there are muscarinic receptors. (3) Among the sympathetic adrenoreceptors, receptor type is related to function. The α receptors and α_1 receptors cause contraction of smooth muscle such as vascular smooth muscle, gastrointestinal and bladder sphincters, pilomotor muscles, and the radial muscle of the iris. The β_1 receptors are involved in metabolic functions such as gluconeogenesis, lipolysis, renin secretion, and in all functions in the heart. The β_2 receptors cause relaxation of smooth muscle in bronchioles, wall of the bladder, and wall of the gastrointestinal tract.

HYPOTHALAMIC AND BRAIN STEM CENTERS

Centers in the hypothalamus and brain stem coordinate the autonomic regulation of organ system functions. Figure 2-5 summarizes the locations of these centers, which are responsible for temperature regulation, thirst, food intake (satiety), micturition, breathing, and cardiovascular (vasomotor) function. For example, the vasomotor center receives information about blood pressure from baroreceptors in the carotid sinus and compares this information to a blood pressure set point. If corrections are necessary, the vasomotor center orchestrates changes in output of both the sympathetic and the parasympathetic innervation of the heart and blood vessels to bring about the necessary change in blood pressure. These higher autonomic centers are discussed throughout this book in the context of each organ system.

Autonomic Receptors

As noted in the preceding discussion, autonomic receptors are present at the neuromuscular junction, on the cell bodies of postganglionic neurons, and in the effector organs. The type of receptor and its mechanism of action determine the nature of the physiologic response. Furthermore, the physiologic responses are tissue-specific and cell type–specific.

To illustrate this specificity, compare the effect of activating adrenergic β_1 receptors in the SA node to the effect of activating β_1 receptors in ventricular muscle. Both the SA node and the ventricular muscle are located in the heart, and their adrenergic receptors and

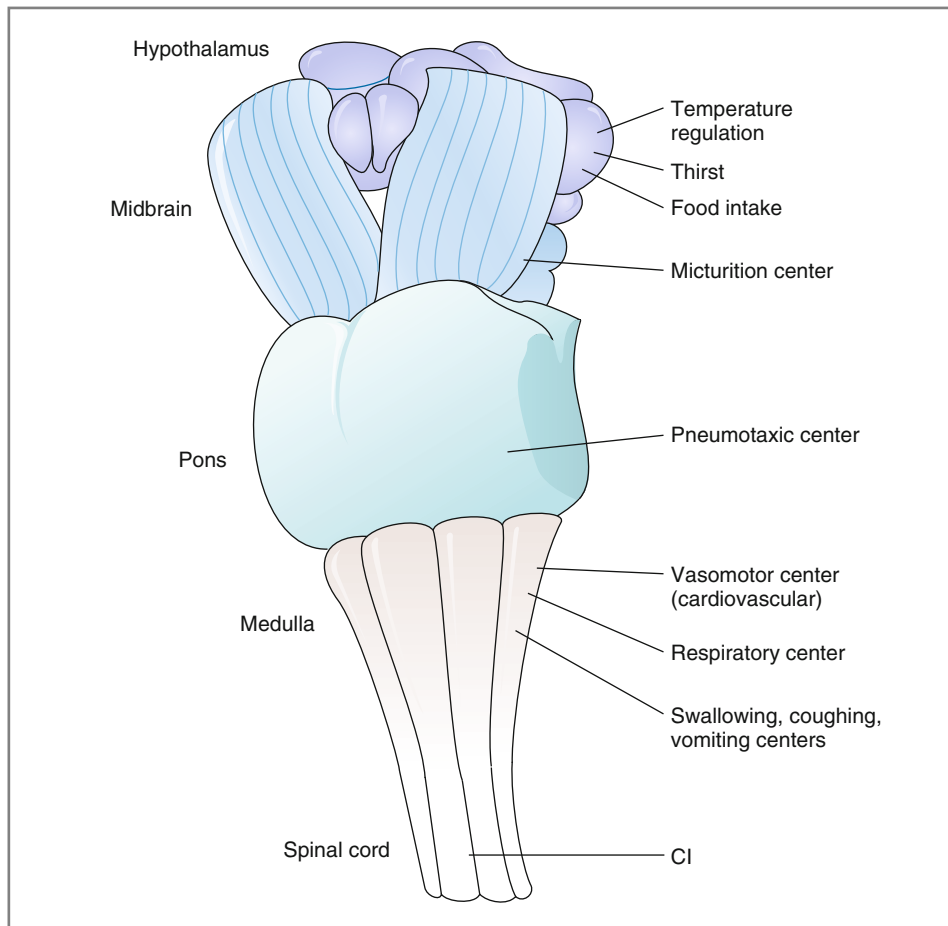**Figure 2-5** **Autonomic centers in the hypothalamus and brain stem.** CI, First cervical spinal cord segment.

mechanisms of action are the same. The resulting physiologic actions, however, are entirely different. The **β$_1$ receptor in the SA node** is coupled to mechanisms that increase the spontaneous rate of depolarization and increase heart rate; binding of an agonist such as norepinephrine to *this* β$_1$ receptor increases the heart rate. The **β$_1$ receptor in ventricular muscle** is coupled to mechanisms that increase intracellular Ca^{2+} concentration and contractility; binding of an agonist such as norepinephrine to *this* β$_1$ receptor increases contractility, but it has no direct effect on the heart rate.

The type of receptor also predicts which pharmacologic agonists or antagonists will activate it or block it. The effects of such drugs can be readily predicted by understanding the *normal* physiologic responses. For example, drugs that are β$_1$ agonists are expected to cause increased heart rate and increased contractility, and drugs that are β$_1$ antagonists are expected to cause decreased heart rate and decreased contractility.

Table 2-4 summarizes the adrenergic and cholinergic receptors, their target tissues, and their mechanisms of action. Table 2-2, its companion, is arranged similarly by receptor type and lists the prototypical drugs that either activate (**agonists**) or block (**antagonists**) the receptors. Together, the two tables should be used as a reference for the following discussion about mechanisms of action. These mechanisms involving guanosine triphosphate (GTP)-binding proteins (G proteins),

adenylyl cyclase, and inositol 1,4,5-triphosphate (IP$_3$) also are discussed in Chapter 9 in the context of hormone action.

G PROTEINS

Autonomic receptors are coupled to GTP-binding proteins (G proteins) and, therefore, are called **G protein–linked receptors**. G protein–linked receptors, including those in the autonomic nervous system, are composed of a single polypeptide chain that winds back and forth across the cell membrane seven times, known as seven-pass transmembrane receptor proteins. The ligand (e.g., ACh, norepinephrine) binds to the extracellular domain of its G protein–linked receptor. The intracellular domain of the receptor binds to (is "linked" to) a G protein.

These G proteins are **heterotrimeric**. In other words, they have three different subunits: α, β, and γ. The α subunit binds either guanosine diphosphate (GDP) or guanosine triphosphate (GTP). When GDP is bound, the α subunit is inactive; when GTP is bound, the α subunit is active. Thus, activity of the G protein resides in its α subunit, and the G protein switches between active and inactive states according to whether it is bound to GDP or GTP. For example, when the G protein releases GDP and binds GTP, it switches from the inactive state to the active state;

Table 2-4 Location and Mechanism of Action of Autonomic Receptors

Receptor	Target Tissue	Mechanism of Action
Adrenoreceptors		
α$_1$	Vascular smooth muscle, skin, renal, and splanchnic Gastrointestinal tract, sphincters Bladder, sphincter Radial muscle, iris	IP$_3$, ↑ intracellular $[Ca^{2+}]$
α$_2$	Gastrointestinal tract, wall Presynaptic adrenergic neurons	Inhibition of adenylyl cyclase, ↓ cAMP
β$_1$	Heart Salivary glands Adipose tissue Kidney	Stimulation of adenylyl cyclase, ↑ cAMP
β$_2$	Vascular smooth muscle of skeletal muscle Gastrointestinal tract, wall Bladder, wall Bronchioles	Stimulation of adenylyl cyclase, ↑ cAMP
Cholinoreceptors		
Nicotinic	Skeletal muscle, motor end plate Postganglionic neurons, SNS and PNS Adrenal medulla	Opening Na^+ and K^+ channels → depolarization
Muscarinic	All effector organs, PNS Sweat glands, SNS	IP$_3$, ↑ intracellular $[Ca^{2+}]$

cAMP, Cyclic adenosine monophosphate; PNS, parasympathetic nervous system; SNS, sympathetic nervous system.

when GTP is converted back to GDP through intrinsic GTPase activity of the G protein, it switches from the active state to the inactive state.

G proteins couple G protein–linked autonomic receptors to enzymes that execute physiologic actions. These enzymes are adenylyl cyclase and phospholipase C, which, when activated, generate a second messenger (cyclic adenosine monophosphate [cAMP] or IP_3, respectively). The second messenger then amplifies the message and executes the final physiologic action. In some cases (e.g., certain muscarinic receptors), the G protein directly alters the function of an ion channel without the mediation of a second messenger.

ADRENORECEPTORS

Adrenoreceptors are found in target tissues of the sympathetic nervous system and are activated by the catecholamines norepinephrine and epinephrine.

Norepinephrine is released from postganglionic neurons of the sympathetic nervous system. Epinephrine is secreted by the adrenal medulla and reaches the target tissues via the circulation. Adrenoreceptors are divided into two types, α and β, which are further designated as α_1, α_2, β_1, and β_2 receptors. Each of the receptor types has a different mechanism of action (except the β_1 and β_2 receptors, which have the same mechanism of action), resulting in different physiologic effects (see Tables 2-3 and 2-4).

α_1 Receptors

α_1 Receptors are found in vascular smooth muscle of the skin, skeletal muscle, and the splanchnic region, in the sphincters of the gastrointestinal tract and bladder, and in the radial muscle of the iris. Activation of α_1 receptors leads to **contraction** in each of these tissues. The mechanism of action involves a G protein called G_q and **activation of phospholipase C**, illustrated in Figure 2-6.
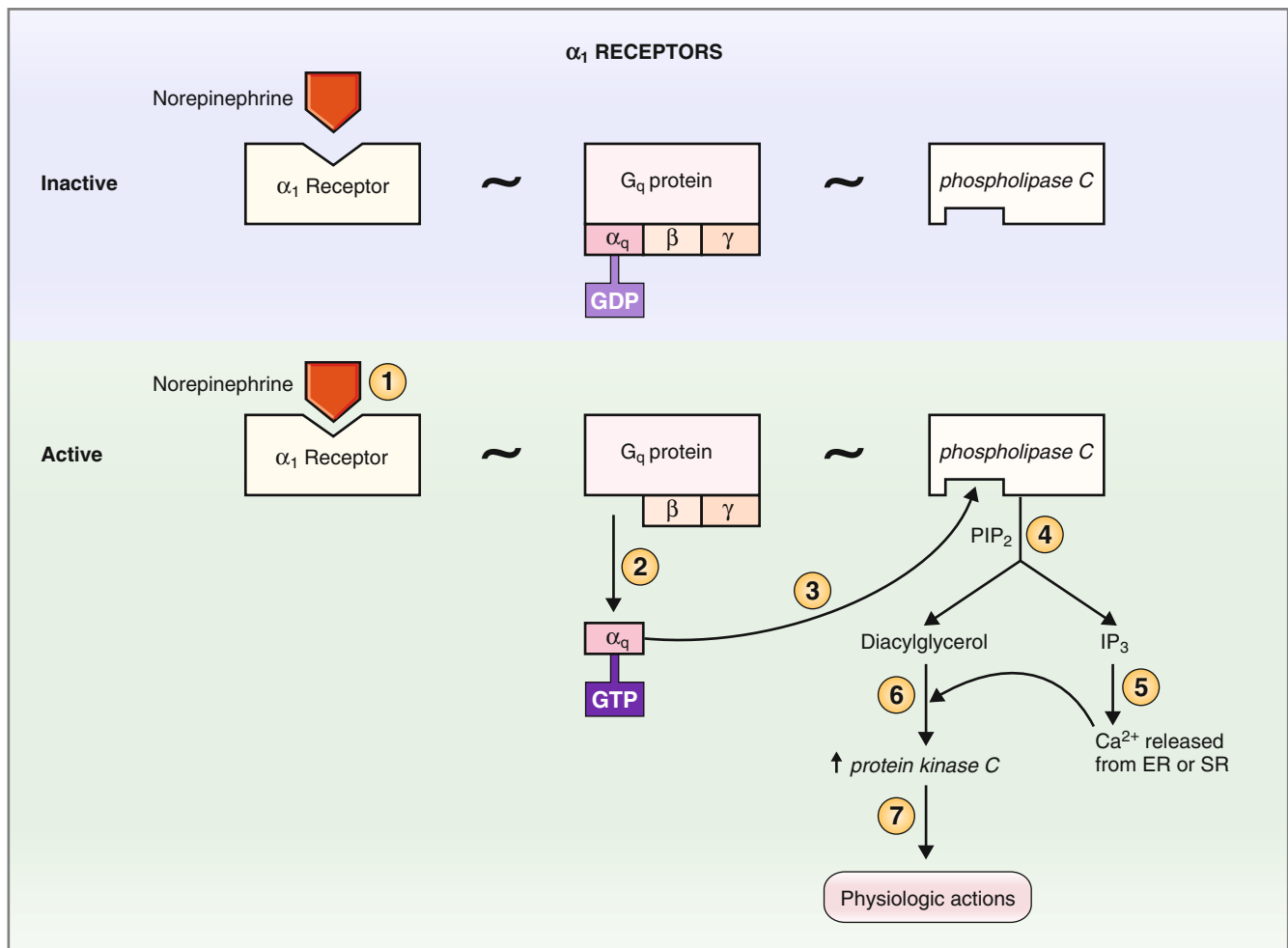

Figure 2-6 **Mechanism of action of α_1 adrenoreceptors.** In the inactive state, the α_q subunit of the G_q protein is bound to GDP. In the active state, with norepinephrine bound to the α_1 receptor, the α_q subunit is bound to GTP. α_q, β, and γ are subunits of the G_q protein. The circled numbers correspond to steps discussed in the text. ER, Endoplasmic reticulum; GDP, guanosine diphosphate; G_q, G protein; GTP, guanosine triphosphate; PIP_2, phosphatidylinositol 4,5-diphosphate; SR, sarcoplasmic reticulum.

The circled numbers in the figure correspond to the steps discussed as follows:

1. The α_1 receptor is embedded in the cell membrane, where it is coupled, via the G_q protein, to phospholipase C. In the inactive state, the α_q subunit of the heterotrimeric G_q protein is bound to GDP.

2. When an agonist such as norepinephrine binds to the α_1 receptor (Step 1), a conformational change occurs in the α_q subunit of the G_q protein. This conformational change has two effects (Step 2): GDP is released from the α_q subunit and replaced by GTP and the α_q subunit (with GTP attached) detaches from the rest of the G_q protein.

3. The α_q-GTP complex migrates within the cell membrane and binds to and activates phospholipase C (Step 3). Intrinsic GTPase activity then converts GTP back to GDP, and the α_q subunit returns to the inactive state (not shown).

4. Activated phospholipase C catalyzes the liberation of diacylglycerol and IP_3 from phosphatidylinositol 4,5-diphosphate (Step 4). The **IP_3** that is generated causes the release of **Ca^{2+}** from intracellular stores in the endoplasmic or sarcoplasmic reticulum, resulting in an increase in intracellular Ca^{2+} concentration (Step 5). Together, Ca^{2+} and diacylglycerol activate protein kinase C (Step 6), which phosphorylates proteins. These phosphorylated proteins execute the final physiologic actions (Step 7), such as contraction of smooth muscle.

α_2 Receptors

α_2 Receptors are inhibitory, are located both pre- and post-synaptically, and are less common than α_1 receptors. They are found on presynaptic adrenergic and cholinergic nerve terminals and in the gastrointestinal tract. α_2 receptors are found in two forms, autoreceptors and heteroreceptors.

α_2 Receptors present on sympathetic postganglionic nerve terminals are called **autoreceptors**. In this function, activation of α_2 receptors by norepinephrine released from pre-synaptic nerve terminals inhibits further release of norepinephrine from the same terminals; this negative feedback conserves norepinephrine in states of high stimulation of the sympathetic nervous system. Interestingly, the adrenal medulla does not have α_2 receptors and, therefore, is not subject to feedback inhibition; consequently, the adrenal medulla can become depleted of catecholamines during periods of prolonged stress.

α_2 Receptors present on parasympathetic postganglionic nerve terminals of the gastrointestinal tract are called **heteroreceptors**. Norepinephrine is released from sympathetic postganglionic fibers that synapse on these parasympathetic postganglionic fibers. When activated by norepinephrine, the α_2 receptors cause inhibition of release of acetylcholine from the parasympathetic postganglionic nerve terminals. In this way, the sympathetic nervous system indirectly inhibits gastrointestinal function (i.e., by inhibiting the parasympathetic activity).

The mechanism of action of these receptors involves the **inhibition of adenylyl cyclase**, described by the following steps:

1. The agonist (e.g., norepinephrine) binds to the α_2 receptor, which is coupled to adenylyl cyclase by an inhibitory G protein, G_i.

2. When norepinephrine is bound, the G_i protein releases GDP and binds GTP, and the α_i subunit dissociates from the G protein complex.

3. The α_i subunit then migrates in the membrane and binds to and **inhibits adenylyl cyclase**. As a result, cAMP levels decrease, producing the final physiologic action.

β_1 Receptors

β_1 Receptors are prominent in the heart. They are present in the SA node, in the atrioventricular (AV) node, and in ventricular muscle. Activation of β_1 receptors in these tissues produces increased heart rate in the SA node, increased conduction velocity in the AV node, and increased contractility in ventricular muscle, respectively. β_1 Receptors also are located in the salivary glands, in adipose tissue, and in the kidney (where they promote renin secretion). The mechanism of action of β_1 receptors involves a G_s protein and **activation of adenylyl cyclase**. This action is illustrated in Figure 2-7 and involves the following steps, which correspond to the circled numbers in the figure:

1. Similar to other autonomic receptors, β_1 receptors are embedded in the cell membrane. They are coupled, via a G_s protein, to adenylyl cyclase. In the inactive state, the α_s subunit of the G_s protein is bound to GDP.

2. When an agonist such as norepinephrine binds to the β_1 receptor (Step 1), a conformational change occurs in the α_s subunit. This change has two effects (Step 2): GDP is released from the α_s subunit and replaced by GTP; the activated α_s subunit detaches from the G protein complex.

3. The α_s-GTP complex migrates within the cell membrane and binds to and activates adenylyl cyclase (Step 3). GTPase activity converts GTP back to GDP, and the α_s subunit is returned to its inactive state (not shown).

4. Activated adenylyl cyclase catalyzes the conversion of ATP to cAMP, which serves as the second messenger
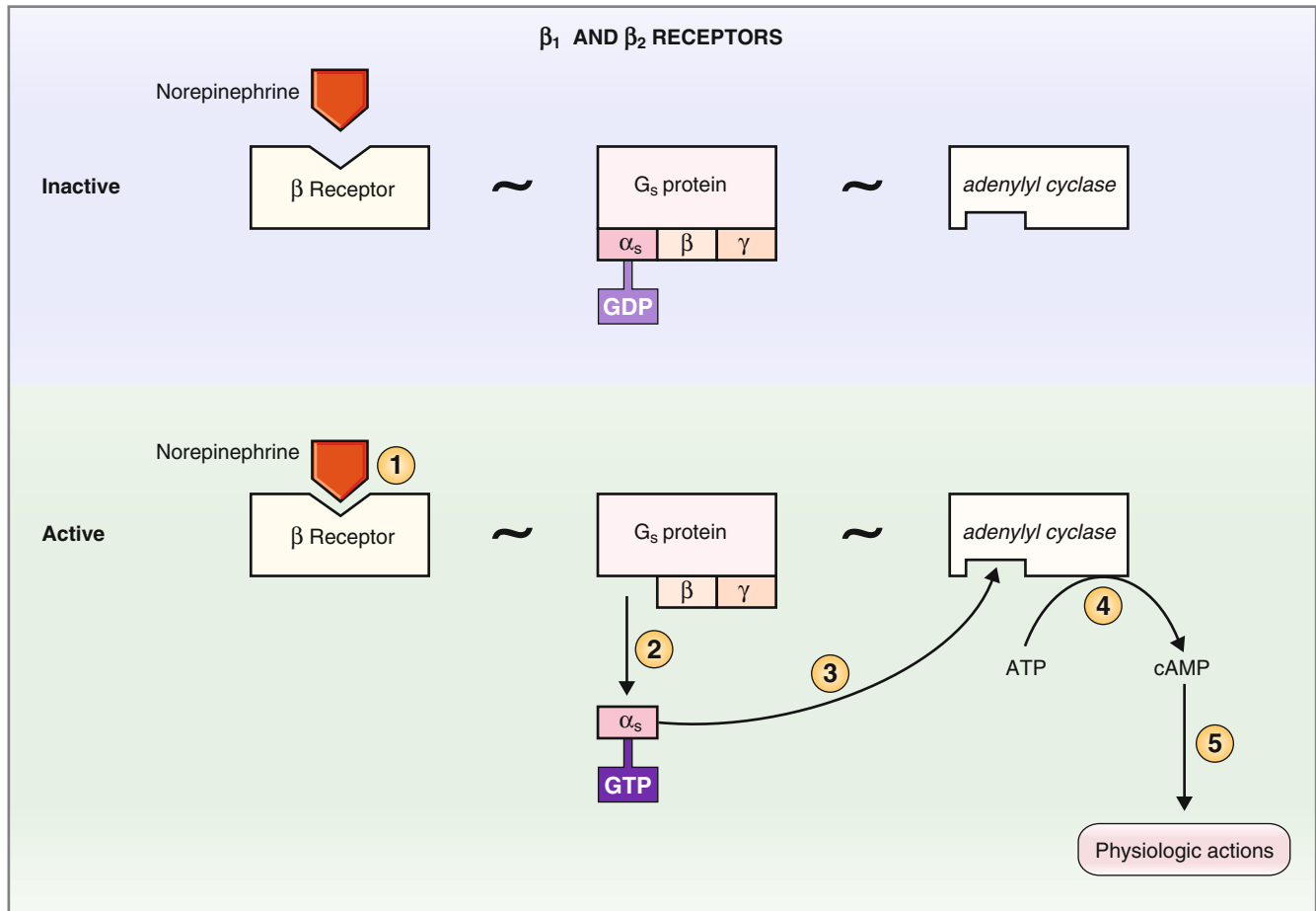
Figure 2-7 **Mechanism of action of β adrenoreceptors.** In the inactive state, the α_s subunit of the G_s protein is bound to GDP. In the active state, with norepinephrine bound to the β receptor, the α_s subunit is bound to GTP. β_1 and β_2 receptors have the same mechanism of action. The circled numbers correspond to steps discussed in the text. ATP, Adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GDP, guanosine diphosphate; GTP, guanosine triphosphate.

(Step 4). **cAMP**, via steps involving activation of protein kinases, initiates the final physiologic actions (Step 5). As previously mentioned, these physiologic actions are tissue-specific and cell type–specific. When β_1 receptors are activated in the SA node, heart rate increases; when β_1 receptors are activated in ventricular muscle, contractility increases; when β_1 receptors are activated in the salivary gland, secretion increases; when β_1 receptors are activated in the kidney, renin is secreted.

β_2 Receptors

β_2 Receptors are found in the vascular smooth muscle of skeletal muscle, in the walls of the gastrointestinal tract and bladder, and in the bronchioles. The activation of β_2 receptors in these tissues leads to **relaxation** or dilation. The β_2 receptors have a mechanism of action similar to that of β_1 receptors: activation of a G_s protein, release of the α_s subunit, **stimulation of adenylyl cyclase**, and generation of cAMP (see Fig. 2-7).

Responses of Adrenoreceptors to Norepinephrine and Epinephrine

There are significant differences in the responses of α_1, β_1, and β_2 adrenoreceptors to the catecholamines epinephrine and norepinephrine. These differences are explained as follows, recalling that norepinephrine is the catecholamine released from postganglionic sympathetic adrenergic nerve fibers, while epinephrine is the primary catecholamine released from the adrenal medulla: (1) Norepinephrine and epinephrine have almost the same potency at **α_1 receptors**, with epinephrine being slightly more potent. However, compared to β receptors, α_1 receptors are relatively insensitive to

catecholamines. Higher concentrations of catecholamines are needed to activate α_1 receptors than to activate β receptors. Physiologically, such high concentrations are reached locally when norepinephrine is released from postganglionic sympathetic nerve fibers but not when catecholamines are released from the adrenal medulla. For example, the amount of epinephrine (and norepinephrine) released from the adrenal medulla in the fight or flight response is insufficient to activate α_1 receptors. (2) Norepinephrine and epinephrine are equipotent at β_1 receptors. As noted previously, much lower concentrations of catecholamines will activate β_1 receptors than will activate α_1 receptors. Thus, norepinephrine released from sympathetic nerve fibers or epinephrine released from the adrenal medulla will activate β_1 receptors. (3) **β_2 receptors** are preferentially activated by epinephrine. Thus, epinephrine released from the adrenal medulla is expected to activate β_2 receptors, whereas norepinephrine released from sympathetic nerve endings is not.

CHOLINORECEPTORS

There are two types of cholinoreceptors: nicotinic and muscarinic. Nicotinic receptors are found on the motor end plate, in all autonomic ganglia, and on chromaffin cells of the adrenal medulla. Muscarinic receptors are found in all effector organs of the parasympathetic division and in a few effector organs of the sympathetic division.

Nicotinic Receptors

Nicotinic receptors are found in several important locations: on the motor end plate of skeletal muscle, on all postganglionic neurons of both sympathetic and parasympathetic nervous systems, and on the chromaffin cells of the adrenal medulla. ACh is the natural agonist, which is released from motoneurons and from all preganglionic neurons.

The question arises as to whether the nicotinic receptor on the motor end plate is identical to the nicotinic receptor in the autonomic ganglia. This question can be answered by examining the actions of drugs that serve as agonists or antagonists to the nicotinic receptor. The nicotinic receptors at the two loci are certainly similar: Both are activated by the agonists ACh, nicotine, and carbachol, and both are antagonized by the drug **curare** (see Table 2-2). However, another antagonist to the nicotinic receptor, **hexamethonium**, blocks the nicotinic receptor in the ganglia but not the nicotinic receptor on the motor end plate. Thus, it can be concluded that the receptors at the two loci are similar but not identical. This pharmacologic distinction predicts that drugs such as hexamethonium will be ganglionic-blocking agents but not neuromuscular-blocking agents.

A second conclusion can be drawn about **ganglionic-blocking agents** such as hexamethonium. These agents should inhibit nicotinic receptors in *both* sympathetic and parasympathetic ganglia, and thus, they should produce widespread effects on autonomic function. However, to predict the actions of ganglionic-blocking agents on a particular organ system, it is necessary to know whether sympathetic or parasympathetic control is dominant in that organ. For example, **vascular smooth muscle** has *only* sympathetic innervation, which causes vasoconstriction; thus, ganglionic-blocking agents produce relaxation of vascular smooth muscle and vasodilation. (Because of this property, ganglionic-blocking agents can be used to treat hypertension.) On the other hand, **male sexual function** is dramatically impaired by ganglionic-blocking agents because the male sexual response has both sympathetic (ejaculation) and parasympathetic (erection) components.

The **mechanism of action** of nicotinic receptors, whether at the motor end plate or in the ganglia, is based on the fact that this ACh receptor is also an ion channel for Na^+ and K^+. When the nicotinic receptor is activated by ACh, the channel opens and both Na^+ and K^+ flow through the channel, down their respective electrochemical gradients.

Figure 2-8 illustrates the function of the nicotinic receptor/channel in two states: closed and open. The nicotinic receptor is an integral cell membrane protein consisting of five subunits: two α, one β, one delta (δ), and one gamma (γ). These five subunits form a funnel around the mouth of a central core. When *no ACh is bound,* the mouth of the channel is closed. When *ACh is bound* to each of the two α subunits, a conformational change occurs in all of the subunits, resulting in opening of the central core of the channel. When the core of the channel opens, Na^+ and K^+ flow down their respective electrochemical gradients (Na^+ into the cell, and K^+ out of the cell), with each ion attempting to drive the membrane potential to its equilibrium potential. The resulting membrane potential is midway between the Na^+ and K^+ equilibrium potentials, approximately 0 millivolts, which is a depolarized state.

Muscarinic Receptors

Muscarinic receptors are located in all of the effector organs of the parasympathetic nervous system: in the heart, gastrointestinal tract, bronchioles, bladder, and male sex organs. These receptors also are found in certain effector organs of the sympathetic nervous system, specifically, in sweat glands.
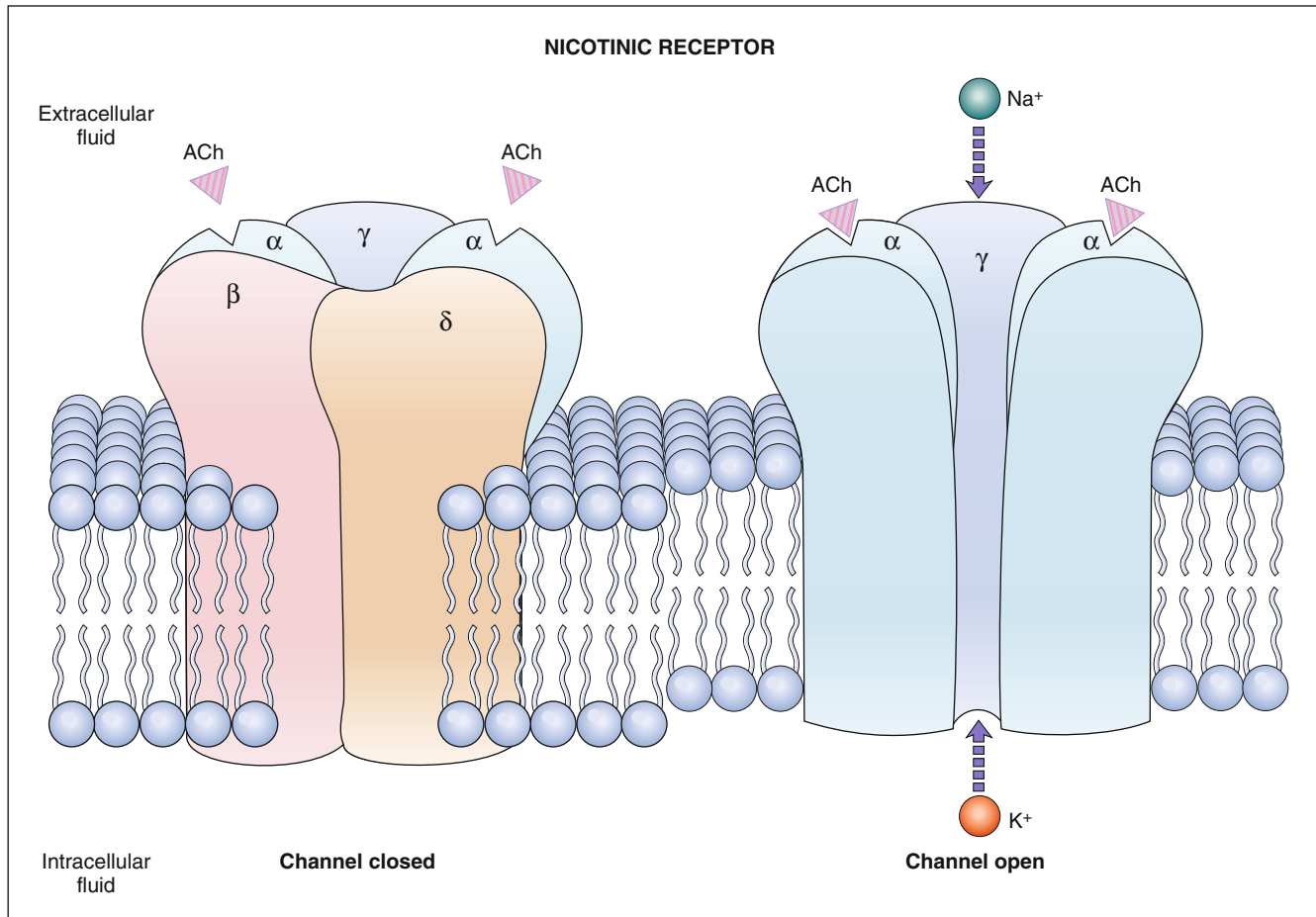
NICOTINIC RECEPTOR

Figure 2-8 **Mechanism of action of nicotinic cholinoreceptors.** The nicotinic receptor for acetylcholine (ACh) is an ion channel for Na$^+$ and K$^+$. The receptor has five subunits: two α, one β, one δ, and one γ. (Modified from Kandel ER, Schwartz JH: Principles of Neural Science, 4th ed. New York, Elsevier, 2000.)

Some muscarinic receptors have the same **mechanism of action** as the α_1 adrenoreceptors (see Fig. 2-6). In these cases, binding of the agonist (ACh) to the muscarinic receptor causes dissociation of the α subunit of the G protein, activation of **phospholipase C**, and generation of **IP$_3$** and diacylglycerol. IP$_3$ releases stored Ca^{2+}, and the increased intracellular Ca^{2+} with diacylglycerol produces the tissue-specific physiologic actions.

Other muscarinic receptors alter physiologic processes via a **direct action of the G protein**. In these cases, no other second messenger is involved. For example, muscarinic receptors in the cardiac **SA node**, when activated by ACh, produce activation of a G$_i$ protein and release of the α_i subunit, which binds *directly* to K$^+$ channels of the SA node. When the α_i subunits bind to K$^+$ channels, the channels open, slowing the rate of depolarization of the SA node and decreasing the heart rate. In this mechanism, there is no stimulation or inhibition of either adenylyl cyclase or phospholipase C, and no involvement of any second messenger; rather, the G$_i$ protein acts directly on the ion channel (Box 2-2).

Summary

■ The autonomic nervous system is composed of two major divisions, the sympathetic and the parasympathetic, which operate in a coordinated fashion to regulate involuntary functions. The sympathetic division is thoracolumbar, referring to its origin in the spinal cord. The parasympathetic division is craniosacral, referring to its origin in the brain stem and sacral spinal cord.

■ Efferent pathways in the autonomic nervous system consist of a preganglionic and a postganglionic neuron, which synapse in autonomic ganglia. The axons of postganglionic neurons then travel