Pharmacology of Cardiac Potassium Channels

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Abstract

Cardiac K^+ channels are cardiomyocyte membrane proteins that regulate K^+ ion flow across the cell membrane on the electrochemical gradient, and determine the resting membrane potential and the cardiac action potential morphology and duration. Several K^+ channels have been well studied in the human heart. They include the transient outward K^+ current I_{to1}, the ultra-rapidly delayed rectifier current I_{Kur}, the rapidly and slowly delayed rectifier currents I_{Kr} and I_{Ks}, the inward rectifier K^+ current I_{K1}, and ligand-gated K^+ channels, including ATP-sensitive K^+ current (I_{KATP}) and acetylcholine-activated current (I_{KACh}). Regional differences of K^+ channel expression contribute to the variable morphologies and durations of cardiac action potentials from sinus node and atrial to ventricular myocytes, and different ventricular layers from endocardium and midmyocardium to epicardium. They also show different responses to endogenous regulators and/or pharmacological agents. K^+ channels are well-known targets for developing novel antiarrhythmic drugs that can effectively prevent/inhibit cardiac arrhythmias. Especially atrial specific K^+ channel currents (I_{Kur} and I_{KACh}) are the targets for developing atrial-selective anti-atrial fibrillation drugs, which has been greatly progressed in recent years. This chapter concentrates on recent advances in intracellular signaling regulation and pharmacology of cardiac K^+ channels under physiological and pathophysiological conditions.

Abbreviations: AF, atrial fibrillation; I_{Kur}, ultra-rapidly delayed rectifier K^+ current; I_{to1}, transient outward K^+ current; I_{KACh}, acetylcholine-activated K^+ current; I_{KATP}, ATP-sensitive K^+ current; I_{Kr}, rapidly delayed rectifier K^+ current; I_{Ks}, slowly delayed rectifier K^+ current; hERG, human *ether-à-go-go*–related gene; Kir, inward rectifier K^+ channels; SUR, sulfonylurea receptor; K_2p, two pore K^+ channels; ECG, electrocardiogram; EADs, early afterdepolarizations; TdPs, Torsade de Pointes; APD, action potential duration; 4-AP, 4-aminopyrodine; ERP, effective refractory period; LQTs, long QT syndrome; SQTs, short QT syndrome; PKA, protein kinase A; PLC, phospholipase C; PKC, protein kinase C; PTK, protein tyrosine kinase; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; PIP2, phosphatidylinositol 4,5-bisphosphate; EGFR, epidermal growth factor receptor; sarcK_{ATP}, sarcolemmal ATP-sensitive K^+ channels; mitoK_{ATP}, mitochondrial ATP-sensitive K^+ channels ; TMD, Transmembrane domains

1. Introduction

Cardiac K^+ channels play a pivotal role in maintaining normal cardiac electrical activity. They regulate the resting membrane potential and excitability, participate in the repolarization and determine the shape and duration of cardiac action potential. Malfunction of K^+ channels, due to either congenital encoded gene mutations or drug blockade, alters not only the cardiomyocyte excitability, but also the electrical balance of depolarization and repolarization and thus causes a long QT interval or short QT interval of the electrocardiogram and underlies different types of cardiac arrhythmias (Kannankeril and Roden, 2007; Zareba and Cygankiewicz, 2008). Therefore, cardiac K^+ channels are important targets of antiarrhythmic drugs.

It is well recognized that the shape and duration of cardiac action potential are determined by a balance (i.e. sequential activation and inactivation) of inward currents and outward currents (Nerbonne and Kass, 2005). Figure 1 schematically illustrates the time course of different current contribution to the action potentials of human atrial and ventricular myocytes. The inward currents include voltage-gated Na^+ current (I_{Na}) responsible for the phase 0 depolarization and L-type Ca^{2+} current ($I_{Ca.L}$) responsible for maintaining plateau (phase 2) of the action potential. The inward component of electrogenic Na^+-Ca^{2+} exchanger may also contribute to the phase 2 of the action potential.

The outward currents are mainly carried by different K^+ channels in human cardiac myocytes. They contribute to repolarization of different phases of the action potential. These K^+ currents include the inward rectified K^+ current I_{K1}, the transient outward K^+ current I_{to1}, the ultra-rapidly delayed rectifier K^+ current I_{Kur}, rapidly and slowly delayed rectifier K^+ currents (I_{Kr} and I_{Ks}), acetylcholine-regulated K^+ current (I_{KACh}), and ATP-sensitive K^+ current ($I_{K.ATP}$).

2. K^+ channel classification.

I. Diversity of K^+ channels

K^+ channels are the most widely distributed type of ion channels composed of α-subunits and β-subunits (Snyders, 1999). The α-subunits of K^+ channels are characterized by 1) an ion conducting pore through which K^+ ions pass through the plasma membrane; 2) a K^+ selectivity filter in the P loop from each subunit which have their electro-negative carbonyl oxygen atoms aligned towards the centre of the filter pore and form an anti-prism similar to a water solvating shell around each K^+ binding site; and 3) a gating machinery that controls the switch between open and close states in response to either changes in membrane potential or a ligand (Snyders, 1999). The cytoplasmic N- and C-termini of α-subunits are also important functional domains. The pore-forming subunits homogenously form functional channels (MacKinnon, 1995). K^+ channels have a tetrameric structure in which four identical α-subunits associate to form a fourfold symmetric complex arranged around a central ion conducting pore (MacKinnon, 1995). Alternatively four related but not identical α-subunits may associate to form heterotetrameric complexes.

The classification of K^+ channels is based upon the primary amino acid sequence of the pore-containing α-subunits. Three groups (Fig. 2) with six, two, or four putative transmembrane segments are recognized, including 1) voltage-gated K^+ (Kv) channels containing six transmembrane regions (S1-S6) with a single pore loop formed by the S5 and S6 segments and S5-S6 linker. The S4 segment is rich in positively charged residues and serves as the voltage sensor (e.g. I_{to1}, I_{Kur}, I_{Kr}, and I_{Ks}); 2) inward rectifier K^+ (Kir) channels containing two transmembrane domains (M1-M2) with intracellular N- and C-termini, and a single pore loop formed by the M1 and M2 domains (e.g. I_{K1}, I_{KACh}, and I_{KATP}); and 3) two-pore K^+ (K_{P2}) channels containing four transmembrane domains (M1-M4), intracellular N- and C-terminus, and two pore regions related to background or leak channels (e.g. TWIK, TASK, TREK and THIK) (Gurney and Manoury, 2009; Snyders, 1999).

II. β-Subunits of K^+ channels

Most K^+ channels heterogeneously assemble with the auxiliary β-subunits in native cells (Fig. 2). The β-subunits are either cytoplasmic proteins (e.g. Kvβ1-4, KChIP) or transmembrane proteins, such as minK and minK-related proteins (MiRPs) encoded by KCNE gene family, and large ATP binding cassette (ABC) transport-related proteins, such as the sulfonylurea receptors (SUR) for the inward rectifiers Kir6.1–6.2 (Snyders, 1999; Stephan et al., 2006). Most β-subunits assemble with α-subunits and act as a molecular chaperone of the α-subunits in regulating the channel gating kinetics, pharmacology, folding/coassembly, trafficking or cell surface expression (Bett and Rasmusson, 2008; Martens et al., 1999; Xu et al., 2009). Both α-subunits and β-subunits are pharmacological targets. Cardiac K^+ channels are also regulated by numerous endogenous molecules and signals. The complex interaction between α-subunits, β-subunits and endogenous modulators represents diversity of native cardiac potassium currents (Snyders, 1999).

3. Cardiac voltage-gated K^+ (Kv) channels

I. The transient outward K^+ current I_{to1}

The transient outward current I_{to}, is composed of two components, i.e. 4-aminopyridine (4-AP) sensitive transient outward K^+ current (I_{to1}) and Ca^{2+}-activated transient outward Cl^- current (I_{to2}) in some species (Li et al., 1995). I_{to2} is not present in human cardiac myocytes, and therefore is not discussed here. I_{to1} is a voltage-gated and Ca^{2+}-independent K^+ current that is rapidly activated and inactivated in response to depolarization, and contributes to the early repolarization (phase 1) of the action potential in human cardiac myocytes (Fig. 1). Density of I_{to1} is greater in atria than ventricles, and is 3-4 folds greater in ventricular midmyocardial (M) cells and/or subepicardial cells than in subendocardial cells (Li et al., 1995; Li et al., 1998), therefore I_{to1} contributes significantly to the phase 1 of the action potentials in these regional myocytes to maintain normal cardiac heterogeneous electrophysiology.

A. Molecular identification of I_{to1}

Kv4.3 (KCND3) is the dominant candidate coding for cardiac I_{to1} in human hearts (Dixon et al., 1996). Kv4.3 channel mRNA and/or protein are significantly expressed in human atrium and ventricle (Gaborit et al., 2007; Kaab et al., 1998) and in canine hearts (Zicha et al., 2004), and display a gradient expression in human and canine ventricular wall from endocardium to epicardium (Zicha et al., 2004), comparable to the region-dependent I_{to1} (Li et al., 1998; Liu et al., 1993; Nabauer et al., 1996). Kv4.3 assembles with cytoplasmic KChIPs to form I_{to1} channels (Zicha et al., 2004). In addition, DPP6 (dipeptidyl aminopeptidase-like protein 6) is another putative subunit of cardiac Kv4.3 (Radicke et al., 2005). Moreover, the potential contribution of Kv1.4 channels to human ventricular I_{to1} can not be excluded (Po et al., 1992; Snyders, 1999).

The downregulation of cardiac I_{to1} frequently occurs in failing hearts associated with a prolonged APD (Li et al., 2002; Li et al., 2004). The reduction of I_{to1} likely contributes to the diminished phase 1 amplitude of action potential, and also partially to the prolonged APD and early afterdepolarizations (EADs) in failing hearts (Li et al., 2002; Li et al., 2004). In patient with chronic atrial fibrillation (AF) and canine with experimental AF, atrial I_{to1} and/or Kv4.3 gene and/or protein are also downregulated (Brundel et al., 2001; Grammer et al., 2000; Yue et al., 1999).

B. Signaling regulation of I_{to1}

The gating properties and kinetics of cardiac I_{to1} are modulated by various endogenous molecules and signal pathways including serine/threonine and tyrosine phosphorylation. α-Adrenergic stimulation inhibits cardiac I_{to1} in rabbit ventricular myocytes (Fedida et al., 1990) and in human cardiac myocytes and cloned hKv4.3 current expressed in mammalian cells (Po et al., 2001), which may be mediated by protein kinase C (PKC), since the PKC activator phorbol 12-myristate 13-acetate (PMA) exhibits a similar inhibition of rat cardiac I_{to1} and Kv4.2/Kv4.3 currents (Nakamura et al., 1997). In addition, c-Src tyrosine kinase increases hKv4.3 current by phosphorylating the channels through the associated macromolecular complex, which is mediated by the SH2 and SH3 domains of c-Src kinases (Gomes et al., 2008).

Activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) slows the inactivation and accelerates the recovery from inactivation of Kv4.3 channels via directly phosphorylating S550 located in C-terminus (Sergeant et al., 2005). SAP97, one of the membrane-associated guanylate kinase proteins, participates in CaMKII dependent regulation of cardiac Kv4.3/Kv4.2 channels (El-Haou et al., 2009). Nitric oxide is a diffusible messenger that inhibits Kv4.3 channels and human I_{to1} mediated by activating adenylate cyclase and the subsequent activation of PKA and the serine/threonine phosphatase 2A (Gomez et al., 2008). The increase of the bioavailability of atrial nitric oxide could partially restore the duration of the plateau phase of remodeled action potential by inhibiting I_{to1}. Angiotensin II regulates the membrane distribution and gating properties of Kv4.3 channels (Doronin et al., 2004).

C. Pharmacology of I_{to1}

4-AP is the first compound used by Kenyon and Gibbon to separate I_{to1} from I_{to2} (or $I_{Ca.Cl}$) in sheep Purkinje fibers (Kenyon and Gibbons, 1979). It is then widely employed as a pharmacological tool to separate I_{to1} from other currents (Li et al., 1995). I_{to1} is a major repolarization current in human atrium. The blockade of I_{to1} is supposed to prolong atrial APD and the refractory period and therefore exert anti-arrhythmic effect. Several antiarrhythmic drugs inhibit I_{to1} in human atrial myocytes (see review by Tamargo et al., 2004). The class I anti-arrhythmic drug flecainide blocks inactivated I_{to1} in a frequency-independent manner (Wang et al., 1995), and quinidine shows an open channel blocker of I_{to1} in a frequency-dependent manner. Propafenone blocks human atrial I_{to1} in a voltage- and use-independent fashion (Seki et al., 1999). Ambasilide inhibits I_{to1} without affecting voltage-dependence of activation, inactivation, or recovery from inactivation, but accelerates the inactivation of I_{to1}, suggesting an open-channel block (Feng et al., 1997).

In addition, Ca^{2+} channel antagonists (diltiazem and nifedipine) inhibit I_{to1} in human atrial myocytes (Gao et al., 2005). Raloxifene, a selective estrogen receptor modulator, directly inhibits human atrial I_{to1} (Liu et al., 2007). The antifungal antibiotic clotrimazole inhibits I_{to1} by accelerating the inactivation and slowing

the recovery from inactivation of the channels (Tian et al., 2006). The antihistamine drug loratadine rate-dependently inhibits I_{to1} at a therapeutic concentration (10 nM) (Crumb, 1999). The omega-3 (n-3) polyunsaturated fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) from fish oil inhibit human atrial I_{to1} in a concentration-dependent manner (Li et al., 2009) (Table 1).

II. The ultra-rapidly delayed rectifier K^+ current I_{Kur}

I_{Kur} is a rapid activation and slow inactivation K^+ current (Snyders et al., 1993; Wang et al., 1993). It is functionally present in the atria but not in the ventricles of human heart (Li et al., 1996). I_{Kur} is thought to be a promising molecular target for atrial arrhythmia (Ford and Milnes, 2008; Kozlowski et al., 2009; Tamargo et al., 2009). I_{Kur} is also observed in canine (Fedida et al., 2003; Yue et al., 1996), pig (Li et al., 2004) and rat (Boyle and Nerbonne, 1992) atrial myocytes.

A. Molecular identification of I_{Kur}

Kv1.5 (KCNA5) encodes the pore-forming subunit of human atrial I_{Kur} (Snyders, 1999; Fedida et al., 1993), which is supported by the evidence that Kv1.5 antisense oligodeoxynucleotides specifically inhibits I_{Kur} density in human atrial myocytes (Feng et al., 1997), and Kv1.5 gene is significantly expressed in human atrium (Gaborit et al., 2007). In canine atrium, I_{Kur} is initially found to be encoded by Kv3.1 (Yue et al., 1996); however, a later study confirms that Kv1.5 does encode the I_{Kur} in canine atrial myocytes (Fedida et al., 2003). The finding of the later study makes it possible to use canine model in evaluating I_{Kur}/Kv1.5 blockers for the treatment of AF (Li et al., 2008). In addition, Kv1.5 mRNA and protein, responsible for I_{Kur}, are present in mouse and rat hearts (Nerbonne, 2000). Moreover, Kv1.5 transcripts are also detected in extracardiac tissues, e.g. pituitary gland, brain, pancreas, etc (Takimoto et al., 1993).

Multiple members of a Kvβ1 subunit family for Kv1.5 have been cloned and multiple N-terminal splice isoforms were detected (Snyders, 1999). Kvβ1 encodes the ancillary subunit (Martens et al., 1999) of I_{Kur} channels. Co-expression of accessory Kvβ-subunits (Kvβ-1.2/1.3) increases the inactivation of Kv1.5 channels and the sensitivity to channel phosphorylation by PKA and/or PKC (Kwak et al., 1999).

In chronic AF, I_{Kur} density, Kv1.5 mRNA and protein (like other ion currents, including I_{to1}, $I_{Ca.L}$, and I_{Na}) are downregulated (Brundel et al., 2001; Grammer et al., 2000). Loss of function of mutant Kv1.5 channels however may lead to inheritable AF (Olson et al.). Loss-of-function mutations of KCNA5 gene located at the N-terminus (A115V), S1 (A251T), S1-S2 linker (P307S, P310L), and C-terminus (P532L and R578K) have been reported in patients with idiopathic AF (Simard et al., 2005). These findings suggest that defective Kv1.5 channels may predispose the atria to electrical instability and arrhythmogenesis.

B. Signaling regulation of I_{Kur}

β-adrenergic stimulation enhances, whereas α-adrenergic stimulation inhibits I_{Kur} in human atrial myocytes mediated by PKA and PKC, respectively (Li et al., 1996). However, in dog atrial myocytes, both β- and α-adrenergic stimulation increases I_{Kur} by activating PKA and PKC (Yue et al., 1999). Whether the different regulation of I_{Kur} by PKC is related to the non-uniform coding (Kv1.5 and Kv3.1) (Fedida et al., 2003; Yue et al., 1996) remains to be studied in canine atrial myocytes. PKA activation reduces the Kvβ-induced fast inactivation of Kv1.5 channels by phosphorylating Kv β-subunit itself (Kwak et al., 1999). Nitric oxide inhibits hKv1.5 channels by a cGMP-dependent mechanism and by S-nitrosylating the channel protein (Nunez et al., 2006). Pyridine nucleotides modulate Kv1.5 channels by regulating the cellular redox state (NADPH-to-NADP$^+$ ratio) (Tipparaju et al., 2007). Moreover, phosphatidylinositol 4,5-bisphosphate (PIP2) regulates the inactivation of Kv1.5 by an equilibrium binding of the N-terminus of Kvβ1.3 between phosphoinositides and the inner pore region of the channels (Decher et al., 2008).

C. Pharmacology of I_{Kur}

Human cardiac I_{Kur} and/or Kv1.5 channels are sensitive to inhibition by 4-AP (Snyders et al., 1993; Wang et al., 1993), but not by tetraethylammonium (TEA) or Ba^{2+} (Wang et al., 1993). Low concentration of 4-AP (less than 50 μM) is used to separate I_{Kur} from I_{to1} in human atrial myocytes (Feng et al., 1997; Li et al., 1996).

The compounds capable of I_{Kur}/Kv1.5 channel block are shown in Table 1. Several antiarrhythmic drugs (see review, Tamargo et al., 2004), including quinidine, flecainide, and ambasilide inhibit I_{Kur} in isolated human atrial myocytes (Feng et al., 1997; Wang et al., 1995) and/or Kv1.5 channel expressed in mammalian cells (Snyders and Yeola, 1995). The L-type Ca^{2+} channel antagonists verapamil, diltiazem and nifedipine reversibly inhibits human atrial I_{Kur} (Gao et al., 2004; Gao et al., 2005). The local anesthetic drugs benzocaine and bupivacaine blocks Kv1.5 channels in a concentration-dependent manner (Caballero et al., 2002). The omega-3 polyunsaturated fatty acids also inhibit human atrial I_{Kur} (Li et al., 2009) (Table 1).

The binding of these drugs is determined by an electrostatic component reflecting the electrical binding distance. The critical residues for hydrophobic binding of quinidine in hKv1.5 channels are located in the

putative S6 of pore-lining region and is important in determining drug affinity and specificity (Snyders and Yeola, 1995). Stereoselective bupivacaine block of hKv1.5 channels is determined by a polar interaction with T507 and two hydrophobic interactions at positions L510 and V514 (Franqueza et al., 1997). The binding sites for quinidine and bupivacaine in the residues of the S6 segment also determine the binding of neutral and acid drugs (e.g. benzocaine) (Caballero et al., 2002; Tamargo et al., 2004). Nonetheless, the external mouth of the channel pore formed by the P-loop and adjacent S5–S6 segments is the potential binding sites for some drugs (Lin et al., 2001; Tamargo et al., 2004). Long-chain polyunsaturated fatty acids bind to an external site to block Kv1.5 channels (Honore et al., 1994).

AVE0118 is one of the most studied novel atrial-selective compounds (Table 1). It blocks human atrial I_{Kur} and Kv1.5 channels (Gogelein et al., 2004; Wettwer et al., 2004) by binding to T479, T480, V505, I508, V512, and V516 within the S6 domain and pore helix region (Decher et al., 2006), and prolongs the APD in atrial myocytes from patients with AF (Wettwer et al., 2004). AVE0118 also inhibits hKv4.3 channels expressed in CHO cells and I_{KACh} in guinea pig atrial myocytes (Gogelein et al., 2004), which may contribute to the atrial-selective effects on APD and ERP (effective refractory period) (Christ et al., 2008). Importantly, AVE0118 terminates AF in a goat model with an intravenous administration (Blaauw et al., 2004; de Haan et al., 2006). However, AVE0118 has a low solubility and undergoes rapid first pass hepatic metabolism with a short half-life in dog and pig (intravenous administration, $T_{1/2}$ = 0.2–0.4 hours) (Ford and Milnes, 2008; Wirth et al., 2007); therefore it has not progressed into phase 3 clinical trial for anti-AF (Ford and Milnes, 2008). AVE1231 is a chemically different compound with similar effects to those of AVE0118 (Ehrlich et al., 2008) on I_{Kur}/Kv1.5, I_{to}, I_{KACh}. It is orally effective and prolongs atrial ERP in pig and goat models with rapid pacing (Wirth et al., 2007). AVE1231 is undergoing phase 1 clinical trial (Ford and Milnes, 2008).

Diphenyl phosphine oxide (DPO) compounds selectively inhibit human atrial I_{Kur} and hKv1.5 current without affecting I_{to1} or prolonging cardiac APD in human ventricular myocytes (Lagrutta et al., 2006). DPO-1 preferentially binds to the open channels of Kv1.5 with putative binding sites T480, L499, L506, I508, L510 and V514 (Du et al., 2010). DPO-1 significantly prolongs atrial ERP in African green monkeys (Regan et al., 2006) and terminates atrial arrhythmia in a canine atrial flutter model without increasing ventricular ERP or PR, QRS or QT interval of ECG (Stump et al., 2005).

ISQ-1 is an isoquinoline Kv1.5 channel blocker, prolongs atrial ERP in African green monkey and dogs, and terminates dog atrial flutter and/or AF (Regan et al., 2008; Regan et al., 2007). Vernakalant (RSD1235) blocks I_{Kur}/Kv1.5 current with a high affinity and binding to T479, T480, I502, V505, and V508 residues (Eldstrom et al., 2007; Fedida et al., 2005). It also inhibits the cardiac I_{to1}, I_{KACh} I_{Kr} and I_{Na} at higher concentrations (Fedida, 2007; Fedida et al., 2005). Clinical trial has demonstrated that vernakalant converts AF rapidly without prolonging QT interval of ECG in patients (Fedida, 2007; Roy et al., 2004), it is under consideration by the FDA of USA for clinical use in treating patients with AF.

Acacetin is a natural flavone compound initially isolated from Chinese traditional medicine Xuelianhua (*Saussurea tridactyla*). It suppresses not only atrial I_{Kur}, but also I_{to1} and I_{KACh}. Acacetin prolongs canine atrial ERP without prolonging QTc interval and effectively prevents AF in a canine model after duodenal administration (Li et al., 2008), suggesting that acacetin may be orally effective.

III. The rapidly delayed rectifier K$^+$ current I_{Kr}

Sanguinetti and Jurkiewicz demonstrate that the class III antiarrhythmic drugs notably E-4031 and sotalol selectively block I_{Kr} and that the drug-sensitive (I_{Kr}) and drug-resistant (I_{Ks}) components of I_K differ in terms of voltage dependence, kinetics, rectification properties, and pharmacological sensitivity (Sanguinetti and Jurkiewicz, 1990). I_{Kr} and I_{Ks} play an important role in cardiac repolarization in different species including human (Li et al., 1996). I_{Kr} channels open rapidly upon depolarization of the action potential, but quickly inactivates. The channel inactivation is released following repolarization with a slow deactivation (Sanguinetti and Jurkiewicz, 1990). Due to this inward rectification property, I_{Kr} contributes a little during the plateau of cardiac action potential, and progressively increases at phase 3 repolarization of the action potential (Fig. 1) (Jost et al., 2005). Therefore, I_{Kr} plays a pivotal role in cardiac repolarization, especially in the later phases of the action potential due to its unique kinetics (Fig. 1).

A. Molecular identification of I_{Kr}

The human *ether-a-go-go*–related gene (hERG or Kv11.1, or KCNH2) coding for the channels carrying the current resembling I_{Kr} has been identified in human heart (Sanguinetti et al., 1995), encodes the α-subunit underlying human cardiac I_{Kr}, and is expressed in both atria and ventricles of human heart (Gaborit et al., 2007). Co-assembly of the regulatory β-subunit MiRP1 (minK-related peptide 1 encoded by KCNE2 gene) with hERG α-subunits is required to form native I_{Kr} (Gordon et al., 2008).

Suppression of I_{Kr}/hERG channels by medications may cause acquired long QT syndrome (LQT) (Farkas and Nattel, 2010; Perrin et al., 2008). Therefore, potential hERG channel blockade has been a

necessary screening procedure at the early stage of developing compounds (Dennis et al., 2007; Farkas and Nattel, 2010). Loss of function mutations of hERG and KCNE2 gene induces congenital LQT2 and LQT6, respectively, which are characterized in patients by prolonged QT interval of ECG, abnormal T waves and a risk of fatal ventricular arrhythmias named Torsades de Pointes (TdPs) (Perrin et al., 2008; Thomas et al., 2006). However, on the other hand, gain of function mutations of hERG (McPate et al., 2009) is responsible for inherited short QT syndrome (SQT1), which is characterized in patients by abnormally short QT interval, and a high risk of atrial/ventricular fibrillation and sudden death (Brugada et al., 2004; Charpentier et al., 2010).

B. Signaling regulation of I_{Kr}

Although it is generally accepted that I_{Kr} and hERG channels are relatively insensitive to signaling modulation, a list of signaling molecules have been reported to regulate I_{Kr}/hERG channels, including cAMP, PKA, PKC, PIP2, etc. (see review, Charpentier et al., 2010). Activation of β- or α-adrenergic receptor suppresses hERG channels by increasing intracellular cAMP levels. PKA decreases the current amplitude, accelerates the deactivation and positively shifts the activation conductance via phosphorylating the hERG channel protein. On the other hand, intracellular cAMP may increase the current by directly binding to the cyclic nucleotide binding domain in C-terminus of hERG channels and negatively shifting the activation conductance (Thomas et al., 2006).

PIP2 up-regulates hERG current by accelerating the activation and slowing the inactivation of the channels (Bian et al., 2004). The polycationic region in C-terminus of hERG channels is the potential electrostatic interaction sites of PIP2 (Bian et al., 2004). Stimulation of α-1_A adrenoceptor decreases hERG current and positively shifts the activation conductance, which is related to the consumption of endogenous PIP2 induced by PLC (phospholipase C) activation (Bian et al., 2004). In addition, hERG channels are also constitutively activated by Src-family kinases and EGFR kinase via phosphorylating the tyrosine residues Y475 and/or Y611 (Zhang et al., 2008). Moreover, nitric oxide inhibits hERG current via an interaction with free radical oxygen species in a cyclic GMP-independent manner (Taglialatela et al., 1999).

A recent study demonstrates that chronic hypokalemia rabbits exhibit a prolonged QT interval of ECG, and a downregulated I_{Kr} without significantly affecting other membrane current in ventricular myocytes isolated from the hypokalemia rabbits. Further investigation indicates that a reduced extracellular K^+ decreases the current amplitude, plasma membrane stability, and expression of hERG channel protein by accelerating internalization and degradation of hERG channels (Guo et al., 2009). This study reveals the potential mechanism why hypokalemia patients are susceptible to LQTs and TdPs tachyarrhythmias (Roden et al., 1986).

C. Pharmacology of I_{Kr}

I_{Kr}/hERG channels are extraordinarily sensitive to block by a large number of structurally diverse drugs/chemicals (Farkas and Nattel, 2010; Raschi et al., 2009). I_{Kr}/hERG blockers such as quinidine, d-sotalol, dofetilide, etc. have been used for many years as class III antiarrhythmic drugs, and they are efficacious in preventing and terminating AF and flutter, but their intrinsic arrhythmogenic activity largely restricts their use due to the well-known major effect of inducing LQTs and TdPs, a substrate of life-threatening ventricular arrhythmia. Therefore, the class III antiarrhythmic drugs with I_{Kr}/hERG channel block are not an ideal medication used for treating AF.

In addition to class III antiarrhymic drugs, many other commonly used clinical medications also block human I_{Kr} and hERG channels (see review, Tamargo et al., 2004), for example (Table 1), the antihistamine drugs terfenadine and loratadine (Crumb, 2000), the antiestrogenic drugs tamoxifen (Thomas et al., 2003) and clomiphene (Yuill et al., 2004), the antifugal drug ketoconazole (Takemasa et al., 2008), the antihypertensive drug ketanserin (Tang et al., 2008) and the antipsychotic drug ziprasidone (Su et al., 2006). These drugs preferentially block the open hERG channels, but also exhibit low affinity for closed and inactivated channels (Tristani-Firouzi and Sanguinetti, 2003). The hERG channel inhibition of the non-antiarrhythmic drugs is the major cause of life-threatening proarrhythmia. This has directly prompted the withdrawal of several clinical drugs from the market (Thomas et al., 2006). Regulatory Agencies therefore request that all new drug candidates be tested for this possibility.

The binding sites of hERG channel blockers are located within the inner cavity of hERG channels. The individual residues that form high-affinity and lower-affinity binding sites have been identified by site-directed mutagenesis approaches, and the gating processes have an important influence on the drug-binding sites (Mitcheson, 2008). The S620 in pore helix of hERG channels is the binding site of dofetilide and verapamil, and an intact C-type inactivation process is also crucial for high-affinity drug binding (Ficker et al., 1998; Zhang et al., 1999). The binding sites of high-affinity hERG blocker MK-499 are located on S6 transmembrane domain (G648, Y652 and F656) and pore helix (T623 and V625) of the

hERG channels that face the vestibule of the channels. Compounds structurally unrelated to MK-499, such as terfenadine and cisapride, also interact with Y652 and F656, but not with V625 (Mitcheson, J. et al., 2005). However, the binding site of propafenone (a lower-affinity hERG blocker) is located in the F656 residue alone (Witchel et al., 2004). When the drug binds within the inner cavity of the channels, they are trapped in the vestibule by closure of the activation gate upon repolarization. So hERG channel blockers such as the methanesulfonanilides MK-499 show a slow recovery from blockade (Mitcheson et al., 2005).

In addition to the direct channel block by binding to the hERG channels, some drugs suppress I_{Kr}/hERG channels and induced acquired long QT syndrome in patients by interrupting the trafficking of hERG channels and reducing the expression of membrane hERG channel protein. The anti-protozoal drug pentamidine is one of examples (Kuryshev et al., 2005). To rescue LQTs, a number of compounds have been developed for activating I_{Kr}/hERG channels (Table 1).

RPR260243 is the first small molecule that activates I_{Kr}/hERG channels. It dramatically slows the deactivation of hERG tail current in a CHO cell line expressing hERG gene. PR260243 reverses the action potential-prolonging effect by dofetilide in guinea pig ventricular myocytes and reduced QT interval of ECG in perfused guinea pig hearts (Kang et al., 2005).

Several potent hERG channel activators developed by Pfizer (Groton, CT) are reported with a distinct mechanism (Zhou et al., 2005). PD-118057 enhances hERG step and tail currents in a HEK 293 stable cell line in a concentration-dependent manner and is able to prevent and reverse QT prolongation and associated arrhythmias induced by a selective I_{Kr} blocker (i.e.dofetilide) in the arterially perfused rabbit ventricular wedge preparation (Zhou et al., 2005).

NS1643 and NS3623 developed by NeuroSearch A/S (Ballerup, Denmark) increases WT hERG current by reducing channel inactivation, while reducing the activation in inactivation-deficient hERG mutants (S620T, S631A) (Hansen et al., 2006). Interestingly, mutation of the high-affinity binding site F656 for hERG channel blocker strengthens the agonist activity of NS1643 and NS3623, suggesting a dual mode of action, being both an activator and an inhibitor of hERG channels (Hansen et al., 2006).

A-935142 is a recently developed compound by Abbott Laboratories (Abbott Park, IL) with significant hERG enhancement by facilitating activation, reducing inactivation, and slowing deactivation of the channels. It shortens cardiac APD in guinea-pig atrial myocytes and canine Purkinje fibers (Su et al., 2009).

The putative binding sites for RPR260243 are located in S5 (L553 and F557) and an adjacent region of S6 (N658, V659) (Perry et al., 2007), while the binding sites of PD-118057 are located in the pore helix (F619) or the S6 segment (L646). Interestingly, the mutants of nearby residues in the S6 segment (C643, M645) enhance the drug activity of PD-118057 (Perry et al., 2009). In contrast, PD-307243, an analog of PD-118057, increases hERG current by remarkably slowing hERG channel deactivation and inactivation and holding the channels in a constitutively open state via binding to the extracellular region of the pore (Gordon et al., 2008).

3-Nitro-*N*-(4-phenoxyphenyl) benzamide (ICA-105574) is an unique and potent hERG channel activator more recently developed by Icagen (Durham, NC) (Gerlach et al., 2010). It steeply increases the hERG current amplitudes by removing the inwardly-rectifying inactivation of the channels, negatively shifting the voltage-dependence of channel activation and slowing channel deactivation. It shortens cardiac APD in ventricular myocytes from guinea pig hearts (Gerlach et al., 2010).

IV. The slowly delayed rectifier K$^+$ current I$_{Ks}$

I_{Ks} activates slowly with almost no inactivation after activation (Charpentier et al., 2010; Sanguinetti and Jurkiewicz, 1990), and contributes to the phase 2 slow repolarization of cardiac action potential (Fig. 1). I_{Ks} has been demonstrated in cardiac tissues/myocytes from different species including human (Charpentier et al., 2010; Jost et al., 2005; Li et al., 1996). The physiological contribution of I_{Ks} to the human ventricular action potential is limited; however, during tonic sympathetic stimulation or when cardiac repolarization reserve is attenuated, I_{Ks} plays an important role in limiting APD prolongation due to its slow deactivation (Jost et al., 2005).

Heterogeneous expression of I_{Ks} is present in different regions of the heart. In the canine ventricle, I_{Ks} density is greater in epicardial and endocardial cells than in the M cells (Li et al., 2002; Liu and Antzelevitch, 1995). The lower I_{Ks} density in M cells is considered to be related to the steeper APD-rate relations and their greater tendency to display longer APD and to develop EADs at slow heart rates or in response to QT prolonging drugs (Liu and Antzelevitch, 1995).

A. I$_{Ks}$ molecular identification

I_{Ks} channels are comprised of four pore-forming α-subunits and two accessory β-subunits, which are encoded by KCNQ1 (Kv7.1 or KvLQT1) and KCNE1 (minK) genes respectively (Barhanin et al., 1996; Sanguinetti et al., 1996). The cytoplasmic C-terminus of KCNQ1 subunit contains a tetramer assembly domain, in which mutations lead to tetramerization deficiency. The KCNE1 subunit dynamically engages in

I_{Ks} gating, and is critical for the biophysical properties of the native cardiac I_{Ks} (Charpentier et al., 2010; Sanguinetti et al., 1996).

I_{Ks} density is down-regulated in failing canine (Li et al., 2002) and human (Li et al., 2004) hearts. A decreased I_{Ks} and KCNQ1/KCNE1 mRNA levels are found in cardiac myocytes from infarcted canine ventricle (Jiang et al., 2000). Loss of function mutations in KCNQ1 gene and KCNE1 gene are associated with congenital LQT1 and LQT5, respectively (Charpentier et al., 2010; Splawski et al., 1997). However, gain of function mutations in KCNQ1 gene causes congenital SQT2 and familial AF (Charpentier et al., 2010; Lundby et al., 2007).

B. Signaling regulation of I_{Ks}

It is well established that catecholamines shorten cardiac APD by enhancing I_{Ks} amplitude mediated by cAMP/PKA and/or PKC via β- and/or α-adrenoceptor stimulation (Sanguinetti et al., 1991; Walsh and Kass, 1991). Activation of PKA by cAMP or phophodiesterase inhibition increases I_{Ks} current and enhances the rate-dependent shortening of cardiac APD (Lo and Numann, 1998; Terrenoire et al., 2005). I_{Ks} is also modulated by EGFR kinase (Dong et al., 2010). In addition, I_{Ks} or KCNQ1/KCNE1 channels are regulated by CaMKII, nitric oxide, and PIP2, etc. Readers are recommended to refer to the recent review (Charpentier et al., 2010) for the detailed information of I_{Ks} regulation.

C. Pharmacology of I_{Ks}

Chromanols (e.g. 293B, HMR-1556) are the first group of relatively selective I_{Ks} blockers (Busch et al., 1996; Thomas et al., 2003) (Table 1), and show stereospecific block on I_{Ks} (Yang et al., 2000). Indapamide (Turgeon et al., 1994) and benzodiazepine compounds (L-735821, L-761334, etc) (Lengyel et al., 2001; Seebohm et al., 2003; Stump et al., 2003) also remarkably block I_{Ks}. Most of them act as open channel blockers. Bepridil, a Ca^{2+} channel blocker, inhibits recombinant cardiac I_{Ks} by binding to the closed state channels (Yumoto et al., 2004). The drug interaction site of I_{Ks} blockers (e.g. 293B and L-735821) is located in the pore loop and S6 domain of KCNQ1. T312 in the pore loop and I337, P339, P340, and A344 in the S6 domain are the most important molecular determinants of channel block (Seebohm et al., 2003).

Blockade of I_{Ks} usually fails to remarkably prolong cardiac APD due to the sufficient repolarization reserve carried by other K^+ channels (Lengyel et al., 2001). However, when the repolarization reserve is attenuated or depleted by inherited disorders, cardiac electrical remodeling or drugs, blockade of I_{Ks} significantly prolongs the ventricular APD (Biliczki et al., 2002). Moreover, β-adrenergic stimulation increases I_{Ks} in epicardial and endocardial cells, but not in M cells. I_{Ks} is intrinsically small, and I_{Ks} block accentuates transmamural dispersion of repolarization (Shimizu and Antzelevitch, 1998). Similar to the I_{Kr} blocker, the I_{Ks} blocker is also proarrhythmic (Cheng and Incardona, 2009). Therefore, I_{Ks} activators, like I_{Kr} activators, may be useful in managing the cardiac arrhythmia related to delayed repolarization.

The Cl^- channel blockers mefenamic acid and dihydro-4,4' diisothiocyanostilbene-2,2'- disulphonic acid (DIDS) are the first group compounds (Table 1) that enhance the recombinant I_{Ks} by reversibly speeding up channel activation in a KCNE1 subunit-dependent manner (Unsold et al., 2000). Thereafter, the novel benzodiazepine compound R-L3 is found to enhance cardiac I_{Ks} or recombinant I_{Ks}. R-L3 stereospecifically activates I_{Ks} and shortens APD in guinea pig cardiac myocytes by slowing the rate of I_{Ks} deactivation and negatively shifting the activation conductance of I_{Ks} (Salata et al., 1998). The interaction sites of R-L3 with I_{Ks} channels are located in the S5 and S6 domains of KCNQ1 subunits (Seebohm et al., 2003).

Several natural compounds are recently demonstrated to up-regulate native cardiac I_{Ks} and/or recombinant I_{Ks}. Tanshinone IIA is one of major active components from the Chinese traditional medicinal herb Danshen (*Salvia miltiorrhiza*), and directly increases recombinant I_{Ks} by accelerating the activation of the channels, and negatively shifting the activation conductance (Sun et al., 2008). Ephedrine, an alkaloid isolated from the Chinese traditional medicinal herb Mahuang (*Ephedra Sinica*) activates recombinant I_{Ks}, and negatively shifts the activation conductance. The binding sites of ephedrine on recombinant I_{Ks} are located in the P-loop helix F296 and Y299 of KCNQ1 (Jing et al., 2009). Ginsenoside Re, a major ingredient of *Panax ginseng*, enhances I_{Ks} via s-nitrosylating the channel protein mediated by nitric oxide in guinea-pig cardiomyocytes (Bai et al., 2004). Moreover, various fatty acids, including docosahexaenoic acid, lauric acid and oleic acid augment I_{Ks} in a KCNE1 subunit-dependent manner (Doolan et al., 2002), and phenylboronic acid is also found to activate recombinant I_{Ks} (Mruk and Kobertz, 2009).

I_{Ks} activators, like the selective I_{Kr}/hERG activators, may also offer a new approach in the treatment of delayed repolarization conditions in patients with acquired long QT syndrome or inherited long QT syndrome. The I_{Ks} activator benzodiazepine R-L3 displays a prominent antiarrhythmic propensity in rescuing cellular models with acquired long QT type 2 (Nissen et al., 2009).

4. Inward rectifier K^+ currents

I. The cardiac inward rectifier K^+ current I_{K1}

Cardiac I_{K1} is a strong inward rectification current, and is believed to contribute only to the phase 3 rapid repolarization of action potential and maintain resting membrane potential in cardiac myocytes (Anumonwo and Lopatin, 2010). However, our recent studies have demonstrated that two components of I_{K1} are activated during cardiac action potential, one is immediately activated by action potential depolarization, and the other is activated at phase 3 repolarization. The I_{K1} activated by depolarization with comparable time course with I_{Na} may also contribute to the maintenance of cardiac excitability (Fig. 1) (Li et al., 1998; Zhang et al., 2009). Thus, I_{K1} plays important roles in stabilizing the resting membrane potential, controlling cardiac APD and excitability (Anumonwo and Lopatin, 2010). I_{K1} density is higher in ventricular than in atrial myocytes, but there is no difference in regional cells through ventricular wall in canine and guinea pig hearts (Schram et al., 2002), and is very low in SA and AV pacemaker cells, and therefore these cells have a more depolarized maximum diastolic potential (Schram et al., 2002).

A. Molecular identification of I_{K1}

Cardiac I_{K1} is encoded by Kir2.1 (KCNJ2), Kir2.3 (KCNJ4), and/or Kir2.2 (KCNJ12) (Dhamoon et al., 2004; Ehrlich, 2008). Heteromeric assemblies of Kir2.1, Kir2.2, and Kir2.3 subunits underlie I_{K1} current. The unique properties of individual Kir2 isoforms, as well as their region- and species-dependent expression patterns determine the heterogeneous profiles of I_{K1} in atrial and ventricular myocytes of the heart (Dhamoon et al., 2004).

Cardiac I_{K1} is altered under different pathophysiological conditions. I_{K1} is downregulated in ventricular myocytes from failing canine (Li et al., 2002) and human (Li et al., 2004) hearts, but no Kir2.1 mRNA reduction is observed (Koumi et al., 1995). In atrial myocytes from patients with chronic AF I_{K1} is up-regulated (Dobrev et al., 2002), which may be related to the selective S-nitrosylation of Kir2.1 Cys76 residue by nitric oxide (Gomez et al., 2009).

Loss of function mutation of KCNJ2 causes inherited Andersen–Tawil syndrome (LQT7), which is characterized by periodic paralysis, specific T-U-wave patterns, and skeletal developmental abnormalities (Anumonwo and Lopatin, 2010; Zhang et al., 2005). On the other hand, gain of function mutation of KCNJ2 causes inherited SQT3 and familial AF (Anumonwo and Lopatin, 2010; Priori et al., 2005; Xia et al., 2005).

B. Signaling regulation of I_{K1}

It is well recognized that the conductance of I_{K1} is highly dependent on extracellular K^+ concentration. An increase in extracellular K^+ concentration enhances the conductance of I_{K1}, while the conductance disappears with removal of extracellular K^+ (Li et al., 1998; Zhang et al., 2009). I_{K1} is uniquely blocked by intracellular polyamines (spermine, spermindine and putrescine) and Mg^{2+} with steep voltage dependence, which is believed to be the molecular mechanism of the inward rectification of I_{K1} (Anumonwo and Lopatin, 2010; Lopatin et al., 1994). However, the conclusion is made under symmetrical K^+ conditions. Under physiological K^+ conditions, an increase of intracellular Mg^{2+} concentration does not induce any block of I_{K1}. instead of an increase in the transient outward component of I_{K1} (Zhang et al., 2009).

Both α- and β-adrenergic stimulation suppress I_{K1} in a PKA and/or PKC-dependent way (Karle et al., 2002; Koumi et al., 1995). PIP2 activates I_{K1} via direct electrostatic interaction between the positively charged residues in the cytoplasmic region of the channels and the negative phosphate head group of PIP2 (Xie et al., 2008). PIP2 is also an important co-factor of other regulators that modulate I_{K1} channels (Xie et al., 2007). Kir2 channels are down-regulated by membrane cholesterol level (Levitan, 2009). The extracellular H^+ regulates I_{K1} in species/tissue-dependent manner, possibly reflecting channel subunit composition (Anumonwo and Lopatin, 2010). Tyrosine kinase activation reduces the membrane density of Kir2.1 channels via promoting channel endocytosis (Tong et al., 2001).

In addition, Kir2.1 channels are post-transcriptionally suppressed by miRNA-1 in ischemia/reperfusion myocardium (Yang et al., 2007). The great reduction of miRNA-1 levels may also contribute to the up-regulation of Kir2.1 subunits and the increased I_{K1} in patients with AF (Girmatsion et al., 2009).

C. Pharmacology of I_{K1}

Ba^{2+} is a well-known I_{K1} blocker with an IC_{50} of 20 μM (Wible et al., 1995) (Table 1). Some antiarrhythmic drugs, such as amiodarone and azimilide, show an inhibitory effect on I_{K1} (see review, Tamargo et al., 2004). Blockade of I_{K1} may cause cardiac diastolic (i.e. resting membrane potential) depolarization, an proarrhythmic effect that offsets the membrane potential more close to the threshold potential of Na^+ channels therefore reduces cardiac excitability. I_{K1} block also slows conduction velocity due to a voltage-dependent inactivation of Na^+ channels, and prolongs the QT interval (Kleber, 1994). Therefore the drug that specifically blocks I_{K1} may not be realistic for antiarrhthima. The compound RP58866 is initially designed to specifically block I_{K1}, and is effective in treating ventricular arrhythmias induced by ischemia/reperfusion in rat, rabbit, and primate (Rees and Curtis, 1993). Later studies demonstrate that

RP58866 is a non-selective K^+ channel blocker. In addition to inhibition of I_{K1}, RP58866 also suppresses I_{to1}, I_{Kr}, I_{Ks}, and I_{KACh} (Brandts et al., 2000; Yang et al., 1999).

II. The acetylcholine-activated K^+ current I_{KACh}

Cardiac I_{KACh} is one of G protein-coupled inwardly-rectifying K^+ channels. It is predominantly present in sinus node, atrial myocardium, and atrioventricular node, but largely sparse in ventricles of the heart (Dobrzynski et al., 2001; Gaborit et al., 2007; Schram et al., 2002). Activation of I_{KACh} by parasympathetic signals such as acetylcholine through M2 muscarinic receptors causes an inward rectifier K^+ current which hyperpolarizes the membrane potential, shortens cardiac APD, slows the spontaneous firing rate of pacemaker cells in sinus and atrial-ventricular nodes, and delays the atrioventricular conduction (Ehrlich, 2008; Tamargo et al., 2004). The heterogeneity of I_{KACh} expression within and between the left and right atria correlates with potentially proarrhythmic ability of vagal nerve stimulation (Arora et al., 2007). In addition, I_{KACh} plays an important role in the generation of AF (Atienza et al., 2006).

A. Molecular identification of I_{KACh}

I_{KACh} channel in the heart is a heterotetramer constituted by two Kir3.1 (KCNJ3/GIRK1) and two Kir3.4 (KCNJ5/GIRK4) subunits (Anumonwo and Lopatin, 2010; Corey et al., 1998).

I_{KACh} is remodeled in heart disorders (Borlak and Thum, 2003; Brundel et al., 2001). I_{KACh} current is transcriptionally down-regulated in chronic AF, but an agonist-independent (i.e., active in the absence of agonist) constitutively active form of I_{KACh} contributes to human chronic AF (Dobrev et al., 2005; Voigt et al., 2007). Loss of function mutation of Kir3.4 gene is detected in, but not associated with clear atrial disorders (Calloe et al., 2007).

B. Signaling regulation of I_{KACh}

In addition to the acetylcholine-muscarinic receptor-G protein pathway, cardiac I_{KACh} may be activated by other G-protein coupled receptors including A1-adenosine, α-adrenergic, etc. Adenosine activates rat atrial I_{KACh} (Bosche et al., 2003). Activation of α1-adrenoceptor reduces I_{KACh} current in atrial myocytes (Anumonwo and Lopatin, 2010). In canine atrial cardiomyocytes, β1-adrenergic stimulation enhances I_{KACh} current via cAMP-induced activation of PKA whereas $\alpha1_A$-adrenergic stimulation suppresses I_{KACh} current via PLC-mediated activation of PKC (Yeh et al., 2007). PIP2 up-regulates I_{KACh} in diverse manners: direct interaction with the channels or with Gβ/γ subunits, and via the downstream PKC action (Keselman et al., 2007). Recombinant Kir3.1/Kir3.4 channels are regulated by PKA phosphorylation. Three phosphorylation sites (Ser385, ser401 and thr407) located within the C-terminus of Kir3.1 are responsible for PKA phosphorylation and the regulation of I_{KACh} channels (Mullner et al., 2009). Gβ/γ also affects the trafficking of I_{KACh} channels by forming Gβ/γ-Kir3.1/Kir3.4 complexes during channel biosynthesis and trafficking (Robitaille et al., 2009).

C. Pharmacology of I_{KACh}

The atrial-specific localization and the functionally upregulation (increased constitutive activity) of I_{KACh} during AF make it possible a promising antiarrhythmic target devoid of ventricular side effects (Ehrlich, 2008; Kozlowski et al., 2009). Much effort is made to develop selective I_{KACh} blockers (Dobrev and Nattel, 2010) (Table 1).

Tertiapin, a 21-residue peptide toxin from honey bee venom, and its derivative tertiapin-Q directly block I_{KACh} with nanomolar affinity by binding to the external end of the ion conduction pore (Jin and Lu, 1998). Tertiapin blocks I_{KACh} current in a receptor- and voltage-independent manner without affecting other cardiac ionic currents (Drici et al., 2000). It has been demonstrated that tertiapin terminates AF without affecting ventricular repolarization in canine AF model (Hashimoto et al., 2006).

The benzopyran compound NIP-151 significantly inhibits I_{KACh}, and effectively terminates AF in canine model with an atrial-specific ERP-prolonging profile and lower risk of proarrhythmia compared with I_{Kr} blockers (Hashimoto et al., 2008). AVE0118, in addition to inhibiting I_{to1} and I_{Kur}, blocks I_{KACh} channels, and demonstrates atrial-specific antiarrhythmic effects in animal models (Blaauw et al., 2004; Gogelein et al., 2004). AVE1231, which has improved pharmacokinetic properties compared to AVE0118, shows similar effects on I_{KACh} current (Wirth et al., 2007). The natural flavone accacetin also inhibits I_{KACh} along with I_{Kur} and I_{to1} and prevents AF in a canine model (Li et al., 2008) (Table 1).

In addition, the benzothiazepine compound JTV-519 (K201) inhibits I_{KACh} and suppresses experimental AF in isolated guinea pig hearts (Nakaya et al., 2000). SD-3212 (levo-semotiadil fumarate), a novel benzothiazine Ca^{2+} channel antagonist, also inhibits I_{KACh} channels by depressing the function of the channel itself and/or associated GTP-binding proteins (Hara and Nakaya, 1995) and shows anti-atrial arrhythmic effect (Fujiki et al., 1997).

Moreover, classical antiarrhythmic agents with a broad channel blockade profile, such as amiodarone

and the structurally related derivatives, dronedarone (SR33589) and KB130015, also block cardiac I_{KACh} with high potency by either disrupting G-protein-mediated activation or directly inhibiting interaction with the channel protein (Guillemare et al., 2000; Mubagwa et al., 2003). Blockade of I_{KACh} by flaceinide contributes at least in part to the anti-AF effect in humans.

III. Cardiac ATP-sensitive K$^+$ current, I_{KATP}

Cardiac I_{KATP} is carried by ATP sensitive K$^+$ channels. K_{ATP} channels are closed at physiological intracellular ATP concentrations, and activated by a decrease in ratio of intracellular ATP/ADP (Noma, 1983). K_{ATP} channels act as a unique metabolic sensor or a coupling between the cell metabolic status and the cellular membrane potential. I_{KATP} plays a pivotal role in maintaining cardiac homeostasis under stress, such as myocardial ischemia/reperfusion and hypoxia, and mediate the ischemia-induced electrophysiological changes and cardioprotective effect of preconditioning (Zingman et al., 2007). Activation of I_{KATP} shortens cardiac APD by accelerating the phase 3 repolarization, reduces Ca^{2+} influx thereby preventing cardiac Ca^{2+} overload, preserves ATP levels (energy-sparing effects) and increases cell survival during myocardial ischemia (Tamargo et al., 2004; Tsuboi et al., 2004). On the other hand, activation of I_{KATP} may also be 'cardiotoxic' by inducing re-entrant ventricular arrhythmias (Tamargo et al., 2004; Zunkler, 2006).

A. Molecular identification of I_{KATP}

K_{ATP} channels are composed of Kir 6.x-type subunits and sulfonylurea receptor (SUR) subunits (Fig. 2), along with additional components (Stephan et al., 2006). They are further identified by their location within the cell as being either sarcolemmal (sarcK_{ATP}) or mitochondrial (mitoK_{ATP}) (Foster et al., 2008; O'Rourke, 2004). Cardiac sarcK_{ATP} channels are a hetero-octameric complex composed of four inwardly-rectifying Kir6.2 channel pore subunits (encoded by KCNJ11), which confer inhibition by ATP, and four modulatory sulfonylurea receptor SUR2A (encoded by ABCC9) subunits (Billman, 2008; Tamargo et al., 2004). However, the subunit of mitoI_{KATP} remains to be determined conclusively (Foster et al., 2008; O'Rourke, 2004). A recent study demonstrated that the SUR2-IES is the β-subunit of mitoKATP channels (Ye et al., 2009). The SUR2A subunit (Fig. 2) has three hydrophobic transmembrane domains (TMD0, TMD1 and TMD2) that likely include five, six and six transmembrane segments respectively, with two hydrophilic nucleotide binding folds (NBF1 and NBF2) following TMD1 and TMD2 (Conti et al., 2001). SUR2A contains ATPase activity harbored within NBF2 and, to a lesser degree, NBF1. NBD1/NBD2 assembly provides a molecular substrate that determines the optimal catalytic activity in SUR2A (Park et al., 2008).

Defective mutations and polymorphisms in Kir6.2 are associated with increased risk of many kinds of metabolic disorders (Reyes et al., 2009). Disruption of sarcl$_{KATP}$ activity impairs cardiac adaptation to stress such as systolic overload (Reyes et al., 2009). Kir6.2$^{-/-}$ mice present with an aberrant regulation of cardiomyocyte membrane excitability and Ca^{2+} handling, and are susceptible to ventricular arrhythmias and sudden death following sympathetic stimulation (Zingman et al., 2002).

B. Signaling regulation of I_{KATP}

In addition to regulation by the intracellular ATP and ADP (Noma, 1983), I_{KATP} is regulated by PKC, PTK, PIP2, nitric oxide, and many other signaling molecules. PKC activates cardiac I_{KATP} channels at near physiological levels of ATP and induces ischemic preconditioning (Light et al., 1996). Isoform-dependent activation of PKC contributes to the persistent opening of I_{KATP} channels during reoxygenation and reperfusion (Ito et al., 2001). Mitochondrial connexin 43 (Cx43) is recently found to regulate mitoK_{ATP} and protects cardiac cells from death. Genetic Cx43 deficiency, pharmacological Cx43 inhibition by carbenoxolone or by mimetic peptide substantially reduces diazoxide-mediated stimulation of mitoK_{ATP} channels. Suppression of mitochondrial Cx43 inhibits mitoK_{ATP} channel activation by PKC (Rottlaender et al., 2010). A recent review (Akrouh et al., 2009) is recommended for the detailed information of K_{ATP} channel regulation.

C. Pharmacology of I_{KATP}

In addition to inhibition by intracellular ATP (Noma, 1983), K_{ATP} channels can be blocked by antidiabetic drugs including the sulfonylureas, e.g. glibenclamide, glicazide, glipizide, glimepiride, tolbutamide and the glinides such as repaglinide, nateglinide, mitiglinide as well as some anti-arrhythmic drugs (e.g. flecainide) (Tamargo et al., 2004). Sulfonylurea drugs bind directly to the SUR region in the loop between TM15 and TM16 in TMD2 and S1237. These drugs have been widely used to regulate K_{ATP} channel activity (Conti et al., 2001)

Because K_{ATP} channels in pancreatic β-cells and smooth muscle regulate insulin secretion and vascular tone (Seino and Miki, 2003), I_{KATP} blockers may therefore induce hypoglycemia and coronary vasoconstriction; however, cardioselective K_{ATP} channel blockers may be beneficial for treating cardiac

disorders. The cardioselective K_{ATP} channel blocker HMR 1098 (clamikalant) (Liu et al., 2001) reduces the cardiac APD shortening induced by hypoxia and prevents ventricular fibrillation induced by coronary artery occlusion in post-infarcted conscious dogs at doses that have no effect on insulin release, blood pressure or coronary blood flow (Grover and Garlid, 2000). Thus, specific cardiac I_{KATP} channel blockers may represent a new therapeutic approach to treat ischemia-induced ventricular arrhythmias with little or no side effects (Billman, 2008).

The K_{ATP} channel activators, e.g. pinacidil, cromakalim, rimakalim and nicorandil, are found to open K_{ATP} channels by binding to two distinct regions of TMD2, the intracellular loop joining TM13 and TM14 and between TM15 and TM16 (residues K1249 and T1253) (Moreau et al., 2000). These compounds have ischemia preconditioning effect and are cardioprotective in experimental myocardial ischemia/reperfusion models and in patients with acute myocardial infarction (Grover and Garlid, 2000). However, they also activate vascular K_{ATP} channels (Kir6.1/SUR2B) and induce hypotension which limits their use in the treatment of myocardial ischemia.

It is believed that sarcK_{ATP} channels are responsible for ischemia preconditioning (Grover and Garlid, 2000). Indeed the mitoK_{ATP} channel activator diazoxide mimics the ischemic preconditioning, and the effect is countered by the selective mitoK_{ATP} blocker 5-hydroxydecanoate (5-HD). The selective mitoKATP opener BMS-191095 exerts cardioprotective effects without shortening APD or inducing hypotension effect (Grover et al., 2001). Therefore, cardioselective and/or mitoK_{ATP} channel blockers and activators (Table 1) would be beneficial in protection of cardiac ischemia/reperfusion.

5. Cardiac two pore K^+ current K_{2P}

The two pore domain K^+ (K_{2P}) channels have been discovered for more than a decade, and they support background K^+ currents and maintain membrane potential in many cell types (see reviews, Gurney and Manoury, 2009; Judge and Smith, 2009). The distinct K_{2P} channels including four subfamilies of TASK, TWIK, TREK and THIK. K_{2P} channels comprise of four transmembrane domains and two pore-forming P loops arranged in tandem (Fig. 2) (Gurney and Manoury, 2009). K_{2P} channels are sensitive to membrane stretch, pH variation, phospholipids, fatty acids, volatile anaesthetics and G-protein coupled receptors (Bayliss and Barrett, 2008); however, they are insensitive to conventional K^+ channel blockers such as 4-AP, TEA, Ba^{2+}, Cs^+ and glibenclamide (Gurney and Manoury, 2009; Tamargo et al., 2004).

In the heart, the resting membrane potential and cell excitability is predominantly contributed by I_{K1}. Although the mRNAs of several K_{2P} channels (e.g. TREK-1 and TASK-1) are detected, the proposed contribution of these channels to cardiac background currents and cellular physiology are still unclear. No functional current has been recorded in human cardiomyocytes (Gurney and Manoury, 2009). However, because K_{2P} channels are sensitive to cellular or extracellular signals (pH level, membrane stretch, etc), so they likely act as cellular sensor and transducers (O'Connell et al., 2002). Effort should be made in the future to find out pharmacological tools that select for these channels in order to further understand the physiological importance and whether these channels regulate cardiac functions (Gurney and Manoury, 2009; O'Connell et al., 2002; Tamargo et al., 2004).

6. Conclusion

The electrical properties of atria and ventricles of human heart are different in the distinct roles of cardiac physiology. Studies on cellular electrophysiology and ion channels have greatly improved our understanding of atrial and ventricular arrhythmias at cellular and molecular levels, including atrial fibrillation and life threatening ventricular arrhythmias. Cardiac K^+ channels have been recognized as potential therapeutic targets. The understanding of the ion channel distribution in the atria and ventricles and the pathophysiological alteration in different ion channels induced by genetics, diseases and/or medications has provided a basis for rational design of safer and more effective K^+ channel blockers and/or activators to prevent/treat atrial fibrillation and/or ventricular arrhythmias.

The improved understanding of molecular basis for cardiac I_{Kr} and I_{Ks} makes it possible for the pharmaceuticals to develop selective I_{Kr}/hERG channel activators (e.g. PR260243, PD-118057, etc.) and/or I_{Ks} activators (e.g. RL-3, tanshinone, etc), which may offer a new approach in the treatment of delayed repolarization conditions in patients with acquired long QT syndrome or inherited long QT syndrome, congestive heart failure, and diabetes. In the last decade, effort has been made to develop new anti-arrhythmic agents with safer and more effective than those presently used, especially 'atrial-selective drugs' that target cardiac ion channel(s) that are exclusively or predominantly expressed in the atria to avoid the proarrhythmic effect of class III antiarrhthmic drugs. I_{Kur} is a major repolarizing current in human atria, but not in the ventricles, so that blocking of I_{Kur} is thought to be a promising target for atrial-specific therapy of AF. I_{KACh} channels are predominantly present in atria, but largely sparse in ventricles of the heart.

Compounds that selectively inhibit I_{Kur} (e.g. DPO-1, ISQ-1, etc.) or I_{KACh} (e.g. tertiapin, tertiapin-Q, etc.) or both I_{Kur} and I_{KACh} (e.g. AVE0118, AVE1231, acacetin, etc.) have been demonstrated to terminate or prevent experimental AF. Therefore, these compounds are thought to be a promising target for atrial-specific therapy of AF. Because I_{to1} channels are more significant for atrial repolarization than that in ventricles, the compounds with I_{to1} block (e.g. vernakalant, AVE0118, acacetin, etc.) would be a plus for anti-AF. These atrial-selective compounds should be further studied to demonstrate whether they are the desired drugs that are not only effective in clinically relevant AF animal models, but also satisfied in oral bioavailability and safe in animals following repeat dosing; and, crucially, clinical efficacy and safety. The studies on cardiac selective K_{ATP} channel inhibitor (e.g. clamikalant) or mitoK$_{ATP}$ activators (e.g. atpenin A5, P1705) (Table 1) are being progressed for the protection of cardiac ischemia/reperfusion. The remained question is whether I_{K1} is a target for developing specific activators to treat certain type of arrhythmias related to delayed repolarization.

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Table 1. Pharmacological blockers and activators of cardiac potassium channels

Drug	I_{to1}/Kv4.3	I_{Kur}/Kv1.5	I_{Kr}/hERG	I_{Ks}	I_{KACh}	I_{KATP}	I_{K1}	Species	References
Blocker									
Acacetin	9.3 μM	3.2 μM			4 μM			Human/GP atrial myocytes	(Li et al., 2008)
Adenosine							20.7 μM	Rat/GP cardiac myocytes	(Wang et al., 2006)
AMP579							4.1 μM	Rat/GP atrial myocytes	(Wang et al., 2006)
AVE0118	3.4 μM	6.2 μM	10 μM					CHO	(Gogelein et al., 2004)
AVE1231	5.9 μM	3.6 μM			8.4 μM			Pig atrial myocytes/CHO	(Wirth et al., 2007)
BaCl$_2$							19.6 μM	hIRK/Oocytes	(Wible et al., 1995)
Cinnamyl-3,4-dihydroxy-alpha-cyanocinnamate		5.7 μM						CHO	(Gong et al., 2008)
Citalopram		2.8 μM						CHO	(Lee et al., 2010)
Clomiphene			180 nM					HEK293 cells	(Yuill et al., 2004)
Clotrimazole	29.5 μM	7.6 μM	3.6 μM	15.1 μM				Human atrial myocytes/HEK293	(Tian et al., 2006)
Diltiazen	29.2 μM	11.2 μM						Human atrial myocytes	(Gao et al., 2005)
DPO-1		20 nM						Human atrial myocytes/CHO	(Lagrutta et al., 2006)
Docosahexaenoic acid	4.1 μM	4.3 μM						Human atrial myocytes	(Li et al., 2009)
Eicosapentaenoic acid	6.2 μM	17.5 μM						Human atrial myocytes	(Li et al., 2009)
JTV-519(K201)					<2.4 μM			GP atrial myocytes	(Nakaya et al., 2000)
KB130015					0.6 μM			GP atrial myocytes	(Brandts et al., 2004)
Ketanserin			110 nM					HEK293	(Tang et al., 2008)
Ketoconazole			1.9 μM					HEK293	(Takemasa et al., 2008)

Table 1 (continued)

Drug	I_{to1}/Kv4.3	I_{Kur}/Kv1.5	I_{Kr}/hERG	I_{Ks}	I_{KACh}	I_{KATP}	I_{K1}	Species	References
LY294002		7.9 μM						CHO cells	(Wu et al., 2009)
Nifendipine	26.8 μM	8.2 μM						Human atrial myocytes	(Gao et al., 2005)
NIP-151					1.6 nM			HEK293 cells	(Hashimoto et al., 2008)
Nordihydroguaiaretic acid		16.4 μM						CHO cells	(Gong et al., 2008)
Quinidine			0.6 μM					CHO cells	(McPate et al., 2006)
Raloxifene	0.9 μM	0.7 μM						Human atrial myocytes	(Liu et al., 2007)
S0100176		0.7 μM						Oocytes	(Decher et al., 2004)
SD-3212					<0.4 μM			GP atrial myovytes	(Hara and Nakaya, 1995)
Spironolactone	27%/1 μM	23%/1 μM		38%/1 μM					(Gomez 2005
Canrenoic acid	27%/1 nM	19%/1 nM	104 nM	223 nM				CHO/Ltk^{-}	Caballero, 2003)
Tertiapin/Tertiapin Q					10 nM			Oocytes	(Jin and Lu, 1998)
U50488H	12.4 μM	3.3 μM						Human atrial myocytes	(Xiao et al., 2003)
U73122/U73343					0.5 μM			HEK293 cells	(Klose et al., 2008)
Verapamil		3.2 μM						Human atrial myocytes	(Gao et al., 2004)
Vernakalant	30 μM	13 μM	21 μM					HEK293 cells	(Fedida et al., 2005)
Verrucotoxin						16 μg/ml		GP atrial myocytes	(Wang et al., 2007)
Ziprasidone			120 nM					HEK293 cells	(Su et al., 2006)

Activator

A-312110						4.3 nM		GP cells	(Davis-Taber et al., 2003)
A-935142			60 μM					HEK293 cells	(Su et al., 2009)
Adenosine	2.3 μM							Rat cardiac myocytes	(Wang et al., 2006)

Table 1 (continued)

Drug	I_{to1}/Kv4.3	I_{Kur}/Kv1.5	I_{Kr}/hERG	I_{Ks}	I_{KACh}	I_{KATP}	I_{K1}	Species/cell type	References
AMP579	8.3 μM							Rat cardiac myocytes	(Wang et al., 2006)
BMS-191095						83 nM		Reconstituted sarcI_{KATP}	(Grover et al., 2001)
Atpenin A5						1 nM		Rat mitoI_{KATP}	(Wojtovich and Brookes, 2009)
Ephedrine				50 nM				HEK293 cells	(Jing et al., 2009)
Ginsenoside Re				3 μM				GP ventricular myocytes	(Bai et al., 2004)
ICA-105574			0.5 μM					HEK293 cells	(Gerlach et al., 2010)
KB130015			12.2 μM					HEK293 cells	(Gessner et al., 2010)
NS1643			10.5 μM					HEK293 cells	(Hansen et al., 2006)
NS3623			79.4 μM					Oocytes	(Hansen et al., 2006)
P1705						68 nM		Rabbit mitoI_{KATP}	(Oldenburg et al., 2003)
PD-118057			3 μM					HEK293 cells	(Zhou et al., 2005)
PD-307243			<1 μM					CHO cells	(Gordon et al., 2008)
Phenylboronic acid				1.6 mM				Oocytes	(Mruk and Kobertz, 2009)
Resveratrol				10 μM				GP ventricular myocytes	(Zhang, Y. et al., 2006)
R-L3				< 1 μM				GP ventricular myocytes/Oocytes	(Salata et al., 1998)
RPR260243			<3 μM					HEK293 cells	(Kang et al., 2005)
Tanshinone IIA				64.5 μM				HEK293 cells	(Sun et al., 2008)
TEA					2.5 mM			GP atrial myocytes	(Wang and Armstrong, 2000)

Data are expressed as IC_{50} (for blockers) or EC_{50} (for activators) values (concentrations producing 50% inhibition or enhancement of the current or half-maximal effects), and some values are estimated according to the reference, which are mainly from the reports after 2003. Please refer to the review (Tamargo et al., 2004) for the information before 2003. GP, guinea pig; CHO, Chinese hamster ovary.
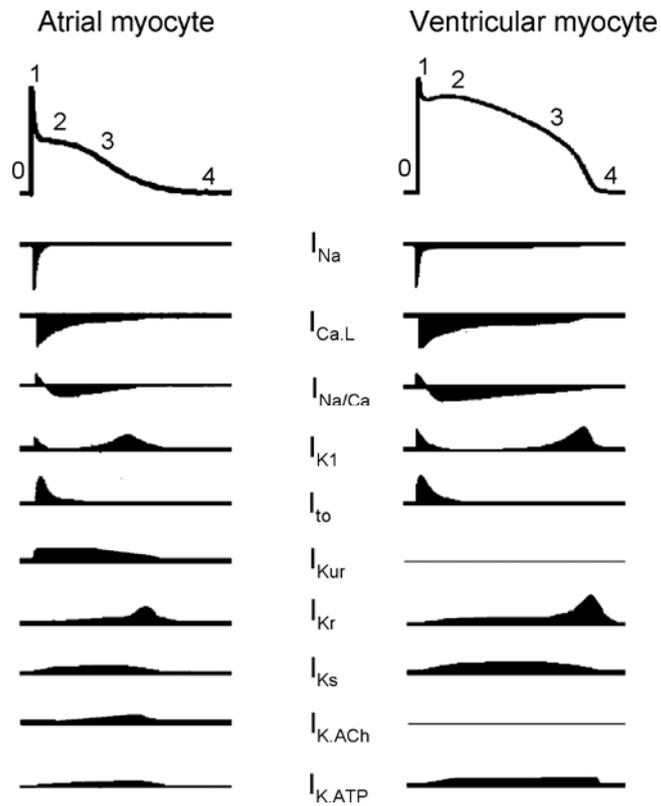
Figure 1. Ionic current contribution to human atrial and ventricular action potentials. The graph schematically shows that the major ionic currents contribute to the action potential waveforms at different phases. The action potentials are recorded from a human atrial myocyte and ventricular myocyte. The depolarizing inward (downward) currents and repolarizing outward (upward) currents represent the potential contribution to the action potentials.
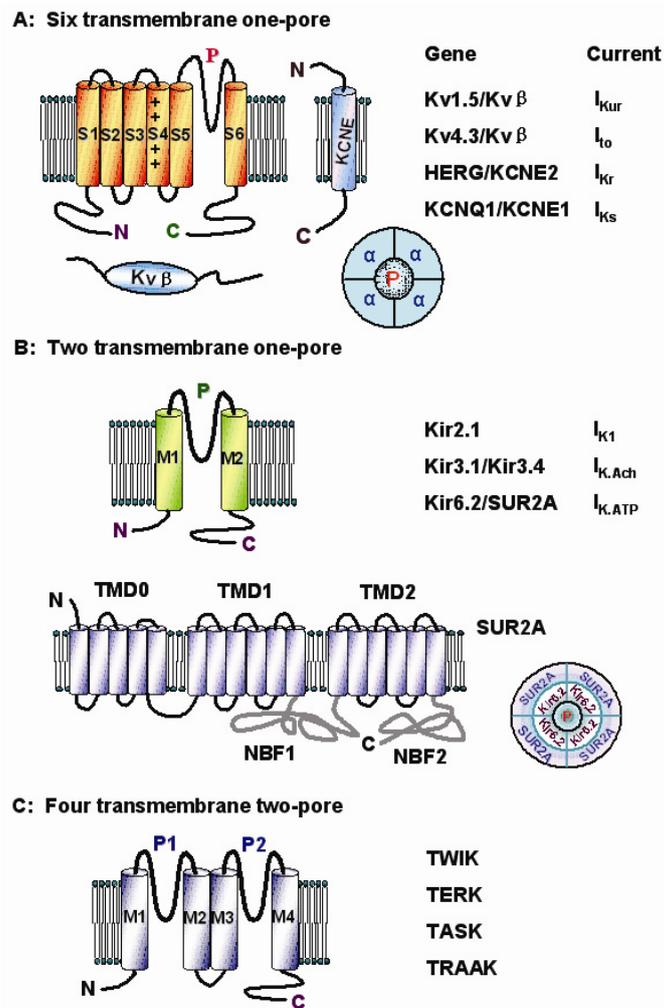
Figure 2. **Schematic topology of the potassium channels subunits. A.** 6-TM subunits, the Kv channels are composed of four subunits each containing six-transmembrane segments (S1-S6) and one conducting pore (P) domain between S5 and S6 with a positively charged voltage sensor S4. The auxiliary β−subunit may be cytoplasmic protein (Kvβ, for I_{Kur} and I_{to1}) or single transmembrane protein (KCNE1, for I_{Kr} and I_{Ks}). The inset shows the general assembly of K^+ channels. The channel tetramer may be homogenous (with four identical α−subunits) or heterogenous (with four different α-subunits). **B.** 2-TM subunits, the α-subunits of the inward rectifier K^+ channels (Kir2.x, Kir 3.x, and Kir6.x) contain four subunits each containing two transmembrane segments (M1 and M2) with one pore. Cardiac I_{KATP} channels are composed of four α−subunits (Kir6.2), and four β −subunits sulfonylurea receptor (SUR2A) containing three transmembrane domains (TMD0-TMD2). **C**, 4-TM subunits. K_{2P} channels have four−transmembrane segments (M1-M4) with two pores.