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Role of Calcium-activated Potassium Channels in Atrial Fibrillation Pathophysiology and Therapy

Jonas G. Diness, PhD, Bo H. Bentzen, PhD,*† Ulrik S. Sørensen, PhD,* and Morten Grunnet, PhD, DrSci*‡*

(See editorial: Innovative therapeutics for atrial fibrillation: Imminent breakthroughs or much ado about nothing? by Stanley Nattel and Dobromir Dobrev. Journal of Cardiovasular Pharmacology, 2015 66:5;409–411)

Abstract: Small-conductance Ca^{2+}-activated potassium (SK) channels are relative newcomers within the field of cardiac electrophysiology. In recent years, an increased focus has been given to these channels because they might constitute a relatively atrial-selective target. This review will give a general introduction to SK channels followed by their proposed function in the heart under normal and pathophysiological conditions. It is revealed how antiarrhythmic effects can be obtained by SK channel inhibition in a number of species in situations of atrial fibrillation. On the contrary, the beneficial effects of SK channel inhibition in situations of heart failure are questionable and still needs investigation. The understanding of cardiac SK channels is rapidly increasing these years, and it is hoped that this will clarify whether SK channel inhibition has potential as a new anti–atrial fibrillation principle.

Key Words: SK channel, atrial fibrillation, supraventricular arrhythmias, SK channel inhibitors, pharmacology

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INTRODUCTION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia; of hospitalizations associated with heart rhythm disturbances, approximately one-third is accounted for by AF. For the general population, the lifetime risk of developing AF is approximately 25% after the age of 40 and with relative incidence increasing with age.[1,2] Although not devastating per se, AF is associated with reduced quality of life and increased risk of stroke. The latter is a consequence of compromised atrial contraction that results in blood stasis and jeopardizes proper ventricular function. In combination, this predisposes to thromboembolic stroke and heart failure (HF).

In addition to a general introduction to the disease and to current surgical and pharmacological treatments of AF, a number of new avenues and biological mechanisms to target AF are presented in this special issue of *Journal of Cardiovascular Pharmacology*. This review is devoted to an in-depth introduction to a relative newcomer in the field of possible targets to treat AF, namely calcium-activated potassium channels. After a general introduction to the family of calcium-activated potassium channels with particular focus on a subclass named the small-conductance Ca^{2+}-activated potassium (SK) channels, a more comprehensive review of cardiac SK channels will be given. Concluding remarks are centered on electrical cardioversion of AF versus corresponding pharmacological cardioversion and a brief account of other alternative ion channel approaches with potential value as AF treatment.

SK CHANNELS: A GENERAL INTRODUCTION

The family of Ca^{2+}-activated K^+ channels has traditionally been divided into 3 classes based on their single channel conductance. Hence, the classes have been named big-conductance Ca^{2+}-activated potassium (BK) channels, intermediate-conductance Ca^{2+}-activated potassium (IK) channels, and small-conductance Ca^{2+}-activated potassium (SK) channels. The corresponding protein and gene names are BK/K_{Ca}1.1/*KCNMA1*, IK/K_{Ca}3.1/*KCNN4*; and SK1, SK2, SK3/K_{Ca}2.1, K_{Ca}2.2, K_{Ca}2.3/*KCNN1, KCNN2, KCNN3*, where SK1-3 denotes the 3 known subtypes of SK channels. Ca^{2+}-activated K^+ channels have traditionally been seen as ubiquitously expressed when it came to tissue expression with the notable exception of being absent from cardiac tissue at least when addressing BK channels.[3] Also, the evidence of cardiac SK channels has been very sparse until recently, and IK channels are still not reported to be present in the cardiac myocytes but play important roles in vessels as key players in blood pressure regulation.[4,5] BK channels play an important role in intracellular compartments such as the mitochondria where they are involved in ischemia–reperfusion injuries.[6–9] Within the family of Ca^{2+}-activated K^+ channels, it is however only the SK channels that seem to be functionally expressed in the plasma membrane of cardiomyocytes and thereby have the possibility to directly impact cardiac action potential morphology. It has furthermore been speculated that functionally, SK channels are

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From the *Acesion Pharma, Copenhagen, Denmark; Departments of †Biomedical Science; and ‡Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark.
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J. G. Diness and B. H. Bentzen contributed equally.
Reprints: Morten Grunnet, PhD, DrSci, CSO, Acesion Pharma, Ole Maaløes Vej 3, 2200 Copenhagen N, Denmark (e-mail: mgr@acesionpharma.com).

a seemingly atrial-selective target. As described in details in the section "Cardiac SK Channels," SK channels are present in both atria and ventricles. However, the functional activation of SK channels and thereby their intrinsic impact on action potential generation are significantly more prominent in atria compared with ventricles.[10–12] This finding has opened up for the notion that SK channels could constitute a potentially interesting target for treating atrial arrhythmias without ventricular adverse effects. Hypothetically, a drug selectively inhibiting SK channels will constitute a traditional class III antiarrhythmic drug, thereby prolonging the effective refractory period (ERP) in the atria by increasing the action potential duration (APD). Another theoretical impact of SK channel inhibition might rely on subtle diastolic depolarization that could increase postrepolarization refractory period, and consequently ERP, by leaving a large proportion of voltage-gated Na^+ channels in their inactivated state.

SK channels consist, as most other K^+ channels, of 6 transmembrane regions (TM) and a single pore loop. To constitute a functional channel, 4 subunits in an arrangement around a central pore are needed.[13] N-termini and C-termini are both oriented toward the cytoplasma. No additional β-subunits have been reported for SK channels, but the calcium-binding protein calmodulin is constitutively associated with the channel by a C-terminal calmodulin-binding domain.[14] As the name implies, Ca^{2+}-activated K^+ channels SK channels are dependent on Ca^{2+} binding to function properly. Ca^{2+} binds to the channel by calmodulin. Biophysically, SK channels are activated almost instantly by increases in intracellular Ca^{2+} with an activation being directly proportional to $[Ca^{2+}]_i$ ($47\ \mu M^{-1}\cdot s^{-1}$). In contrast, the deactivation rate is independent on $[Ca^{2+}]_i$ (13/s).[15] The activation kinetics upon Ca^{2+} activation of SK channels is steeply Ca^{2+}-dependent with a Hill coefficient of 4–5. SK channels are believed to be quiescent at resting concentrations of intracellular Ca^{2+} (approximately 100 nM) and have a half-maximal Ca^{2+} activation at ~300 nM.[14] This Ca^{2+} dependency is equal among the 3 SK channel subtypes, SK1, SK2, and SK3. More specifically, the most likely mechanism behind SK channel activation is a conformation where 4 calmodulin molecules, each potentially binding 2 Ca^{2+} ions, accounts for channel activation.[16] The channels have no charged amino acids in the fourth TM domain that is usually an important component of the voltage sensor of voltage-gated channels. Whereas BK channels are activated both by Ca^{2+} and by voltage, SK and IK channels are activated and deactivated solely as a consequence of binding and unbinding of Ca^{2+}. SK and IK channels thereby represent a unique family of K^+ channels as they are gated only by intracellular Ca^{2+} in a voltage-independent manner and are able to integrate changes in intracellular Ca^{2+} to changes in K^+ conductance.[17] SK channels have a small single-channel conductance of 8–10 pS (0 mV, symmetrical 150 mM K^+).[18] Despite a complete lack of voltage sensors, SK channels demonstrate inward-rectifying current–voltage relationship when recorded in symmetrical K^+ solutions, a phenomenon that is almost absent under physiological ion concentrations. In all likelihood, the rectification is a consequence of voltage-dependent inhibition by intracellular Mg^{2+} and Ca^{2+}.[19] Moreover, SK2 channels have been shown to be part of larger macromolecular protein complexes, consisting of a protein kinase (CK2), a phosphatase (PP2A), calmodulin, and scaffolding proteins. This complex dynamically influences the phosphorylation state of calmodulin and thereby also the Ca^{2+}-sensitivity of SK2 channels.[20] Despite the lack of voltage sensitivity, these possibilities for additional regulation impose state-dependent control of the Ca^{2+} sensitivity of SK channels.[21] One could speculate that this constitutes part of an explanation for the different functional effects observed between atrial and ventricular SK channels and for the varying function during sinus rhythm (SR) and under AF due to different Ca^{2+} dynamics in these situations.

The tight control of regulation of the Ca^{2+}-activated K^+ channels by Ca^{2+} has prompted a search for the source of Ca^{2+} necessary for activation. One obvious possibility is the direct coupling to other membrane proteins permeable to Ca^{2+}. Such interactions have initially been demonstrated for Ca^{2+}-activated K^+ channels localized in the brain. Examples are the direct coupling to voltage-gated Ca^{2+} channels and the coupling to ionotropic receptors in various neurons.[22,23] Similar interactions have been demonstrated in cardiac tissue by coupling of the SK channels and L-type Ca^{2+} channels through a cytoskeletal linker protein named α-actinin2.[24,25] Other sources of intracellular Ca^{2+} could be speculated to come from direct release from intracellular organelles in close proximity to the Ca^{2+}-activated K^+ channel, but this remains to be proven. From a physiological and pathophysiological perspective, the exact source of Ca^{2+} activation of SK channels seems interesting. The apparent functional difference between atrial and ventricular SK channels despite the molecular evidence of messenger RNA and protein expression in both atria and ventricles might rely on different Ca^{2+} handling. This notion is however currently speculative as is the notion that such differences in Ca^{2+} handling could be important during arrhythmic events such as AF.

As mentioned, the SK channel current (I_{SK}) has only recently been seriously considered relevant for electrical activity in the heart. Most knowledge on SK channels is from brain tissue where a widespread but distinct expression patterns is observed in species such as mice and rats. The general picture is that the SK1 and SK2 subtypes are coexpressed in hippocampal, neocortical, and cerebellar regions, whereas SK3 is confined to expression in evolutionary more original brain structures such as the basal ganglia and thalamus regions.[26–28] Whether native channels express as homomers or heteromers is debatable, but at least in brain, functional heteromers seem to be of importance.[29] The wide expression of SK channels in the brain has importance in the development of safe drugs using SK channels as targets because unintended inhibition in the brain may result in central nervous system–mediated adverse effects. Outside the central nervous system and the heart, SK channels are also found in the liver, sensory nerves, vascular endothelium, skeletal and smooth muscle cells, and adrenal cromaffine cells.[30,31]

SK CHANNEL PHARMACOLOGY

A number of naturally occurring peptides and synthetic organic molecules have historically provided valuable information about SK channel function. The bee toxin apamin has traditionally been used in the identification of current component conducted by SK channels because of the combination of

highly potent and selective SK channel inhibition. Apamin inhibits SK channels at low nanomolar concentrations. In addition, the toxin demonstrates no affinity for all other Ca^{2+}-activated, constitutively active, and voltage-gated K^+ channels as well as other Na^+, Ca^{2+}, and Cl^- channels.[32] Apamin inhibits all 3 subtypes of SK channels with the selectivity sequence: SK2 < SK3 < SK1.[33] It is however noteworthy that a changeable fraction of SK channels might become insensitive to apamin (and to the small-molecule *N*-methyl-bicuculline) in heterologous expression systems,[32,34] a phenomenon that is currently unexplained.

Apamin has also demonstrated various degrees of potency in different types of organs with cardiac tissue being no exception.[17,35] Some toxins, such as scyllatoxin/leiurotoxin, and tamapin are also potent SK channel inhibitors.[36,37] An artificial peptide LeiDap7 has been generated based on the structure of scyllatoxin and exhibits improved selectivity for SK2 over SK3/SK1.[38] In addition to peptides, also small molecules, such as UCL1684, D-tubocurarine, dequalinium, methyl-laudanosine, and methyl-noscapine are SK channel inhibitors.[39] These compounds mimic some of the structural elements responsible for toxin binding,[40] and a common feature of these small organic molecules and toxins is their ability to displace [^{125}I]-apamin binding. A common denominator is thereby that all act as pore blockers although apamin apparently binds to a more remote outer part of the pore compared with traditional pore blockers like tetraethylammonium (TEA).[41–43] A completely different class of compounds is represented by the small molecule NS8593.[44,45] This compound is able to interact with gating structures deep within the channel pore structure albeit in a manner that does not share binding site with apamin. NS8593 is a pan-selective SK channel modifier that acts as a negative allosteric modulator by decreasing the affinity for Ca^{2+} binding and thereby channel activation.

Physiological and Pathophysiological Roles of Cardiac SK Channels

Shortly, after the partitioning of bee venom into its chemical constituents was accomplished, the cardiac effects of apamin both in vivo and ex vivo were studied and reported at Edgewood Arsenal, Maryland.[46] At this time, the pharmacological actions of apamin were not known, but apamin was found to be clearly antiarrhythmic as well as increasing the heart rate and the force of contraction with no effects on blood pressure or electrocardiogram in both monkeys and dogs.[46] The apamin used for those experiments was, however, not completely pure, and the results did not lead to follow-up studies of this interesting effect of apamin.[47]

The idea of Ca^{2+}-activated K^+ channels linking free intracellular Ca^{2+} to the opening of K^+ channels is not new and could explain a number of effects on TM currents by free cytosolic Ca^{2+}. During the 1970s, numerous findings of supposed calcium-activated potassium currents were made but however also rejected.[48] It was not until 1999 that the first convincing evidence of cardiac Ca^{2+}-activated K^+ channels was presented.[49]

In 2003, with a concentration as remarkably low as 50 pM apamin, Xu et al demonstrated apamin-sensitive current in atrial myocytes from both mice and men. The apamin-sensitive current was shown to be significantly larger in atrial myocytes compared with ventricular myocytes in mice in line with the discovery that SK2 channels were preferentially expressed in atria as compared with ventricles of human and mouse hearts.[50] All 3 SK channel subtypes were found in mouse hearts by Chiamvimonvat et al in 2005, showing an atrial-selective distribution for the SK1 and SK2 subtypes.[51]

Role of Atrial I_{SK}

The first indication that I_{SK} might play a role in AF was presented in 2007 by Ozgen et al[52] who showed that the recurrent burst pacing of pulmonary vein sleeves resulted in increased trafficking of SK2 to the cell membranes, which in turn shortened pulmonary vein action potentials due to increased I_{SK}. In 2009, Chiamvimonvat et al provided evidence of a more direct connection between I_{SK} and AF by showing that atrial cardiomyocytes from SK2 knockout mice had prolonged atrial APD and early afterdepolarizations (EADs) when recording from isolated atrial cardiomyocytes. Such EADs were not observed in control conditions. Furthermore, SK2 KO mice had higher propensity for developing AF after programmed extrastimulations and bursts compared with wild-type mice.[53] Surprisingly, AF could be induced in these mice by premature electrical stimulation protocols although these procedures usually cause reentry rather than EAD arrhythmias, and prolongation of the atrial effective refractory period (aERP) would be expected to decrease the risk of reentry arrhythmias.[10] The Chiamvimonvat group also examined another genetic mouse model that overexpress the SK3 channel unless they are given dietary tetracycline or doxycycline in which case SK3 expression is lowered. In this model, it was shown that atrial myocytes from the homozygous $SK3^{T/T}$ mice overexpressing SK3 have significantly shortened APD_{90}, and dietary doxycycline leads to prolongation of the APD_{90}. Furthermore, in intact hearts from the overexpressing SK3 mice, it was possible to induce atrial arrhythmias, whereas this was not possible in the wild-type littermates.[54]

In 2010, Ellinor et al[55] presented the first connection between SK channels and clinical AF by identifying the gene encoding SK3, KCNN3, as a common genetic variant underlying lone AF in a meta-analysis of genome-wide association studies. The link between clinical AF and I_{SK} has later been confirmed in studies of larger populations[56] and populations of non-European ancestry.[57]

Following the publication in 2010 by Ellinor et al, I_{SK} inhibition was shown to be antiarrhythmic in isolated heart models of AF in a range of species and in in vivo rats without any ventricular effects.[58] These findings were further supported in 2011 with 2 publications providing evidence from in vivo rats that I_{SK} inhibition prolongs aERP correlating with antiarrhythmic activity.[35,58] I_{SK} inhibition was furthermore shown to be effectively antiarrhythmic in hypertension-induced atrial remodeling in rats in vivo.[59] Moreover, when combining low doses of inhibitors of I_{SK} and I_{Na}, potent antiarrhythmic effects can be obtained in isolated guinea pig hearts.[60]

There is however also evidence of proarrhythmic effects of reduced SK channel expression. In a transgenic

mouse study, it has been demonstrated that SK knockout resulted in increased atrial action potential triangulation and augmented AF propensity.[53] It should be considered that also genetic overexpression of SK in mice seems proarrhythmic, and in general, cardiac electrophysiology in mice is significantly different from larger mammalian species, including humans, because of very fast heart rate and a corresponding different composition of cardiac ion channels.[54]

Another report of proarrhythmic effects of SK channel blockade has been generated in dogs. Hsueh et al investigated the effects of blocking I_{SK} in optically mapped isolated canine atria in 2013.[61] In this study, the main conclusion was that I_{SK} blockade promotes atrial arrhythmia especially at slow heart rates by increasing APD heterogeneity in the atrial tissue. It should however be noted that apparently no time-matched controls were used, and that the number of experiments where the induction of reentrant arrhythmias was attempted was too small to be statistically significant (n = 2 for apamin and n = 4 for UCL1684).

In 2013, the laboratory of Dr Nattel published data on the role of cardiac I_{SK} from a canine in vivo model of tachypacing-induced atrial remodeling.[11] In this study, it is documented that SK channel expression and I_{SK} are greater in canine pulmonary vein sleeves versus left atrial wall and that both are upregulated by atrial tachypacing. In contrast to the findings by Hsueh et al in isolated canine atria, the study clearly demonstrates that negative allosteric modulation of SK channels with NS8593 increases atrial APD and ERP at different heart rates and has distinct anti-AF effects with apparently no effects on ventricular ERP, AV-nodal conductance, or blood pressure. The discrepancy between these studies might rely on the isolated heart preparation and incubation with voltage-sensitive dyes in contrast to the in vivo setting. For example, it has been demonstrated that such dyes can have pharmacological or photodynamic effects in themselves, such as slowing of conduction velocity, prolongation of APD, reduction of resting membrane potential, and inexcitability.[62,63] It is still an open question how SK channel inhibition benchmark against other antiarrhythmic principles with regard to efficacy. In the dog model used in Dr Nattel's group to profile SK channel inhibition, efficacy was addressed as the ability to convert tachypaced-induced AF. The efficacy of SK channel inhibition was 100% in this model, but other compounds tested in the same model, including vernakalant, have had similar efficacy. Relative efficacy of SK channel inhibition will therefore have to await models of more severe tachypacing than what is applied in the dogs from Dr Nattel's laboratoy.

The functional role of SK channels in human hearts was addressed by Skibsbye et al[12] who obtained right atrial appendages from 65 patients in SR and 22 patients with chronic (>6 months) AF undergoing cardiac valve replacement and/or coronary artery bypass surgery. From 15 patients undergoing aortic valve replacement, biopsies from the interventricular septum were obtained. In concordance with other studies,[64,65] transcripts for SK2 and SK3 channels were found to be downregulated in long-standing (>6 months) AF. However, I_{SK} has in another study been shown to be upregulated in persistent AF[66] and in animal models of AF,[11,52] suggesting that after an initial upregulation, SK channels are instead downregulated during the extensive electrical and structural atrial remodeling during long-standing AF.

In the study by Skibsbye et al, sharp electrode recordings from right atrial appendages revealed that patients with AF >6 months had significantly shorter APD_{90} versus patients in SR. It was also demonstrated that NS8593 and another SK selective compound called ICAGEN prolonged atrial APD significantly (11%–19%) in tissue from SR patients. In tissue from chronic AF patients, there was however only very minor atrial effect of NS8593, whereas ICAGEN had lost the ability to affect the APD. No effects were seen on APD in ventricular septal tissue with NS8593 or ICAGEN. In recapitulation, studies performed in different species, including humans, point to the fact that SK channels constitute an integrated part of the phase 3 repolarization capacity in normal hearts. Furthermore, SK channels also seem to have prominent function in diseased heart with modest remodeling and here constitute a valid target for treating of AF. In situations of more severe remodeling, the relative impact of SK channels seems to be minor at least in humans.

Interestingly, I_{SK} was recently shown to be present in equine hearts, and the inhibition of I_{SK} in horse in vivo was shown to possess prominent antiarrhythmic properties.[67]

Role of Ventricular I_{SK}

Although the atrial expression of SK channels is apparently abundant, the ventricular expression of these channels is relatively sparse.[12,50,51] Many of the studies described in the previous section found atrial-selective effects of I_{SK} with no or diminutive effects in the ventricles when I_{SK} was altered by either pharmacological tools or by genetic upregulation or downregulation.[11,12,50,53,54,58] Nagy et al[68] published a study in which they reported no functional role for I_{SK} in ventricular cells from rats, dogs, and human under normal conditions. In both atrial and ventricular multicellular preparations and isolated cardiomyocytes from these species, no effects were observed by 100 nM apamin on action potentials.

Under normal physiological conditions, there seems to be general consensus that I_{SK} plays a very minor role in ventricular tissue. However, the case might be different under pathophysiological conditions, such as HF or acute myocardial infarction (AMI). From 2011 to 2013, Chen et al published 3 articles on cardiac SK channels in a rabbit model of tachycardia-induced HF.[69–71] In this model, they demonstrate that I_{SK} is upregulated in failing rabbit ventricles. In agreement with previous findings, these studies demonstrate that inhibition of I_{SK} has very diminutive effects in nonfailing rabbit ventricles. However, in failing rabbit ventricles, apamin prolongs APD at fast and slow heart rates but not at intermediate heart rates.[71] The APD prolongation was reported to be antiarrhythmic at fast hearts rates[70] but proarrhythmic at slow heart rates.[69]

Bonilla et al[72] also examined the electrophysiological consequences of ventricular I_{SK} inhibition in HF. Inhibition of Isk was tested in canine atrial and ventricular myocytes from control, 1 month of HF, and 4 months HF with AF as well as in human atrial and ventricular myocytes that were isolated

from explanted end-stage failing hearts obtained from transplant recipients. Quite surprisingly, the only effect on atrial cardiomyocytes that was found by I_{SK} inhibition with 100 nM apamin in any of the tested groups was a shortening of APD90 in the control animals rather than a prolongation. Although SK2 and SK3 were significantly increased in atrial cardiomyocytes from end-stage HF patients as compared with nonfailing individuals, no effects by apamin were seen in human atrial cardiomyocytes from either group in this study. More in agreement with the findings by other groups, no effects were found by the inhibition of I_{SK} in ventricular cardiomyocytes from control animals, whereas it caused prolongation of the APD in ventricular cardiomyocytes from HF animals and patients. The prolongation of APD by I_{SK} inhibition in ventricular myocytes from failing hearts was associated with proarrhythmia markers, such as increased beat-to-beat variability and an increase in the risk of EADs. Thus, SK channel inhibition in association with HF calls for some caution and thorough investigation. Interestingly, Chen et al have published evidence that amiodarone, the only antiarrhythmic drug recommended for AF treatment in cases of significant structural heart disease, acts as an I_{SK} blocker with an IC50 <3 μM, suggesting that some degree of I_{SK} is not contraindicated in AF with underlying HF.[73,74]

Gui et al[75] investigated the role of ventricular I_{SK} in an in vivo rat model of AMI. Compared with controls, the AMI rats had shortened ventricular refractory periods, increased duration, and episodes of spontaneous ventricular tachycardia and ventricular fibrillation (VF). The 2 SK channel blockers, UCL1684 and apamin, had protective effects in the AMI rats, increasing the ventricular refractory period and decreasing the inducibility of ventricular arrhythmia in a dose-dependent manner, whereas I_{SK} inhibition showed no ventricular effects in the sham-operated controls.

Thus, although it seems that while there is common agreement that ventricular I_{SK} plays a very minor role under normal physiological conditions, there are data pointing in different directions under pathophysiological conditions, such as HF and AMI, where I_{SK} inhibition can seemingly be both proarrhythmic[69,72] and antiarrhythmic.[70,75] The exact mechanistical explanation for the apparent functional atrial selectivity of SK channels is at present unknown. Although some studies point toward a difference in expression levels, other studies cannot reproduce these findings. Also, the exact nature of the Ca^{2+} regulation between atrial and ventricular SK channels might be different, but this notion is currently only speculation.

Status on Atrial-selective/Atrial-specific Drug Targets and Future Perspectives

Management of AF often involves attempts to restore and maintain SR, and strategies may use a combination of interventions, including cardioversion, catheter ablation, and antiarrhythmic drugs.[76] Cardioversion can be achieved by direct current conversion or by antiarrhythmic drugs. The former is highly effective but requires that the patient is anesthetized and may lead to thromboembolism, tachyarhhythmias and bradyarhhythmias, skin burns, and soreness. Antiarrhythmic drugs for cardioversion are most effective in recent onset AF (<7 days). There is no need for sedation, but because of the risk of QT prolongation and torsades de pointes, hypotension, and other adverse effects with current drugs, novel safer and more effective antiarrhythmic drugs are needed. Currently marketed drugs for pharmacological cardioversion include ibutilide, flecainide, dofetilide, propafenone, amiodarone, and vernakalant.[76]

As for pharmacological cardioversion, the antiarrhythmic drugs used for maintaining the patient in SR are hampered by poor efficacy or safety concerns. To minimize the risk of drug-induced ventricular proarrhythmia, a search for drugs that modulates atrial-specific/atrial-selective ion channels is ongoing. So far, focus has mainly been on ion channels that are predominantly expressed in atria (atrial-specific targets) as compared with ventricles. A wealth of preclinical data has established both $K_V1.5$ (I_{Kur}) and $K_{ir}3.1$/$K_{ir}3.4$ ($I_{K,ACh}$) as promising drug targets for the treatment of AF, including efficacy in sophistical large animal models of AF and APD prolongations in recordings from human atrial tissue.[77] Lately, the SK channel was added to this list of potentially atrial-selective targets. Atrial selectivity of Na^+ channel blockers has also been suggested as a strategy to avoid ventricular proarrhythmic effects. This is possible because $Na_V1.5$ channels are preferentially blocked in their active/inactive state, which is a more common conformation during AF as a consequence of the rapid activation rates and more depolarized resting membrane potential of the atria as compared with ventricles.[78,79] Atrial-selective $Na_V1.5$ channel blockers include ranolazine and vernakalant.[78,80] Finally, modulators of gap junctions that enhance electrical coupling have been found to be antiarrhythmic in ischemia, but their role in AF is still debated.[81] Two-pore K^+ channels have also been suggested as novel targets in AF, but this still needs further validation.[82]

Results from clinical trials are also emerging, addressing the safety and efficacy of targeting ion channels with atrial-selective mechanisms. Ranolazine is an antianginal drug, which also possesses antiarrhythmic properties, most likely by inhibition of the late $Na_V1.5$ current and by atrial-selective inhibition of the channel.[78] The clinical usefulness of ranolazine in AF still needs confirmation in a large randomized clinical study, but a number of smaller randomized or retrospective cohort studies would suggest a modest beneficial effect.[83] Recently, Gilead Sciences announced results from a phase 2 study demonstrating a reduction of AF burden by combining ranolazine and low-dose dronedarone.[84] Another chapter in this review issue describes combination therapy as an approach to AF treatment in more detail.

AstraZeneca recently reported on a small first-time-in-man clinical investigation of their selective $I_{K,ACh}$ blocker AZD2927. In atrial flutter patients undergoing an invasive electrophysiological investigation, the $I_{K,ACh}$ blocker was found to be safe and well tolerated. Although AZD2927 in tachypaced canine AF models was found to be antiarrhythmic and to increase aERP, no effect on aERP was observed in the patients as compared with placebo. Based on this finding, the authors concluded that an important role of $I_{K,ACh}$ in human atrial electrophysiology, and as a potential target for effective management of AF, may be questioned.[85] Likewise, data

from a small (n = 20), randomized, placebo-controlled, double-blind study on AF burden in patients with paroxysmal AF demonstrated that the specific $I_{K,ACh}$ blocker BMS914392 was well tolerated but did not result in the reduction of AF burden or AF frequency as compared with placebo.[86]

In 2012, the results of the first-time-in-man investigation of a selective $K_v1.5$ inhibitor, MK-0448, were published. Preclinical data demonstrated that MK-0448 was a potent I_{Kur} blocker with limited off-target effects. MK-0448 prolonged the aERP and only produced minimal lengthening of ventricular effective refractory period (vERP) in dogs and in conscious HF dogs with sustained AF infusion of MK-0448-terminated AF. In clinical trials on healthy males, MK-0448 was well tolerated with mild adverse effects. In contrast to the canine findings, ascending doses of MK-0448 did not increase atrial or ventricular refractoriness, even at plasma concentrations many folds higher than the in vitro IC_{50} value. The authors concluded that I_{Kur} block would likely have limited value in the prevention of AF.[87] One explanation of the lack of effect in healthy humans was addressed by performing in vitro intracellular recordings on atrial trabecula from patients in SR, intermittent AF, and permanent AF, respectively. Significant prolongations of APD and aERP after application of MK-0448 were only observed in tissue from patients in permanent AF.[88] Concerns about the slow pacing frequency used for the clinical evaluation of MK-0448 effects on aERP have also been raised, and whether the inhibition of I_{Kur} could cardiovert AF or reduce AF burden remains to be investigated. Whether the disappointing clinical findings are a result of study design, including which patients to enroll, potency of the drug, dosing regimen, endpoints, and power of the study or if it reflects that the drug targets are not as important in humans as expected from preclinical efficacy findings is still up for debate.

Phase 2 clinical trials on the efficacy of the $K_V1.5$ inhibitor XEN-D0103 in patients with paroxysmal AF have been commenced,[89] and the outcome is much anticipated. At this point, no clinical trials on the efficacy or safety of SK channel inhibitors have been performed, wherefore it is unknown if the encouraging preclinical data will translate to clinical efficacy in AF patients.

For now, the jury is still out on whether successful rhythm control can be achieved by pharmacological inhibition of atrial-selective ion channel targets. Future clinical trials will help reaching a verdict.

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