Review

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Ventricular ion channels and arrhythmias: an overview of physiology, pathophysiology and pharmacology

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Abstract: Cardiac ion channels are critical transmembrane proteins that mediate almost all aspects of cardiac function including generation and propagation of cardiac action potential (AP) as well as maintenance of normal heart excitability and contraction. In addition, the pivotal role of cardiac ion channels in cardiac health and disease is underscored by the profound effects of their dysfunctional mutations on various arrhythmias. Hence, ion channels are vital targets for antiarrhythmic drugs. In this review, we first summarize the characteristics, structure of the various cardiac ion channels and their specific roles in cardiac electrophysiology. Subsequently, we highlight the implications of genetic mutations that disrupt ion channel function, which are associated with inherited cardiac arrhythmias. Finally, we address antiarrhythmic drugs acting on cardiac ion channels respectively, according to their therapeutic targets. In conclusion, this manuscript aims to review the physiology, pathophysiology and pharmacology of the most prominent ventricular Na_V, Ca_V, K_V, and K_{ir} ion channels.

Keywords: ion channels; action potential; arrhythmias; antiarrhythmic drugs

Introduction

Ion channels are ubiquitous transmembrane proteins embedded within living cells, selectively permitting the passage of charged ions (e.g., sodium, potassium, calcium, and chloride) across the cell membrane. These orchestrated movements of ions, driven by electrical and chemical gradients, underpin a myriad of physiological processes, including cellular secretion, nerve signal transmission, and muscle contraction.

Meanwhile, the rhythmic and coordinated contraction of the heart are governed by the precise flow of ions across the cell membranes. This electrical activity is shaped by a complex interplay of various ion channels, with specific channels responsible for the distinct phases of cardiac action potential (AP). Cardiac AP originates in the sinoatrial node (SAN) and travels through the specialized conduction system, ensuring coordinated contraction of the atria and ventricles [1].

These numerous ion channels expressed in the heart or in the vasculature are the target for clinical antiarrhythmic drugs. Understanding the functions and dysfunctions of cardiac ion channels, as well as their impact on the cardiac AP, is of paramount importance for treating inherited arrhythmias. In the following chapters, we aim to briefly discuss the structure, expression profiles, physiological roles and pharmacology of predominant subtype of Na_V, Ca_V, K_V, and K_{ir} channels which contribute to ventricular AP.

Fast action potential of cardiomyocytes

In ventricular myocytes, cardiac AP depolarizes rapidly due to a high density of voltage-gated sodium $Na_V1.5$ channels which allow sodium ions to enter cardiac cells within 1 ms. This fast response AP can be divided into five distinct phases (P0–P4) that are facilitated by different cardiac ion channels [2] (Figure 1).

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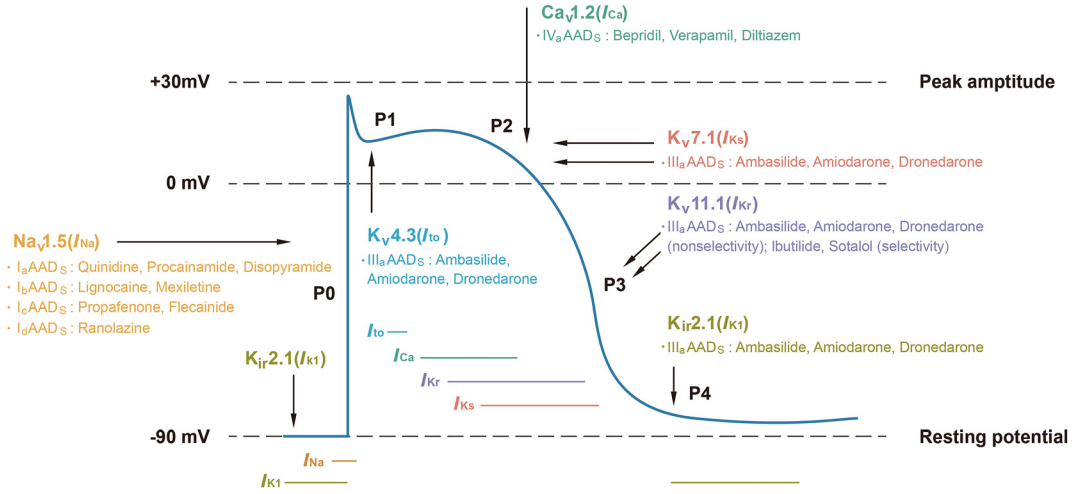

Figure 1: Fast action potential and ionic currents. Schematic of the five phases (0, 1, 2, 3 and 4) of the fast AP. The contribution of different ion channels to the generation of a fast AP and their representative antiarrhythmic drugs are included. The segments with different color represent the corresponding time periods of different currents in the fast AP. I_{Na}, voltage gated sodium current. I_{Ca}, voltage gated calcium current. I_{to}, transient outward potassium current. I_{Ks}, slow delayed rectifier potassium current. I_{Kr}, rapid delayed rectifier potassium current. I_{k1}, inward rectifier potassium current.

Phase 4 represents the resting state of APs during which ventricular cells maintain a resting membrane potential (-90 mV). The outward I_{K1} current [3] facilitated by the inward rectifier potassium channels ($K_{ir}2.1/2.2$) is the primarily current that mediate this phase. Phase 0, the fast depolarization, occurs as myocardial cells are excited by appropriate stimulation, which triggers the opening of voltage-dependent sodium channels ($Na_V1.5$) and the entry of sodium ions. Then, the membrane potential shifts from resting state (-90 mV) into positive voltage range (+30 mV) [4]. Phase 1 presents an initial and rapid repolarization induced by the inactivation of sodium channels and transient outward potassium currents I_{to} mediated by voltage-dependent potassium channels ($K_V4.2/4.3$, $K_V1.4$). The outward I_{to} current conduces the membrane potential to decline to about 0 mV. During Phase 2, or the plateau, calcium ions enter the cells through the L-type voltage-gated calcium channels ($Ca_V1.2/1.3$), while the voltage-dependent potassium channels ($K_V11.1$, $K_V7.1$) produce the outward I_{Kr} and I_{Ks} currents which is approximately equal to I_{Ca}. Phase 3 shows the rapid terminal repolarization facilitated by the increased outward I_{Kr} and I_{Ks} currents as well as the lessened inward I_{Ca}. Then the K_{ir} channels ($K_{ir}2.1/2.2$) mediate the I_{K1} currents that complete repolarization phases, allowing the membrane potential to return to its resting state.

Arrhythmogenic ventricular ion channels

The voltage variations in cardiac AP are generated by ions flowing through specific selectively permeable ion channels whose dysfunctions are associated with cardiac arrhythmias [5, 6]. Here, we list the clones of the α subunits of the major arrhythmogenic ventricular ion channels (Table 1). In particular, these ion channels are the main therapeutic targets of antiarrhythmic drugs. Meanwhile, the tremendous development in structural and molecular biology has significantly facilitated the investigation of protein structures and the elucidation of drug-binding sites.

Table 1: Main arrhythmogenic ventricular ion channels and their currents, genes and functional phases in fast action potential [4].

Current	Ion	Direction	Functional phases	α subunits	Gene
I_{Na}	Na^+	Inward	Phase 0	$Na_V1.5$	SCN5A
$I_{to,fast}$	K^+	Outward	Phase 1	$K_V4.2/K_V4.3$	KCND2/KCND3
$I_{to,slow}$	K^+	Outward	Phase 1	$K_V1.4$	KCNA4
$I_{Ca,L}$	Ca^{2+}	Inward	Phase 2	$Ca_V1.3/Ca_V1.2$	CACNA1D/CACNA1C
I_{Kr}	K^+	Outward	Phase 2, 3	$K_V11.1$	KCNH2
I_{Ks}	K^+	Outward	Phase 2, 3	$K_V7.1$	KCNQ1
I_{K1}	K^+	Outward	Phase 3, 4	$K_{ir}2.1/K_{ir}2.2$	KCNJ2

$I_{to,fast}$, fast transient outward potassium current; $I_{to,slow}$, slow transient outward potassium current.

Voltage-dependent sodium channels

In cardiac myocytes, the $Na_V1.5$ channel is the predominant subtype of voltage-gated sodium channels family ($Na_V1.1$–1.9). The channel exists as a protein complex consisting of a

large α subunit (>260 kDa) encoded by the SCN5A gene, along with β1 and β2 subunits, encoded by SCN1B and SCN2B, respectively [13]. The α subunit consists of four homologous domains (DI–DIV) [14] and it is the major functional subunit capable of independently forming channels and generating sodium current [15]. Each domain contains six transmembrane segments (S1–S6), and the S4 segment acts as the voltage sensor domain (VSD). The extracellular loops (P loops) between the S5 and S6 segments of four homologous domains form the pore region, where the Asp (D), Glu (E), Lys (K), Ala (A) residues from each domain contribute to the selectivity filter of the sodium channel [16] (Figure 2B).

$Na_V1.5$ channels are closed in the resting state. In response to membrane depolarization, these channels generate a depolarization within 200–300 μs and the majority are inactivated rapidly within 2–5 ms [13], while a small number of channels remain in open state in the later phases, contributing to late sodium current (late sodium current, $I_{Na,\ Late}$). Though $I_{Na,\ Late}$ is only about 5 % of the I_{Na} peak current, it still plays a significant role in maintaining the AP plateau phase and duration [33, 34].

Due to the crucial role of the $Na_V1.5$ channel in cardiac AP, many mutations in the SCN5A gene are associated with inherited arrhythmogenic diseases (IADS), including long QT syndrome type 3 (LQT3), Brugada syndrome (BrS), sick sinus syndrome (SSS), dilated cardiomyopathy (DCM), atrial fibrillation (AF), and progressive cardiac conduction disease (PCCD) [24]. To date, more than 700 SCN5A mutations have been identified as being related to cardiac diseases. Among them, LQT3 is characterized by prolonged QT intervals, accentuated QT dispersion, late onset of T wave and frequent prominent U wave which is related to over 300 SCN5A variants. Five to ten percentage of LQT3 patients possess gain-of-function variants in SCN5A resulting in a more rapid AP initiation and enhancing $I_{Na,\ Late}$. On the other hand, loss-of-function variants in SCN5A cause synthesis deficiency or trafficking defects, permeation disruption, slower activation or faster inactivation of $Na_V1.5$ channels. These dysfunctional behaviors primarily induced BrS which is characterized by ST segment elevation on electrocardiogram (ECG). These loss-of-function mutations ruin the transmembrane ion flux balance and damage the depolarization in phase 1 (Figure 2). In addition, ischemic cardiomyopathy, myocardial infarction and heart failure are associated with reduced $Na_V1.5$ peak current or enhanced late current through metabolic changes or specific signaling pathways, contributing to arrhythmic risk [35–37].

Therefore, the $Na_V1.5$ channel is a crucial therapeutic target for antiarrhythmic medications. The updated Singh–Vaughan Williams classification system [38] categorizes antiarrhythmic drugs into five classes (Class I–V) based on

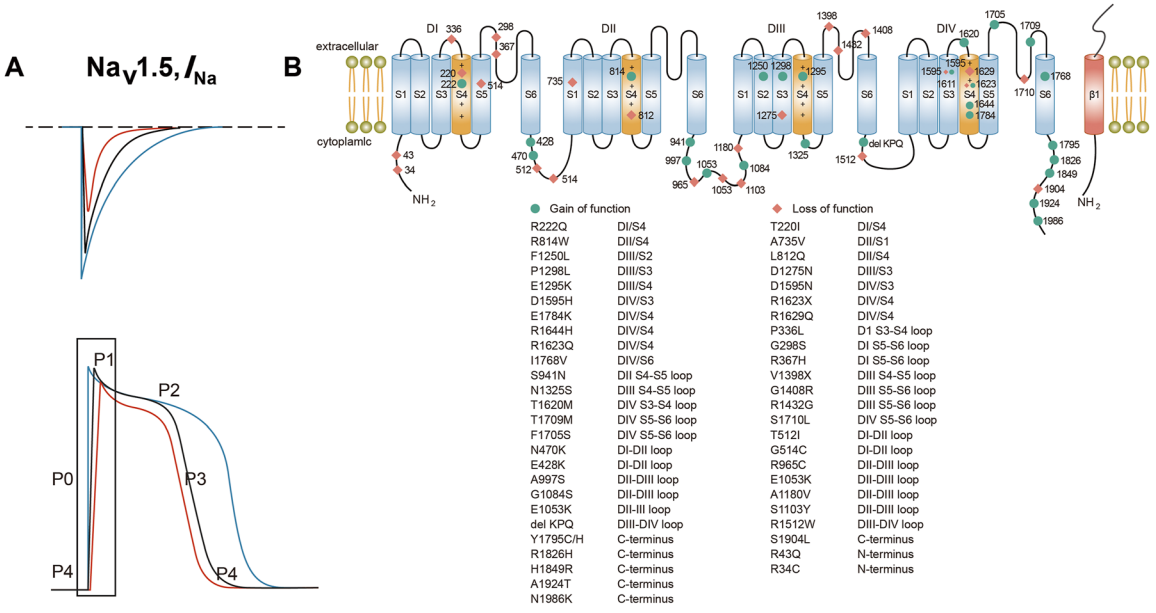

Figure 2: Cardiac voltage-gated sodium channel ($Na_V1.5$) and its typical gain-of-function or loss-of-function SCN5A mutations. (A) schematic representation of I_{Na} corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) schematic of $Na_V1.5$ protein structure and some typical GOF and LOF mutations [17–32]. $Na_V1.5$ comprises one α subunit consisting of four homologous domains (DI-DIV) and one or two auxiliary β subunits. The transmembrane segments S1-S6 in each domain are indicated by numbered cylinders and the fourth positively charged S4 segment as the voltage sensor domain is depicted in orange. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

Table 2: Class I antiarrhythmic drugs [7–10].

Class	Drug exemplars	Pharmacological targets	Therapeutic action	Clinical indications
I_a	Quinidine Procainamide Disopyramide	$Na_V1.5$ channel open state blocker; intermediate ($\tau \approx 1$–10 s) dissociation kinetics; often concomitant K^+ channel block	Reduces peak I_{Na}, AP generation and $(dV/dt)_{max}$; slows action potential conduction down; often accompanies I_K inhibition and prolongs APD, ERP, QT interval	Supraventricular tachyarrhythmias, recurrent atrial fibrillation; ventricular tachycardia, ventricular fibrillation (SQTS and BrS)
I_b	Lignocaine Mexiletine	$Na_V1.5$ channel open state blocker; rapid ($\tau \approx 0.1$–1 s) dissociation kinetics	Reduces peak I_{Na}, AP generation and $(dV/dt)_{max}$; slows action potential conduction down; prolongs APD, ERP	Ventricular tachyarrhythmias; ventricular fibrillation (particularly after myocardial infarction)
I_c	Propafenone Flecainide	$Na_V1.5$ channel inactivated state blocker; slow ($\tau \approx 0.1$–1 s) dissociation kinetics	Reduces peak I_{Na}, AP generation and $(dV/dt)_{max}$; slows action potential conduction down; reduces overall excitability; prolongs APD (at high heart rates) and ERP	Supraventricular tachyarrhythmias; premature ventricular contraction; ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease; CPVT
I_d	Ranolazine	$Na_V1.5$ channel $I_{Na,\ Late}$ blocker	Reduces $I_{Na,\ Late}$; affects AP plateau, duration and QT interval	Stable angina; ventricular tachycardia; LQT3; AF; heart failure

their primary mechanisms of AP. Class I antiarrhythmic drugs (Table 2), also known as sodium channel blockers, constitute the largest group and are further subdivided into I_a, I_b, and I_c subclasses based on the distinct effects on sodium current [39]. Moreover, a growing body of evidence has implicated the late sodium current ($I_{Na,\ Late}$), which remains during the late phases of the AP, in the pathogenesis of various arrhythmias, including AF and LQT3. Ranolazine, a selective blocker of $I_{Na,\ Late}$ current without significantly affecting I_{Na} current, has been identified as I_d antiarrhythmic drug demonstrating efficacy in treating AF, LQT3 and heart failure [7, 8].

Beyond the well-characterized $Na_V1.5$ channel, the heart harbors a diverse array of additional sodium channels, including $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.6$, $Na_V1.8$, and $Na_V2.1$ [13]. While their precise roles in cardiac physiology remain to be fully elucidated, emerging evidence suggests that these channels play crucial yet often underappreciated roles in regulating electrical activity and contributing to various cardiac pathologies.

In heart failure, $Na_V1.1$ channel expression is significantly upregulated in ventricular cardiomyocytes [40], contributing to the $I_{Na,\ Late}$ current. Similarly, $Na_V1.8$ channel expression is upregulated in cases of cardiac hypertrophy and heart failure [41]. Blocking $Na_V1.8$ currents reduces $I_{Na,\ Late}$ and shortens AP duration [42], suggesting that $Na_V1.8$ channel contributes to $I_{Na,\ Late}$ current and plays a potential role in regulating cardiac excitability. Notably, many mutations in SCN10A gene which encodes the $Na_V1.8$ channel have been reported in patients with AF [43] and sudden cardiac death [44].

Voltage-dependent calcium channels

In 1989, Reuter first reported the existence of two distinct types of voltage-gated calcium (Ca_V) channels in mammalian hearts: T-type and L-type voltage-gated calcium channels [45, 46]. Cardiac Ca_V channels are composed of a pore-forming α1 subunit along with auxiliary β and α2δ subunits, while lacking the γ subunit found in skeletal muscle Ca_V channels (Figure 3B). Among these, the L-type voltage-gated calcium channel $Ca_V1.2$ encoded by the CACNA1C gene is the predominant α1 subunit in cardiac system [47, 48], which requires assembly with auxiliary β and α2δ subunits to function properly [1].

The structure of the $Ca_V1.2$ channel resembles that of the Na_V channel [53, 54]. The α1 subunit consists of four homologous domains (DI–DIV), each containing six transmembrane helices (S1–S6). The S4 segment serves as the voltage sensor domain (VSD), S5 and S6 segments form the structure of pore region. The glutamate residues (EEEE) in the four extracellular loops constitute pore filter and determine the ion selectivity of calcium channels [55]. $I_{Ca,L}$ current contributed by $Ca_V1.2$ channels plays a crucial role in maintaining the plateau of AP and in excitation–contraction coupling of cardiomyocytes [12, 56].

As reported, G406R and G402S mutations in CACNA1C gene are associated with Timothy syndrome (TS) which is often accompanied with long QT syndrome 8 (LQT8), ventricular arrhythmias and structural heart disease [56]. These gain-of-function (GOF) mutations lead to delayed inactivation of the $I_{Ca,L}$ current [56] and enhance gating coupling [57] of the $Ca_V1.2$ channel. In addition, the loss-of-function (LOF) mutations, such

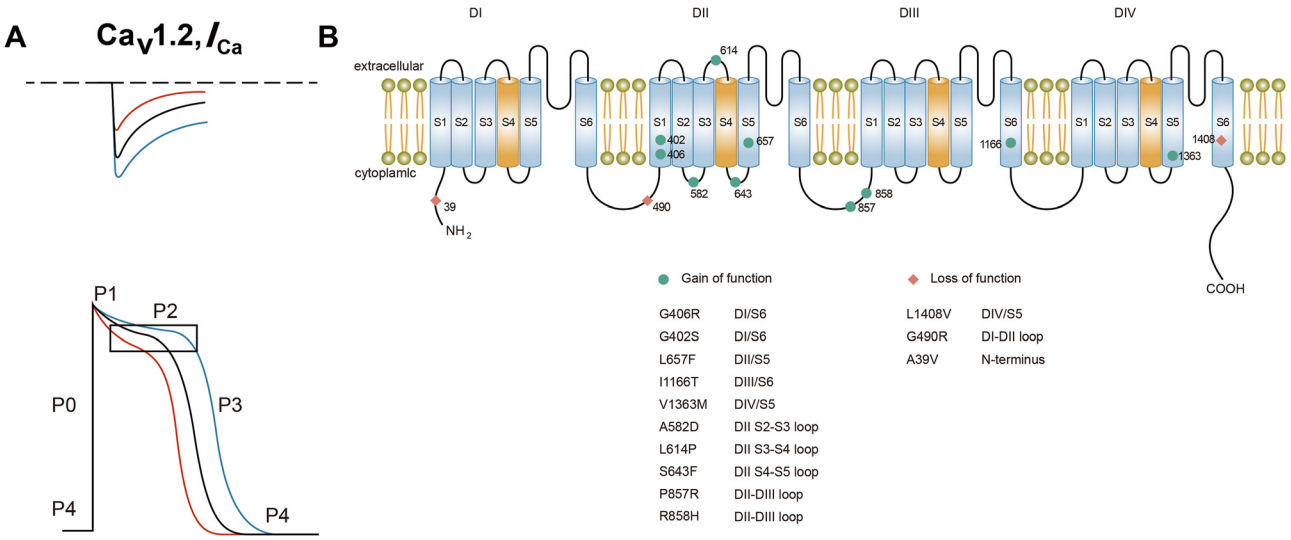

Figure 3: Cardiac L-type voltage-gated calcium channel ($Ca_V1.2$) and its typical gain-of-function or loss-of function CACNA1C mutations. (A) schematic representation of $I_{Ca,L}$ corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) schematic of $Ca_V1.2$ protein structure and some typical GOF and LOF mutations [49–52]. $Ca_V1.2$ comprises one α subunit consisting of four homologous domains (DI-DIV). The transmembrane segments S1-S6 in each domain are indicated by numbered cylinders and the fourth positively charged S4 segment as the voltage sensor domain is depicted in orange. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

as A39V and G490R, drastically reduce the amplitudes of $I_{Ca,L}$ current, resulting in familial cardiac arrhythmia syndromes [49] (Figure 3).

The Singh-Vaughan Williams classification initially defined Class IV antiarrhythmic drugs as non-dihydropyridine calcium channel blockers [9]. This concept has since been expanded to drugs acting on calcium homeostasis related targets. The traditional surface membrane Ca^{2+} channel blockers are classified as Class IV_a (Table 3), while the updated classification includes Intracellular Ca^{2+} channel blockers (Class IV_b), sarcoplasmic reticular Ca^{2+}-ATPase activators (Class IV_c), surface membrane ion exchange inhibitors (Class IV_d), and phosphokinase and phosphorylase inhibitors (Class IV_e). However, no clinical drugs are currently available for Class IV_c, IV_d, and IV_e.

Voltage-dependent potassium channels

Voltage-gated potassium channels (K_V) share similar structural compositions, consisting of α-subunits which form the pore region of channels and multiple auxiliary β subunits. In contrast to Na_V channels which are homotetramers, K_V channels are hereotetramers composed of four distinct α subunits.

Table 3: Class IV_a antiarrhythmic drugs [9, 11].

Class	Drug exemplars	Pharmacological targets	Therapeutic action	Clinical indications
IV_a	Bepridil	Nonselective surface membrane Ca^{2+} channel blockers	Reduces I_{Ca}, resulting in inhibition of SAN pacing, inhibition of AVN conduction; prolongs ERP, APD, PR interval; diminishes repolarization reserve and suppression of intracellular Ca^{2+} signaling	Angina pectoris; supraventricular tachyarrhythmias
	Verapamil Diltiazem	Selective L-type Ca^{2+} channel blockers	Reduces I_{Ca}, resulting in inhibition of SAN pacing, inhibition of AVN conduction; prolongs ERP, APD, PR interval; diminishes repolarization reserve and suppression of intracellular Ca^{2+} signaling	Supraventricular arrhythmias and ventricular tachycardia (without structural heart disease); rate control of atrial fibrillation
	–	Selective T-type Ca^{2+} channel blockers	Inhibition of SAN pacing; prolongs His-Purkinje phase 4 repolarization	–

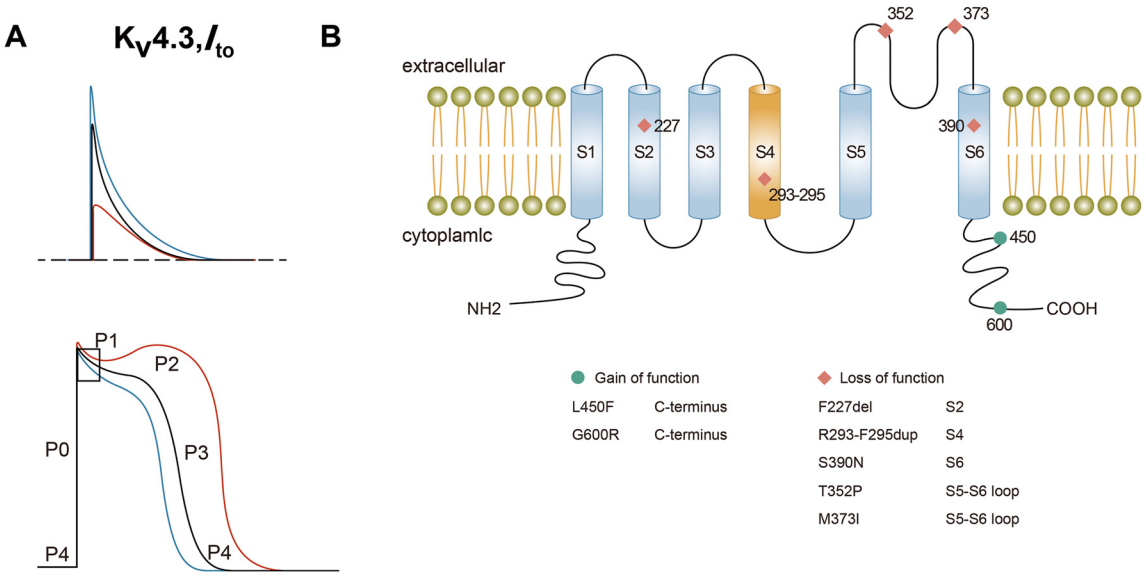

Figure 4: Cardiac voltage-gated potassium channel ($K_V4.3$) and its typical gain-of-function or loss-of function KCND3 mutations. (A) Schematic representation of I_{to} corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) Schematic of $K_V4.3$ α subunit structure and some typical GOF and LOF mutations [58–61]. $K_V4.3$ comprises four α subunits which are heterotetramers and interacting auxiliary subunits. Each α subunit consists of six segments (S1-S6) which are indicated by numbered cylinders and the fourth positively charged S4 segment as the voltage sensor domain is depicted in orange. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

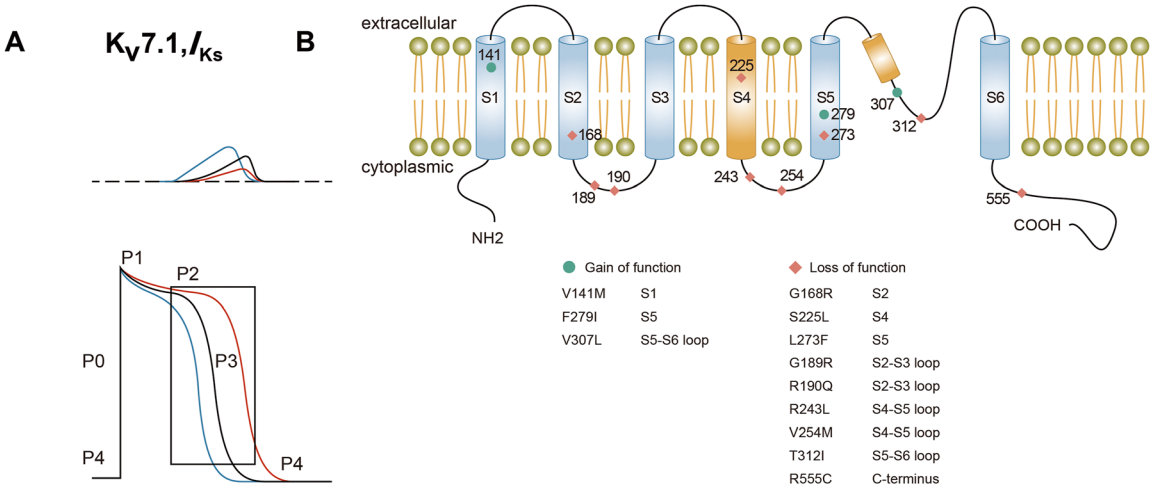

Figure 5: Cardiac voltage-gated potassium channel ($K_V7.1$) and its typical gain-of-function or loss-of function KCNQ1 mutations. (A) Schematic representation of I_{Ks} corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) Schematic of $K_V7.1$ α subunit structure and some typical GOF and LOF mutations [62–67]. $K_V7.1$ comprises four α subunits which are heterotetramers and interacting auxiliary subunits. Each α subunit consists of six segments (S1-S6) which are indicated by numbered cylinders and the fourth positively charged S4 segment as the voltage sensor domain is depicted in orange. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

Each α subunit consists of six transmembrane helices (S1–S6), in which S4 segment serves as the voltage-sensing domain, while the extracellular domain between S5 and S6 forms the pore region. The conserved threonine (T), valine (V), glycine (G), tyrosine (Y), and glycine (G) residues on each P-loop create a narrow pore filter determining its potassium ion selectivity [11] (Figure 4B, Figure 5B, and Figure 6B).

K_V channels provide the outward current necessary for phase 2 plateau and early phase 3 rapid repolarization of the AP. The primary cardiac K_V channel α-subunits and their

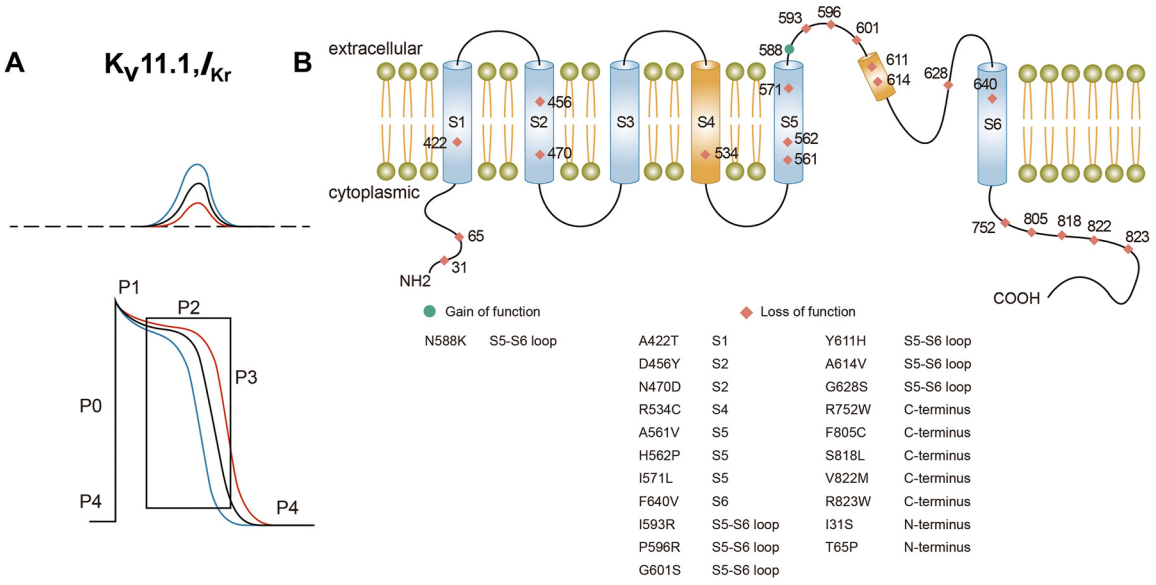

Figure 6: Cardiac voltage-gated potassium channel ($K_V11.1$) and its typical gain-of-function or loss-of function KCNH2 mutations. (A) Schematic representation of I_{kr} corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) Schematic of $K_V11.1$ α subunit structure and some typical GOF and LOF mutations [68–71]. $K_V11.1$ comprises four α subunits which are heterotetramers and interacting auxiliary subunits. Each α subunit consists of six segments (S1-S6) which are indicated by numbered cylinders and the fourth positively charged S4 segment as the voltage sensor domain is depicted in orange. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

currents include $K_V4.3/K_V1.4$ (I_{to}), $K_V7.1$ (I_{Ks}), $K_V11.1$ (I_{Kr}), and $K_V1.5$ (I_{Kur}, only in the atria [72]).

$K_V4.3$ channels

The $K_V4.3$ channels, encoded by the KCND3 gene, play a crucial role in regulating cardiac repolarization. GOF mutations in KCND3 gene lead to I_{to} current increasing, which have been reported to result in BrS, early repolarization syndrome (ERS), and sudden cardiac death (SCD) [73, 74] while LOF mutations cause spinocerebellar ataxia type 19 [58] and type 22 [59] (Figure 4). Additionally, studies suggest an intricate interplay between $K_V4.3$ and $Na_V1.5$ channels [75, 76]. This interaction is supported by their close proximity on the cell membrane (<40 nm) [75] and the observation that overexpressing $K_V4.3$ channels significantly reduces $Na_V1.5$ current density and the degree of depolarization of AP [76]. Moreover, the β subunits KchIP2 and $Na_Vβ1$ can modulate the I_{Na}/I_{to} balance by increasing I_{Na} and decreasing I_{to} [75], while GOF mutations in KCNE3, the gene encoding the $K_V4.3$ channel β subunit MiRP2, are also associated with BrS [77]. In addition, $K_V4.2$ and $K_V1.4$ are also involved in the formation of I_{to}, and typical GOF S447R mutation of KCND2 encoding $K_V4.2$ causes autosomal dominant early-onset nocturnal paroxysmal AF while the LOF W362F mutation prolongs the APD in mouse atrial myocytes *in vitro* [78, 79].

$K_V7.1$ channels

Dysfunctions of the $K_V7.1$ channels are implicated in various cardiac diseases [80]. LOF mutations in KCNQ1 and KCNE1 genes, which encode $K_V7.1$ channel and its auxiliary subunit respectively, cause $K_V7.1$ channels dysfunction or restrict protein kinase A (PKA) activation of the channels [81]. These result in reduced I_{Ks} and trigger long QT syndrome 1 (LQT1). Conversely, GOF mutations in KCNQ1 gene accelerate $K_V7.1$ channels activation or slow channels inactivation, enhancing I_{Ks} and associating with short QT syndrome 2 (SQT2) [80] (Figure 5).

$K_V11.1$ channels

The $K_V11.1$ channels are encoded by KCNH2 gene (human ether-à-go-go-related gene, hERG). LOF mutations in $K_V11.1$, associated with long QT syndrome 2 (LQT2) [68, 82], perhaps conduce reduction of protein folding efficiency and increase retention in the endoplasmic reticulum that disrupts $K_V11.1$ channel trafficking [68, 82]. Conversely, GOF mutations are linked to sudden death associated with short-QT syndrome [69]

(Figure 6). Furthermore, LOF mutations in KCNE2 gene encoding its β subunit MiRP1 heighten the channel inactivation and induce long QT syndrome 6 (LQT6), a rare type of LQT. The K_V11.1 channels are also well known for its association with drug cardiotoxicity, inhibition of which is the foremost mechanism responsible for torsades de pointes and QT prolongation that led to the withdrawal of many non-cardiovascular drugs and hERG assays have been mandated to evaluate potential proarrhythmic risk of new drugs since 2005 [83].

K_V1.5 channels

K_V1.5 channels are the gene products of KCNA5 which are responsible for the ultra-rapid delayed-rectifier current (I_{Kur}) characterized by the rapid depolarization and sluggish inactivation [84]. The I_{Kur} is almost exclusively in atrial myocytes and plays a critical role in repolarization of atrial AP. LOF mutations in KCNA5 gene are characterized by reduced I_{Kur}, thus most prolong atrial AP duration and induce early after depolarizations [85, 86]. These LOF mutations have been identified in multiple familial AF patients. In addition, P91L and E33V mutations [87] in KCNA5 gene which are observed in LQT and SCD cases do not affect the expression or gating of K_V1.5 channels, leaving the exact pathogenic mechanism unclear.

The modernized classification of clinical Class III agents includes wide ranges of nonselective and selective voltage-dependent potassium channel blockers (Class III_a, Table 4), as well as drugs opening metabolically dependent potassium channel (K_{ir}6.2, Class III_b), investigational drugs blocking transmitter-dependent potassium channel (GIRK1/GIRK4, Class III_c).

Besides, the original Class I_a antiarrhythmic drug quinidine has been suggested that its clinical antiarrhythmic effects in BrS perhaps not only include inhibition of I_{Na} but also I_{to} [88].

Inwardly rectifying potassium channels

The cardiac potassium channel landscape extends beyond voltage-gated potassium channels, encompassing a diverse array of inward rectifying potassium (K_{ir}) channels that play equally crucial roles in regulating cardiac function. K_{ir} channels conduct I_{K1} current at hyperpolarized membrane potentials (MP), contributing in repolarization during phases 3 and 4 of AP and stabilization of resting MP.

K_{ir} channels are characterized by their unique inward rectification property, exhibiting a greater conductance for inward potassium currents compared to outward currents. Unlike K_V channels that open and close in response to changes in membrane potential, K_{ir} channels are constitutively active and their conductance is modulated by various factors, including intracellular signaling molecules and second messengers. This rectification arises from voltage-

Table 4: Class III_a antiarrhythmic drugs [9, 12].

Class	Drug exemplars	Pharmacological targets	Therapeutic action	Clinical indications
III_a	Ambasilide Amiodarone Dronedarone	Nonselective K^+ channel blockers	Blocks multiple K^+ channel; prolongs AP recovery, ERP and QT intervals; diminishes repolarization reserve	Ventricular tachycardia (without structural heart disease or with remote myocardial infarction); tachyarrhythmias with Wolff–Parkinson–White syndrome; atrial fibrillation with atrioventricular conduction via accessory pathway; ventricular fibrillation; premature ventricular contraction; tachyarrhythmias associated with supraventricular arrhythmias and atrial fibrillation
	Ibutilide Sotalol	Selective K_V11.1 (hERG) channel blockers	Reduces I_{Kr}; prolongs AP recovery, ERP and QT intervals; diminishes repolarization reserve	Ventricular tachycardia (without structural heart disease or with remote myocardial infarction); tachyarrhythmias with Wolff–Parkinson–White syndrome; atrial fibrillation with atrioventricular conduction via accessory pathway; ventricular fibrillation; premature ventricular contraction; tachyarrhythmias associated with supraventricular arrhythmias and atrial fibrillation
	Vernakalant	Selective K_V1.5 channel blockers	Reduces I_{Kur}; prolongs atrial AP recovery, ERP and QT intervals; diminishes atrial repolarization reserve	Immediate conversion of atrial fibrillation

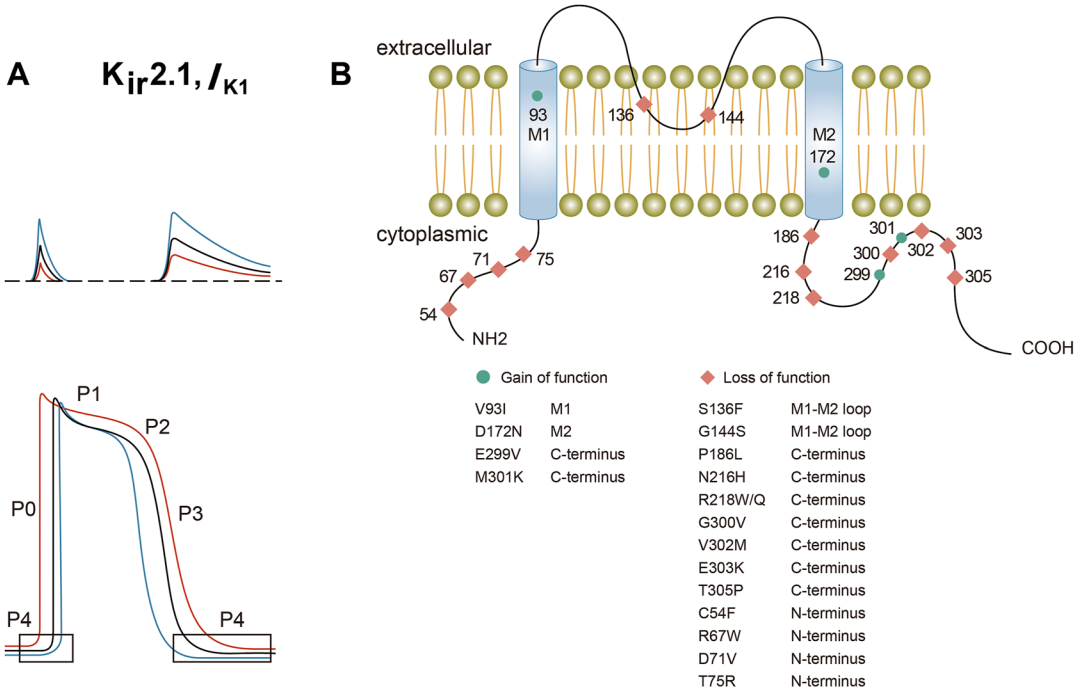

Figure 7: Cardiac inwardly rectifying potassium channel ($K_{ir}2.1$) and its typical gain-of-function or loss-of function KCNJ2 mutations. (A) Schematic representation of I_{k1} corresponding to WT (in black, upper), gain-of function mutations (in blue, upper) and loss-of-function mutations (in red, upper) and their related ventricular AP (lower). (B) Schematic of $K_{ir}2.1$ protein structure and some typical GOF and LOF mutations [90–97]. $K_{ir}2.1$ are functional tetramers consisting of two membrane-spanning domains (M1 and M2). The p-loop forms the ion selectivity filter. The locations of the GOF mutations are shown in green circle while the locations of LOF mutations are shown in orange rhombus.

dependent blockade of the channel pore by intracellular magnesium ions and polyamines that occlude the channels pore and reduce outward I_{K1} current at positive MP [72, 89]. Besides, phosphatidylinositol (4, 5)-bisphosphate (PIP_2) can activate K_{ir} channels.

$K_{ir}2.1$, encoded by the KCNJ2 gene, is the predominant K_{ir} channel subtype in the heart. Each α subunit comprises two transmembrane segments (M1 and M2) and assembles into functional tetramers [89] (Figure 7B).

Most LOF mutations in KCNJ2 genes induce Andersen-Tawil syndrome (ATS) which is associated with type 7 long QT syndrome (LQT7), skeletal abnormalities, and periodic paralysis [98]. These arise from dysfunctional $K_{ir}2.1$ subunits encoded by LOF mutant KCNJ2 genes, leading to the formation of nonfunctional K_{ir} channels and reduced I_{K1}. Conversely, GOF mutations have been associated with short QT syndrome 3 (SQT3) [99] (Figure 7).

Potent blockers of $K_{ir}2$ channels are rare currently, while nonselective potassium channel blockers in Class III_a antiarrhythmic drugs exert inhibitory effects on K_{ir} channels. Additionally, Class III_b antiarrhythmic drugs, nicardipine and pinacidil, act as openers of $K_{ir}6.2$ channels and are used in the treatment of angina pectoris.

Conclusions

Cardiac ion channels, act as gatekeepers, selectively permitting the passage of ions, thereby governing the cardiac AP and maintaining the delicate balance of cardiac rhythm. Dysfunction in these channels invariably leads to various arrhythmias.

This review has delved into the realm of arrhythmogenic ion channels in ventricular myocytes, exploring their corresponding currents in shaping the different phases of the AP and their involvement in the pathogenesis of cardiac arrhythmias. We provide an overview of the predominant subtype of Na_V, Ca_V, K_V, and K_{ir} channels, along with the diverse antiarrhythmic drugs that targeting cardiac ion channels based on the updated Singh-Vaughan Williams classification system which categorized antiarrhythmic drugs according to their primary mechanism of action on ion channels. In addition, some other channels that are not mentioned in detail are involved in the physiologic activity of the cardiac AP. For example, the hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels mediate a mixed sodium/potassium inward I_f current which is responsible for the early part of the diastolic depolarization in

the SAN, and dysfunctional HCN4 channels might directly cause rhythm disorders which can be treated with ivabradine as a new approach in selective HR reduction [100, 101].

However, the quest for more effective and targeted antiarrhythmic therapies continues. Traditional medications do not provide complete protection and can have serious side effects while Ablation techniques are also tissue-breaking and invasive. Device therapy like pacemakers have a limited range of indications, and patients can get infections when devices are implanted and in the long term there are also risks such as device failure [102]. Research into novel therapeutic strategies, such as gene therapy and small molecule modulators, holds great promise for the future management of cardiac arrhythmias. For instance, there are six fundamental strategies for gene and cell therapy: gene transfer, allele-specific silencing, gene editing, modulation of signal pathways, differentiation of stem cells, and hybrid gene-gene/cell, which is therapeutic approaches of introducing specific genetic material into cells or directly replacing dysfunctional cells with healthy cells to correct the underlying case of disease [102]. Furthermore, advancements in computational modeling and structural biology will pave the way for the development of personalized antiarrhythmic therapies, minimizing side effects. The high-resolution structure of the cardiac channels can give detailed insights into voltage-dependent activation, ion selectivity, arrhythmia mechanisms, and antiarrhythmic drug action at the atomic level, such as a pathogenic gating pore ~2 Å in diameter created by an arrhythmia mutation of SCN5A(9), the same conformation of $Ca_V1.2$ that is bound by calciseptin [54], amiodarone and dihydropyridine drugs, the unique properties of the central cavity of the hERG channel which likely contribute to hERG block by many drugs [103] and so on [89, 104].

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