5.5 The Cardiac Action Potential

Learning Objectives

- Identify an action potential as originating from SA nodal cells, atrial cells, or ventricular cells
- Distinguish between T-type and L-type calcium channels
- Describe what is meant by "pacemaker potential"
- Describe the general effects of sympathetic and parasympathetic stimulation of the SA node
- Identify the signaling pathways used by sympathetic and parasympathetic nervous systems for the electrical system of the heart
- Identify phases 0, 1, 2, 3, and 4 of the ventricular action potential
- Describe the major ion fluxes in phases 0, 1, 2, 3, and 4
- Define "chronotropic" and "inotropic" effects
- Describe the effect of epinephrine on the ventricular myocyte action potential

DIFFERENT CARDIAC CELLS DIFFER IN THEIR RESTING MEMBRANE POTENTIAL AND ACTION POTENTIAL

As described in Chapter 5.4, the heart consists of three main muscle types: atrial muscle, ventricular muscle, and specialized muscle that coordinates electrical signals through the heart. These cells are all excitable, meaning that they can produce a brief, pulse-like change in their membrane potential, and this **action potential** can be conducted over the surface of the cell to activate all parts of the cell nearly simultaneously.

The different cell types have different sets of ion channels on their membranes. The different ion channels have different conductances and these conductances respond differently over time and to changes in membrane potential. These differences cause differences in the resting membrane potentials and the action potentials. Figure 5.5.1 shows the action potentials of sino atrial (SA) nodal cells, atrial muscle cells, and ventricular muscle cells. The resting membrane potentials of the contractile cells are stable and stay at −80 to −90 mV until stimulated by depolarization. The SA nodal cells, on the other hand, have unstable resting membrane potentials that begin at about −60 mV and gradually depolarize and reach threshold.

SA NODAL CELLS SPONTANEOUSLY GENERATE ACTION POTENTIALS WHEREAS CONTRACTILE CELLS HAVE STABLE RESTING MEMBRANE POTENTIALS

The SA nodal cells have a resting membrane potential of about −60 mV. This potential is due to a larger conductance to K^+ ions compared to Na^+ or Ca^{2+} ions. Recall that the resting membrane potential is the chord conductance-weighted average of the equilibrium potentials for all diffusable ions:

$$E_m = \frac{g_{Na}}{(g_{Na}+g_K+g_{Ca})}E_{Na} + \frac{g_K}{(g_{Na}+g_K+g_{Ca})}E_K + \frac{g_{Ca}}{(g_{Na}+g_K+g_{Ca})}E_{Ca} \quad [5.5.1]$$

where E_m is the membrane potential; E_i is the equilibrium potential for the ith ion; g_i is the conductance for the ith ion. Recall here that the chord conductance is a coefficient that relates the current carried by a particular ion to its driving force:

$$I_i = g_i(E_m - E_i) \quad [5.5.2]$$

where I_i is the current carried by the ith ion, g_i is its conductance, E_m is the membrane potential, and E_i is the equilibrium potential for the ith ion. This is a variant of Ohm's law for ions moving across a membrane. The net driving force for the ion is $E_m - E_i$. **Current flow is always taken as the direction of positive ion flow, outward flow being positive**.

Like most excitable cells, the SA nodal cell at rest has a larger g_K than g_{Na} or g_{Ca}, but the channel responsible for g_K is different from that in nerve or in the contractile cells of the ventricle. The stable E_m in contractile cardiac cells is produced by the **inward rectifying K^+ channel** (carrying the current I_{K1}) which SA nodal cells lack. Instead, SA nodal cells have a **delayed rectifying K^+ channel** (carrying the current I_K) that opens slowly upon depolarization and deactivates with time. The initial negative membrane potential depolarizes slowly with time toward a threshold of about −40 to −55 mV. This slow depolarization is called the **pacemaker potential**. Potentials of about −60 mV activate an inward Na^+ current called I_f—for **"funny" current**. It earns this name because it has the peculiar property of being activated by hyperpolarization

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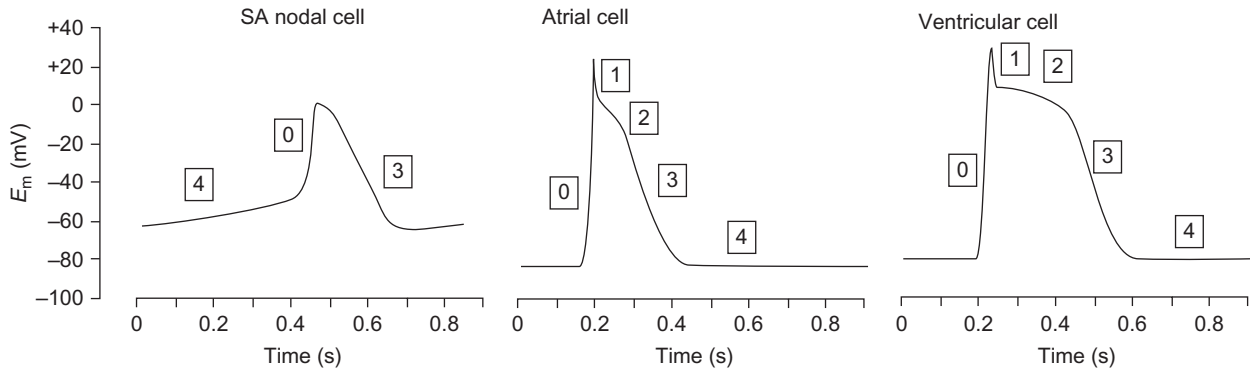

FIGURE 5.5.1 Action potentials in SA nodal cells, atrial muscle cells, and ventricular muscle cells. The SA nodal cell resting membrane potential initially is about −60 mV. It is unstable, gradually spontaneously depolarizing toward threshold at about −50 mV. The gradual increase is called the pacemaker potential. Each of the action potentials occurs in phases numbered 0–4.

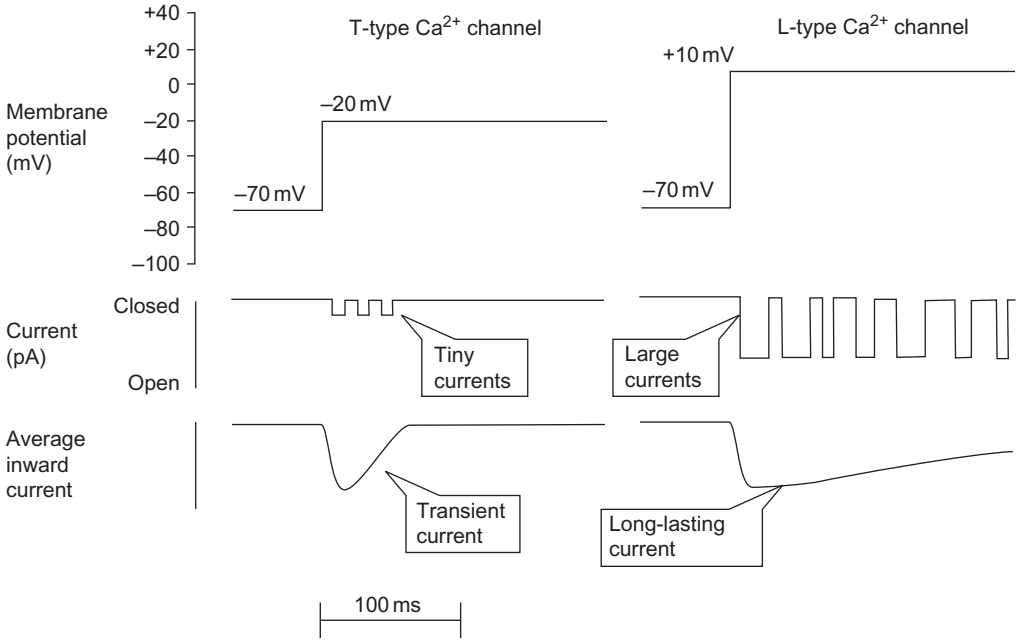

FIGURE 5.5.2 Recordings of the currents passing through single Ca^{2+} channels in small patches of membranes as studied by the patch clamp method. When the membrane is depolarized above about −55 mV, a single Ca^{2+} channel opens sporadically, admitting tiny currents (left, middle). The average response of many of these channels produces the ensemble response of a larger patch of membrane (left, bottom). These T-type channels open transiently. When the membrane is depolarized further, a single L-type Ca^{2+} channel opens. It also flickers between open and closed states, but its open state current is larger (right, middle). Also, the average of many channels produces a longer lasting current (right, bottom), although it also eventually inactivates. Thus the T-type channel's name derives from its tiny current and transient opening, and the L-type channel's name derives from its larger current and its long-lasting openings.

rather than by depolarization, whereas most channels in excitable tissues are activated by depolarization. The membrane potential gradually depolarizes from a combination of the inward Na^+ current (I_f) and from a decay in the outward K^+ current (I_K). When the potential reaches about −55 mV, voltage-gated Ca^{2+} channels contribute to an inward current that depolarizes the membrane potential. Two types of Ca^{2+} channels work here: **T-type Ca^{2+} channels** have tiny conductances that transiently open; **L-type Ca^{2+} channels** have large conductances with long-lasting openings. The T-type Ca^{2+} channels contribute to the last third of the pacemaker potential, whereas the inward Ca^{2+} current from L-type Ca^{2+} channels largely forms the upstroke of the action potential. Traces showing the differences between T-type and L-type channels are shown in Figure 5.5.2. The approximate time course of changes in membrane currents that produce the SA node action potential are shown in Figure 5.5.3.

AUTONOMIC NERVES ALTER THE HEART RATE BY AFFECTING THE PACEMAKER POTENTIAL

SYMPATHETIC STIMULATION ACCELERATES THE HEART BY INCREASING THE SLOPE OF THE PACEMAKER POTENTIAL

As described in Chapter 4.9, sympathetic nerves originating in spinal segments T1–T5 travel to the sympathetic chain where they ascend to the superior cervical

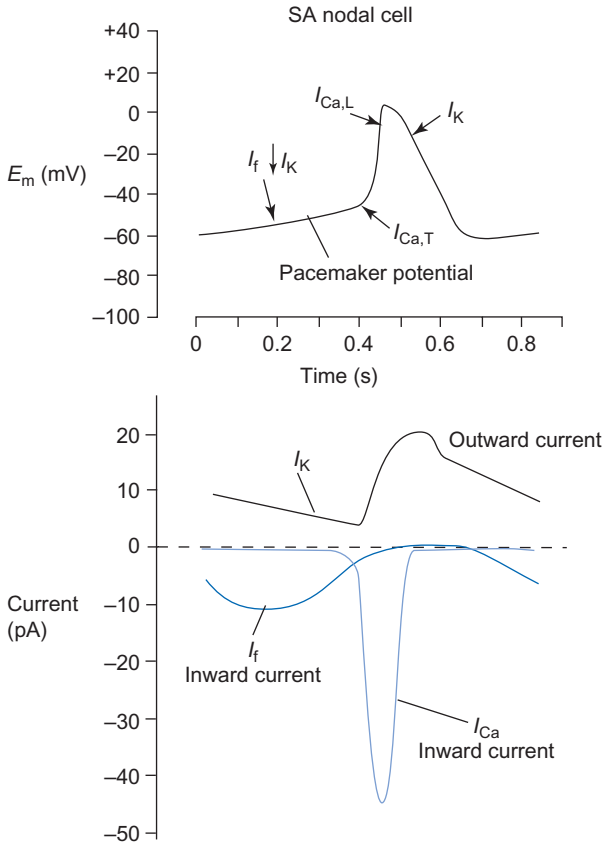

FIGURE 5.5.3 SA nodal currents that produce the SA node action potential. Recall that a positive current is an outward current. Thus, a negative current in the figure denotes an inward flow of positive charge. The pacemaker potential is caused by a decreased outward K^+ current as I_K falls and by an increased inward current of Na^+ as the "funny" current, I_F, increases. As the membrane reaches about −55 mV, T-type and then L-type Ca^{2+} channels open, carrying an inward Ca^{2+} current that contributes to the last third of the pacemaker potential and which produces the rapid upstroke of the SA nodal action potential. Then the delayed rectifying K channel opens and increases outward K^+ current at the same time that I_f and I_{ca} are decreasing. Thus, I_K returns the membrane potential toward its original −60 mV. (Source: *Redrawn from J.R. Levick,* An Introduction to Cardiovascular Physiology, *Arnold, London, 2000.*)

ganglia where they synapse with ganglion cells. These ganglion cells send postganglionic fibers along the great vessels to the heart where they release **norepinephrine**. Norepinephrine released from these terminals, and circulating epinephrine, bind to β_1 **receptors** on SA nodal cells, on AV nodal cells, and on contractile cardiomyocytes. As described in Chapter 2.8, the β_1 receptors are linked to a G_s mechanism. Occupancy of the β_1 receptor causes exchange of GTP for GDP on the α subunit of the heterotrimeric G_s protein. The α subunit dissociates from the β and γ subunits and binds to adenylyl cyclase, activating it. This increases the production of **3′,5′-cyclic AMP** from ATP. The increased concentration of cAMP activates **protein kinase A**, which phosphorylates a number of protein targets within nodal or contractile cells. This increases L-type I_{Ca} and the hyperpolarizing I_K. Cyclic AMP directly activates I_f. This increases the slope of the pacemaker potential, thereby reducing the time required for the SA nodal cells to reach threshold. Increasing the hyperpolarizing I_K current also shortens the time for repolarization. All of these effects increase the frequency of action potentials produced from the SA node (see Figure 5.5.4) and forms the basis for the **chronotropic effects** of the sympathetic stimulation, referring to its ability to accelerate the heart rate. Sympathetic stimulation has a positive chronotropic effect because it accelerates the heart rate. Sympathetic stimulation has other chronotropic effects: it decreases AV nodal delay and shortens the action potential on the contractile cells. If sympathetic stimulation did not shorten the contractile cells' action potential, the long duration of the action potential could limit the heart rate.

PARASYMPATHETIC STIMULATION SLOWS THE HEART RATE BY DECREASING THE SLOPE OF THE PACEMAKER POTENTIAL

Parasympathetic nerves to the heart originate from the vagal motor nuclei in the brainstem and travel over the **vagus nerve** (cranial nerve X) to the heart. The right vagus nerve supplies the SA node and slows its pacemaker; the left vagus innervates the AV node and slows its conduction of the cardiac impulse to the bundle of His. The vagus fibers are preganglionic; they make synapses with parasympathetic neurons within the heart. These ganglionic fibers send short postganglionic fibers to the nodal and muscle tissue. These terminals release **acetylcholine**, the main neurotransmitter for postganglionic parasympathetic nerves. Acetylcholine can bind to a variety of receptors. In the heart, its main receptor is the **M2 receptor**. Binding to the M2 receptor has two main effects:

1. It activates a G_i mechanism that inhibits adenylyl cyclase, in opposition to the β_1 mechanism that norepinephrine activates.
2. Second, the $\beta\gamma$ subunits released by acetylcholine binding to G_i activates an acetylcholine-sensitive K^+ channel that carries a current called $\boldsymbol{I_{K-ACh}}$.

These two effects slow the heart rate by:

- hyperpolarizing the SA nodal cells, thereby increasing the time required to depolarize to threshold;
- decreasing the slope of the pacemaker potential by decreasing cAMP and decreasing phosphorylation of target proteins.

The overall effects of sympathetic and parasympathetic stimulation on the SA node action potential are shown in Figure 5.5.4. The subcellular basis for these effects is shown in Figure 5.5.5.

THE IONIC BASIS OF THE VENTRICULAR CARDIOMYOCYTE ACTION POTENTIAL

THE RESTING MEMBRANE POTENTIAL, PHASE 4, IS SET BY E_K AND LARGE G_K

The resting membrane potential of ventricular contractile cells is determined by the conductance-weighted average of the equilibrium potentials for all of the diffusable

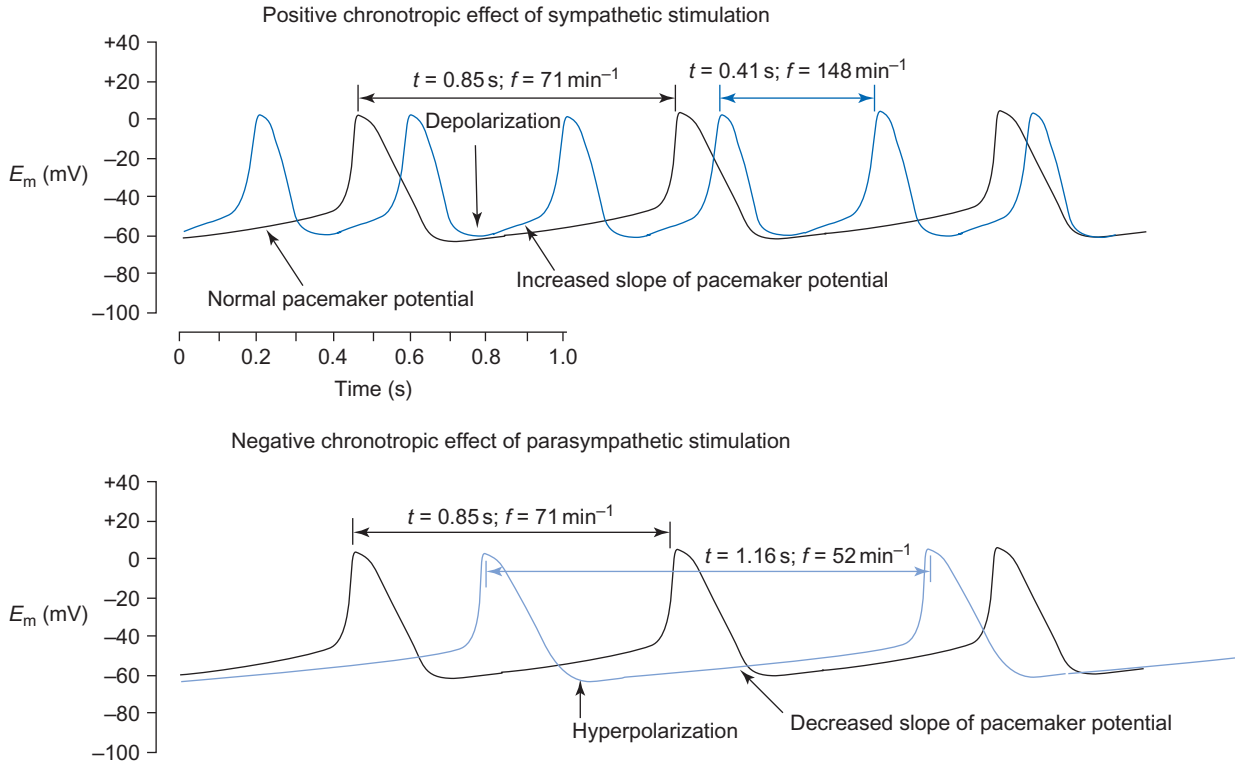

FIGURE 5.5.4 Effects of sympathetic (top) and parasympathetic (bottom) stimulation on the SA nodal action potential. Since the SA node is the pacemaker of the heart, the heart rate depends directly on the rate of action potential production by the SA node. Sympathetic stimulation causes phosphorylation of membrane channels that alters their conductance. The result is a depolarization, an increase in the slope of the pacemaker potential, a shorter time to reach threshold resulting in an increase in the rate of firing of action potentials, and consequently a higher heart rate. Parasympathetic stimulation decreases phosphorylation and independently stimulates a K^+ channel that carries I_{K-ACh}. These effects cause a hyperpolarization, a decrease in the slope of the pacemaker potential, a decrease in the rate of firing of action potentials, and a decreased heart rate.

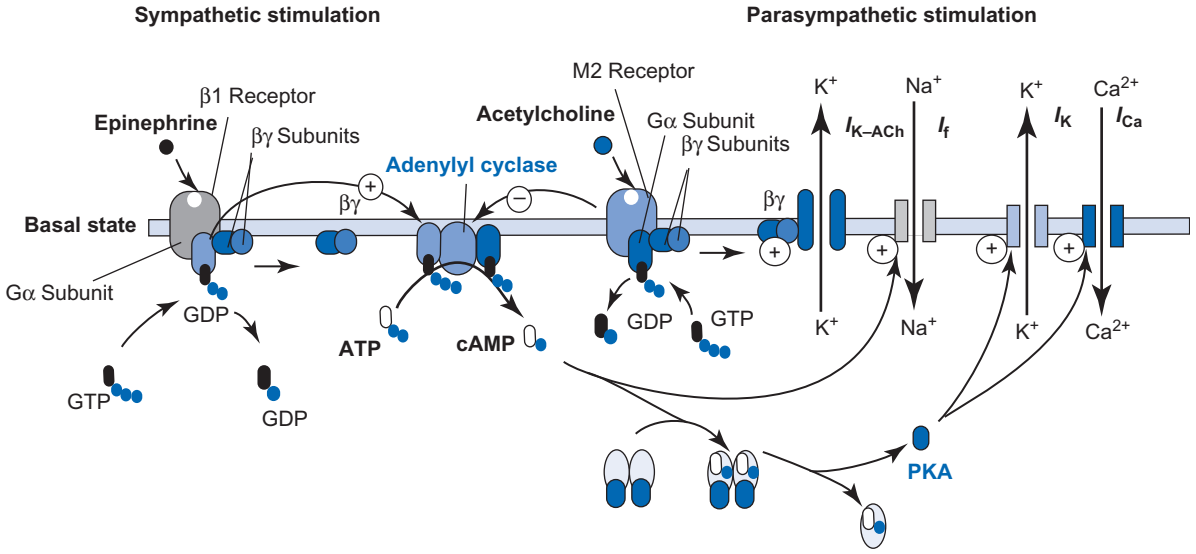

FIGURE 5.5.5 Molecular mechanism of action of sympathetic and parasympathetic stimulation of SA nodal cells. See text for details.

ions, as described in Eqn [5.5.1]. The equilibrium potential for Na^+ is given by the Nernst Equation, whose derivation was described in Chapter 3.1:

$$E_{Na} = \frac{RT}{z\Im} \ln \frac{[Na^+]_o}{[Na^+]_i} \quad [5.5.3]$$

where E_{Na} is the equilibrium potential for Na^+, R is the gas constant, which in electrical units is 8.314 J mol^{-1} K^{-1}, T is the temperature in K, z is the valence on the Na^+ ion, which is 1.0, and $\Im$ is the faraday = 9.649×10^4 C mol^{-1}. The logarithm is the natural log. Expressions such as that in Eqn [5.5.3] can

TABLE 5.5.1 Concentrations of Selected Ions in the Extracellular Fluid and Intracellular Fluid and Their Calculated Equilibrium Potentials for Cardiomyocytes

Ion, X	$[X_o]$ (M)	$[X_i]$ (M)	E_x (V)
K^+	4×10^{-3}	140×10^{-3}	−0.094
Na^+	145×10^{-3}	10×10^{-3}	+0.071
Ca^{2+}	1.2×10^{-3}	1×10^{-7}	+0.125
Cl^-	114×10^{-3}	30×10^{-3}	−0.036

be used for each ion, and the resulting equilibrium potentials are listed in Table 5.5.1 for the ionic conditions in the cardiomyocytes.

The resting membrane potential in the ventricular cells is −0.080 to −0.090 V. This is because at rest in these cells, $g_K >> g_{Na}$, g_{Ca}, and g_{Cl}, so by Eqn [5.5.1] the resting membrane potential is closer to E_K than to E_{Na}, E_{Ca}, or E_{Cl}. Two specific channels account for the large resting g_K. These channels carry the **delayed rectifying K^+ current** (I_K) and the **inwardly rectifying K^+ current** (I_{K1}). The resting E_m is never as negative as E_K, however, because there is residual conductance to Na^+ that carries the **background current**, I_b. This is the stable situation that pertains to the resting cell and accounts for phase 4 of the action potential for ventricular cells shown in Figure 5.5.1.

THE UPSTROKE OF THE ACTION POTENTIAL, PHASE 0, IS DUE TO INWARD Na^+ CURRENT

Ventricular muscle cells contain Na^+ channels like those in nerve tissue (Chapter 3.2). These voltage-gated channels open upon depolarization, causing an inward Na^+ current (because E_m at rest is −85 mV and E_{Na} is +71 mV, the driving force for Na^+ is: $E_m - E_{Na} = -156$ mV; the negative sign means the Na^+ current enters the cell). This I_{Na} causes a further depolarization, opening still more Na^+ channels and increasing I_{Na} still further. This causes an explosive depolarization of the cell, reaching about +50 mV in less than 2 ms. Like the regenerative Na^+ channels in nerve, the Na^+ channels close spontaneously. The model for the Na^+ channel is the Hodgkin–Huxley model, in which the Na^+ channel acts as if it had two gates, called m and h. The m gate is the activation gate, and the h gate is the inactivation gate. At rest, the h gate is open and the m gate is closed. Depolarization activates the channel by opening the m gate. Since both m and h gates are open, the channel conducts Na^+ into the cell, depolarizing it further. Depolarization also causes the delayed inactivation of the channel by closing the h gate. Thus, I_{Na} is transient. This Na^+ channel is blocked by **tetrodotoxin**. The channel returns to its resting configuration first by closing the m gate and then by opening the h gate. In this state it is closed but activatable. According to this scheme, there is a time when the channel has a closed inactivation gate. During this time, it cannot be opened and so the membrane is **refractory** to excitation: it cannot be excited to form an action potential when the Na^+ channel is in the inactivated state. We can identify an **absolute refractory period** (ARP) during which no stimulus, no matter how large, can induce the cell to fire an action potential. During the **relative refractory period**, the cell can fire an action potential but a larger than normal stimulus is required to excite the cell. The states of the channel and refractory periods are shown in Figure 5.5.6.

PHASE 1 REPOLARIZATION IS CAUSED BY K^+ OUTWARD CURRENT (I_{to}) WHILE THE Na^+ CHANNEL INACTIVATES

Repolarization occurs when the outward current exceeds the inward current. At the membrane potential at the end of phase 0, the driving force for Na^+ is inward, but not so strong because E_m is closer to E_{na}, and the driving force for K^+ entry is large because $E_m - E_K$ is large. The falling Na^+ conductance alone would tend to repolarize the cell. However, the conductance of the channel carrying I_{K1} is **inwardly rectified**. Inwardly rectifier K^+ channels derive their name from the fact that they pass much larger inward currents at negative E_m than outward currents at positive E_m, even in symmetrical $[K^+]$ solutions. Thus, at positive E_m the outward current I_{K1} is suppressed by reducing the conductance of its channel. This prevents the immediate repolarization of the action potential and allows the rest of the action potential to develop.

Another channel, the transient outward K^+ channel, causes a current called I_{to} that contributes to the repolarization of phase 1. Depolarization rapidly but transiently activates this channel, which inactivates over about 100 ms, thereby contributing to net membrane current over phases 1 and 2 of the action potential.

Ca^{2+} INWARD CURRENT MAINTAINS THE PLATEAU OF PHASE 2

The L-Type Ca^{2+} Channels Conduct Inward Ca^{2+} Current During the Early Plateau

Up to now, the action potential that we have described is similar to that in nerve: the resting membrane potential is set by a large g_K compared to g_{Na} or g_{Ca}; the upstroke is due to rapidly but transiently increasing g_{Na}, followed by a repolarization due to the decreased g_{Na}

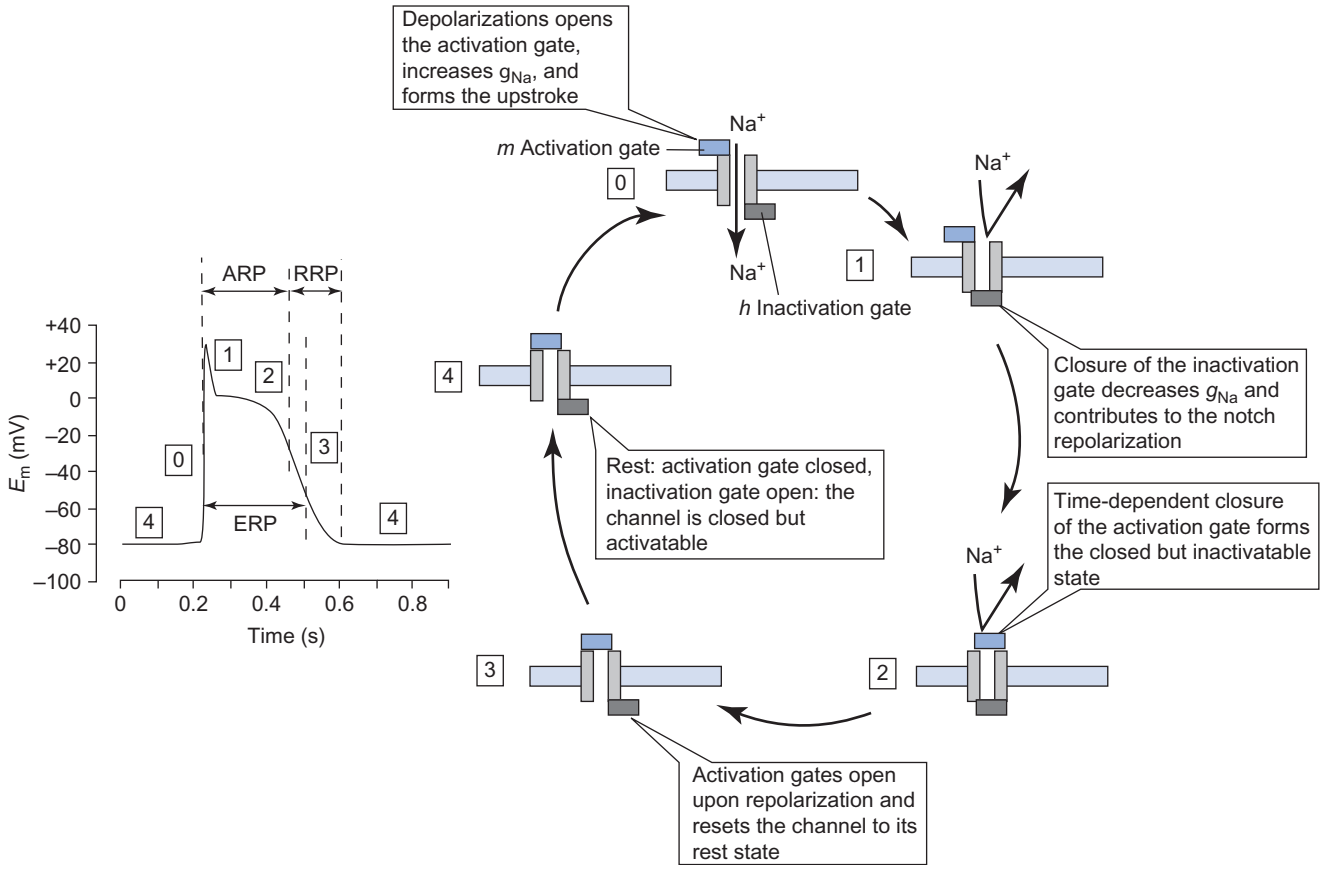

FIGURE 5.5.6 States of the fast Na^+ channel during the action potential. During phase 4, the channel is closed but activatable, meaning that the activation gate, *m*, is closed, whereas the inactivation gate, *h*, is open. Upon depolarization, the activation gate opens regeneratively, causing a rapid increase in g_{Na} that produces the upstroke of the action potential, phase 0. During phase 1, the Na^+ channels close their inactivation gates. This is followed by closure of the activation gates. During repolarization in phase 3 the inactivation gates open in a progressively larger fraction of the channels, leading to the resting state with activation gate closed but activatable. When the inactivation gate is closed, opening of the activation gate still does not produce an open channel. Thus, when the inactivation gate is closed, the Na^+ channel cannot be activated, and the membrane containing Na^+ channels in this state cannot elicit an action potential. This state of the cell membrane is called a refractory state. The absolute refractory period (ARP) corresponds to the period in which no action potential can be elicited, regardless of the depolarization. The relative refractory period (RRP) indicates that an action potential can be elicited but at higher thresholds. The effective refractory period (ERP) corresponds to the time during which an action potential will not have sufficient current to depolarize adjacent cells.

and brief increase in I_{to}, carried by K^+. In ventricular cells, however, repolarization is delayed. There is a plateau phase that keeps the membrane potential elevated for 200–400 ms and constitutes most of the **action potential duration** (**APD**). The inward current during the plateau phase is primarily due to L-type Ca^{2+} channels. These channels open upon depolarization but more slowly than the Na^+ channels that produce the upstroke of the action potential. The L-type Ca^{2+} channels inactivate slowly during the plateau.

$I_{Ca,L}$ Is Balanced in Part by the Delayed Rectifier K^+ Channel

The plateau phase is characterized by a nearly steady membrane potential between about 0 and −20 mV. This slowly changing membrane potential means that the inward $I_{Ca,L}$ must be balanced by some outward current. The outward current is a K^+ current carried by the delayed rectifier (I_K), so-named because they activate slowly upon depolarization. The amplitude and time course of $I_{Ca,L}$ and I_K set the time course of phases 2 and 3.

CLOSURE OF THE L-TYPE CHANNEL AND INCREASED g_K CAUSE REPOLARIZATION IN PHASE 3

During the plateau phase, $I_{Ca,L}$ decays and I_K increases, leading to an acceleration of the rate of repolarization. As the membrane repolarizes, I_{K1}, the inwardly rectifying K^+ current, increases. This further increases g_K and further accelerates repolarization. During this time, the Na^+ and Ca^{2+} channels reset themselves. These channels need repolarization to recover from the closed and inactivated state to the closed but activatable state.

THE Na^+–Ca^{2+} EXCHANGER PASSES A CURRENT

The Ca^{2+} carried by I_{Ca} that enters the cardiac myocytes with each contraction must be pumped out again during some other part of the cycle or else Ca^{2+}

would accumulate indefinitely. There are two mechanisms on the surface membrane of the cells that pump out Ca^{2+} ions: a plasma membrane Ca-ATPase (PMCA) and a Na^{+}–Ca^{2+} exchanger (NCX). The PMCA couples uphill Ca^{2+} transport to the chemical energy in ATP hydrolysis, and thus it is a primary active transport mechanism. The NCX was discussed in Chapter 2.6 as an example of secondary active transport, which derives its energy for Ca^{2+} extrusion from the energy of the Na^{+} gradient. It transports three Na^{+} ions for each Ca^{2+}, so each turnover is accompanied by a net movement of one positive charge. The NCX is reversible, depending on the electrochemical potentials for each ion on both sides of the membrane. During the plateau phase, NCX transports Ca^{2+} in and Na^{+} out, and thereby it contributes an outward current. This is the NCX reverse mode. During the latter stages of the plateau, $I_{Ca,L}$ gradually inactivates and the NCX pumps one Ca^{2+} out and three Na^{+} in, producing an inward current that delays repolarization.

Figure 5.5.7 reprises the ventricular action potential, the conductance changes, and the currents that produce the action potential.

EPINEPHRINE ENHANCES THE L-TYPE Ca^{2+} CHANNELS, WHICH ELEVATES THE ACTION POTENTIAL PLATEAU

β_1 Adrenergic stimulation of the heart activates adenylyl cyclase through a G_s-coupled system, as illustrated in Figure 5.5.5. Increased adenylyl cyclase activity increases cytoplasmic [cAMP], which in turn activates PKA that phosphorylates target proteins. One of these target proteins is the L-type Ca^{2+} channel. Its phosphorylation increases $I_{Ca,L}$ during the plateau phase, causing a dome-shaped action potential (see Figure 5.5.8). There are multiple effects of β_1 adrenergic agonists on the heart. We have already discussed the chronotropic effects that increase the heart rate through effects on the SA nodal cells. β_1 Adrenergic agonists also exert a **positive inotropic effect**, which refers to their ability to increase the strength of myocardial contraction. Part of this derives from the extra Ca^{2+} that enters during the plateau phase of the action potential. Like skeletal muscle, cardiac muscle is activated by a transient increase in cytoplasmic $[Ca^{2+}]$. In skeletal muscle, all of this cytoplasmic Ca^{2+} derives from sarcoplasmic reticulum (SR) stores. The skeletal muscle system is geared for total or near total activation of the actomyosin cross bridges by having large Ca^{2+} transients from an abundant SR. Fine control of the force of skeletal muscle is provided by neural control. In cardiac muscle, the strength of contraction is regulated in large part by the size of the Ca^{2+} transient, and it has two sources: the intracellular stores in the SR and influx into the cell across the cell membrane, the sarcolemma. When Ca^{2+} entry increases, it increases the Ca^{2+} transient and increases the number of actomyosin cross bridges, thereby increasing the force of cardiac muscle contraction. Thus, increasing $I_{Ca,L}$ by β_1 adrenergic stimulation increases the force of cardiac muscle contraction.

THE ACTION POTENTIAL IS CONDUCTED TO NEIGHBORING CELLS THROUGH GAP JUNCTIONS IN THE INTERCALATED DISKS

The space constant in cardiac tissue is some 20 times the length of an individual cell in the longitudinal direction and many times the cell diameter in the transverse direction. The cells are electrically coupled through **gap junctions** where they join at the intercalated disks. As in the nervous system, gap junctions in cardiac tissue form when **connexin** hexamers on one cell membrane join up with connexin hexamers on an adjacent membrane. Each hexamer forms a hemi-channel, and together they form a complete channel that allows diffusion of ions and small molecular weight signaling molecules between cells. There are at least six different isoforms of connexin, and four of these are expressed in heart. The gap junctions allow the action potential to spread passively from one cell to another without using neurotransmitters and without using large numbers of conducting fibers. A schematic diagram of a gap junction is shown in Figure 5.5.9.

SUMMARY

The cardiac action potential takes a different form in different cardiac cells, which include SA nodal cells, atrial muscle cells, AV nodal cells, Purkinje fibers, and ventricular muscle cells. We consider here the action potential of SA nodal cells and ventricular muscle cells. The SA node contains the most excitable cells in the heart, and so it sets the pace of the heart. The SA nodal cells have an unstable resting membrane potential that spontaneously depolarizes due to a pacemaker potential. This is caused by the "funny" Na^{+} current and a decrease in the conductance of the inward rectifier K^{+} channel. On reaching a threshold of about −55 mV, an action potential begins by the progressive opening of T-type and L-type Ca^{2+} channels. The spike returns to baseline because of an increase in the delayed rectifier K^{+} current. The slope of the pacemaker potential and the resting membrane potential determine the time necessary to reach threshold: the sooner threshold is reached, the sooner an action potential is fired and the faster the heart rate. Sympathetic stimulation increases the slope of the pacemaker potential and depolarizes the resting membrane potential. Both of these help increase the heart rate. Sympathetic stimulation releases norepinephrine that acts on the SA node through β_1 receptors that are coupled to a G_s protein. This increases [cAMP] within the cell, which activates protein kinase A that subsequently phosphorylates a number of target proteins. Parasympathetic stimulation is coupled to M2 receptors that decrease [cAMP] and therefore opposes the positive chronotropic effect of sympathetic stimulation. Parasympathetic stimulation releases acetylcholine at terminals of the vagus nerve in the heart, which lowers the pacemaker potential and hyperpolarizes the cell. This reduces the frequency of action potentials originating at the SA node.

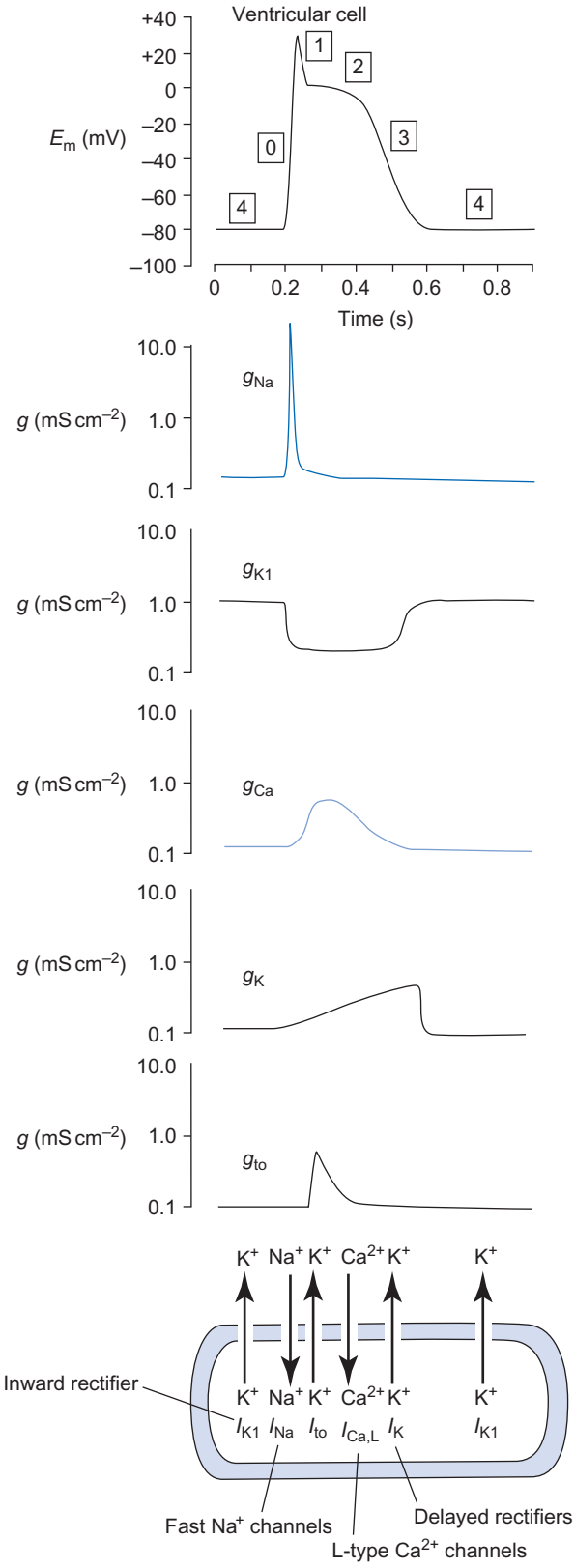

FIGURE 5.5.7 Conductance changes and currents responsible for the major features of the ventricular myocyte action potential. The action potential consists of five phases; phase 4 is the resting phase, produced largely by inward rectifying K^+ channels that keep g_K greater than g_{Na} or g_{Ca} at rest. These channels carry I_{K1}. Phase 0 is the upstroke of the action potential, caused by the opening of fast Na^+ channels that carry I_{Na}. These open transiently, and a notch in the action potential (phase 1) is formed when the fast Na^+ channels close and L-type Ca^{2+} channels open and I_{to} contributes to phase 1. The plateau phase (phase 2) is maintained by a combination of $I_{Ca,L}$, the delayed rectifier (I_K) and the current carried by the NCX I_{NaCa}. Repolarization in phase 3 is brought about by inactivation of $I_{Ca,L}$ and increases in I_K (the delayed rectifier current) and I_{K1} (the inward rectifier current). The time courses of the conductance changes for each of the main currents involved in the ventricular myocyte action potential are shown individually. The main currents that produce the action potential are shown in the bottom of the figure.

The action potential in ventricular cardiomyocytes begins with a rapid upstroke (phase 0) caused by the regenerative opening of fast Na^+ channels. This is followed by a partial repolarization (phase 1) caused by closing of the fast channels, opening of a transient outward K^+ channel, and reduced conductance of the inward rectifier K^+ channel. The membrane potential enters the plateau phase (phase 2) due to inward Ca^{2+} currents carried by

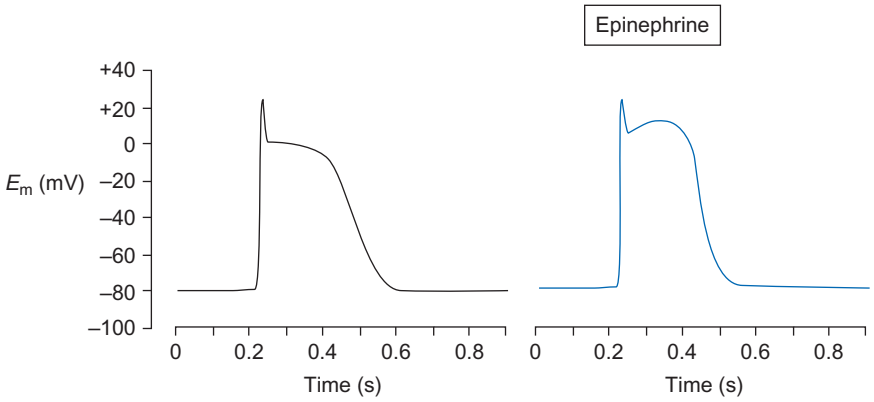

FIGURE 5.5.8 Effect of epinephrine, which stimulates β receptors, on the cardiomyocyte action potential. Epinephrine begins a signal cascade that results in the phosphorylation of the L-type Ca^{2+} channel, among other targets. Its effects include an increase in inward Ca^{2+} current during the plateau phase (phase 2) that results in an elevation of the plateau. Left, normal ventricular cardiomyocyte action potential; right, after exposure to epinephrine.

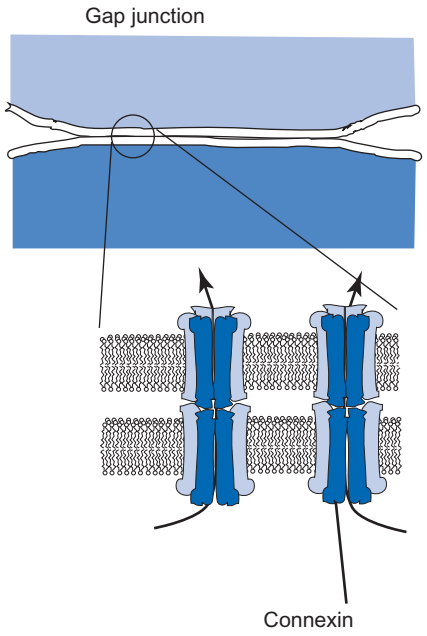

FIGURE 5.5.9 The gap junction. A small conductive, aqueous pathway is available between adjoining heart cells by the juxtapositioning of two hemi-channels consisting of connexin hexamers. Two hemi-channels from adjacent membranes can align, forming a direct aqueous channel between the two cells.

the L-type Ca^{2+} channel. The repolarization phase, phase 3, occurs because these Ca^{2+} channels gradually inactivate and delayed rectifier K^+ channels contribute to an outward K^+ current. During repolarization, the fast Na^+ channels revert to their resting state of closed but activatable.

The action potential spreads passively throughout regions of ventricular cardiomyocytes through the gap junction connections between cells.

REVIEW QUESTIONS

1. Draw and label the phases of the action potentials for SA nodal cells, atrial cells, and ventricular cells.
2. What is responsible for the pacemaker potential? How does sympathetic stimulation alter it? How does parasympathetic stimulation alter it? What does sympathetic stimulation do the resting membrane potential in SA nodal cells? What does parasympathetic stimulation do? How do these stimulations alter heart rate?
3. What currents are responsible for the upstroke of the action potential in SA nodal cells and in ventricular muscle cells?
4. What is phase 1 of the ventricular myocyte action potential, and what causes it?
5. What causes the plateau of the action potential?
6. What currents are responsible for repolarization of the ventricular myocyte (phase 3)?
7. During what part of the action potential do the Na channels inactivation gates close and activation gates open?