We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



3

The Cardiac Ion Channels

Thomas Jespersen
Danish Arrhythmia Research Centre
Department of Biomedical Sciences
University of Copenhagen
Denmark

1. Introduction

Action potentials are mediated by transient changes in ion conductance across the cell surface membrane. These changes in conductance are primarily mediated by ion channels. Ion channels are membrane-embedded proteins that selectively pass specific ions upon opening. Some ion channels are constitutively open; however, most channels open following stimulation, such as through voltage changes, intracellular messengers, neurotransmitters, or shear stress. In the heart, voltage gated ion channels, conducting sodium, calcium and potassium ions, are primarily important in generating and shaping the action potential as well as exchangers and pumps that contribute to ion fluxes.

The most prominent features of the cardiac action potential is the synchronised depolarisation of all the cardiomyocytes and the very long lasting depolarisation period, which in humans lasts 200-450 ms, depending on the beating frequency. The electrical impulse is generated in the pacemaker cells in the sinoatrial node located at the junction of the superior vena cava and right atrium. The electrical signal spreads to the right and left atria, thereby initiating muscular contraction and resulting in additional filling of the ventricles. When the depolarisation reaches the atrioventricular node, conduction is slowed before the depolarisation progresses to the ventricular cardiomyocytes. The electrical impulse is spread to the ventricles through a specialised conduction system formed by the His bundle branches and the Purkinje fibres, resulting in the depolarisation of the ventricular cardiomyocytes within a relatively short time span. The very long cardiac action potential mediates a long lasting increase in cytosolic calcium and, thereby, a long lasting contraction. Furthermore, the long action potential duration makes the myocardium refractory, whereby under normal physiological conditions no new action potentials will disturb the ongoing contraction. After the depolarisation phase and the plateau phase, the myocardium repolarises such that the contraction cesses and the ventricular chambers can be refilled. Disturbances in this highly fine-tuned electrical-contraction pattern - termed arrhythmia - can be detrimental since unorganised electrical impulse propagation in the musculature will lead to uncoordinated muscle contraction and therefore a loss of pumping function (Jespersen, 2011).

The cardiac action potential is the summarised output of several different types of ion channels. The functional significance of the different ion channels depends on both the subcardial location and the biophysical configuration of the channels, as well as the

physiological demands to be fulfilled. This is illustrated by the fact that the action potential morphology differs whether it is recorded in nodal tissue, in atria or else in either the subendocardial or subepicardial myocytes in the ventricle.

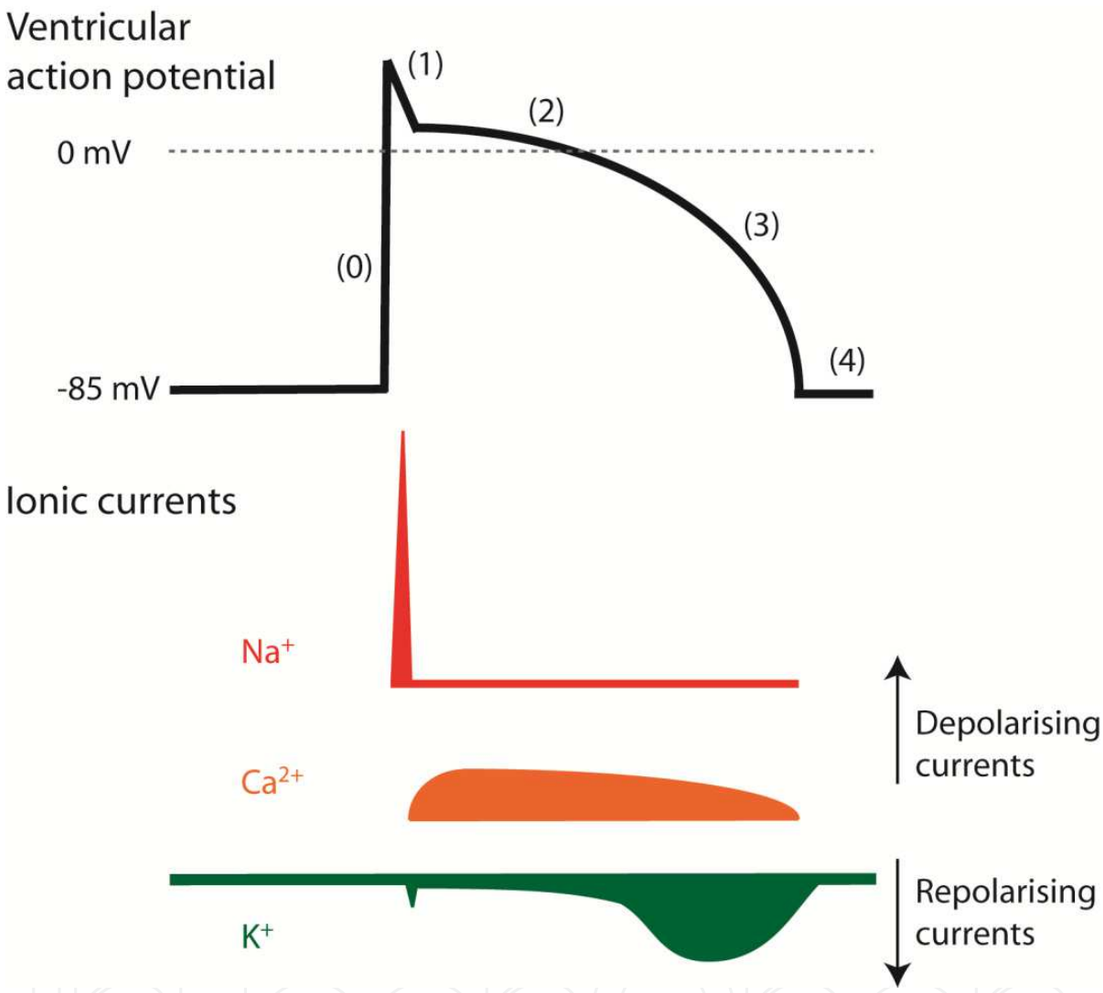


Fig. 1. Ionic currents shape the cardiac action potential. Illustration of a ventricular action potential and the underlying currents.

Ion channels consist of a central protein, named the α-subunit, where ions pass through a pore. Cardiac sodium and calcium channel α-subunits are composed of a single protein constituting a functional channel, while the potassium channels are tetrameric complexes of either homomeric or heteromeric composition. The pore contains a selectivity filter which ensures, for most channels, a high selectivity of one ion over the others (Hille, 2001). The opening, closing and inactivation of the channels are managed in a number of different ways. The voltage-gated channels contain a voltage sensor - primarily located in transmembrane segment 4 - which detects voltage changes, thereby initiating a conformational change in the protein leading to the opening and closing of the channel (Gouaux & Mackinnon, 2005). The inactivation of channel conductance - which is important

for the physiological functions of a number of the cardiac channels - can be induced either by fast intramolecular changes or by slower extramolecular regulation, such as through the binding of calcium ions to calmodulin, which interacts with the channel. A number of different classes of proteins interact with the cardiac ion channels. Closely associated proteins which are believed to be specific to the ion channels are termed β-subunits. β-subunits can regulate both surface expression and opening and inactivation kinetics (Isom *et al.*, 1992). Many of these β-subunits have been suggested as being promiscuous since they can interact with several different α-subunits (Panaghie & Abbott, 2006). In addition to the β-subunits, a growing number of regulatory and scaffolding proteins have been found to interact with the different cardiac ion channel complexes.

This chapter will provide an overview of the major cardiac currents, the protein complexes constituting the ion channels and the regulatory mechanisms of these channels which are of crucial importance for controlling the progression, synchronisation and rhythmicity of the cardiac action potentials.

1.1 Impulse generation

The sinoatrial node, the atrioventricular node and the purkinje fibres all show spontaneous beating activity, but because the sinoatrial node normally has the highest frequency this is considered the primary pacemaker of the heart. The automaticity of the sinoatrial node is thus the basis for the rhythm and rate of the heart. The nodal action potential is initiated by a slow increase in depolarisation - driven by a sodium influx - followed by a faster depolarisation due to a calcium influx and terminated by a potassium ion efflux (reviewed by Mangoni & Nargeot, 2008a).

One of the important ion currents participating in generating the spontaneous impulse is the hyperpolarisation activated current I_f (f for 'funny'), which is conducted through the hyperpolarisation-activated cyclic nucleotide-gated channels (HCN) of which four members are known (HCN1-4). HCN4 is the primary expressed pacemaker channel, but HCN1 and HCN2 are also present in the sinoatrial node (Marionneau *et al.*, 2005; Moosmang *et al.*, 1999; Moroni *et al.*, 2001; Shi *et al.*, 1999; Sizarov *et al.*, 2011). HCN channels are permeable to both sodium and potassium (Xue *et al.*, 2002). However, as the channels deactivate at depolarising potentials, the predominant conductance is an inward sodium current. These channels are activated by cyclic nucleotides and hyperpolarisation potentials negative to ~-55 mV (Gauss *et al.*, 1998; Ludwig *et al.*, 1998; Santoro *et al.*, 1998). The one transmembrane spanning β-subunit, KCNE2 (MiRP1), has been reported to increase the surface expression and accelerate the kinetics of the HCN channels and has, therefore, been proposed as playing a role in generating the pacemaker signal (Macri *et al.*, 2002; Qu *et al.*, 2004; Yu *et al.*, 2001).

In the sinoatrial and atrioventricular nodes, the activation of the HCN channels leads to a gradual depolarisation. This depolarisation is counteracted by an acetylcholine-activated potassium current ($I_{K,Ach}$) conducted through the G-protein coupled inward rectifier (GIRK) (Noma & Trautwein, 1978). The cardiac $I_{K,Ach}$ channels are heteromeric complexes consisting of Kir3.1 (GIRK1) and Kir3.4 (GIRK4) subunits (Wickman *et al.*, 1999). The Kir3 channels are activated by various heptahelical receptors coupled to G proteins of the pertussis toxin class (G_i/G_o). Upon receptor activation, the heterotrimeric G protein complex is dissociated in its α and ßγ subunits, where the latter interacts with Kir3 subunits inducing an increased open probability of the channel complex (Logothetis *et al.*, 1987). The activation of cardiac GIRK

channels by acetylcholine, adenosine and ATP mediates a negative chronotropic effect (Friel & Bean, 1990; Kurachi *et al.*, 1986a; Kurachi *et al.*, 1986b; Medina *et al.*, 2000; Ravens & Dobrev, 2003). Vagal stimulation activates cardiac muscarinic M2 receptors whereby $I_{K,Ach}$ increases. This results in a slowing of the depolarising phase of the sinoatrial action potential and thereby provides a reduced action potential frequency. In contrast, the sympathetic stimulation of β-adrenergic receptors in the sinoatrial node mediates a positive chronotropic effect by increasing the cAMP levels, which reduces the GIRK-mediated current and - at the same time - increases the activity of the HCN and Ca^{2+} channels (see below), whereby the diastolic depolarisation phase is shortened and the spike frequency is increased (Baruscotti *et al.*, 2005; Bucchi *et al.*, 2003; DiFrancesco & Tromba, 1988; DiFrancesco, 1993; Noma *et al.*, 1980; Zaza *et al.*, 1996). Although HCN and GIRK channel regulation is considered central to setting the firing frequency of the sinoatrial node, other ion channels, including the ryanodine receptors (calcium-activated calcium channels located in the sarcoplasmic reticulum), I_{ST} channels with unknown molecular correlates and voltage-gated sodium channels (probably of the neuronal type) have also been found to play a role (Lakatta & DiFrancesco, 2009; Mangoni & Nargeot, 2008b).

The increasing depolarisation triggers the activation of T-type and L-type calcium channels (Fermini & Nathan, 1991; Hagiwara *et al.*, 1988; Vuill & Hancox, 2002), whereby an action potential is generated. The repolarisation of the nodal cells is controlled by voltage-gated potassium channels. Both the rapid and slow inward rectifying current (I_{Kr} and I_{Ks}) as well as the transient outward current (I_{To}) are present, but further investigation is necessary to establish the relative and spatial importance of these currents (Mangoni & Nargeot, 2008b). As both the calcium and potassium currents play prominent roles in shaping the atrial and ventricular action potentials, they will be described below.

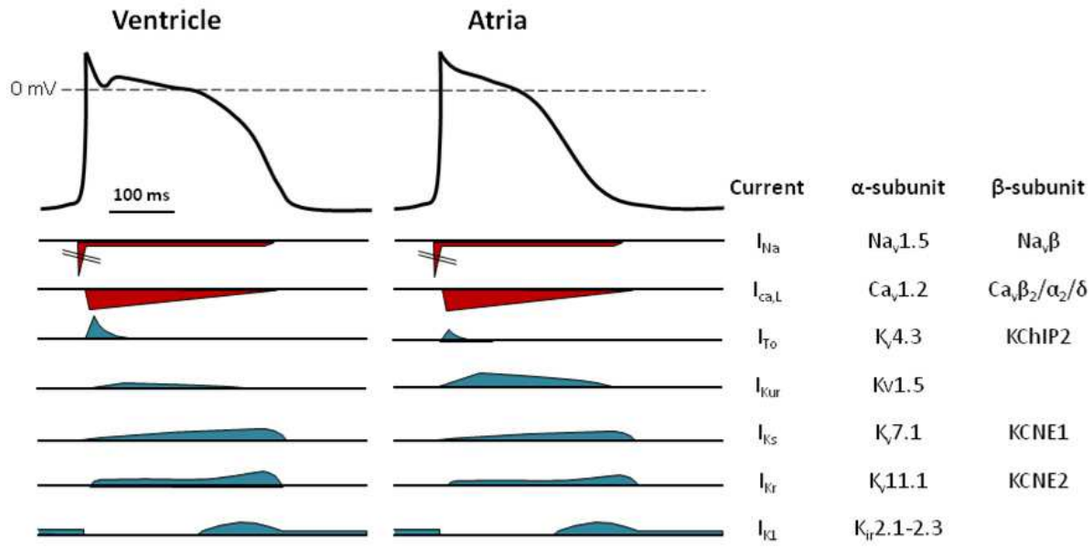


Fig. 2. The major ion channels responsible for the ventricular and atrial action potentials.
An illustration of the different depolarising (red) and repolarising (blue) currents underlying the action potential in the ventricle and the atria. The current names, together with the major proteins constituting the channels conducting these currents, are listed to the right.

1.2 The atrial and ventricular action potentials

The majority of the ion channels responsible for determining the action potential in atrial and ventricular myocytes are the same (Nerbonne & Kass, 2005). However, the relative expression level and means of being regulated differ for several of them (Gaborit *et al.*, 2007). The action potential can be divided into 5 phases (Fig. 1). Propagation and the rapid depolarisation (phase 0) of the cardiac action potential is mediated by a voltage-gated sodium current. $Na_v1.5$ is the predominant α-subunit responsible for conducting the sodium current, but recently several reports have suggested other channels within the same voltage-gated sodium channel family to be important. The fast activation of the sodium channels drives the membrane potential towards the equilibrium potential of sodium - which is quite positive - depolarising the membrane. Partial repolarisation (phase 1), after a few milliseconds, happens due to inactivation of the sodium channels together with the somewhat slower activation of L-type calcium channels (Striessnig, 1999). The depolarising sodium and calcium currents are countered by a repolarising potassium flux. In the ventricular subepicardium, the transient outward potassium current (I_{To}) - conducted through a multimeric complex with Kv4.x α-subunits - induces a notch in the beginning of the plateau phase (phase 2). In the atria, the ultra-rapid potassium current (I_{Kur}) - conducted through the Kv1.5 channels, potentially together with I_{To} - induces a partial repolarisation early in the action potential. The L-type calcium channels undergo a slow calcium and voltage-dependent inactivation and, at the same time, an increase in the rapid and slow delayed rectifier potassium currents, I_{Kr} and I_{Ks}, respectively, is observed. This moves the action potential into phase 3. The inward rectifier current I_{K1} participates in the latter part of phase 3, together with I_{Kr} and I_{Ks}, in driving the membrane potential towards the equilibrium potential of potassium and thereby terminating the action potential. I_{Kr} is conducted through human the ether-a-go-go-related gene channel 1 (hERG1, also called Kv11.1), while I_{Ks} is conducted through the Kv7.1/KCNE1 channels and I_{K1} through the Kir2.x channels. Together with the sodium potassium exchanger 1 (NCX1), I_{K1} is the current that is primarily responsible for setting the resting membrane potential (phase 4). Several other ion channels, including the K_{ATP} channels, the T-type calcium channels, the GIRK channels and the small conductance potassium channels, have been reported to be present in atrial and ventricular myocytes, but a thorough review these channels is beyond the scope of this chapter .

2. Sodium channels

The primary determinant in depolarising the surface membrane in the atrial and ventricular myocytes is the sodium current. the activation of the sodium channels leads to a very fast depolarisation of the myocytes, changing the membrane potential from approximately –85 mV to approximately +25 mV within 10^{th} of milliseconds (Petitprez *et al.*, 2008) (phase 0, Fig. 1). The sodium channels inactivate equally fast and only a small fraction of the channels are open during what remains of the action potential (Fig. 3).

2.1 $Na_v1.5$ voltage-gated sodium channels

The voltage-gated sodium channel $Na_v1.5$ is the primary component in generating the cardiac sodium current. This is proved by the fact that several cardiac syndromes, including long QT syndrome and Brugada Syndrome, have been linked to mutations in SCN5A, which is the

gene encoding $Na_v1.5$ (Jespersen, 2011; Tfelt-Hansen *et al.*, 2009). The $Na_v1.5$ protein is a relatively large glycosylated membrane protein consisting of 2015 or 2016 residues (depending on the splice variant) with a molecular weight of ~220 kilo Dalton (Makielski *et al.*, 2003). The $Na_v1.5$ protein comprises 4 homologue domains (I to IV), each consisting of 6 transmembrane segments (TM1 to TM6) forming a functional channel (Fig. 3). The channel can be found in three confirmations: closed, open and inactivated. Around the resting membrane potential, the majority of channels are in the closed state. When a depolarising pulse reaches the $Na_v1.5$ channels - which are embedded in the cardiomyocyte plasma membrane - the channels undergo a very fast transition, rendering the channels open.

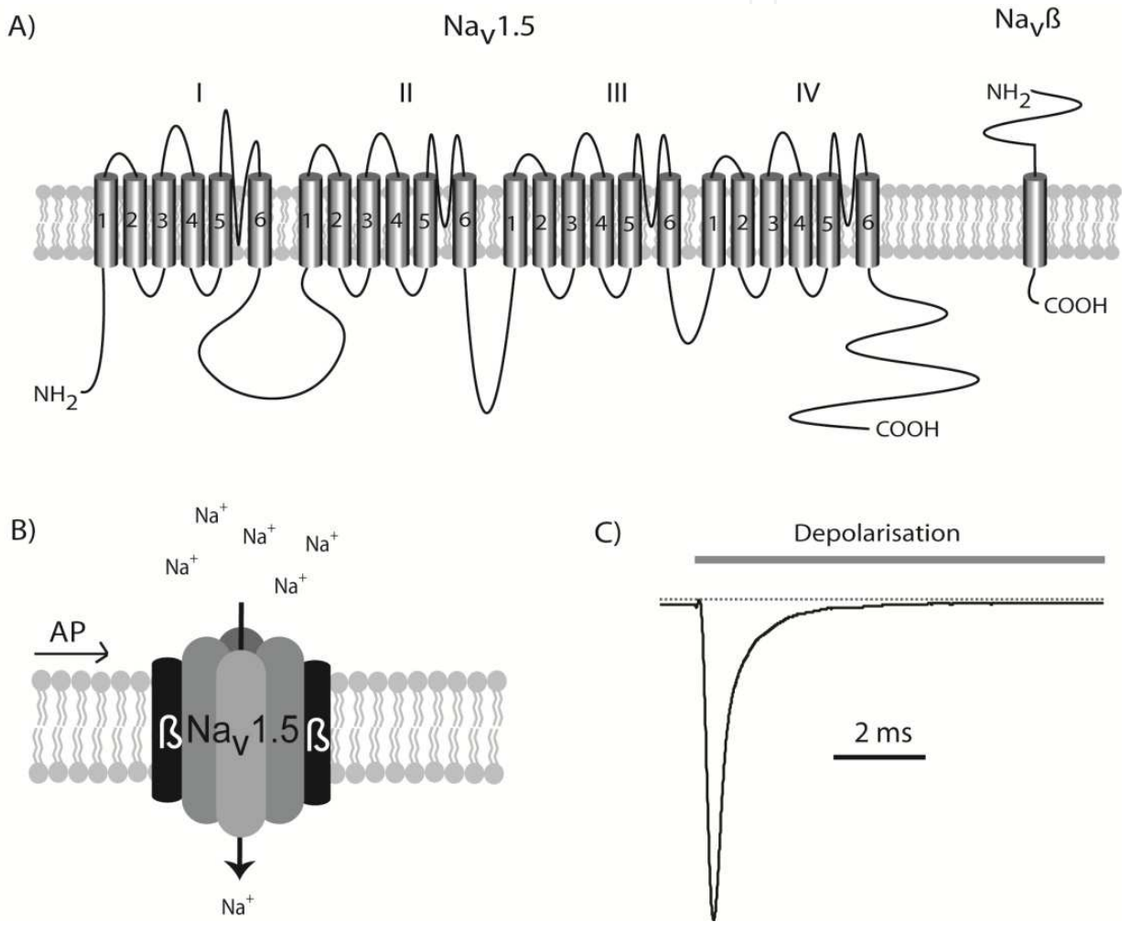


Fig. 3. The cardiac $Na_v1.5$ sodium channel. A) The SCN5A gene is transcribed into the large $Na_v1.5$ protein containing 24 transmembrane domains. B) This protein can fold up into a functional channel, but it is believed to be modulated by the Navβ one-transmembrane spanning β-subunits *in vivo*. When an action potential (AP) induces a depolarisation of the membrane, $Na_v1.5$ is activated and a transient influx of sodium begins. C) Illustration of the current conducted through $Na_v1.5$ channels following a depolarising pulse. The channels will activate very quickly, but as soon as the action potential has commenced a fast inactivation is also initiated. After approximately 10 milliseconds, only a small fraction of the channels will be open.

This opening is, however, only transient as the inactivation of the channels is also a fast process, beginning immediately after depolarisation and making almost all of the channel complexes non-conducting after a few milliseconds. Although the vast majority of sodium conductance is within the first few milliseconds of the action potential sustained - or late - the inward sodium current is also observed. This sustained current, which is in the range of 5 ‰ of the peak current, participates in determining the action potential duration, which is illustrated in long QT syndrome 3 patients who have mutations in *SCN5A* resulting in an increased sustained sodium current (~1-3 % of peak current) (Bennett *et al.*, 1995). In cardiomyocytes with an increased sustained sodium current, the depolarising power of this current will lead to a longer depolarisation time and as the QT interval reflects the ventricular action potential duration, a prolonged QT interval is observed. This sodium ion selectivity is due to peptide sequences located in the pore between TM5 and TM6, while TM4 is involved in the activation of the channel. Furthermore, an intracellular sequence between domain 3 and 4 is important for the inactivation (West *et al.*, 1992).

2.2 Na_vβ1-β4 subunits interact with Na_v1.5

Four sodium channel β-subunits, Na_vβ1-β4, are encoded by *SCN1-4B* and have been identified (Meadows & Isom, 2005). *SCN1-4B* all comprise large extracellular immunoglobulin-like domains, a single transmembrane spanning segment and intracellular C-terminal domains. The β-subunits have been found implicated in sodium channel expression at the cell surface, the modulation of channel gating and the voltage dependency of the sodium current. All *SCNB* transcripts are present in the heart, but thorough investigations of protein expression have not been performed (Gaborit *et al.*, 2007; Olesen *et al.*, 2011). *In vivo* investigations of the cardiac role of Na_vβs are restricted to knock-out mice, and the reported *in vitro* effects inflicted by these β-subunits often depend on the cellular expression system applied; further studies in native settings are needed. However, the fact that mutations in the genes underlying the β-subunits have been linked to a number of arrhythmic disorders (reviewed in detail by Abriel, 2010) underlines the importance of these proteins in the heart.

SCN1B is spliced into two variants, β1 (Isom *et al.*, 1992) and β1A in rats (Kazen-Gillespie *et al.*, 2000), and β1B in humans (Qin *et al.*, 2003). While the rat and human β1 proteins have a high degree of similarity, the alternatively spliced part of rβ1A and hβ1B only shows a 33% sequence homology. In heterologous expression systems, the two most consistent findings with Navβ1 co-expressed with Na_v1.5 are a positive voltage shift in the steady-state inactivation and an increase in peak current (Dhar *et al.*, 2001; Herfst *et al.*, 2003; Qu *et al.*, 1995). *SCN1B* mutations have been associated with atrial fibrillation and Brugada syndrome, both of which can be caused by a reduced sodium conductance, indicating that the *in vitro* observations can - at least to some extent - be translated into a functional myocyte context (Watanabe *et al.*, 2008; Watanabe *et al.*, 2009).

In most studies, the expression of Na_vβ2 in various cell systems does not promote changes in the electrophysiological properties of Na_v1.5, but it has been suggested that Na_vβ2 is involved in linking sialic acids to Na_v1.5, which alters the activation properties (Johnson & Bennett, 2006). *SCN2B* mutations have been found in patients with atrial fibrillation (Watanabe *et al.*, 2009). The Na_vβ3 subunit is reported to modify a number of biophysical properties - depending on expression system - including both activation and inactivation voltage dependence, as well as reducing the sustained current of Na_v1.5 (Fahmi *et al.*, 2001; Ko *et al.*, 2005). *SCN3B* knock-down mice show a reduced sodium current and a negative

voltage shift in steady-state inactivation, indicating that this subunit augments sodium conductance in the heart. The observations are supported by the fact that mutations in *SCN3B* have been associated with both Brugada Syndrome and atrial fibrillation (Hu *et al.*, 2009; Olesen *et al.*, 2011).

The studies performed with heterologous expression systems and transgenic mice have so far been inconclusive in determining the role of $Na_v\beta4$ in the heart. However, *SCN4B* mutations have been linked to both long QT syndrome and sudden infant death syndrome, as *in vitro* electrophysiological investigations revealed an increased sustained current of $Na_v1.5$ when these $Na_v\beta4$ mutant proteins were co-expressed (Medeiros-Domingo *et al.*, 2007; Tan *et al.*, 2010).

2.3 Phosphorylation of $Na_v1.5$

Phosphorylation is a well-known regulatory mechanism of ion channels, often resulting in altered biophysical properties. Protein kinase C (PKC) activation provokes a drastic reduction in $Na_v1.5$ current amplitude as well as a negative shift in steady-state inactivation (Qu *et al.*, 1994). This effect is believed to be primarily mediated through the phosphorylation of serine residue 1503 (Murray *et al.*, 1997; Qu *et al.*, 1996). The function of glycerol 3-phosphate dehydrogenase 1-like (GPD1L) has recently been linked to the PKC phosphorylation of $Na_v1.5$ (Valdivia *et al.*, 2009). GPD1L catalyses the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate. Glycerol-3-phosphate stimulates - through several intermediate proteins - PKC and thereby feeds the PKC-mediated phosphorylation of $Na_v1.5$. Mutations in GPD1L have been associated to Brugada (London *et al.*, 2007; Weiss *et al.*, 2002) and sudden infant death syndromes (Van Norstrand *et al.*, 2007), and Valdivia and colleagues have shown this to be related to the decreased activity of GPD1L, inducing higher PKC activity and a reduced sodium current (Valdivia *et al.*, 2009).

The tyrosine phosphorylation of $Na_v1.5$ has also been found to promote changes in the channel kinetics. The cardiac-expressed protein kinase Fyn induces a depolarising shift in steady-state inactivation (Ahern *et al.*, 2005). By mutating tyrosine residue 1495, located in the linker between domains 3 and 4 and in close proximity to residues involved in inactivation (Patton *et al.*, 1992), the authors found the effect of Fyn to be abolished. In contrast, the expression of the protein tyrosine phosphatase PTPH1 - which is also expressed in the heart - induced a hyperpolarisation shift in steady-state inactivation (Jespersen *et al.*, 2006). PTPH1 interacts with the 14-3-3β regulatory protein suggest that 14-3-3β functions as a regulator or adapter protein of the phosphatase (Zhang *et al.*, 1997). Another member of the 14-3-3 family, namely 14-3-3η, has been found to interact with the Nav1.5 cytoplasmic I inter-domain, modifying the biophysical properties of the channel (Allouis *et al.*, 2006). Whether or not this interaction modulates the level of $Na_v1.5$ phosphorylation is unknown.

2.4 Plasma membrane stability of $Na_v1.5$

$Na_v1.5$ holds a C-terminal PDZ domain-binding motif. This domain binds syntrophin, which again interacts with dystrophin (Gavillet *et al.*, 2006). The most prominent role of dystrophin is to provide a structural link between the cytoskeleton and the extracellular matrix in order to maintain muscle integrity. However, experiments performed by Abriel and co-workers on dystrophin-deficient mdx mice indicated the cardiac sodium channel to be regulated through a syntrophin/dystrophin complex (Gavillet *et al.*, 2006). A significant reduction in $Na_v1.5$ protein and current levels - together with ECG alterations - was found when the hearts from these mdx mice were analysed. The functional importance of this

interaction has been confirmed in humans, where mutations in α1-syntrophin have been associated with long QT syndrome and sudden infant death syndrome (Cheng *et al.*, 2009; Ueda *et al.*, 2008; Wu *et al.*, 2008).

For an increasing number of ion channels, Nedd4/Nedd4-like ubiquitin-protein ligase mediated internalisation has been found to be important (review by Abriel & Staub, 2005). This class of protein ligases - counting 9 members - interacts with membrane proteins holding a PY-motif (Staub *et al.*, 1996). Ubiquitin is a 76 amino acid protein which can be covalently linked to lysine residues on target proteins, marking them for internalisation, followed by either degradation or intracellular storage (Hershko & Ciechanover, 1998; Hicke, 1999). $Na_v1.5$ is regulated by Nedd4/Nedd4-like mediated ubiquitylation (Rougier *et al.*, 2005; van Bemmelen *et al.*, 2004). *In vitro* electrophysiological experiments revealed that a down-regulation in current density - without altering the biophysical properties - to be was induced by Nedd4-2 through a PY-motif located in the C-terminal tail of $Na_v1.5$. Nedd4-2 induces an increase in the ubiquitylation of $Na_v1.5$, which leads to a drastic redistribution, where Nav1.5 proteins are almost absent from the surface membrane but are instead found in intracellular compartments.

2.5 Other sodium channels in the heart

Although $Na_v1.5$ is the most important sodium channel in the heart, other voltage-gated sodium channels may also play a role in generating the cardiac I_{Na}. Neuronal sodium channels do, in contrast to $Na_v1.5$, have a very high sensitivity to tetrodotoxin. This has been used to investigate the potential function of neuronal voltage-gated sodium channels in the heart. Although present at a relatively low mRNA level (Gaborit *et al.*, 2007) neuronal sodium channels have been suggested to play a role in electrical-chemical coupling, as low tetrodotoxin concentrations lead to a reduction in sercoplasmic reticulum calcium release (Torres *et al.*, 2010) and thereby reduce left ventricular functioning (Maier *et al.*, 2002). Brette & Orchad found that TTX-sensitive I_{Na} makes up approximately 15% of the total I_{Na} in isolated rat ventricular cells, which decreased the rate of the depolarisation of the action potential by 10% (Brette & Orchard, 2006). Further, the sodium current in Purkinje fibres has been shown to be sensitive to low concentrations of tetrodotoxin (Carmeliet, 1987), indicating that the neuronal sodium channels participate in the propagation of the cardiac action potential.

Recently, genome-wide association studies have revealed that *SCN10A* - encoding the $Na_v1.8$ sodium channel - seems to participate in determining the conduction velocity in both atria (PR interval) and the ventricles (QRS duration) (Chambers *et al.*, 2010; Holm *et al.*, 2010; Pfeufer *et al.*, 2010). $Na_v1.8$ has a low sensitivity to tetrodotoxin, as with $Na_v1.5$, and it can therefore be speculated that this channel has been overlooked up until now.

3. L-type calcium channels

The fast depolarisation (phase 0) driven by the influx of sodium through the voltage-gated sodium channels triggers the activation of voltage-gated calcium channels. Both voltage-gated T-type and L-type calcium channels have been reported to be expressed in the heart. The T-type channels are low voltage-activated transient Ca^{2+} channels which are functionally expressed during development, while they are drastically down-regulated in adult myocytes (Ono & Iijima, 2010). However, these T-type calcium channels may still play a role in impulse generation in the sinoatrial node (Hagiwara *et al.*, 1988). The long lasting,

high voltage-activated L-type Ca^{2+} channels are both abundant and ubiquitously expressed in the heart (Bodi *et al.*, 2005). These voltage-dependent calcium channels (VDCC) bind dihydropyridine and have, therefore, also been named dihydropyridine receptors (Taira *et al.*, 1987; Tanabe *et al.*, 1987). The L-type Ca^{2+} channels are the primary source of extracellular calcium influx. The opening of L-type Ca^{2+} channels is delayed when compared with Na^{+} channels and in contrast to the voltage-gated sodium channels, the L-type Ca^{2+} channels inactivate slowly (<100 ms) in a voltage- and calcium-dependent manner (Bean, 1985). This slowly inactivated calcium current is - together with the fine-tuned regulation of sodium and potassium conductance - the basis for the action potential plateau observed in ventricular myocytes (phase 2). The ryanodine receptor calcium channels (RYR2) - which are located in the sarcoplasmic reticulum in close proximity to the L-type Ca^{2+} channels - is activated by the calcium influx (Bers, 2004). This RYR2-mediated sarcoplasmic calcium release is the major contributor in the activation of the contractile machinery (Bers, 2002).

The cardiac L-type calcium channel consists of a pore-forming α-subunit, the $Ca_v1.2$ protein, which is encoded by Cacna1c. $Ca_v1.2$ has a similar topology to $Na_v1.5$ (Fig. 3). A functional cardiac channel complex is composed of four polyproteins which, apart from Cav1.2, form the β and α_2/δ auxiliary subunits (Bodi *et al.*, 2005). The α_2 and δ subunits are encoded by the same gene and are separated by proteolytic cleavage (De Jongh *et al.*, 1990). Several different isoforms of this protein are known. The $\alpha_{2/}\delta$ subunits are linked together by a disulphide bridge and are closely associated with the $Ca_v1.2$ α-subunit by surface interaction. The α_2 subunit is entirely extracellular, and the δ subunit has a single transmembrane region with a very short intracellular part. The $\alpha_{2/}\delta$ subunits have been suggested to increase the membrane density of the channel complex, and mice lacking this gene have a tendency to have bradycardia (Ivanov *et al.*, 2004). All four calcium channel β-subunits (CACNB1-4) are known to modify the currents; however, it has been suggested that β_2 is the primary subunit in the heart (Colecraft *et al.*, 2002). The β-subunits play a prominent role in the trafficking of the channel complexes to the cell surface membrane (Bichet *et al.*, 2000; Chen *et al.*, 2004; Van *et al.*, 2004). Furthermore, the absence of β-subunits renders the channel insensitive to β-adrenergic stimulation (Mikala *et al.*, 1998).

One of the important regulatory mechanisms of L-type calcium channels is cAMP-dependent phosphorylation, which increases the amplitude of the calcium current (McDonald *et al.*, 1994). An increase in cAMP is induced by the β-adrenergic control of cardiac functions. β-adrenergic stimulation thereby leads to an increased calcium influx through the L-type channels, which facilitates an increased calcium release from the ryanodine receptors. Other important regulators of L-type calcium channels are calmodulin-dependent protein kinase II (CaMKII) (Maier & Bers, 2007) and calcium-induced inactivation through binding to calmodulin (Bodi *et al.*, 2005).

4. Potassium channels

In the heart, potassium conductance is conducted through a number of different potassium channels. All of the potassium channels described below consist of six transmembrane domains - except for Kir2.x which has two - and assembles into tetrameric complexes, which can either be homo- or heteromeric (Nerbonne & Kass, 2005) (Fig. 4). In the early phase of the action potential, the transient outward potassium current (I_{To}) is important in the atria and in subepicardial ventricular myocytes. The ultra-rapid potassium current (I_{Kur}) - which is also a fast activating current present early on in the action potential - is predominantly

expressed in the atria. The rapid and slow delayed rectifier potassium currents, I_{Kr} and I_{Ks}, respectively, are, together with the inward rectifier current I_{K1}, the primary currents responsible for repolarising the myocyte membranes in the final part of the action potential and thereby terminating it (phase 3). All three of these currents are important in both atria and the ventricles.

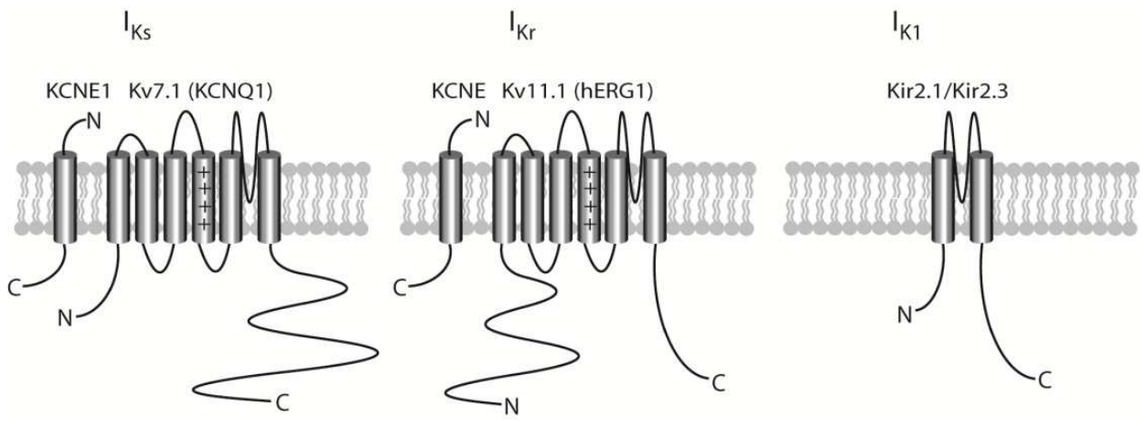


Fig. 4. Topology of the major repolarising potassium channels and their β-subunits.

4.1 The transient outward (Kv4.x/I_{To}) potassium channels

The transient outward current I_{To} is composed of two different components, namely a calcium-dependent chloride current and a calcium-independent potassium current. While the molecular components underlying the chloride current are unknown, several recently published reports have revealed a detailed picture of the proteins involved in forming the potassium transient outward current (reviewed by Patel & Campbell, 2005). This current can be divided into a rapidly activating and inactivating current - named $I_{To,f}$ - and a current with slow recovery kinetics - named $I_{To,s}$. $I_{To,s}$, conducted through Kv1.4 channels - which are regulated by Kvβ cytosolic proteins (Morales *et al.*, 1995). Kv1.4 channels are expressed throughout the ventricular wall as well as in the atria, where it is suggested that they participate to a minor extent with I_{To} (Calloe *et al.*, 2010; Calloe *et al.*, 2011). The $I_{To,f}$ channels activate rapidly (in the order of milliseconds) in a voltage-dependent manner and are inactivated through a somewhat slower process (in the order of tens of milliseconds). The pore-forming subunit in $I_{To,f}$ which is predominantly present in larger mammals is Kv4.3, which when co-expressed with the Kv channel interacting protein 2 (KChiP2) recapitulates most of the features of the native current (An *et al.*, 2000; Deschenes *et al.*, 2002). Kv4.3 is homogenously expressed in the ventricle. The KChiP2 auxiliary protein potentiates the current conducted through the Kv4.3 channels by promoting cell surface expression. In fact, in human and canine ventricles, a transmural expression gradient of KChiP2 has been found to correlate with a much higher $I_{To,f}$ in the subepicardial layer than in the subendocardial layer (Calloe *et al.*, 2010; Deschenes *et al.*, 2002; Gaborit *et al.*, 2007; Soltysinska *et al.*, 2009; Zicha *et al.*, 2004). This large expression of $I_{To,f}$ is responsible for the characteristic notch (phase 1 repolarisation) observed in subepicardial cardiomyocytes (Calloe *et al.*, 2009; Di Diego *et al.*, 2002). $I_{To,f}$ is also prominently expressed in the atria, where it likewise participates in early repolarisation (Calloe *et al.*, 2010; Calloe *et al.*, 2011; Gaborit *et al.*, 2007).
While KChIP2 has the most prominent effect on Kv4.3 channels, with altered current levels as well as inactivation and recovery parameters (Patel & Campbell, 2005), other auxiliary

subunits have also been shown to be important for $I_{To,f}$. Dipeptidyl aminopeptidase-related proteins (DPPs) affect the biophysical properties of the Kv4.3 channels in a manner very similar to KCHiP2 proteins, with the important difference that they also accelerate activation, thereby providing current properties resembling native $I_{To,f}$ (Cotella *et al.*, 2010; Nadal *et al.*, 2003; Radicke *et al.*, 2005). Kvβ cytosolic proteins, which increase the expression of Kv4.3, have been suggested to regulate this transient outward potassium current (Yang *et al.*, 2001). KCNE β-subunits, of which 5 different subtypes exit, have also been suggested to interact with Kv4.3/KCHiP2 channels as they modify the channel kinetics in *in vitro* studies (Radicke *et al.*, 2006; Radicke *et al.*, 2008). Recently, mutations in KCNE3 and KCNE5 have been linked to Brugada syndrome, which is a syndrome associated with an increased risk of ventricular fibrillation (Brugada & Brugada, 1992; Delpon *et al.*, 2008; Ohno *et al.*, 2011). Both KCNE3 and KCNE5 decrease the I_{To} current level when co-expressed, and as the mutations found in Brugada Syndrome patients provide an increase in current level compared to controls, it is suggested that this inhibitory effect of I_{To} is important in maintaining the current balance between the sodium and potassium currents in the early part of the ventricular action potential.

4.2 The ultra-rapid (Kv1.5/I_{Kur}) potassium channels

The ultra rapid potassium current I_{Kur} is well-expressed in the atria, where it contributes to repolarisation (Amos *et al.*, 1996). This current activates early during an action potential and inactivates slowly. Hence, I_{Kur} is an important repolarising current throughout most of the atrial action potential. The molecular constituent of I_{Kur} is the Kv1.5 potassium channel (Wang *et al.*, 1993). Although, I_{Kur} has predominantly been reported in atria, this current has also been suggested to play a role in canine and human ventricles (Calloe *et al.*, 2010; Nielsen *et al.*, 2007; Sridhar *et al.*, 2007).

4.3 The fast delayed rectifier (hERG1/I_{Kr}) potassium channels

The rapid delayed rectifier current I_{Kr} is present in nodal tissue, atria, purkinje fibres and ventricles. The molecular correlate of I_{Kr} is the ether-a-go-go-related gene 1 product ERG1, also termed Kv11.1 (Sanguinetti *et al.*, 1995; Trudeau *et al.*, 1995). It is the unique biophysical features - with fast inactivation followed by slow deactivation - of the ERG1 potassium channel which makes it pivotal in cardiac repolarisation (Grunnet, 2010; Spector *et al.*, 1996). Upon depolarisation, the ERG1 channels open but inactivate very quickly and at the same time display marked inward rectification (Grunnet *et al.*, 2008b). This means that the ERG1 channel complexes conduct a minor potassium current during the initial depolarisation and the plateau phase of the cardiac action potential. However, when the membrane potential moves slightly towards the repolarisation potential - partly due to L-type calcium channel inactivation and partly due to I_{Ks} activation - then ERG1 channels are released from inactivation. As ERG1 channels only slowly progress into a closed state (deactivation) – and, therefore, are kept in an open state (Piper *et al.*, 2005) - a relatively large potassium current is conducted and the membrane potential is accelerated towards the resting membrane potential. The inactivation of ERG1 channels is called C-type inactivation, which involves a change at the extracellular mouth of the pore modulated by the extracellular potassium concentration (Baukrowitz & Yellen, 1995). A low concentration of potassium will lead to a pore collapse. Hence, the external potassium concentration is an important regulator of potassium conductance, where low concentrations will reduce activity and high concentrations will increase activity. Loss-of-function mutations in hERG1 are associated

with long QT syndrome type 2 (Sanguinetti *et al.*, 1996a), while gain-of-function mutations have been found in short QT syndrome type 1 (Brugada *et al.*, 2004; Cordeiro *et al.*, 2005; Grunnet *et al.*, 2008a).

Two splice variants of ERG1 have been reported. The originally identified ERG1 protein is termed ERG1a while an alternatively spliced variant, termed ERG1b, has a much shorter intracellular N-terminal with a unique 36 residue sequence (Lees-Miller *et al.*, 1997; London *et al.*, 1997). ERG1b displays different deactivation kinetics to ERG1a (Lees-Miller *et al.*, 1997; London *et al.*, 1997). The co-expression of mRNA levels corresponding to the levels found in the human ventricles of the two variants alter several of the kinetic parameters (Larsen *et al.*, 2008), and this may explain a reported dispersion of I_{Kr} deactivation kinetics observed between myocytes isolated from the subepicardium and the mid-myocardium (Szabo *et al.*, 2005).

The membrane-spanning KCNE2 β-subunits have been found to modify the kinetics of the hERG1 channel (Abbott *et al.*, 1999; McDonald *et al.*, 1997). KCNE2/hERG1 expression in heterologous expression systems has been found to provide currents partly resembling native I_{Kr}, and as KCNE2 mutations found in long QT syndrome patients alter the channel properties it has been suggested that KCNE2 interacts with ERG1 in the heart (Abbott *et al.*, 1999). However, another report has not found KCNE2 to act as an essential constituent of the ERG1 channel complex carrying native I_{Kr} (Weerapura *et al.*, 2002).

4.4 The slow delayed rectifier (Kv7.1/I_{Ks}) potassium channels

The KCNQ1 gene, encoding Kv7.1 proteins, was cloned by Wang and co-workers using linkage analyses on genomic material from Long QT syndrome patients (Wang *et al.*, 1996), and was, therefore, originally named KvLQT1. The voltage-gated Kv7.1 channel is progressively opened by increasing membrane depolarisations. The channel gives rise to slowly activating and deactivating potassium currents. Upon longer depolarising steps, a fraction of the KCNQ1 channels inactivate (Pusch, 1998). KCNQ1 potassium channels are expressed in several tissues throughout the body and regulate key physiological functions. The two most important roles of KCNQ1 channels are: i) the repolarisation of the cardiac tissue following an action potential, and ii) water and salt transport across epithelial tissues (reviewed by Jespersen *et al.*, 2005).

The five relatively small one-transmembrane spanning KCNE proteins - KCNE1-5 - have been found to be highly promiscuous with respect to modulating the biophysical properties of Kv potassium channels as well as HCN pacemaker channels (McCrossan & Abbott, 2004). All five members of the KCNE family modify the properties of Kv7.1 channels (Jespersen *et al.*, 2005). The co-expression of Kv7.1 with KCNE1 - formerly known as minK - recapitulates native I_{Ks} (Barhanin *et al.*, 1996; Sanguinetti *et al.*, 1996b), which not only plays a pivotal role in repolarising the myocardium but which is also important in transporting potassium across the strial marginal cells in the inner ear (Sunose *et al.*, 1997). The co-assembly of Kv7.1 and KCNE1 results in an increase in single channel conductance, a positive shift in the voltage activation threshold, the slowing of activation and deactivation, and an almost complete absence of inactivation (Splawski *et al.*, 1997). In long QT syndromes 1 and 5, which are caused by mutations in Kv7.1 and KCNE1, a reduced I_{Ks} current is observed (Wang *et al.*, 1996; Wang *et al.*, 1999).

I_{Ks} is the only potassium current which is upregulated with increased beating frequency. The upregulation of I_{Ks} is orchestrated by sympathetic mediated β-adrenergic receptor activation. The β-adrenergic receptor activation results in an increased level of cAMP and PKA stimulation, which interacts with the I_{Ks} channel complex through an A-kinase

anchoring protein (AKAP) called 'yotiao' (Marx *et al.*, 2002; Potet *et al.*, 2001). PKA and protein phosphatase 1 interact with the C-terminal tail of KCNQ1 through yotiao, which leads to a phosphorylation of serine 27 in the N-terminus. cAMP-induced regulation of Kv7.1 is dependent on KCNE1 and Long QT mutations in both KCNQ1 and KCNE1 have been shown to disrupt this regulation (Kurokawa *et al.*, 2004; Marx *et al.*, 2002). The β-adrenergic activation increases the activation and slows the deactivation kinetics of I_{Ks}, and these features - together with the increased beating frequencies - have been suggested to underlie the profoundly augmented cardiac I_{Ks} current (Marx *et al.*, 2002; Terrenoire *et al.*, 2005). I_{Ks} is therefore essential for action potential shortening at increased beating frequencies. The importance of β-adrenergic stimulation is underlined by the fact that in humans I_{Ks} is almost absent without sympathetic stimulation (Jost *et al.*, 2005).

KCNE2-5 β-subunits also interact with Kv7.1 channels, modifying the biophysical parameters (Angelo *et al.*, 2002; Bendahhou *et al.*, 2005; Grunnet *et al.*, 2002; Jespersen *et al.*, 2004; Mazhari *et al.*, 2002; Tinel *et al.*, 2000). Although KCNE2 is primarily believed to be of importance in the stomach, it has also been suggested as modifying I_{Ks} properties in the heart (Jiang *et al.*, 2009; Wu *et al.*, 2006). A polymorphism in KCNE4 has been associated with atrial fibrillation through a proposed gain-of-function mechanism (Ma *et al.*, 2007), but solid evidence is still missing concerning a potential physiological function of the Kv7.1/KCNE4 interaction in the heart. KCNE5 expression drastically reduces the I_{Ks} current amplitude (Angelo *et al.*, 2002). A KCNE5 mutation found in a patient with atrial fibrillation has been shown to increase I_{Ks} and it has therefore been suggested that KCNE5 β-subunits regulate the current conducted through Kv7.1/KCNE1 channels (Ravn *et al.*, 2005; Ravn *et al.*, 2008).

Under pathophysiological conditions, such as during ischemia, cell volume and pH may undergo considerable alterations. KCNQ1 channels have been found to be activated by a drastic increase in extracellular hyperosmolarity in cardiomyocytes (Sasaki *et al.*, 1994; Vandenberg *et al.*, 1996). In heterologous expression systems, it has been shown that hyperosmolar-induced swelling increases the Kv7.1 current while hyperosmolar shrinkage decreases the current (Grunnet *et al.*, 2003). The ability of Kv7.1 to sense volume changes depends on an intact cytoskeleton which interacts with the N-terminal part of Kv7.1. As with volume changes, internal and external acidification also modifies the Kv7.1 current density. Homomeric KCNQ1 channels are inhibited by both intracellular and extracellular acidic pH (Freeman *et al.*, 2000; Peretz *et al.*, 2002; Unsold *et al.*, 2000). KCNE β-subunits enforce differential effects on the Kv7.1 channel complex following acidification. While KCNE3 renders Kv7.1 insensitive to external acidification, KCNE2 induces an increase in the current level following such acidification, which seems to be determined by the extracellular and transmembrane domains of KCNE2 (Heitzmann *et al.*, 2007). The pH-dependent regulation induced by KCNE1 has been disputed, as both a small decrease (Peretz *et al.*, 2002) and an increase (Heitzmann *et al.*, 2007) in current amplitude has been found; however, both external and internal acidification seem to modify the Kv7.1/KCNE1 current kinetics by changing the slow activation kinetics to an instantaneous onset (Heitzmann *et al.*, 2007; Unsold *et al.*, 2000).

4.5 The inward rectifier (Kir2.X/I_{K1}) potassium channels

The resting membrane potential of cardiomyocytes - being between -80 and -90 mV - is close to the equilibrium potential of potassium, partly due to relatively large resting K^+ conductance through inward rectifier potassium channels (I_{Kir}) (phase 4) (Dhamoon & Jalife,

2005). I_{Kir} channels are composed of four pore-forming subunits, being either homomeric or heteromeric and characterised by a preferentially conducting current at potentials below –50 mV (Lu, 2004). I_{Kir} is not, in contrast to the above described currents, voltage gated. The inward rectification profile, where much less current is passing when the membrane is depolarised than when it is repolarised, is not an inherent property of the channel protein itself, but reflects strong voltage dependence of channel block by intracellular cations, such as Mg^{2+} and polyamines (Ficker *et al.*, 1994; Lopatin *et al.*, 1994; Matsuda *et al.*, 1987; Vandenberg, 1987). The primary inward rectifying current responsible for terminating the action potential - as well as for setting the resting membrane potential - is I_{K1}, constituted by Kir2.1 and, to a lesser extent, the Kir2.2 and Kir2.3 proteins (Preisig-Muller *et al.*, 2002; Zaritsky *et al.*, 2001). Regional differences in the expression of I_{K1} have been described (Dhamoon *et al.*, 2004; Samie *et al.*, 2001) (Samie *et al.*, 2001; Dhamoon *et al.*, 2004) and the modulation of this current affects cardiac excitability and arrhythmogenesis (Nakamura *et al.*, 1998; Plaster *et al.*, 2001; Poelzing & Veeraraghavan, 2007; Warren *et al.*, 2003).

I_{K1} channels, such as ERG1 (I_{Kr}) channels, are regulated by extracellular potassium (Dhamoon *et al.*, 2004; Hume & Uehara, 1985; Knot *et al.*, 1996). Increased extracellular potassium augments potassium conductance - even though the potassium driving force is decreased - while a decreased concentration reduces the current. This biophysical property of I_{K1} and I_{Kr} channels is important in a clinical setting, as a patient with hypokalaemia will have a reduction in two of the three major repolarising cardiac currents which will lead to action potential prolongation as potentially being the trigger of arrhythmia. Another important regulator of the I_{K1} function is phosphatidylinositol 4,5-bisphosphate (PIP2) (Soom *et al.*, 2001; Takano & Kuratomi, 2003). PIP_2 is a quantitatively minor membrane component, although its local concentration may be relatively high. PIP is a key signalling phospholipid, whereby its hydrolysis by phospholipase C as well as its phosphorylation by PI3 kinases generates important second messengers. PIP2 binds directly to Kir channels, where it stabilises the open state. PIP2 has a high affinity with Kir2.X channels, which probably underlies the almost constitutive active I_{K1} (Lopes *et al.*, 2002).

5. Summary

The length and morphology of cardiac action potential are shaped by the expression and fine-tuning of a number of ion channels. Sodium channels are responsible for the rapid depolarisation of the myocardium. The influx of sodium is followed by an influx of calcium through L-type calcium channels, contributing to keeping the depolarisation for several hundred milliseconds. The cardiac action potential is terminated by an increased efflux of potassium driving the membrane potential towards repolarisation. The dynamic properties of the action potential are obtained through a number of regulatory mechanisms maintaining the delicate balance between the different depolarising and repolarising ionic currents. Many of the primary regulatory mechanisms - such as β-subunits and phosphorylation sites - have been established. However, below the direct channel interacting proteins there is a whole network of modulatory mechanisms, and we are only just on the brink of discovering their role in regulating the cardiac action potential.

6. References

Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, & Goldstein SA (1999). MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 97, 175-187.

Abriel H (2010). Cardiac sodium channel Na(v)1.5 and interacting proteins: Physiology and pathophysiology. *J Mol Cell Cardiol* 48, 2-11.

Abriel H & Staub O (2005). Ubiquitylation of ion channels. *Physiology (Bethesda)* 20, 398-407.

Ahern CA, Zhang JF, Wookalis MJ, & Horn R (2005). Modulation of the cardiac sodium channel NaV1.5 by Fyn, a Src family tyrosine kinase. *Circ Res* 96, 991-998.

Allouis M, Le BF, Wilders R, Peroz D, Schott JJ, Noireaud J, Le MH, Merot J, Escande D, & Baro I (2006). 14-3-3 is a regulator of the cardiac voltage-gated sodium channel Nav1.5. *Circ Res* 98, 1538-1546.

Amos GJ, Wettwer E, Metzger F, Li Q, Himmel HM, & Ravens U (1996). Differences between outward currents of human atrial and subepicardial ventricular myocytes. *J Physiol* 491 (Pt 1), 31-50.

An WF, Bowlby MR, Betty M, Cao J, Ling HP, Mendoza G, Hinson JW, Mattsson KI, Strassle BW, Trimmer JS, & Rhodes KJ (2000). Modulation of A-type potassium channels by a family of calcium sensors. *Nature* 403, 553-556.

Angelo K, Jespersen T, Grunnet M, Nielsen MS, Klaerke DA, & Olesen SP (2002). KCNE5 induces time- and voltage-dependent modulation of the KCNQ1 current. *Biophys J* 83, 1997-2006.

Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, & Romey G (1996). K(V)LQT1 and lsK (minK) proteins associate to form the I(Ks) cardiac potassium current. *Nature* 384, 78-80.

Baruscotti M, Bucchi A, & DiFrancesco D (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. *Pharmacol Ther* 107, 59-79.

Baukrowitz T & Yellen G (1995). Modulation of K+ current by frequency and external [K+]: a tale of two inactivation mechanisms. *Neuron* 15, 951-960.

Bean BP (1985). Two kinds of calcium channels in canine atrial cells. Differences in kinetics, selectivity, and pharmacology. *J Gen Physiol* 86, 1-30.

Bendahhou S, Marionneau C, Haurogne K, Larroque MM, Derand R, Szuts V, Escande D, Demolombe S, & Barhanin J (2005). In vitro molecular interactions and distribution of KCNE family with KCNQ1 in the human heart. *Cardiovasc Res* 67, 529-538.

Bennett PB, Yazawa K, Makita N, & George AL, Jr. (1995). Molecular mechanism for an inherited cardiac arrhythmia. *Nature* 376, 683-685.

Bers DM (2002). Cardiac excitation-contraction coupling. *Nature* 415, 198-205.

Bers DM (2004). Macromolecular complexes regulating cardiac ryanodine receptor function. *J Mol Cell Cardiol* 37, 417-429.

Bichet D, Cornet V, Geib S, Carlier E, Volsen S, Hoshi T, Mori Y, & De WM (2000). The I-II loop of the Ca2+ channel alpha1 subunit contains an endoplasmic reticulum retention signal antagonized by the beta subunit. *Neuron* 25, 177-190.

Bodi I, Mikala G, Koch SE, Akhter SA, & Schwartz A (2005). The L-type calcium channel in the heart: the beat goes on. *J Clin Invest* 115, 3306-3317.

Brette F & Orchard CH (2006). No apparent requirement for neuronal sodium channels in excitation-contraction coupling in rat ventricular myocytes. *Circ Res* 98, 667-674.

Brugada P & Brugada J (1992). Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 20, 1391-1396.

Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A,

Bianchi F, Giustetto C, Schimpf R, Brugada P, & Antzelevitch C (2004). Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 109, 30-35.

Bucchi A, Baruscotti M, Robinson RB, & DiFrancesco D (2003). I(f)-dependent modulation of pacemaker rate mediated by cAMP in the presence of ryanodine in rabbit sino-atrial node cells. *J Mol Cell Cardiol* 35, 905-913.

Calloe K, Cordeiro JM, Di Diego JM, Hansen RS, Grunnet M, Olesen SP, & Antzelevitch C (2009). A transient outward potassium current activator recapitulates the electrocardiographic manifestations of Brugada syndrome. *Cardiovasc Res* 81, 686-694.

Calloe K, Nof E, Jespersen T, Diego JM, Chlus N, Olesen SP, Antzelevitch C, & Cordeiro JM (2011). Comparison of the Effects of a Transient Outward Potassium Channel Activator on Currents Recorded from Atrial and Ventricular Cardiomyocytes. *J Cardiovasc Electrophysiol* 22:1057-66.

Calloe K, Soltysinska E, Jespersen T, Lundby A, Antzelevitch C, Olesen SP, & Cordeiro JM (2010). Differential effects of the transient outward K(+) current activator NS5806 in the canine left ventricle. *J Mol Cell Cardiol* 48, 191-200.

Carmeliet E (1987). Voltage-dependent block by tetrodotoxin of the sodium channel in rabbit cardiac Purkinje fibers. *Biophys J* 51, 109-114.

Chambers JC, Zhao J, Terracciano CM, Bezzina CR, Zhang W, Kaba R, Navaratnarajah M, Lotlikar A, Sehmi JS, Kooner MK, Deng G, Siedlecka U, Parasramka S, El-Hamamsy I, Wass MN, Dekker LR, de Jong JS, Sternberg MJ, McKenna W, Severs NJ, de SR, Wilde AA, Anand P, Yacoub M, Scott J, Elliott P, Wood JN, & Kooner JS (2010). Genetic variation in SCN10A influences cardiac conduction. *Nat Genet* 42, 149-152.

Chen YH, Li MH, Zhang Y, He LL, Yamada Y, Fitzmaurice A, Shen Y, Zhang H, Tong L, & Yang J (2004). Structural basis of the alpha1-beta subunit interaction of voltage-gated Ca2+ channels. *Nature* 429, 675-680.

Cheng J, Van Norstrand DW, Medeiros-Domingo A, Valdivia C, Tan BH, Ye B, Kroboth S, Vatta M, Tester DJ, January CT, Makielski JC, & Ackerman MJ (2009). Alpha1-syntrophin mutations identified in sudden infant death syndrome cause an increase in late cardiac sodium current. *Circ Arrhythm Electrophysiol* 2, 667-676.

Colecraft HM, Alseikhan B, Takahashi SX, Chaudhuri D, Mittman S, Yegnasubramanian V, Alvania RS, Johns DC, Marban E, & Yue DT (2002). Novel functional properties of Ca(2+) channel beta subunits revealed by their expression in adult rat heart cells. *J Physiol* 541, 435-452.

Cordeiro JM, Brugada R, Wu YS, Hong K, & Dumaine R (2005). Modulation of I(Kr) inactivation by mutation N588K in KCNH2: a link to arrhythmogenesis in short QT syndrome. *Cardiovasc Res* 67, 498-509.

Cotella D, Radicke S, Bortoluzzi A, Ravens U, Wettwer E, Santoro C, & Sblattero D (2010). Impaired glycosylation blocks DPP10 cell surface expression and alters the electrophysiology of Ito channel complex. *Pflugers Arch* 460, 87-97.

De Jongh KS, Warner C, & Catterall WA (1990). Subunits of purified calcium channels. Alpha 2 and delta are encoded by the same gene. *J Biol Chem* 265, 14738-14741.

Delpon E, Cordeiro JM, Nunez L, Thomsen PE, Guerchicoff A, Pollevick GD, Wu Y, Kanters JK, Larsen CT, Hofman-Bang J, Burashnikov E, Christiansen M, & Antzelevitch C

(2008). Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol* 1, 209-218.

Deschenes I, DiSilvestre D, Juang GJ, Wu RC, An WF, & Tomaselli GF (2002). Regulation of Kv4.3 current by KChIP2 splice variants: a component of native cardiac I(to)? *Circulation* 106, 423-429.

Dhamoon AS & Jalife J (2005). The inward rectifier current (IK1) controls cardiac excitability and is involved in arrhythmogenesis. *Heart Rhythm* 2, 316-324.

Dhamoon AS, Pandit SV, Sarmast F, Parisian KR, Guha P, Li Y, Bagwe S, Taffet SM, & Anumonwo JM (2004). Unique Kir2.x properties determine regional and species differences in the cardiac inward rectifier K+ current. *Circ Res* 94, 1332-1339.

Dhar MJ, Chen C, Rivolta I, Abriel H, Malhotra R, Mattei LN, Brosius FC, Kass RS, & Isom LL (2001). Characterization of sodium channel alpha- and beta-subunits in rat and mouse cardiac myocytes. *Circulation* 103, 1303-1310.

Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS, & Antzelevitch C (2002). Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation* 106, 2004-2011.

DiFrancesco D (1993). Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol* 55, 455-472.

DiFrancesco D & Tromba C (1988). Muscarinic control of the hyperpolarization-activated current (if) in rabbit sino-atrial node myocytes. *J Physiol* 405, 493-510.

Fahmi AI, Patel M, Stevens EB, Fowden AL, John JE, III, Lee K, Pinnock R, Morgan K, Jackson AP, & Vandenberg JI (2001). The sodium channel beta-subunit SCN3b modulates the kinetics of SCN5a and is expressed heterogeneously in sheep heart. *J Physiol* 537, 693-700.

Fermini B & Nathan RD (1991). Removal of sialic acid alters both T- and L-type calcium currents in cardiac myocytes. *Am J Physiol* 260, H735-H743.

Ficker E, Taglialatela M, Wible BA, Henley CM, & Brown AM (1994). Spermine and spermidine as gating molecules for inward rectifier K+ channels. *Science* 266, 1068-1072.

Freeman LC, Lippold JJ, & Mitchell KE (2000). Glycosylation influences gating and pH sensitivity of I(sK). *J Membr Biol* 177, 65-79.

Friel DD & Bean BP (1990). Dual control by ATP and acetylcholine of inwardly rectifying K+ channels in bovine atrial cells. *Pflugers Arch* 415, 651-657.

Gaborit N, Le BS, Szuts V, Varro A, Escande D, Nattel S, & Demolombe S (2007). Regional and tissue specific transcript signatures of ion channel genes in the non-diseased human heart. *J Physiol* 582, 675-693.

Gauss R, Seifert R, & Kaupp UB (1998). Molecular identification of a hyperpolarization-activated channel in sea urchin sperm. *Nature* 393, 583-587.

Gavillet B, Rougier JS, Domenighetti AA, Behar R, Boixel C, Ruchat P, Lehr HA, Pedrazzini T, & Abriel H (2006). Cardiac sodium channel Nav1.5 is regulated by a multiprotein complex composed of syntrophins and dystrophin. *Circ Res* 99, 407-414.

Gouaux E & Mackinnon R (2005). Principles of selective ion transport in channels and pumps. *Science* 310, 1461-1465.

Grunnet M (2010). Repolarization of the cardiac action potential. Does an increase in repolarization capacity constitute a new anti-arrhythmic principle? *Acta Physiol (Oxf)* 198 Suppl 676, 1-48.

Grunnet M, Diness TG, Hansen RS, & Olesen SP (2008a). Biophysical characterization of the short QT mutation hERG-N588K reveals a mixed gain-and loss-of-function. *Cell Physiol Biochem* 22, 611-624.

Grunnet M, Hansen RS, & Olesen SP (2008b). hERG1 channel activators: a new anti-arrhythmic principle. *Prog Biophys Mol Biol* 98, 347-362.

Grunnet M, Jespersen T, MacAulay N, Jorgensen NK, Schmitt N, Pongs O, Olesen SP, & Klaerke DA (2003). KCNQ1 channels sense small changes in cell volume. *J Physiol* 549, 419-427.

Grunnet M, Jespersen T, Rasmussen HB, Ljungstrom T, Jorgensen NK, Olesen SP, & Klaerke DA (2002). KCNE4 is an inhibitory subunit to the KCNQ1 channel. *J Physiol* 542, 119-130.

Hagiwara N, Irisawa H, & Kameyama M (1988). Contribution of two types of calcium currents to the pacemaker potentials of rabbit sino-atrial node cells. *J Physiol* 395, 233-253.

Heitzmann D, Koren V, Wagner M, Sterner C, Reichold M, Tegtmeier I, Volk T, & Warth R (2007). KCNE beta subunits determine pH sensitivity of KCNQ1 potassium channels. *Cell Physiol Biochem* 19, 21-32.

Herfst LJ, Potet F, Bezzina CR, Groenewegen WA, Le MH, Hoorntje TM, Demolombe S, Baro I, Escande D, Jongsma HJ, Wilde AA, & Rook MB (2003). Na+ channel mutation leading to loss of function and non-progressive cardiac conduction defects. *J Mol Cell Cardiol* 35, 549-557.

Hershko A & Ciechanover A (1998). The ubiquitin system. *Annu Rev Biochem* 67, 425-479.

Hicke L (1999). Gettin' down with ubiquitin: turning off cell-surface receptors, transporters and channels. *Trends Cell Biol* 9, 107-112.

Hille B (2001). *Ion Channels of Excitable Membranes*, third ed. Sunderland, Mass: Sinauer Associates.

Holm H, Gudbjartsson DF, Arnar DO, Thorleifsson G, Thorgeirsson G, Stefansdottir H, Gudjonsson SA, Jonasdottir A, Mathiesen EB, Njolstad I, Nyrnes A, Wilsgaard T, Hald EM, Hveem K, Stoltenberg C, Lochen ML, Kong A, Thorsteinsdottir U, & Stefansson K (2010). Several common variants modulate heart rate, PR interval and QRS duration. *Nat Genet* 42, 117-122.

Hu D, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A, Pfeiffer R, Koopmann TT, Cordeiro JM, Guerchicoff A, Pollevick GD, & Antzelevitch C (2009). A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ Cardiovasc Genet* 2, 270-278.

Hume JR & Uehara A (1985). Ionic basis of the different action potential configurations of single guinea-pig atrial and ventricular myocytes. *J Physiol* 368, 525-544.

Isom LL, De Jongh KS, Patton DE, Reber BF, Offord J, Charbonneau H, Walsh K, Goldin AL, & Catterall WA (1992). Primary structure and functional expression of the beta 1 subunit of the rat brain sodium channel. *Science* 256, 839-842.

Ivanov SV, Ward JM, Tessarollo L, McAreavey D, Sachdev V, Fananapazir L, Banks MK, Morris N, Djurickovic D, vor-Henneman DE, Wei MH, Alvord GW, Gao B, Richardson JA, Minna JD, Rogawski MA, & Lerman MI (2004). Cerebellar ataxia, seizures, premature death, and cardiac abnormalities in mice with targeted disruption of the Cacna2d2 gene. *Am J Pathol* 165, 1007-1018.

Jespersen T (2011). Regulation and physiological function of Na(v)1.5 and KCNQ1 channels. *Acta Physiol (Oxf)* 202 Suppl 683, 1-26.

Jespersen T, Gavillet B, van Bemmelen MX, Cordonier S, Thomas MA, Staub O, & Abriel H (2006). Cardiac sodium channel Na(v)1.5 interacts with and is regulated by the protein tyrosine phosphatase PTPH1. *Biochem Biophys Res Commun* 348, 1455-1462.

Jespersen T, Grunnet M, & Olesen SP (2005). The KCNQ1 potassium channel: from gene to physiological function. *Physiology (Bethesda)* 20, 408-416.

Jespersen T, Rasmussen HB, Grunnet M, Jensen HS, Angelo K, Dupuis DS, Vogel LK, Jorgensen NK, Klaerke DA, & Olesen SP (2004). Basolateral localisation of KCNQ1 potassium channels in MDCK cells: molecular identification of an N-terminal targeting motif. *J Cell Sci* 117, 4517-4526.

Jiang M, Xu X, Wang Y, Toyoda F, Liu XS, Zhang M, Robinson RB, & Tseng GN (2009). Dynamic partnership between KCNQ1 and KCNE1 and influence on cardiac IKs current amplitude by KCNE2. *J Biol Chem* 284, 16452-16462.

Johnson D & Bennett ES (2006). Isoform-specific effects of the beta2 subunit on voltage-gated sodium channel gating. *J Biol Chem* 281, 25875-25881.

Jost N, Virag L, Bitay M, Takacs J, Lengyel C, Biliczki P, Nagy Z, Bogats G, Lathrop DA, Papp JG, & Varro A (2005). Restricting excessive cardiac action potential and QT prolongation: a vital role for IKs in human ventricular muscle. *Circulation* 112, 1392-1399.

Kazen-Gillespie KA, Ragsdale DS, D'Andrea MR, Mattei LN, Rogers KE, & Isom LL (2000). Cloning, localization, and functional expression of sodium channel beta1A subunits. *J Biol Chem* 275, 1079-1088.

Knot HJ, Zimmermann PA, & Nelson MT (1996). Extracellular K(+)-induced hyperpolarizations and dilatations of rat coronary and cerebral arteries involve inward rectifier K(+) channels. *J Physiol* 492 (Pt 2), 419-430.

Ko SH, Lenkowski PW, Lee HC, Mounsey JP, & Patel MK (2005). Modulation of Na(v)1.5 by beta1-- and beta3-subunit co-expression in mammalian cells. *Pflugers Arch* 449, 403-412.

Kurachi Y, Nakajima T, & Sugimoto T (1986a). Acetylcholine activation of K+ channels in cell-free membrane of atrial cells. *Am J Physiol* 251, H681-H684.

Kurachi Y, Nakajima T, & Sugimoto T (1986b). On the mechanism of activation of muscarinic K+ channels by adenosine in isolated atrial cells: involvement of GTP-binding proteins. *Pflugers Arch* 407, 264-274.

Kurokawa J, Motoike HK, Rao J, & Kass RS (2004). Regulatory actions of the A-kinase anchoring protein Yotiao on a heart potassium channel downstream of PKA phosphorylation. *Proc Natl Acad Sci U S A* 101, 16374-16378.

Lakatta EG & DiFrancesco D (2009). What keeps us ticking: a funny current, a calcium clock, or both? *J Mol Cell Cardiol* 47, 157-170.

Larsen AP, Olesen SP, Grunnet M, & Jespersen T (2008). Characterization of hERG1a and hERG1b potassium channels-a possible role for hERG1b in the I (Kr) current. *Pflugers Arch* 456, 1137-1148.

Lees-Miller JP, Kondo C, Wang L, & Duff HJ (1997). Electrophysiological characterization of an alternatively processed ERG K+ channel in mouse and human hearts. *Circ Res* 81, 719-726.

Logothetis DE, Kurachi Y, Galper J, Neer EJ, & Clapham DE (1987). The beta gamma subunits of GTP-binding proteins activate the muscarinic K+ channel in heart. *Nature* 325, 321-326.

London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE, Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Ackerman MJ, McNamara DM, Weiss R, & Dudley SC, Jr. (2007). Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation* 116, 2260-2268.

London B, Trudeau MC, Newton KP, Beyer AK, Copeland NG, Gilbert DJ, Jenkins NA, Satler CA, & Robertson GA (1997). Two isoforms of the mouse ether-a-go-go-related gene coassemble to form channels with properties similar to the rapidly activating component of the cardiac delayed rectifier K+ current. *Circ Res* 81, 870-878.

Lopatin AN, Makhina EN, & Nichols CG (1994). Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. *Nature* 372, 366-369.

Lopes CM, Zhang H, Rohacs T, Jin T, Yang J, & Logothetis DE (2002). Alterations in conserved Kir channel-PIP2 interactions underlie channelopathies. *Neuron* 34, 933-944.

Lu Z (2004). Mechanism of rectification in inward-rectifier K+ channels. *Annu Rev Physiol* 66, 103-129.

Ludwig A, Zong X, Jeglitsch M, Hofmann F, & Biel M (1998). A family of hyperpolarization-activated mammalian cation channels. *Nature* 393, 587-591.

Ma KJ, Li N, Teng SY, Zhang YH, Sun Q, Gu DF, & Pu JL (2007). Modulation of KCNQ1 current by atrial fibrillation-associated KCNE4 (145E/D) gene polymorphism. *Chin Med J (Engl)* 120, 150-154.

Macri V, Proenza C, Agranovich E, Angoli D, & Accili EA (2002). Separable gating mechanisms in a Mammalian pacemaker channel. *J Biol Chem* 277, 35939-35946.

Maier LS & Bers DM (2007). Role of Ca2+/calmodulin-dependent protein kinase (CaMK) in excitation-contraction coupling in the heart. *Cardiovasc Res* 73, 631-640.

Maier SK, Westenbroek RE, Schenkman KA, Feigl EO, Scheuer T, & Catterall WA (2002). An unexpected role for brain-type sodium channels in coupling of cell surface depolarization to contraction in the heart. *Proc Natl Acad Sci USA* 99, 4073-4078.

Makielski JC, Ye B, Valdivia CR, Pagel MD, Pu J, Tester DJ, & Ackerman MJ (2003). A ubiquitous splice variant and a common polymorphism affect heterologous expression of recombinant human SCN5A heart sodium channels. *Circ Res* 93, 821-828.

Mangoni ME & Nargeot J (2008). Genesis and regulation of the heart automaticity. *Physiol Rev* 88, 919-982.

Marionneau C, Couette B, Liu J, Li H, Mangoni ME, Nargeot J, Lei M, Escande D, & Demolombe S (2005). Specific pattern of ionic channel gene expression associated with pacemaker activity in the mouse heart. *J Physiol* 562, 223-234.

Marx SO, Kurokawa J, Reiken S, Motoike H, D'Armiento J, Marks AR, & Kass RS (2002). Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. *Science* 295, 496-499.

Matsuda H, Saigusa A, & Irisawa H (1987). Ohmic conductance through the inwardly rectifying K channel and blocking by internal Mg2+. *Nature* 325, 156-159.

Mazhari R, Nuss HB, Armoundas AA, Winslow RL, & Marban E (2002). Ectopic expression of KCNE3 accelerates cardiac repolarization and abbreviates the QT interval. *J Clin Invest* 109, 1083-1090.

McCrossan ZA & Abbott GW (2004). The MinK-related peptides. *Neuropharmacology* 47, 787-821.

McDonald TF, Pelzer S, Trautwein W, & Pelzer DJ (1994). Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. *Physiol Rev* 74, 365-507.

McDonald TV, Yu Z, Ming Z, Palma E, Meyers MB, Wang KW, Goldstein SA, & Fishman GI (1997). A minK-HERG complex regulates the cardiac potassium current I(Kr). *Nature* 388, 289-292.

Meadows LS & Isom LL (2005). Sodium channels as macromolecular complexes: implications for inherited arrhythmia syndromes. *Cardiovasc Res* 67, 448-458.

Medeiros-Domingo A, Kaku T, Tester DJ, Iturralde-Torres P, Itty A, Ye B, Valdivia C, Ueda K, Canizales-Quinteros S, Tusie-Luna MT, Makielski JC, & Ackerman MJ (2007). SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. *Circulation* 116, 134-142.

Medina I, Krapivinsky G, Arnold S, Kovoor P, Krapivinsky L, & Clapham DE (2000). A switch mechanism for G beta gamma activation of I(KACh). *J Biol Chem* 275, 29709-29716.

Mikala G, Klockner U, Varadi M, Eisfeld J, Schwartz A, & Varadi G (1998). cAMP-dependent phosphorylation sites and macroscopic activity of recombinant cardiac L-type calcium channels. *Mol Cell Biochem* 185, 95-109.

Moosmang S, Biel M, Hofmann F, & Ludwig A (1999). Differential distribution of four hyperpolarization-activated cation channels in mouse brain. *Biol Chem* 380, 975-980.

Morales MJ, Castellino RC, Crews AL, Rasmusson RL, & Strauss HC (1995). A novel beta subunit increases rate of inactivation of specific voltage-gated potassium channel alpha subunits. *J Biol Chem* 270, 6272-6277.

Moroni A, Gorza L, Beltrame M, Gravante B, Vaccari T, Bianchi ME, Altomare C, Longhi R, Heurteaux C, Vitadello M, Malgaroli A, & DiFrancesco D (2001). Hyperpolarization-activated cyclic nucleotide-gated channel 1 is a molecular determinant of the cardiac pacemaker current I(f). *J Biol Chem* 276, 29233-29241.

Murray KT, Hu NN, Daw JR, Shin HG, Watson MT, Mashburn AB, & George AL, Jr. (1997). Functional effects of protein kinase C activation on the human cardiac Na+ channel. *Circ Res* 80, 370-376.

Nadal MS, Ozaita A, Amarillo Y, Vega-Saenz de ME, Ma Y, Mo W, Goldberg EM, Misumi Y, Ikehara Y, Neubert TA, & Rudy B (2003). The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K+ channels. *Neuron* 37, 449-461.

Nakamura TY, Artman M, Rudy B, & Coetzee WA (1998). Inhibition of rat ventricular IK1 with antisense oligonucleotides targeted to Kir2.1 mRNA. *Am J Physiol* 274, H892-H900.

Nerbonne JM & Kass RS (2005). Molecular physiology of cardiac repolarization. *Physiol Rev* 85, 1205-1253.

Nielsen NH, Winkel BG, Kanters JK, Schmitt N, Hofman-Bang J, Jensen HS, Bentzen BH, Sigurd B, Larsen LA, Andersen PS, Haunso S, Kjeldsen K, Grunnet M, Christiansen

M, & Olesen SP (2007). Mutations in the Kv1.5 channel gene KCNA5 in cardiac arrest patients. *Biochem Biophys Res Commun* 354, 776-782.

Noma A, Kotake H, & Irisawa H (1980). Slow inward current and its role mediating the chronotropic effect of epinephrine in the rabbit sinoatrial node. *Pflugers Arch* 388, 1-9.

Noma A & Trautwein W (1978). Relaxation of the ACh-induced potassium current in the rabbit sinoatrial node cell. *Pflugers Arch* 377, 193-200.

Ohno S, Zankov DP, Ding WG, Itoh H, Makiyama T, Doi T, Shizuta S, Hattori T, Miyamoto A, Naiki N, Hancox JC, Matsuura H, & Horie M (2011). KCNE5 (KCNE1L) variants are novel modulators of Brugada syndrome and idiopathic ventricular fibrillation. *Circ Arrhythm Electrophysiol* 4, 352-361.

Olesen MS, Jespersen T, Nielsen JB, Liang B, Moller DV, Hedley P, Christiansen M, Varro A, Olesen SP, Haunso S, Schmitt N, & Svendsen JH (2011). Mutations in sodium channel beta-subunit SCN3B are associated with early-onset lone atrial fibrillation. *Cardiovasc Res* 89, 786-793.

Ono K & Iijima T (2010). Cardiac T-type Ca(2+) channels in the heart. *J Mol Cell Cardiol* 48, 65-70.

Panaghie G & Abbott GW (2006). The impact of ancillary subunits on small-molecule interactions with voltage-gated potassium channels. *Curr Pharm Des* 12, 2285-2302.

Patel SP & Campbell DL (2005). Transient outward potassium current, 'Ito', phenotypes in the mammalian left ventricle: underlying molecular, cellular and biophysical mechanisms. *J Physiol* 569, 7-39.

Patton DE, West JW, Catterall WA, & Goldin AL (1992). Amino acid residues required for fast Na(+)-channel inactivation: charge neutralizations and deletions in the III-IV linker. *Proc Natl Acad Sci USA* 89, 10905-10909.

Peretz A, Schottelndreier H, haron-Shamgar LB, & Attali B (2002). Modulation of homomeric and heteromeric KCNQ1 channels by external acidification. *J Physiol* 545, 751-766.

Petitprez S, Jespersen T, Pruvot E, Keller DI, Corbaz C, Schlapfer J, Abriel H, & Kucera JP (2008). Analyses of a novel SCN5A mutation (C1850S): conduction vs. repolarization disorder hypotheses in the Brugada syndrome. *Cardiovasc Res* 78, 494-504.

Pfeufer A, van NC, Marciante KD, Arking DE, Larson MG, Smith AV, Tarasov KV, Muller M, Sotoodehnia N, Sinner MF, Verwoert GC, Li M, Kao WH, Kottgen A, Coresh J, Bis JC, Psaty BM, Rice K, Rotter JI, Rivadeneira F, Hofman A, Kors JA, Stricker BH, Uitterlinden AG, van Duijn CM, Beckmann BM, Sauter W, Gieger C, Lubitz SA, Newton-Cheh C, Wang TJ, Magnani JW, Schnabel RB, Chung MK, Barnard J, Smith JD, Van Wagoner DR, Vasan RS, Aspelund T, Eiriksdottir G, Harris TB, Launer LJ, Najjar SS, Lakatta E, Schlessinger D, Uda M, Abecasis GR, Muller-Myhsok B, Ehret GB, Boerwinkle E, Chakravarti A, Soliman EZ, Lunetta KL, Perz S, Wichmann HE, Meitinger T, Levy D, Gudnason V, Ellinor PT, Sanna S, Kaab S, Witteman JC, Alonso A, Benjamin EJ, & Heckbert SR (2010). Genome-wide association study of PR interval. *Nat Genet* 42, 153-159.

Piper DR, Hinz WA, Tallurri CK, Sanguinetti MC, & Tristani-Firouzi M (2005). Regional specificity of human ether-a'-go-go-related gene channel activation and inactivation gating. *J Biol Chem* 280, 7206-7217.

Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, Clark J, Deymeer F, George AL, Jr., Fish FA, Hahn A, Nitu A, Ozdemir C, Serdaroglu P, Subramony SH, Wolfe G, Fu YH, & Ptacek LJ (2001). Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 105, 511-519.

Poelzing S & Veeraraghavan R (2007). Heterogeneous ventricular chamber response to hypokalemia and inward rectifier potassium channel blockade underlies bifurcated T wave in guinea pig. *Am J Physiol Heart Circ Physiol* 292, H3043-H3051.

Potet F, Scott JD, Mohammad-Panah R, Escande D, & Baro I (2001). AKAP proteins anchor cAMP-dependent protein kinase to KvLQT1/IsK channel complex. *Am J Physiol Heart Circ Physiol* 280, H2038-H2045.

Preisig-Muller R, Schlichthorl G, Goerge T, Heinen S, Bruggemann A, Rajan S, Derst C, Veh RW, & Daut J (2002). Heteromerization of Kir2.x potassium channels contributes to the phenotype of Andersen's syndrome. *Proc Natl Acad Sci USA* 99, 7774-7779.

Pusch M (1998). Increase of the single-channel conductance of KvLQT1 potassium channels induced by the association with minK. *Pflugers Arch* 437, 172-174.

Qin N, D'Andrea MR, Lubin ML, Shafaee N, Codd EE, & Correa AM (2003). Molecular cloning and functional expression of the human sodium channel beta1B subunit, a novel splicing variant of the beta1 subunit. *Eur J Biochem* 270, 4762-4770.

Qu J, Kryukova Y, Potapova IA, Doronin SV, Larsen M, Krishnamurthy G, Cohen IS, & Robinson RB (2004). MiRP1 modulates HCN2 channel expression and gating in cardiac myocytes. *J Biol Chem* 279, 43497-43502.

Qu Y, Isom LL, Westenbroek RE, Rogers JC, Tanada TN, McCormick KA, Scheuer T, & Catterall WA (1995). Modulation of cardiac Na+ channel expression in Xenopus oocytes by beta 1 subunits. *J Biol Chem* 270, 25696-25701.

Qu Y, Rogers J, Tanada T, Scheuer T, & Catterall WA (1994). Modulation of cardiac Na+ channels expressed in a mammalian cell line and in ventricular myocytes by protein kinase C. *Proc Natl Acad Sci USA* 91, 3289-3293.

Qu Y, Rogers JC, Tanada TN, Catterall WA, & Scheuer T (1996). Phosphorylation of S1505 in the cardiac Na+ channel inactivation gate is required for modulation by protein kinase C. *J Gen Physiol* 108, 375-379.

Radicke S, Cotella D, Graf EM, Banse U, Jost N, Varro A, Tseng GN, Ravens U, & Wettwer E (2006). Functional modulation of the transient outward current Ito by KCNE beta-subunits and regional distribution in human non-failing and failing hearts. *Cardiovasc Res* 71, 695-703.

Radicke S, Cotella D, Graf EM, Ravens U, & Wettwer E (2005). Expression and function of dipeptidyl-aminopeptidase-like protein 6 as a putative beta-subunit of human cardiac transient outward current encoded by Kv4.3. *J Physiol* 565, 751-756.

Radicke S, Vaquero M, Caballero R, Gomez R, Nunez L, Tamargo J, Ravens U, Wettwer E, & Delpon E (2008). Effects of MiRP1 and DPP6 beta-subunits on the blockade induced by flecainide of Kv4.3/KChIP2 channels. *Br J Pharmacol* 154, 774-786.

Ravens U & Dobrev D (2003). Cardiac sympathetic innervation and control of potassium channel function. *J Mol Cell Cardiol* 35, 137-139.

Ravn LS, Aizawa Y, Pollevick GD, Hofman-Bang J, Cordeiro JM, Dixen U, Jensen G, Wu Y, Burashnikov E, Haunso S, Guerchicoff A, Hu D, Svendsen JH, Christiansen M, &

Antzelevitch C (2008). Gain of function in IKs secondary to a mutation in KCNE5 associated with atrial fibrillation. *Heart Rhythm* 5, 427-435.

Ravn LS, Hofman-Bang J, Dixen U, Larsen SO, Jensen G, Haunso S, Svendsen JH, & Christiansen M (2005). Relation of 97T polymorphism in KCNE5 to risk of atrial fibrillation. *Am J Cardiol* 96, 405-407.

Rougier JS, van Bemmelen MX, Bruce MC, Jespersen T, Gavillet B, Apotheloz F, Cordonier S, Staub O, Rotin D, & Abriel H (2005). Molecular determinants of voltage-gated sodium channel regulation by the Nedd4/Nedd4-like proteins. *Am J Physiol Cell Physiol* 288, C692-C701.

Samie FH, Berenfeld O, Anumonwo J, Mironov SF, Udassi S, Beaumont J, Taffet S, Pertsov AM, & Jalife J (2001). Rectification of the background potassium current: a determinant of rotor dynamics in ventricular fibrillation. *Circ Res* 89, 1216-1223.

Sanguinetti MC, Curran ME, Spector PS, & Keating MT (1996a). Spectrum of HERG K+-channel dysfunction in an inherited cardiac arrhythmia. *Proc Natl Acad Sci USA* 93, 2208-2212.

Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, & Keating MT (1996b). Coassembly of K(V)LQT1 and minK (IsK) proteins to form cardiac I(Ks) potassium channel. *Nature* 384, 80-83.

Sanguinetti MC, Jiang C, Curran ME, & Keating MT (1995). A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell* 81, 299-307.

Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER, Siegelbaum SA, & Tibbs GR (1998). Identification of a gene encoding a hyperpolarization-activated pacemaker channel of brain. *Cell* 93, 717-729.

Sasaki N, Mitsuiye T, Wang Z, & Noma A (1994). Increase of the delayed rectifier K+ and Na(+)-K+ pump currents by hypotonic solutions in guinea pig cardiac myocytes. *Circ Res* 75, 887-895.

Shi W, Wymore R, Yu H, Wu J, Wymore RT, Pan Z, Robinson RB, Dixon JE, McKinnon D, & Cohen IS (1999). Distribution and prevalence of hyperpolarization-activated cation channel (HCN) mRNA expression in cardiac tissues. *Circ Res* 85, e1-e6.

Sizarov A, Devalla HD, Anderson RH, Passier R, Christoffels VM, & Moorman AF (2011). Molecular analysis of patterning of conduction tissues in the developing human heart. *Circ Arrhythm Electrophysiol* 4, 532-542.

Soltysinska E, Olesen SP, Christ T, Wettwer E, Varro A, Grunnet M, & Jespersen T (2009). Transmural expression of ion channels and transporters in human nondiseased and end-stage failing hearts. *Pflugers Arch* 459, 11-23.

Soom M, Schonherr R, Kubo Y, Kirsch C, Klinger R, & Heinemann SH (2001). Multiple PIP2 binding sites in Kir2.1 inwardly rectifying potassium channels. *FEBS Lett* 490, 49-53.

Spector PS, Curran ME, Zou A, Keating MT, & Sanguinetti MC (1996). Fast inactivation causes rectification of the IKr channel. *J Gen Physiol* 107, 611-619.

Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, & Keating MT (1997). Mutations in the hminK gene cause long QT syndrome and suppress IKs function. *Nat Genet* 17, 338-340.

Sridhar A, da Cunha DN, Lacombe VA, Zhou Q, Fox JJ, Hamlin RL, & Carnes CA (2007). The plateau outward current in canine ventricle, sensitive to 4-aminopyridine, is a constitutive contributor to ventricular repolarization. *Br J Pharmacol* 152, 870-879.

Staub O, Dho S, Henry P, Correa J, Ishikawa T, McGlade J, & Rotin D (1996). WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na+ channel deleted in Liddle's syndrome. *EMBO J* 15, 2371-2380.

Striessnig J (1999). Pharmacology, structure and function of cardiac L-type Ca(2+) channels. *Cell Physiol Biochem* 9, 242-269.

Sunose H, Liu J, & Marcus DC (1997). cAMP increases K+ secretion via activation of apical IsK/KvLQT1 channels in strial marginal cells. *Hear Res* 114, 107-116.

Szabo G, Szentandrassy N, Biro T, Toth BI, Czifra G, Magyar J, Banyasz T, Varro A, Kovacs L, & Nanasi PP (2005). Asymmetrical distribution of ion channels in canine and human left-ventricular wall: epicardium versus midmyocardium. *Pflugers Arch* 450, 307-316.

Taira N, Takahashi K, & Hosono M (1987). Effect of DHP-218, a novel dihydropyridine phosphonate, on atrioventricular nodal conductivity compared with its vascular effect in dogs. *J Cardiovasc Pharmacol* 10, 274-279.

Takano M & Kuratomi S (2003). Regulation of cardiac inwardly rectifying potassium channels by membrane lipid metabolism. *Prog Biophys Mol Biol* 81, 67-79.

Tan BH, Pundi KN, Van Norstrand DW, Valdivia CR, Tester DJ, Medeiros-Domingo A, Makielski JC, & Ackerman MJ (2010). Sudden infant death syndrome-associated mutations in the sodium channel beta subunits. *Heart Rhythm* 7, 771-778.

Tanabe T, Takeshima H, Mikami A, Flockerzi V, Takahashi H, Kangawa K, Kojima M, Matsuo H, Hirose T, & Numa S (1987). Primary structure of the receptor for calcium channel blockers from skeletal muscle. *Nature* 328, 313-318.

Terrenoire C, Clancy CE, Cormier JW, Sampson KJ, & Kass RS (2005). Autonomic control of cardiac action potentials: role of potassium channel kinetics in response to sympathetic stimulation. *Circ Res* 96, e25-e34.

Tfelt-Hansen J, Winkel BG, Grunnet M, & Jespersen T (2009). Inherited Cardiac Diseases Caused by Mutations in the Nav1.5 Sodium Channel. *J Cardiovasc Electrophysiol* 21:107-15.

Tinel N, Diochot S, Borsotto M, Lazdunski M, & Barhanin J (2000). KCNE2 confers background current characteristics to the cardiac KCNQ1 potassium channel. *EMBO J* 19, 6326-6330.

Torres NS, Larbig R, Rock A, Goldhaber JI, & Bridge JH (2010). Na+ currents are required for efficient excitation-contraction coupling in rabbit ventricular myocytes: a possible contribution of neuronal Na+ channels. *J Physiol* 588, 4249-4260.

Trudeau MC, Warmke JW, Ganetzky B, & Robertson GA (1995). HERG, a human inward rectifier in the voltage-gated potassium channel family. *Science* 269, 92-95.

Ueda K, Valdivia C, Medeiros-Domingo A, Tester DJ, Vatta M, Farrugia G, Ackerman MJ, & Makielski JC (2008). Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci USA* 105, 9355-9360.

Unsold B, Kerst G, Brousos H, Hubner M, Schreiber R, Nitschke R, Greger R, & Bleich M (2000). KCNE1 reverses the response of the human K+ channel KCNQ1 to cytosolic pH changes and alters its pharmacology and sensitivity to temperature. *Pflugers Arch* 441, 368-378.

Valdivia CR, Ueda K, Ackerman MJ, & Makielski JC (2009). GPD1L links redox state to cardiac excitability by PKC-dependent phosphorylation of the sodium channel SCN5A. *Am J Physiol Heart Circ Physiol* 297, H1446-H1452.

van Bemmelen MX, Rougier JS, Gavillet B, Apotheloz F, Daidie D, Tateyama M, Rivolta I, Thomas MA, Kass RS, Staub O, & Abriel H (2004). Cardiac voltage-gated sodium channel Nav1.5 is regulated by Nedd4-2 mediated ubiquitination. *Circ Res* 95, 284-291.

Van Norstrand DW, Valdivia CR, Tester DJ, Ueda K, London B, Makielski JC, & Ackerman MJ (2007). Molecular and functional characterization of novel glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) mutations in sudden infant death syndrome. *Circulation* 116, 2253-2259.

Van PF, Clark KA, Chatelain FC, & Minor DL, Jr. (2004). Structure of a complex between a voltage-gated calcium channel beta-subunit and an alpha-subunit domain. *Nature* 429, 671-675.

Vandenberg CA (1987). Inward rectification of a potassium channel in cardiac ventricular cells depends on internal magnesium ions. *Proc Natl Acad Sci USA* 84, 2560-2564.

Vandenberg JI, Rees SA, Wright AR, & Powell T (1996). Cell swelling and ion transport pathways in cardiac myocytes. *Cardiovasc Res* 32, 85-97.

Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de JT, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, & Keating MT (1996). Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 12, 17-23.

Wang Z, Fermini B, & Nattel S (1993). Sustained depolarization-induced outward current in human atrial myocytes. Evidence for a novel delayed rectifier K+ current similar to Kv1.5 cloned channel currents. *Circ Res* 73, 1061-1076.

Wang Z, Tristani-Firouzi M, Xu Q, Lin M, Keating MT, & Sanguinetti MC (1999). Functional effects of mutations in KvLQT1 that cause long QT syndrome. *J Cardiovasc Electrophysiol* 10, 817-826.

Warren M, Guha PK, Berenfeld O, Zaitsev A, Anumonwo JM, Dhamoon AS, Bagwe S, Taffet SM, & Jalife J (2003). Blockade of the inward rectifying potassium current terminates ventricular fibrillation in the guinea pig heart. *J Cardiovasc Electrophysiol* 14, 621-631.

Watanabe H, Darbar D, Kaiser DW, Jiramongkolchai K, Chopra S, Donahue BS, Kannankeril PJ, & Roden DM (2009). Mutations in sodium channel beta1- and beta2-subunits associated with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2, 268-275.

Watanabe H, Koopmann TT, Le SS, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kaab S, Wichmann HE, Hasdemir C, Aizawa Y, Wilde AA, Roden DM, & Bezzina CR (2008). Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 118, 2260-2268.

Weerapura M, Nattel S, Chartier D, Caballero R, & Hebert TE (2002). A comparison of currents carried by HERG, with and without coexpression of MiRP1, and the native rapid delayed rectifier current. Is MiRP1 the missing link? *J Physiol* 540, 15-27.

Weiss R, Barmada MM, Nguyen T, Seibel JS, Cavlovich D, Kornblit CA, Angelilli A, Villanueva F, McNamara DM, & London B (2002). Clinical and molecular

heterogeneity in the Brugada syndrome: a novel gene locus on chromosome 3. *Circulation* 105, 707-713.

West JW, Patton DE, Scheuer T, Wang Y, Goldin AL, & Catterall WA (1992). A cluster of hydrophobic amino acid residues required for fast Na(+)-channel inactivation. *Proc Natl Acad Sci USA* 89, 10910-10914.

Wickman K, Krapivinsky G, Corey S, Kennedy M, Nemec J, Medina I, & Clapham DE (1999). Structure, G protein activation, and functional relevance of the cardiac G protein-gated K+ channel, IKACh. *Ann N Y Acad Sci* 868, 386-398.

Wu DM, Jiang M, Zhang M, Liu XS, Korolkova YV, & Tseng GN (2006). KCNE2 is colocalized with KCNQ1 and KCNE1 in cardiac myocytes and may function as a negative modulator of I(Ks) current amplitude in the heart. *Heart Rhythm* 3, 1469-1480.

Wu G, Ai T, Kim JJ, Mohapatra B, Xi Y, Li Z, Abbasi S, Purevjav E, Samani K, Ackerman MJ, Qi M, Moss AJ, Shimizu W, Towbin JA, Cheng J, & Vatta M (2008). alpha-1-syntrophin mutation and the long-QT syndrome: a disease of sodium channel disruption. *Circ Arrhythm Electrophysiol* 1, 193-201.

Xue T, Marban E, & Li RA (2002). Dominant-negative suppression of. *Circ Res* 90, 1267-1273.

Yang EK, Alvira MR, Levitan ES, & Takimoto K (2001). Kvbeta subunits increase expression of Kv4.3 channels by interacting with their C termini. *J Biol Chem* 276, 4839-4844.

Yu H, Wu J, Potapova I, Wymore RT, Holmes B, Zuckerman J, Pan Z, Wang H, Shi W, Robinson RB, El-Maghrabi MR, Benjamin W, Dixon J, McKinnon D, Cohen IS, & Wymore R (2001). MinK-related peptide 1: A beta subunit for the HCN ion channel subunit family enhances expression and speeds activation. *Circ Res* 88, E84-E87.

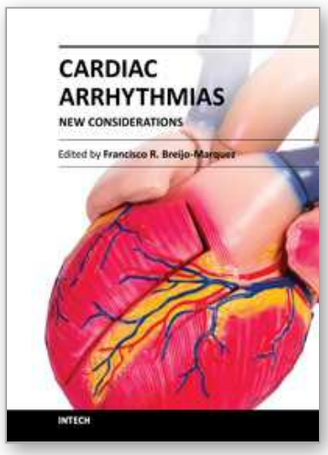
Yuill KH & Hancox JC (2002). Characteristics of single cells isolated from the atrioventricular node of the adult guinea-pig heart. *Pflugers Arch* 445, 311-320.

Zaritsky JJ, Redell JB, Tempel BL, & Schwarz TL (2001). The consequences of disrupting cardiac inwardly rectifying K(+) current (I(K1)) as revealed by the targeted deletion of the murine Kir2.1 and Kir2.2 genes. *J Physiol* 533, 697-710.

Zaza A, Robinson RB, & DiFrancesco D (1996). Basal responses of the L-type Ca2+ and hyperpolarization-activated currents to autonomic agonists in the rabbit sino-atrial node. *J Physiol* 491 (Pt 2), 347-355.

Zhang SH, Kobayashi R, Graves PR, Piwnica-Worms H, & Tonks NK (1997). Serine phosphorylation-dependent association of the band 4.1-related protein-tyrosine phosphatase PTPH1 with 14-3-3beta protein. *J Biol Chem* 272, 27281-27287.

Zicha S, Xiao L, Stafford S, Cha TJ, Han W, Varro A, & Nattel S (2004). Transmural expression of transient outward potassium current subunits in normal and failing canine and human hearts. *J Physiol* 561, 735-748.



Cardiac Arrhythmias - New Considerations

Edited by Prof. Francisco R. Breijo-Marquez

ISBN 978-953-51-0126-0

Hard cover, 534 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

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 electrocardiographyc 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!

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Thomas Jespersen (2012). The Cardiac Ion Channels, Cardiac Arrhythmias - New Considerations, Prof. Francisco R. Breijo-Marquez (Ed.), ISBN: 978-953-51-0126-0, InTech, Available from: http://www.intechopen.com/books/cardiac-arrhythmias-new-considerations/the-cardiac-ion-channels

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen