Cardiac potassium channels: physiological insights for targeted therapy.

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Abstract

The development of novel drugs specifically directed at the ion channels underlying particular features of cardiac action potential (AP) initiation, recovery and refractoriness would contribute to an optimised approach to anti-arrhythmic therapy that minimises potential cardiac and extra-cardiac toxicity. Of these, K^+ channels contribute numerous and diverse currents with specific actions on different phases in the time course of AP repolarisation. These features as well as their site-specific distribution make particular K^+ channel types attractive therapeutic targets for the development of pharmacological agents attempting anti-arrhythmic therapy in conditions such as atrial fibrillation. However, progress in the development of such temporally and spatially selective antiarrhythmic drugs against particular ion channels has been relatively limited, particularly in view of our incomplete understanding of the complex physiological roles and interactions of the

various ionic currents. This review summarises the physiological properties of the main cardiac potassium channels and the way in which they modulate cardiac electrical activity, then critiques a number of available potential antiarrhythmic drugs directed at them.

Keywords

Potassium channels, repolarisation, physiological mechanisms, currents, ion channel, drug target

1.0 Introduction

Orderly propagation of cardiac electrophysiological excitation and recovery depends on a normal sequence of cardiac action potential (AP) generation through its component myocytes. AP depolarisation and repolarisation is mediated by multiple, interacting, inward and outward currents mediated by different ion charge carriers dependent on the action of specific membrane ion channels (Figure 1). The initial depolarisation phase takes the form of a rapid upstroke and is mainly driven by inward Na^+ current (I_{Na}) through voltage-gated sodium channels ($Na_v1.5$). The succeeding plateau phase is dominated by inward Ca^{2+} current (I_{Ca}). The resulting entry of extracellular Ca^{2+} induces release of sarcoplasmic reticular Ca^{2+} stores, thereby activating excitation-contraction coupling. Repolarisation, ultimately returning the membrane to the resting potential, is principally driven by outward current through voltage-gated K^+ channels (K_v)[1]. K^+ channel activity is thus a principal determinant of AP duration (APD) as it limits the depolarisation duration and therefore both the time course of the Ca^{2+} mediated contraction and the refractory period. There are numerous and diverse K^+ channels types, each with particular kinetic and voltage-dependent properties. These result in numerous and diverse current contributions each with specific roles at different phases of repolarisation. Together these determine the relatively prolonged but finely tuned repolarisation time course, and the repolarization reserve following recovery of the resting membrane potential. The repolarisation reserve refers to the partly overlapping function of these currents, namely $I_{Kr,}$ I_{Ks} and $I_{K1,}$ that gives a limited level of redundancy to the system [2]. The kinetics of repolarisation varies greatly with cardiac region and species. This reflects variations in the occurrence and density of the different K^+ channel subtypes. All these characteristics suggest that explorations of K^+ channels may yield a useful group of pharmacological targets for arrhythmic conditions.

1. Potassium channels

K^+ channels represent the most functionally diverse cardiac ion channel type [3-6]. Together, they tightly regulate cardiac repolarisation thus ensuring stable and consistent AP signalling. The different K^+ channel types have overlapping functions [2,7] resulting in some degree of functional redundancy [2] which in turn contributes to repolarisation reserve. Table 1 summarises their encoding genes with their chromosomal locations, and the structural properties of their pore-forming α and accessory β-subunits. The α-subunit of different K^+ channel types all possess a conserved pore-forming region allowing K^+ movement across the plasma membrane down an electrochemical gradient possessing a selective permeability to K^+ attributable to a specific structural motif. They may also exhibit gating mechanisms responsive to membrane depolarisation and ligand binding sites whose occupancy could alter channel conformation. Finally, individual monomeric α-subunits may assemble into functional dimers or tetramers due to the presence of one or more subunit-assembly domains [6,8-10]. K^+ channel α–subunits fall into three structural types based on subunit topology (Figure 2). The first has one pore-forming region with six or seven transmembrane regions (Figure 2a), the second has one pore-forming region and two transmembrane regions (Figure 2b) and the third has two pore-forming and four transmembrane regions (Figure 2c) [5,6,10].

K^+ channel β-subunits encompass many molecular groups, such as ATP-binding cassette transport-related proteins (e.g sulfonylurea receptors) for inward rectifiers, cytoplasmic proteins (KChIP, KChAP and K_v β1-3) and single transmembrane spanning proteins (minK) [10]. These β-subunits form complexes with the α–subunits and can modify the channel's functional properties. For example, K_vβ subunits can alter channel trafficking and the kinetics of current activation and inactivation when interacting with K_v1.5 [11]. More specifically, Kvβ2.1 and Kvβ4.1 behave as chaperone proteins [12]. Furthermore, the N-terminus of K_Vβ1.2 and K_Vβ1.3 has an inactivation domain resembling the inactivation particle of the α–subunit, allowing it to modulate channel inactivation [12-14].

2. Cardiac potassium currents

Cardiac K^+ channels vary in their permeability properties, membrane potential dependence and their opening or closing activation and inactivation kinetics. The major currents are classified into the transient outward currents, delayed rectifier outward currents and the inward rectifiers (Figure

3). Advances in electrophysiological and molecular biology techniques have demonstrated additional currents that may fall outside this basic classification. Some brief notes on the major cardiac K^+ currents, their role in the cardiac AP, and their functional importance follow.

3.1 Transient outward K^+ (I_{to1}) currents

When first described, the transient outward currents (I_{to}) were attributed to two distinct channels, one blocked by 4-aminopyridine (4-AP) and unaffected by extracellular Ca^{2+} (I_{to1}) and the other not blocked by 4-AP but sensitive to Ca^{2+} (I_{to2}) [6]. I_{to} drives the initial rapid repolarisation phase of the AP. Regions with shorter APDs such as the epicardium, right ventricle and septum have higher I_{to} expression. It was later discovered that I_{to2} is a Cl^- rather than a K^+ current [15]. Further characterisations subdivided I_{to1} into fast (I_{tof}) and slow (I_{tos}) currents (Figure 3). I_{tof} predominates in the atria whereas both I_{tof} and I_{tos} occur in the ventricles [16]. Whilst I_{tos} requires longer recovery times, its classification as 'slow' is relative only to I_{tof}. Thus both I_{tof} and I_{tos} channels activate and inactivate rapidly in comparison to the corresponding processes in other K^+ channels [15]. Due to differences in the biophysical properties of I_{tof} and I_{tos}, the existence of molecular heterogeneity between these two channels has been previously suggested [15].

3.2 Ultra-rapid delayed rectifier currents (I_{Kur})

In addition to I_{to}, the ultra-rapid delayed rectified K^+ current *(I_{Kur})* plays a role in the initial rapid Phase 1 AP repolarisation. I_{Kur} activates rapidly in under 10 msec at voltages in the plateau range and deactivates slowly over the course of the AP [17-19]. I_{Kur} is the predominant delayed rectifier current for the atria and thus results in the shorter APD seen in the atria compared to the ventricles [10,16,17,19]. Where I_{Kur} is present, its channels are not evenly distributed over the myocyte surface but instead found at high densities in the intercalated disk [6]. This pattern of distribution is often disrupted after cardiac ischemic damage [10]. The selective presence of I_{Kur} in the atria makes it an interesting target for atria selective therapy whereby inhibition of I_{Kur} would prolong the APD in the atria but not the ventricles [4].

3.3 Rapid delayed rectifier K^+ currents (I_{Kr})

The voltage-gated rapid delayed rectifier outward K^+ current (I_{Kr}) is critical to Phase 3 repolarisation. It shows a relatively rapid activation with depolarisation. However, its inactivation

rate is around ten times faster than its activation rate due to voltage-dependent C-type inactivation. This renders it relatively non-conducting in Phase 1 and 2 of the cardiac AP [20-23]. Thus, although termed a delayed rectifier current, it also shows an inward rectification property at positive potentials [22,24]. However, with the end of Phase 1 and 2 as the membrane potential becomes negative to 0 mV, I_{Kr} becomes activated once again but the deactivation during this phase is much slower. This results in a large outward K^+ efflux during Phase 3 repolarisation [2,10]. I_{Kr} is found in both human atria and ventricles but is differentially expressed with higher levels in the left atrium and ventricular endocardium [16].

3.4 Slowly activating delayed rectifier K^+ *current (*I_{Ks}*)*

Cardiac repolarisation is also influenced by a third, slowly activating delayed rectifier K^+ current (I_{Ks}). I_{Ks} slowly activates at potentials positive to –20 mV. Unlike I_{Kr}, I_{Ks} barely inactivates [25,26] and consequently accumulates over Phase 2 repolarisation, significantly influencing Phase 3 repolarisation [2]. This feature of I_{Ks} is particularly important during atria and ventricular APs of long duration. It is also involved in APD shortening during physiological increases in heart rate. An increase in heart rate thus reduces the time required for I_{Ks} inactivation. In consequence, more I_{Ks} accumulates leading to a steeper drop in the repolarisation rate [27,28]. Blocking I_{Ks} results in an APD prolongation at increased heart rates [21,28]. Inhibition of I_{Ks} will increase the vulnerable window for reactivation of voltage-gated Ca^{2+} channels, thereby increasing the risk for arrhythmic trigger events [2]. I_{Ks} is found in all cardiac cell types but its expression is significantly reduced in the mid-myocardial wall; this accounts for the long APD seen in this region [16].

3.5 Inward rectifying K^+ *current (*I_{K1}*)*

The inward rectifying K^+ current (I_{K1}) functions over a narrow membrane potential range. Its rectifying property results in a marked reduction of I_{K1} conductance at positive, depolarised, membrane potentials and an increase of I_{K1} at negative membrane potentials, with the effect of stabilising the membrane resting potential close to the K^+ equilibrium potential (E_K) [10]. The channel mediating I_{K1} does not show voltage-dependent gating and does not possess a voltage sensor. Nevertheless, I_{K1} modulation associated with movement of Mg^{2+} and polyamines result in an indirect sensitivity to voltage [29-32]. Between Phase 0 to Phase 2 of the AP, the membrane potential is more positive than -20 mV and at this potential there is no conductance of I_{K1} as the

channel is inhibited by Mg^{2+} and polyamines. The resulting marked inward rectification property limits the outward current at these positive potentials. This in turn minimises the inward depolarising current, which confers energetic efficiency for AP generation as it minimises changes to ionic gradients that would need to be restored [16]. As the potential returns to more negative values (typically around -40 mV), the inhibition by Mg^{2+} and polyamines is reversed. I_{K1} conductance then resumes and this contributes to the Phase 3 cardiac repolarisation [31]. I_{K1} occurs in both atria and ventricles and is thereby involved in setting their resting membrane potentials. Channels conducting I_{K1} are expressed in greater density in the ventricles making the ventricles less susceptible to pacemaker influence [16].

3.6 Acetylcholine-activated K^+ *current (*I_{KACH}*)*

The inwardly rectifying acetylcholine-activated K^+ current (I_{KACH}) is regulated by G-proteins rather than voltage gating. Cardiac parasympathetic nerve endings release acetylcholine (ACh) thereby activating M2 muscarinic receptors. This reduces the depolarising effect of the pacemaker current (I_f), reducing firing rates of pacemaker cells, and in turn reducing heart rate [6]. ACh also opens muscarinic sensitive I_{KACH} channels allowing the inward rectification of K^+. The inward rectifying current shortens the AP and hyperpolarises the membrane potential [16]. Membrane hyperpolarisation reduces the rate at which the sinoatrial (SA) and atrio-ventricular (AV) nodes drive pacemaker depolarisation in addition to reducing AV conduction velocity [6,33]. I_{KACH} is thought to be specific to the atria [2] but there has been a suggestion that it may exist both in the atria and ventricle [16] but with densities 6 times greater in the atria than the ventricles [34].

3.7 ATP-activated K^+ *current (*I_{KATP}*)*

The ATP-activated K^+ current (I_{KATP}) occurs at both the sarcolemmal (sarc-K_{ATP}) and mitochondrial inner membrane (mito-K_{ATP}) of cardiomyocytes. The sarc-K_{ATP} channels are highly expressed in cardiomyocytes and are composed of $K_{ir}6.2$ and SUR2A subunits. There may also be contributions from $K_{ir}6.1$ and SUR1 [35]. In contrast, although the subunits of mito-K_{ATP} channels have been difficult to identify due to the challenge of isolating pure mitochondrial membrane fractions, ROMK2 pore-forming subunits and SUR2 regulatory subunits have been suggested to contribute [36,37].

Both channels are controlled by adenosine triphosphate (ATP) and are thus directly responsive to the cell's metabolic status, thereby influencing cell membrane potential [6]. I_{KATP} is inhibited by physiological intracellular ATP levels but this reverses with ATP depletion. Thus, under normal energetic circumstances, there is limited I_{KATP} current. However, under both physiological and pathological conditions that reduce ATP, there is increased I_{KATP} current that is essential for adaptation to stress. For example, compared to wild-type controls, mice lacking $K_{ir}6.2$-containing K_{ATP} channels perform less well in acute treadmill exercise testing [38]. The increased I_{KATP} has a cardioprotective role in ischemia by shortening the cardiac AP, thus limiting calcium influx into the cytosol [39-41]. Specifically, studies have suggested that mito-K_{ATP} rather than sarc-K_{ATP} channel opening has an energy-modulating property that confers cardioprotection in ischaemic hearts [42,43].

In some situations, the I_{KATP}-mediated APD shortening and corresponding heterogeneities in repolarization can create a substrate for cardiac re-entry arrhythmia. In other situations, K_{ATP} channel openers have been described to have antiarrhythmic effects [44-48], and evidence suggests that activation and block of K_{ATP} can be pro or antiarrhythmic depending on the arrhythmogenic mechanism in different animal models [49]. For example, selective sarcolemma K_{ATP} channel blockers, such as HMR 1883, confer antiarrhythmic effects in the short-term [50] although this could be metabolically disadvantageous in the long-term due to the abolished adaptive response to stresses. Finally, it is important to note that the channel involved in the conductance of I_{KATP} is also thought to be involved in regulation of smooth muscle tone and insulin secretion in pancreatic β-cells [6].

3.8 Other K^+ channel family: Ca^{2+}-activated K^+ current (I_{KCa}), 2-pore domain K^+ current (I_{K2p}) and HCN channels

Recently, several further currents have been characterised. The Ca^{2+}-activated K^+ current also known as the small-conductance Ca^{2+}-activated K^+ (SK) current, I_{KCa}, and the 2-pore domain K^+ current, I_{K2p} have attracted considerable physiological and pharmacological interest. I_{KCa} was initially thought to not exist in the human heart [51]. Subsequent studies however demonstrated the presence of I_{KCa} with a higher density in the atria than the ventricle. Various subtypes of Ca^{2+}-activated K^+ channels exist in different tissues; the channel subtype conducting the cardiac I_{KCa} is the SK channel [51,52]. In neuronal cell, SK channels are involved in modulating the tonic firing

frequency and activation of these channels cause membrane hyperpolarisation thus limiting neuronal AP firing frequency [51]. In contrast, cardiac SK channels and consequently I_{KCa} are involved in late AP repolarisation and controlling the resting membrane potential in human atria [52]. I_{KCa} appears to not play physiologically significant roles in the ventricle [52]. I_{KCa} is accordingly of particular pharmacological interest for atrial fibrillation therapy. Thus, I_{KCa} occurs during late repolarisation, when the atrial AP is susceptible to irregular or abnormal excitation such as that resulting from early-after-depolarisations (EADs) [51].

I_{K2p} contributes to the background current, the resting membrane potential and cellular excitability. The channel involved in the conductance of this current has no voltage dependence but its activity is modulated by lipids, particularly fatty acids, pH, drugs, particularly local and inhalation anaesthetics, and membrane stretch [53,54]. These mediators act upon the channel via secondary messenger phosphorylation [55]. I_{K2p} is a background current that persists through all phases of the cardiac AP. It thus stabilises the membrane potential towards E_m. I_{K2p} may also prevent the occurrence of EADs and it may be involved in fine tuning of Na^+ channel availability for Phase 0 depolarisation [56]. The current has been found to occur selectively in the atria and AV node also making it a target for drug development [57-59]. Although not entirely new but only recently well characterised, the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is instrumental in conducting the inward funny current (I_f) in the heart. The channel is activated by the hyperpolarization of the membrane and is additionally stimulated by intracellular cyclic nucleotides [60,61]. The generation of I_f is attributable to the inward permeability of both Na^+ and K^+ and occurs at threshold close to the resting membrane potential [62]. Although the HCN channel under physiological circumstances conducts both Na^+ and K^+, the primary sequence of the HCN pore region suggest that is primarily related to a selective potassium channel [63]. In certain pathological conditions such as atrial fibrillation and myocardial infarction, I_f is increased unusually outside the pacemaker cells leading to increased propensity to arrhythmia. Thus targeting the I_f in such pathological conditions has proven to be therapeutically advantageous [64].

4.0 Cardiac K^+ channel as targets for drug development

Although there have been significant recent advances in the development and use of cardiological devices and procedures directed at arrhythmic conditions, anti-arrhythmic drugs continue to be

important whether by themselves or as adjunct therapy to such interventions. These include situations involving acute management of potentially fatal arrhythmic events, particularly where such procedures are contraindicated. Yet progress in anti-arrhythmic drug development has been relatively limited. This likely reflects a lack of understanding of cardiac arrhythmic mechanisms. However, recent developments of our understanding of the role of the ion channels in normal AP generation has led to a specific interest into ion channels and their associated currents whose abnormal activity potentially leads to arrhythmia. This would encourage interest in the development of cardiac ion channel activator or blockers directed at modulating the cardiac AP or its refractory period. Introduction of drugs acting specifically on ion channels would optimise the efficacy of therapeutic actions on arrhythmogenic tendency whilst minimising problems arising from potential cardiac and extra-cardiac toxicity. K^+ channels play a vital role in cardiac AP repolarisation and thus naturally form potential targets for the development of ion channel specific anti-arrhythmic therapy, such as for atrial fibrillation (AF). However, a limitation of this approach is that arrhythmic conditions, such as AF, are heterogeneous and the efficacy of targeting ion channels varies according to the cause and extent of the arrhythmia.

This is complicated by the fact that in various physiological and pathological conditions, remodelling of K^+ channel expression can occur, which can alter the AP and increase risk of sudden cardiac death [65]. For example, AF is maintained and progressed partly due to electrical remodelling, mediating APD shortening [66]. Thus, in chronic AF, there is upregulation of I_{K1}, I_{Ks} and $I_{K2P}3.1$, which offsets the possible downregulation of I_{Kur} and I_{to} [67-69]. Nevertheless, the experimental evidence for the reduction of I_{Kur} during remodelling is conflicting, as some reports suggest reduced I_{Kur} density [70,71] and others suggest no change [72,73]. It has been suggested that receptor-activated I_{KACH} (rI_{KACH}) mediates AF induced by vagal stimulation while constitutive I_{KACH} (c I_{KACH}) develops in the timecourse of AF remodelling [67,74].

In physiological cardiac hypertrophy, induced by chronic exercise for example, there is an increase in I_K density [75]. This contrasts with pathological cardiac hypertrophy caused by pressure overload where a reduced I_K density is noted that was attributable to cellular hypertrophy rather than gene expression changes in I_{tof} and I_{K1} [76]. In heart failure, AP prolongation is associated with downregulation of several genes, leading to reduced $I_{to,f}$, I_{Ks}, I_{Kr} and I_{K1} [65,77,78]. Considering the

changes in K^+ channel expression in remodelling is clinically important as the sensitivity and efficacy of blocking these channels will change.

Table 2 outlines selected drugs that have been experimentally proven to target different K^+ channels, using either native cardiac myocytes or human cell line expression systems. Some of these drugs presently in clinical use have been primarily developed for other ion channels such as the Na^+ or Ca^{2+} cardiac ion channel but have corresponding effects on K^+ channels. Several drugs have been proposed to be selective to specific K^+ channels, such as A935142, XEN-D0103 and XEN-D0101. However, despite promising experimental findings, many of these drugs have not progressed to clinical use. This may be attributable to limitations associated with experimental studies. Expression systems can often produce off target effects or non-specific interactions which may mask the true effect of these drugs. Additionally, expression systems may run the risk of either over or under expressing the channel of interest. On the other hand, native cardiac myocytes, whilst more physiologically representative, may not provide the right platform for the study of specific targets. Additionally, acquisition of viable native cardiac myocytes from a minimally heterogenous population remains a challenge and it is widely accepted that channel functions can differ by gender and age. Consequently, whilst experimental studies may suggest potentially promising options to selectively target K^+ channels, the translational capacity of such studies remain limited.

Furthermore, these activators and blockers often target more than one K^+ channel species, and thus are not entirely specific [10,79]. However, a large proportion of these drugs also typically target I_{Kr} (known to be present in all cardiac regions) and as such do not constitute ideal candidates for targeted therapy. Nevertheless, mechanisms of cardiac arrhythmia are likely to be region-dependent. Drugs that may be anti-arrhythmic in some cardiac regions may potentially be pro-arrhythmic in others. Thus, the presence of atrial specific K^+ channels has provided focus on developing drugs that could specifically increase refractory periods thus preventing atrial re-entry arrhythmia which is the most common mechanism for AF [80].

Of ion channels specific to the atrium that might offer specific therapeutic targets, the channel conducting I_{Kur} tends to prolong repolarisation and effective refractory period (ERP) without altering QT intervals [81,82]. The experimental drugs AVE0118 and XEN-D101 are thought to be I_{Kur} selective blockers with both prolonging APD in atrial tissue from patients with permanent AF in common with the known I_{Kur} blocker 4-aminopyridine [83-87]. However, a subsequent 'first-in-

human' study using the highly selective I_{Kur} blocker MK-0448 (N-{6-[(1S)-1-(4-fluorophenyl)-2,2-di (pyridine-3-1) ethyl] pyridine2yl} methane sulphonamide) did not reveal any increase in atrial ERP. This led to the conclusion that selective blocking of I_{Kur} may have limited clinical value [88]. I_{KACH} channels are also atrium specific or at least predominantly occur in the atria and have minimal physiological function in the ventricle [87]. Opening of the I_{KACH} channel will lead to the shortening of atrial APD and thus increase the likelihood of AF. Therefore, blocking the opening of I_{KACH} channels will prevent such shortening of APD with minimal effect on ventricular APD in turn reducing the chances of AF. Several drugs block I_{KACH}, but have limited specificity. Nevertheless, selective blocking of I_{KACH} has been experimentally achieved using the compound NTC-801. The compound was found to have selective anti-fibrillatory properties, achieved by prolonging the atrial ERP [89]. Another potential atrial-specific therapeutic target of interest is the I_{KCa} current conducted by SK channels. The selective presence of this current in the atria has recently led to several investigative drugs beings explored. NS8593 is a selective SK channel inhibitor demonstrating significant atrial antiarrhythmic effects in canine and equine experimental models. Experiments using human atrial cardiac myocytes from patients with normal sinus rhythm demonstrated reduction in K^+ currents and prolongation in APD. No such changes were observed in intraventricular myocytes [52].

5.0 Conclusion

There is currently an incomplete understanding of the cellular physiological role of the various cardiac potassium currents and their interacting effects and how dysregulation of their function and expression can provide arrhythmogenic mechanisms. It is thought that the site-specific distribution of some K^+ channels could allow targeted therapy to be more spatially selective. However, complex electrical remodelling events that occur in disease states may change channel expression levels to the extent that the selectivity of the drug is hindered, making even this potential therapeutic strategy challenging. While targeting ion channels responsible for discrete parts of the cardiac AP to modulate the system towards a more physiological state has therapeutic appeal, there are inherent difficulties in developing successful drugs. This is because the ion channels targeted are functionally complex and are inter-dependent thus adding a dynamic situation in which function and expression are altered depending on the cell environment. Furthermore, pathophysiological processes of arrhythmic disease may involve functional

alterations in one or more ion channels. Such single or multiple ion channel functional abnormalities may therefore warrant corresponding use of a single or multichannel activator/blocker approach. This approach however will only be possible if we are able to identify the specific pathophysiological process affecting individual patients (i.e. is this arrhythmic disease related to a single or multichannel abnormality). Thus, whilst we may be able to develop single or multichannel activators/blockers, actual clinical use will be dependent on a detailed understanding of the exact arrhythmogenic mechanisms affecting individual patients, which thus far is limited. Presently, decisions to use single or multichannel activators/blockers are largely dependent on resolution of clinical signs or the actual arrhythmia rather than a therapeutic approach targeting ion channel functional abnormality. Furthermore, the availability of truly specific ion channel activators/blockers is limited as these agents tend to have off-target actions with corresponding side effects, and this limits the clinical use of selective agents. Focusing on understanding the system at a cellular physiological level through further experimental and computational modelling is needed to enable development of novel insights at a pharmacological level.

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figure legends

Figure 1. The ventricular action potential as a paradigm for cardiac electrophysiological activity

In the resting state, the voltage of the cell intracellular space is negative to the external environment. This reflects its higher K^+ but lower Na^+ and Ca_2^+ concentrations, and its lower membrane permeability to Na^+ and Ca^{2+} in comparison to K^+. K^+ efflux from the cell is then controlled by the inward rectifying K^+ channel (I_{K1}). When excitation threshold is reached, a large Na^+ influx (I_{Na}) into the cell through Na^+ channels produces phase 0 depolarization. This is followed by activation of fast and slow transient outward K^+ currents (I_{tof} and I_{tos}) mediating a K^+ efflux driving a rapid phase I repolarisation. There is also an activation of a depolarizing inward Ca^{2+} current through L-type Ca^{2+} channels (I_{Ca}) which initiates excitation contraction coupling. The reduced membrane K^+ permeability due to I_{K1} rectification combined with I_{Ca} maintains the action potential phase 2 plateau phase. Phase 3 repolarization is driven by K^+ efflux through the rapid and slow delayed rectifier K^+ channels (I_{Kr} and I_{Ks}), as well as I_{K1}. At the end of Phase 3, the Na^+ and Ca^{2+} that has accumulated in the cells are removed by the Na^+, K^+ pump and the Na^+,Ca^{2+}-exchanger (NCX). The atrial action potential shows greater contributions to recovery from the ultra-rapid delayed rectifier outward currents (I_{Kur}) and acetylcholine-activated inward rectifying K^+ channel (I_{KACh}).Adapted by permission.[1]

Figure 2. Structure of different cardiac potassium channel species

Schematic representation of selected potassium channel α subunits. (a) the six-transmembrane one-pore-region voltage-dependent K^+-channel (Kv) α-subunits mediating I_{Kur}, I_{to}, I_{Ks}, I_{Kr}, and I_f, (b) the two-transmembrane one-pore-region inward-rectifying K^+-channel (*K*ir) α subunits mediating I_{K1}, I_{KATP}, and I_{KAch}, and (c) the four-transmembrane two-pore-region K^+ channel (K2P) mediating 'leak' K^+ currents. The arrows indicate the location of the pore-forming region(s). Abbreviations: HCN, hyperpolarization-activated cyclic-nucleotide-gated channel; I_f, inward-rectifier mixed Na^+ and K^+ 'funny' current; I_{K1}, inward-rectifier K^+ current; I_{KAch}, acetylcholine-activated inward-rectifier K^+ current; I_{KATP}, ATP-sensitive K^+ current; I_{Kr}, rapid component of the delayed-rectifier K^+ current; I_{Ks}, slow component of the delayed-rectifier K^+ current; I_{Kur}, ultra-rapid component of the delayed-rectifier K^+ current; I_{to}, transient outward K^+ current. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Cardiology, Giudicessi & Ackerman, copyright 2012.[3]

Figure 3. Classification of K^+ currents

General classification of the main cardiac K^+ currents. The relatively new additions to the K^+ channel family (*Ca^{2+}-activated K^+ current (I_{KCa}) and 2-pore domain K^+ current (I_{K2p})* have not been grouped under this scheme. Most K^+ currents are grouped according to the direction of their overall rectification property. In some instances, this may vary. With the inward rectifying K^+ channels, the name refers to the unusual characteristic whereby net potassium flow is into the cell at potentials lower than the reversal potential where channel conductance is high. As the channel potential becomes more positive, channel conductance decreases. Net ion flow direction reverses at the reversal potential, meaning that net potassium flow is outward at potentials more positive than this. Therefore at depolarised potentials, potassium loss from the cell is low as conductance through the channel is low.

Tables

Table 1. Molecular details and activation mechanisms of the cardiac potassium channels.[2]

Current	Gene	Chromosomal location	Associated protein	Type of subunit
I_{tof}	*KCND3*	1p13.2	K_v4.3	α
	KCNIP2	10q24.32	KChIP2	β
	KCNE3	11q13.4	MiRP2	β
I_{tos}	*KCNA4*	11p14.1	K_v1.4	α
I_{Ks}	*KCNQ1*	11p15.5-p15.4	K_v1.7.1/K_vLQT1	α
	KCNE1	21q22.12	minK	β
	AKAP9	7q21.2	AKAP-9	β
I_{Kr}	*KCNH2*	7q36.1	K_v11.1/hERG	α
	KCNE2	21q22.11	MiRP1	β
I_{K1}	*KCNJ2*	17q24.3	K_{ir}2.1/IRK1	α
	KCNJ12	17p11.2	K_{ir}2.2/IRK2	α
I_{KATP}	*KCNJ8*	12p12.1	K_{ir}6.1	α
	KCNJ11	11p15.1	K_{ir}6.2	α
	ABCC9	12p12.1	SUR2A/SUR2B*	β
I_{Kur}	*KCNA5*	12p12.32	K_v1.5	α
	KCNAB1-B3	N/A	K_vβ1-3	β
I_{KAch}	*KCNJ3*	2q24.1	K_{ir}3.1/GIRK1	α
	KCNJ5	11q24.3	K_{ir}3.4/GIRK4	α

*SUR2A and SUR2B are splice variant of ABCC9 and considered as cardiac (SUR2A) and vascular (SUR2B) isoforms.

Table 2. Selected pharmacological agents affecting the human K^+ channels

Current	Pharmacological agent (expression system) [reference]
	Activators
I_{Kr}	A-935142 (HEK) [90], ICA-105574 (HEK) [91], NS1643 (HEK) [92], PD-118057 (HEK) [93],
I_{Ks}	Ephedrine (HEK) [94], Tanshinone IIA (HEK) [95]
I_{Kca}	NS1619 (HEK) [96]
	Blockers
I_{to}	Chromanol 293B (HVM) [97], Flecainide* (nHAM) [98]
I_{Kur}	Amiodarone* (HEK) [99], Bepridil (HEK) [99], DPO-1 (nHAM) [100], MK-0448 (nHAM) [101], NIP-142 (HEK) [102], Papaverine (nHAM) [103], Pimozide (HEK) [104], Sertindole (HEK) [105], XEN-D0103 (HAM) [106]
I_{Kr}	Cocaine (HEK) [107], Fluvoxamine (HEK) [108], Ketoconazole (HEK) [109], Ketanserin (HEK) [110], Ziprasidone (HEK) [111]
I_{Ks}	HMR 1556 (HEK) [112], SKF-96365 (HEK) [113]
I_{KACH}	NIP-151 (HEK) [114], U73122/U73343 (HEK) [115]
I_{KATP}	5-Hydroxydecanoate (HEK) [116], HMR1098 (HEK) [116]
I_{to}, I_{Kur}	AVE-0118 (nHAM) [83], Acacetin (nHAM) [117], Ambasilide (nHAM) [118,119], 4-aminopyridine (nHAM) [98], Diltiazem$^{\delta}$ (nHAM) [120], Docosahexaenoic acid (nHAM) [121], Eicosapentaenoic acid (nHAM) [121], Nifedipine$^{\delta}$ (nHAM) [120], Quinidine* (nHAM) [98], Raloxifene (nHAM) [122], U50488H (nHAM) [123], XEN-D0101 (HAM) [124], Vernakalant (RSD1235) (HEK) [125]
I_{to}, I_{Kur}, I_{K1}	Propafenone* (nHAM) [126]
I_{to}, I_{Kur}, I_{Kr}, I_{Ks}	Clotrimizole (nHAM) [127]
I_{to}, I_{Kur}, I_{Kr}, I_{Ks}, I_{K1}	Azimilide (nHAM) [128]
I_{Kur}, I_{Kr}	Cisapride (HEK) [129], Verapamil $^{\delta}$ (HAM, HEK) [130,131]
I_{Kr}, I_{Ks}	Sotalol (nHAM) [21,118]

HVM = human ventricular myocyte, HAM= human atrial myocyte, nHAM = native human atrial myocyte, HEK = human embryonic kidney.
* = primary Na^+ channel blocker, $^{\delta}$ = primary Ca^{2+} channel blocker