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The Cardiac Ion Channels

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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.

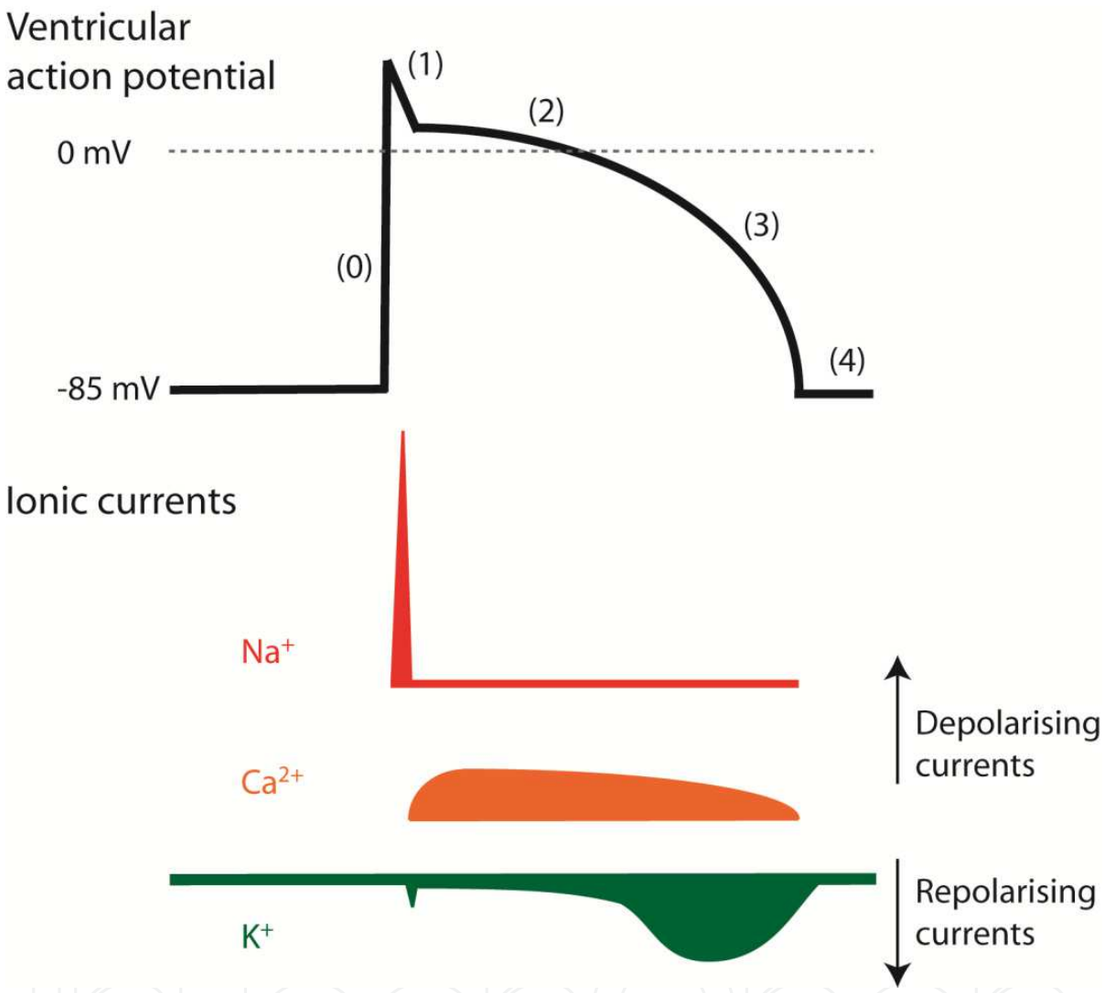

Fig. 1. Ionic currents shape the cardiac action potential. Illustration of a ventricular action potential and the underlying currents.

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.

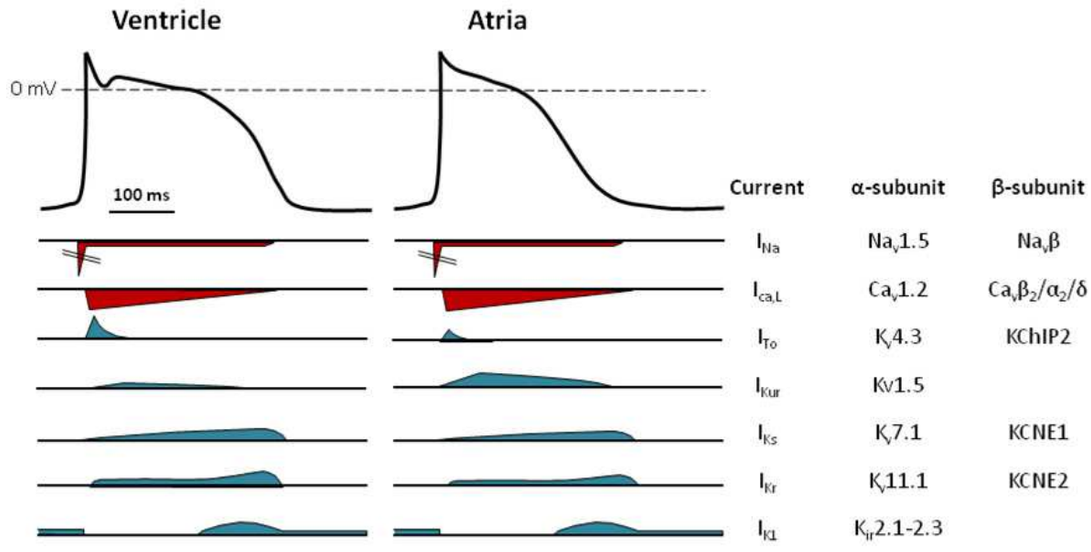

Fig. 2. The major ion channels responsible for the ventricular and atrial action potentials.
An illustration of the different depolarising (red) and repolarising (blue) currents underlying the action potential in the ventricle and the atria. The current names, together with the major proteins constituting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

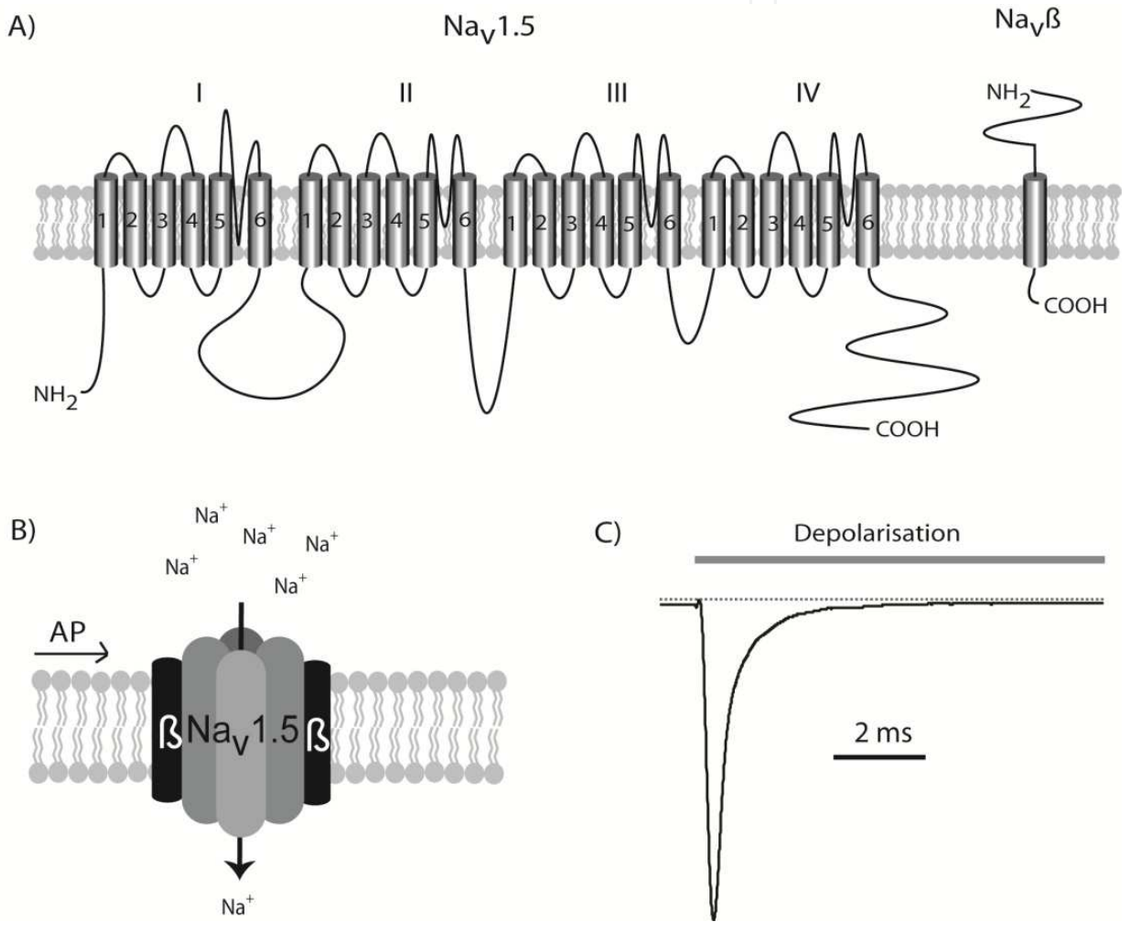

Fig. 3. The cardiac $Na_v1.5$ sodium channel. A) The SCN5A gene is transcribed into the large $Na_v1.5$ protein containing 24 transmembrane domains. B) This protein can fold up into a functional channel, but it is believed to be modulated by the Navβ one-transmembrane spanning β-subunits *in vivo*. When 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.

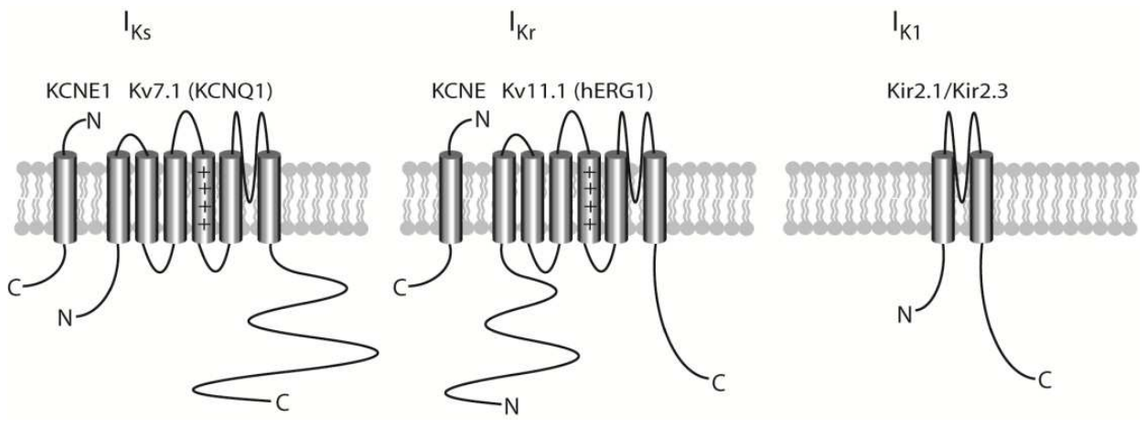

Fig. 4. Topology of the major repolarising potassium channels and their β-subunits.

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.

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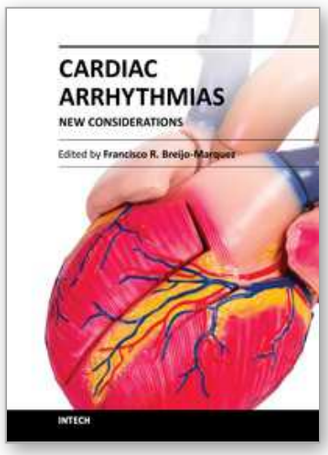

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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five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

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