

Contributions of Ion Channels in Cardiac Arrhythmias

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1. Introduction

The cardiac action potential is arised by the highly orchestrated activity of dozens of ion channel proteins. These transmembrane proteins govern the influx of ion across the sarcolemma of cardiomyocytes generating the ionic currents responsible for excitation. In order to myocardium contract and ensure rhythmic pump function, the long-lasting action potential of the working myocardium maintains a refractory state. Because some channels must recover from inactivation after-repolarization before they have ability of re-opening, and during this time, the myocardial cells remain refractory for re-excitation.

Typical normal action potentials consist of five distinct phases (Figure 1). Na⁺ influx triggers a rapid depolarization (phase 0) followed by an early fast repolarization phase (phase 1) and

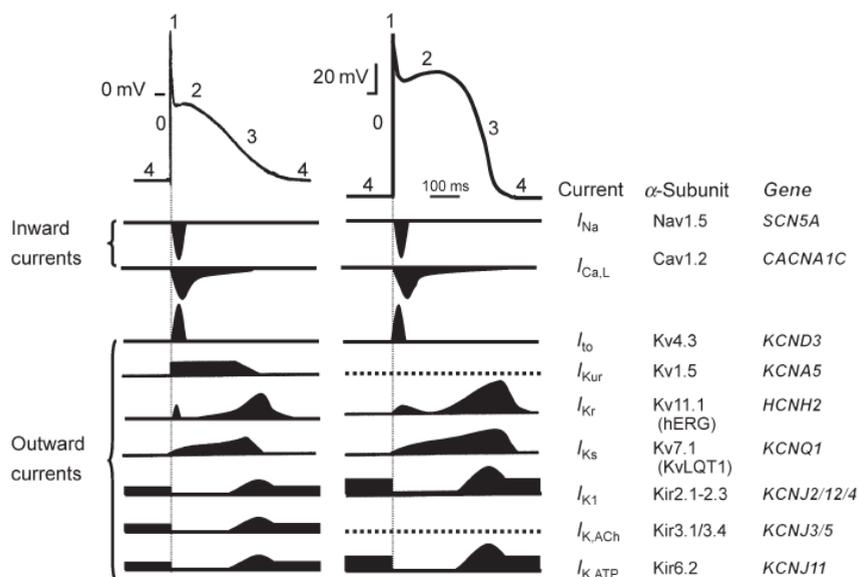


Fig. 1. (cited from The Sicilian gambit, 2008). Currents of sodium, calcium and potassium channels underlie the atrial and ventricular action potential.

a plateau phase (phase 2), in which repolarization is slowed due to the activation of inward Ca^{2+} current. During the final rapid repolarization phase (phase 3), membrane potential returns to the resting level (phase 4). Therefore, normal action potentials attributed to the normal function of ion channel participated to formation of action potentials.

1.1 Ion channels in human heart disease

Regular excitation is formed by normal AP which generated in the sino-atrial node and spreads throughout the heart in an orderly manner. Oppositely, disorganization of electrical activity is the basis of cardiac arrhythmias. Arrhythmias are caused by the perturbation of physiological impulse formation, impaired impulse conduction, or disturbed electrical recovery. Abnormal excitability of myocardial cells may give rise to kinds of cardiac diseases.

The most ordinary cardiac arrhythmia diseases was inherited long QT syndrome (LQTS) which was recognized 40 years ago as 2 distinct clinical phenotypes, such as the Romano-Ward and the Jervell and Lange-Nielsen syndromes. Interestingly, while LQTS was initially thought to be a pure cardiac channelopathy, it is now clear that non-ion-channel encoding genes may also cause the disease. Nevertheless, LQTS attributed to dysfunctions of ionic currents, either directly (ion channel) or indirectly (chaperones and/or other modulators).

To date, 12 forms of inherited LQTS described because LQTS arise from polygenic causes and 9 of them directly combine with ion channels (Table 1). LQT1, 2, 5, and 6 are referred to prolong the plateau of cardiac APs (phase 2) by reducing K^+ channel currents activated during depolarization. LQT1 and 5 are caused by mutations in *KCNQ1* (*KvLQT1*) and *KCNE1* (*MinK*), which encode the α and ancillary β subunits, respectively and together form the slowly activating delayed rectifier K^+ current (I_{Ks}). LQT2 and 6 are caused by mutations in *KCNH2* (human-ether a-go-go-related gene; *HERG*) and *KCNE2* (*MiRP1*), which encode the α and putative β subunits, respectively and together form the rapidly activating delayed rectifier K^+ current (I_{Kr}). LQT7 is characterized by mutations in *KCNJ2* (*Kir2.1*), which reduces the inward rectifier K^+ channel current (I_{K1}) to slow the return of the membrane to the resting potential. These cause failure of normal inactivation to decrease of K^+ current (loss of function) and abbreviate action potentials. Besides potassium channel, LQT3, 10 attributed to mutations in *hNav1.5* (*SCN5a*), and *SCN4b*, which encode α and ancillary β subunits of Na^+ channel. LQT8 are determined by mutation in *CACNA1c*, which encode alpha subunit of calcium channel. LQT3,10 and LQT8 arise from the increase of Na^+ currents and Ca^{2+} currents, respectively, for prolong action potential. Therefore, "loss of function" or "gain of function" mutations in the affected ion channels are often formed different phenotypes of cardiac arrhythmia disease.

Except the mentioned above, LQT4,9,11,12 are determined by mutation in *ANK2*, *Cav3*, *AKAP9* and *SNTA1*, which encode ankyrin B, caveolin, A-kinase-anchoring protein and alpha1-syntrophin, respectively. All proteins increase or decrease the ionic currents (loss of function or gain of function). Although the remarkable genetic heterogeneity in LQT, three genes, such as *KCNQ1* (LQT1), *KCNH2* (LQT2) and *SCN5A* (LQT3), are dominant and cover more than 90 percentage of LQTS patients with identified mutations.

With exception of LQTS, some of these involve gain of function mutations in K^+ channels (short QT syndrome) and loss of function mutations in Ca channel and Na^+ channels (Brugada syndrome, cardiac conduction disease, etc). Additional congenital arrhythmia syndromes continue to be described, and these are summarized in Table 1.

current	disease	gene name	chromosomal locus	Protein	functional effect	inheritance
I _{Na}	LQT3	SCN5A	3p21	sodium channel alpha subunit (Nav1.5)	gain of function	AD
	BrS1	SCN5A	3p21	sodium channel alpha subunit (Nav1.5)	loss of function	AD
	AF3	SCN5A	3p21	sodium channel alpha subunit (Nav1.5)	loss of function	AD
	PCCD	SCN5A	3p21	sodium channel alpha subunit (Nav1.5)	loss of function	AD
	SSS	SCN5A	3p21	sodium channel alpha subunit (Nav1.5)	loss of function	AD
	LQT10	SCNβ4	11q23.3	sodium channel beta subunit	increases sodium channel	AD
I _{Ca,L}	TS/LQT8	CACNA1C	12p13.3	calcium channel alpha subunit	gain of function	AD/mosaicism
	BrS3	CACNA1C	12p13.3	calcium channel alpha subunit	loss of function	AD
	BrS4	CACNB2b	10p12	calcium channel alpha subunit		AD
I _{Ks}	LQT1	KCNQ1	11p15.5	I _{Ks} potassium channel alpha subunit (KvLQT1)	loss of function	AD
	JLN1	KCNQ1	11p15.5	I _{Ks} potassium channel alpha subunit (KvLQT1)	gain of function	AR
	AQT2	KCNQ1	11p15.5	I _{Ks} potassium channel alpha subunit (KvLQT1)	gain of function	AD
	AF1	KCNQ1	11p15.5	I _{Ks} potassium channel alpha subunit (KvLQT1)	gain of function	AD
	LQT5	KCNE1	21q21.1-q22.2	I _{Ks} potassium channel beta subunit (Mink)	loss of function	AD
	JLN2	KCNE1	21q21.1-q22.2	I _{Ks} potassium channel beta subunit (Mink)	gain of function	AR
	AF5	KCNE1	21q21.1-q22.2	I _{Ks} potassium channel beta subunit (Mink)	gain of function	AD

current	disease	gene name	chromosomal locus	Protein	functional effect	inheritance
I _{Kr}	LQT2	KCNH2	7q35-q36	I _{Kr} potassium channel alpha subunit (hERG)	loss of function	AD
	SQT1	KCNH2	7q35-q36	I _{Kr} potassium channel alpha subunit (hERG)	gain of function	AD
	AF2	KCNH2	7q35-q36	I _{Kr} potassium channel alpha subunit (hERG)	gain of function	AD
	LQT6	KCNE2	21q21.1-q22.2	I _{Kr} potassium channel beta subunit (MiRP)	loss of function	AD
	AF6	KCNE2	21q21.1-q22.2	I _{Kr} potassium channel beta subunit (MiRP)	gain of function	AD
I _{K1}	AND/LQT&	KCNJ2	17q23.2-q24.2	I _{K1} potassium channel (Kir2.1)	loss of function	AD
	SQT3	KCNJ2	17q23.2-q24.2	I _{K1} potassium channel (Kir2.1)	gain of function	AD
	AF4	KCNJ2	17q23.2-q24.2	I _{K1} potassium channel (Kir2.1)	gain of function	AD

Table 1. Mutations of ion channels

1.2 Mechanism of ion channels dysfunction

Based on the discussion mentioned above we can easy to understand the mutation how reduce or increase the currents and lead the kinds of cardiac arrhythmia. The change of the magnitude of currents in cardiac is based on the below three factors. For instance, the total number of channels on the membrane (N), the open probability of the channel (P_0) and the conductance of single channel (i). Gain of function or loss of function mutations of ion channel through changing of N, P_0 and I alone or all contribute to kinds of congenital cardiac arrhythmia.

1.2.1 Change of the channel number

There are two distinct process in which can change the number of channel in the plasma membrane, one is in the synthesis channel process and another is during the channel trafficking.

About defective synthesis of mutations contained the premature termination codons is maybe the most mutations of ion channel. For example, there are one fourths of all mutations of hERG channel (<http://www.fsm.it/cardmoc>). The protein encoded by the mutation with premature termination codon is a truncated one which can be eliminated by nonsense-mediated mRNA decay. And the hERG truncation mutation is proved to be clear by the nonsense-mediated mRNA decay in recently.

Exception of the nonsense-mediated mRNA decay, another important clear mechanism is at mRNA level by microRNA (miRNA) mediated mRNA silencing. The degradation of the target

mRNA is through partial complementary combination with the miRNA followed binding with kinds of protein or nucleotide to form a huge ribosome. To date, many miRNA are detected in heart and decrease of ion channel protein at translation or/and transcript levels.

There are three steps during the process of ion channel synthesis: i) the formation of core-glycosylated monomer in ER followed the correct to the tetramer ii), iii) then complex glycosylation to form the mature subunit in Golgi. Accordingly, Western blot check can be used to detect whether composition of the channel protein is complete. The primary channel protein is commonly synthesized in ER.

In order to export completely from the synthesis location (ER), each channel subunit protein contained more than one of the ER exit signal (D/E-X-D/E) motif which can guide the protein correctly from ER to Golgi, where X represents any kind of amino acid. To ensure the channel deviated from ER, channel forms a tetramer in ER by masking or shielding the ER retention signal. Therefore, mutations in ER exit signal or with correlation of the assembly of channel may lead to the retention in ER then decrease the number of channels in the membrane.

1.2.2 Change of channel open probability

Change of activation and inactivation may be two ways of altering of channel open probability. In *Xenopus laevis* oocytes system, to date many mutations have been detected to alter the channel gating. But there are much difference between the oocytes system and the mammalian system. In addition, there are many mutations that have been expressed in mammalian and shown to result in gating defects.

1.2.3 Change of single channel conductance

To alter the conductance of single channel, the mutation sites of ion channel exits in the vicinity of the selective filter. Owing to the selective filter of ion channel is determined the kinds of ions across the channel. Accordingly, the single channel conductance change may be attributed to the conformation altering of the selective filter.

2. Sodium channel

Cardiac voltage-gated sodium channel has critical role in excitability of myocardial cells and proper conduction of the electrical impulse within the heart. Influx of Na^+ across sodium channel is responsible for the initial fast upstroke of the cardiac action potential. Therefore, this inward sodium channel triggers the initiation and propagation of action potential throughout the myocardium. The gene of *SCN5A* encodes the major sodium channel in heart.

2.1 Structure of sodium channel

The voltage-gated sodium channel is composed by a pore-forming α subunit and an ancillary β subunit. Nav1.5 encoded by *SCN5A* consists of four homologous domains (D I - D II) and each domain has six transmembrane segments (S1-S6). Similar to other voltage-gated ion channel, the S4 contained many positive residues in each domain forms the voltage sensor and the S4 and S5 in all domains together make up ion-conductance pore including the selectivity filter. When sodium channel is activated, influx of Na^+ begins, thereby the depolarizing of the membrane until the activation of L-calcium channel, at last forming the upstroke of action potential. Continue to depolarization, the fast and low inactivation happens causing the sodium channel close. Sodium channel gating properties and current kinetics may be altered when channel is dysfunction.

Cardiac sodium channel function can be regulated by a vast number of proteins. The single transmembrane β -subunit consists of a small C-terminal cytoplasmic domain and a large glycosylated N-terminal extracellular domain. The ancillary subunit alters the currents density and kinetics by physical interaction with the α subunit. Other proteins regulating Nav1.5 by directly binding include ankyrins, fibroblast growth factor homologous factor 1B, calmodulin, caveolin-3, Nedd4-like ubiquitin-protein ligases, dystrophin, and syntrophin, as well as glycerol-3-phosphate dehydrogenase 1-like protein and MOG1. In addition, sodium channel density and kinetics are furthermore also regulated by phosphorylation and glycosylation, even by changes in temperature.

2.2 Functions of sodium channel in heart

During myocardial ischemia, the mechanisms involved in arrhythmogenesis are complex, but excitability and conduction are considered as the major determinants. During ischemia, local metabolic changes within the myocardium lead to inactivation of the sodium current and consequent repression of cardiac excitability and slowing of conduction. In clinical, slowing conduction produced by sodium channel blockers application has been shown to be proarrhythmic. Some papers have reported an association between *SCN5A* loss-of-function mutations and the occurrence of ischemia-induced severe episodes of ventricular tachyarrhythmias. It is as yet unknown whether *SCN5A* mutations and/or polymorphisms play a substantial role in the prevalence of sudden arrhythmic death in the setting of myocardial infarction,

2.3 Cardiac sodium channelopathies

To date, more than 150 mutations in *SCN5A* have been reported, the vast majority of them caused either LQTS3 and Brugada syndrome. Some patients with LQTS can be healing well whereas most of them may increase risk for sudden death due to ventricular tachyarrhythmias, in particular torsades de pointes. The character of LQTS3 is that display arrhythmias predominantly during rest or sleep videlicet at slow heart rate. Therefore, the first clinical event of the patient with LQTS3 often is cardiac arrest rather than syncope. About the molecular mechanism of LQTS, vast majority of mutations in *SCN5A* produced the disruption of the fast inactivation but not the slow inactivation. The disruption allows the sodium channel reopen and produces the persistent inward current during the action potential plateau phase. Gain of function mutations in sodium channel delays the depolarization of the action potential and causes the prolongation of the action potential.

Brugada syndrome, a familial disease which characterized by ventricular arrhythmia and sudden cardiac death even occurring in healthy person at relatively young age (mainly between 30 to 40) and more in male, is first raised by brothers of Brugada in 1992. The features on ECG show the elevation of ST segments in the precordial line. Mutation in *SCN5A* is acquired as original of the SQT3 in a familial disorder in 1998. More than 100 mutations in *SCN5A* is related the Brugada syndrome. Besides the mutation in *SCN5A*, mutations in the β -subunits *SCN1B* and *SCN3B*, and the regulatory protein GPD1-L have been described in some Brugada syndrome patients. In a word, mutations in *SCN5A* or ancillary subunit caused to Brugada syndrome because of the reduction of sodium channel availability, loss of function. Some factors cause loss of function in ion channel. For example the decreased trafficking will degrade the number of sodium channel (N) in membrane surface, or disruption of activation, accelerated inactivation, and impaired

recovery from inactivation will alter channel gating properties (the open probability and the single channel conductance).

Loss of mutations in *SCN5A* underlies the mechanism of progressive cardiac conduction defect (PCCD) due to reduction the sodium channel availability. PCCD is characterized by progressive conduction slowing through the His-Purkinje system, leading to the complete AV block, syncope and sudden death. Same to PCCD, Sick Sinus Syndrome is also caused by the mutations in *SCN5A* by decreasing the current of inward sodium currents. Sodium channel contribute to the cardiac automaticity owe to the inward sodium currents in depolarizing progress. Therefore, automaticity of sinoatrial pacemaker can also be regulated by the sodium channel. Atrial fibrillation is often happened in elderly person with the abnormal heart and younger person with normal structure. In recent, both loss of function and gain of function mutations in *SCN5A* have been identified as atrial fibrillation due to decrease atrial conduction velocity attributed to the degrade of sodium inward currents and increase atrial action potential duration and excitability owe to the raise of sodium channel availability, respectively. In addition, the patients with dilated cardiomyopathy are evoked by the mutations in *SCN5A*.

In recent years, "overlap syndrome" of cardiac sodium channel diseases have known to exist. The term of "overlap syndrome" is referred to extensive clinical and biophysical overlap. For example, the patients with the mutation *SCN5A-1795insD*^{+/-} shows extensive variability in type and severity of symptoms of sodium channel disease. Otherwise, the single mutation in *SCN5A* alone but express pleiotropic effects make further verified through a transgenic mice *SCN5A-1798insD*^{+/-} (equal to human *SCN5A-1795insD*^{+/-}). It is further confirmed that a single *SCN5A-1795insD*^{+/-} mutation is sufficient to express the overlap syndrome of the sodium channel. Heterogeneous biophysical properties of ion channel mutations causing the mixed disease expressively are now increasing recognized. Therefore, it is necessary that improve diagnosis for the sodium channelopathies.

3. Calcium channel

Voltage gated calcium channel is the main channel across by Ca^{2+} into the intracellular in many excited cell. L-type $\text{Ca}_v1.2$ channel is an important voltage gated calcium channel and have been detected in many organs. Notwithstanding the widespread important function of the L-type calcium channel, the mutations have been identified is very rare. Mutations of deletion of the pore forming part in $\text{Ca}_v1.2$ channel change significantly the properties of the channel leading to the embryonically lethal. On the contrary, mutations associated with mild effects on $I_{\text{Ca,L}}$ kinetics is well adapted and the patients with no obvious symptoms.

3.1 Structure of L-type $\text{Ca}_v1.2$ channel

Similar to the voltage-gated sodium channel, structure of L-type $\text{Ca}_v1.2$ channel is formed by a pore-forming subunit divided for four domains (from I to IV). Each domain consists of six transmembrane segments (S1 to S6). As the common to other voltage gated channel, the S4 of each domain is the voltage sensor moving across the membrane corresponding to the depolarization of the membrane potential. The part of S5, S6 and the linker S5-6 in each domain are composed to the ion conduction pathway.

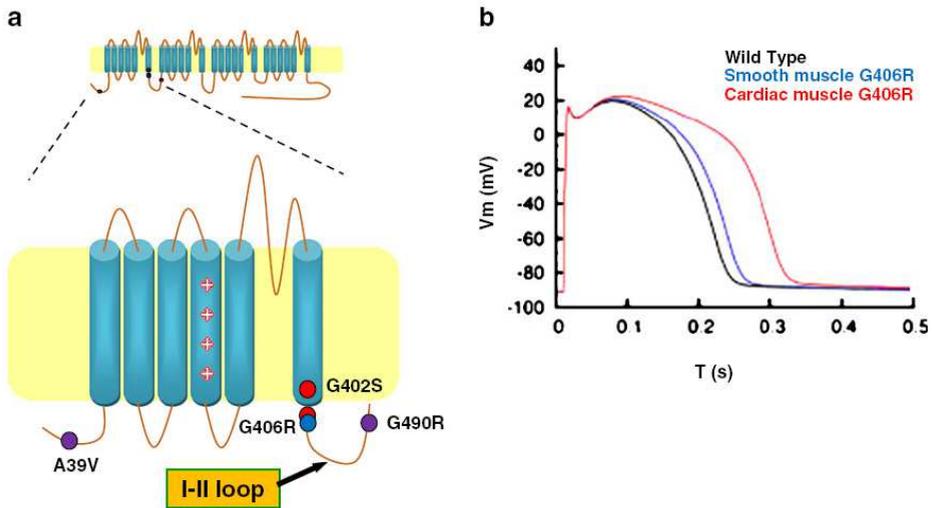


Fig. 2. a (cited from Liao and Soong, 2010). Location of the mutations identified in Cav1.2 pore-forming $\alpha 1$ subunit. Red circles (G402S and G406R) represents spliced cardiac exon. Blue circle (G406R) is located in smooth muscle exon. Purple circles (A39V and G490R) represents constitutive exons. b Computer modeling revealed cardiac action potential when the mutation in smooth muscle exon and in cardiac exon.

3.2 Ancillary subunits

To date, four β subunits of calcium channel genes are expressed in the heart. The ancillary subunits can in theory bind to the Cav1.2 subunit at the $\alpha 1$ interaction domain (AID). The domain is highly conserved binding motif of 18 amino acid residues present in the cytoplasmic linker between repeat I and II of $\alpha 1$ subunits. The $\beta 2$ subunit is generally believed to constitute the intracellular, accessory subunit of the Cav1.2 channel in adult mammalian myocardium.

There are two distinct function of β subunit binding with the pore-forming subunit: before binding as a chaperone helping α subunit correct location at the membrane, after binding as an allosteric modulator to regulate the kinetic of the currents. Otherwise, different β subunit increase the currents of $I_{Ca,L}$ at different levels by increasing the the channel opening probability, produce distinctive effects on channel inactivation kinetics and induce hyperpolarizing shifts in the voltage-dependence of channel activation.

Recent studies have shown that the ancillary subunits are members of the membrane-associated guanylate kinase (MAGUK) family of proteins by crystallographic information. Therefore, the ancillary subunits, as a ideal targets, interact with other protein such as ahnak or various members of the Gem/kir family of small Ras-like GTPase.

3.3 Functions of L-type Cav1.2 in heart

The L-type Cav1.2 channel plays a critical and dominant role in triggering excitation-contraction coupling in cardiomyocytes through the influx of the calcium ions to form the plateau of the ventricular action potential. Otherwise, the L-type Cav1.2 channel contribute to the trigger of the contraction when initiate the Ca^{2+} from the sarcoplasmic reticulum.

LQTS8 (also called Timothy syndrome) is first reported in 1990s with the symptoms of syndactyly. The molecular basis of Timothy Syndrome is the mutations in L-type Cav1.2 at IS6 segment encoded by the two mutually exclusive exons 8/8a. Timothy syndrome is several features. Firstly, mutations are common caused by the deamination of a methylated cytosine to a thymine at de novo. Secondly, gain of function of L-type Cav1.2 lead to the increase of current density of $I_{Ca,L}$ through slowing the inactivation of the channel. The net effects of the mutations increase of intracellular calcium ion. Thirdly, mutations are common in the mutually exclusive exons. The mutation of exons alters dramatically channel properties and the unaffected exon function normally. Lastly, mutation in Cav1.2 is also related to normal function of immune system.

Different Cav1.2 variants are formed by the extensive alternative splicing by changing the pattern of splicing causing a series of disease. Among of them, only a few major splicing site can be divided to the cardiac and smooth muscle subfamily. In human heart, Cav1.2 channel contained cardiac exon may be 77 percent of all Cav1.2 channel. The first Timothy Syndrome mutation G406R is at the smooth muscle exon whereas other mutation G406R and F402s is at the cardiac exon. The latter can be named as TS2 and the cardiac arrhythmia of what is more serious than TS.

TS2 mutant Cav1.2 belong to gain of function mutation leading to more calcium ion into the cytoplasm. Therefore, the action potential duration are be prolonged and a longer QT interval on ECG is shown. Comparison with TS (mutations at smooth muscle exon), TS2 (mutations at cardiac exon) produces more effects on action potential duration and excitability. For example, the prolongation of action potential duration by mutation at cardiac exon and smooth muscle exon is 30% and 8% by computer analysis, respectively. Therefore, symptom of patient with TS is milder than one with TS2.

Otherwise, loss of function mutation in Cav1.2 or ancillary subunit cause to Brugada syndrome characterized by the elevating QT segments and shortening QT interval on ECG. The ages of the patients with Brugada syndrome is ranging from 21 to 44 years old which is elder than TS patients. Besides the dysfunction in cardiac tissues, other organs are nearly normal in patient with Brugada syndrome.

4. Potassium channel

Potassium channel is the largest family of ion channel protein and divided into voltage- and ligand- potassium channel owing to activating by voltage and ligand, respectively. Most of potassium channel are determined and depended by membrane potential. The ion-conducting pore of a K^+ channel is formed by four α -subunits that co-assemble as homo- or hetero-tetramers with different biophysical properties. Their gating characteristics can also be modulated by ancillary subunits or all kinds of blocker or activator.

4.1 Classification of the cardiac potassium channel

On the basis of their function, cardiac K^+ channels are further classified into the transient outward channels, the delayed rectifier channels and the inward rectifier channels (*Figure 1*). Firstly, the transient outward current (I_{to}) formed by Kv4.3 manifests rapid activation and subsequent inactivation during the early repolarization phase (at phase 1). (ii) The delayed rectifier channels consist of at least three members Kv1.5, Kv11.1 and Kv7.1, for three different currents I_{Kur} , I_{Kr} , and I_{Ks} , respectively. All three channels activate at positive potentials but with distinct time courses, for example ultrarapid, rapid, and slow,

respectively. Inactivation of I_{Kur} and I_{Ks} is slow, on the contrary that of I_{Kr} is extremely fast. (iii) The cardiac inward rectifier potassium channels have more than three components. The major classical of one is Kir2,1-2.3 which form I_{K1} currents. This channel is always open and conducts K^+ better into than out of the cell. Another channel expressed in atrial myocytes is an acetylcholine-dependent channel which conducts $I_{K,ACh}$ corresponding with the stimulation of G-protein-coupled muscarinic (M2) and adenosine (A1) receptors. The activation of $I_{K,ACh}$ shortens the active potential duration (APD). The third one in cardiomyocytes is ordinary closed under physiological metabolic conditions and is activated when the cells are deprived of intra-cellular adenosine triphosphate (ATP). Similar to $I_{K,ACh}$, $I_{K,ATP}$ causes profound APD shortening.

Notwithstanding general similarity in the mechanism of action potential arising, the distribution of potassium channel in cardiac ventricular myocardium and cardiac atrium is the most striking difference. For example, I_{Kur} and $I_{K,ACh}$ currents are both detected just in atrial but not in ventricular. Under the positive potential I_{Kur} is activated rapidly followed by $I_{Ca,L}$ activation and therefore lead to less positive plateau phase in atrial than ventricular cells.

4.2 Structure of potassium channel

Remarkable advances about the structure-function relationship in ion channel have great progress in over past 30 years. Especially the progress in two experimental techniques, one is the single channel conductance recorded limpidly and plainly by patch clamp and another is the first determination at atomic-resolution of the structure of potassium channel protein. By means of these techniques, we can monitor real-time behaviour of single macromolecule in cell membrane and associate the behaviour with the molecular architecture of the protein

4.2.1 Structures of voltage gated potassium channel

Voltage-gated potassium channel is a homotetramer formed by each subunit containing six transmembrane domains (S1-S6). The pore domain comprise of the S5, the pore helix and S6 segment. The S1-S4 segments of each subunit form the voltage sensor domains (VSD). The part of VSD regulates the open and close of the pore domain through moving across membrane in response to change of membrane potential. The channel pore is anisomeric and its dimensions change when the transition of channel gates from a closed to an open state. The K^+ -selectivity filter, a narrow cylinder, exists in the extracellular end of the pore that optimally utilize for conduction of K^+ ions. The difference of the selectivity filter of Kv channels with other channel is characterized by the highly conserved sequence Thr-Val-Gly-Tyr-Gly (the K^+ signature sequence), located at the carboxy-terminal end of the pore helix. In hERG channel, the Thr and Tyr residues are substituted with Ser and Phe. The hydroxyl group of Thr in side-chain and the carbonyl oxygen atoms of the other four residues in each subunit all expose to the narrow K^+ selectivity filter. These atoms mentioned above (OH- and O) encircle several octahedral binding sites that compete with the single water molecule of hydrated K^+ ions and make a single water molecule alone arranged in a single line pass across the filter.

The central cavity under the selectivity filter is much more widen and is a filled water region boundary by the S6 α -helices. In the closed state, the four S6 domains criss-cross near the cytoplasmic interface to form a narrow aperture that is too small to permit entry of ions from the cytoplasm. In response to membrane depolarization, the S6 α -helices splay outwards and increase the diameter of the aperture to allow passage of ions.

4.2.2 Structures of Kir channel

Inward rectifier K^+ channels (Kirs) consist of two transmembrane domains (M1 and M2). M1 and M2, equal to the S5 and S6 part of voltage-gated potassium channel, is connected by a pore containing the G(Y/F)G sequence. In addition, the Kirs channels comprise of intracellular N- and C-termini. This architecture is typical structure of K_{ATP} and K_{ir} channels. They conduct K^+ currents more in the inward direction than the outward and play an important role in setting the resting potential close to the equilibrium potential for K^+ (E_K , approximately -90 mV for $[K^+]_o = 5$ mM) and in repolarization. Kir channels form either homo- or heterotetramers.

About the essential properties of rectification which attributed to blocking of Kir2 channels by intracellular organic cations called polyamines response to potent and strongly voltage-dependent. Of the polyamines, free spermine in cell is the most potent inducer of inward rectification, followed by spermidine, putrescine, and then Mg^{2+} . Accordingly, the "activation" of inward rectifiers upon membrane hyperpolarization is essentially uncoupling of polyamines or Mg^{2+} from the Kir channel pore.

The general architecture of the Kir channels and the key structures involved in permeation and block is well established. Similar to bacterial homologs, the Kir channel in mammalian has a selective filter at the extracellular of the membrane with a signature sequence GYG. Under the filter there are a widen water cavity towards the intracellular of the membrane. There are a number of residues in Kir2 critical for inward rectification. For example, Mutations of D172 located at the level of the water cavity is firstly identified, a 'rectification controller'. Spermine has high affinity with D172 in the vicinity of the filter and unbinding from the residues highly voltage-dependent. Another important residue in rectification is E224 and E299 in the cytoplasmic region which form a ring of acidic. Contrast to D172, spermine has a low-affinity binding with E224 and E299 and low voltage-dependent. Spermine, as the largest (~16–18 Å) polyamine, the pore of the Kir2 is long enough to easily accommodate two or more spermine.

In native $I_{K,ACh}$ channels, spermine can also induce strong inward rectification. There are half of the residues in underlying Kir3.1/Kir3.4 channels equal to D172 and E224 in Kir2.1. The negative residues in Kir3.1/Kir3.4 channels have important role causing strong inward rectification. Although Kir2 and Kir3 have many common similarities there are lots of differences in the kinetical properties between both of them (Anumonwo and Lopatin, 2011).

5. Kv11.1

Kv11.1 formed a kind of the delayed rectifier currents I_{Kr} encoded by *KCNH2* which is identified as the molecular basis of LQT2 in 1995. To date, nearly 300 different mutations of Kv11.1 is the direct reason of congenital LQTS (<http://www.fsm.it/cardmoc/>; see Table 1) and almost all drugs induced acquired LQTS do so through interaction with the hERG channel. Besides that, dysfunction of Kv11.1 may cause short QT syndrome and atrial fibrillation. Therefore, Kv11.1 has vital role in excitability and action potential conductance in heart

5.1 The features of the structure

Differences from other Kv potassium channel, hERG channel has a unique extracellular part between S5 and the "pore", so called "S5P linker" that contained an amphipathic helix. With

exception of transmembrane segment, hERG has intracellular N-terminal and C-terminal. The N-terminal has a Per-Arnt-Sim (PAS) domain which is unique to hERG channel in mammalian ion channel and play a role in deactivation of the channel. The C-terminal has a cyclic nucleotide binding domain (CNBD) which has relatively little effect on gating by binding with cAMP. However, mutation of the domain cause trafficking defects followed by loss of function of hERG channel and the last lead to cardiac arrhythmia.

5.2 Kinetic characters of Kv11.1

Similar to other Kv potassium channel, hERG channel exists at least three distinct conformational states: closed, open and inactivated. Transition from closed to open states or from open to inactivated state of channel attributed to the activation or inactivation which evokes the constrain of the conduction pathway and disrupted ion translocation. hERG channel have significant homology to other Kv family members by sequence analysis. However, kinetics characters of hERG channel activation and inactivation is distinct with other Kv channel. Contrast with other Kv channel, activation of hERG channel is much slower (t_{on} ranging from 100s of ms to many second) and inactivation is more rapid (t_{off} ranging from 1 to 10 ms) and voltage-dependent. Because of the slow activation of hERG at depolarized potentials, little outward currents produced by the channel flows through the phase 1 and 2 of cardiac action potential. Reduced outward currents conduce to the maintenance of the plateau of cardiac action potential by allowing Ca^{2+} entry and avoid the cell refractory to premature excitation. In addition, the increase outward currents, due to the much faster recovering from inactivation, is the most important determination of the plateau of cardiac action potential. Besides that the distinct gating kinetics of hERG channel leads to form the character I_{Kur} currents which is help for suppression of propagation of premature beats. Therefore, hERG channel has crucial role in normal or abnormal cardiac action potential.

5.2.1 Activation

The gate of potassium channel is the bundle crossing formed by four the intracellular parts of S6 transmembrane helices of each subunit. The gate at closed state is too narrow to allow transverse of K^+ ions. Transition to open state attribute to these helices which kink at a gate hinge revoking to enlargement of the pore and allow potassium ion pass it. In the bacterial KcsA, MthK and KvAP channels, a conserved Gly residue in S6 is proposed to serve as the hinge for the activation gate. Mutation of the putative Gly hinge in hERG alters gating but does not prevent channel opening. Although Kv1-Kv4 channels also have a Gly in the same location, a different molecular hinge may mediate channel activation. Therefore, the gating hinge, common formed by PVP motif in Kv1-Kv4, has vital roles in change of channel gate whereas the second proline of PVP motif was replaced by glycine in hERG channel.

The S1-S4 VSDs also have important role in regulating the transition from closed to open state in voltage-gated potassium channel. The voltage sensor in hERG channel which is the six basic positive amino acid every 3 residues localized in the position between 525 and 538 of the S4 domain Especially, the most important amino acid is the K525, R528 and K538 conducting to voltage sensing for slow activation. With exception of the positive residues, the acidic amino acid in S1-S4 stablize the VSD at open and closed conformation through forming salt bridge with S4 residues.

It is well known that the voltage sensing regulating the channel open or closed by voltage sensor domain (VSDs) up or down across the transmembranes. However, to date the exact rearrangement of the structure between up or down and the exact magnitude of movement of VSD is still debated. For instance, although the structure of mammalian Kv1.2 channel at open state, especially the location of VSD up relative to the membrane have revealed. But crystal structure of the channel at closed state scilicet the down relative to the membrane do not still detected. Another meaning thing is about the distinct kinetics of the hERG channel because the overall of SVD is high homology with other members of Kv channel family by analysis sequence and hydrophathy plots.

To find the reason that the kinetics of hERG is so different, many scientists are attracted in the field and find several key pieces of evidence. When the gating currents corresponding to the movement of voltage sensor domain are measured at the same time the results show that a slow time course corresponding with the slow the activation. From the results we can conclude that the slow activation of hERG attribute to the slow movements of VSDs

5.2.2 Inactivation

About the hERG channel, the mechanism of the inactivation is the C-type at original stage. However, hERG inactivation is orders of magnitude faster than C-type inactivation and its intrinsically voltage-dependent. Many papers pay attention to the molecular basis of the voltage-sensitive of channel inactivation and the relationship between activation and inactivation gating, whether the process are couple or completely separate. Some data indicate that other part but not the S4 contribute to regulate the hERG inactivation. Ser620 and Ser 631 in the P-domain are vital for inactivation. In addition, the charge change of S5P can markedly alter the inactivation of hERG. Therefore, Perrin conclude that different parts of voltage sensor domain participate in regulate the channel activation and inactivation. The amphipathic α -helix of S5P contain in the regulation of hERG inactivaon, due to the relative movements between the α -helix of S5P and the pore domain.

5.2.3 The regulation of KCNE2

It is well known that KCNE2 (Mirp1) was described as a modulator of the ether-à-go-go-related gene 1 (ERG1) potassium current. The protein of KCNE2 is a single transmembrane peptide with an intracellular C-terminal and an extracellular N-terminal. Coexpression with Kv11.1 increase the currents of I_{Kr} owing to increasing the single conductance, altering the kinetic characters of inactivation and inactivation. Later KCNE2 was found to also change the KCNQ1 potassium current by drastically changing the gating properties. Mutations in KCNE2 are associated with long QT syndrome (LQT6) (<http://www.fsm.it/cardmoc/>) because of a decreasing influence on both ERG1 and KCNQ1 currents by KCNE2 mutation. Accordingly, both types of complexes KCNQ1/KCNE1 and KCNH2/KCNE2 could play a functional role in the heart.

5.3 Functions of Kv11.1 in heart

Loss of function and gain of function mutations in Kv11.1 produce to the formation and conductance of action potential in cardiac tissues. Loss of function mutations decreases the currents of I_{Kr} due to decrease of channel number, channel open probability and single channel conductance as mentioned above.

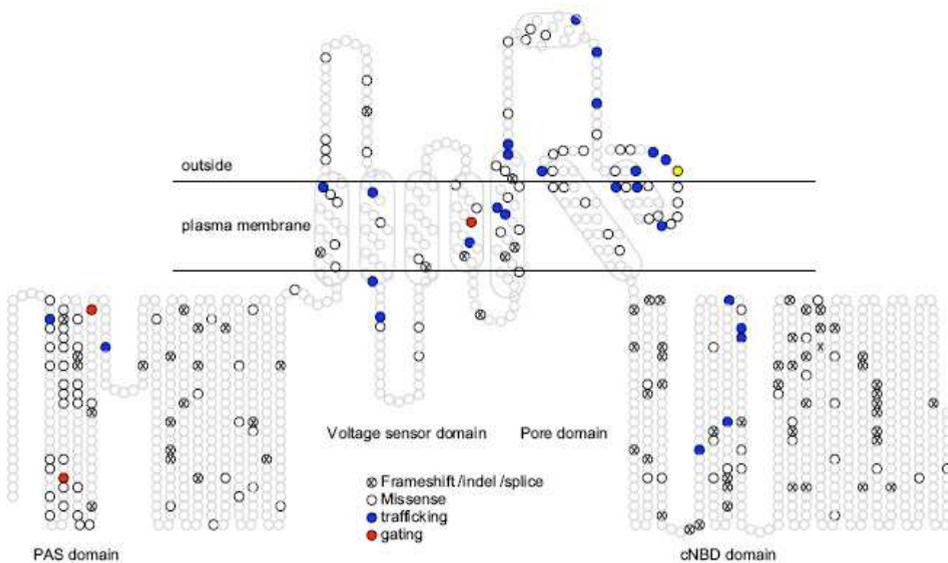


Fig. 3. (adapted from Perrin et al, 2008) Topological map of position of nearly 300 different mutations in hERG in LQTS2.

5.3.1 Congenital cardiac arrhythmia

LQTS is characterized by the prolongation of QT interval on ECG of the patients. Loss of function in Kv11.1 caused LQT2. Defective synthesis of mutations contained the premature termination codons is maybe the one fourths of all mutations of hERG channel (<http://www.fsm.it/cardmoc>). Otherwise, hERG mutation of R534C display an increased open probability expressed in *Xenopus laevis* oocytes whereas in clinically the mutant induces the gain of function. Therefore, it is importance of detecting the mutations in mammalian system.

Gain of function mutation in KCNH2 cause increasing of currents amplitude I_{Kr} which lead to shorten the action potential duration and in final to decurtate the QT interval on ECG. Some patients with SQT will be healing well in the future through the regulation of themselves. However, if the cardiac action potential is persistent shorten and produce diminishing of refractory period between the continual bisaction potential. At last, SQT may be get worse the atrial fibrillation and sudden death or syncope.

5.3.2 Acquired LQTS

Comparison with congenital LQTS, acquired LQTS is more common cause of TdP. Lots of factors can induce to form acquired LQTS, such as myocardial ischemia, electrolyte disturbances, bradycardia and so on. Of the most important factors is drug. Accordingly, the drug-induced LQTS is equal to the acquired LQTS in most case. However, acquired LQTS and drug-induced LQTS is essential two different concepts.

Many kinds of drug can induce the acquired LQTS, for instance antiarrhythmia drug, antibiotic, antihistamine and so on. Antiarrhythmia drug quinidine is a relatively frequent side effects, caused 2-9% of treated patient induced RdP. Other drugs induced TdP is less

than antiarrhythmia drugs. The compounds (dofetilide, sotalol and ibutilide), predictable designed to block cardiac repolarizing currents, can induce the prolongation of the QT interval which unfortunately arises as a side effect of the compound treated for non-cardiac diseases. Therefore, the compound in already marketed drugs will be withdrawal or restriction. In order to the expenses of the pharmaceutical companies, it is now common practice to screen for compound for hERG-channel activity early during preclinical safety assessment. However, in clinical the blockage of hERG can counteract by blocking of L-type of calcium channel.

Most of drugs which can induce acquired LQTS can also block of hERG channel. Contrast to other Kv channel, the hERG is unusually susceptible to blockage by drugs is unknown, suggesting that it has a unique binding site. In order to find the interact sites hERG with the blockers, an ala-scanning mutagenesis approach is used. Mutations of two polar residues (Thr 623 and Ser 624) located at the base of the pore helix and mutations two aromatic residues Tyr652 and Phe656 located in the S6 domain of hERG has vital roles in combination with the compounds. The side chains of all four residues are oriented toward the large central cavity of the channel and can block the transmembrane pass of potassium ions by combining with the blocker.

5.4 Future perspectives

Over the past 16 years a great deal of discovery of hERG channel has been detected but there is still much to explore about the channel.

6. Kv7.1

Kv7.1 (also known as KCNQ1, KvLQT1) is the α -subunit of a voltage-gated potassium channel cloned in 1996 by Wang and co-workers using linkage analyses of LQTS1 patients and expressed in several tissues including cardiac myocytes and epithelial cells. The most important roles of KCNQ1 channels are repolarization of the cardiac tissue following an action potential. In cardiac myocytes, the KCNQ1 subunit assembles with the KCNE1 β -subunit (minK) to form a channel complex. The channel complex of KCNQ1/KCNE1 produce the delayed rectifier current I_{Ks} , which is partly responsible for terminating the cardiac action potential during phase 2. Up to now, there are nearly three hundred mutation of KCNQ1 have been detected. Most of the mutations produce the loss of function of KCNQ1, lead to the LQTS (<http://www.fsm.it/cardmoc/>), a most kind of cardiac arrhythmia characterized by prolongation of QT interval in electrocardiogram, syncope and sudden death. Only a few gain-of function mutations have been verified and have correlate with the atrial fibrillation or the short QT syndrome (SQTs).

Based on the molecular mechanism of altering of KCNQ1 currents, mutations of the channel are divided into impaired trafficking, impaired voltage dependence, impaired selectivity and impaired tetramerization. For the majority of these three hundred KCNQ1 mutations, little is known about the molecular mechanism producing to the pathologies or limited to which of the categories. Therefore, there are many unknown knowledge about the three hundred KCNQ1 mutations and make further progress in the future with the application of new technology of structure prediction in study.

6.1 Structure and electrophysiological characters of KCNQ1

As a member of Kv potassium channel, KCNQ1 channel show a high similarity to voltage-gated potassium channels of the Kv type which assemble a tetramer, with each subunit of

KCNQ1 contained S1-S6 trans-membrane. Different from other Kv members, KCNQ1 often form heterotetramer with auxiliary subunits contained one-transmembrane in vivo. To date, there are five member of KCNE family have been detected and in *Xenopus laevis* oocytes or mammalian system the α subunit of KCNQ1 channel can combine with any one of them to form miscellaneous kinds heterotetramer with distinct kinetic characters of channel such as activation, inactivation or deactivation and so on. Accordingly, α subunit of KCNQ1 channel has been checked in lots of tissues in the body and with different physiological characters.

In the full-length human KCNQ1 gene, 16 exons constitute of KCNQ1 with the very GC-rich 5'-end. The translated protein is composed of 676 residues and has six transmembrane domains S1-S6, a pore loop with a typical potassium-channel pore signature sequence (GYGD), and intracellular NH₂ and COOH terminals covering 122 and 322 residues, respectively. To date, with the exception of KCNQ1, there are other four members in the KCNQ family have been detected, such as KCNQ2-5. Comparison with other members of KCNQ family, KCNQ can not assemble a heterotetramer with other members and just forming a homotetramer only with themselves.

As a voltage-gated potassium channel, KCNQ1 was activated by decreasing of depolarization. And similar the other voltage-gated potassium channel, the voltage sensor is located in the S4. However, mutations in the linker of between S4 and S5 still have effect on activation of the KCNQ1 channel. When KCNQ1 channel are fully open at the positive potential followed by a strikingly repolarization produces a hook currents which represent a fraction of KCNQ1 channel inactivation. Because the channel will be open again from the closed state. Researches show that the five transmembrane and the pore part of each subunit have vital roles in the inactivation of KCNQ1 channel.

6.2 Regulation of KCNQ1 channel activation and inactivation

As mentioned above, the KCNQ1 subunit and the ancillary subunit KCNE1 collect together to form the currents of I_{Ks} in cardiac tissues. The KCNE1 subunit has important roles in regulation of kinetical properties of KCNQ1 channel. For example, the currents formed by KCNQ1 subunit alone is activated rapidly whereas ones formed by coexpressed of KCNQ1 and KCNE1 is activated very slowly. In addition, the presence of KCNE1 produce a large increase in the macroscopic KCNQ1 currents, a positive shift of voltage-dependence curves, slowing of the activation and deactivation and almost of absent of inactivation. Some researches have shown that the distinguished increase of the magnitude of currents of KCNQ1/KCNE1 complex is owing to increase the single channel conductance for four to sevenfold and almost eliminate the inactivation the channel by KCNE1 subunit. As for the exact combination of KCNQ1 and KCNE1 subunit, there are distinct views about it. Some results display that KCNE1 lines to the conductance pathway. On the contrary other results show the combination site is out of the conductance pathway. Van Horn proposes a Q1/E1-TMD model, a new model to elucidate the interaction of protein-protein about KCNQ1 and KCNE1 in recent researches. The emphasis of the new model is on the KCNE1 transmembrane domain (also called TMD). It is generally accepted that in closed state the S4-S5 linker interact with the C-end of S6 from another subunit to lock it in the closed configuration. In response to depolarization, the change of conformation of S4 voltage sensor, the S4-S5 linker pull off and deviate from the S6 inducing the channel open. The Q1/E1-TMD model consider that the C-terminal end of KCNE sits on the end of the S4-S5 linker while simultaneously N-terminal end makes extensive (and presumably adhesive)

contacts in the cleft between the voltage sensor and pore domains of the channel. Therefore, during the transition of the channel from closed to open state, the presence of KCNE1 TMD will interfere with the S4-S5 linker deviating from the S6. Uniformly, because of the KCNE1 presence, transition state open to close become very slow and is help for maintenance of the open state of the channel.

Besides the ancillary subunit of KCNE1, there are other members (KCNE2-5) in the family. It is interesting that all ancillary subunits can co-assemble with KCNQ1 channel in different tissue and alter the kinetic characters of KCNQ1 channel. In cardiac tissue, besides of KCNE2, KCNE2 is another important ancillary subunit. KCNE2 (also named Mirp1), originally described as a ancillary of the ether-à-go-go-related gene 1 (ERG1) potassium current, was later found to change the KCNQ1 potassium current though drastically changing the gating properties. Otherwise, in organs such as stomach and intestine, Moreover, the mRNA of KCNE4 and KCNE5 has been detected in the heart. They may be has vital roles in maintaneine of the ordinary function of the heart. However, there is no relative report about it.

6.3 Functions of KCNQ1 channel in heart

Currents of I_{Ks} formed by KCNQ1/KCNE1 have slow activation, whereas I_{Kur} and I_{K1} constituted by ERG1 and Kir2.x, respectively, have rapide activation kinetics. The three repolarizing potassium currents together have been called the repolarization reserve because to some extent they can substitute for each other. However, in the fast heart beat, only I_{Ks} currents are upregulated by phosphorylation and by current accumulation due to slow deactivation. In addition, In heart tissue, distribution of KCNQ1 through the cardiac wall is also inhomogeneous and the expression of KCNQ1 is less in medmyocardium than epi- and endomyocardium.

The cardiac function of KCNQ1 and its accessory subunits is emphasized by the functional impact of numerous mutations in these proteins (<http://www.fsm.it/cardmoc/>). Mutations in KCNQ1 causing loss of function by trafficking defective, assembly defective, or single channel conductance lead to prolonged action potentials and LQTS. A domain located near the COOH terminal (residues 589–620) is responsible for this assembly specificity, and deletion of a part of this domain leads to an impaired assembly of the channel complexes followed by mistrafficking. Mutations in ancillary subunits such as KCNE1 and KCNE1 also cause LQTS4 and LQTS5, respectively.

KCNQ1 mutation (S140G), as a gain of function mutation, is detected in a family with arterial fibrillation inherited as an autosomal dominant way through four generations. The mutation shortens the action potential through increasing the currents of I_{Ks} . Similarly, a gain-of-function mutation in KCNE2 (R27C) increasing the activity of the KCNQ1/KCNE2 channel has also been implicated in atrial fibrillation.

Acquired LQTS is predominantly found when the patients take the blocker of hERG channel as medicine. Because the currents of I_{Kr} are blocked, the repolarization reserve is decreased and the disperation of repolarization is leaded to a further increase due to the inhomogeneous distribution of KCNQ1 in heart wall.

7. Kv4.3

Kv4.3 is formed the rapid activated currents I_{to} (encoded by *KCND3*) which is a voltage-dependent, 4-aminopyridine (4-AP) sensitive, calcium-independent K^+ current (I_{to}). I_{to} have

been detected in human atrial and ventricular myocytes and is responsible for the early rapid depolarization (at phase 1) so determining the height of plateau. Therefore, I_{to} will influence of other ion channel activation such as the L-type calcium channel and the delayed rectifier channel (KCNQ1). Distribution of Kv4.3 is heterogeneous through the cardiac tissue. For example, I_{to} density in atrial tissue, Purkinje fibers, epicardial and midmyocardial (M) cells is higher than in the endocardial cells. The prominent epicardial I_{to} conduce to the depression of epicardial in ischemia and to the progress of a significant dispersion of repolarization between normal and ischemic epicardium, between epicardium and endocardium.

7.1 Regulation of Kv4.3

Kv4.3 can be blocked by many compounds but which bind with the channel either at open state or at close state. It has been raised that blocker of I_{to} prolong the action potential duration in atria or in ischemic ventricular tissues. However, blockage of I_{to} subsequently changes the other potassium channel underlying during repolarization of cardiac action potential. Reduction of I_{to} magnitude can shorten the duration of ventricular action potential. Therefore, it is still unclear that the exact role in control human cardiac action potential.

Channel properties of Kv4.3 is modified by the phosphorylation, mediated by protein kinase A (PKA) and C (PKC) through altering the channel kinetic (activation, inactivation or single channel conductance) and the expression of active channel in the membrane. Decrease in I_{to} by PKC attributed to enhance the inactivation and step down the time of deactivate of the channel Kv4.3. α -adrenergic agonists reduce I_{to} magnitude in rat ventricular myocytes and oppositely the β -adrenergic agonists has no effect on I_{to} currents.

7.2 Functions of Kv4,3 in heart

Heart failure, cardiac hypertrophy and myocardial ischemia and infarction decrease the magnitude of I_{to} resulting in the prolongation of action potential. The degrade in I_{to} in heart failure may be adaptive in the short-term because increased depolarization during the cardiac cycle means that more time is available for excitation-contraction coupling, which moderate the decrease in cardiac output, however it becomes maladaptive in the long-term, because a prolongation of the APD may contribute to arrhythmogenesis, either by causing inhomogeneous repolarization or by increasing the likelihood of early afterdepolarizations. On the contrary, it is proved that up-regulation of I_{to} in cardiac hypertrophy and in cardiac myocytes after induced myocardial infarction. Increase in I_{to} presents as a protector moderating the excessive prolongation of action potential duration and Ca^{2+} inflow to minimize the incidence of ventricular arrhythmia. In addition, the patients with chronic atrial fibrillation decrease the currents of I_{to} and downregulate the mRNA.

8. Kv1.5

I_{kur} currents in human atrium are formed by the α subunit (Kv1.5) and β ancillary subunit (Kv β 1.2). The features of I_{kur} , as outward rectified currents, are activated rapidly in the plateau range and inactivation slowly. Interestingly, currents of I_{kur} just have been detected in human atria rather than cardiac ventricle. Therefore, currents of I_{kur} have vital roles during the atrial repolarization. There is a huge difference of Kv1.5 from other ion cardiac channel. Distribution of Kv1.5 is homogeneous across the atrial wall.

8.1 Regulations of Kv1.5

hKv1.5 can be regulated by both PKA and PKC. One consensus site in Kv1.5 for phosphorylation by PKC is located on the extracellular S4-S5 linker and 4 consensus sites for PKA is located in the N- and C-terminal domains. Isoproterenol and adenylate cyclase both increase the magnitude of $I_{K_{ur}}$ and the increase can be counteracted by PKA inhibitor. Otherwise, propranolol and phenylephrine decrease the amplitude of $I_{K_{ur}}$ moderating by the PKC inhibitor. Accordingly, β -adrenergic stimulation enhances the currents of $I_{K_{ur}}$ by PKA. Oppositely, α -adrenergic stimulation inhibits $I_{K_{ur}}$ currents by PKC. Human thrombin or rat 5-HT_{1c} receptors inhibits the currents of $I_{K_{ur}}$ by increasing phospholipase C (PLC). Moreover, the Src tyrosine kinase inhibits the hKv1.5 by phosphorylation of the N-terminus proline-rich sequences mediated by SH3 domain of the tyrosine kinase.

8.2 Functions of $I_{K_{ur}}$ in heart

$I_{K_{ur}}$ is relatively insensitive to TEA, Ba²⁺ and class III antiarrhythmics of the methanesulfonanilide group. Antiarrhythmia drug is often weak bases that predominant cationic ion at pH7. At the channel open state, the cationic ion can bind with the pore and/or selective filter domain of the channel leading to the blockage of the channel. The binding site for some drugs is existed at the external mouth of the channel pore formed by the P loop and adjacent S5-S6 segments.

Because of the Kv1.5 just located in atria, the channel is a promising target for the development of new safe antiarrhythmic drugs to prevent atrial fibrillation and without a risk of ventricular proarrhythmia. However, In patients in chronic atrial fibrillation, the action potential duration in atria is significantly prolonged due to both blockage of $I_{Ca,L}$ and $I_{K_{ur}}$. Accordingly, it is not expected what will be happened by use of $I_{K_{ur}}$ blocker to treat the patient with chronic AF. In a rat, rapid atrial pacing just immediately and transiently increases the mRNA of Kv1.5 rather than the ones of KCNQ1 and hERG. It shows that Kv4.3 at least in part contribute to the rapid shortening of the atrial refractoriness at the onset of AF. Therefore, the selective blockers of $I_{K_{ur}}$ counteract the shortening of atrial action potential duration at rapid rate state. From mentioned above, application of $I_{K_{ur}}$ selective blocker in clinical is a challenge job in the future.

9. Kir2.1 and Kir3

Inward rectifiers (Kir) is composed of a large family of potassium channel. Among them, only two subfamilies (Kir2 and Kir3) share great structural similarity and underlie classical 'strong inwardly rectifying currents' originally observed in skeletal and cardiac muscle. In cardiac tissue, there are only two similar types of these currents: (1) I_{K1} , as a constitutively active Kir current, is more prominent in ventricular tissue, and (2) $I_{K,ACh}$, as a receptor-activated Kir current, is more prominent in atrial tissue, as well as in SA node and AV node. There are two common features of the kir2 and Kir3. one is a strongly voltage-dependent decline of potassium conductance upon membrane depolarization producing a characteristic region of so-called 'negative slope' conductance. Another unique property of Kir currents is the unusual dependence of rectification on extracellular K⁺. In order to comprehend the two characters of Kir channel, firstly to fully the molecular basis of the channels.

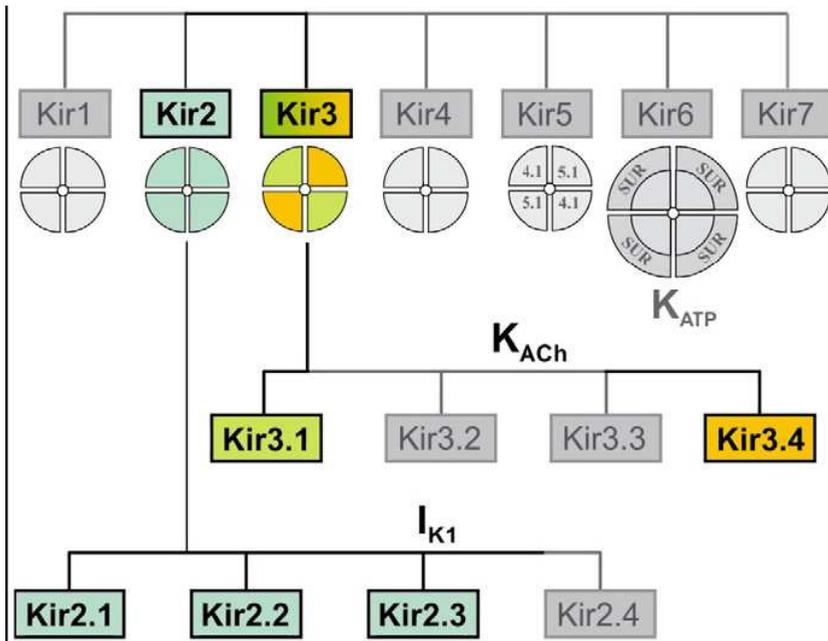


Fig. 4. (cited from Anumonwo et al, 2009). The family of inward rectifier potassium channels. All members of this family share significant structural similarity, but only Kir2 and Kir3 subfamilies represent channels carrying classical strongly rectifying currents.

In human heart, the distribution of I_{K1} and $I_{K_{ACh}}$ has distinct region. I_{K1} is more prominent in the ventricles, including Purkinje myocytes. $I_{K_{ACh}}$ has generally an opposite distribution to that of I_{K1} . It is more prominent in the atria than in ventricles. Similarity, the current density of I_{K1} and $I_{K_{ACh}}$ may vary across the ventricular or atrial tissues, distinctively. About the subunit composition of $I_{K_{ACh}}$, under normal conditions native $I_{K_{ACh}}$ channels are heteromers of Kir3.1/ Kir3.4 subunits. However, recent data suggest that Kir3.4 subunit alone has similar function with the native $I_{K_{ACh}}$. Comparison with $I_{K_{ACh}}$, I_{K1} is formed by coassembly of the Kir2.1.x subfamily of proteins (Kir 2.1, 2.2, and 2.3) with Kir2.1 the most abundant subtype in ventricular tissue.

9.1 Functions of Kir2 and Kir3 in heart

To date, I_{K1} , formed by coassembly of the Kir2.1.x subfamily of proteins (Kir 2.1, 2.2, and 2.3) in cardiac tissue, is the major component of inward rectifier potassium current and has a vital role in determinant of the resting membrane potential and conduces to the terminal phase of repolarization (phase 3). Loss of function of Kir2 channel $\geq 90\%$, the heart of transgene (TG) mice led to prolongation of QRS and QT intervals as well as expected prolongation of action potential. Surprisingly, resting membrane potential in TG ventricular myocytes was nearly unaffected. It is unexpectedly that upregulation of I_{K1} in TG mice expressing Kir2.1 subunits, gain of function, cause to multiple abnormalities of cardiac excitability contained significant AP shortening and various types of atrial and ventricular arrhythmias.

In heart, another contribution of I_{K1} to excitability is through an unusual and strong dependence on extracellular K^+ . During repetitive firing, cardiac activity is followed by markedly changes in the concentration of K^+ in the restricted (0.01–5 μM) intercellular space, even more accumulation in the t-tubules. Increase of extracellular K^+ should be accompanied by the increase of I_{K1} conductance with results on electrical activity, e.g., AP duration and propagation

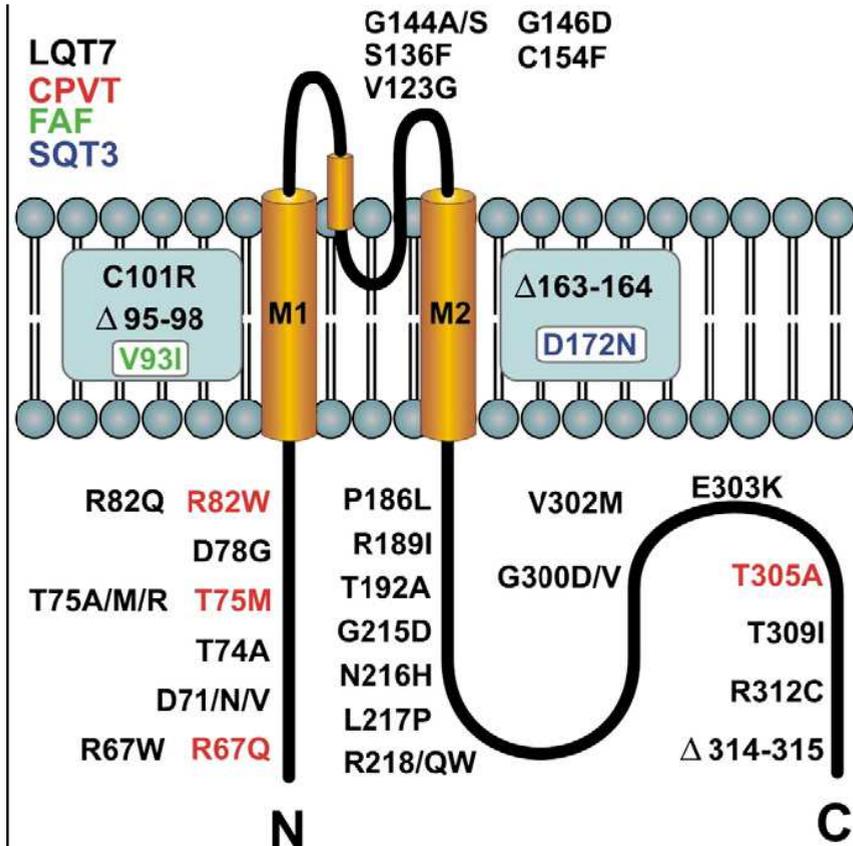


Fig. 5. (cited from Anumonwo et al, 2009). Mutations on Kir2.1 protein associated with channelopathies of the classical inward rectifier channel. Mutant residues are color coded to represent the long QT7 (LQT7; black), catecholaminergic polymorphic ventricular tachycardia (CPVT; red), familial atrial fibrillation (FAF; green), and short QT3 (SQT3; blue).

To date, four channelopathies related with inward rectifier currents have been detected, all due to loss of function or gain of function of I_{K1} currents (encoded by *KCNJ2*), LQT7, catecholaminergic polymorphic ventricular tachycardia (CPVT), familial atrial fibrillation (FAF), and short QT3. LQT7 at early is also called Andersen syndrome (AS) or Andersen-Tawil syndrome (ATS). Symptoms of the disease are characterized by a triad of clinical phenotypes affecting morphogenesis as well as the functioning of skeletal and cardiac

muscles. ATS patients are often accompanied by features that include scoliosis, cleft palate, and short stature and display skeletal muscle weakness. Besides that, cardiac electrical abnormalities include prolongation of the QT interval, short runs of ventricular tachycardia, ventricular bigeminy and multi-focal ventricular ectopy mediated by adrenergic stimulation. However, recent works suggest that classification of ATS into LQTS is incorrect because of the former largely related to the abnormalities of the T-U complex. Because more than half of ATS is the mutations in KCNJ2 the term AST1 is referred to the disease of $I_{K_{ir2}}$. To date, more than 33 mutation in KCNJ2 is related to AST1 and the mutations have been identified as the autosomal-dominant. Some of mutations, such as D71V in AST1 patients, can decrease by ~94% of the magnitude of wild type currents $I_{K_{ir2}}$. Several of ATS1 mutations, such as R21Q/W mutations, result in a loss-of function in the $K_{ir2.1}$ channels due to reduced interaction with membrane PIP_2 .

Short QT syndrome (SQTS) is characterized by the shorten of QT interval on ECG. SQTS is an inherited abnormality that predisposes afflicted individuals to a high risk of having fibrillation (atrial/ventricular) and sudden death. Three forms of SQTS have been identified and SQTS3 is caused by the gain of function of mutations in inward rectifier channel gene, KCNJ2. SQTS3, characterized by electrocardiographic phenotype with asymmetrical T waves, is distinguished with other two kinds of SQTS. The molecular basis of SQTS3 is the mutation D172N at a position critical for inward rectification of $K_{ir2.1}$ channel. Heterologous coexpression of wild type and mutant $K_{ir2.1}$ subunits showed increased outward currents in mutant channels which account for the tall, asymmetrical T waves on the ECG of LQTS3 patients. Researches by computer simulations suggest that mutations in SQT3 might predispose patients to a higher risk of reentrant arrhythmias.

Mutation of V93I in $K_{ir2.1}$ is associated with familial atrial fibrillation, thereby implicating I_{K1} in this disease. In addition, the mutant channels have larger outward currents by whole-cell patch-clamp studies, however the underlying mechanism(s) responsible for the increase remains unknown.

In a recent study, three novel (R67Q, R85W, and T305A) mutations belonged to CPVT3 and one previously described (T75M) mutations in KCNJ2 are identified. ECG analysis reveals prominent U-waves, ventricular ectopy, and polymorphic ventricular tachycardia. It is interestingly that there were no dysmorphic features or skeletal muscle abnormalities in the patients. Whole-cell patch-clamp experiments revealed that mutant channels had significantly reduced by $\geq 95\%$ amplitude of wild type outward current and that T75M and R67Q mutations had dominant negative effects when co-expressed with wild type channels. Importantly, the study showed that the T305A mutation selectively affected channel rectification properties.

Cardiac strong inward rectifier potassium channels continue to surprise researchers with their novel roles in cardiac excitability, complex structure, function, and regulation. While significant progress has been made in recent years, clearly, many questions still remain to be answered and we certainly will soon witness new, and likely unexpected, discoveries in this field.

10. $K_{ir6.2}$

ATP-sensitive potassium (K_{ATP}) channels (encoded by KCNJ11) are evolutionarily conserved and are first discovered in the cardiac sarcolemma where they are expressed in high density.

$I_{K_{ATP}}$ is formed by the complex protein composed by the pore-forming subunit and the regulatory sulfonyleurea receptor which is an ATPase-harboring ATP-binding cassette protein. To date, members of the inwardly rectifying K^+ channel family (Kir6.1 and Kir6.2) and the sulfonyleurea receptor isoforms (SUR1, SUR2A and SUR2B) have been identified. In cardiac tissue, K_{ATP} channel is a hetero-octameric complex composed of four pairs of these two distinct subunits Kir6.2 and SUR2A. The structure of K_{ATP} channel is very similar to Kir3 and Kir2. Therefore, there is no redundant description in this part.

10.1 Functions of K_{ATP} channels in heart

K_{ATP} channels, as a cardio-protective role, were recognized early in ischemia heart. The channel can mediate shortening of the cardiac action potential by increase of the $I_{K_{ATP}}$ currents then control calcium influx into the cytosol. Moreover, when the heart expose to a brief periods of ischemia causing a sustained ischemic insult K_{ATP} channel activity can depress significantly the injury produced by ischemia such as infarct size, coined ischemic preconditioning. Therefore, in ischemia heart, K_{ATP} channel can degrade markedly heart injure caused by ischemia.

Another important function of K_{ATP} channel is during the process of stress without distress in heart. The concept of "stress without distress" is referred to describe the ability of an organism to confront and/or escape imposed threat. The concept is very likewise to the "flight-or-fight" response, through the general adaptation syndrome. For example, acute exercise-stress causes a systemic sympathetic stimulation that raises cardiac contractility, heart rate and thereby provides the necessary higher cardiac output. How huge change of the heart excitability has happened after acute exercise. Many researches suggest that stress without distress is dependent in the K_{ATP} channel in heart. The change of this enhanced cardiac output imposes a significant metabolic in large part of the heart due to the highly energy consuming calcium handling machinery. A compensatory increase in outward potassium current formed by K_{ATP} channel is normally activated to offset the resulting calcium influx in order to reducing energy-demanding myocardial calcium overload.

K_{ATP} channel also has important roles in heart failure. Heart failure has no effect on the intrinsic biophysical properties of the cardiac K_{ATP} channel whereas the structural remodeling disrupts communication of energetic signal and channel. Then the disruption leads to interfere markedly the metabolic regulation of the channel at last. Accordingly, metabolic dysregulation of K_{ATP} channels created by the disease-induced structural remodeling appears to contribute to the dysfunction of heart failure.

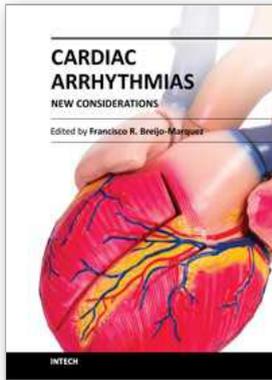
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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographic features, ion channel alterations, heart diseases still unknown, and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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