase occurs in the cytoplasm. Activation of preganglionic nerves results in the liberation of ACh, depolarization of the chromaffin cells, calcium influx, and release of the contents of the storage granules: catecholamines (primarily epinephrine), ATP, chromogranin, and enkephalins (24). Although epinephrine can markedly influence many organ systems, the precise physiologic role of the adrenal medulla remains obscure.

Receptors

Biologically active substances (transmitters, hormones, some drugs) interact with specific proteins called "receptors," resulting in various biophysical, biochemical, and ultimately physiologic consequences (25–27). Three general classes of receptors have been identified: (a) receptors located on the external surface of the plasma membrane in nerves, muscle, and glands activated by amines and peptides; chemically, these are glycoproteins associated with lip-

ids; (b) receptors for steroids that are located intracellularly in the soluble compartment; (c) receptors located within the cell nucleus (e.g., for thyroid hormone). In some instances, the agonist-receptor complex (e.g., peptides, insulin, growth hormone, prolactin, as well as low-density lipoproteins) can be internalized by endocytosis to form a vesicle within the cell (25–28).

Ligands interact with receptors by highly specific binding processes resulting in changes in the conformation or charge distribution of the receptor or neighboring region. These, in turn, result in changes in membrane permeability, alteration of the conformation of enzymes, or alteration of their associated regulatory subunits. Quantitatively, binding of agonists to membrane receptors depends on the number of receptors present and their affinity state. Binding of several classes of agonists (β-adrenergic, opiate) is markedly attenuated by guanosine triphosphate (GTP) and by sodium. GTP converts these receptors from high-affinity states to low-affinity states. In contrast, GTP does not alter binding of antagonists.

Physiologic responses vary with the number of receptors occupied. However, activation of a relatively small proportion of membrane receptors usually results in maximal physiologic responses.

The number and affinity of receptors are subject to negative feedback, leading to desensitization (down-regulation) or supersensitivity (up-regulation). Down-regulation may involve reduced synthesis of receptors. Not all agonist-receptor interactions are subject to down-regulation (e.g., aldosterone release by AII). Binding can alter the conformation of receptors in such a manner that the affinity of remaining receptors decreases (negative cooperativity). Large numbers of receptor systems utilizing amines, peptides, and steroids as agonists have been identified. These include receptors for NE, epinephrine, dopamine, ACh, 5HT, histamine, adenosine, AII, vasopressin, oxytocin, γ-aminobutyric acid, enkephalins, substance P, glycine, glutamate, etc. (25–30).

Antagonists can inhibit the actions of agonists by combining with agonist binding sites on the receptor or by binding to adjacent (allosteric) sites. Competitive blockade is surmountable, and the usual organ responses are obtained if the concentration of the agonist is increased; i.e., the dose–response curve is shifted to the right, but the maximum obtainable response remains unaltered. Noncompetitive blockade involves covalent binding to receptors. Maximum responses are depressed, and restoration of activity requires synthesis of new receptors.

Cholinergic Receptors

Acetylcholine is an agonist for two major types of receptors. These were originally classified as "muscarinic" or "nicotinic" on the basis of their similarities to responses to the alkaloid muscarine and nicotine. Cholinergic receptors in skeletal muscle and most of those on the cell bodies of postganglionic neurons and on nonmyelinated C fibers respond to nicotine and are considered "nicotinic." In contrast, receptors innervated by postganglionic cholinergic fibers, such as in smooth muscle and glands, are termed "muscarinic" (Table 1). Nicotinic receptors in ganglia and skeletal muscle are inhibited by competitive blockers such as hexamethonium and *d*-tubocurarine, respectively. Atropine exemplifies a blocker of muscarinic receptors (Table 2).

Activation of cholinergic receptors results in changes in cell membranes ultimately leading to various responses such as hyperpolarization of cells in the sinoatrial node or depolarization of ganglia (as indicated earlier) and intestinal smooth muscle. Biochemically, muscarinic receptors (e.g., in the heart) may be negatively coupled to