Cardiac Ion Channels
Augustus O. Grant, MB, ChB, PhD

The analysis of the molecular basis of the inherited cardiac arrhythmias has been the driving force behind the identification of the ion channels that generate the action potential. The genes encoding all the major ion channels have been cloned and sequenced. The studies have revealed greater complexity than heretofore imagined. Many ion channels function as part of macromolecular complexes in which many components are assembled at specific sites within the membrane. This review describes the generation of the normal cardiac action potential. The properties of the major ionic currents are examined in detail. Special emphasis is placed on the functional consequences of arrhythmia-associated ion channel mutations. The review concludes with a glimpse of the directions in which this new electrophysiology may lead.

The Cardiac Action Potential
The normal sequence and synchronous contraction of the atria and ventricles require the rapid activation of groups of cardiac cells. An activation mechanism must enable rapid changes in heart rate and also respond to the changes in autonomic tone. The propagating cardiac action potential fulfils these roles. Figure 1 illustrates the 5 phases of the normal action potential:

1. Phase 4, or the resting potential, is stable at \(-90 \text{ mV}\) in normal working myocardial cells.
2. Phase 0 is the phase of rapid depolarization. The membrane potential shifts into positive voltage range. This phase is central to rapid propagation of the cardiac impulse (conduction velocity, \(\theta = 1 \text{ m/s}\)).
3. Phase 1 is a phase of rapid repolarization. This phase sets the potential for the next phase of the action potential.
4. Phase 2, a plateau phase, is the longest phase. It is unique among excitable cells and marks the phase of calcium entry into the cell.
5. Phase 3 is the phase of rapid repolarization that restores the membrane potential to its resting value.1

The action potentials of pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes are significantly different from those in working myocardium. The membrane potential at the onset of phase 4 is more depolarized (\(-50\) to \(-65 \text{ mV}\)), undergoes slow diastolic depolarization, and gradually merges into phase 0. The rate of depolarization in phase 0 is much slower than that in the working myocardial cells and results in slow propagation of the cardiac impulse in the nodal regions (\(\theta = 0.1\) to 0.2 m/s). Cells in the His-Purkinje system may also show phase 4 depolarization under special circumstances. The characteristics of the action potential change across the myocardial wall from endocardium, midmyocardium, to epicardium. Epicardial cells have a prominent phase 1 and the shortest action potential. The action potential duration is longest in the midmyocardial region.2 The average duration of the ventricular action potential duration is reflected in the QT interval on the ECG. Factors that prolong the action potential duration (eg, a decrease in outward K\(^+\) currents or an increase in inward late Na\(^+\) current) prolong the action potential duration and the QT interval on the ECG. The QT interval of males and females is equal during early childhood. However, at puberty the interval of males shortens.3 Studies have focused on the longer QT interval of females and the possible reduction in K\(^+\) channel function. However, a definitive conclusion has not been made.

General Properties of Ion Channels
The generation of the action potential and the regional differences that are observed throughout the heart are the result of the selective permeability of ion channels distributed on the cell membrane. The ion channels reduce the activation energy required for ion movement across the lipohilic cell membrane. During the action potential, the permeability of ion channels changes and each ion, eg, X, moves passively down its electro-chemical gradients (\(\Delta V = [V_m - V_x]\) where \(V_m\) is the membrane potential and \(V_x\) the reversal potential of ion X) to change the membrane potential of the cell. The electrochemical gradient determines whether an ion moves into the cell (depolarizing current for cations) or out of the cell (repolarizing current for cations). Homeostasis of the intracellular ion concentrations is maintained by active and coupled transport processes that are linked directly or indirectly to ATP hydrolysis.

Ion channels have 2 fundamental properties, ion permeation and gating.4 Ion permeation describes the movement through the open channel. The selective permeability of ion channels to specific ions is a basis of classification of ion channels (eg, Na\(^+\), K\(^+\), and Ca\(^{2+}\) channels). Size, valency, and hydration energy are important determinants of selectivity. The selectivity ratio of the biologically important alkali cations is high. For example, the Na\(^+\):K\(^+\) selectivity of...
sodium channels is 10:1. Ion channels do not function as simple fluid-filled pores, but provide multiple binding sites for ions as they traverse the membrane. Ions become dehydrated as they cross the membrane as ion-binding site interaction is favored over ion–water interaction. Like an enzyme–substrate interaction, the binding of the permeating ion is saturable. Most ion channels are singly occupied during enzyme–substrate interaction, the binding of the permeating ion is saturable. Most ion channels are singly occupied during 

for ions as they traverse the membrane. This property becomes evident when the membrane potential is abruptly returned to its hyperpolarized (resting) value while the channel is open, closes by deactivation, a reversal of the normal activation process. The multiple mechanisms of inactivation are discussed below. If the membrane potential is abruptly returned to its hyperpolarized (resting) value while the channel is open, closes by deactivation, a reversal of the normal activation process. These transitions may be summarized by the following state diagram (as proposed for the Na\(^+\) channel): 

The C→I transition may occur from multiple closed states. However, because these states are nonconducting, the kinetics of transition between them are difficult to resolve with certainty.

Ligand-dependent gating is the second major gating mechanism of cardiac ion channels. The most thoroughly studied channel of this class is the acetylcholine (Ach)-activated K\(^+\) channel. Acetylcholine binds to the M-2 muscarinic receptor and activates a G protein–signaling pathway, culminating in the release of the subunits Goi and Gβγ. The Gβγ subunit activates an inward-rectifying K\(^+\) channel, \(I_{\text{Kach}}\) that abbreviates the action potential and decreases the slope of diastolic depolarization in pacemaker cells. \(I_{\text{Kach}}\) channels are most abundant in the atria and the SA and atrioventricular nodes. \(I_{\text{Kach}}\) activation is a part of the mechanism of the vagal control of the heart. The ATP-sensitive K\(^+\) channel, also termed the ADP-activated K\(^+\) channel, is a ligand-gated channel distributed abundantly in all regions of the heart. The open probability of this channel is proportional to the [ADP]/[ATP] ratio. This channel couples the shape of the action potential to the metabolic state of the cell. Energy depletion
during ischemia increases the [ADP]/[ATP] ratio, activates $I_{K_{ATP}}$, and abbreviates the action potential. The abbreviated action potential results in less force generation and may be cardioprotective. This channel also plays a central role in ischemic preconditioning.

The mechanosensitive or stretch-activated channels are the least studied. They belong to a class of ion channels that can transduce a physical input such as stretch into an electric signal through a change in channel conductance. Acute cardiac dilatation is a well-recognized cause of cardiac arrhythmias. Stretch-activated channel are central to the mechanism of these arrhythmias. Blunt chest wall impact at appropriately timed portions of the cardiac cycle may also result in PVCs or ventricular fibrillation (the VF of commotio cordis). The channels that transduce the impact into an electric event are unknown.

The major ion channels that shape the action potential have been cloned and sequenced. Table 1 lists the clones of the $\alpha$-subunits of the major ion channels. The sodium channel consists of 4 homologous domains, DI – DIV, arranged in a 4-fold circular symmetry to form the channel (Figure 2). Each domain consists of 6 membrane-spanning segments, S1 through S6. The membrane-spanning segments are joined by alternating intra- and extracellular loops. The loops between S5 and S6 of each domain termed the P loops curve back into the membrane to form the pore. Each S4 segment has a positively charged amino acid at every third or fourth position and acts as the sensor of the transmembrane voltage. The movement of these charges across the membrane during channel gating generates small currents that can be recorded at high resolution. Transmission of the voltage sensor transition to S-5 has been suggested as the critical element of channel gating.

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The highly potent neurotoxin tetrodotoxin (TTX) and the systematic mutation of residues in the loop have enabled the tentative identification of the amino acid residues that are critical for ion permeation; these residues include aspartate, glutamate, lysine, and alanine (D, E, K, and A) contributed by D1 through D4, respectively. The lysine (K) in domain III is critical for Na:K selectivity. Mutation of multiple residues in D4 renders the channel noncation selective.

Each sodium channel opens very briefly (<1 ms) during more than 99% of depolarizations. The channel occasion-
ally shows alternative gating modes consisting of isolated brief openings occurring after variable and prolonged latencies and bursts of openings during which the channel opens repetitively for hundreds of milliseconds. The isolated brief openings are the result of the occasional return from the inactivated state. The bursts of openings are the result of occasional failure of inactivation. Sodium channel mutations that favor these slow gating modes are the basis of a subgroup of the long QT syndromes (LQT3). Sodium channel inactivation is a multifaceted process that may occur in the time frame of milliseconds, seconds, or tens of seconds, depending on the duration of the antecedent depolarization. In response to depolarization lasting tens of milliseconds, the process is fast. Intermediate and slow inactivation develops over hundreds of milliseconds, for example during the course of the normal action potential and inactivation develops over hundreds of milliseconds. The isolated brief openings occurring after variable and prolonged latencies may occur in the time frame of milliseconds, seconds, or tens of seconds, depending on the duration of the antecedent depolarization. In response to depolarization lasting tens of milliseconds, the process is fast. Intermediate and slow inactivation develops over hundreds of milliseconds, for example during the course of the normal action potential and in response to trains of action potentials. The fraction of channels available for opening (1-the inactivated fraction), denoted by h, varies from ≈1 at −90 mV to zero at ≈−40 mV. The structural basis of fast sodium channel inactivation resides in the interdomain linker between DIII and DIV (ID111/IV). The primary amino acid sequence of this region is highly conserved between species and sodium channel subtypes. The tertiary structure of the region has been resolved by NMR spectroscopy. The putative form is that of a tilting disk that folds into the membrane to occlude the pore. The amino acid triplet isoleucine, phenylalanine, methionine (IFM) is crucial for inactivation; the mutation IFM→QQQ abolishes inactivation. The receptor site to which the triplet binds has not been identified. The carboxyl terminus also plays an important role in sodium channel inactivation.

The cardiac sodium channel has consensus sites for phosphorylation by protein kinase (PKA), protein kinase C (PKC), and Ca-calmodulin kinase. Data on the effects of PKA on the I_{Na} are controversial, with some studies reporting a decrease in current whereas others report an increase. Phosphorylation of the channel by PKC results in a decrease in I_{Na}. Modulation the Na^{+} channel by glycerol-3-phosphate dehydrogenase like1 kinase was recently established by the identification of a kindred with Brugada syndrome and a mutation in the enzyme. In vitro expression showed that enzyme action is associated with a decrease in I_{Na}.

Mutations in cardiac sodium channel gene SCN5A have been associated with LQTS, Brugada syndrome, primary cardiac conduction system disease (PCCP), and dilated cardiomyopathy (Table 4). The long QT syndrome is the result of defects in inactivation that enhance the late component of sodium current. The late component of current is more sensitive to block by class 1 antiarrhythmic drugs than the peak current. Mexiletine and flecainide decrease the late component of sodium current and restore the QT interval toward normal. They have been used to treat patients with LQT3, particularly in the neonatal period and in children when ICD implantation may prove technically challenging. Sodium channel mutations have been described in 20% of patients with Brugada syndrome. The mutations reduce the Na^{+} current as a result of synthesis of nonfunctional proteins, failure of the protein to be targeted to the cell membrane or accelerated inactivation of the channel. As a subgroup, the patients with Na^{+} channel mutations that produce Brugada syndrome have H-V interval prolongation at electrophysiology study. The mechanism of ST segment elevation and T wave inversion in the syndrome is controversial. One group view the syndrome as primarily a repolarization abnormality; others view the Na^{+} channel variant as a conduction defect. Slow conduction from endocardium to epicardium results in delayed epicardial activation. The sequence of transmural repolarization is reversed, resulting in the ST-T wave changes. The mutations associated with primary cardiac conduction disease also reduce the Na^{+} current. The clinical syndromes include sinus node dysfunction, atrial standstill, AV block, and fascicular (infra-Hisian) block. Overlap syndromes of LQT3, Brugada syndrome, and PCCD may occur in the same kindred or individual. The mechanisms by
which Na⁺ defects result in dilated cardiomyopathy are not well understood.  Long standing conduction delay and asynchrony of contraction may be contributory.

The cardiac sodium channel is the substrate for the action of class 1 antiarrhythmic drugs (Table 3). Open and inactivated channels are more susceptible to block than resting channels. The differential block may be the result of a difference in binding affinity or state-dependent access to the binding sites. Binding of antiarrhythmic drug occurs primarily during the action potential. This block is dissipated in the interval between action potentials. Because a fast heart rate is associated with abbreviation of the diastolic period and insufficient time for recovery, block accumulates (ie, it is use-dependent). Class 1 antiarrhythmic drugs may be classified according to the kinetics of unbinding, with various drugs showing fast, intermediate, or slow unbinding kinetics.

### Calcium Channels

Calcium ions are the principal intracellular signaling ions. They regulate excitation–contraction coupling, secretion, and the activity of many enzymes and ion channels. [Ca²⁺]ᵢ, is highly regulated despite its marked fluctuation between systole and diastole. Calcium channels are the principal portal of entry of calcium into the cells; a system of intracellular storage sites, and transporters such as the sodium-calcium exchanger (NCX), also play important roles in [Ca²⁺]ᵢ regulation. In cardiac muscle, 2 types of Ca²⁺ channels, the L- (low threshold type) and T-type (transient-type), transport Ca²⁺ into the cells. The L-type channel is found in all cardiac cell types. The T-type channel is found principally in pacemaker, atrial, and Purkinje cells. The unqualified descriptor Ca²⁺ channel refers to the L-type channel. Table 2 contrasts the properties of the two types of channels.

A combination of as many as 5 subunits, α₁, α₂, β, γ, and δ, unite to form the channel in its native state. The α₁c subunit, Ca₁.2, is the cardiac-specific subunit. The β subunit increases channel expression ≈10-fold and accelerates the activation and inactivation kinetics. Ca²⁺ channels have a similar structure to the sodium channel: 4 homologous domains each consisting of 6 membrane-spanning segments.

### Table 2. A Comparison of the L-Type and T-Type Ca²⁺ Channels

<table>
<thead>
<tr>
<th>Activation</th>
<th>L-Type</th>
<th>T-Type</th>
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<tbody>
<tr>
<td>Range</td>
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<td>High Em (~ −60 mV)</td>
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<table>
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<tr>
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<tr>
<td>Voltage dependence</td>
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<td>[Ca²⁺]ᵢ, dependent</td>
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</tr>
<tr>
<td>N₄</td>
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<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
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### Table 3. Classification of Antiarrhythmic Drug Actions

<table>
<thead>
<tr>
<th>Class</th>
<th>Unbinding Kinetics</th>
<th>Effect on APD</th>
<th>Example</th>
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<tr>
<td>1A</td>
<td>Intermediate</td>
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<td>Procainamide</td>
</tr>
<tr>
<td>1B</td>
<td>Fast</td>
<td>APD →</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>1C</td>
<td>Slow</td>
<td>APD ↓ ,→</td>
<td>Flecainide</td>
</tr>
<tr>
<td>II (β-blocker)</td>
<td>APD ↑</td>
<td>Metoprolol</td>
<td></td>
</tr>
<tr>
<td>III (K⁺ channel blocker)</td>
<td>APD ↑</td>
<td>Dofetilide, Ibutilide</td>
<td></td>
</tr>
<tr>
<td>IV (Ca²⁺ channel blocker)</td>
<td>Slow</td>
<td>APD ↑ ,→</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

The P-loop of each domain contributes a glutamate residue (E) to the pore structure. These residues (EEEE) are critical for calcium selectivity; the channel can be converted from a Ca²⁺-sensitive channel to one with high monovalent cation sensitivity by mutating a glutamate residue. Several molecular mechanisms contribute to a complex system of inactivation. Membrane depolarization decreases the fraction (dₜ) of channels available for opening; dₜ varies from 1 at −45 mV to 0 at zero mV. The carboxyl terminus has multiple Ca²⁺ binding sites and Ca-calmodulin– dependent kinase activity. Ca²⁺ in the immediate vicinity of the channel and phosphorylation also play roles in the inactivation of the channel. Reuptake of Ca²⁺ by the sarcoplasmic reticulum during prolonged depolarization can result in the recovery from Ca²⁺-dependent inactivation and enable secondary depolarization. This may be the basis for the early afterdepolarizations, EADs that trigger polymorphic VT in LQTS. The overall kinetics of the Ca channel is important in controlling contractility in response to various patterns of stimulation. At low (depolarized) membrane potentials, recovery of Iₐ from inactivation between action potentials is slow; Iₐ declines in response to repetitive stimulation and a negative staircase of contractility is observed. At normal resting potentials, recovery of Iₐ from inactivation is fast, and Iₐ may increase progressively during repetitive stimulation. This positive staircase or rate-dependent potentiation of contractility is Ca²⁺-dependent. It is the result of enhanced loading of the sarcoplasmic reticulum and may be facilitated by calmodulin kinase II–dependent phosphorylation.
they cause use-dependent block of conduction in cells with Ca\textsuperscript{2+}-dependent action potentials such those in the SA- and AV nodes and slow the sinus node rate. However, the hypotensive effects of verapamil may cause an increase in sympathetic tone and increase the heart rate. A third class of Ca\textsuperscript{2+} channel blockers, the dihydropyridines, block open Ca\textsuperscript{2+} channels. However, the kinetics of recovery from block is sufficiently fast that they produce no significant cardiac effect but effectively block the smooth muscle Ca\textsuperscript{2+} channel because of its low resting potential.

**Potassium Channels**

Cardiac K\textsuperscript{+} channels fall into 3 broad categories: Voltage-gated (I\textsubscript{to}, I\textsubscript{kur}, I\textsubscript{ks}, and I\textsubscript{k}), inward rectifier channels (I\textsubscript{K1}, I\textsubscript{KATP}), and the background K\textsuperscript{+} currents (TASK-1, TWIK-1/2). It is the variation in the level of expression of these channels that account for regional differences of the action potential configuration in the atria, ventricles, and across the myocardial wall (endocardium, midmyocardium, and epicardium). K\textsuperscript{+} channels are also highly regulated and are the basis for the change in action potential configuration in response to variation in heart rate.

Voltage-gated K\textsuperscript{+} channels consist of principal \( \alpha \)-subunits and multiple \( \beta \)-subunits. The channel functional units also include the complementary proteins K\textsubscript{v}-channel associated protein, KChAP, and the K\textsubscript{v} channel interacting protein, KChIP. The major subfamilies of \( \alpha \)-subunits include K\textsubscript{v}1.x (n = 1 to 4), the HERG channel (gene KCNH2), and KvLQT1 (gene KCNQ1). They are important in generating outward current in the heart. Members of the K\textsubscript{v}1.x subfamily may coassemble to form hetero-multimers through conserved amino-terminal domains. In contrast, members of the HERG and KvLQT1 subfamilies assemble as homotetramers. The \( \alpha \)-subunits that coassemble to form the various types of K\textsuperscript{+} channels and their role in the generation of the action potential are summarized in Table 1. Most \( \beta \)-subunits have been cloned and sequenced. They have o xo-reductase activity. The \( \alpha \)-subunits can generate voltage dependent K\textsuperscript{+} current when expressed in heterogenous systems. However, the accessory subunits are required to recapitulate the K\textsuperscript{+} currents seen in native cells. KChAP (KCHAP) and KChIP (KCNIP2) may increase channel activity independent of transcription and alter channel kinetics. The structure of voltage-gated K\textsuperscript{+} channels is similar to 1 of the 4 domains of voltage-gated Na\textsuperscript{+} and Ca\textsuperscript{2+}. The amino acid sequence glycine-tyrosine-glycine GYG is the sequence requirement for K\textsuperscript{+} selectivity.

The transient outward current is composed of a K\textsuperscript{+} current I\textsubscript{to1} and a Ca\textsuperscript{2+}-activated chloride current, I\textsubscript{to2}. The former has fast and slow components, I\textsubscript{kur} and I\textsubscript{k}, is the principal subtype expressed in human atrium; I\textsubscript{to1} and I\textsubscript{to2} are expressed in the ventricle. Myocardial regions with relatively short action potentials such as the epicardium, right ventricle, and endocardium. K\textsubscript{ATP} has fast and slow components, and the septum have higher levels of I\textsubscript{to} expression. Compared to other voltage-gated K\textsuperscript{+} channels, activation of I\textsubscript{to} is fast (activation time constant <10 ms). The rate of inactivation is variable and highly voltage-dependent. \( \alpha \)-adrenergic stimulation reduces I\textsubscript{to} in human myocytes through PKA-dependent phosphorylation. Chronic \( \alpha \)-adrenergic stimulation and angiotensin II also reduces channel expression. The influence of a reduction of I\textsubscript{to} on the action potential duration varies with species; in rodents, a reduction in I\textsubscript{to} prolongs the action potential duration. In large mammals, a reduction in I\textsubscript{to} shifts the plateau to more positive potentials increasing the activation of the delayed rectifier and promoting faster repolarization. In a rodent model of hypothyroidism the action potential prolongation is associated with a reduction of I\textsubscript{to}. The current is also reduced in human heart failure but is associated with a prolongation of the action potential duration. Because the level of the plateau is set by I\textsubscript{to}, modulators that decrease I\textsubscript{to} shift the plateau into the positive range of potentials. This decreases the electro-chemical driving force for Ca\textsuperscript{2+} and hence I\textsubscript{Ca}.

The delayed rectifier K\textsuperscript{+} currents I\textsubscript{kur}, I\textsubscript{k1}, and I\textsubscript{k} are slowly activating outward currents that play major roles in the control of repolarization. The deactivation of these channels is sufficiently slow that they contribute outward current throughout phase 3 repolarization. I\textsubscript{kur} is highly expressed in atrial myocytes and is a basis for the much shorter duration of the action potential in the atrium. I\textsubscript{k1} is differentially expressed, with high levels in the left atrium and ventricular endocardium. I\textsubscript{k} is expressed in all cell types, but is reduced in midmyocardial myocytes. These cells have the longest action potential duration across the myocardial wall. The \( \alpha \)-subunits that make up the delayed rectifier currents are summarized in Table 1. \( \beta \)-subunits are associated with I\textsubscript{k1} and I\textsubscript{k}. MinK-Related Peptide-1 (MiRP-1) and MinK are the most thoroughly studied. MiRP-1 and MinK are single-membrane spanning peptides with extracellular amino termini. The \( \beta \)-subunits are nonconducting but regulate \( \alpha \)-subunit function, including gating, response to sympathetic stimulation, and drugs. \( \beta \)-adrenergic stimulation regulates I\textsubscript{k1} through activation of protein kinase A and elevation of c-AMP. The former effect is inhibitory; the latter is stimulatory through binding to the cyclic nucleotide binding domain of the channel. \( \alpha \)-adrenergic stimulation is inhibitory.

\( \beta \)-adrenergic stimulation increases I\textsubscript{k1} through PKA-dependent phosphorylation. This action involves a complex of PGA, protein phosphatase1, and the adaptor protein yotai.\textsuperscript{7} Ion channel mutations that disrupt the function of the complex result in the action potential prolongation of LQT1. \( \beta \)-adrenergic blockers indirectly regulate this complex and are important therapeutic options in LQT1.

The inward rectifier channel current I\textsubscript{k} sets the resting membrane potential in atrial and ventricular cells. Channel expression is much higher in the ventricle and protects the ventricular cell from pacemaker activity. The strong inward rectification of the I\textsubscript{k} limits the outward current during phases 0, 1, and 2 of the action potential. This limits the outward current during the positive phase of the action potential and confers energetic efficiency in the generation of the action potential. Because block of the outward current by intracellular Mg\textsuperscript{2+} and the polyamines is relieved during repolarization, I\textsubscript{k1} makes a significant contribution to phase 3 repolarization.

The acetylcholine-activated K\textsuperscript{+} channel is a member of the G protein–coupled inward rectifying potassium channels. The channel is highly expressed in the SA and AV nodes, and
atria, but low in ventricle. Activation of $I_{K_{Ach}}$ hyperpolarizes
the membrane potential and abbreviates the action potential.
Phase 4 depolarization of pacemaker cells is slowed. The
channel structure is similar to that of $I_{K_1}$. The binding of
acetylcholine to the M2 muscarinic receptor activates the G
protein $G_i$ and the release of the subunits $G_{i1}$ and $G_{i2}$. The
dissociated $G_{i2}$ subunit binds to the channel and activates it.
The binding of adenosine to the P1 receptor also results in the
release of $G_{i2}$ and activation of the channel. Methylxanthines
such as theophylline block the P1 receptor and antagonized
the effects of adenosine. Coexpression of the inward rectifier
$K_{1}$ channel Kir6.1 and sulfonylurea receptor yield channels
with properties similar to the native $I_{K_{ATP}}$.

Mutations of the genes encoding cardiac $K^{+}$ channels are
the principal causes of arrhythmias that result from abnormal
repolarization (Table 4). Mutations of KCNQ1, the gene
encoding $K_{r,LQT1}$, and KCNH2, the gene encoding HERG,
account for more than 80% of autosomal dominant LQTS
(Romano-Ward syndrome). Bilateral neurosensory deafness
is a part of the autosomal recessive form (Jervell and
Lange-Nielsen syndrome). Mutations of the $\alpha$-subunit
KCNJ2 and the $\beta$-subunits of KVLQT1 and HERG are minor
causes of LQTS. A majority of these mutations have a
dominant negative effect, coassembling with normal sub-
units, but impairing their function. Polymorphisms of the
genes encoding the $K^{+}$ channels may increase susceptibility
to drug-induced LQTS. Gain of function mutations of
$I_{Kr}$, $I_{Ks}$, $I_{K_1}$ cause marked acceleration of repolarization and the short
QT syndrome. Mutations of these subunits have also been
associated with familial atrial fibrillation.

Cardiac $K^{+}$ channels are the targets for the action of class
III antiarrhythmic drugs. The HERG channel is very suscep-
tible to block by a broad range of drugs that are not primarily
used to treat cardiac arrhythmias, including antipsychotics,
and the macrolide antibiotics. The potent $K^{+}$ channel block-
ing action of quinidine, procainamide, and disopyramide
account for their QT- prolonging action and occasionally
torsade de pointes. HERG blockers produce greater blockade

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Protein</th>
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<tbody>
<tr>
<td>LQTS</td>
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<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>$I_{K_1}$</td>
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at slow heart rates; block tends to dissipate during the rapid heart rates of a tachycardia, so called reverse-use dependence. Amiodarone is exceptional in that it produces K+ channel blockade that shows little use dependence. Although antiarrhythmic drugs have fallen out of favor for the management for ventricular tachycardia, they retain an important role in the prevention of recurrences of atrial fibrillation. The discovery of the atrial-specific distribution of IKur has made this channel a target for novel therapies for atrial fibrillation. The drug vernakalant is a IKur/Na channel blocker and is undergoing review by the FDA for the acute termination of atrial fibrillation.

Hyperpolarization-Activated Cyclic Nucleotide Gated Channel

Autorhythmicity is one of the most characteristic features of cardiac cells and resides in the pacemaker cells of the specialized conducting system, including the SA and AV nodes, and His-Purkinje system. Pacemaker activity initiates and sustains electric activity of the heart independent of the underlying innervation. Phase 4 diastolic depolarization is characteristic of pacemaker cells. Many ion channels contribute to phase 4 depolarization: the K+ channel current activated during the preceding action potential, a background Na+ current, the sodium-calcium exchange, the I\textsubscript{f} channel, and the L- and T-type Ca\textsuperscript{2+} channels. However, the I\textsubscript{f} current unique is to this process. Unlike other voltage-gated channels, I\textsubscript{f} is activated by hyperpolarization negative to \textsim 40 mV. The channel is not very selective for Na\textsuperscript{+} over K\textsuperscript{+} and has a reversal potential (Er) of \textsim 10 to \textsim 20 mV. Therefore, it carries inward current throughout the range of pacemaker potential. The phase 4 depolarization reduces the membrane to the threshold for the regenerative activation of IC\textsubscript{a,t} and IC\textsubscript{a,i}.

The genes encoding I\textsubscript{f} channels have been cloned and sequenced in the past decade. I\textsubscript{f} channels (hyperpolarization-activated cyclic nucleotide gated [HCN]-H4CN) are members of a family of cyclic nucleotide activated voltage-gated channels. Although members of this family of channels are expressed in heart and brain, HCN2 and HCN4 are expressed in the heart. Expression is both developmentally and regionally regulated. Neonatal cardiac ventricular myocytes that show pacemaker activity predominantly expressed HCN2. Expression of HCN2 declines in adulthood. HCN4 is the subtype primarily expressed in the sinus node, AV node, and ventricular conducting system. Knockout of the HCN4 gene is embryonic lethal. Channels are formed by the assembly of 4 \textalpha-subunits, each with a structure analogous to that of the voltage gated K\textsuperscript{+} channels. Binding of cAMP to this domain shift the voltage dependence of I\textsubscript{f} activation to more depolarized potentials and increase the rate of pacemaker discharge. Protons shift the activation of I\textsubscript{f} to more hyperpolarized potentials and slow pacemaker activity. The I\textsubscript{f} channel is the target for a new class of bradycardic agents, eg, ivabradine. They have the advantage over \beta-blockers in that they slow the heart rate without the disadvantage of negative inotropy or hypotension. They have proved effective in the management of patients with chronic stable angina.

Isolated reports of mutations in the HCN4 gene have appeared recently. One kindred had idiopathic sinus brady-
Future Directions

The cloning and sequencing of the ion channel genes that regulate the action potential hold the promise that these genes could be manipulated to treat arrhythmias. Proof of principle has been established. The initial problem approached is the control of the ventricular response in atrial fibrillation. β-adrenergic blockers are the most widely used drugs used to control the ventricular response in atrial fibrillation. Adrenergic inhibition decreases intracellular [cAMP] and the Ca2+ current. This would slow conduction over the AV node. Donahue and colleagues developed an indirect strategy to regulate the action potential hold the promise that these genes provided a state of the art review on the genetic approach to the control of the ventricular response in atrial fibrillation. This would slow conduction over the AV node. Donahue and colleagues developed an indirect strategy to decrease sympathetic activity in AV nodal cells. They inserted the inhibitory G protein Gαi into an adenoviral vector. The adenoviral vector-Gαi construct was infused in the AV nodal artery of pigs with atrial fibrillation. Gαi over expression decreased the heart rate in atrial fibrillation by 20% compared to the drug-free state. Persistence of the effect was limited and the delivery of vector would be challenging in the clinical situation.

Sick sinus syndrome is the most common cause for permanent pacemaker implantation. A genetic strategy to treat sinus node failure would be attractive. In an earlier contribution to this series, Rosen and colleagues have provided a state of the art review on the genetic approach to the development of biological pacemakers by manipulating the HCN4 gene. The biological pacemakers have relatively slow rates. The initial effort is focused on biological pacemaker that will complement rather than replace the normal sinus node pacemaker.

Disclosures

Dr Grant has received honoraria from Boston Scientific, Medtronic, St Jude Medical, and Sanofi Aventis.

References


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