12 Cardiac Muscle: The Autonomic Nervous System

The motor functions we have described so far in this part of the book have been concerned with the control of skeletal muscles. These are the muscles that produce overt movements of the body and give rise to the observable external actions that we normally think of as the "behavior" of an animal. However, even in an animal that appears to an external observer to be quiescent, the nervous system is quite busy coordinating many ongoing motor actions that are as important for survival as skeletal muscle movements. These motor activities include such things as regulating digestion, maintaining the proper glucose balance in the blood, regulating heart rate, and so on. The part of the nervous system that controls these functions is called the **autonomic nervous system**. The motor targets of the autonomic nervous system include gland cells, cardiac muscle cells, and smooth muscle cells such as those found in the gut. To distinguish it from the autonomic nervous system, the parts of the nervous system we have been discussing up to this point whose motor targets are the skeletal muscles are collectively called the **somatic nervous system**.

In addition to the differences in their target cells, there are other differences between the autonomic and somatic nervous systems. As we have seen, in the somatic nervous system, the cell bodies of the motor neurons are located within the central nervous system, either in the spinal cord or in the nuclei of cranial nerves in the brainstem. By contrast, the cell bodies of the motor neurons in the autonomic nervous system are located outside the central nervous system altogether, in a system of **autonomic ganglia** distributed throughout the body. The central nervous system controls these autonomic ganglia by way of output neurons called **preganglionic neurons**, which are located in the spinal cord and brainstem. This arrangement is illustrated in Figure 12-1. The motor neurons in the autonomic ganglia are also called **postganglionic neurons**. The axons of the preganglionic neurons entering the ganglia are referred to as the **preganglionic fibers**, while the axons of the autonomic motor neurons carrying the output to the target cells are called the **postganglionic fibers**. Thus, in the

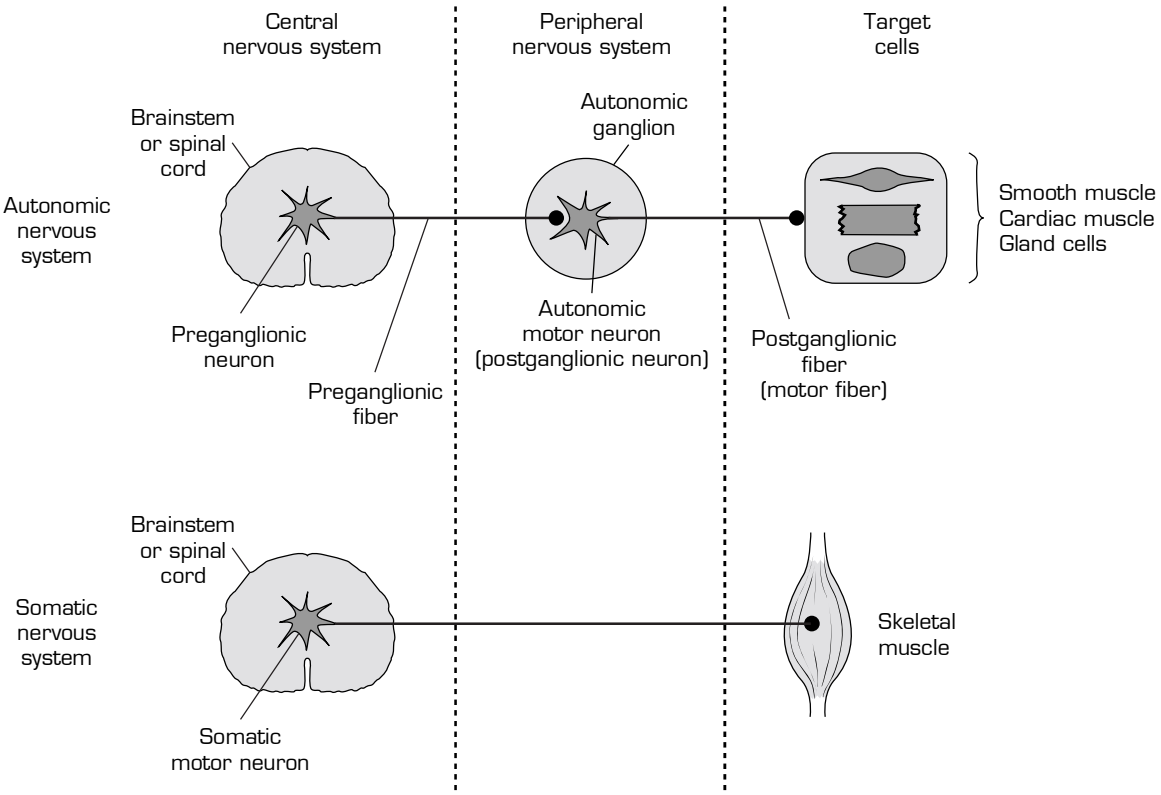

Figure 12-1 Differences between autonomic and somatic nervous systems. In the autonomic nervous system, the motor neurons are located outside the central nervous system, in autonomic ganglia. The motor neurons contact smooth muscle cells, cardiac muscle cells, and gland cells. The central nervous system controls the ganglia via preganglionic neurons. In the somatic nervous system, the motor neurons are located within the central nervous system and contact skeletal muscle cells.

somatic nervous system, the motor commands exiting from the central nervous system go directly to the target cells, while in the autonomic nervous system, the motor commands from the central nervous system are relayed via an additional synaptic connection in the peripheral nervous system.

The autonomic and somatic nervous systems also differ in the effects that the motor neurons have on the target cells. In Chapter 8, we discussed in detail the synaptic interaction between motor neurons and skeletal muscle cells at the neuromuscular junction. All of the somatic motor neurons release ACh as their neurotransmitter, and the effect on the skeletal muscle cells is always excitatory: contraction is stimulated. In the autonomic nervous system, however, some motor neurons release ACh and other motor neurons release the neurotransmitter norepinephrine (see Chapter 9), instead of ACh. Further, an

autonomic motor neuron may either excite or inhibit its target cell. In general, if norepinephrine excites the target cells, then ACh inhibits them, and vice versa. For example, norepinephrine increases the rate of beating of the heart, while ACh decreases the heart rate, as we will examine in detail shortly.

The norepinephrine-releasing and ACh-releasing motor neurons are organized into anatomically distinct divisions of the autonomic nervous system, called the **sympathetic division** (norepinephrine-releasing) and the **parasympathetic division** (ACh-releasing). The ganglia containing the sympathetic motor neurons are called sympathetic ganglia, and those containing parasympathetic motor neurons are called parasympathetic ganglia. Most of the sympathetic ganglia are arrayed parallel to the spinal cord, one ganglion on each side just outside the vertebral column. There is one pair of these **paravertebral ganglia** for each vertebral segment. The ganglia are interconnected by thick, longitudinal bundles of axons containing the preganglionic fibers exiting from the spinal cord. Because of these connectives, the paravertebral ganglia form two long chains parallel to the spinal column, sometimes referred to as the **sympathetic chains**. In addition to the paravertebral ganglia that make up the chains, there are also sympathetic ganglia called the **prevertebral ganglia**, located within the abdomen.

The parasympathetic ganglia are distributed more diffusely throughout the body and tend to be located closer to their target organs. In some cases, the parasympathetic ganglia are actually located within the target organ itself. This is the case, for example, in the heart. Because the sympathetic ganglia are located predominantly near the central nervous system while the parasympathetic ganglia are located mostly near to their target organs, the preganglionic fibers of the sympathetic nervous system are usually much shorter than the preganglionic fibers of the parasympathetic nervous system, which must extend all the way from the central nervous system to the near vicinity of the target organ in order to reach the postganglionic neurons. Conversely, the postganglionic fibers are typically much longer in the sympathetic nervous system than in the parasympathetic nervous system.

Most target organs receive inputs from both the sympathetic and parasympathetic divisions of the autonomic nervous system. As noted above, the sympathetic and parasympathetic inputs produce opposing effects on the target. In general, excitation of the sympathetic nervous system has the overall effect of placing the organism in "emergency mode," ready for vigorous activity. The parasympathetic nervous system has the opposite effect of placing the organism in a "vegetative mode." For example, sympathetic activity increases the heart rate and blood pressure, diverts blood flow from the skin and viscera to the skeletal muscles, and reduces intestinal motility, all appropriate preparations for rapid reaction to an external threat. Parasympathetic activity, on the other hand, decreases heart rate and blood pressure, and promotes blood circulation to the gut and intestinal motility. All of these actions are appropriate for resting and digesting, in the absence of any threatening situation in the environment.

Autonomic Control of the Heart

To see how the motor neurons of the sympathetic and parasympathetic divisions exert their actions on target cells, it will be useful to examine a particular example in detail. The example we will explore is the neural control of the heart. The heart is made up of muscle cells, which are in some ways similar to the skeletal muscle cells we learned about in Chapter 10. However, there are some important differences, which we must understand before we can examine the effects that the sympathetic and parasympathetic neurons have on the heart. Thus, we will first discuss the electrical and mechanical properties of the heart muscle, and then return to the modulation of those properties by norepinephrine and ACh, which are the neurotransmitters released by the sympathetic and parasympathetic inputs to the heart, respectively.

The Pattern of Cardiac Contraction

Cardiac muscle cells contain a contractile apparatus like that of other striated muscle, being made up of bundles of myofilaments with a microscopic structure like that discussed in Chapter 10. Unlike other striated muscles in the body, the heart muscle is specialized to produce a rhythmic and coordinated contraction in order to drive the blood efficiently through the blood vessels. The heart has a number of tasks to accomplish in order to carry out its role in providing oxygen to the cells of the body. It must receive the oxygen-poor blood returning from the body tissues via the venous circulation and send that blood to the lungs for oxygenation. It must also receive the oxygenated blood from the lungs and send it out through the arterial circulation to the rest of the body. Carrying out these tasks requires precise timing of the contractions of the various heart chambers; otherwise, the flow of oxygenated blood will not occur efficiently or will cease altogether with disastrous consequences. What is the normal timing sequence of the heart contractions underlying the coordinated pumping of the blood?

A schematic diagram of the flow of blood through a human heart during a single contraction cycle is shown in Figure 12-2. Humans, like all other mammals, have a four-chambered heart, consisting of the left and right **atria** and the left and right **ventricles**. The two atria can be thought of as the receiving chambers, or "priming" pumps, of the heart, while the two ventricles are the "power" pumps of the circulatory system. The right atrium receives the blood returning from the body through the veins, and the left atrium receives the freshly oxygenated blood from the lungs. During the phase of the heartbeat when the atria are filling with blood, the valves connecting the atria with the ventricles are closed, preventing flow of blood into the ventricles. When the atria have filled with blood, they contract and the increase in pressure opens the valves leading to the ventricles and drives the collected blood into the ventricles. At this point, the muscle of the ventricles is relaxed, and the valves

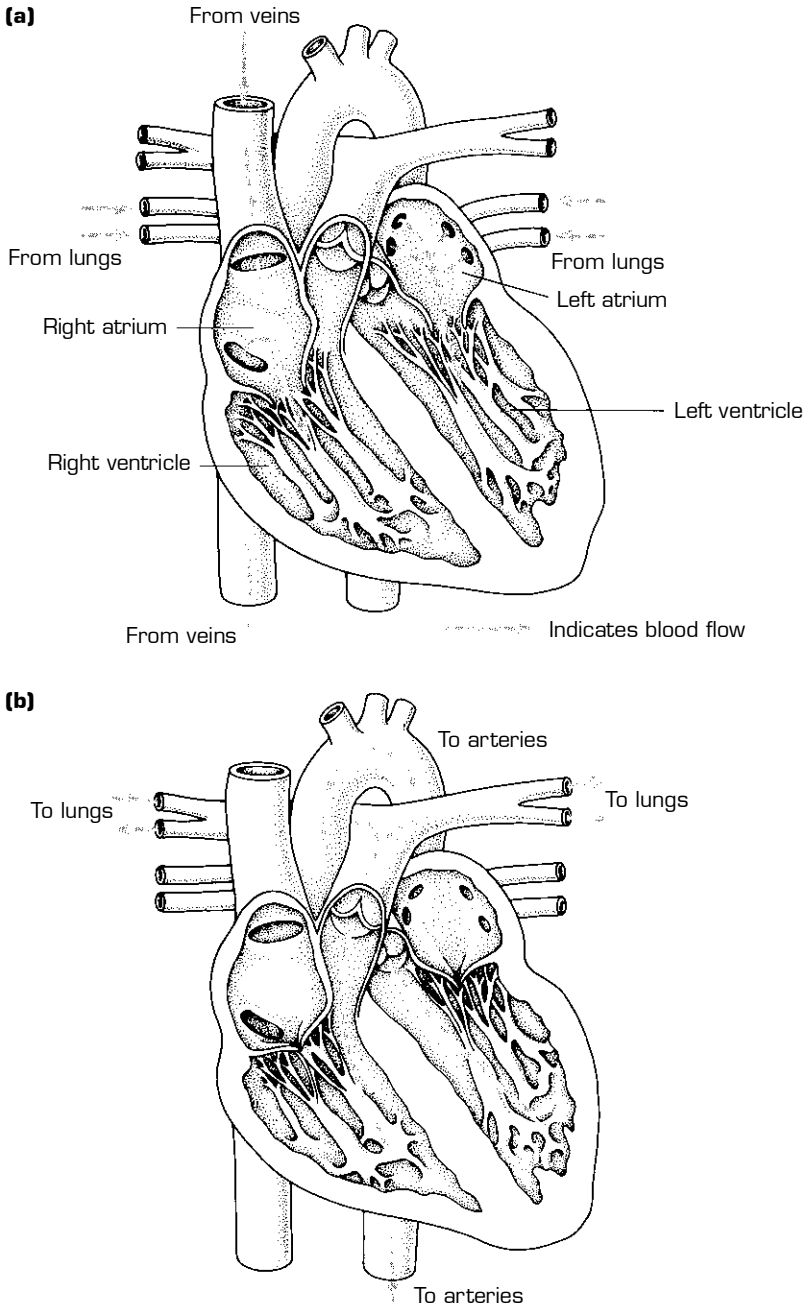

Figure 12-2 Schematic drawings of the state of the heart valves and the direction of blood flow during two stages in a single heartbeat. (a) The atria are contracting and the ventricles are filling with blood. (b) The valves between the atria and ventricles are closed and the ventricles are contracting, forcing the blood from the right ventricle to the lungs and from the left ventricle to the arteries supplying the rest of the body.

connecting the ventricles to the vessels leaving the heart are closed. When the ventricles have filled with blood, they contract, opening these valves and delivering the power stroke to drive the blood out to the lungs and to the rest of the body, as shown in Figure 12-2b. Thus, during a normal heartbeat the two atria

contract together, followed after a delay by the simultaneous contraction of the two ventricles.

Coordination of Contraction Across Cardiac Muscle Fibers

In order for the contraction of a heart chamber to be able to propel the expulsion of fluid, all the individual muscle fibers making up the walls of that chamber must contract together. It is this unified contraction that constricts the cavity of the chamber and drives out the blood into the blood vessels of the circulation. In skeletal muscles, an action potential in one muscle fiber is confined to that fiber and does not influence neighboring fibers; therefore, contraction is restricted to the particular fiber undergoing an action potential. In cardiac muscle, however, the situation is quite different. When an action potential is generated in a cardiac muscle fiber, it causes action potentials in the neighboring fibers, which in turn set up action potentials in their neighbors, and so on. Thus, the excitation spreads rapidly out through all the muscle fibers of the chamber. This insures that all the fibers contract together.

What characteristic of cardiac muscle fibers allows the action potential to spread from one fiber to another? The answer can be seen by looking at the microscopic structure of the cells of cardiac muscle, shown schematically in Figure 12-3. At the ends of each cardiac cell, the plasma membranes of neighboring cells come into close contact at specialized structures called **intercalated disks**. The contact at this point is sufficiently close that electrical current flowing inside one fiber can cross directly into the interior of the next fiber; in electrical terms, it is as though the neighboring cells form one larger cell. Recall from Chapter 6 that an electrical current flowing along the interior of a fiber has at each point two paths to choose from: across the plasma membrane or continuing along the interior of the fiber. The amount of current taking each path at a particular point depends on the relative resistances of the two paths; the higher the resistance, the smaller the amount of current taking that path. Normally, at the point where one cell ends and the next begins, there is little opportunity for current to flow from one cell to the other because the current would have to flow out across one cell membrane and in across the other in order to do so; this is a high resistance path because current must cross two membranes. At the specialized structure of the intercalated disk, however, the resistance to current flow across the two membranes is low, so that the path to the interior of the neighboring cell is favored. This means that depolarizing current injected into one cell during the occurrence of an action potential can spread directly into neighboring cells, setting up an action potential in those cells as well. The low resistance path from one cell to another is through membrane structures called **gap junctions**. These structures consist of arrays of small pores directly connecting the interiors of the joined cells. The pores are formed by pairs of protein molecules, one in each cell, that attach to each other and bridge the small extracellular gap between the two cell membranes (Figure 12-3). The pores at the center of each of these **gap junction channels** are

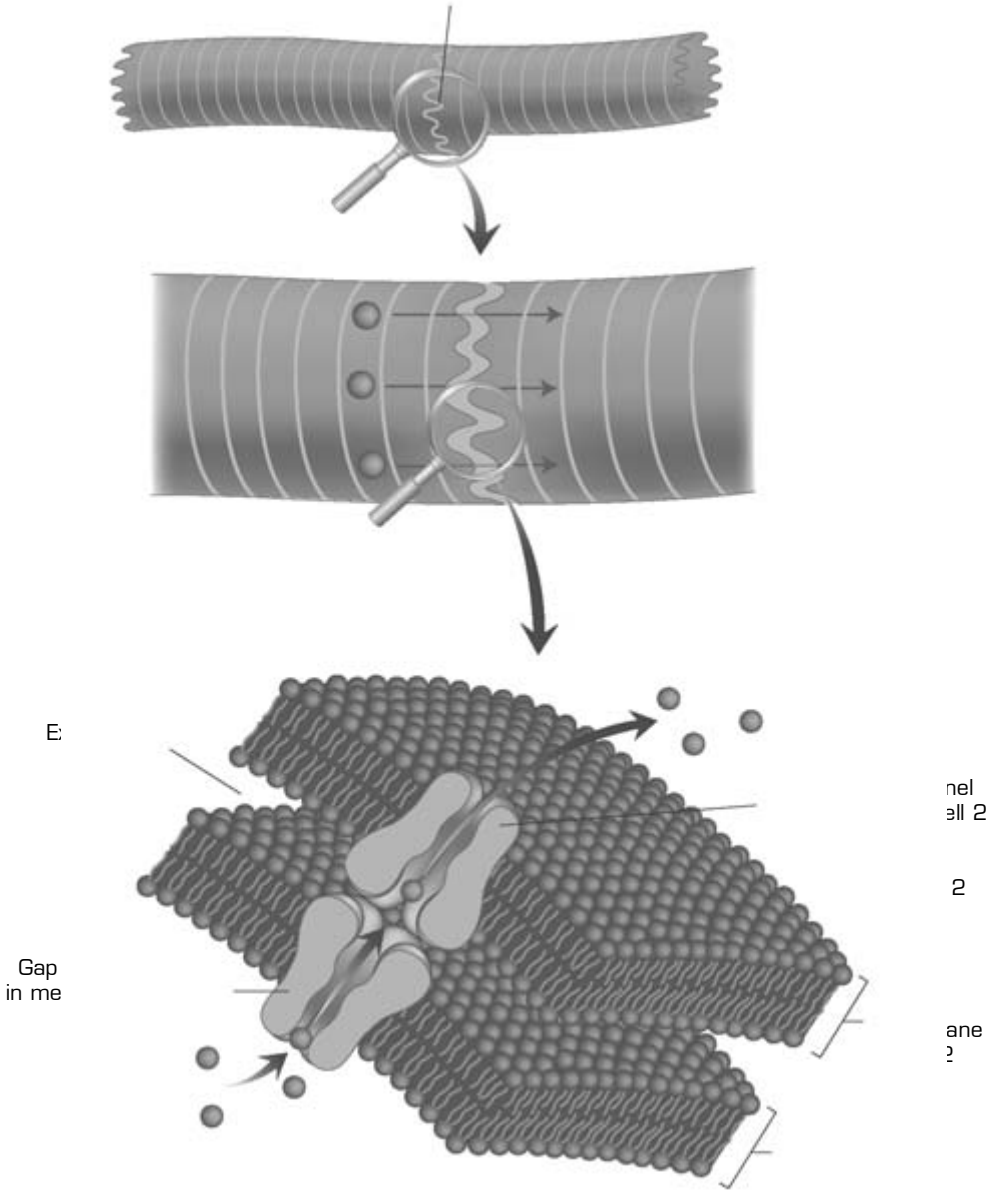

Figure 12-3 Electrical current can flow from one cardiac muscle cell to another through specialized membrane junctions located in a region of contact called the intercalated disk. The current flows through pores formed by pairs of gap junction channels that bridge the extracellular space at the intercalated disk.

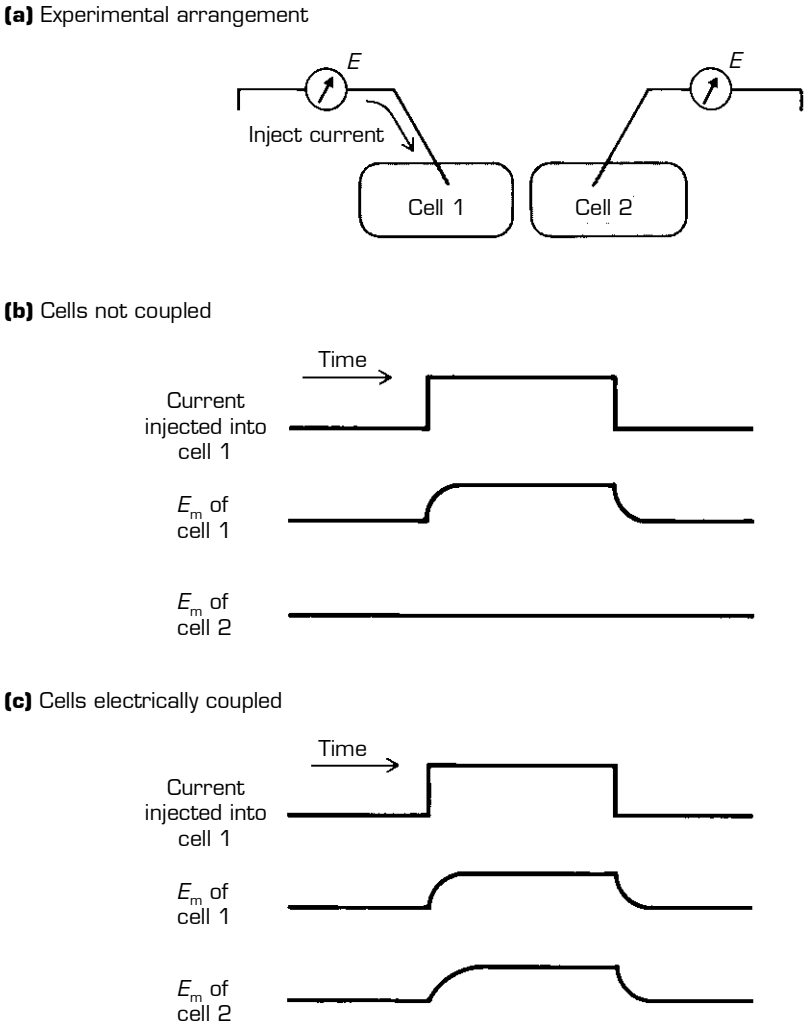

Figure 12-4 An experiment in which the membrane potentials of two cells are measured simultaneously with intracellular microelectrodes. (a) A depolarizing current is injected into cell 1. (b) If the cells are not electrically coupled, the depolarization occurs only in the cell in which the current was injected. (c) If the cells are electrically coupled via gap junctions, a depolarization occurs in cell 2, as well as in cell 1.

aligned, permitting small molecules like ions to pass directly from one cell to the other.

When electrical current can pass from one cell to another, as in cardiac muscle, those cells are said to be **electrically coupled**. Figure 12-4 illustrates an electrophysiological experiment to demonstrate this behavior. When current is injected into a cell, no response occurs in a neighboring cell if the cells are not electrically coupled. If the two cells are coupled via gap junctions, a response to the injected current occurs in both cells because the ions carrying the current inside the cell can pass directly through the gap junction. If the depolarization is large enough, an action potential will be triggered in both cells at the same time.

Generation of Rhythmic Contractions

The electrical coupling among cardiac muscle fibers can explain how contraction occurs synchronously in all the fibers of a chamber. We will now consider the control mechanisms responsible for the repetitive contractions that characterize the beating of the heart. If a heart is removed from the body and placed in an appropriate artificial environment, it will continue to contract repetitively even though it is isolated from the nervous system and the rest of the body. By contrast, a skeletal muscle isolated under similar conditions will not contract unless its nerve is activated. The rhythmic activity of the heart muscle is an inherent property of the individual muscle fibers making up the heart, and this constitutes another important difference between cardiac muscle fibers and skeletal muscle fibers. This difference can be demonstrated dramatically in experiments in which muscle tissue is dissociated into individual cells, which are placed in a dish isolated from each other and from the influence of any other cells, like nerve cells. Under these conditions, muscle cells from skeletal muscles are quiescent; they do not contract in the absence of their neural input. Cells from cardiac muscle, however, continue to contract rhythmically even in isolation. Thus, rhythmic contractions of heart muscle are due to built-in properties of the cardiac muscle cells. Before we can examine the membrane mechanism underlying this autorhythmicity, it will be necessary to look first at the action potential of cardiac muscle cells. In keeping with the different behavior of cardiac cells, this action potential has some different characteristics from the action potentials of neurons or skeletal muscle cells.

The Cardiac Action Potential

In Chapters 6 and 7, we discussed the ionic mechanisms underlying the action potential of nerve membrane. The action potential of skeletal muscle fibers is fundamentally the same as that of neurons. The cardiac action potential, however, is different from these other action potentials in several important ways. Figure 12-5 compares the characteristics of action potentials of skeletal and cardiac muscle cells. One striking difference is the difference in time-scale: cardiac action potentials can last several hundred milliseconds, while skeletal muscle action potentials are typically over in 1–2 msec. As we saw in Chapter 6, a long-lasting plateau like that of the cardiac action potential can arise from a calcium component in the action potential, resulting from the opening of voltage-dependent calcium channels. These channels open upon depolarization and allow influx of positively charged calcium ions. In addition, the plateau of the cardiac action potential is also associated with a reduction in the potassium permeability. This is due to a type of potassium channel that is open as long as the membrane potential is near its normal resting level and closes upon depolarization. This is the reverse of the behavior of the gated potassium channel we are familiar with from our discussion of nerve action potential. The reduction in potassium permeability caused by the closing of this channel

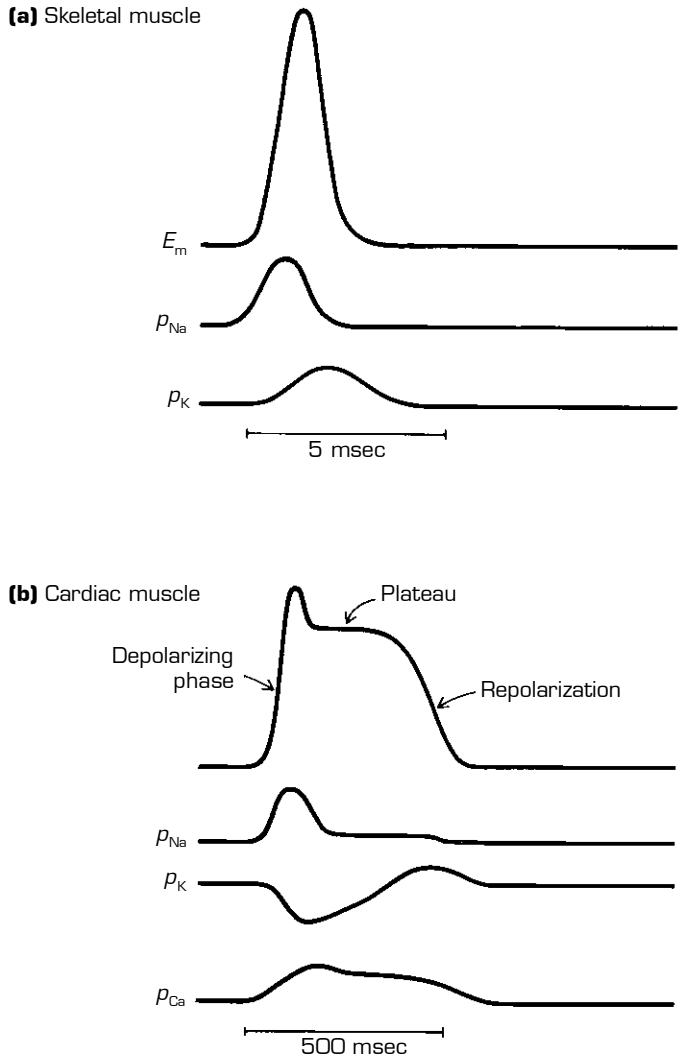

Figure 12-5 The sequence of permeability changes underlying the action potentials of (a) skeletal muscle fibers and (b) cardiac muscle fibers. Note the greatly different time-scales.

tends to depolarize the cardiac muscle fiber. Both the opening of the calcium channels and the closing of the potassium channels contribute to the plateau.

The initial rising phase of the cardiac action potential is produced by voltage-dependent sodium channels very much like those of nerve membrane. The sodium channels drive the rapid initial depolarization and are responsible for the brief initial spike of the cardiac action potential before the plateau phase sets in. Like the sodium channel of neuronal membrane, this channel rapidly closes (inactivates) with maintained depolarization. However, unlike the nerve sodium channel, this inactivation is not total; there is a small, maintained increase in sodium permeability during the plateau.

What is responsible for terminating the cardiac action potential? First, the calcium permeability of the plasma membrane slowly declines during the maintained depolarization. This decline might be a consequence of the gradual build-up of internal calcium concentration as calcium ions continue to enter the muscle fiber through the open calcium channels. Internal calcium ions are thought to have a direct or indirect action on the calcium channels, causing them to close. In addition, the potassium permeability of the plasma membrane increases, as in the nerve and skeletal muscle action potentials. This increase in potassium permeability tends to drive the membrane potential of the cardiac fiber toward the potassium equilibrium potential and thus to repolarize the fiber. There is evidence that part of this increase in potassium permeability is due to voltage-sensitive potassium channels that open in response to the depolarization during the action potential (like the *n* gates of the nerve membrane). However, the increased potassium permeability is also caused by calcium-activated potassium channels (see Chapter 6), which open in response to the rise in internal calcium concentration during the prolonged action potential.

One functional implication of the prolonged cardiac action potential is that the duration of the contraction in cardiac muscle is controlled by the duration of the action potential. The action potential and contraction of cardiac muscle fibers are compared with those of skeletal muscle fibers in Figure 12-6. In skeletal muscle, the action potential acts only as a trigger for the contractile events; the duration of the contraction is controlled by the timing of the release and

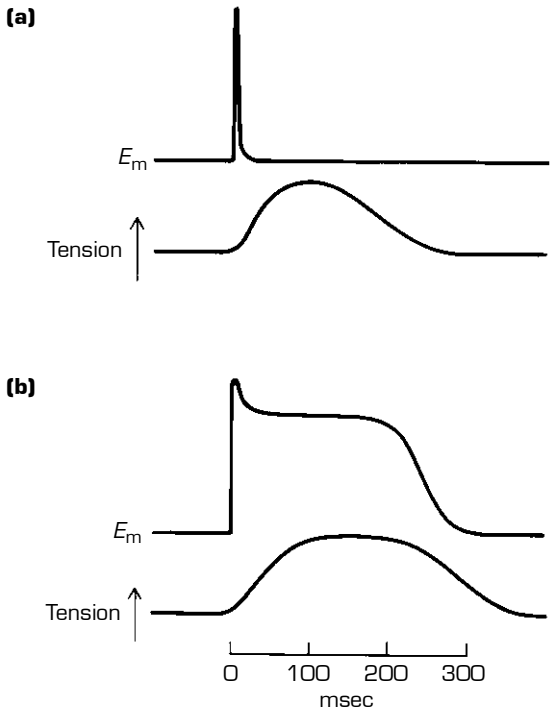

Figure 12-6 (a) In a skeletal muscle fiber, the action potential is much briefer than the resulting contraction. Thus, the action potential acts only as a trigger for the contraction, which proceeds independently of the duration of the action potential. (b) In a cardiac muscle fiber, the duration of the contraction is closely related to the duration of the action potential because of the maintained calcium influx during the plateau of the action potential. Thus, characteristics of the action potential can influence the duration and strength of the cardiac contraction.

reuptake of calcium by the sarcoplasmic reticulum, not by the duration of the action potential. In cardiac muscle fibers, however, only the initial part of the contraction is controlled by sarcoplasmic reticulum calcium; the contraction is maintained by the influx of calcium ions across the plasma membrane during the plateau phase of the cardiac action potential. For this reason, the duration of the contraction in the heart can be altered by changing the duration of the action potential in the cardiac muscle fibers. This provides an important mechanism by which the pumping action of the heart can be modulated.

The Pacemaker Potential

Although the ionic mechanism of the cardiac action potential differs in important ways from that of other action potentials, nothing in the scheme presented so far would account for the endogenous beating of isolated heart cells discussed earlier. If we recorded the electrical membrane potential of a spontaneously beating isolated heart cell, we would see a series of spontaneous action potentials, as shown in Figure 12-7. After each action potential, the potential falls to its normal negative resting value, then begins to depolarize slowly. This slow depolarization is called a **pacemaker potential**, and it is caused by spontaneous changes in the membrane ionic permeability. Voltage-clamp experiments on single isolated muscle fibers from the ventricles suggest that the pacemaker potential is due to a slow decline in the potassium permeability coupled with a slow increase in sodium and calcium permeability. When the depolarization reaches threshold, it triggers an action potential in the fiber, with a rapid upstroke caused by opening of sodium channels and a prolonged plateau produced by calcium channels. Part of the early phase of the pacemaker potential represents the normal undershoot period of an action potential (see Chapter 6), when potassium channels that were opened by depolarization during the action potential slowly close again. As these potassium channels close, the membrane potential will move in a positive direction, away from the potassium equilibrium potential.

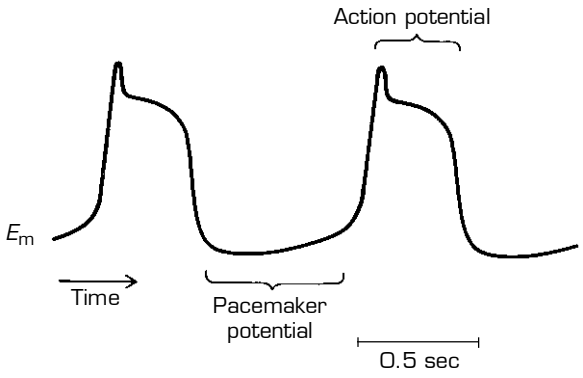

Figure 12-7 A recording of the membrane potential during repetitive, spontaneous beating in a single cardiac muscle fiber. The repolarization at the end of one action potential is followed by a slow, spontaneous depolarization called the pacemaker potential. When this depolarization reaches threshold, a new action potential is triggered.

Later phases of the pacemaker potential represent increases in sodium and calcium permeability, both of which move the membrane potential more positive, toward the sodium and calcium equilibrium potentials. The sodium permeability increases during the pacemaker potential because of the opening of nonspecific cation channels, which open at more hyperpolarized membrane potentials. As described in Chapter 8, the opening of channels with equal permeability to sodium and potassium ions (like the ACh-activated channels at the neuromuscular junction) will produce depolarization of a cell. These hyperpolarization-activated cation channels are opened in response to the membrane hyperpolarization during the undershoot of the action potential. Together with the decrease in potassium permeability, the resulting influx of sodium ions moves the membrane potential of the cardiac cell in a positive direction, toward the threshold for firing an action potential. As the membrane potential becomes more positive during the pacemaker potential, voltage-dependent calcium channels open in response to the depolarization. The resulting influx of positively charged calcium ions produces even more depolarization, ultimately triggering the next action potential in the series.

The rate of spontaneous action potentials in isolated heart cells varies from one cell to another; some cells beat rapidly and others slowly. In the intact heart, however, the electrical coupling among the fibers guarantees that all the fibers will contract together, with the overall rate being governed by the fibers with the fastest pacemaker activity. In the normal functioning of the heart, the overall rate of beating is controlled by a special set of pacemaker cells, called

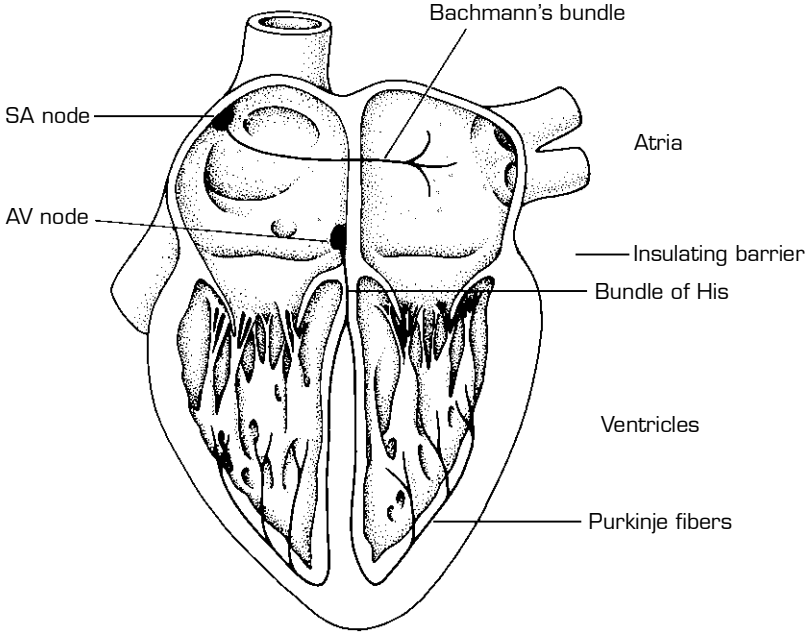

Figure 12-8 Diagram of the spread of action potentials across the heart during a single heartbeat. The excitation originates in the sinoatrial (SA) node of the right atrium and spreads throughout the atria via electrical coupling among the atrial muscle fibers. The fibers of the atria are not electrically connected to those of the ventricles. The action potential spreads to the ventricles via the atrioventricular (AV) node, which introduces a delay between the atrial and ventricular action potentials. When the wave of action potentials leaves the AV node, its spread throughout the ventricles is aided by the rapidly conducting Purkinje fibers of the bundle of His.

the **sinoatrial (SA) node**, which is located in the upper part of the right atrium. This node is indicated in the diagram of the heart in Figure 12-8. The action potential of cells in the SA node is a bit different from that of other cardiac cells. In the SA node, calcium channels play a larger role than sodium channels in triggering the action potential, as well as in sustaining the depolarization during the action potential. In the normal resting human heart, the cells of the SA node generate spontaneous action potentials at a rate of about 70 per minute. These action potentials spread through the electrical connections among fibers throughout the two atria, generating the simultaneous contraction of the atria as discussed in the first section of this chapter. This helps insure that the two atria contract together. The atrial action potentials do not spread directly to the fibers making up the two ventricles, however. This is a good thing, because we know that the contraction of the ventricles must be delayed to allow the relaxed ventricles to fill with blood pumped into them by the atrial contraction. In terms of electrical conduction, the heart behaves as two isolated units, as shown in Figure 12-8: the two atria are one unit and the two ventricles are another. The electrical connection between these two units is made via another specialized group of muscle fibers called the **atrioventricular (AV) node**. Excitation in the atria must travel through the AV node to reach the ventricles. The fibers of the AV node are small in diameter compared with other cardiac fibers. As discussed in Chapter 6, the speed of action potential conduction is slow in small-diameter fibers. Therefore, conduction through the AV node introduces a time delay sufficient to retard the contraction of the ventricles relative to the contraction of the atria. Excitation leaving the AV node does not travel directly through the muscle fibers of the ventricles. Instead, it travels along specialized muscle fibers that are designed for rapid conduction of action potentials. These fibers are called **Purkinje fibers**, and they form a fast-conducting pathway through the ventricles called the **bundle of His**. The Purkinje fibers carry the excitation rapidly to the apex at the base of the heart, where it then spreads out through the mass of ventricular muscle fibers to produce the contraction of the ventricles.

Actions of Acetylcholine and Norepinephrine on Cardiac Muscle Cells

Each muscle fiber of a skeletal muscle receives a direct synaptic input from a particular motor neuron; without this synaptic input, a skeletal fiber does not contract unless stimulated directly by artificial means. Nevertheless, we have seen that cardiac muscle fibers generate spontaneous contractions that are coordinated into a functional heartbeat by the electrical conduction mechanisms inherent in the heart itself. This does not mean, however, that the activity of the heart is not influenced by inputs from the nervous system. The heart receives two opposing neural inputs that affect the heart rate. One input comes from the cells of the parasympathetic nervous system, whose synaptic terminals in the heart release the neurotransmitter ACh. The effect of ACh is to

slow the rate of depolarization during the pacemaker potential of the SA node. This has the effect of increasing the interval between successive action potentials and thus slowing the rate at which this master pacemaker region drives the heartbeat. Acetylcholine acts by increasing the potassium permeability of the muscle fiber membrane. This tends to keep the membrane potential closer to the potassium equilibrium potential and thus retard the growth of the pacemaker potential toward threshold for triggering an action potential. The second neural input to the heart comes from neurons of the sympathetic nervous system, whose synaptic terminals release the neurotransmitter norepinephrine. Activation of this input speeds the heart rate and also increases the strength of contraction. This effect is mediated via an increase in the calcium permeability that is activated upon depolarization. Thus, the parasympathetic and sympathetic divisions of the autonomic nervous system have opposite effects on the heart, just as they typically do in all other target organs as well.

Both the effect of ACh on potassium channels and the effect of norepinephrine on calcium channels are indirect effects. Recall from Chapter 9 that neurotransmitters can affect ion channels either directly (as is the case for ACh at the neuromuscular junction) or indirectly via intracellular second messengers. In the heart, the ACh released by the parasympathetic neurons binds to and activates a type of ACh receptor quite different from the nonspecific cation channel that is directly activated by ACh at the neuromuscular junction. This type of receptor is called the **muscarinic acetylcholine receptor** (because it is activated by the drug muscarine and related compounds, as well as by ACh). The ACh receptor at the neuromuscular junction is called the **nicotinic acetylcholine receptor** (because it is activated by the drug nicotine and related compounds). Muscarinic receptors are not themselves ion channels. Instead, the activated receptor binds to and stimulates GTP-binding proteins (G-proteins, see Chapter 9) that are attached to the inner surface of the membrane near the receptors. This sequence is diagrammed in Figure 12-9. In their active form, with GTP bound, the G-proteins then cause potassium channels to open, increasing the potassium permeability of the muscle cell and slowing the rate of action potentials. The effect of the G-proteins on the channel may be direct, by binding of the channel protein to one or more subunits of the active G-protein, or it may be indirect by stimulation of arachidonic acid, a second messenger produced by enzymatic cleavage of membrane lipids. The muscarinic receptor activates the G-protein by inducing the replacement of GDP by GTP at the GTP binding site. The G-protein remains active interacting with and opening potassium channels as long as GTP occupies the binding site on the G-protein. The activity of the G-protein is terminated by the intrinsic GTPase activity of the G-protein itself, which ultimately hydrolyzes the terminal phosphate of the GTP, converting it to the inactive GDP.

The linkage between the norepinephrine receptor of the cardiac muscle cells and the calcium channels is also mediated via G-proteins. This is summarized in Figure 12-10. The receptor on the cell surface that detects norepinephrine is a type called the **β-adrenergic receptor** (there is also a different

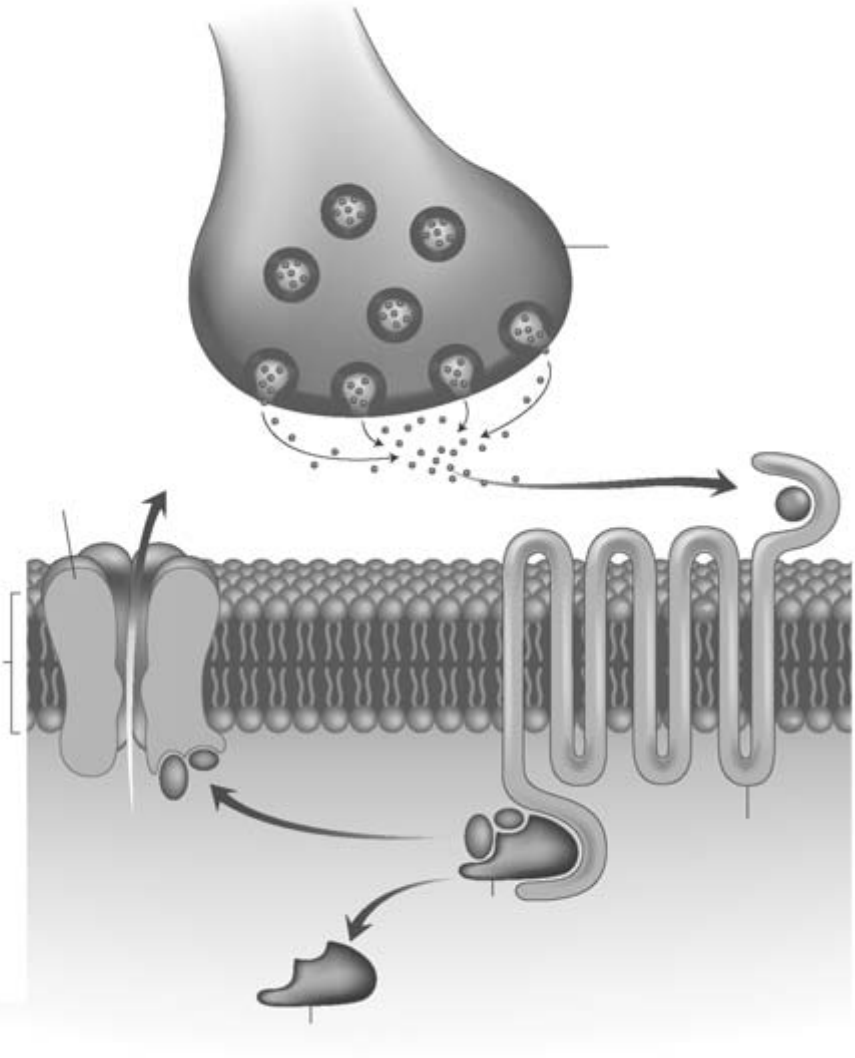

Figure 12-9 Acetylcholine indirectly opens potassium channels in cardiac muscle cells. The synaptic terminals of parasympathetic neurons release ACh, which binds to muscarinic ACh receptor molecules in the membrane of the postsynaptic muscle cell. The receptor then activates G-proteins, by catalyzing the replacement of GDP by GTP on the GTP-binding site on the α-subunit of the G-protein. The β- and γ-subunits dissociate from the α-subunit when GTP binds. The potassium channel is thought to open when the β- and γ-subunits directly interact with the channel. (Animation available at www.blackwellscience.com)

class of norepinephrine receptor called the α-adrenergic receptor, but that class is not involved in the effects of norepinephrine we are discussing here). β-Adrenergic receptors are members of the same family of receptors as the muscarinic cholinergic receptors we discussed above. Like the muscarinic

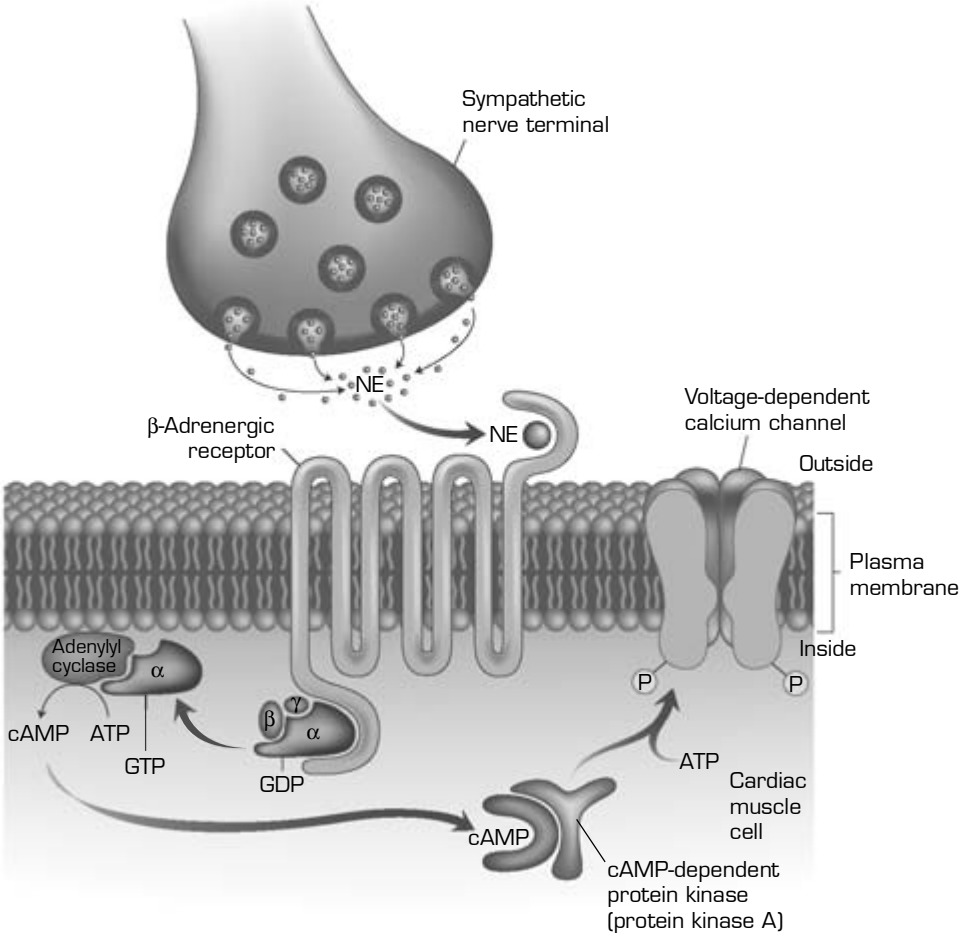

Figure 12-10 Norepinephrine promotes the activation of voltage-dependent calcium channels in cardiac muscle cells. When norepinephrine is released from the synaptic terminals of sympathetic neurons, it combines with β-adrenergic receptors in the postsynaptic membrane of the cardiac muscle cells. The activated receptor stimulates G-proteins, by catalyzing binding of GTP to the α-subunit, which then dissociates from the β- and γ-subunits. The α-subunit of the G-protein activates adenylyl cyclase, an enzyme that converts ATP into cyclic AMP. Cyclic AMP then stimulates protein kinase A, which phosphorylates calcium channel molecules. Phosphorylated calcium channels open more readily during depolarization and also remain open for a longer time. As a result, calcium influx increases during depolarization of the heart cell. (Animation available at www.blackwellscience.com)

receptor, the β-adrenergic receptor is not itself an ion channel. The receptor activates G-proteins inside the cell when norepinephrine occupies its binding site on the outside of the cell. In this case in the heart, the G-protein is a member of a class that exerts its cellular actions by changing the level of **cyclic AMP** inside the cell. The synthetic enzyme for cyclic AMP, **adenylyl cyclase**, is activated by the G-protein, causing cyclic AMP levels to rise inside the cardiac

cell. Cyclic AMP binds to and stimulates **protein kinase A** (also called **cyclic-AMP-dependent protein kinase**), which in turn attaches a phosphate group to (**phosphorylates**) specific amino-acid groups of the calcium channel protein. Phosphorylation of the calcium channel is thought to be required for the channel to be able to open in response to depolarization, so an increase in cyclic AMP inside the cell translates into a greater number of openable calcium channels in the cell. In addition, each channel remains open for a longer time, on average, when it opens. Thus, phosphorylation of the channels greatly potentiates the inward calcium current that flows when the cardiac muscle cells are depolarized.

In the SA node, the triggering of the action potential depends on calcium channels. If there are more calcium channels available, the threshold potential for triggering the action potential will be lower and so the action potential will be triggered earlier during the pacemaker potential in the presence of norepinephrine. Outside of the SA node, in the muscle cells of the atria and ventricles, the role of the calcium channels is to produce the plateau phase of the action potential and to allow calcium influx, which contributes to the muscle contraction. An increase in the number of available calcium channels in these cells will increase the calcium influx during the plateau and thus increase the strength of contraction of the overall heart muscle. The combination of the increase in heart rate and the increase in strength of contraction makes the β-adrenergic receptors a powerful regulator of the amount of blood volume circulated per minute through the heart. The β-adrenergic receptors which ultimately exert their effect by increasing the phosphorylation of voltage-activated calcium channels are therefore targeted by many drugs that are used clinically to increase the heart output in human patients whose heart muscle has been damaged by disease.

One advantage of having the autonomic neurotransmitters exert their actions through G-protein-linked receptors, rather than by direct binding to ion channels, is that the nervous system can produce rather long-term effects on the ion channels of the heart without having to continuously provide an ongoing neural signal. Once the G-proteins are activated, they can affect channel activity for several seconds, until their activation terminates when GTP is hydrolyzed by the G-protein. Thus, ACh can be released briefly from parasympathetic nerve terminals (or norepinephrine from sympathetic nerve terminals) and still affect the heart rate for several seconds after the ACh stops being released. If instead, ACh bound to and opened a ligand-gated potassium channel in order to increase potassium permeability, the neurotransmitter would have to be continuously present, requiring the nervous system to continuously send signals from the central nervous system to the autonomic ganglia to produce a steady train of action potentials in the autonomic motor neurons. In the somatic nervous system, this is exactly what happens. Somatic motor neurons are tightly temporally coupled to the activation of their targets, the skeletal muscle fibers. This allows rapid, sub-second turn-on and turn-off of muscle activity under the control of the somatic nervous system. In general, the targets

controlled by the autonomic nervous system are involved in much slower activities that are typically sustained for longer periods. Therefore, the slower and more sustained activation produced by indirect linkage between neurotransmitter receptor and ion channels seems well suited for the autonomic nervous system.

Summary

Motor systems of the nervous system can be divided into two parts, based on the motor targets that are innervated. The somatic nervous system is responsible for the control of the skeletal musculature, and thus for most of what we normally think of as the behavior of the organism. The autonomic nervous system is responsible for controlling other important organ systems, involved in maintaining the internal homeostasis of the organism. The autonomic nervous system controls the cardiovascular system, the respiratory system, the digestive system, etc. The autonomic nervous system is organized differently from the somatic nervous system. The motor neurons of the autonomic nervous system are located outside the central nervous system, in autonomic ganglia. The somatic motor neurons, by contrast, are located within the spinal cord and are thus part of the central nervous system. The autonomic nervous system is divided into the parasympathetic and the sympathetic divisions. The parasympathetic autonomic ganglia are located close to or in the target organs themselves. The sympathetic ganglia are typically located close to the central nervous system, and most of them found in two chains of ganglia, called the paravertebral ganglia, that parallel the spinal column on each side of the spinal cord.

The nerve terminals of the parasympathetic postganglionic neurons release the neurotransmitter ACh in the target organ. Acetylcholine typically acts on the target cells by activating muscarinic cholinergic receptors, which exert their postsynaptic actions by altering the level of internal second messengers such as cyclic AMP in the postsynaptic cell. The nerve terminals of the sympathetic postganglionic neurons release the transmitter norepinephrine, which also exerts its postsynaptic effect by altering the levels of internal second messengers. In organs that receive both sympathetic and parasympathetic innervation, the actions of ACh and norepinephrine on the target cells are usually opposite. In the heart, for example, ACh decreases heart rate and reduces cardiac output, while norepinephrine increases heart rate and cardiac output.

The muscle fibers making up the heart are specialized in a number of ways to carry out their function of efficiently pumping blood through the vessels of the circulatory system. These specializations lead to a number of differences between cardiac muscle fibers and skeletal muscle fibers, which are summarized in Table 12-1. In addition, the heart as an organ contains specific structures whose function is to coordinate the pumping activity. These structures include the SA node, the AV node, and the Purkinje fibers. The SA node is the

Table 12-1 Comparison of some properties of skeletal and cardiac muscle fibers.

Property	Skeletal muscle	Cardiac muscle
Striated	Yes	Yes
Electrically coupled	No	Yes
Spontaneously contract in absence of nerve input	No	Yes
Duration of contraction controlled by duration of action potential	No	Yes
Action potential is similar to that of neurons	Yes	No
Calcium ions make an important contribution to the action potential	No	Yes
Effect of neural input	Excite	Excite or inhibit
Division of nervous system that provides neural control	Somatic	Autonomic (parasympathetic and sympathetic)
Neurotransmitter released onto muscle fibers by neurons	ACh	ACh (parasympathetic) or Norepinephrine (sympathetic)
Effect of neurotransmitter on postsynaptic ion channels	Direct	Indirect (via G-proteins)

master pacemaker region of the heart, which controls the heart rate during normal physiological functioning of the heart. The AV node provides a path for electrical conduction between the atria and the ventricles and is responsible for the delay between atrial and ventricular contractions. The Purkinje fibers provide a rapidly conducting pathway for distributing excitation throughout the ventricles during the power stroke of a single heartbeat.

The activity of the heart is controlled by both the sympathetic and parasympathetic divisions of the autonomic nervous system. Acetylcholine released by the parasympathetic nerve terminals in the heart causes slowing of the heart rate by opening potassium channels. Norepinephrine released by the sympathetic nerve terminals increases the response of voltage-dependent calcium channels to depolarization, which increases the rate of beating and the strength of contraction. Both effects of neurotransmitters are indirect, mediated via receptors that act via GTP-binding proteins. These receptors are muscarinic receptors in the case of ACh and β-adrenergic receptors in the case of norepinephrine. The effect of the β-adrenergic receptors is to increase the levels of cyclic AMP inside the cardiac cells, which in turn promotes phosphorylation of calcium channels by protein kinase A.

appendix A

Derivation of the Nernst Equation

The Nernst equation is used extensively in the discussion of resting membrane potential and action potentials in this book. The derivation presented here is necessarily mathematical and requires some knowledge of differential and integral calculus to understand thoroughly. However, I have tried to explain the meaning of each step in words; hopefully, this will allow those without the necessary background to follow the logic qualitatively.

This derivation of the Nernst equation uses equations for the movement of ions down concentration and electrical gradients to arrive at a quantitative description of the equilibrium condition. The starting point is the realization that at equilibrium there will be no net movement of the ion across the membrane. In the presence of both concentration and electrical gradients, this means that the rate of movement of the ion down the concentration gradient is equal and opposite to the rate of movement of the ion down the electrical gradient. For a charged substance (an ion), movement across the membrane constitutes a transmembrane electrical current, I. Thus, at equilibrium

$$I_C = -I_E \tag{A-1}$$

or

$$I_C + I_E = 0 \tag{A-2}$$

where I_C and I_E are the currents due to the concentrational and electrical gradients, respectively.

Concentrational Flux

Consider first the current due to the concentration gradient. which will be given by

$$I_C = A\Phi_C ZF \tag{A-3}$$