CONTEMPORARY REVIEW

Cardiac ion channels in health and disease

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Cardiac electrical activity depends on the coordinated propagation of excitatory stimuli through the heart and, as a consequence, the generation of action potentials in individual cardiomyocytes. Action potential formation results from the opening and closing (gating) of ion channels that are expressed within the sarcolemma of cardiomyocytes. Ion channels possess distinct genetic, molecular, pharmacologic, and gating properties and exhibit dissimilar expression levels within different cardiac regions. By gating, ion channels permit ion currents across the sarcolemma, thereby creating the different phases of the action potential (e.g., resting phase, depolarization, repolarization). The importance of ion channels in maintaining normal heart rhythm is reflected by the increased incidence of arrhythmias in inherited diseases that are linked to mutations in genes encoding ion channels or their accessory proteins and in acquired diseases that are associated with changes in ion channel expression levels or gating properties. This review discusses ion channels that contribute to action potential formation in healthy hearts and their role in inherited and acquired diseases.

KEYWORDS Action potential; Atrial fibrillation; Brugada syndrome; Current; Heart failure; Inherited arrhythmia; Ion channel; Long QT syndrome; Myocardial infarction

ABBREVIATIONS **AF** = atrial fibrillation; **AP** = action potential; **AVN** = atrioventricular node; **cAMP** = cyclic adenosine monophosphate; **EAD** = early afterdepolarization; **HCN** = hyperpolarization-activated cyclic nucleotide gated; **LQTS** = long QT syndrome; **SAN** = sinoatrial node

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Cardiac electrical activity starts by the spontaneous excitation of "pacemaker" cells in the sinoatrial node (SAN) in the right atrium. By traveling through intercellular gap junctions, the excitation wave depolarizes adjacent atrial myocytes, ultimately resulting in excitation of the atria. Next, the excitation wave propagates via the atrioventricular node (AVN) and the Purkinje fibers to the ventricles, where ventricular myocytes are depolarized, resulting in excitation of the ventricles. Whereas on the surface electrocardiogram, atrial and ventricular excitation are represented by the P wave and the QRS complex, respectively, depolarization of each atrial or ventricular myocyte is represented by the initial action potential (AP) upstroke (phase 0), where the negative resting membrane potential (approximately −85mV) depolarizes to positive voltages. Restitution of the resting membrane potential during AP phases 1, 2, and 3 results in atrial and ventricular repolarization (Figures 1A and 1B).

APs constitute changes in the membrane potential of cardiomyocytes. The membrane potential is established by an unequal distribution of electrically charged ions across the sarcolemma (electrochemical gradient) and the presence of conducting ion channels in the sarcolemma. Opening and closing (gating) of ion channels enable transmembrane ion currents and, as a result, AP formation. Ion channels consist of pore-forming α-subunits and accessory β-subunits.[1] Commonly, α-subunits and β-subunits are members of large protein families that evolutionary possess comparable amino acid sequences. This is reflected in the names of the subunits and their genes. For example, the gene encoding the α-subunit of the cardiac Na^+ channel is called SCN5A: sodium channel, type 5, α-subunit. The α-subunit is termed $Na_v1.5$: Na^+ channel family, subfamily 1, member 5; the subscript "V" means that channel gating is regulated by transmembrane voltage changes (voltage dependent).

The direction of ion currents (into the cell [inward] or out of the cell [outward]) is determined by the electrochemical gradient of the corresponding ions. The current amplitude (I) depends on the membrane potential (V) and the conductivity (G) of the responsible ion channels. This relation is expressed in equation form as $I = V \cdot G$ (as resistance [R] is the reverse of conductivity: $I = V/R$ [Ohm's law]), implying that the current amplitude reacts linearly ("ohmically") in response to membrane potential changes. However, some currents do not act ohmically (so-called rectifying currents). The conductivity of channels carrying such currents is not constant but alters at different membrane potentials. Rectifying currents in the heart are the inward rectifying current (I_{K1}) and the outward rectifying currents

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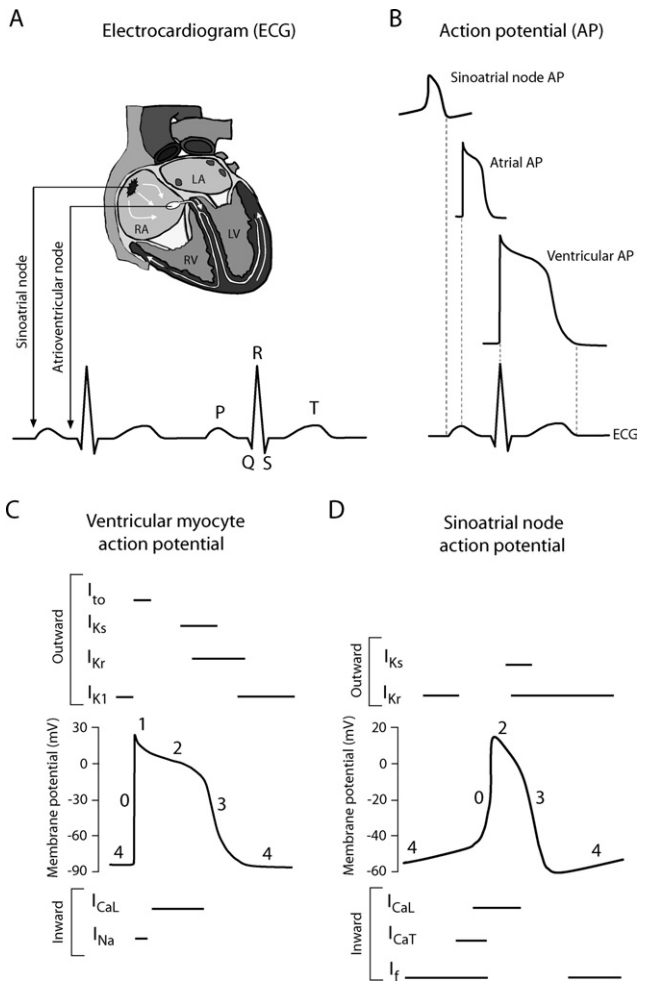

Figure 1 Cardiac electrical activity. **A:** Schematic representation of the electrical conduction system and its corresponding signal on the surface electrocardiogram (ECG). **B:** Relationship between ECG and action potentials (APs) of myocytes from different cardiac regions. **C, D:** Schematic representation of inward and outward currents that contribute to action potential formation in sinoatrial node and ventricular myocytes.

(see below). Channels carrying outward rectifying currents preferentially conduct K^+ ions during depolarization (potentials positive to K^+ equilibrium potential [approximately −90 mV]) when the currents are outwardly directed. Channels carrying I_{K1} preferentially conduct K^+ ions at potentials negative to K^+ equilibrium potential when the currents are inwardly directed. Nevertheless, I_{K1} channels also conduct a substantial outward current at membrane potentials between −40 and −90 mV. Within this voltage range, outward I_{K1} is larger at more negative potentials. Because membrane potentials negative to the K^+ equilibrium potential are not reached in cardiomyocytes, only the outward I_{K1} plays a role in AP formation.

Cardiac AP

In general, the resting potential of atrial and ventricular myocytes during AP phase 4 (resting phase) is stable and negative (approximately −85 mV) due to the high conductance for K^+ of the I_{K1} channels. Upon excitation by electrical impulses from adjacent cells, Na^+ channels activate (open) and permit an inward Na^+ current (I_{Na}), which gives rise to phase 0 depolarization (initial upstroke). Phase 0 is followed by phase 1 (early repolarization), accomplished by the transient outward K^+ current (I_{to}). Phase 2 (plateau) represents a balance between the depolarizing L-type inward Ca^{2+} current ($I_{Ca,L}$) and the repolarizing ultra-rapidly (I_{Kur}), rapidly (I_{Kr}), and slowly (I_{Ks}) activating delayed outward rectifying currents. Phase 3 (repolarization) reflects the predominance of the delayed outward rectifying currents after inactivation (closing) of the L-type Ca^{2+} channels. Final repolarization during phase 3 is due to K^+ efflux through the I_{K1} channels (Figure 1C).

In contrast to atrial and ventricular myocytes, SAN and AVN myocytes demonstrate slow depolarization of the resting potential during phase 4. This is mainly enabled by the absence of I_{K1}, which allows inward currents (e.g., pacemaker current [I_f]) to depolarize the membrane potential. Slow depolarization during phase 4 inactivates most Na^+ channels and decreases their availability for phase 0. Consequently, in SAN and AVN myocytes, AP depolarization is mainly achieved by $I_{Ca,L}$ and the T-type Ca^{2+} current ($I_{Ca,T}$; Figure 1D).[2]

Substantial differences in the expression levels of ion channels underlie substantial heterogeneity in AP duration and configuration between cardiomyocytes located in different cardiac regions.[1] Changes in expression levels or gating properties of ion channels in pathologic conditions may aggravate such regional heterogeneities, thereby generating spatial voltage gradients that are large enough to initiate excitation waves from regions with more positive potentials to regions with less positive potentials. Such excitation waves may travel along a constant or variable circuit to excite cells repeatedly (reentry); this represents the arrhythmogenic mechanism of many inherited and acquired cardiac diseases.[1]

Na^+ current (I_{Na})

By enabling phase 0 depolarization in atrial, ventricular, and Purkinje APs, I_{Na} determines cardiac excitability and electrical conduction velocity. The α-subunit of cardiac Na^+ channels ($Na_v1.5$, encoded by *SCN5A*) encompasses four serially linked homologous domains (DI–DIV), which fold around an ion-conducting pore (Figure 2A). Each domain contains six transmembrane segments (S1–S6). S4 segments are held responsible for voltage-dependent activation. At the end of phase 0, most channels are inactivated and can be reactivated only after recovery from inactivation during phase 4. Some channels remain open or reopen during phases 2 and 3, and they carry a small late Na^+ current (I_{NaL}).[3] Despite its minor contribution in healthy hearts, I_{NaL} may play an important role in diseased hearts. Cardiac Na^+ channels are blocked by high concentrations of tetrodotoxin. Their gating properties usually are studied by expression of *SCN5A* in heterologous systems (e.g., *Xenopus* oocytes or human embryonic kidney cells). I_{Na} amplitude increases and its gating properties accelerate when *SCN5A* is co-expressed with its β-subunits (Table 1). $Na_v1.5$ also interacts with several regulatory proteins that can alter its expression or function.[3–5]

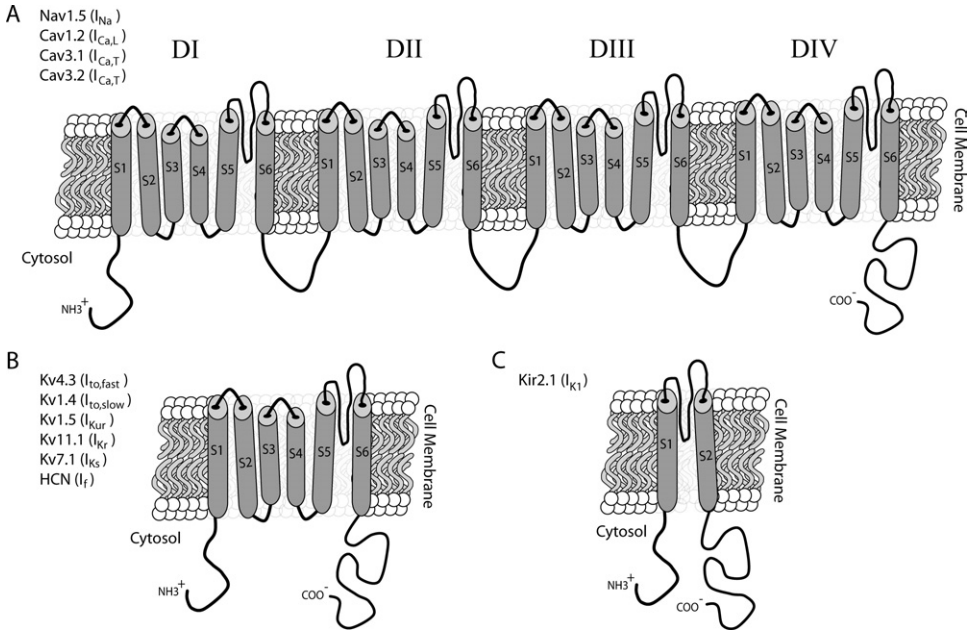

Figure 2 α-Subunits of cardiac ion channels. **A:** α-Subunits of Na^+ and Ca^{2+} channels consists of four serially linked homologous domains (DI–DIV), each containing six transmembrane segments (S1–S6). **B, C:** α-Subunits of channels responsible for I_{to}, I_{Kur}, I_{Kr}, I_{Ks}, I_{K1}, and I_f consist of one single domain with six (B) or two (C) (I_{K1}) transmembrane segments. Four subunits (domains) co-assemble to form one functional channel.

Inherited diseases

Na^+ channel dysfunction is linked to several inherited arrhythmia syndromes, emphasizing the important role of this channel in cardiac electrical activity. Long QT syndrome (LQTS) is a repolarization disorder with QT interval prolongation and increased risk for torsades de pointes ventricular tachycardia and ventricular fibrillation. In LQTS type 3 (LQT3), mutations in *SCN5A* delay repolarization, mostly by enhancing I_{NaL} (Figure 3). Delayed repolarization may trigger early afterdepolarizations (EADs; abnormal depolarizations during phase 2 or 3 due to reactivation of L-type Ca^{2+} channels). EADs are believed to initiate torsades de

Table 1 Genetic and molecular basis of cardiac ion currents

Current	α-Subunit	Gene	β-subunit(s)/accessory proteins	Gene	Blocking agent
I_{Na}	$Na_v1.5$	*SCN5A*	$\beta1$	*SCN1B*	Tetrodotoxin
			$\beta2$	*SCN2B*	
			$\beta3$	*SCN3B*	
			$\beta4$	*SCN4B*	
$I_{to,fast}$	$K_v4.3$	*KCND3*	MiRP1	*KCNE2*	4-aminopyridine
			MiRP2	*KCNE3*	*Heteropoda* spider toxins
			KChIPs	Multiple genes	
			DPP6	*DPP6*	
$I_{to,slow}$	$K_v1.4$	*KCNA4*	$K_v\beta1$	*KCNB1*	4-aminopyridine
			$K_v\beta2$	*KCNB2*	
			$K_v\beta3$	*KCNB3*	
			$K_v\beta4$	*KCNB4*	
$I_{Ca,L}$	$Ca_v1.2$	*CACNA1C*	$Ca_v\beta2$	*CACNB2*	Cations (Mg^{2+}, Ni^{2+}, Zn^{2+})
			$Ca_v\alpha2\delta1$	*CACNA2D1*	Dihydropyridines
					Phenylalkylamines
					Benzothiazepines
$I_{Ca,T}$	$Ca_v3.1$	*CACNA1G*			Similar as $I_{Ca,L}$ (potency may differ)
	$Ca_v3.2$	*CACNA1H*			
I_{Kur}	$K_v1.5$	*KCNA5*	$K_v\beta1$	*KCNAB1*	4-aminopyridine
			$K_v\beta2$	*KCNAB2*	
I_{Kr}	$K_v11.1$	*KCNH2*	MiRP1	*KCNE2*	E-4031
I_{Ks}	Kv7.1	*KCNQ1*	minK	*KCNE1*	Chromanol-293B
I_{K1}	Kir2.1	*KCNJ2*			Ba^{2+}
I_f (pacemaker current)	HCN1-4	*HCN1-4*			Cs^+

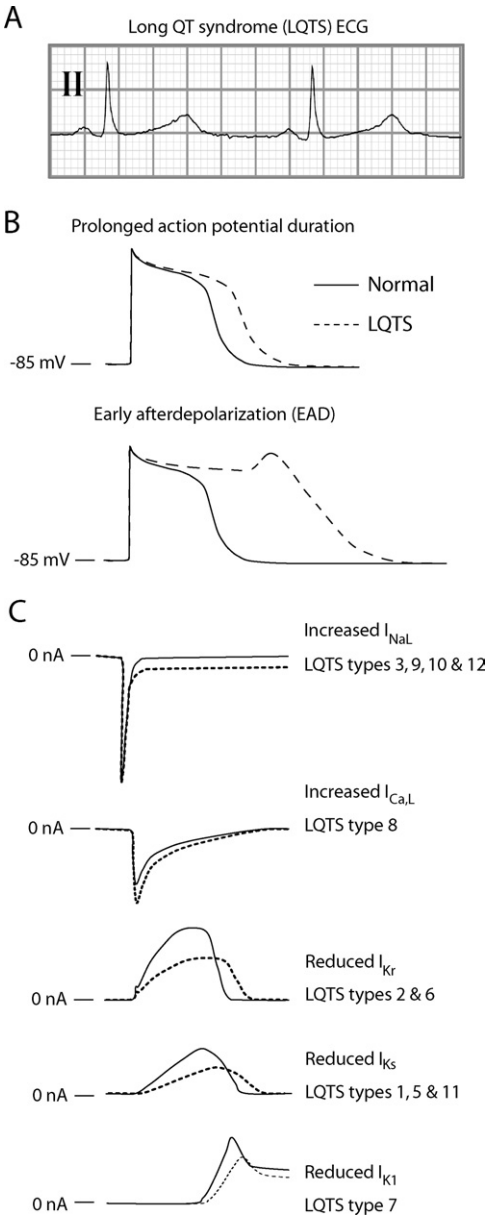

Figure 3 Long QT syndrome (LQTS). **A:** Typical ECG abnormalities in LQTS type 2. **B:** QT prolongation corresponds to prolonged action potential duration, which may induce early afterdepolarizations (EADs). **C:** Ion current dysfunctions linked to different types of LQTS.

pointes.[5] Accordingly, drugs that block I_{NaL} (e.g., ranolazine, mexiletine) may effectively shorten repolarization in LQT3 patients.[6] Moreover, mutations in genes encoding Na^+ channel regulatory proteins may cause rare types of LQTS (Table 2), indicating the importance of these proteins for normal channel function.[4,5]

Brugada syndrome is traditionally linked to mutations in *SCN5A* that reduce I_{Na} by different mechanisms (Figure 4). Brugada syndrome is characterized by prolonged conduction intervals, right precordial ST-segment elevation, and increased risk for ventricular tachyarrhythmia. Prolonged conduction intervals are attributed to conduction slowing due to I_{Na} reduction (Figure 5). ST-segment elevation is hypothesized to be due to preferential conduction slowing in the right ventricle and/or aggravation of transmural voltage gradients (AP shortening in epicardial but not endocardial myocytes).[3] Recently, Brugada syndrome has also been linked to mutations in genes encoding Na^+ channel β-subunits or a protein involved in intracellular $Na_v1.5$ trafficking (Table 2).[7–9] Of note, use of Na^+ channel blocking drugs may evoke or aggravate Brugada syndrome (see http://www.brugadadrugs.org) and is discouraged in patients (suspected of) having Brugada syndrome.

Cardiac conduction disease is manifested by progressive conduction defects at the atrial, atrioventricular, and/or ventricular level and is commonly associated with *SCN5A* mutations that are also linked to Brugada syndrome. How a single mutation may cause different phenotypes or combinations thereof is often not known.[3] Dilated cardiomyopathy is a familial disease with ventricular dilation and failure. The few reported cases with *SCN5A* mutation display atrial and/or ventricular arrhythmia. Dilated cardiomyopathy–linked *SCN5A* mutations cause divergent changes in gating, but how such changes evoke contractile dysfunction and arrhythmia is not understood.[10] Finally, mutations in *SCN5A* have occasionally been linked to sick sinus syndrome, which includes sinus bradycardia, sinus arrest, and/or sinoatrial block. *SCN5A* mutations may impair sinus node function by slowing AP depolarization or prolonging AP duration in SAN cells.[11]

Acquired diseases

I_{Na} reduction and/or I_{NaL} increase may contribute to arrhythmogenesis in acquired diseases. In atrial fibrillation (AF), chronic tachyarrhythmia alters expression levels of several ion channels in atrial myocytes, which may promote and maintain AF ("electrical remodeling"). $Na_v1.5$ expression is reduced as part of this process, leading to I_{Na} reduction.[12] Moreover, AF (either familial or secondary to cardiac diseases [nonfamilial]) is linked to both *SCN5A* loss-of-function mutations and gain-of-function mutations.[13] I_{Na} loss of function may provoke AF by slowing atrial electrical conduction, whereas gain of function may induce AF by enhancing spontaneous excitability of atrial myocytes.[14] In heart failure, peak I_{Na} is reduced, while I_{NaL} is increased. Decreased *SCN5A* expression may underlie peak I_{Na} reduction. I_{NaL} increase is attributed to increased phosphorylation of Na^+ channels, when intracellular Ca^{2+} in heart failure rises.[12] In myocardial infarction, myocytes in the surviving border zone of the infarcted area exhibit decreased I_{Na} due to reduced Na^+ channel expression and altered gating.[12] Moreover, Na^+ channel blocking drugs increase the risk for sudden death in patients with ischemic heart disease, possibly by facilitating the initiation of reentrant excitation waves. Finally, I_{NaL} increases during myocardial ischemia, explaining why I_{NaL} inhibition may be an effective therapy for chronic stable angina.[6]

Transient outward K^+ current (I_{to})

I_{to} supports early repolarization during phase 1. The transient nature of I_{to} is secondary to its fast activation and inactivation upon depolarization. I_{to} displays two pheno-

Table 2 Genetic basis of inherited cardiac diseases

Type	Occurrence (or % of genotyped)	Gene	Protein	Protein function	Affected current
Long QT Syndrome					
1	42%–54%	*KCNQ1*	$K_v7.1$	α-subunit I_{Ks} channel	I_{Ks} decrease
2	35%–45%	*KCNH2*	$K_v11.1$	α-subunit I_{Kr} channel	I_{Kr} decrease
3	1.7%–8%	*SCN5A*	$Na_v1.5$	α-subunit Na^+ channel	I_{NaL} increase
4	<1%	*ANK2*	Ankyrin-B	Adaptor protein	None
5	<1%	*KCNE1*	minK	β-subunit I_{Ks} channel	I_{Ks} decrease
6	<1%	*KCNE2*	MiRP1	β-subunit I_{Kr} channel	I_{Kr} decrease
7	Rare	*KCNJ2*	Kir2.1	α-subunit I_{K1} channel	I_{K1} decrease
8	Rare	*CACNA1C*	$Ca_v1.2$	α-subunit Ca^{2+} channel	$I_{Ca,L}$ increase
9	Rare (1.9% in one study)	*CAV3*	Caveolin-3	Component of caveolae (co-localizes with $Na_v1.5$ at sarcolemma)	I_{NaL} increase
10	<0.1%	*SCN4B*	$\beta4$	β-subunit Na^+ channel	I_{NaL} increase
11	Rare (2% in one study)	*AKAP9*	Yotiao	Mediates I_{Ks} channel phosphorylation	Inadequate I_{Ks} increase during β-adrenergic stimulation
12	Rare (2% in one study)	*SNTA1*	α1-syntrophin	Regulates Na^+ channel function	I_{NaL} increase
Short QT Syndrome					
1	Three families	*KCNH2*	$K_v11.1$	α-subunit I_{Kr} channel	I_{Kr} increase
2	Two case reports	*KCNQ1*	$K_v7.1$	α-subunit I_{Ks} channel	I_{Ks} increase
3	One family (two members)	*KCNJ2*	Kir2.1	α-subunit I_{K1} channel	I_{K1} increase
Brugada Syndrome					
—	10%–30%	*SCN5A*	$Na_v1.5$	Na^+ channel (I_{Na})	I_{Na} decrease
—	Rare (one family)	*GPD1-L*	GPD1-L	Regulates intracellular $Na_v1.5$ trafficking	I_{Na} decrease
—	<1%	*SCN1B*	$\beta1$	β-subunit Na^+ channel	I_{Na} decrease
—	<1%	*SCN3B*	$\beta3$	β-subunit Na^+ channel	I_{Na} decrease
—	<1%	*KCNE3*	MiRP2	β-subunit $I_{to,fast}$ channel	$I_{to,fast}$ increase
—	<8.5%	*CACNA1C*	$Ca_v1.2$	α-subunit Ca^{2+} channel	$I_{Ca,L}$ decrease
—	<8.5%	*CACNB2*	$Ca_v\beta2$	β-subunit Ca^{2+} channel	$I_{Ca,L}$ decrease
Familial Atrial Fibrillation					
—	One (small) family	*KCNE3*	MiRP2	β-subunit $I_{to,fast}$ channel	$I_{to,fast}$ increase
—	Three families	*KCNA5*	$K_v1.5$	α-subunit I_{Kur} channel	I_{Kur} increase
—	One family	*KCNH2*	$K_v11.1$	α-subunit I_{Kr} channel	I_{Kr} increase
—	Two families	*KCNE2*	MiRP1	β-subunit I_{Kr} channel (may modulate I_{Ks} channel)	I_{Ks} increase
—	One family	*KCNQ1*	$K_v7.1$	α-subunit I_{Ks} channel	I_{Ks} increase
—	One family	*KCNJ2*	Kir2.1	α-subunit I_{K1} channel	I_{K1} increase

types. $I_{to,fast}$ recovers rapidly from inactivation, and its α-subunit ($K_v4.3$) is encoded by *KCND3*. $I_{to,slow}$ recovers slowly from inactivation; its α-subunit ($K_v1.4$) is encoded by *KCNA4*.[1] Like other members of the voltage-gated K^+ channel family (Kv family; Table 1), $K_v4.3$ and $K_v1.4$ contain one domain with six transmembrane segments (Figure 2B). Four subunits co-assemble to form one channel. $K_v4.3$ is abundantly expressed in the epicardium and is responsible for shorter AP duration there compared to endocardium, where $K_v1.4$ is expressed to a much lesser extent. This creates a transmural voltage gradient between epicardium and endocardium. I_{to} is blocked by 4-aminopyridine, whereas $I_{to,fast}$ is selectively blocked by *Heteropoda* spider toxins.[15] Heterologous expression of *KCND3* or *KCNA4* does not fully recapitulate native I_{to} phenotypes unless co-expressed with their accessory proteins. For $K_v1.4$, four β-subunits have been identified (Table 1). For $K_v4.3$, gating properties are modulated by MiRP1 and MiRP2 (encoded by *KCNE2* and *KCNE3*), intracellular K_v channel interacting proteins (KChIPs), and dipeptidyl-aminopeptidase-like protein-6 (DPP6; encoded by *DPP6*).[15,16]

Inherited diseases

To date, only mutations in *KCNE3* are linked to inherited arrhythmia. An *KCNE3* mutation was found in five related patients with Brugada syndrome. When expressed with $K_v4.3$, the mutation increased $I_{to,fast}$.[16] It was speculated that increased $I_{to,fast}$ induces ST-segment elevation in Brugada syndrome by aggravating transmural voltage gradients. Another *KCNE3* mutation was identified in one patient with familial AF.[17] The mutation was found to increase $I_{to,fast}$ and postulated to cause AF by shortening AP duration and facilitating atrial reentrant excitation waves.

Recently, a genome-wide haplotype-sharing study associated a haplotype on chromosome 7, harboring *DPP6*, with idiopathic ventricular fibrillation in three distantly related families. Risk-haplotype carriers had increased DPP6 mRNA levels.[18] Although, *in vitro,* DPP6 decreases I_{to} and modulates its

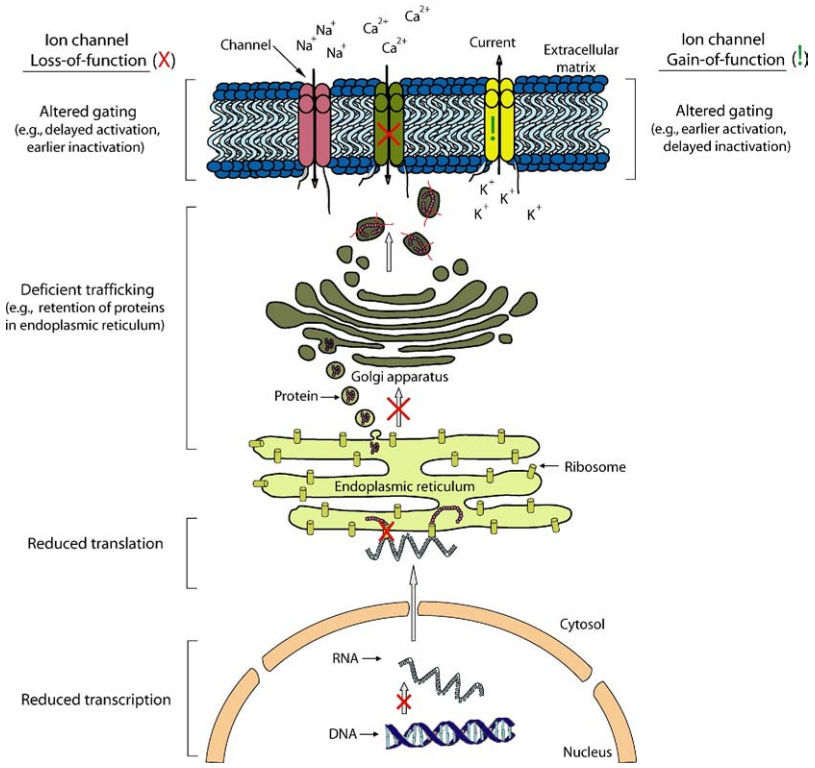

Figure 4 Common molecular mechanisms responsible for ion channel loss of function or gain of function in inherited and/or acquired cardiac diseases.

gating,[16] how potential DPP6 overexpression causes ventricular fibrillation is unresolved.

Acquired diseases

I_{to} is reduced in AF, myocardial infarction, and heart failure.[12] In myocardial infarction, I_{to} is down-regulated by the increased activity of calcineurin, a phosphatase that regulates gene transcription by dephosphorylating transcription factors.[2,12] Sustained tachycardia in heart failure reduces I_{to}, probably through a similar mechanism.[12] However, I_{to} may be increased in the hypertrophic phase preceding heart failure. Accordingly, $K_v4.3$ mRNA and protein levels decrease during progression of hypertrophy to heart failure. Finally, I_{to} may be reduced and contribute to QT interval prolongation in diabetes. Importantly, with certain delay, insulin therapy partially restores I_{to}, maybe by enhancing $K_v4.3$ expression.[15]

Cardiac Ca^{2+} current (I_{Ca}) and intracellular Ca^{2+} transients

The L-type (long-lasting) inward Ca^{2+} current ($I_{Ca,L}$) is largely responsible for the AP plateau. Ca^{2+} influx by $I_{Ca,L}$ activates Ca^{2+} release channels (ryanodine receptor [RyR2]), located in the sarcoplasmic reticulum membrane. Sarcoplasmic reticulum Ca^{2+} release (Ca^{2+} transients) via RyR2 channels couples excitation to contraction in myocytes.[1] *CACNA1C* encodes the α-subunit ($Ca_v1.2$) of L-type channels (Figure 2A). $Ca_v1.2$ gating is voltage dependent. $I_{Ca,L}$ is blocked by several cations (e.g., Mg^{2+}, Ni^{2+}, Zn^{2+}) and drugs (dihydropyridines, phenylalkylamines, benzothiazepines). Its amplitude increases markedly during β-adrenergic stimulation and in the presence of *CACNB2*-encoded $Ca_v\beta2$ (β-subunit) and *CACNA2D1*-encoded $Ca_v\alpha2\delta1$ (accessory protein). Beside $I_{Ca,L}$, T-type (tiny) Ca^{2+} current ($I_{Ca,T}$) is identified in SAN and AVN myocytes.[1] $I_{Ca,T}$ is believed to contribute to AP formation in pacemaker cells.

Inherited diseases

CACNA1C mutations are linked to Timothy syndrome, a rare multisystem disease with QT interval prolongation (LQTS type 8), ventricular tachyarrhythmia, and structural heart disease. In Timothy syndrome, *CACNA1C* mutations delay repolarization by increasing $I_{Ca,L}$ (Figure 3C).[19] Reversely, in one study, loss-of-function mutations in *CACNA1C* or *CACNB2* were found in 7 of 82 patients with Brugada syndrome, three of whom had mildly shortened QT intervals. It was speculated that these mutations cause Brugada syndrome by aggravating transmural voltage gradients.[8]

RyR2 mutations cause catecholaminergic polymorphic ventricular tachycardia, a disease associated with exercise- and emotion-induced arrhythmia. Mutant RyR2 channels permit Ca^{2+} leakage from the sarcoplasmic reticulum into the cytoplasm.[20] Ca^{2+} leakage induces extrusion of Ca^{2+} to the extracellular matrix by the Na^+/Ca^{2+} exchanger, which exchanges one Ca^{2+} ion for three Na^+ ions (Figure 6). By doing so, the Na^+/Ca^{2+} exchanger generates an inward Na^+ current, which underlies delayed afterdepolarization (abnormal depolarization during phase 4 due to activation of Na^+ channels). Delayed afterdepolarizations are believed to cause ventricular tachyarrhythmia.

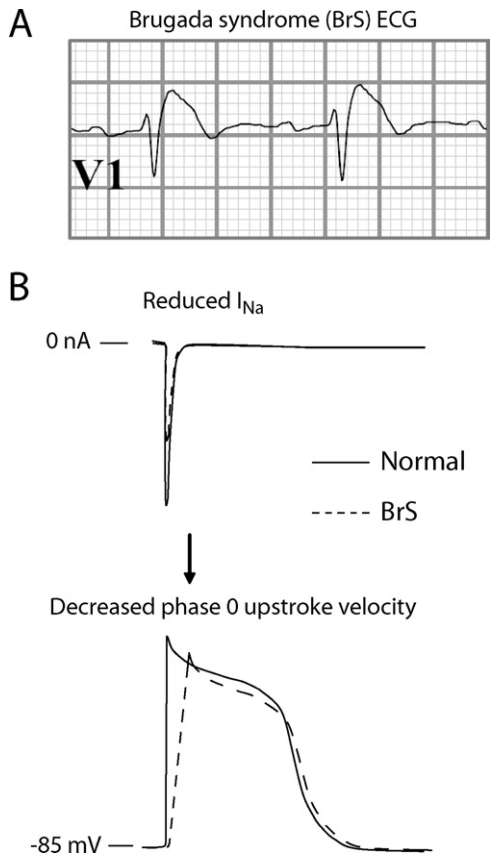

Figure 5 Brugada syndrome (BrS). **A:** Typical ECG abnormalities in Brugada syndrome. **B:** Brugada syndrome is often linked to I_{Na} loss of function, leading to slowed action potential depolarization.

Acquired diseases

Abnormalities in Ca^{2+} currents and/or intracellular Ca^{2+} transients in acquired diseases may induce both arrhythmia and contractile dysfunction. In AF, $Ca_v1.2$ mRNA and protein levels are down-regulated, resulting in $I_{Ca,L}$ reduction, which contributes to AP shortening.[2,21] In heart failure, $Ca_v1.2$ expression is reduced but $I_{Ca,L}$ density remains unchanged due to increased phosphorylation and, consequently earlier activation, of Ca^{2+} channels.[12] Despite unchanged $I_{Ca,L}$, sarcoplasmic reticulum Ca^{2+} transients are smaller and slower in heart failure, causing contractile dysfunction.[21] In myocardial infarction, $I_{Ca,L}$ is reduced in the border zone of the infarcted area.[12] Additionally, acute ischemia inhibits $I_{Ca,L}$ via extracellular acidosis and intracellular Ca^{2+} and Mg^{2+} accumulation.[2]

Ultra-rapidly activating delayed outward rectifying current (I_{Kur})

KCNA5 encodes the α-subunit ($K_v1.5$) of the channel carrying I_{Kur}. $K_v1.5$ is mainly expressed in the atria, and I_{Kur} is detected only in atrial myocytes. Thus, I_{Kur} plays a role in atrial repolarization. It activates rapidly upon depolarization but displays very slow inactivation.[15] Inactivation accelerates when $K_v1.5$ is co-expressed with its β-subunits (Table 1). I_{Kur} is highly sensitive to 4-aminopyridine and is completely blocked by much lower concentrations than is I_{to}.

Inherited diseases

Genetic studies identified *KCNA5* mutations in individuals with familial AF. Heterologous expression of these mutations revealed complete I_{Kur} loss of function, which may cause AF through AP prolongation and EAD occurrence.[22] Interestingly, *KCNA5* missense mutations were found in two patients with long QT intervals and cardiac arrest. Because both of these mutations did not change $K_v1.5$ expression and/or channel gating and because I_{Kur} is detected only in the atria, the contribution of *KCNA5* mutations to ventricular arrhythmogenesis remains controversial.[23]

Acquired diseases

I_{Kur} may be affected in myocardial ischemia. Decreased $K_v1.5$ mRNA levels were reported for the epicardial border zone of infarcted hearts.[12] Moreover, ischemic damage disrupted the normal location of $K_v1.5$ in the intercalated disks.[15] Whereas I_{Kur} defects may be arrhythmogenic in ischemia, I_{Kur} block may act therapeutically in AF. Because I_{Kur} is atrium-specific, a drug specifically targeting $K_v1.5$ channels could terminate AF by preventing reentry through atrial AP prolongation. However, because $K_v1.5$ mRNA and

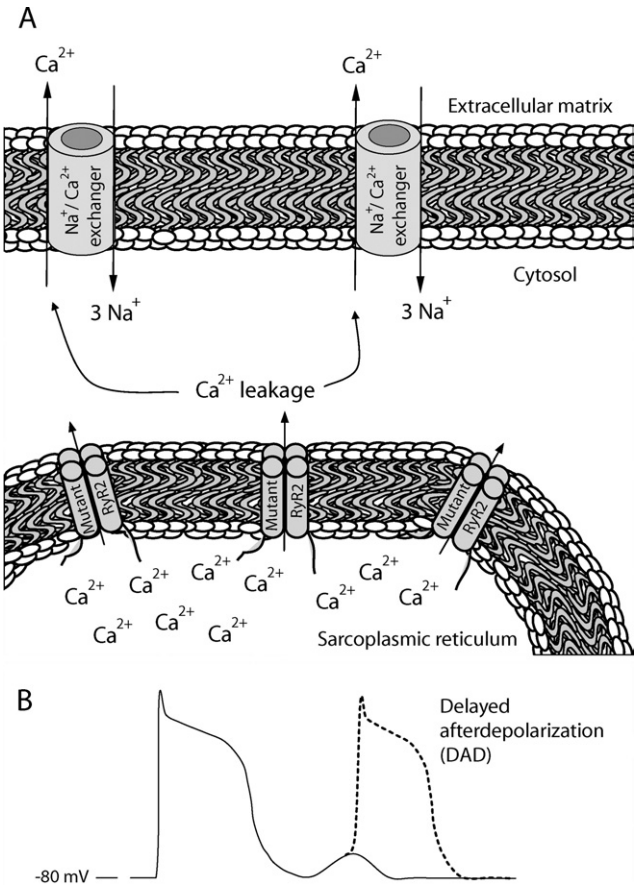

Figure 6 In catecholaminergic polymorphic ventricular tachycardia, A: Mutant RyR2 channels permit Ca^{2+} leakage from the sarcoplasmic reticulum into the cytoplasm, thereby inducing Ca^{2+} extrusion to the extracellular matrix by the Na^+/Ca^{2+} exchanger. **B:** The Na^+/Ca^{2+} exchanger generates an inward Na^+ current, which underlies delayed afterdepolarization (DAD).

protein levels are down-regulated in AF, the beneficial effect of I_{Kur} block becomes less certain. Furthermore, because $K_v1.5$ is also expressed in other organs (e.g., brain), discovery of drugs that selectively inhibit atrial $K_v1.5$ channels remains necessary.[15]

Rapidly activating delayed outward rectifying current (I_{Kr})

KCNH2, also called the *human-ether-a-go-go-related gene (hERG)*, encodes the α-subunit ($K_v11.1$) of the channel carrying I_{Kr}. Belying its name, I_{Kr} activation upon depolarization is not rapid, but inactivation thereafter is very fast, resulting in a small outward K^+ current near the end of the AP upstroke. However, during early repolarization, the channel rapidly recovers from inactivation to produce large I_{Kr} amplitudes during AP phases 2 and 3. Next, the channel deactivates (closes) slowly (in contrast to inactivation, deactivation is a voltage-independent process).[24] Under normal conditions, I_{Kr} is largely responsible for repolarization of most cardiac cells.[1] Interaction of $K_v11.1$ with its β-subunit MiRP1 (encoded by *KCNE2)* induces earlier activation and accelerates deactivation. I_{Kr} is blocked by E-4031.

Inherited diseases

LQTS type 2, the second most prevalent type of LQTS, is caused by *KCNH2* loss-of-function mutations (Figure 3C). This translates into AP and QT interval prolongation and may generate EADs to trigger torsades de pointes. *KCNH2* mutations reduce I_{Kr}, mostly by impairing the trafficking of $K_v11.1$ proteins to the sarcolemma (Figure 4). Moreover, mutations in *KCNE2* also reduce I_{Kr} and cause the less prevalent LQTS type 6.[5]

Short QT syndrome is a rare disease associated with short QT intervals and increased risk for atrial and ventricular fibrillation. A gain-of-function mutation in *KCNH2* is linked to short QT syndrome type 1.[5] The resulting I_{Kr} increase achieved by altered gating hastens repolarization, thereby shortening AP duration and facilitating reentrant excitation waves to induce atrial and/or ventricular arrhythmia. Accordingly, gain-of-function mutations in *KCNE2* have been found in two families with AF.[13]

Acquired diseases

I_{Kr} may not be changed in AF or heart failure.[12] In myocardial infarction, $K_v11.1$ mRNA levels and I_{Kr} are reduced, and AP duration is prolonged. Conversely, during acute ischemia, I_{Kr} is increased and APD is shortened. Such changes may be arrhythmogenic during ischemia. In diabetes, I_{Kr} reduction contributes to QT interval prolongation. Accordingly, $K_v11.1$ levels are down-regulated; this may be due to reduced protein synthesis, as *KCNH2* mRNA levels are normal. Importantly, hyperglycemia depresses I_{Kr}, whereas insulin therapy prevents or restores I_{Kr} function and shortens QT intervals.[25]

Finally, by blocking I_{Kr}, a large variety of drugs prolong QT interval and increase the risk for torsades de pointes (see http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm).[15] Typical structural features of the I_{Kr} channel are held responsible for its remarkable susceptibility to be blocked by drugs. Particularly, individuals with preexisting repolarization defects (e.g., patients with LQTS or diabetes) may be at risk when using such drugs.

Slowly activating delayed outward rectifying current (I_{Ks})

$K_v7.1$, encoded by *KCNQ1,* is the α-subunit of the channel responsible for I_{Ks}. However, only co-expression of *KCNQ1* with minK-encoding *KCNE1* yields currents that resemble I_{Ks}: a K^+ current that activates slowly upon depolarization, displays no inactivation, and deactivates slowly during repolarization.[1] I_{Ks} is markedly enhanced by β-adrenergic stimulation through channel phosphorylation by protein kinase A (requiring A-kinase anchoring proteins [AKAPs]) and protein kinase C (requiring minK).[15] This implies that I_{Ks} contributes to repolarization, especially when β-adrenergic stimulation is present. Accordingly, selective blocking of I_{Ks} by chromanol-293B prolongs AP duration minimally under baseline conditions but markedly under β-adrenergic stimulation.[15] Interestingly, *KCNQ1* and *KCNE1* are also expressed in the inner ear, where they enable endolymph secretion.

Inherited diseases

The most common type of LQTS, type 1 (LQT1), is caused by loss-of-function mutations in *KCNQ1* (Figure 3C). The resulting I_{Ks} reduction is responsible for prolonged AP durations and QT intervals.[5] Arrhythmia usually occurs during exercise or emotional stress, probably because mutant I_{Ks} does not increase sufficiently during β-adrenergic stimulation. Accordingly, β-adrenergic blocking drugs suppress arrhythmic events in LQT1. Individuals with the less prevalent LQTS type 5 carry loss-of-function mutations in *KCNE1* and display a similar phenotype as LQT1 patients.[5] A mutation in *AKAP9*, encoding Yotiao (AKAP9), was described in two related patients with LQTS type 11. The mutation inhibited the β-adrenergic response of I_{Ks} by disrupting the interaction between Yotiao and $K_v7.1$.[26] Yotiao mediates phosphorylation of $K_v7.1$ by protein kinase A upon β-adrenergic stimulation.

Loss-of-function mutations in both alleles of *KCNQ1* or *KCNE1* cause the very rare Jervell and Lange-Nielsen syndrome (JLNS) type 1 or 2, respectively.[5] JLNS encompasses 1% to 7% of all genotyped LQTS patients and is characterized by, in addition to QT interval prolongation, arrhythmia and congenital deafness, the latter due to deficient endolymph secretion.

KCNQ1 gain-of-function mutations are anecdotally linked to short QT syndrome (type 2).[5] Moreover, an *KCNQ1* gain-of-function mutation is reported to cause familial AF by shortening atrial AP duration and facilitating reentry.[13]

Acquired diseases

Animal models of AF-related sustained atrial tachyarrhythmia do not display alterations in I_{Ks} amplitude. However,

genetic association studies in patients with nonfamilial AF have linked increased risk for AF to *KCNE1* polymorphisms.[13] Heterologous co-expression of one such polymorphism with *KCNQ1* resulted in I_{Ks} reduction. Such contradictory reports of *KCNQ1* mutation causing familial AF by increasing I_{Ks} and *KCNE1* polymorphisms increasing AF risk by decreasing I_{Ks} suggest that multiple mechanisms underlie AF. Several studies reported that heart failure reduces I_{Ks} in atrial, ventricular, and SAN myocytes.[12] Given that I_{Kr} is unchanged, I_{Ks} reduction may largely account for prolonged AP duration in heart failure. Finally, I_{Ks} density and *KCNQ1*/*KCNE1* mRNA levels were decreased in myocytes from infarcted border zones 2 days postinfarction. However, *KCNQ1* expression was restored 5 days postinfarction, while *KCNE1* expression remained decreased.[12,15]

Inward rectifying current (I_{K1})

I_{K1} stabilizes the resting membrane potential of atrial and ventricular myocytes during phase 4 and contributes to the terminal portion of phase 3 repolarization (Figure 1C). I_{K1} channels are closed during AP phases 1 and 2. Voltage-dependent block by intracellular Mg^{2+} underlies channel closing, while unblocking enables channel opening.[15] I_{K1} is almost absent in SAN and AVN myocytes. Its α-subunit (Kir2.1) is encoded by *KCNJ2* and consists of one domain with two transmembrane segments (Figure 2C). Blocking I_{K1} by extracellular Ba^{2+} results in depolarization of the resting potential and mild AP prolongation.[27]

Inherited diseases

Loss-of-function mutations in *KCNJ2* are linked to Andersen-Tawil syndrome, a rare disease characterized by skeletal developmental abnormalities, periodic paralysis, and usually nonsustained ventricular arrhythmia, often associated with prominent U waves and mild QT interval prolongation (LQTS type 7; Figure 3C).[27] *KNCJ2* mutations reduce I_{K1} by encoding defective Kir2.1 subunits, which generate nonfunctional channels and/or bind to normal subunits to disrupt their function ("dominant-negative effect"). I_{K1} reduction may trigger arrhythmia by allowing inward currents, which are no longer counterbalanced by the strong outward I_{K1}, to gradually depolarize the membrane potential during phase 4. Membrane depolarization during phase 4 induces arrhythmia by facilitating spontaneous excitability.[5] Alternatively, I_{K1} reduction may trigger arrhythmia by prolonging AP duration and triggering EADs.

To date, one *KCNJ2* gain-of-function mutation, found in one small family, is linked to short QT syndrome type 3. When expressed heterologously, the mutation increased I_{K1} and was predicted to shorten AP duration and QT interval by accelerating the terminal phase of repolarization.[5] Another *KCNJ2* gain-of-function mutation was described in one single family with AF. The affected members had normal QT intervals. The mutation was speculated to cause AF by shortening atrial AP duration and facilitating reentrant excitation waves.[13]

Acquired diseases

In chronic AF, I_{K1} is increased and Kir2.1 mRNA and protein levels are elevated. Increased I_{K1} corresponds to more negative resting potentials and, together with reduced $I_{Ca,L}$, accounts for AP shortening in AF.[12] Reduced I_{K1} densities are reported in animal models of ventricular failure.[15] This may be secondary to increased intracellular Ca^{2+} because Ca^{2+} blocks the outward component of I_{K1}.[28] Reduced I_{K1} densities are also measured in myocytes of animal hearts postinfarction. Moreover, various factors during ischemia (e.g., intracellular Ca^{2+}, Mg^{2+}, and/or Na^{+} accumulation, and acidosis) may inhibit I_{K1}.[2] I_{K1} reduction in heart failure or ischemia may facilitate spontaneous excitability and trigger arrhythmia.

Pacemaker current (I_f)

The pacemaker current enables spontaneous initiation of cardiac electrical activity. It is also called the funny current (I_f) because it displays unusual gating properties. I_f is a mixed Na^{+}/K^{+} current, which activates slowly upon hyperpolarization and inactivates slowly in a voltage-independent manner (deactivation) upon depolarization. I_f conducts an inward current during phases 3 and 4 and may underlie slow membrane depolarization in cells with pacemaker activity (i.e., cells with I_f and little or no I_{K1}).[29] I_f activation is accelerated when intracellular cyclic adenosine monophosphate (cAMP) levels are increased. Thus, I_f mediates heart rate regulation by sympathetic and parasympathetic activity, which control synthesis and degradation of intracellular cAMP, respectively. Accordingly, channels responsible for I_f are named hyperpolarization-activated cyclic nucleotide-gated (HCN) channels.[2] Four α-subunit isoforms are described (HCN1-4, encoded by *HCN1-4*), which are preferentially expressed in SAN and AVN myocytes, and Purkinje fibers (Figure 2B). HCN channels are blocked by Cs^{+}. Their intracellular C-terminus contains cyclic nucleotide-binding domains (CNBDs), which enable direct cAMP binding. HCN isoforms differ in the extent of voltage-dependent gating and sensitivity to cAMP, and HCN4 channels are considered the best candidate to carry I_f.

Inherited diseases

Heterozygous *HCN4* mutations were found in individuals with mild to severe sinus bradycardia.[30] Heterologous expression revealed that these mutations decrease HCN channel expression, decelerate I_f activation, or, when located in CNBDs, abolish sensitivity of HCN channels to cAMP. These effects imply that *HCN4* mutations cause bradycardia by reducing I_f and the speed of membrane depolarization during phase 4; this results in slower pacemaking rates in SAN myocytes.

Acquired diseases

Increased HCN expression in atrial or ventricular myocytes in pathologic conditions could initiate arrhythmia by triggering spontaneous excitation of nonpacemaker myocytes.[2] Indeed, increased HCN2/HCN4 mRNA and protein levels

are found in atria of patients with AF and in ventricular tissues of heart failure patients. Accordingly, larger I_f amplitudes were recorded in myocytes that were obtained from failing hearts.[12]

I_f recently has become a target for pharmacologic studies aimed at discovering drugs to decrease heart rates in patients with ischemic heart disease. Elevated heart rates in these patients are associated with increased risk for mortality. Whereas current heart rate lowering drugs adversely affect cardiac contractility, selective I_f inhibition is believed to lower heart rate without impairing contractility. To date, ivabradine is the only I_f blocker registered for treatment of chronic stable angina.[29]

Study limitations and future research

This review has focused on ion channels that contribute to AP formation in normal adult hearts. However, several ion channels play only a role in disease or during early development. Emerging studies have indicated that ion channels function properly only in the presence of various regulatory molecules. Moreover, next to exonic mutations and polymorphisms, ion channel expression may be influenced by variants in intronic regions of the responsible genes and/or small noncoding RNAs (microRNAs) that control expression by regulating mRNA translation. Thus, ion channels act in close interaction with multiple genetic and nongenetic modifiers, which possibly contribute to interindividual phenotype differences in individuals with the same disease. Nevertheless, the majority of the available literature about ion currents is obtained from electrophysiologic studies of the responsible channels in heterologous expression systems, isolated myocytes from animal hearts, or, to a lesser extent, myocytes from explanted human hearts, where the effects of such modifiers is greatly lost. Exploring these effects on channel expression and function may provide novel mechanistic insights into the pathophysiology of diseases. Moreover, it may introduce new and more specific targets to treat arrhythmia, especially as currently used antiarrhythmic drugs are insufficiently effective and may cause serious adverse effects, including arrhythmias.

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