Chapter 2
Potassium Channels Implicated in the Short QT Syndrome

The work presented in this thesis centres on the in silico investigation of arrhythmia substrates in an inherited cardiac condition: the short QT syndrome (SQTS). Chapter 3 provides detailed background information on this syndrome (which consequently will be discussed only briefly here). The three variants of the SQTS examined in this thesis—SQT1, SQT2 and SQT3—involve gene mutations that affect proteins forming different potassium channels [1–6]. SQT1 affects the *hERG* channel, which is responsible for the rapid-delayed outward rectifier potassium current (I_{Kr}) [7–9], SQT2 affects the *KCNQ1* gene, which encodes the α-subunit of channels mediating slow-delayed outward rectifier potassium channel (I_{Ks}) [10]. SQT3 affects *KCNJ2*, which encodes the Kir2.1 protein that contributes to inwardly-rectifying potassium channel current (I_{K1}) [11]. Building upon the brief descriptions of these channels in Chap. 1, this chapter gives a detailed consideration of their structure and characteristics.

2.1 Rectification

In Sect. 1.3, it was established that the lipid bilayer of the cell membrane can be thought of as a capacitor that separates charges in the intracellular and extracellular regions. The charges separated are the ions in intracellular/extracellular fluid that can flow across the membrane through ion channels, when these are in a conducting state. The ion channels are thus resistors. Simple resistors follow Ohm's law:

$$V = IR \tag{2.1}$$

where V is the voltage (membrane potential), I is the current and R is the resistance. To describe the biophysical properties of ion channels during voltage clamp experiments, the conductance of the channels (inverse of resistance) is normally employed. If an ion channel has a linear current-voltage (I–V) relationship, i.e., the slope (conductance) is linear, the channel is said to show 'ohmic' behaviour (Fig. 2.1).

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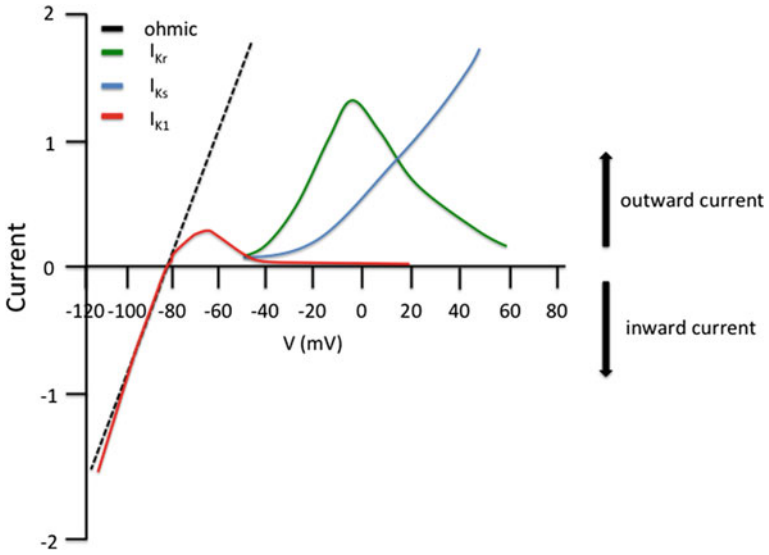

Fig. 2.1 Schematic representation of the I–V relationship for an ohmic channel and channels showing rectification. The black dashed line represents an ohmic channel with a linear I–V relationship. The green line shows the I–V relationship for I_{Kr}, which shows outward rectification. The blue line represents the I–V relationship for I_{Ks}, which also shows outward rectification and the red line represents I_{K1}, which is an inwardly rectifying current because it passes current preferentially in the inward direction. Note that currents are not drawn to scale

When the I–V relationship of the channel is nonlinear, i.e., channel conductance changes with voltage, the channel is said to show voltage-dependent rectification (Fig. 2.1). In this event, the channel passes current preferentially in one direction over another. For example, Fig. 2.1 shows a schematic representation of the I–V relationships for four channels: an ohmic channel, hERG/I_{Kr} (outward rectifier), KCNQ1-KCNE1/I_{Ks} (outward rectifier) and KCNJ2/I_{K1} (inward rectifier). hERG/I_{Kr} and KCNQ1-KCNE1/I_{Ks} pass current preferentially in the outward direction while KCNJ2/I_{K1} passes current preferentially in the inward direction over the outward direction.

2.2 The hERG/I_{Kr} Potassium Channel

The significance of the hERG/I_{Kr} channel for normal human cardiac electrical activity was discovered when inherited gene mutations to hERG resulted in long QT syndrome (LQTS) [12–14]; a cardiac repolarization disorder. In the LQTS, patients have a lengthened QT interval on the ECG and become susceptible to the potentially fatal arrhythmia *torsades de pointes* [15–17]. hERG is also now known to be responsible for pharmacologically induced (“acquired”) Long QT syndrome

[16, 18–20]. This is due to structural features of the channel that have been established to render it particularly susceptible to pharmacological blockade [15, 16, 21, 22]. The consideration of hERG here focuses on its electrophysiological properties and for detailed consideration of the basis of its pharmacological promiscuity the reader is referred to [15, 16, 21, 22]. Some antihistamines and antibiotics have also been known to cause arrhythmia and sudden death through blockade of the hERG/I_{Kr} channel [23].

hERG/I_{Kr} is expressed in several tissue and cell types including cardiac [13], neurons, neuroendocrine glands [24, 25], smooth muscle [26] and tumour cells [27, 28]. Its expression is greatest in cardiac cells and this is the region that has received the greatest research focus and from which its properties and function are best understood. Heterologous expression studies have shown that hERG encodes the α-subunit of the I_{Kr} channel [13, 14, 29–31].

2.2.1 *hERG/I_{Kr} Potassium Channel Gating*

hERG/I_{Kr} plays a significant role in cardiac action potential repolarization; it is the channel that is largely responsible for the early and middle stages of ventricular action potential repolarization (phase 3; Fig. 1.1) after which I_{K1} (being responsible for terminal repolarization) takes over, bringing the membrane potential back to its normal resting value (phase 4; Fig. 1.1) [13, 14]. It is characterised by slow activation but fast and profound voltage-dependent inactivation [14, 29, 32–35]. Its inactivation (a non-conducting state) is considerably faster than its activation.

Figure 2.2 shows characteristic features of I_{hERG}. With depolarisation to more positive membrane potentials, outward I_{hERG} is elicited, which increases rapidly and then plateaus for the duration of the pulse. A step repolarization of the membrane potential (to a negative potential) results in a resurgent increase in I_{hERG} (tail current); this increase in I_{hERG} is despite the decrease in the driving force for K^+ out of the cell membrane. This is due to the rapid recovery of I_{hERG} from inactivation [13, 14, 33]. Eventually, via channel deactivation, I_{hERG} decreases bi-exponentially [36].

Further insight can be gleaned from the current-voltage (I–V) relation of I_{hERG}/I_{Kr} (Fig. 2.3). At the membrane resting potential (~ -80 mV), hERG/I_{Kr} channels are closed and in that state conduct no current. As the membrane is depolarised to more positive membrane potentials greater than ~ -60 mV, the channels get activated (open) and conduct current (Fig. 2.3); K^+ ions flow out of the cell across the cell membrane according to their electrochemical gradient. At the same time, the channel begins to inactivate. As hERG/I_{Kr} inactivation with progressive depolarisation is faster than its activation, channel inactivation with increasing depolarisation eventually overtakes channel activation resulting in the channel entering the non-conducting, inactivated state. This gives the current-voltage relationship a region of negative slope (Fig. 2.3). This helps to prolong phase 2 of the action potential. Eventually, the channel begins to deactivate (close) and also

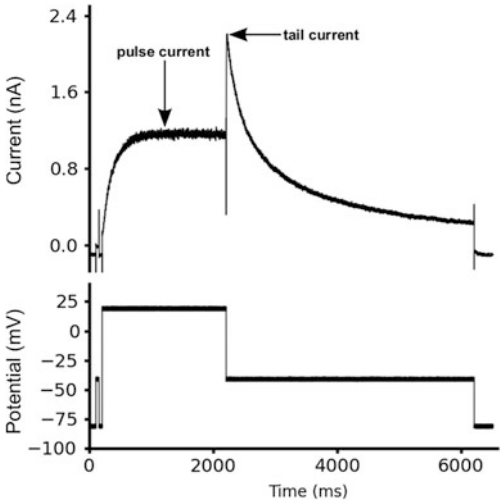

Fig. 2.2 Representative current trace for hERG elicited by a standard voltage protocol from a hERG-expressing Chinese Hamster Ovary (CHO) cell (recording made at 37 °C). Outward I_{hERG}/I_{Kr} current is elicited when the membrane potential is stepped to 20 mV from a holding potential of −80 mV. On stepping the membrane potential to −40 mV, I_{hERG}/I_{Kr} (tail current) of greater amplitude than that seen at the 20 mV are produced. Modified from [35]

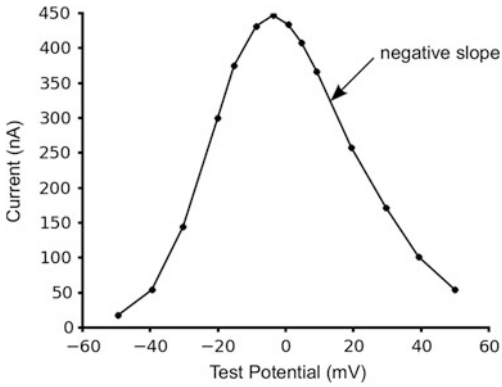

Fig. 2.3 Current-voltage (I–V) relationship for I_{hERG}/I_{Kr} (recorded in Xenopus oocytes). Depolarisation activates I_{hERG}/I_{Kr} causing an increase in outward current. At around 0 mV, I_{hERG}/I_{Kr} reaches a maximum then declines in amplitude with further depolarisation (negative slope region). Modified from [13]

begins to recover from inactivation. However, recovery from inactivation for hERG/I_{Kr} is faster than deactivation, thus allowing the channel to again conduct current, which repolarises the cell membrane (phase 3 of the action potential), returning it to its resting state (phase 4).

2.2.2 *hERG/I_{Kr} Channel Structure*

The hERG/I_{Kr} K^+ channel is a comprised of a protein tetramer consisting of four identical α-subunits [29, 37–39]. Each subunit contains six α-helical transmembrane domains (S1–S6). Functionally, each α-subunit can be divided into two parts: a voltage-sensing region and a pore-forming K^+-selective filter (Fig. 2.4). Segments S1–S4 form the transmembrane potential sensor region with S4 in particular having

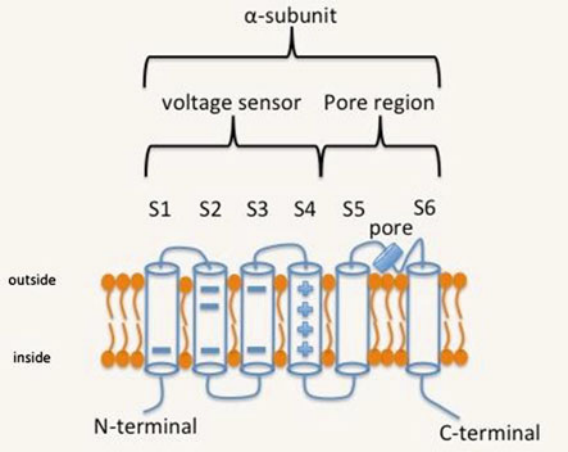

Fig. 2.4 Schematic diagram showing a representative hERG/I_{Kr} α-subunit. hERG channels consist of four identical α-subunits. Each subunit contains six transmembrane segments S1–S6. S4 has positively charged amino acids and acts as the main voltage sensor for transmembrane potential changes. The blue cylinder indicates the pore of the P-loop that acts as a K^+ selectivity filter by blocking or unblocking the pore. Intracellularly, the α-subunit has N and C termini

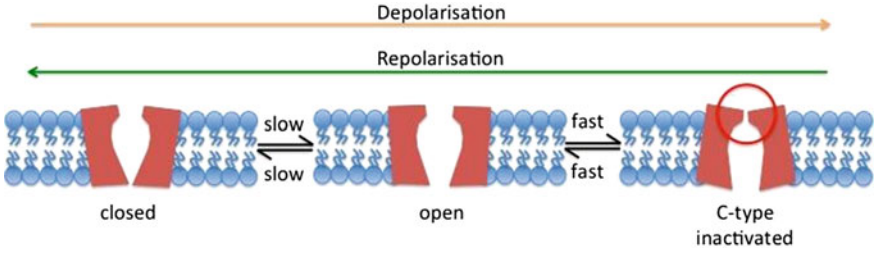

Fig. 2.5 Membrane depolarisation to voltages more positive than ~ -60 mV activates (opens) the channel slowly. With greater depolarisation, the channel rapidly inactivates (it undergoes C-type inactivation—a slight constriction of the K^+ selectivity filter). Repolarization reverses the whole process

positive charges, which allow it to react to a change in membrane potential by moving its position [40–43]. Voltage-sensor movement leads to conformational changes that open, inactivate or close the channel (Fig. 2.5). Segments S5–S6 form the ion permeation pathway and consist of the P-loop (S5) that penetrates the membrane and creates a pore through which ions enter or leave. Together, these traits confer voltage dependence and ion selectivity on the channel [40–43].

Below the P-loop is a water-filled cavity that is lined by S6 α-helices. In a conducting (open) state, i.e., in response to membrane depolarisation, all four S6 α-helices are spread out allowing the passage of K^+ ions. They crisscross in the closed state, forming a narrow cleft that blocks entry of K^+ ions [41]. hERG also

has a pair of intracellular termini (an N terminus and a C terminus), which contribute to its function. The N-terminus is responsible for channel deactivation following membrane depolarisation while mutations to the C-terminus affect trafficking and disrupt the processing of hERG channels [44, 45].

Voltage-gated K^+ channels can inactivate via two different mechanisms: rapid 'N-type' inactivation (also known as "ball and chain" type) and slow 'C-type' inactivation. N-type inactivation occurs when a ball-like structure (an intracellular protein segment) anchored to the channel's N-terminus blocks the channel pore [33] whereas 'C-type' inactivation has been suggested to occur via a slight narrowing of the K^+-selectivity filter [46] at the extracellular mouth. Deletion of the N-terminus removes 'N-type' inactivation but has no significant effect on hERG inactivation [33, 47] suggesting that hERG inactivates via 'C-type' inactivation. This was confirmed by removing 'C-type' inactivation via the Ser 631 Val mutation [48], which resulted in the elimination hERG inactivation. In addition, application of extracellular tetraethylammonium (TEA) blockade but not intracellular TEA blockade has been shown to slow inactivation suggesting that the process involves changes towards the channel exterior [49].

In addition to the four α-subunits, hERG also interacts with a β–subunit, MiRP1 (minK-related protein 1) in heterologous expression systems. The expression of MiRP1 in atrial or ventricular tissue is quite low but it is highly expressed in Purkinje fibres and the atrial pacemaking cells [50, 51]. The effect of this co-expression of the hERG α-subunit and MiRP1 is to reduce the trafficking of the channel to the cell membrane surface, reduce channel conductance and to increase channel deactivation [52]. As MiRP1 expression is low outside of the conduction system [53], it has been suggested that it may not function as hERG β–subunit in other regions and comparison of hERG with and without MiRP1 has shown that when hERG is heterologously expressed in mammalian instead of amphibian cells (*Xenopus* oocytes), it adequately recapitulates I_{Kr} [54]. Also, MiRP1 can co-assemble with a variety of other cardiac ion channels [53, 55], and so may exhibit broad interactions rather than being specific for hERG.

hERG is heteromeric and consists of two isoforms: hERG 1a (the major isoform) and hERG 1b, which differ by a truncated N-terminus in the latter. This heteromeric form of hERG (hERG 1a/1b) has recently been proposed to recapitulate native I_{Kr} more accurately than hERG 1a expressed alone [56, 57].

2.3 The KCNQ1-KCNE1/I_{Ks} Potassium Channel

Similar to the hERG/I_{Kr} potassium channel, the KCNQ1 potassium channel also plays a significant role in cardiac repolarization. The KCNQ1 α-subunit co-expresses with the KCNE1 β–subunit (minK) [40, 58, 59], the result of which is a protein complex that is responsible for the slow-delayed rectifier potassium channel I_{Ks}, which is partially responsible for action potential repolarization (phase 3) along with hERG/I_{Kr} [40, 58, 59]. In the event of an impairment to I_{Kr},

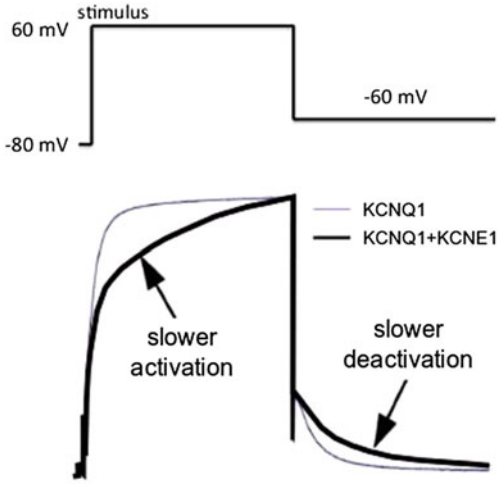

Fig. 2.6 Representative superimposed current traces for KCNQ1 (*purple*) and KCNQ1 + KCNE1 (black) elicited by a standard voltage protocol from KCNQ1-expressing oocytes (recording made at 36 °C). The *left arrow* shows the slower activation of KCNQ1 when co-expressed with KCNE1 when the membrane potential is stepped to 60 mV from a holding potential of −80 mV. On stepping the membrane potential to −60 mV, KCNQ1-KCNE1/I_{Ks} (tail current) deactivates more slowly than KCNQ1 (*right arrow*). Modified from [78]

e.g., channel block or gene mutation, I_{Ks} is a key component of repolarization reserve [40, 60, 61]. A *loss-of-function* mutation to the channel results in the first variant of the long QT syndrome LQTS1 [62–64].

In the ventricular wall, KCNQ1-KCNE1/I_{Ks} is heterogeneously distributed with its expression being very low in the mid-myocardial cells [60, 65–67]. Consequently, mid-myocardial cells have the longest APD and repolarise later than epicardial and endocardial cells. This leads to a transmural dispersion of repolarization across the ventricular wall [68–70] (meaning repolarization occurs at different rates in the different cell types that make up the wall of the myocardium), which is a substrate for re-entry. Re-entry is the continuous (usually several cycles) re-excitation of a cardiac tissue region by a single electrical signal and it usually results in arrhythmias.

In addition to being expressed in cardiac tissue, the *KCNQ1* protein is also expressed in epithelial tissue of different organs: stomach, cochlea, lungs, intestine and kidney. Its function in these tissue types is the transport of salt and water [65]. In humans, impairment to *KCNQ1* expression in epithelial tissue has been known to cause deafness [65, 71, 72], while in knockout mice, it causes deafness, balance problems and morphological abnormalities in the gastrointestinal tract and inner ear [65, 73, 74].

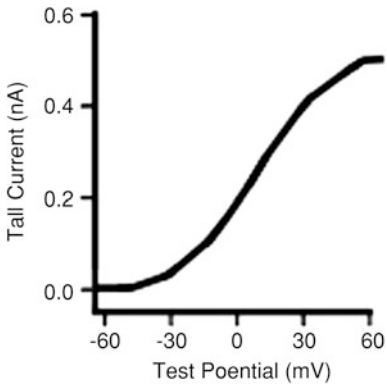

Fig. 2.7 I–V relationship of I_{Ks} tail current (recording in HEK 293 cells at 36 °C) measured from peak tail current to complete deactivation. Depolarisation activates KCNQ1-KCNE1/I_{Ks} causing an increase in outward current. Modified from [79]

2.3.1 KCNQ1-KCNE1/I_{Ks} Potassium Channel Gating

Similar to hERG, KCNQ1 is a voltage-gated channel, though its kinetic properties differ considerably from those of hERG (Fig. 2.8). Depolarisation activates (opens) KCNQ1 channels but very slowly. Upon further depolarisation, a fraction of the open channels inactivates [40, 60, 75–77] (Fig. 2.6). The channel is also characterised by slow deactivation kinetics [40, 60, 75–77]. Recovery from inactivation, however, is faster than deactivation and is seen as a hook on the current trace during the repolarization (Fig. 2.6). On co-expression with KCNE1, thus reproducing I_{Ks}, the current is enhanced (Fig. 2.6) because KCNE1 increases the single channel conductance causing a positive shift in voltage activation threshold, i.e., KCNE1 slows activation (Fig. 2.6) considerably and inactivation is completely eliminated [28, 60, 76]. Figure 2.7 shows the tail current I–V relationship for KCNQ1-KCNE1/I_{Ks} measured from peak tail current to complete deactivation.

2.3.2 KCNQ1-KCNE1/I_{Ks} Channel Structure

Structurally, KCNQ1 is a voltage-gated potassium channel like hERG described in Sect. 2.2.2 above. It consists of four identical subunits, each of which is comprised of six α-helical transmembrane domains (S1–S6). Segments S1–S4 form the voltage sensor while segments S5 and S6 form the ion permeation pathway with a pore loop and K^+ selectivity filter [58, 59, 65, 80] (Fig. 2.8). Each α-subunit also has intracellular 'N' and 'C' terminals. A major difference from hERG is KCNQ1's co-assembly with KCNE1 β–subunit, which together encode the human I_{Ks}. A representation of the KCNQ1-KCNE1 structure is shown in Fig. 2.8. The effect of the KCNE1 subunit is to stabilise the open state of the channel by altering the interaction between the pore loop, the K^+ selectivity filter and the S5/S6

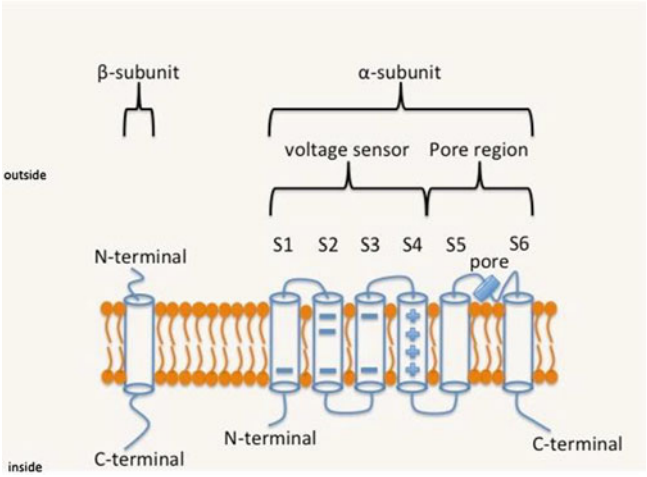

Fig. 2.8 A structural representation of the α and 0-subunits KCNQ1-KCNE1/I_{Ks}. KCNQ1 channels consist of four identical α-subunits. Each subunit contains six transmembrane segments S1−S6. S4 has positively charged amino acids and acts as the main voltage sensor for transmembrane potential changes. The blue cylinder indicates the pore of the P-loop that acts as a K^+ selectivity filter by blocking or unblocking the pore. KCNQ1 has intracellular N and C termini

segment [81]. However, the stoichiometry of KCNQ1:KCNE1 is still a matter of debate because there is no extant crystal structure for KCNQ1 with or without KCNE1 [82, 83]. Stoichiometries of 4:4 [84], 4:2 [85] and other forms [77, 83] have been proposed. A recent review can be found in [83].

2.4 The KCNJ2/I_{K1} Potassium Channel

The KCNJ2-encoded Kir2.1 protein belongs to the family of inwardly rectifying potassium (Kir) channels [86, 87]. Specifically, it belongs to the Kir2.x channel family. It is expressed in skeletal muscle, blood vessels, neurons and richly in cardiac tissue, where it is expressed in Purkinje fibres, atrial and ventricular tissues [87–92]. This family of channels allows K^+ to flow more easily into the cell than out of it. They therefore, preferentially pass current in the inward direction over the outward direction. A schematic representation of the I–V relation for I_{K1} is shown in Fig. 2.1 (red line) and an experimentally observed I–V relation is shown in Fig. 2.9.

Unlike voltage-gated K^+ channels such as I_{Kr} and I_{Ks}, the behaviour of Kir channels depends not only on the membrane potential but also predominantly on the electrochemical gradient of K^+ in the cell, i.e., the difference between the membrane potential and the K^+ reversal potential (E_K). They therefore have greater K^+ conductance at potentials negative to E_K and pass comparatively little current at depolarised membrane potentials, i.e., potentials positive to E_K (see red

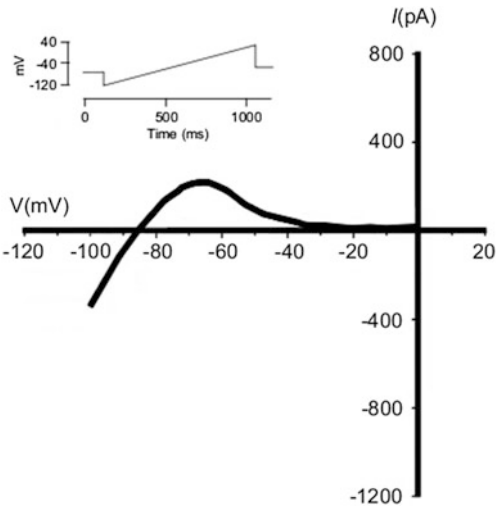

Fig. 2.9 Current-voltage (I-V) relations of the KCNJ2-encoded Kir2.1 channel expressed in HEK cells elicited by the ascending voltage ramp command shown inset. Modified from [93]

line in Figs. 2.1 and 2.9) [86–88, 94–97]. As membrane depolarisation increases further, the outward I_{K1} current decreases due to its inward rectification.

These characteristics make myocardial cells expressing I_{K1} have resting potentials close to E_K whereas cells without I_{K1} or those with an insignificant expression of I_{K1} have depolarised resting potentials and tend to show spontaneous activity, e.g., the SAN [98]. This is because with little I_{K1} present, the cells have high membrane resistances at negative voltages and so small changes in current can produce substantial changes in voltage (i.e. membrane potential is more 'labile' in the absence of I_{K1}). Consequently, in cardiac cells, I_{K1} plays a role in stabilizing the resting potential of the cell and in the duration of the action potential [86–88, 94–97]. As I_{K1} channels pass little outward current at depolarised potentials, there is little K^+ efflux through I_{K1} channels during phase 2 (the plateau phase) of the ventricular action potential [99] (Fig. 2.10b); therefore, the rectification property of I_{K1} channels also serves to maintain membrane depolarisation, thereby facilitating prolonged action potential duration. When phase 3 repolarization commences (via I_{Kr} and $I_{Ks)}$ and the membrane becomes more and more hyperpolarised, relatively large outward I_{K1} current is generated. This serves to accelerate terminal repolarization [100–103]. Figure 2.10b shows the I–V relationship of I_{K1} and relates it to the action potential, which is drawn sideways to give a better indication of the current amplitude at different phases of the action potential.

2.4.1 Kir2.1/I_{K1} Potassium Channel Gating

The inward rectification of I_{K1} and Kir2.x channels is due to blockade of outward K^+ movement through the channel pore by intracellular Mg^{2+} ions and polyamines

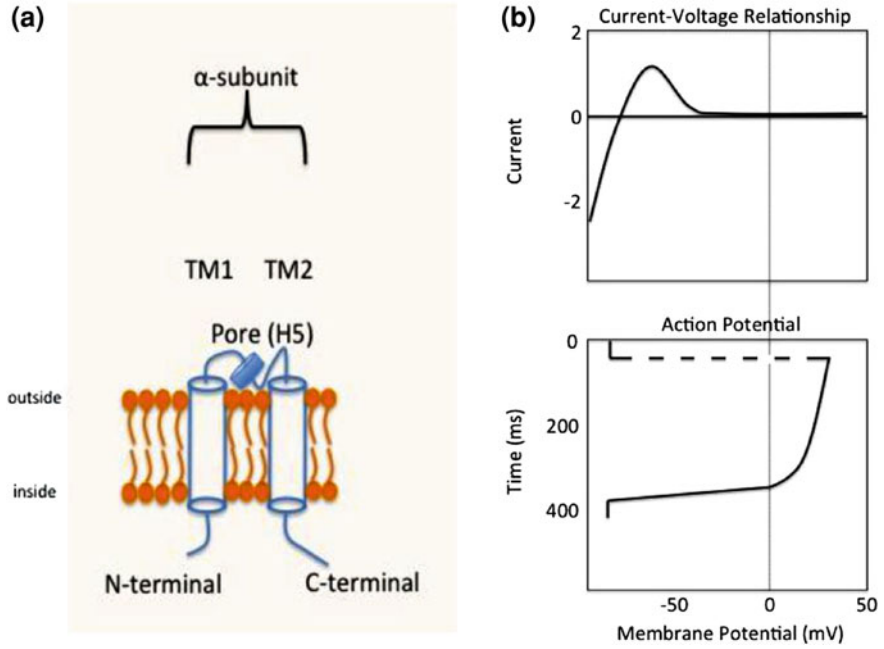

Fig. 2.10 A: structure of the Kir2.1/KCNJ2/I_{K1} channel. Each of its four α-subunits consists of two transmembrane segments (TM1 and TM2), a pore-forming loop (H5) and intracellular N and C terminals. B: I_{K1} current-voltage relationship related to the membrane action potential. The action potential is drawn sideways to give a better understanding of the contribution of I_{K1} during the action potential. The reader should focus on the repolarization phase and resting potential (the *non-dashed* parts of the action potential

[87, 97, 104–107]. At depolarised membrane potentials, the Mg^{2+} ions and polyamines such as spermine and spermidine, which are present in sub-micromolar quantities within the cell, reduce outward K^+ current. On hyperpolarisation, the Mg^{2+} ions and polyamines unblock the pore, thereby leading to increased current. This inward current first increases time-independently due to the unblocking of Mg^{2+} ions and then increases time-dependently due to unblocking of the polyamines. The unblocking of the Mg^{2+} ions is fast while the polyamine unblocking is slow [87, 108].

2.4.2 KCNJ2/I_{K1} Channel Structure

Functional Kir2.x channels (similarly to hERG/I_{Kr} and KCNQ1/I_{Ks}) also have four α-subunits but each subunit consists of only two transmembrane segments, TM1 and TM2 (Fig. 2.10a), which are highly homologous to the S5 and S6 domains of the K^+ channels discussed previously [87, 109, 110]. These two segments are

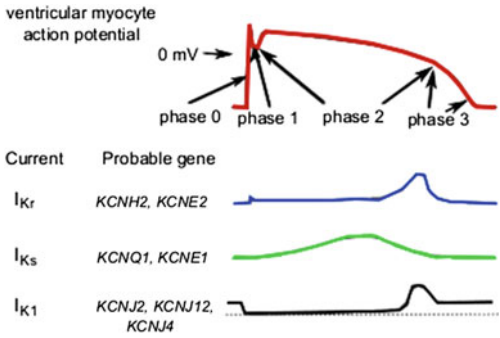

Fig. 2.11 A schematic diagram of the current profiles of I_{Kr}, I_{Ks} and I_{K1} ionic currents during a ventricular action potential. Also shown are the major gene candidates responsible for these currents. Modified from [111]

linked by the extracellular pore-forming loop or P-loop (H5), which acts as the K^+ selectivity filter. The intracellular 'N' and 'C' termini are also present. Unlike hERG/I_{Kr} and KCNQ1/I_{Ks}, there is no voltage sensor region or S4 segment; hence the channel is not truly voltage-gated in a traditional sense, with voltage-dependence instead occurring through voltage-dependent channel block/unblock by Mg^{2+} and polyamines (as described above).

2.5 Current Profiles During an Action Potential

Figure 2.11 shows a schematic diagram of the current profiles of each potassium channel currents discussed in this chapter during a ventricular action potential. I_{Kr} contributes during most of phase 3 repolarization, I_{K1} contributes later in phase 3 than I_{Kr} while I_{Ks} contributes earlier during phase 3 and some part of phase 2.

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