Differential Distribution of Cardiac Ion Channel Expression as a Basis for Regional Specialization in Electrical Function

Gernot Schram, Marc Pourrier, Peter Melnyk, Stanley Nattel

Abstract—The cardiac electrical system is designed to ensure the appropriate rate and timing of contraction in all regions of the heart, which are essential for effective cardiac function. Well-controlled cardiac electrical activity depends on specialized properties of various components of the system, including the sinoatrial node, atria, atrioventricular node, His-Purkinje system, and ventricles. Cardiac electrical specialization was first recognized in the mid 1800s, but over the past 15 years, an enormous amount has been learned about how specialization is achieved by differential expression of cardiac ion channels. More recently, many aspects of the molecular basis have been revealed. Although the field is potentially vast, an appreciation of key elements is essential for any clinician or researcher wishing to understand modern cardiac electrophysiology. This article reviews the major regionally determined features of cardiac electrical function, discusses underlying ionic bases, and summarizes present knowledge of ion channel subunit distribution in relation to functional specialization. (Circ Res. 2002;90:939-950.)

Key Words: ion channels / molecular biology / conduction / cardiac arrhythmias / antiarrhythmic drugs

Cardiac function depends on the appropriate timing of contraction in various regions, as well as on appropriate heart rate. To subserve these functions, electrical activity in each region is adapted to its specialized function. Regionally specialized cardiac electrical function was recognized in the mid 1800s, when Stannius demonstrated that ligatures in the superior vena caval sinus region of the frog caused cardiac asystole, with the sinus continuing to beat. With the widespread application to cardiac ion channel study of patch-clamp methodologies in the 1980s and molecular biology in the 1990s, many underlying mechanisms have been unraveled. The present article reviews the major regionally determined features of cardiac electrical function and the present knowledge regarding ionic and molecular bases.

Overview of Regional Functional Specificity

Figure 1 illustrates typical regional action potential (AP) properties in the heart. The normal cardiac impulse originates in the sinoatrial node (SAN) and propagates through the atria to reach the atrioventricular node (AVN). From the AVN, electrical activity passes rapidly through the cable-like His-Purkinje system to reach the ventricles, triggering cardiac pumping action. Figure 2 shows the ionic currents involved in a schematic cardiac AP, provides standard abbreviations for currents and their corresponding subunits, and summarizes principal localization data discussed elsewhere in the present review.

Ionic and Molecular Basis of Functional Specificity

Sinoatrial Node

Cellular Electrophysiology and Function

The SAN, located in the right atrial (RA) roof between the venae cavae, is specialized for physiological pacemaker function. Heart rate control is achieved through autonomic regulation of SAN pacemaking. SAN APs have a relatively positive maximum diastolic potential (MDP) of $\approx -50$ mV, a small phase 0 upstroke velocity ($V_{\text{up}} < 2$ V/s), and prominent phase-4 depolarization maintaining SAN pacemaker dominance. The cell type changes from the typical nodal cell at the center of the SAN to the atrial cell toward the periphery. The longest AP durations (APDs) are in the central pacemaking zone, preventing invasion by ectopic impulses and preserving SAN dominance. The SAN contains both spider and spindle pacemaker cell types. Spider cells have a faster intrinsic rate, a less negative MDP, and a longer APD, suggesting they are primary pacemaking cells of the central node. Cholinergic and $\beta$-adrenergic stimulation slow and accelerate spontaneous SAN activity, respectively. Electrical coupling to the atrium is designed to drive the large atrial muscle mass while insulating the SAN from hyperpolarizing atrial muscle influences. SAN dysfunction causes bradyarrhythmias that are associated with syncope but rarely with death.
Ionic Mechanisms

Ionic properties underlying SAN function are indicated in Figure 3. Many varieties of time-dependent currents contribute to SAN pacemaking.8 A key time-dependent inward current, sometimes called the pacemaker current, is the nonselective cation current (I_f).9,10 I_f density is ~70% greater in spider than in spindle cells.5 Several other currents flowing between the time of MDP and the phase-0 take off, including L-type Ca^{2+} current (I_{CaL}), T-type Ca^{2+} current (I_{CaT}), and the delayed rectifier K^+ current (I_K), influence pacemaking activity: inward Ca^{2+} current activation and outward K^+ current deactivation contribute to diastolic depolarization.5–10 I_{CaT} is particularly large in the SAN. One study found SAN pacemaker cells to lack the background K^+ current predominantly governing MDP (I_K) and the transient outward current (I_{to}).11 The lack of I_K explains the positive MDP of SAN cells. A smaller rapid I_K component (I_{Ks}) in central SAN cells compared with peripheral cells may contribute to their more positive MDP and longer APD.12 A smaller sustained I_to component may also contribute to longer APD in central SAN.13 I_{CaT} underlies AP upstrokes in primary SAN pacemaking tissue.10,11 The Na^+ current (I_Na) may contribute to subsidiary pacemaker activity in peripheral regions, providing a backup mechanism.14 A sustained inward component (I_{st}) related to I_{CaT} may also contribute to SAN depolarization,11 but this remains controversial.15

Autonomic regulation of I_f and I_{CaT} controls heart rate. β-adrenergic stimulation positively shifts I_f activation volt-

**Principal Ion-channel Subunits and their Localization**

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Corresponding Current</th>
<th>Primary Function</th>
<th>Demonstrated Localization</th>
</tr>
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<tbody>
<tr>
<td>HCN</td>
<td>I_p (pacemaking)</td>
<td>Diastolic depolarization</td>
<td>SAN&gt;AP&gt;A-V</td>
</tr>
<tr>
<td>Kv2.1</td>
<td>I_{K1}</td>
<td>Resting potential, terminal repolarization</td>
<td>V&gt;AS&gt;SAN</td>
</tr>
<tr>
<td>Kv3.3/3.4</td>
<td>I_{KCaCh}</td>
<td>Mediates acetylcholine effects</td>
<td>SAN&gt;AS&gt;V</td>
</tr>
<tr>
<td>ERG</td>
<td>I_{Ks} (s-subunit)</td>
<td>Phase-3 repolarization</td>
<td>Present in all tissues. LA&gt;RA; 70%PF</td>
</tr>
<tr>
<td>MRP1</td>
<td>Modulates I_{Ks}, I_{Kr}</td>
<td>?</td>
<td>SAN&gt;AP&gt;A-V</td>
</tr>
</tbody>
</table>
| KvLoT1  | I_{Ks} (s-subunit)    | Phase-3 repolarization (esp. with β-adrenergic stimulation, I_{Ks} inhibition) | Abundant in A and V. 70%PF. |%
| minK    | I_{Ko} (β-subsunit)   | Necessary to form I_{Ko} with KvLoT1 | SAN>A-V            |
| Kv4.2/4.3 | I_p (s-subunit)       | Early (phase-1) repolarization | Present in A and V. Species-specific. 70%PF. |%
| Kv1.4   | I_p (s-subunit)       | Early (phase-1) repolarization | Important in some species (rabbit). 70%PF. |%
| KChP2   | I_p (β-subsunit)      | Necessary to form I_{Ko} | Epinephrine in man and dog. |%
| Kv1.5/3.1 | I_{Kur}               | Phase 1-2 repolarization. | Atinal-specific. (Kv1.5 man; Kv3.1 dog). |%
| Cq_{1.2} | I_{CaL} (s-subunit)   | Maintenance of plateau. Electromechanical coupling. Automotility, conduction SAN, AVN | SAN>AV. 70%PF. |
| Cq_{1.3} | I_{Cal} component     | Role in SAN function in mice. | ?Weakly expressed in SAN, A. |%
| Cq_{3.1-3.3} | I_{CaT}               | ?Role in pacemaking | SAN>AV. 70%PF. |
| Na_{1.5} | I_{Na}                | Conduction A, V, PF | Strong in A. Absent in compact AVN. |%
| Cx_{40,43,45} | I_{Cj}            | Inter cellular conduction | Cx40 strong in A, V, PF. Absent in central SAN, AVN. Cx43 strong in IN peripheral SAN, central AVN, PF. |%

**Figure 1.** Schematic diagram of AP properties in different regions of the heart.

**Figure 2.** Principal cardiac ion channel subunits, corresponding currents, and localization. Inset shows schematic diagram of cardiac AP and currents involved in different phases. Outward currents correspond to upward arrows; inward currents correspond to downward arrows.
Molecular Basis

Hyperpolarization-activated cation channel (HCN)1-HCN4 cDNAs encode If-like currents. HCN transcripts are 25-300 times more abundant in the SAN than in Purkinje cells (PCs) and ~140 times more abundant than in ventricular myocardium. HCN1 protein and message and HCN4 transcripts are abundant in rabbit SAN, whereas HCN2 protein expression is weak, and HCN3 mRNA is absent. In the mouse, SAN HCN4 transcripts are abundant, HCN2 levels are moderate, and HCN1 levels are low. HCN1 and HCN2 coassemble to form functionally distinct channels. The minK-related protein, MiRP1, increases the density and activation rate of If, resulting from HCN expression. MiRP1 mRNA is highly expressed in rabbit SAN, likely contributing to SAN pacemaker function.

Expression of Kir2.1, the predominant cardiac IK subunit, is very limited in ferret SAN, which is consistent with the virtual absence of IK1 in ferrets. IK1, formed by complexes containing Kir3.1 and Kir3.4 subunits. Kir3.1 protein is present in rat, ferret, and guinea pig SAN. Kir3.1 and m2-receptor proteins colocalize. Kir3.4 protein is present in rat SAN.

Four subunits are believed to contribute to IK: the ether-a-go–go–related (ERG) and MiRP1 subunits (thought to be α and β subunits of IKr, respectively) and KvLQT1 and minK (α and β subunits of IKs, respectively), although the role of MiRP1 remains controversial. MinK transcripts are more abundant in the SAN than in the atrium or ventricle. ERG protein and transcript are correlated with the presence of IKs in ferret and rabbit SAN.

Voltage-activated Ca2+ channel (CaV)3.1 and CaV3.2 encode ICaL α subunits. CaV3.1 mRNA expression is 30-fold greater in mouse SAN than in mouse atrium. CaV3.2 expression is lower than CaV3.1 expression, but it is also greater in the SAN. CaV1.2 and CaV1.3 are ICaL α subunits. CaV1.3 mRNA expression is low in mouse SAN and atrium, but CaV1.3 knockout creates marked SAN dysfunction. CaV1.2 transcripts are more numerous and are more strongly expressed in the SAN than in the atrium. Subunits β and δ modulate the density, kinetics, and activation/inactivation of ICaL. Little is known about their cardiac localization.

Gap-junctional hemichannel connexin (Cx) proteins are the basis of intercellular electrical coupling. The SAN is shielded against hyperpolarizing atrial influences by compartmentalization of Cx expression. Many studies report that Cx43, the major cardiac Cx, is absent in the central SAN. Cx40, Cx45, and Cx40 are expressed in the SAN of rabbit and human hearts. Cx46 is present in rabbit SAN. In canine SAN, 55% of the cells express Cx40 alone; 35% express Cx43, Cx45, and Cx40; and 10% show no Cx. Cells expressing all 3 connexins are located in bundles abutting atrial tissue, whereas Cx40-expressing cells are located in the central SAN. Myocytes coexpressing Cx40, Cx43, and Cx45 extend from the SAN into the atrium, transmitting pacemaker impulses that drive the atrium.
nary veins have APs similar to those in atrial myocytes, whereas more distally located cells have less negative MDP, shorter APD, and slow pacemaker activity.56

Animal models57–59 and clinical studies60 suggest an important role of the LA in atrial fibrillation. This may partly be due to accelerated LA repolarization,49 which shortens ERPs, favoring reentry.61 LA pulmonary vein activity also triggers atrial fibrillation.62 In guinea pigs, pulmonary vein cells generate atrial tachyarrhythmias that are due to digitalis-induced triggered activity.63 Parasympathetic stimulation shortens atrial APD in a spatially heterogeneous fashion,64 producing important proarrhythmic effects.65

Ionic Mechanisms

The ionic mechanisms of atrial cell APs are summarized in Figure 4. I_F is present in atrial myocytes.56,67 A role for I_F in atrial ectopy has been suggested,66 but atrial I_F function has been questioned because of limited activation at atrial MDP.67 Atrial cells have large inward I_Ka,68 providing energy for rapid conduction.

Atrial I_Ka is 6- to 10-fold smaller than ventricular I_Ka,69,70 explaining the less negative atrial MDP and slower phase-3 repolarization. Ultrarapid delayed rectifier current (I_Kur), activating two orders of magnitude faster than I_Ka, has been described in rat,71 mouse,72 human,73 and canine74 atria. In humans and dogs, I_Kur is present in atria but not in ventricles.75–78 Atrial I_Ka includes both I_Ka and the slow component, I_Kc.77–79 Unlike normal ventricular myocytes, in which I_CaT is lacking in the absence of cardiac hypertrophy,80 I_CaT is readily detectable in atrial myocytes48 and may be important in atrial tachycardia–induced ionic remodeling.81 Atrial tachyarrhythmias and heart failure produce discrete atrial ionic remodeling.48,82,83 which is important in arrhythmogenesis.61 A recent study suggests that atrial tachycardia causes ionic remodeling and afterdepolarizations in pulmonary vein myocytes.84 A number of discrepancies make that study difficult to interpret; these discrepancies include an I_Kc reversal potential of −40 mV in cells with a resting potential of −65 mV, the simultaneous measurement of inward and outward currents with similar kinetics at the same test potentials with no attempt to isolate components, and the generation of 25-mV delayed afterdepolarizations by transient inward currents <10 pA.

Myocytes from different RA regions show discrete ionic current distributions that explain their AP properties.52 LA free-wall myocytes have larger I_K compared with RA, accounting for their shorter APDs and ERPs.49 I_KACh density is 6 times greater in the atrium than in the ventricle.85

Molecular Basis

HCN2 and HCN4 are expressed in the atrium.86 HCN4 message levels are much lower in the atrium than in the SAN.21

Kir2.1 is the most abundant Kir2-family (I_K1) subunit mRNA in the atrium and ventricle and is equally expressed in each.70 Kir2.3 transcripts are more concentrated in human atrium than ventricle, and Kir2.2 transcripts are equal and sparse in both.70 Kir2-subunit mRNA expression does not account for atrioventricular I_K1 differences. Kir2.1 protein expression is ~80% greater in the ventricle than in the atrium, whereas Kir2.3 protein expression is 228% greater in the atrium.87 Kir2.3 protein localizes to transverse tubules of most atrial but few ventricular cells, whereas the converse is true of Kir2.1.87 The role of these atrioventricular differences in Kir2 protein expression in the much weaker atrial I_K1 is uncertain.

Kir3.1 mRNAs are expressed strongly in rat atria but not ventricles,88,89 and Kir3.1 and Kir3.4 proteins are abundant in the atrium and sparse in the ventricle,27 consistent with predominantly atrial I_KACh expression.85 Recent work suggests that homomeric Kir3.4 channels may also contribute to atrial I_KACh.80,91

The principal subunits thought to encode I_K include Kv1.4, Kv4.2, and Kv4.3.92 Kv4.2 contributes to rat atrial I_Ka,93 localizing to the sarcolemma and T tubules.94 Kv1.4 transcript expression is stronger in rat atrium than ventricle,95 but Kv4.2 protein is almost undetectable in both.96 In rabbit atrium, Kv1.4 is a major contributor to I_Ka whereas in human atrium, I_Ka is encoded entirely by Kv4.3.97
The molecular basis of atrial $I_{\text{Kur}}$ varies widely among species. $^{98}$ Kv1.2 and Kv1.5 contribute to rat atrial $I_{\text{Kur}}$. $^{93}$ Human atrial $I_{\text{Kur}}$ is encoded by Kv1.5, with no corresponding component in the ventricle. $^{99}$ Kv3.1 is the molecular basis of canine atrial $I_{\text{Kur}}$ and, like the corresponding current, it is absent in the ventricle. $^{76}$

KvLQT1 transcripts are abundant in ferret RA. $^{100}$ MinK is less abundant in the atrium than in the SAN. $^{100}$ ERG mRNA is abundantly expressed in the atrium, as is the longer (ERG1a) variant, with larger expression in the ventricle versus atrium in humans and larger expression in the atrium versus ventricle in rats. $^{101}$

ERG protein levels in dogs are larger in the LA than in the RA, consistent with a larger LA $I_{\text{ERG}}$. $^{49}$ No information is available about the molecular basis of intra-atrial regional differences in $I_{\text{K,S}}$ and $I_{\text{K,at}}$. $^{52}$ Cardiomyocytes in pulmonary veins contain Kir2.1 subunits and show $I_{\text{K1}}$-like currents, $^{102}$ but otherwise, little is known about their molecular electrophysiology.

Ca.3.1 and Ca.3.2 transcripts are found in mouse atrium, $^{35}$ consistent with the atrial presence of $I_{\text{Ca.L}}$. $^{34}$ Ca.1.2 transcripts are abundant in the atria, and their downregulation is believed to be central to atrial electrical remodeling. $^{103,104}$ The Na$^{+}$ channel α subunit, Na.a1,5, is abundantly expressed in atrial myocytes, on the atrial surface, and in T-tubular membranes and intercalated disks, consistent with large $I_{\text{Na}}$. $^{105}$

Cx43 protein is present on bovine, guinea pig, and human atrial myocytes, $^{106-108}$ with a distinct transitional zone containing interdigitating Cx43-expressing atrial and Cx43-lacking nodal cells at the periphery of the SAN. $^{45,106,108}$ Canine and rabbit RA gap junctions contain mainly Cx40 and Cx43, and less Cx45. $^{39,109}$ Cx40 expression in the atrium is much stronger than in the ventricle (where it is virtually undetectable) in humans, rabbits, guinea pigs, and mice. $^{107,109-111}$

Cx40 is more abundant in human RA than LA. $^{107}$

Atrophicventricular Node

Cellular Electrophysiology and Function

The primary function of the AVN is to govern the ventricular response to supraventricular activation. AVN cells have low excitability and postrepolarization refractoriness, $^{112}$ which limit the maximum number of impulses that can traverse to the ventricles $^{113}$ and prevent dangerously rapid ventricular rates in response to supraventricular tachyarrhythmias.

The AVN has a complex 3D structure. APs from intact AVN have slow upstrokes and small amplitudes. $^{114}$ Within the compact AVN, MDPs are $\approx -64$ mV, phase-4 depolarization results in takeoff potentials of $\approx -60$ mV, and $V_{\text{max}}$ is $<20$ V/s. $^{115}$ Cell types include N cells in the compact node and NH cells at the junction with the His bundle. $^{115}$ A modern classification divides the AVN into a transitional cell area, compact node, posterior nodal extension, and lower nodal cell bundle. $^{116}$

Ovoid and rod-shaped cells have been isolated from the compact AVN. $^{117}$ Ovoid cells have N- or NH-like APs showing postrepolarization refractoriness and no AP abbreviation with increased frequency, less negative MDPs, faster diastolic-depolarization, and smaller $V_{\text{max}}$ than those in rod-shaped cells. Rod-shaped cells display APs intermediate between typical AVN and atrial cells (AN type). $^{117}$ AVN cells have pacemaking activity, $^{117,118}$ particularly in the midnodal and lower nodal regions. $^{119}$ Spontaneous activity in AN cells is suppressed by atrial electrotonic influences. $^{120}$

AV node reentrant arrhythmias were classically related to the presence of dissociable AVN pathways, $^{121}$ which are typically manifested clinically as a faster conducting pathway with a longer refractory period and a slower conducting pathway with more brief refractoriness. $^{122}$ Although the detailed physiology is not completely clear, there is evidence that the posterior nodal extension may form the slow pathway substrate. $^{116}$

Ionic Mechanisms

The ionic basis of AVN properties is illustrated in Figure 5. $I_{\text{f}}$ is present in 95% of ovoid cells versus $\approx 10\%$ of rod-shaped cells, and $I_{\text{f}}$ density is $\approx$ 25-fold larger in ovoid cells, which is consistent with the much greater ovoid cell pacemaker activity. $^{117}$ $I_{\text{Na}}$ and $I_{\text{Ks}}$ are present in few ovoid cells but in almost all rod-shaped cells. $^{117}$ $I_{\text{f}}$ underlies the compact AVN AP upstroke. $^{123}$ 4-Aminopyridine inhibits spontaneous AVN APs, which is consistent with a role for $I_{\text{f}}$ in AVN pacemaking. $^{124}$ $I_{\text{Kr}}$ elimination in transgenic mice causes atrioventricular block. $^{125}$

$I_{\text{Kr}}$ deactivates faster in AVN than in ventricular myocytes. $^{126}$ Contrary to the SAN, where both $I_{\text{Kr}}$ and $I_{\text{Ks}}$ are important, $I_{\text{Kr}}$ predominates in the AVN. $^{127}$ $I_{\text{Kr}}$ activation contributes to AVN repolarization and deactivation to diastolic depolarization. $^{123}$ There is little $I_{\text{K1}}$ in the AVN, $^{123}$ consistent with its positive MDP.

Molecular Basis

Data regarding ion channel subunit distribution in the AVN are limited. As opposed to transitional or lower nodal cells, midnodal cells of the rabbit AVN display little or no Na$^{+}$ channel α subunit or Cx43 protein. $^{128}$ Cx43 expression is sparse or absent in the AVN. $^{129-132}$ Low-level Cx43 expression colocalizes with Cx40 in the rat. $^{132}$ Targeted disruption
of Cx40-subunit expression impairs atrioventricular conduction in the mouse,\textsuperscript{133–135} although much of the delay is attributable to slowing in the ventricular conduction system.\textsuperscript{136} Cx45 is strongly expressed in the rodent AVN and conducting system.\textsuperscript{137}

His-Purkinje System

Ionic Mechanisms

Multicellular Purkinje fiber preparations were used for classic voltage-clamp studies because of favorable geometry; however, because of the difficulty of isolating PCs, much less work has been done recently. Ionic bases for PC AP properties are specialized for rapid conduction. PC MDP is 5 to 10 mV more negative (averaging $\approx -90$ mV) than working ventricular MDP.\textsuperscript{138,139} $V_{\text{max}}$ is also greater in PCs ($\approx 400$ to $800$ V/s) than in the ventricle (150 to 300 V/s), and the PC plateau voltage is lower.\textsuperscript{138,139} APD is more prolonged in PCs than in ventricular muscle at slow rates.\textsuperscript{140,141} PCs show prominent phase-4 depolarization, providing ventricular escape pacemakers.\textsuperscript{142} PCs preferentially generate drug-induced early afterdepolarizations that excite adjacent ventricular muscle,\textsuperscript{143} likely explaining endocardial early afterdepolarizations that trigger torsade de pointes arrhythmias.\textsuperscript{143,144}

Ventricular Muscle

Ionic Mechanisms

Multicellular Purkinje fiber preparations were used for classic voltage-clamp studies because of favorable geometry; however, because of the difficulty of isolating PCs, much less work has been done recently. Ionic bases for PC AP properties are specialized for rapid conduction. PC MDP is 5 to 10 mV more negative (averaging $\approx -90$ mV) than working ventricular MDP.\textsuperscript{138,139} $V_{\text{max}}$ is also greater in PCs ($\approx 400$ to $800$ V/s) than in the ventricle (150 to 300 V/s), and the PC plateau voltage is lower.\textsuperscript{138,139} APD is more prolonged in PCs than in ventricular muscle at slow rates.\textsuperscript{140,141} PCs show prominent phase-4 depolarization, providing ventricular escape pacemakers.\textsuperscript{142} PCs preferentially generate drug-induced early afterdepolarizations that excite adjacent ventricular muscle,\textsuperscript{143} likely explaining endocardial early afterdepolarizations that trigger torsade de pointes arrhythmias.\textsuperscript{143,144}

The information available about the ionic bases of transmural AP heterogeneity in the ventricles is summarized in Figure 7. $I_{\text{to}}$ differences between epicardium and endocardium were originally inferred from phase-1 repolarization properties.\textsuperscript{159} $I_{\text{to}}$ is larger in epicardium than endocardium for dogs, cats, and other species.\textsuperscript{166}
Molecular Basis

HCN2 is the only isoform in rabbit ventricle, and its mRNA expression is minimal.\textsuperscript{20} HCN4 mRNA has been detected in rat ventricle.\textsuperscript{20} HCN2 and HCN4 have been detected in human ventricle but have not been quantified.\textsuperscript{180} HCN1 and HCN3 were not detected in the ventricle.\textsuperscript{19,21} Low-level HCN mRNA is not detectable in canine RV.\textsuperscript{162} A tremendous amount has been learned over the last 10 to 15 years regarding the ionic and molecular basis of cardiac regional electrical specialization. Nevertheless, many aspects remain unexplained. The molecular biology of ion channel expression in the AVN and Purkinje fibers remains largely unexplored. The basis of intra-atrial and intraventricular

Conclusions

A tremendous amount has been learned over the last 10 to 15 years regarding the ionic and molecular basis of cardiac regional electrical specialization. Nevertheless, many aspects remain unexplained. The molecular biology of ion channel expression in the AVN and Purkinje fibers remains largely unexplored. The basis of intra-atrial and intraventricular
regional variations in ion channel function remains poorly understood, and the distribution of ion channel subunits in specific cellular subtypes in complex regions such as the SAN and AVN remains largely unknown. Species differences in ion channel distribution are incompletely understood and complicate extrapolations of experimental findings to humans. The effects of disease states on regional ion channel function are virtually unknown. Targeted modulation of regional ion channel function by genetic engineering approaches may open up entirely new therapeutic vistas, and its feasibility has been demonstrated.201

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