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Cardiac Strong Inward Rectifier Potassium Channels

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Abstract

Cardiac I_{K1} and I_{KACh} are the major potassium currents displaying classical strong inward rectification, a unique property that is critical for their roles in cardiac excitability. In the last fifteen years, research on I_{K1} and I_{KACh} has been propelled by the cloning of the underlying inwardly rectifying potassium (Kir) channels, the discovery of the molecular mechanism of strong rectification and the linking of a number of disorders of cardiac excitability to defects in genes encoding Kir channels. Disease-causing mutations in Kir genes have been shown experimentally to affect one or more of the following channel properties: structure, assembly, trafficking and regulation, with the ultimate effect of a gain-, or a loss-of-function of the channel. It is now established that I_{K1} and I_{KACh} channels are heterotetramers of Kir2 and Kir3 subunits, respectively. Each homomeric Kir channel has distinct biophysical and regulatory properties, and individual Kir subunits often display different patterns of regional, cellular and membrane distribution. These differences are thought to underlie important variations in the physiological properties of I_{K1} and I_{KACh}. It has become increasingly clear that the contribution of I_{K1} and I_{KACh} channels to cardiac electrical activity goes beyond their long recognized role in the stabilization of resting membrane potential and shaping the late phase of action potential repolarization in individual myocytes, but extends to being critical elements determining the overall electrical stability of the heart.

Keywords

Kir channels; I_{K1}; I_{KACh}; cardiac excitability

Introduction

The year 2009 is the 60th anniversary of the phenomenon of inward rectification. In 1949 Bernard Katz [1] described a novel potassium conductance in skeletal muscle which, in contrast to known, at that time, outwardly rectifying potassium conductance, increased at potentials negative to E_K equilibrium potential and decreased upon membrane depolarization. Inwardly rectifying potassium conductance was soon described in various types of cardiac muscle [2–6] and the following years witnessed great deal of early phenomenological work including establishment of major properties of inward rectification. Then cloning of the first members of inward rectifier channels in early 1990s [7,8] was followed by the discovery of the molecular

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mechanism of inward rectification [9–12], ultimately leading to genetic studies in experimental animals and identification and characterization of mutations in inward rectifier genes underlying various abnormalities of cardiac excitability.

Although inward rectifiers (Kir) comprise a large family of potassium channels (Figure 1) and share great structural similarities, only two subfamilies, Kir2 and Kir3, underlie classical 'strong inwardly rectifying currents' originally observed in skeletal and cardiac muscle. In the heart, there are only two similar types of these currents: (1) I_{K1}, a constitutively active Kir current which is more prominent in ventricular tissue, and (2) I_{KACh}, a receptor-activated Kir current which is more prominent in atrial tissue, as well as in SA node, where it plays critical role in the regulation of heart rate by vagal nerve activity, and AV node. This review will focus only on these two currents while another prominent cardiac Kir current carried by weakly rectifying K_{ATP} channels is covered separately in this issue.

Basic properties of classical inward rectification

General features of strong inward rectification are similar, but not identical, between I_{K1}, I_{KACh} and those produced by exogenously expressed Kir channels. Inward rectification is a *strongly voltage-dependent* decline of potassium conductance upon membrane depolarization producing a characteristic region of so-called '*negative slope*' conductance (Figure 2B). Another unique property of Kir currents is the *unusual dependence of rectification on extracellular* K^+ (K_{OUT}). Specifically, upon increase in K_{OUT} the Kir current/voltage relationship shifts nearly in parallel with the reversal potential for K^+ (E_K) leading to a 'crossover' phenomenon (Figure 2B). One important consequence of such behavior is that at potentials positive to the crossover, potassium conductance increases rather than decreases, against an expectation based on a reduced driving force for K^+ ions due to elevated K_{OUT}.

A Family of Inward Rectifier Potassium Channels

Currently, the family of Kir channels is comprised of seven subfamilies (Figure 1) [13], with distinct properties and relatively clear physiological roles. Only Kir2 and Kir3 channels, however, fit the definition of strong inward rectifiers. To date, 4 members of Kir2 subfamily and 4 members of Kir3 subfamily were cloned from mammals (Figure 1). A fifth member of Kir2 subfamily, Kir2.5, was cloned from the fish [14], and a fifth member of Kir3 subfamily, Kir3.5, was cloned from the *Xenopus laevis* [15]. Kir2 subfamily members are expressed in the heart, although levels of expression and localization of individual subunits is (cardiac) region- and species-dependent. Importantly, in the guinea-pig heart, Kir2.4 subunit has been localized to neuronal cells only [16], thus potentially reducing the candidate genes for mammalian I_{K1} channels to Kir2.1–2.3. Also, Kir3.2 and Kir3.3 were not detected in atrial tissue [17] leaving Kir3.1 and Kir3.4 as the only candidates for mammalian cardiac I_{KACh} [18].

Molecular mechanisms of strong inward rectification

Significant advances in our understanding of molecular mechanism of strong inward rectification were made in 1994 [9–12]. The studies showed that the essential properties of rectification could be explained by potent and strongly voltage-dependent block of Kir2 channels by intracellular organic cations called polyamines – spermine, spermidine and putrescine [19]. Earlier studies with cardiac I_{K1} indicated that block by intracellular Mg^{2+} ions may be the cause of rectification [20,21] but a number of quantitative characteristics of Mg^{2+} block have discounted it as the primary mechanism. In Kir2 channels variable weak residual rectification frequently observed in the nominal absence of polyamines and Mg^{2+} was shown to be largely due to the presence of impurities found in chemicals commonly used in electrophysiological experiments [22]. Polyamines are found in all cell types and total cellular

levels are in the low millimolar range [19]. Most of polyamines, however, are bound to intracellular agents such as RNA, DNA and ATP [23] while only free polyamines can cause rectification in Kir channels [24]. Of the polyamines, spermine is the most potent inducer of inward rectification, followed by spermidine, putrescine and then Mg^{2+} ions [9]. According to the above mechanism of inward rectification the 'activation' of inward rectifiers upon membrane hyperpolarization reflects unbinding of polyamines and Mg^{2+} from the Kir channel pore. Spermine unbinds the slowest and unbinding of Mg^{2+} and putrescine is quasi-instantaneous [25,26].

The general architecture of the Kir channels and key structures involved in permeation and block are well established. It follows from the crystallographic data obtained for transmembrane domains of bacterial homologs [27,28] that the selectivity filter containing a GYG signature motif is located close to the extracellular side of the membrane. It is then followed by a water cavity of ~10 Å in diameter and the pore then narrows toward the intracellular side of the membrane (Figure 2A). Cytoplasmic domains of mammalian Kir channels [29,30] have been crystallized as well, and the data suggest significant widening of the intracellular part of the pore (Figure 2A) which is likely to be as long as its transmembrane counterpart. Early studies have identified a number of residues critical for inward rectification, including D172 [31], a 'rectification controller' located at the level of the water cavity, and the two acidic residues in the cytoplasmic region, E224 [32] and E299 [33] (aa numbering for Kir2.1 sequence; Figure 2A). In Kir2 channels D172 is responsible for so-called 'steep' (highly voltage-dependent) part of the rectification, while E224 and E299 are involved in the 'shallow' (less voltage-dependent) part of rectification. There is strong evidence that polyamines (e.g. spermine) bind with strong affinity at the deep binding site in the vicinity of D172 and selectivity filter. In contrast, a ring of acidic (E224 and E299) residues provides a low-affinity binding site for polyamines. The pore is long enough to easily accommodate two or more polyamines like spermine, the longest (~16–18 Å) of the polyamines. Neither of the above residues is unique in rectification process. Introducing a negative charge at any position facing the inner cavity in a non-rectifying Kir channel (e.g. Kir6.2) confers strong inward rectification [34], and D255 and D259 have also been shown to be involved in rectification [30].

Spermine can also induce strong inward rectification in native I_{KACh} channels [35] although in underlying Kir3.1/Kir3.4 channels only half of the residues equivalent to D172 and E224 in Kir2.1 are present (all originating from Kir3.1 subunit). Importantly, neutralization of the above negative charges in Kir3.1/Kir3.4 channels has little effect on rectification [36] suggesting the involvement of other residues including those at the base of the selectivity filter [37].

Despite the formal simplicity of the phenomenon of polyamine-induced rectification, details of the mechanism of block, e.g., origin of strong voltage dependence of rectification [38], location of polyamine binding sites [39], are unclear. It should be noted that a number of experimental and theoretical findings cannot be easily reconciled with the pore blocking mechanism of strong rectification and therefore other mechanisms have been proposed [40, 41].

Differential properties of Kir2 and Kir3 channels

The single channel conductances of exogenously expressed Kir2 and Kir3 channels generally fall in distinct groups: ~20–31 pS for Kir2.1 [8,16,42–44], ~34–42 pS for Kir2.2 [16,45,46], ~10–14 pS for Kir2.3 [16,47–49], ~15 pS for Kir2.4 [50] and ~42 pS for Kir3.1 [7].

The sensitivity to extracellular Ba^{2+}, a potent and selective blocker of strong inward rectifiers, is different among the members of Kir2 and Kir3 subfamilies. In Kir2 channels the following

sequence of Ba^{2+} sensitivity has been established: (most to least sensitive): Kir2.2>Kir2.1>Kir2.3>Kir2.4 [16,51,52]. Different isoforms of Kir3 channels display similar sensitivities to extracellular Ba^{2+} [53] but ~100 fold less sensitive than Kir2.1 [54] when tested under similar recording conditions (−120 mV).

Kir2 channels display differential sensitivity to inhibition by intracellular pH with the following sequence within Kir2 subfamily: Kir2.3>Kir2.2>Kir2.1 (no data are available for Kir2.4) [55,56]. Kir2.3 displays a pKa of ~6.8–6.9 which is within the physiological/ pathophysiological range. Kir2.3 (and Kir2.4 [57]) is also very sensitive to inhibition by extracellular protons with a pKa of ~7.35 while Kir2.1 and Kir2.2 are virtually insensitive to pH_o within comparable range [24,58].

Both steady-state rectification profiles and kinetics of Kir2 and Kir3 channels activation add more to their differential properties. When the strength of rectification is compared under similar conditions, Kir2.2 channels pass less outward current than Kir2.1 and Kir2.3 at any depolarized potential (‘strong’ and ‘steep’ rectification). Further, while the relative amplitudes of Kir2.1 and Kir2.3 outward currents are similar, Kir2.3 channels carry substantially larger current at far depolarized potentials than Kir2.1 (‘shallow’ rectification) [59,60]. Currents through Kir3.1/Kir3.4 channels (a heteromeric assembly underlying I_{KACh} [18]) rectify much weaker than those mediated by Kir2.1 channels [61]. Although rectification of Kir3.1/Kir3.4 currents was not directly compared to that of Kir2.3, it is clearly weaker even when compared to the ‘weakest’ Kir2 member and the I/V relationships display small or no negative slope even over extended depolarized potentials (Figure 2C). There is evidence that rectification of Kir3 currents is affected by the subunit composition [62].

Opening of cardiac Kir channels upon membrane hyperpolarization is characterized by a quasi-instantaneous phase followed by slower time-dependent relaxation (activation) with relative amplitudes of each phase depending on the type of the channel and experimental conditions. In general, the contribution of quasi-instantaneous phase in Kir2 channels is relatively small and the activation kinetics is primarily determined by spermine unblock rate. Activation times are similar in Kir2.1 and Kir2.2 channels but ~7 fold longer in Kir2.3 channels when measured under high K_{OUT} [60]. Activation times strongly depend on the membrane potential and K_{OUT}, and for Kir2 channels the values fall in low msec/sub msec range. In contrast, opening of Kir3.1 channels is characterized by prominent quasi-instantaneous phase followed by much slower weakly voltage-dependent activation characterized by two time constants of ~50 ms and 400 ms [63]. Similar activation kinetics is observed upon co-expression of Kir3.1 and Kir3.4 [18]. Kurachi and co-workers provided evidence that activation of Kir3 currents can be modulated by G proteins through a complex mechanism involving Regulators of G Protein Signaling (RGS proteins) [64,65].

Inward rectification and cardiac excitability

The nature of inward rectification implies that Kir channels should contribute mostly to stabilization of the resting membrane potential and to the repolarization phase (phase 3) of the action potential (AP) with little or no effect on the plateau of the AP. Accordingly, Zaritsky et al [66,67] showed that suppression of I_{K1} in *Kir2.1* knock-out mice led to an increased number of spontaneously active isolated ventricular myocytes and broader APs, although no ectopic or re-entrant arrhythmias were observed. Similarly, >90% suppression of I_{K1} in adult transgenic (TG) mice expressing dominant negative Kir2.1-AAA subunits (channels have disrupted selectivity filter) in the heart led to prolongation of QRS and QT intervals as well as expected prolongation of AP [68]. Surprisingly, resting membrane potential in TG ventricular myocytes was nearly unaffected. More sever phenotype of I_{K1} suppression by adenoviral expression of Kir2.1-AAA subunits was observed in guinea-pig hearts [69,70]. In addition to

prolongation of AP, some isolated myocytes displayed pacemaker-like activity, and in 40% of Kir2.1-AAA animals ECG recordings revealed premature beats of ventricular origin.

Importantly, and somewhat unexpectedly, upregulation of I_{K1} in TG mice expressing Kir2.1 subunits led to multiple abnormalities of cardiac excitability including significant AP shortening and various types of atrial and ventricular arrhythmias [71,72]. Noujaim et al [73] also showed that hearts isolated from I_{K1} overexpressing TG mice could sustain stable high frequency re-entrant activity which could be terminated by application of low concentration of Ba^{2+}. Similarly, in mice, atrial fibrillation could be induced only in the presence of carbachol, and could not be induced in Kir3.4 knock-out mice deficient in I_{KACh} [74].

It becomes increasingly clear that heterogeneous repolarization may contribute to electrical instability of the heart, and therefore I_{K1} may play a significant role here as well. Consistent with this, experiments show that a LV/RV gradient of the outward I_{K1} may contribute to stabilization of reentrant arrhythmias in the guinea-pig heart [75], and the induced ventricular fibrillation could be terminated by I_{K1} blockade [76]. Studies using Kir2.1 channels in a tissue model of cultured neonatal rat ventricular myocytes also showed the contribution of I_{K1} heterogeneity to the genesis and stability of reentrant activity [77]. Similarly, a LA/RA gradient of I_{KACh} may also contribute to proarrhythmic phenotype [78].

I_{K1} also contributes to excitability in another unique way - through an unusual and strong dependence on K_{OUT}. Cardiac activity is accompanied by significant changes in the concentration of K^+ in the restricted (0.01 – 5 μm) intercellular space [79,80] during repetitive firing [80]. K^+ accumulation in the t-tubules may be even more significant [81]. Increase in K_{OUT} should be associated with increase in I_{K1} conductance with consequences on electrical activity, e.g., AP duration and propagation [82].

Despite the established role of I_{K1} in the terminal phase of AP repolarization and the representation of I_{K1} -dependent part of an AP in the human T-wave, the origin of even slower part of the ECG, known as U-wave, was not that clear. It seems, however, that this ‘100-year-old enigma’ might have been resolved. Recently, a thorough analysis of ECGs from patients carrying mutations in Kir2.1 showed that U-wave is strongly modulated by I_{K1} [83].

Localization

I_{K1} and I_{KACh} currents have a distinct regional distribution in the heart. I_{K1} is more prominent in the ventricles, including Purkinje myocytes [84], and significantly smaller in atria [59,85–87] with the exception of the mouse heart [88,89]. Further, I_{K1} density is small in pacemaker cells of the sinoatrial node (SAN) of mice and rats [90,91] and undetectable in the rabbit SAN [90]. I_{K1} is apparently absent in atrioventricular node (AVN) of rabbit [92,93] but is significant in the guinea-pig AVN [94]. The density of I_{K1} is also different in various regions of the ventricular myocardium. Significant differences in inward I_{K1} were observed across left ventricular tissue in the mouse heart with lager currents in apical myocytes compared to epicardial cells [95]. Generally, in the mouse heart inward I_{K1} is larger in RV than in LV myocytes [95,96]. In cat left ventricular myocytes, both inward and outwards I_{K1} are larger in endocardial compared to epicardial cells [97]. In the guinea-pig heart, however, outward I_{K1} is larger in cells from left ventricular wall compared to those from right ventricular wall [76].

I_{KACh} has generally an opposite distribution to that of I_{K1} - it is more prominent in the atria than in ventricles [98] although its amplitude in the ventricles might have been underestimated due to the presence of a large I_{K1} [99]. I_{KACh} channels are also expressed in SAN and AVN cells [100,101]. Similar to ventricular I_{K1}, I_{KACh} density may vary across the atrial tissue. In the mouse, I_{KACh} current density is larger in RA than in LA myocytes [102], and the gradient

is reversed in the sheep [78]. I_{KACh} is significantly larger in SAN cells compared to atrial myocytes [102].

Functional I_{K1} and I_{KACh} channels were found using patch-clamp technique in the outer sarcolemmal membrane of nearly all relevant types of cardiac myocytes. It is nearly indisputable that I_{K1} channels are expressed in the t-tubular membrane. It has been shown that the loss of t-tubules in ventricular myocytes during short-term culture is accompanied by the reduction of I_{K1} [103,104]. Experiments with fast application of Ba^{2+} ions also showed a significant delay in Ba^{2+}-induced inhibition consistent with location of significant part of I_{K1} in narrow t-tubular space [104]. Strong evidence also comes from experiments employing the effect of potassium accumulation/depletion in t-tubules, a phenomenon long known in skeletal muscle (e.g. [105,106]). Clark et al [81] showed that in mouse ventricular myocytes significant increase in the amplitude of I_{K1} tail currents can be observed in response to a preceding flow of large outward K^+ currents, consistent with both the K^+ accumulation and presence of I_{K1} in the restricted t-tubular space. Antibody labeling experiments also support t-tubular localization of Kir2.1, Kir2.2 and Kir2.3 subunits in ventricular myocytes [81,87, 107]. Interestingly, in canine ventricular and atrial myocytes Kir2.3 was also highly expressed (relative to Kir2.1), in the intercalated disks membranes [87].

Subunit composition

It is well established that members of Kir2 subfamily underlie I_{K1} channels although their exact subunit composition varies among animal species, cell types and also likely depends on the membrane location. A recent study using high-throughput real-time RT-PCR provided a detailed pattern of Kir2 transcript expression in atria, ventricular epicardium and endocardium, and Purkinje fibers [108]. No specific patterns were found for epicardium *vs* endocardium and left- *vs* right-sided chambers although the following significant regional differences were observed: in Purkinje fibers - Kir2.1~Kir2.3>Kir2.2, in RV - Kir2.1>Kir2.2>Kir2.3, and the sequence was reversed in RA - Kir2.3>Kir2.2>Kir2.1. Expression of Kir2.4 was not reported in this study. The data are nevetheless inconsistent with an earlier study by Wang et al [109].

In the guinea-pig heart, all three transcripts were detected in a mixed suspension of cardiac cells, with Kir2.1>Kir2.2~Kir2.3. Interestingly, analysis of RNA from intact ventricular and atrial tissue revealed the presence of Kir2.4 as well [16]. Antibody labeling experiments however, showed that Kir2.4 expression is restricted to neuronal cells in the heart [16]. Whether this is a property of Kir2.4 across the species is unclear. The data in guinea-pig are also somewhat controversial with respect to Kir2.2 since in the study by Dhammon et al [59] Kir2.2 transcript was not detected. Kir2.2 transcript was also not detected in the sheep atrial and ventricular myocytes [59]. In the mouse (whole) heart, Kir2.1 transcript was the most abundant, although Kir2.2 was also present, and very little amount of Kir2.3 transcript was found [66].

Subunit composition of channels underlying I_{K1} has also assessed using functional approaches based on the differential properties of individual Kir2 channels. In cardiac atrial and ventricular myocytes, unitary conductances usually display a wide spectrum ranging from ~10–15 pS corresponding to low conductance Kir2.3 channels up to ~40–45 pS corresponding to high conductance Kir2.2 channels (human atria [46]; guinea-pig ventricle [16]). The frequency of appearance of individual conductances, however, is tissue- and species-dependent and the exact contribution of Kir2 subunits to the conductance of heteromeric channels is not known. Ba^{2+} sensitivity of Kir2 heteromeric channels is quite complex and the data are conflicting. For example, Preisig-Muller et al [52] showed that Kir2.2 subunits may exert dominant effect on Ba^{2+} sensitivity of Kir2.1/Kir2.2 heteromeric channels, and Schram et al [51] showed that Ba^{2+} sensitivity of Kir2.1/Kir2.3 heteromers is significantly higher than that of individual channels, matching that of the most sensitive Kir2.2 channels. Nevertheless, experiments with

Ba^{2+} provide evidence that, I_{K1} in human right ventricular myocytes is likely composed of various Kir2 subinits [51]. Kinetics of activation in Kir2.1/Kir2.3 heteromers, however, is reasonably 'proportional' to the number of 'slow' Kir2.3 subunits in a heteromeric channel [96]. Using 'activation kinetics' approach it was shown, that the contribution of Kir2.3 subunit to I_{K1} in mouse and guinea-pig hearts is likely to be minor [24,96]. In contrast, analysis of pH sensitivity of I_{K1} in sheep ventricular myocytes shows significant functional expression of Kir2.3 subunits [58].

In contrast to I_{K1}, the subunit composition of I_{KACh} is relatively well established. There is compelling evidence that under normal conditions native I_{KACh} channels are heteromers of Kir3.1 and Kir3.4 subunits [18]. Recent data, however, suggest that the subunit stoicheometry of I_{KACh} channels may vary. First, Bender et al (2001) [62] showed using overexpression approach that Kir3.4 subunits may form fully functional homomeric channels in rat atrial myocytes. Second, Mintert et al (2007) [110] found that Kir3.4 current shares some properties with Kir3-like currents found in atrial myocytes from patients with chronic atrial fibrillation [110,111].

Regulation

Adrenergic

It is generally agreed upon that I_{K1} is suppressed by α [112,113] and β [114] adrenergic stimulation although opposite effects were also described [115]. Importantly, in most studies only inward I_{K1} currents were analyzed and little attention was paid to the outward, physiologically relevant component of I_{K1}. For example, in guinea-pig ventricular myocytes inhibition of inward I_{K1} by β adrenergic stimulation was accompanied by little, if any, decrease in peak outward I_{K1} [114]. The added complexity arises from the co-existence of different types of adrenergic receptors in the heart. For example, in *Xenopus* oocytes expression system stimulation of β_3 receptors leads to upregulation of Kir2.1 and Kir2.2 (but not Kir2.3) channels [116], and the stimulation of α_{1A} receptors downregulates Kir2.2 and Kir2.3 but not Kir2.1 channels [117].

Polyamines

There is no evidence that polyamines play a role in physiological responses involving I_{K1} or I_{KACh}. However, Kir currents can be affected through modulation of polyamines using pharmacological tools [118,119] as well as by their manipulation in transgenic animals [120]. For example, experiments with mice with disrupted spermine synthase gene showed a significant decrease in the strength of rectification and faster I_{K1} activation kinetics, consistent with undetectable levels of spermine and ~5-fold increase in the level of spermidine [120]. Overall, the evidence is consistent with spermine being the major polyamine in Kir channel rectification, with little contribution of putrescine.

Cations (Ca^{2+}, Mg^{2+}, H^+)

Intracellular Ca^{2+} (Ca_i) can also block I_{K1} channels in a voltage-dependent manner [121]. Although the potency of Ca_i block is even less than that of Mg^{2+}, and the average concentrations of Ca_i are quite low, there is evidence that Ca_i may have significant dynamic effects on I_{K1}. For example, in guinea-pig ventricular myocytes a transient increase in Ca_i during an AP leads to I_{K1} inhibition of a physiologically significant magnitude [122]. The data suggest that significant Ca_i effects may be due to tight co-localization of I_{K1} channels and Ca^{2+} release/Ca^{2+} entrance sites in a highly restricted space.

Another important phenomenon of dynamic regulation of I_{K1} involving intracellular Mg^{2+} (and polyamines) was described by Ishihara et al [25,123]. It was found that the amplitude of

the outward I_{K1} depends strongly on the speed of the membrane potential repolarization (and thus AP repolarization). The data suggest that the effect is due to a fine interplay between Mg^{2+} and polyamine blocking/unblocking reactions.

I_{K1} sensitivity to extracellular H^+ is species/tissue-dependent, possibly reflecting channel subunit composition. In rat and guinea-pig ventricular myocytes I_{K1} is insensitive to H^+ [124] [125,126]. In contrast, Munoz et al [58] reported that in sheep ventricular myocytes I_{K1} can be inhibited by H^+ within physiological range (pKa=7.4). Consistent with this, Kir2.3 subunit, the most H^+-sensitive isoform [24], confers pH sensitivity to heteromeric Kir2.1/Kir2.3 channels [58] and contributes significantly to I_{K1} in sheep myocardium [59].

PIP_2

Phosphatidylinositol-4,5-bisphosphate (PIP_2) is an important component in membrane-delimited second messenger signaling systems [127,128]. Regulation of an ion channel by PIP_2 was first described for IK_{ATP} [129], and subsequent studies have shown that PIP_2 modulates all Kir channels in native cells as well as in heterologous expression systems [130,131]. Kir2 and Kir3 channels, similar to most members of the Kir family are preferentially activated by PIP_2 [130,132]. Rohacs et al [133] reported that PIP_2 interacted strongly with Kir2.1 but weakly with Kir3.1/3.4. Furthermore, Kir2.1, but not Kir3.1/3.4, had a marked specificity for phosphates in the 4,5 head group positions of the PIP_2 molecule. The study showed that phosphatidylinositol was inactive for both channels.

Functional properties of Kir2 subfamily members are sensitive to interactions with PIP_2. There is evidence that regulation of Kir2.3 by pH, acetylcholine or by phorbol myristate acetate is dependent on channel-PIP_2 interactions [130]. Similarly, activation of Kir3 channels by $G_{\beta\gamma}$ and Na^+ ions is also PIP_2-dependent [134]. A molecular model of how PIP_2 may control Kir channel proposes that PIP_2 strengthens Kir N- and C-termini interactions, tethering them to the cytoplasmic face of the membrane, and mechanically gating (opening) the channel. Kir2.1-PIP_2 interactions were recently shown to increase channel availability and to favor transitions to the fully open state over various subconductance levels [135].

General Pathophysiology

Atrial I_{K1} is upregulated in patients with chronic atrial fibrillation [136,137], although I_{KACh} is downregulated [137] but constitutively active [111]. In congestive heart failure (CHF) conflicting results were reported with respect to both ventricular and atrial I_{K1}. In ventricular myocytes, both a moderate (~2-fold) decrease [138–140] or no change [141,142] in I_{K1} density were observed. Similar, atrial I_{K1} in patients with symptomatic CHF was also found to be reduced ~ 2 fold [143] but it was not affected in dogs with experimental CHF [144]. Decrease of I_{K1} was also observed in subendocardial Purkinje myocytes from the infarcted dog heart [145]. The general pattern is reversed in hypertrophy: I_{K1} was increased in isolated right ventricular myocytes from cats with experimentally induced right ventricular hypertrophy [146] but not affected in left ventricular myocytes with induced lefty ventricular hypertrophy [147].

During metabolic stress, e.g., ischemia, activation of large K_{ATP} conductance masks many potassium currents, including I_{K1}. Nevertheless, in experiments using glibenclamide to block K_{ATP} channels, Xie et al [148] showed that metabolic stress caused by application of iodoacetic acid leads to inhibition of I_{K1}. Interestingly, suppression of I_{K1} in rabbit ventricular myocytes abolishes protection by ischemic preconditioning, a role commonly assigned to K_{ATP} channels [149]. In contrast, several isolated reports indicate that I_{K1} may be upregulated during acute hypoxia/anoxia [150] or cyanide poisoning [151]. Recently, a strong evidence for this

phenomenon was provided by Piao et al [152] who showed that in mice the early AP shortening during acute hypoxia is mediated by I_{K1} but not K_{ATP} channels.

Channelopathies

In 1995, the identification of two defective ion channel genes responsible for abnormal prolongation of the QT interval on the ECG was key to our present knowledge on channelopathies [153,154], and was followed by the reports of disease-causing mutations in many other ion channels [155,156]. It is noteworthy, however, that there are cardiac channelopathies associated with genes encoding non-ion channel proteins [155], which presumably reflects channel dysfunction resulting from abnormal protein-protein interactions. To date, four channelopathies associated with inward rectifier channels have been identified, all originating from loss-of-function or gain-of-function mutations in *KCNJ2* (Kir2.1): Type 1 Andersen Syndrome (see note on Long QT7 later), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Familial Atrial Fibrillation (FAF) and Short QT3 (Figure 3).

Long QT, Short QT

In Long QT syndrome (LQTS), QT prolongation can lead to polymorphic ventricular tachycardia, or torsades de pointes, ventricular fibrillation and sudden cardiac death [157]. The arrhythmias are thought to be precipitated by early afterdepolarizations (EADs) as a consequence of a prolongation of the ventricular AP duration. To date, 11 different LQTS (LQT1-11) subtypes have been identified [158] [159] [160] with LQT7 (see below) linked to abnormalities in the function of I_{K1} [161].

LQT7 is related to Andersen's Syndrome (AS) or Andersen-Tawil Syndrome (ATS; this term will be used hereafter) which is characterized by a triad of clinical phenotypes affecting morphogenesis as well as the functioning of skeletal and cardiac muscles. ATS patients are dysmorphic, with features that include scoliosis, cleft palate and short stature, and display skeletal muscle weakness [161] [162]. Cardiac electrical abnormalities include short runs of ventricular tachycardia, ventricular bigeminy and multi-focal ventricular ectopy mediated by adrenergic stimulation, as well as originally reported prolongation of the QT interval. Recent work by Zhang et al (2005) [163] showed, however, that classification of ATS syndrome as LQT7 may be incorrect since specific ECG patterns in this syndrome were found to be largely related to the abnormalities of the T-U complex. A genome-wide linkage analysis performed to identify the disease locus of the ATS established a link between the disease and the long arm of chromosome 17. Because of the coincidence with the locus of *KCNJ2* encoding for Kir2.1, the gene was examined for possible mutations. The original study showed that more than half of ATS patients have mutations in the *KCNJ2* gene [164], and thus the term Andersen-Tawil Syndrome Type I, or ATS1, specifically linking the disease to Kir2.1 channels, seems the best option [163]. Furthermore, given over twenty distinct missense mutations in the heterozygote state, allelic heterogeneity is indicated in ATS1 [161,165] [166].

More than 33 *KCNJ2* mutations are now associated with ATS1 (Figure 3) and heterologous expression studies of mutant channels show that mutations result in loss-of-function of Kir2.1 channels. Because ATS1 is an autosomal-dominant disorder (ATS1 patients have one mutant and one wild type allele), the study of Plaster et al (2001) [164] examined the effects of coexpressing equal amounts of wild type and mutant channels for two ATS1 mutations (D71V and R218Q) in *Xenopus* oocytes. Properties of inwardly rectifying currents from heteromeric assembly of wild type and each mutant Kir2.1 subunits showed that mutant channels had a dominant negative effect on wild type channels. The effect was more dramatic for the D71V where current amplitude was reduced by ~94% of wild type current amplitude. Several of ATS1 mutations result in a loss-of-function in the Kir2.1 channels due to reduced interaction with membrane PIP_2 [162,167]. Thus, it was shown that the ATS1 associated R21Q/W mutations

are located within a group of residues putatively involved in PIP_2 interactions with the channel [161,167].

Short QT syndrome (SQTS) is an inherited abnormality that predisposes afflicted individuals to a high risk of having fibrillation (atrial/ventricular) and sudden death. SQTS is characterized by an abnormally short QT interval (<300 ms) on the ECG [168,169], with a marked acceleration of repolarization. Three forms of SQTS (SQT1-3) have now been described [170–172]. SQT1 and SQT2 are a result of mutations, respectively, in two voltage-gated potassium channel genes KCNH2 (HERG channel) and KCNQ1 (I_{Ks} channel). Priori and colleagues (2005) [172] described the third variant of the syndrome as resulting from a mutation in inward rectifier channel gene, KCNJ2 (Kir2.1). In all three cases, the mutations resulted in gain-of-function channels that provided excessive outward current leading to accelerated repolarization.

SQT3 has a characteristic electrocardiographic phenotype with asymmetrical T waves [172]. Amazingly, genetic analysis of affected members of a single family showed a mutation in *KCNJ2*, which resulted in the substitution of an aspartic acid residue for an asparagine (D172N; Figure 3) at a position critical for inward rectification of Kir2.1 channel. Heterologous coexpression of wild type and mutant Kir2.1 subunits showed increased outward currents in mutant channels. Further analysis in computer simulations showed that the mutant-induced increase in outward currents could account for the tall, asymmetrical T waves on the ECG of affected individuals [172]. While arrhythmia susceptibility tests could not be performed on SQT3 patients, computer simulations predicted a steeper steady-state restitution curve (AP duration as a function of diastolic interval) for D172N and WT/D172N mutation when compared to wild type channels, or to mutations in SQT1and SQT2. It was therefore suggested that mutations in SQT3 might predispose patients to a higher risk of reentrant arrhythmias [172].

Familial Atrial Fibrillation

Previous studies on atrial fibrillation have implicated gain-of-function mutations in the genes underlying I_{Ks} channel (KCNQ1 and KCNE2) [173,174], as well loss of function in Kv1.5 channels encoded by *KCNA5* [175]. Xia et al (2005) [176] reported that a single valine to isolucine substitution in Kir2.1 (V93I; Figure 3) was associated with familial atrial fibrillation, thereby implicating I_{K1} in this disease [176]. In line with this, whole-cell patch clamp studies showed that the mutant channels have larger outward currents, although the underlying mechanism(s) responsible for the increase remains unknown.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable arrhythmia and patients frequently present with ventricular arrhythmias and sudden cardiac death associated with physical activity such as in exercise or adrenergic stimulation [177,178]. Abnormalities in calcium handling involving the ryanodine receptors (CPVT1; [179]) or calsequestrin (CPVT2; [180]) may be responsible for CPVTs. In a recent study, a cohort of 541 unrelated patients were referred for genetic arrhythmia testing and when genotyped for KCNJ2, three novel (R67Q, R85W, T305A) and one previously described (T75M) mutations were identified [181]. ECG analysis revealed prominent U-waves, ventricular ectopy and polymorphic ventricular tachycardia. Interestingly, there were no dysmorphic features or skeletal muscle abnormalities in the patients. Whole-cell patch-clamp experiments revealed that mutant channels had significantly reduced outward current (had <5% of wild type current amplitude), and that two of the mutations (T75M, R67Q) had dominant negative effects when coexpressed with wild type channels [181]. Importantly, the study showed that the T305A mutation selectively affected channel rectification properties. Because the tested patients lacked the

criteria for ATS, it was suggested that the three novel mutations be classified as CPVT3 [181].

Conclusion

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

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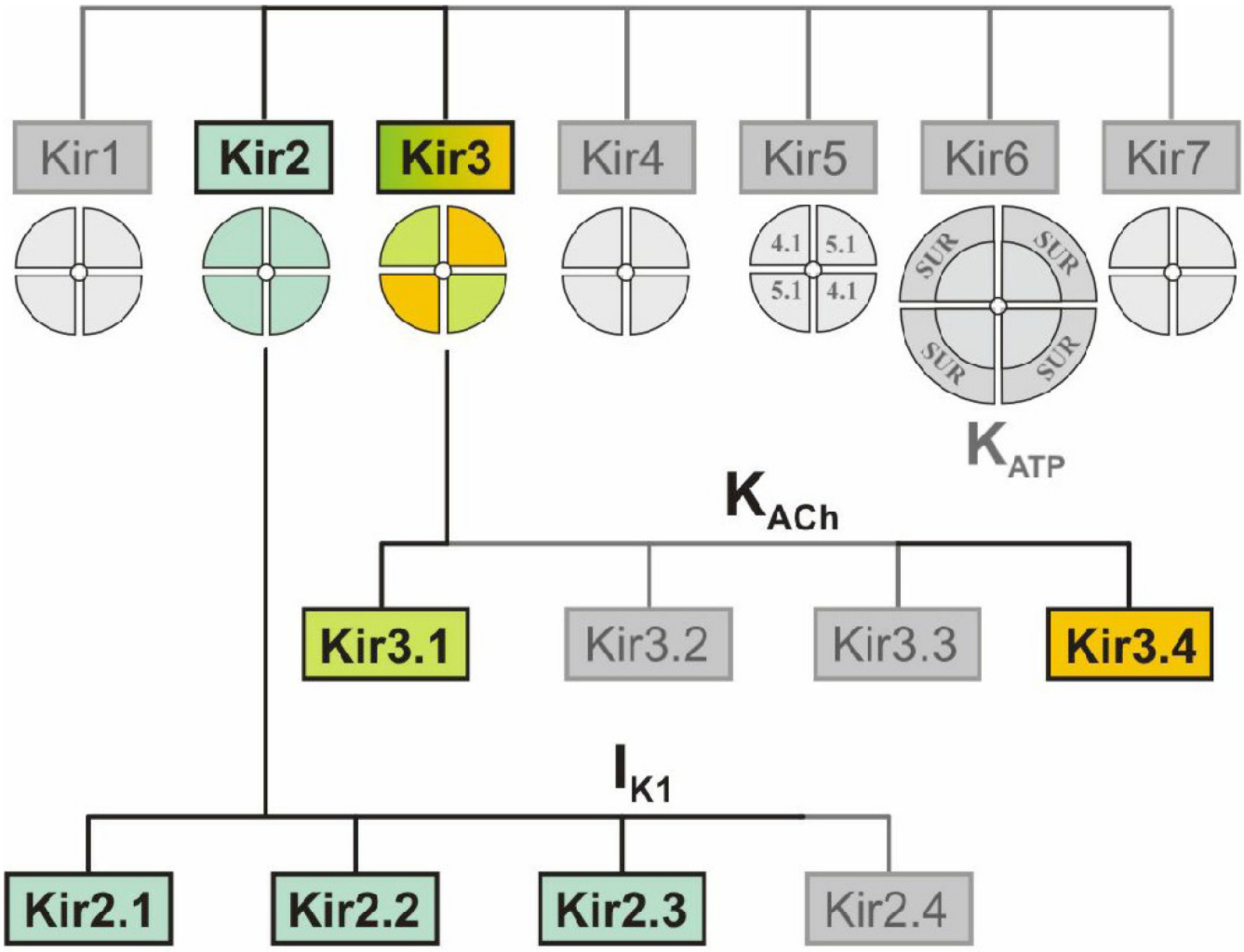

Figure 1. The family of inward rectifier potassium channels

All members of this family share significant structural similarity but only Kir2 and Kir3 subfamilies represent channels carrying classical strongly rectifying currents. Four members of each Kir2 and Kir3 subfamilies were cloned in mammals. Heteromeric assemblies of Kir2.1, Kir2.2 and Kir2.3 subunits underlie I_{K1} current, and heteromeric assembly of Kir3.1 and Kir3.4 subunits underlies I_{KACh} current. Other nomenclatures of Kir channels can be found in IUPHAR database (http://www.iuphar-db.org), and in the 'International Union of Pharmacology. LIV'[13].

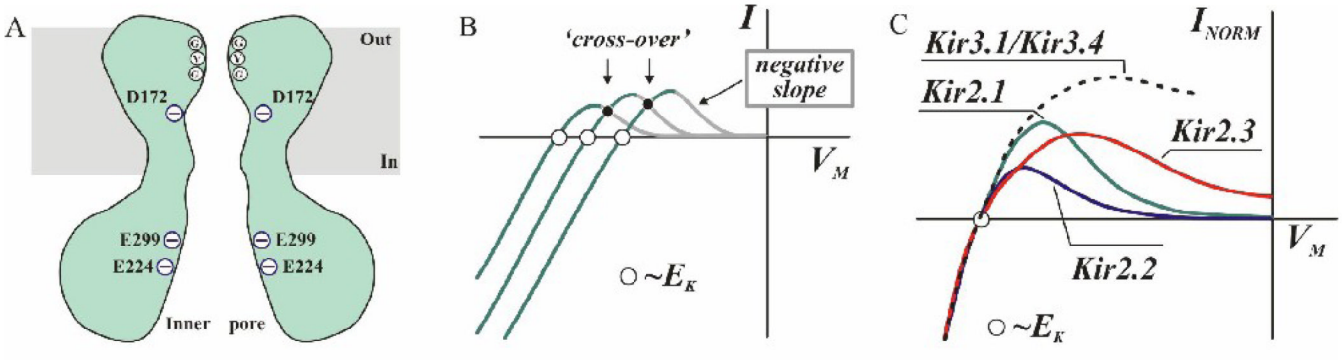

Figure 2. Essential properties of classical inward rectification

(A) The pore of a prototypic inward rectifier channel consists of long tunnel extending far inside the cell. A 'ring' of negatively charged residues at the level of intra-membrane water cavity (D172 in Kir2.1) is critical for high-affinity strongly-voltage dependent block of Kir channels by intracellular polyamines (e.g. spermine). Another ring of negatively charged residues (including but not limited to E224 and E299 in Kir2.1) is essential for a low-affinity weak-voltage-dependent block by polyamines. (B) Block of the Kir channel pore by intracellular polyamines and Mg^{2+} ions in response to membrane depolarization leads to a voltage-dependent decline of K^+ conductance producing a region of 'negative slope' conductance. Increase in the concentration of extracellular K^+ leads to a near parallel shift of current/voltage relationships and their 'crossover'. (C) Rectification profiles are distinct in different Kir channels. When current amplitudes are normalized at far negative membrane potentials the outward currents are the smallest for Kir2.2 and the largest for Kir3.1/Kir3.4 channels.

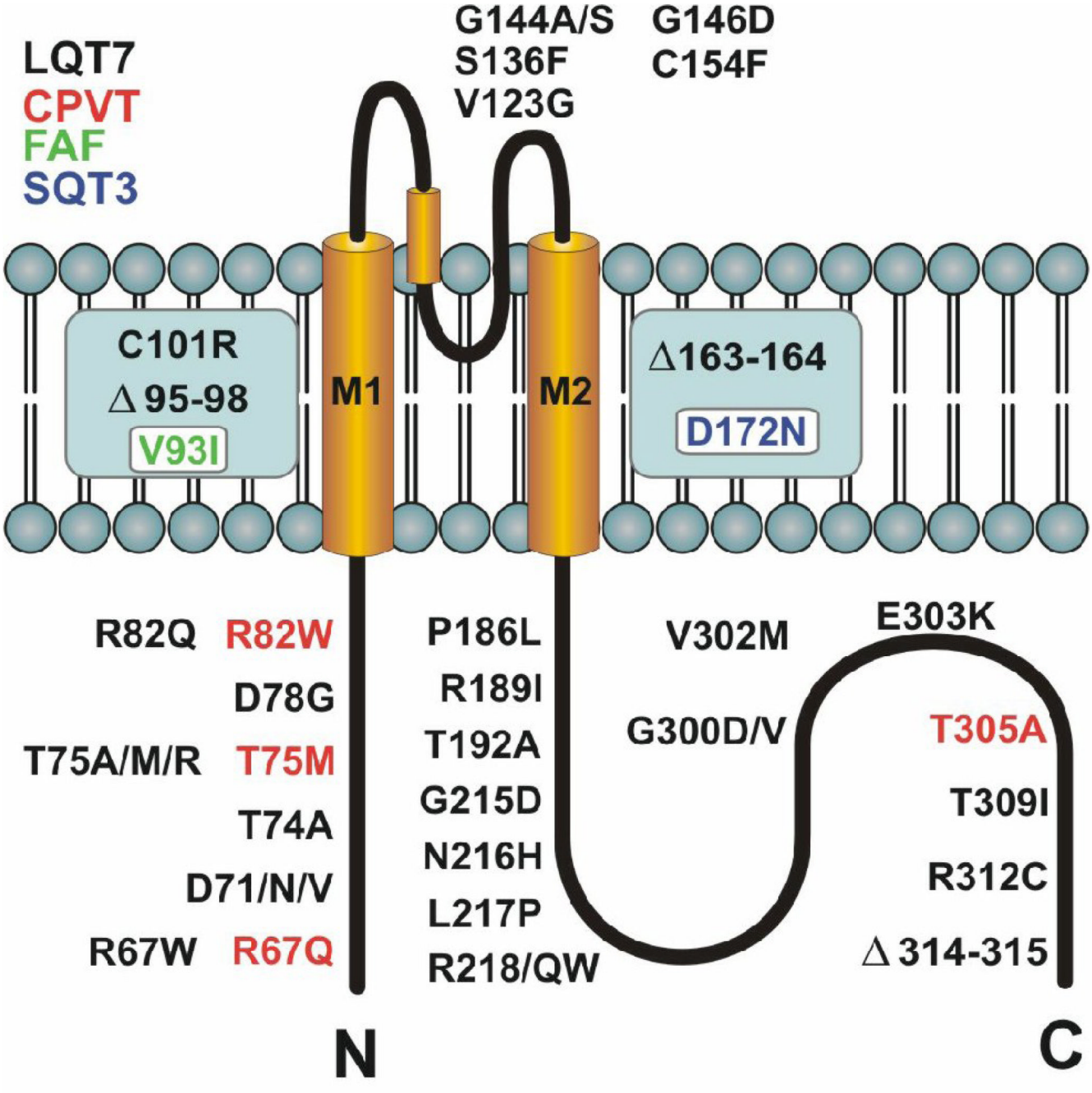

Figure 3. Mutations on Kir2.1 protein associated with channelopathies of the classical inward rectifier channel

Mutant residues are color coded to represent the Long QT7 (LQT7; black), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT; red), Familial Atrial Fibrillation (FAF; green) and Short QT3 (SQT3; blue).