Acetylcholine stimulates cholinergic receptors in the gut to promote normal secretory and motor activity. Cholinergic stimulation results in increased peristalsis and relaxation of the smooth muscle in sphincters to facilitate movement of flatus and feces. The secretory functions of the salivary and gastric glands are also stimulated.

Acetylcholine stimulates cholinergic receptors in the urinary system to promote normal urination. Cholinergic stimulation results in contraction of the detrusor muscle and relaxation of the urinary sphincter to facilitate emptying the urinary bladder.

Mechanisms of Action and Effects

Direct-acting cholinergic drugs are synthetic derivatives of choline. Most direct-acting cholinergic drugs are quaternary amines, carry a positive charge, and are lipid insoluble. They do not readily enter the central nervous system; thus, their effects occur primarily in the periphery. These drugs can exert their therapeutic effects because they are highly resistant to metabolism by acetylcholinesterase, the enzyme that normally metabolizes acetylcholine. Their action is longer than that of acetylcholine. They have widespread systemic effects when they combine with muscarinic receptors in cardiac muscle, smooth muscle, exocrine glands, and the eye (Fig. 20–1). Specific effects include:

1. Decreased heart rate, vasodilation, and unpredictable changes in blood pressure
2. Increased tone and contractility in gastrointestinal (GI) smooth muscle, relaxation of sphincters, increased salivary gland and GI secretions
3. Increased tone and contractility of smooth muscle (detrusor) in the urinary bladder and relaxation of the sphincter
4. Increased tone and contractility of bronchial smooth muscle
5. Increased respiratory secretions
6. Constriction of pupils (miosis) and contraction of ciliary muscle, resulting in accommodation for near vision

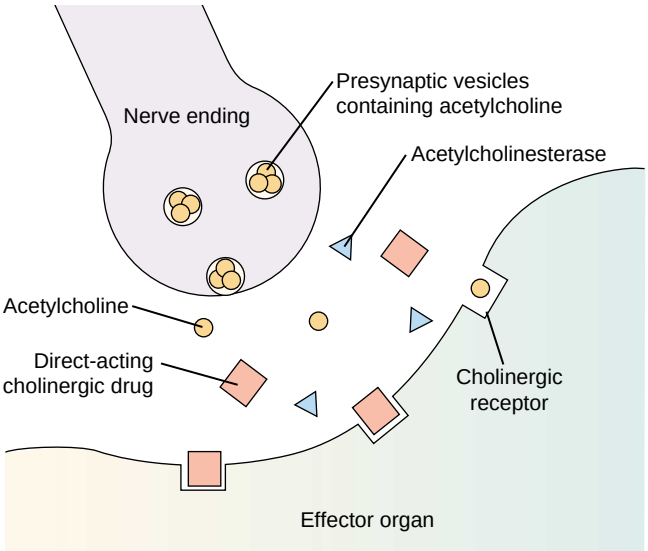

Figure 20–1 Mechanism of direct cholinergic drug action. Direct-acting cholinergic drugs interact with postsynaptic cholinergic receptors on target effector organs, activating the organ in a similar fashion as the neurotransmitter acetylcholine.

Indirect-acting cholinergic or *anticholinesterase drugs* decrease the inactivation of acetylcholine in the synapse by the enzyme acetylcholinesterase. Acetylcholine can then accumulate in the synapse and enhance the activation of postsynaptic muscarinic and nicotinic receptors (Fig. 20–2). This improves cholinergic neurotransmission in the brain and the force of muscle contraction in peripheral tissues.

Anticholinesterase drugs are classified as either reversible or irreversible inhibitors of acetylcholinesterase. The reversible inhibitors exhibit a moderate duration of action and have several therapeutic uses, as described later. The irreversible inhibitors produce prolonged effects and are highly toxic. These agents are used primarily as poisons (ie, insecticides and nerve gases). Their only therapeutic use is in the treatment of glaucoma (see Chap. 65).

Indications for Use

Cholinergic drugs have limited but varied uses. A direct-acting drug, bethanechol, is used to treat urinary retention due to urinary bladder atony and postoperative abdominal distention due to paralytic ileus. The anticholinesterase agents are used in the diagnosis and treatment of myasthenia gravis and to reverse the action of nondepolarizing neuromuscular blocking agents (eg, tubocurarine and related drugs) used in surgery (see Chap. 14). The drugs do not reverse the neuromuscular blockade produced by depolarizing agents, such as succinylcholine. In addition, tacrine, donepezil, and rivastigmine are anticholinesterase agents approved for treatment of Alzheimer's disease. Cholinergic drugs may also be used to treat glaucoma (see Chap. 65).

Contraindications to Use

These drugs are contraindicated in urinary or GI tract obstruction, asthma, peptic ulcer disease, coronary artery disease, hyperthyroidism, pregnancy, and inflammatory abdominal conditions. Tacrine is also contraindicated in previous users in whom jaundice or a serum bilirubin level above 3 mg/dL developed.

INDIVIDUAL CHOLINERGIC DRUGS

These drugs are described in the following sections. Trade names, clinical indications, and dosage ranges are listed in Drugs at a Glance: Selected Cholinergic Drugs.