choline acetyltransferase. After its release from the nerve ending, acetylcholine acts briefly (milliseconds), then is rapidly metabolized by acetylcholinesterase (an enzyme present in the nerve ending and on the surface of the receptor organ). Acetylcholinesterase splits the active acetylcholine into inactive acetate and choline; the choline is taken up again by the presynaptic nerve terminal and reused. Acetylcholine exerts excitatory effects at nerve synapses and nerve–muscle junctions and inhibitory effects at some peripheral sites such as the heart.

Cholinergic Receptors

When acetylcholine acts on body cells that respond to parasympathetic nerve stimulation, it interacts with two types of cholinergic receptors: nicotinic and muscarinic. Nicotinic receptors are located in motor nerves and skeletal muscle. When they are activated by acetylcholine, the cell membrane depolarizes and produces muscle contraction. Muscarinic receptors are located in most internal organs, including the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. When muscarinic receptors are activated by acetylcholine, the affected cells may be excited or inhibited in their functions. These receptors have been further subdivided, with two types of nicotinic and five types of muscarinic receptors identified.

Although the subtypes of cholinergic receptors have not been as well characterized as those of the adrenergic receptors, the intracellular events (of signal transduction) after stimulation are thought to include the following mechanisms:

- *Muscarinic$_1$ receptors:* Activation of these receptors results in a series of processes during which phospholipids in the cell membrane and inside the cell are broken down. One of the products of phospholipid metabolism is inositol phosphate. The inositol phosphate acts as a second messenger to increase the intracellular concentration of calcium. Calcium also acts as a second messenger and functions to activate several intracellular enzymes, initiate contraction of smooth muscle cells, and increase secretions of exocrine glands.
- *Muscarinic$_2$ receptors:* Activation of these receptors results in inhibition of adenyl cyclase in the heart, smooth muscle, and brain. As a result, less cAMP is formed to act as a second messenger and stimulate intracellular activity. Receptor stimulation also results in activation of potassium channels in cell membranes of the heart. The overall consequence of M_2 activation is inhibition of affected cells.
- *Muscarinic$_3$ receptors:* Activation apparently causes the same cascade of intracellular processes as with activation of the M_1 receptors. In addition, nitrous oxide is generated from vascular endothelial cells, resulting in dilation of vessels.
- *Muscarinic$_4$ Receptors:* Activation results in a molecular response similar to M_2 receptor activation. Their location and function have not yet been delineated.
- *Muscarinic$_5$ receptors:* Receptor activation results in a molecular response similar to M_1 receptor activation. The receptor has been identified in central nervous system tissues; however, its function has not been delineated.
- *Nicotinic$_n$ receptors:* These receptors are located on autonomic ganglia and the adrenal medulla. Activation results in enhanced transmission of nerve impulses at all parasympathetic and sympathetic ganglia, and release of epinephrine from the adrenal medullae.
- *Nicotinic$_m$ receptors:* These are located at neuromuscular junctions in skeletal muscle. Their activation causes muscle contraction.
- *Nicotinic$_{CNS}$ receptors:* These receptors are located on presynaptic nerve fibers in the brain and spinal cord. Their activation promotes the release of acetylcholine in the cerebral cortex.

CHARACTERISTICS OF AUTONOMIC DRUGS

Many drugs are used clinically because of their ability to stimulate or block activity of the SNS or PNS. Drugs that stimulate activity act like endogenous neurotransmitter substances; drugs that block activity prevent the action of both endogenous substances and stimulating drugs.

Drugs that act on the ANS usually affect the entire body rather than certain organs and tissues. Drug effects depend on which branch of the ANS is involved and whether it is stimulated or inhibited by drug therapy. Thus, knowledge of the physiology of the ANS is required if drug effects are to be understood and predicted. In addition, it is becoming increasingly important to understand receptor activity and the consequences of stimulation or inhibition. More drugs are being developed to stimulate or inhibit particular subtypes of receptors. This is part of the continuing effort to design drugs that act more selectively on particular body tissues and decrease adverse effects on other body tissues. For example, drugs such as terbutaline have been developed to stimulate beta$_2$ receptors in the respiratory tract and produce bronchodilation (a desired effect) with decreased stimulation of beta$_1$ receptors in the heart (an adverse effect).

The terminology used to describe autonomic drugs is often confusing because different terms are used to refer to the same phenomenon. Thus, *sympathomimetic*, *adrenergic*, and *alpha-* and *beta-adrenergic agonists* are used to describe a drug that has the same effects on the human body as stimulation of the SNS. *Parasympathomimetic*, *cholinomimetic*, and *cholinergic* are used to describe a drug that has the same effects on the body as stimulation of the PNS. There are also drugs that oppose or block stimulation of these systems. *Sympatholytic*, *antiadrenergic*, and *alpha-* and *beta-adrenergic blocking drugs* inhibit sympathetic stimulation. *Parasympatholytic*, *anticholinergic*, and *cholinergic blocking drugs* inhibit parasympathetic stimulation. This book uses the terms *adrenergic*, *antiadrenergic*, *cholinergic*, and *anticholinergic* when describing medications.