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Atrial-selective K⁺ channel blockers – potential antiarrhythmic drugs in atrial fibrillation?¹

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Abstract

In the wake of demographic change in Western countries atrial fibrillation has reached an epidemiological scale, yet current strategies for drug treatment of the arrhythmia lack sufficient efficacy and safety. In search of novel medications, atrial-selective drugs that specifically target atrial over other cardiac functions have been developed. Here, I will address drugs acting on potassium (K^+) channels that are either predominantly expressed in atria or possess electrophysiological properties distinct in atria from ventricles. These channels include the ultra-rapidly activating, delayed outward-rectifying Kv1.5 channel conducting I_{Kur} , the acetylcholine-activated inward-rectifying Kir3.1/Kir3.4 channel conducting $I_{K,ACh}$, the Ca^{2+} -activated K^+ channels of small conductance (SK) conducting I_{SK} , and the two pore domain K^+ (K2P) channels [tandem of P domains, weak inward-rectifying K^+ channels (TWIK-1), TWIK-related acid-sensitive K^+ channels (TASK-1 and TASK-3)] that are responsible for voltage-independent background currents I_{TWIK-1} , I_{TASK-1} , and I_{TASK-3} . Direct drug effects on these channels are described and their putative value in treatment of atrial fibrillation is discussed. Although many potential drug targets have emerged in the process of unravelling details of the pathophysiological mechanisms responsible for atrial fibrillation, we do not know whether novel antiarrhythmic drugs will be more successful when modulating many targets or a single specific one. The answer to this riddle can only be solved in a clinical context.

Key words

Atrial fibrillation – antiarrhythmic drugs – voltage-dependent K^+ channels - two-pore domain K^+ channels – Ca^{2+} - activated K^+ channels

Introduction

Atrial Fibrillation (AF) affects more than 6 million Europeans (European Heart Rhythm et al. 2010) worsening their quality of life and increasing their mortality due to elevated risk of stroke and heart failure (Benjamin et al. 1998). Therefore, the two major treatment goals are prevention of stroke with novel oral anticoagulants and prevention of heart failure by normalizing heart rhythm or if that is not feasible, by reducing heart rate (Kirchhof et al. 2016).

Pacemaker cells within the sinus node generate excitatory action potentials that first activate the atria and are then conducted to the ventricles via the atrio-ventricular node. During an action potential, pore-containing proteins within the lipid membrane (ion channels) open and close in a voltage- and time-dependent manner in order to allow ionic current flow. The sum of all current flow via Na^+ , Ca^{2+} and K^+ channels gives rise to the specific shape of action potential (see **Figure 1**) with its characteristic spike-and dome configuration in healthy atrial tissue (Ravens and Cerbai 2008).

Atrial fibrillation is initiated when a pathophysiological trigger encounters a vulnerable substrate allowing conduction within re-entry circuits to perpetuate the arrhythmia. The high frequency of aberrant excitation leads to characteristic electrical and structural changes in the atrial tissue (electrical and structural “remodelling”), including changes in atrial action potentials and tissue morphology. The hallmark of electrical remodelling is the change of the action potential from a spike-and-dome to a typical triangular shape (Dobrev and Ravens 2003).

Antiarrhythmic strategies target suppression of ectopic foci and disruption of re-entry either by ablation techniques or by electrical and pharmacological cardioversion to sinus rhythm. In particular, drugs may suppress ectopic and triggered activity (Na^+ channel blockers), disrupt re-entry by prolongation of action potential duration (APD) and effective refractory period (K^+ channel blockers), and restore compromised cellular Ca^{2+} handling (experimental drugs) [for reviews see (Burashnikov and Antzelevitch 2009; Heijman and Dobrev 2015; Heijman et al. 2014; Ravens 2010)].

The currently registered antiarrhythmic drugs, however, lack sufficient efficacy and safety due to cardiac and extracardiac side effects. In particular, all available antiarrhythmic drugs, on their own terms, can also produce proarrhythmic effects that

may eventually lead to ventricular arrhythmia. For instance, excessive prolongation in ventricular APD by conventional class III antiarrhythmic drugs, mainly human ether-a-go-go related gene (hERG) channel blockers, is associated with a high risk of life-threatening torsades de pointes arrhythmias that may exacerbate into ventricular fibrillation (Sanguinetti and Mitcheson 2005). Therefore, the idea of “atrial selective” drugs was conceived (Ehrlich et al. 2007) which implies that drugs for treating atrial fibrillation should aim at specific targets that are expressed only in the atria but not in the ventricles thereby sparing the ventricles of unwanted proarrhythmic effects [for reviews see (El-Haou et al. 2015; Hancox et al. 2016; Ravens et al. 2013)]. In my lecture held in honour of Professor Naranjan Dhalla, founder of the 20-years old International Academy for Cardiovascular Sciences, I provided an update of the recent developments in the search for new atria-targeting antiarrhythmic drugs that are directed at various K^+ channels predominantly expressed in atrial cardiomyocytes (Ravens and Odening 2016; Voigt and Dobrev 2016).

Atrial-selective drug targets

Although most ion currents that constitute the action potential resemble each other in atrial and ventricular cardiomyocytes, there are sufficient differences to allow atrial-selective drug targeting. While the upstroke and plateau phase are similar, distinct K^+ channels or K^+ channel properties are responsible for the profound differences in action potential shapes (see Roman numbers I-IV in **Figure 1**). For instance, the robust expression of Kv1.5 channels in atrial cardiomyocytes gives rise to an ultra-rapidly activating outward current carried by K^+ (I_{Kur}) that contributes to the large rapid early repolarization of the atrial action potential before the inwardly directed L-type Ca^{2+} current is activated. Thus the atrial plateau phase occurs at more negative voltage in atrial than in ventricular cardiomyocytes. Kir3.1/3.4 channels are predominantly expressed in atria and cause robust action potential shortening following their activation by acetylcholine. Atrial fibrillation triggered by vagal nerve stimulation is mediated by excessive action potential shortening, and hence also shortening of the effective refractory period, which promotes reentry (Kovoor et al. 2001). Other channels more prevalent in atria than in ventricles are two-pore domain potassium (K2P) channels belonging to the tandem of P domains, weak inward-rectifying K^+ (TWIK) and the TWIK-related acid-sensitive K^+ (TASK) channel families

(Duprat et al. 1997; Lesage et al. 1996). Current flow through these channels contributes to background conductance in human atrial cardiomyocytes (Limberg et al. 2011). Finally, Ca^{2+} -activated K^+ channels of small conductance, SK1, SK2 and SK3, contribute to cardiac background current (Kohler et al. 1996). They are activated by submicromolar concentrations of intracellular Ca^{2+} and abbreviate the action potential duration.

Here, I will confine myself to the discussion of atrial-selective K^+ channels as putative drug targets. Blocking any of these channels is expected to produce an antiarrhythmic effect by prolongation of action potential duration and effective refractory period thereby disrupting re-entry and possibly re-establishing sinus rhythm. A vast number of experimental drugs have been extensively investigated for their putative potential in the therapy of atrial fibrillation (El-Haou et al. 2015; J. W. Ford and Milnes 2008). Since ion channels are not confined to the heart but also expressed in the brain, putatively useful cardiac drugs should not pass the blood brain barrier in order to avoid unwanted side effects in the central nervous system.

Blockers of Kv1.5 channels

The first human atrial-selective K^+ channel discovered was Kv1.5 (Fedida et al. 1993). Block of Kv1.5 channels in computer models or in patch-clamped human atrial cardiomyocytes did in fact prolong action potential duration in atrial fibrillation cardiomyocytes. In sinus rhythm, however, the major result was a marked elevation of the action potential plateau with prolongation in action potential duration in computer models and actually *shortening* of action potential duration measured in physiologically paced native atrial tissue (Courtemanche et al. 1998; Ravens and Wettwer 2011; Wettwer et al. 2004). Interestingly, the first clinically studied Kv1.5 blocker MK-0448 failed to produce a significant effect on atrial refractoriness in healthy subjects at heart rates up to 150 beats per minute (Pavri et al. 2012). One possible explanation for this lack of efficacy could lie in the strong frequency-dependency of Kv1.5 blockers that we found in human atrial tissue (J. W. Ford et al. 2016). MK-0448 and XEN-D0103 shortened sinus rhythm action potential duration at frequencies below 3 Hz, but clearly prolonged this parameter at faster frequencies (see **Figure 2**). Action potentials remodelled by atrial fibrillation were always

prolonged (J. W. Ford et al. 2016; Loose et al. 2014). However, clinical trials clearly demonstrating reduction of AF burden by Kv1.5 blockers have not been reported.

Blockers of Kir3.1/Kir3.4 channels

Under physiological conditions, the hetero-tetrameric Kir3.1/Kir3.4 channels are activated by the neurotransmitter acetylcholine. The channels conduct a much larger inwardly rectifying K⁺ current in atrial than in ventricular cardiomyocytes (Koumi and Wasserstrom 1994), which is responsible for the robust shortening in atrial action potential duration upon vagal nerve stimulation. Interestingly, during atrial fibrillation-induced remodeling, these channels become constitutively active (Dobrev et al. 2005), that is, their open probability increases in the absence of any acetylcholine or related compound (**Figure 3**). The resulting increase in K⁺ conductance contributes to the short action potential in atrial fibrillation. Therefore, selective block of Kir3.1/Kir3.4 channels could have beneficial effects by preventing atrial fibrillation episodes caused by vagal activation or by reversing AF-induced action potential shortening due to constitutive channel activity. In fact, the bee venom constituent tertiapin, a selective Kir3.1/Kir3.4 channel blocker, suppresses the arrhythmia in a dog model of atrial fibrillation (Cha et al. 2006). Numerous additional experimental drugs, such as AZ2927, NTC-801 (renamed BMS914392) or XEN-R0706 have been tested in dog and human atrial tissue, with convincing effects in dog but little evidence for antiarrhythmic efficacy in man (Machida et al. 2011; Walfridsson et al. 2015). One reason could be, that Kir3.1/Kir3.4 blockers, like Kv1.5 blockers, exhibit more robust prolongation of action potential duration and refractoriness at high frequencies. In a recent clinical study with BMS914392 dosage was limited by central nervous side effects before any significant increase in atrial refractoriness occurred (Podd et al. 2016).

Blockers of TASK-1/TASK-3 channels

Compelling evidence has been provided during the past two decades that the K2P channels TWIK-1, TASK-1 and TASK-3 are expressed in the heart and contribute to background current (Decher et al. 2015) In particular, TWIK-1 and TASK-1 are more abundant in human atria than ventricles (Gaborit et al. 2007; Limberg et al. 2011), although the opposite is the case for TASK-1 in murine hearts (Donner et al. 2011).

Conflicting results were reported for the role of TASK-1 in atrial fibrillation: whilst Schmidt et al. (Schmidt et al. 2015) reported up-regulation of the *KCNK3* gene encoding for TASK-1 in atrial tissue from patients with permanent atrial fibrillation that was accompanied by increased current, Harleton et al. reported reduced current despite unchanged expression of channel protein (Harleton et al. 2015). Instead, they found robust phosphorylation of TASK-1 channel protein, accompanied by impaired channel function that could be rescued by activation of phosphatases, suggesting that AF-induced electrical remodelling of this current involves regulatory processes rather than changes in gene expression. Interestingly, Schmidt et al. (Schmidt et al. 2015) also did not find any change in TASK-1 expression in the left atrial appendage from atrial fibrillation patients, so that some of these discrepancies may be due to different chamber origin of the biopsies (right atrial appendage versus left atrial free wall). Clearly, more research is required to resolve this issue.

Notwithstanding these difficulties TASK-1 current appears to contribute to repolarization of human atria, since pharmacological inhibition of $I_{\text{TASK-1}}$ prolongs APD [(Schmidt et al. 2014), see also **Figure 4A**]. Many clinically used and experimental antiarrhythmic drugs are TASK-1 channel blockers, as for instance amiodarone (Gierten et al. 2010), dronedarone (Schmidt et al. 2012) or carvedilol (Staudacher et al. 2011), and also Kv1.5 blockers (Kiper et al. 2015). However, there are only few selective TASK-1 channel blockers amongst which the Sanofi-Aventis compound A293 has been most extensively investigated (Putzke et al. 2007). Recent pharmaceutical efforts aim at developing new agents, also to avoid possibly the risk of pulmonary hypertension inherent with TASK-1 channel block (Flaherty et al. 2014).

Blockers of SK channels

During the contractile cycle free intracellular Ca^{2+} changes between nano- and sub-micromolar concentrations. This concentration range is sufficient to activate K^+ channels of small conductance, SK channels, which contribute to cardiac background current (Kohler et al., 1996). Since SK channels are more abundant in atrial than in ventricular tissue (Tuteja et al. 2005) they qualify as atrial-selective drug targets. The most abundant α -subunits isoforms in human atria are SK2 and SK3 channels (Skibsbjerg et al. 2014). When all SK channel isoforms are present they usually form heteromers in a 2:2 stoichiometry (Church et al. 2015).

The contribution of SK channel current to the atrial action potential is controversial, with positive as well as negative results [compare, for instance, (Skibsbjerg et al. 2014) versus (Bonilla et al. 2014)]. Since these studies rely on drugs to block SK channels, differences between various agents in selectivity or pharmacokinetic distribution within the tissue may lead to discrepant interpretations.

There is also conflicting evidence as to the role of SK channels in chronic atrial fibrillation-induced remodelling which may not only affect channel expression but also regulation of channel activity due to impairment of Ca^{2+} handling that is associated with the tachyarrhythmia (Dobrev and Nattel 2008) thereby indirectly affecting SK channel activity. In the atrial fibrillation model of tachy-paced dog atria, SK channels were reported to be up-regulated (Qi et al. 2014), and in the burst-pacing rabbit model, trafficking of SK channels to the plasma membrane was found to be enhanced (Ozgen et al. 2007). In our own studies in atrial biopsies from patients, however, SK2 and SK3 channels were down-regulated at the messenger mRNA level in chronic atrial fibrillation (Skibsbjerg et al. 2014).

The SK channel inhibitors best characterised are apamin, UCL1684, NS8593, and ICAGEN. Theoretically, inhibition of SK channels is expected to prolong the atrial action potential duration and therefore protect against re-entry due to increased wavelength (Diness et al. 2010; Qi et al. 2014) but proarrhythmic effects due to increased electrophysiological heterogeneity in the presence of SK channel blockers have also been reported (Hsueh et al. 2013). Using ICAGEN, we observed prolongation of action potential duration in SR preparations, but no effect in AF preparations [(Skibsbjerg et al. 2014); **Fig. 4B**]. Therefore, whether or not block of SK channels is in fact useful in atrial fibrillation still has to be demonstrated in a clinical setting.

Conclusion

Having restricted myself to the brief characterization of a few atrial K^+ channels and the effects of potential drugs that target them is, of course, an oversimplification. The drugs reviewed exhibited in-vitro electrophysiological effects that are considered to be antiarrhythmic and showed promising antiarrhythmic activity in animal models, but clinical efficacy could not convincingly be demonstrated. Drug failure may, at least

partially, be due to the heterogeneity of atrial fibrillation, since the efficacy of modification of expression/function of individual ion channels may vary according to the aetiology and severity of the arrhythmia (Kirchhof et al. 2012). In view of the fact that one of the most efficient antiarrhythmic drugs currently in use is the multichannel blocker amiodarone, one could speculate that blocking more than one atrial-selective channel or a combination of an atrial-selective drug with a low concentration of a Na⁺ channel blocker may be a potentially beneficial treatment option. In addition numerous other atria-associated or even systemic drug targets are being considered, including in the former case components of channel-protein macrocomplexes, channel trafficking, calcium handling, mitochondria or fibroblast-cardiomyocyte interactions (Nattel et al. 2008), and in the latter case systemic inflammation, endothelial dysfunction, oxidative stress, diffuse and focal myocardial fibrosis (Wijesurendra and Casadei 2015). Therefore, in order to develop specific novel drugs, more research is required for full elucidation of all mechanisms contributing to the development and progression of atrial fibrillation from a molecular to a macroscopic level.

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Legends to Figures

Figure 1. Electrical activity in human myocardium: comparison of atrial with ventricular tissue. Top: Action potentials with phase 0, rapid depolarization; phase 1, rapid early repolarization; phase 2, slow repolarization ('plateau' phase); phase 3, rapid late repolarization; phase 4, resting membrane potential. Middle: Inward, depolarizing currents (blue background); Bottom: outward, repolarizing currents (red background). I_{Na} sodium current; $I_{Ca,L}$ L-type calcium current; I_{to} transient outward current; I_{Kur} ultrarapidly activating delayed rectifier current; I_{Kr} and I_{Ks} rapidly and slowly activating delayed rectifier current, respectively; I_{K1} inward rectifier current; $I_{K,ACh}$ acetylcholine-activated potassium current. $I_{K,ATP}$, ATP-dependent K^+ current; I_{K2P} , background current flowing through TASK1/3 channels; $I_{SK,Ca}$, current flowing through Ca^{2+} -activated K^+ channels of small conductance. Note, that I_{Kur} , $I_{K,ACh}$, I_{K2P} , and $I_{SK,Ca}$ are predominantly present in atria only. Adapted from (Ravens and Cerbai 2008).

Figure 2. Proposed antiarrhythmic mechanism of selective I_{Kur} blockers in non-remodelled human atria from patients in sinus rhythm or paroxysmal atrial fibrillation. Blockade of Kv1.5 channels induces APD shortening at low stimulation rate (1 Hz) but prolongation at higher rate (4 Hz and higher) leading to suppression of action potentials and failure to capture electrical excitation (red arrow; (J. W. Ford et al. 2016). Black and red traces: action potentials from patients in SR and AF, respectively. Reproduced from (Ravens and Odening 2016), with permission of the publishers.

Figure 3. Single channel activity in atrial cardiomyocytes from a patient in sinus rhythm (SR, left) and atrial fibrillation (AF, right). A downward deflection from the zero-level denotes inward current flow through an open channel. Two activity patterns with distinctly different characteristics are observed: low-amplitude, long-lasting channel openings predominate in SR under control conditions (upper left tracing) and are due to opening of inward rectifier K^+ channels Kir2.1/Kir2.3. Upon addition of carbachol, acetylcholine-activated Kir3.1/Kir3.4 channels show large-amplitude, short-lasting openings (lower left tracing). In AF controls, however, these

large-amplitude, short-lasting openings in the absence of any drug (i.e. constitutive activity) occur in addition to the low-amplitude, long-lasting openings of Kir2.1/Kir2.3 channels (upper right tracings).

Figure 4

Effects of selective TASK-1 and SK channel blockers on human right atrial action potentials. (A) Patch-clamp, single cell recordings in the absence (black) and presence of A293 (200 nM; red, dashed), stimulation rate 0.2 Hz. Note, that A293 mainly prolongs action potential duration in atrial fibrillation, where TASK-1 channels are up-regulated. Data redrawn from (Schmidt et al. 2015). (B) Sharp microelectrode recordings in atrial trabeculae without and in the presence of the selective SK channel blocker ICAGEN (10 μ M), stimulation frequency 1 Hz. Note that ICAGEN has little effect in atrial fibrillation action potentials, where SK-2 and SK-3 are down-regulated. Data redrawn from (Skibsbjerg et al. 2014).

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