Chapter

SK Channels and Heart Disease

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Abstract

Extensive evidence indicates that small-conductance Ca^{2+}-activated K^+ channels (SK channels) help regulate cardiac rhythm and myocardial function in physiological and pathophysiological conditions. This chapter will begin by discussing the basic physiology of SK channel expression, localization, and activation under normal conditions, before proceeding to address the impact of SK channel dysfunction on a variety of cardiac pathologies including atrial fibrillation (AF), ventricular arrhythmias (VA), cardiac hypertrophy/heart failure (HF) and myocardial ischemia/reperfusion (IR) injury. The critical role of aberrant SK channel regulation will also be discussed to establish unifying mechanisms of SK channel pathology across these different conditions. Several animal model and human tissue experiments suggest that pharmacologic modulation of SK channel function may be beneficial in controlling AF, VA, cardiomyopathy and myocardial IR injury. Therefore, targeting SK channels may represent a promising new therapeutic avenue for treating a variety of cardiovascular disease states.

Keywords: SK channel, small-conductance Ca^{2+}-activated K^+ channels, cardiac rhythm, cardiac function, atrial fibrillation, ventricular arrhythmias, cardiac hypertrophy, heart failure, ischemia reperfusion injury

1. Introduction

The coordinated activity of cell membrane ion channels forms the basis of the cardiomyocyte action potential sequence, driving myocardial contractility and resulting in cardiac output. Each stage of the myocardial action potential relies on opening and closing of specific groups of ion channels to propagate excitatory stimuli through the heart [1–4]. Most myocardial action potentials begin with transmission of spontaneous impulses generated by pacemaker cells (e.g., the sinoatrial node [SAN] and atrioventricular node [AVN]) to atrial and ventricular myocytes that are at resting membrane potential (phase 4, around −85 to −90 mV). Sinus node impulses reach atrial myocytes via intercellular gap junctions, leading to depolarization to threshold. Myocytes then transition to phase 0, a fast upstroke driven by opening of voltage-gated sodium channels that facilitate a strong inward sodium current that rapidly depolarizes the cardiomyocyte to a membrane potential of over 20 mV, at which point sodium channels close and transient outward potassium channels open, producing a brief repolarizing current (phase 1).

However, the strongly depolarized cardiomyocyte membrane also triggers opening of L-type voltage gated calcium channels (LTCC) that facilitate influx of calcium.

Calcium influx balances potassium efflux through transient outward and delayed-rectifier potassium channels (which also open during this period), leading to the phase 2 plateau of the cardiac action potential. It is during phase 2 that calcium entering cardiomyocytes triggers calcium-induced calcium release from sarcoplasmic reticulum (SR) stores via calcium-induced calcium release, mediated by calcium interaction with ryanodine receptor (RyR) calcium channels located on the SR [2]. Increasing levels of intracellular calcium relieves troponin-tropomyosin inhibition of cardiomyocyte actin-myosin cross bridge formation, leading to cross-bridge cycling and myocardial contraction. Finally, cardiomyocytes transition to phase 3 repolarization, where calcium channels close and delayed rectifier potassium channels remain open, allowing membrane potential to return to its resting state (phase 4) and terminating the action potential.

The repolarization phase of the myocardial action potential has received extensive attention in biomedical research because aberrations in this phase are intimately related to disruptions in myocardial excitability and overall control of synchronous, regulated myocardial contraction. Until recently, phase 3 repolarization was thought to be almost entirely driven by delayed rectifier potassium channels that opened alongside calcium channels during phase 2 and remained open following calcium channel closure, subsequently driving membrane potential towards the potassium equilibrium potential.

However, a growing body of evidence suggests that another type of potassium channel, the small-conductance Ca^{2+}-activated K^+ channels (SK channel), might also have an important role in myocardial repolarization [5–8]. SK channels are cell membrane potassium channels that are exquisitely sensitive to calcium, opening in response to elevated intracellular calcium and facilitating an outward potassium current. Several studies have shown that SK channels are active during the late repolarization phase of the cardiac action potential, likely assisting delayed rectifier potassium channels by amplifying the outward potassium current [5, 6]. On their own, SK channels may represent a form of feedback control of excess myocardial excitability, given their close responsiveness to calcium—which governs cardiomyocyte contraction.

Conversely, SK channel dysfunction may contribute to cardiovascular pathology in a manner reminiscent of how dysfunction of other major myocardial ion channels (especially the delayed rectifier potassium channel) is implicated in cardiovascular disease. Indeed, the past two decades have given rise to an abundance of research attempting to characterize the role of SK channels in numerous cardiovascular disease states and explore whether modulation of SK channels may be a potential therapeutic tool that deserves clinical attention. Hence the focus of this chapter, which will discuss the history and basic physiology of myocardial SK channels before delving into the current literature concerning SK channel dysfunction in four major areas: atrial fibrillation (AF), ventricular tachyarrhythmias (VA), heart failure (HF), and ischemia-reperfusion (IR) injury.

2. Identification of SK channels in the heart

Small-conductance Ca^{2+}-activated K^+ channels (SK channels), encoded by KCNN genes, are a family of K^+ channels that have a small single channel conductance (10–20 pS with symmetrical solutions), and are gated by intracellular Ca^{2+} concentrations [9]. SK channels were identified using apamin, a bee venom toxin that selectively

blocks SK channels [9]. SK channels were first identified in rat and human brain tissue [10]. Since their discovery, SK channels have been identified in a variety of tissues including the nervous system, blood, epithelial cells, skeletal muscle and endothelial (vessel) cells [11, 12]. SK channels are classified into three isoforms: SK1, SK2 and SK3, based on their gene origins and different sensitivities to apamin. The SK1 channel is encoded by the KCNN1 gene, located on chromosome 19, and is moderately sensitive to apamin. The SK2 channel is encoded by the KCNN2 gene located on chromosome 5 and has the strongest affinity for apamin. The SK3 channel is encoded by the KCNN3 gene located on chromosome 1 and is moderately sensitive to apamin [8, 13]. The intermediate-conductance Ca^{2+}-activated K^+ channel (IK or SK4) is similar to SK channels and is encoded by the KCNN4 gene. SK4 has a slightly larger single conductance (12–42 pS) and a higher affinity for intracellular Ca^{2+} than other SK channels [8, 13].

SK channels were first identified in the heart in 2003 [14, 15], and their distribution and functions in heart tissue have since been extensively studied [16–18]. SK channels have been found in both atrial and ventricular tissues in animals and humans [7, 12, 19–33]. In mouse atrial and ventricular myocytes, quantification of SK1 and SK3 transcripts showed a higher level of SK1 expression in atria versus ventricles, while SK3 is expressed at a simar level in atria and ventricles [12]. Apamin-sensitive Ca^{2+}-activated K^+ currents (SK currents) have been detected in the pulmonary veins (PV), Bachmann's bundle (BB), sinoatrial node (SAN) myocytes, and mouse atrioventricular nodes (AVN) [34–36]. SK channels have also been found expressed intracellularly in the ventricular mitochondrial membranes of guinea pigs, rats and humans [37, 38]. Indeed, transcripts of both SK2 and SK3 isoforms are found in the inner mitochondrial membrane (IMM), but not SK1 [38]. Notably, although there are fewer SK channels in the ventricles, under certain pathological conditions such as HF and chronic myocardial infarction (MI), SK currents in ventricles are upregulated [39, 40]. The results are summarized in **Table 1**.

Species	Tissue/ cardiomyocyte	mRNA	Protein	Ion channel recording	SK channels	Reference
Mouse	Atrial and ventricular myocytes	Higher level of expression of SK1 in atria versus ventricles; SK3 is expressed at a simar level in both	Protein expression of SK1 and low level of SK3	SK current is more prominent in atria than in ventricles	SK1, SK3	[12]
	Anatomical atrioventricular nodes (AVN)	N/A	SK2 channel protein detected in AVN cells	SK current recorded in AVN cells	SK2	[36]
	SAN cells	Presence of the transcripts of SK1, SK2 and SK3	All three isoforms are present and are preferentially distributed along the Z line, especially SK3	SK currents recorded	SK1, SK2, SK3	[41]

Species	Tissue/ cardiomyocyte	mRNA	Protein	Ion channel recording	SK channels	Reference
Rabbit	Pulmonary vein (PV) and Bachmann's bundle (BB)	SK2 and SK3 mRNA detected in both PV and BB	Presence of SK2 and SK3 protein in both PV and BB	SK current recorded in both PV and BB	SK2, SK3	[6]
	Ventricles	N/A	N/A	SK currents are not significant in normal ventricles but are upregulated in failing ventricles	N/A	[39]
	Pulmonary vein (PV) and sinoatrial node (SAN) myocyte	N/A	N/A	SAN exhibits greater SK currents than PV	N/A	[35]
	Ventricles	N/A	SK2 are more abundantly present in the Purkinje cells (PCs) than in the ventricular myocytes	Apamin prolonged APD in PCs. SK current density was larger in PCs than in ventricular myocytes	SK2	[42]
Guinea pig	Ventricular mitochondria	N/A	SK2 and SK3 channel proteins were present in IMM	SK current recorded	SK2, SK3	[16]
Human	Right and left atrial appendages	mRNAs of SK1, SK2 and SK3 were detected	SK1, SK2 and SK3 were expressed in human atrial myocytes	SK current detected	SK1, SK2, SK3	[27]
	Atrial and ventricular tissue	SK1 had a higher level of expression in atria compared to ventricle, while the expression level of SK2 and SK3 were not different in atria vs. ventricle	N/A	N/A	SK1, SK2, SK3	[25]
	Atrial tissues	N/A	SK3 polypeptide level was unchanged pre- and post-cardioplegic arrest	N/A	SK3	[19]
	Right atrial tissues	N/A	Insignificant decrease in SK3	Diabetes significantly	SK3	[20]

Species	Tissue/ cardiomyocyte	mRNA	Protein	Ion channel recording	SK channels	Reference
			protein level in diabetic myocardium vs. nondiabetics	reduced SK currents		
	Right atrial tissues	N/A	Neither cardioplegic arrest nor diabetes resulted in a significant change of SK3 protein level	N/A	SK3	[21]
	Human atrial tissue, coronary arterioles and coronary artery endothelial cells	No significant difference in SK3 mRNA levels in diabetic atrial tissues and endothelial cells vs. nondiabetics	No significant difference in SK3 protein levels in diabetic atrial tissues and endothelial cells vs. nondiabetics	N/A	SK3	[33]
Multiple species	Mouse atrial and ventricular and human atrial myocytes	Presence of SK2 mRNA in human and mouse cardiac myocytes	Presence of SK2 channel	SK current was more prominent in atria versus ventricles	SK2	[14]
	Guinea pig, rat and human ventricular mitochondria	mRNAs of SK2 and SK3, but not SK1, are present in guinea pig ventricular myocytes. SK3 mRNAs are present in human ventricular tissues.	SK3 is expressed in human and guinea pig ventricular IMM	N/A	SK3	[38]

Table 1.
Functional expression of SK channels in the heart.

3. Physiological functions of SK channels in the heart

In neuronal cells, SK channels contribute to the slow afterhyperpolarization following an action potential [43]. The physiologic functions of SK channels in the heart were not clear until Xu et al. first reported their role in the repolarization of cardiac myocytes. Apamin-treated cardiac cells show significantly longer action potential durations (APD) due to slower repolarization compared to control groups, indicating SK channel involvement in cardiac repolarization. These effects are more prominent in atrial versus ventricular cells, likely due to the higher level of expression of SK

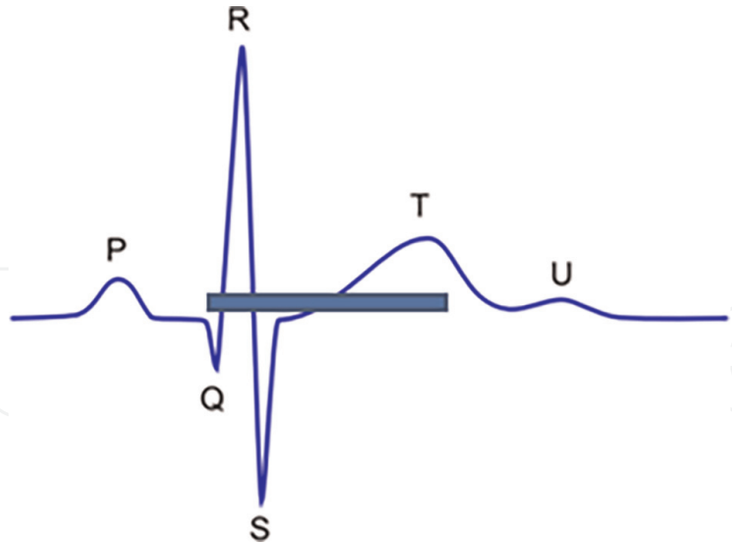

Figure 1.
Cardiac action potential. P = atrial depolarization; QRS = ventricular depolarization; T = ventricular repolarization. The significance of the U wave is largely unknown, although may represent Purkinje fiber repolarization. The QT interval indicated by the dark bar between "Q" and "T". SK channels have been shown to influence the duration of the QT interval of cardiomyocyte action potentials. Diagram courtesy of ECGpedia.org (https://en.ecgpedia.org/wiki/Action_potential) [45].

channels in atria [14]. In another study, the AVN in SK2-null mutant mice show decreased firing frequency and longer APD compared with controls, while mice overexpressing SK2 channels show shorter APD [36]. Apamin application results in decreased action potential firing frequency akin to that seen in SK2-null mutants [36].

Consistently, overexpression of SK3 channels also results in significantly shorter APD, suggesting a similar role for different isoforms of SK channels in the repolarization process in cardiac cells [44]. The prolongation of APD resulting from apamin has also been recorded in human right and left atrial appendages, rabbit PV and SAN, and mouse SAN cells [27, 35, 41]. These studies consistently show that SK channels contribute to repolarization and shorten the action potentials in normal hearts, especially in the atria where they are more densely expressed than in the ventricles. In SAN, SK blockade also leads to significant depolarization of the maximal diastolic potential (MDP) and a decrease in the diastolic depolarization slope [41]. Notably, in PVs with intact endothelium, SK channels contribute to hyperpolarization and vessel dilation [35]. **Figure 1** shows the cardiac action potential including the QT interval affected by SK channels.

Meanwhile, with respect to mitochondria, DCBE, an SK channel opener, reduces mitochondrial injury when given before cardiac ischemia, suggesting that SK channel opening may protect the heart and mitochondria against ischemia-reperfusion (IR) injury. SK channels have also been found to reduce oxidative stress by reducing mitochondrial Ca^{2+} overload [38].

4. Signaling pathway

The Ca^{2+} that activates SK channels comes from various intracellular and extracellular sources. In hippocampal neurons, SK channels are coupled to the LTCC using microdomains of submembrane calcium, and Ca^{2+} influx through LTCC activates SK channels [46]. Similar co-localization of LTCC and SK channels can be found in

cardiac myocytes, where SK2 channels couple with LTCCs through α-actinin2. This suggests that, in cardiac myocytes, SK2 channels are activated by local subsarcolemmal Ca^{2+} that enters the cell through LTCCs [47]. Besides LTCCs, the SR also plays a role in providing the Ca^{2+} needed for activating SK channels. In mouse cardiac myocytes, the type 2 ryanodine receptor (RyR2) mediates intracellular Ca^{2+} release from the SR, which activates SK channels [48]. It is possible that in cardiac myocytes, SK channels could be activated by either Ca^{2+} influx through voltage-gated Ca^{2+} channels or through release of intracellular Ca^{2+} from SR stores.

SK channels are gated by intracellular Ca^{2+} through interactions between the channel α-subunits and calmodulin (CaM) [49]. The intracellular C-terminal domain of the SK channels immediately adjacent to the sixth transmembrane segment (S6) consists of four α-helices, named A, B, C and D, that are critical to the channel gating. CaM binds to channel regions A-D constitutively, whereas CaM binding to regions B-C and B-D is Ca^{2+} dependent. This indicates that regions B-C and B-D are involved in the Ca^{2+} gating mechanism [49]. Ca^{2+} binds to the EF hands in the N-lobe of CaM, which leads to conformational changes and opening of SK channels [50].

Besides Ca^{2+}-activated channel gating, CaM is also critical in the regulation of cell surface expression of the SK channels, independent of the binding of Ca^{2+} [51]. Several cytoskeletal proteins, including α-actinin2, filamin A, and MLC2, are important in SK2 channel trafficking [52–54]. Notably, cell membrane localization of SK2 channels is Ca^{2+}-dependent when the channels are co-expressed with α-actinin2. An increase in intracellular Ca^{2+} such as in AF is predicted to increase the expression of SK2 channels and lead to shortened APD and maintenance of the arrhythmias [54].

Casein kinase 2 (CK2) and protein phosphatase 2A (PP2A) are critical components of the SK channels that regulate the Ca^{2+} sensitivity of the channels by phosphorylating or dephosphorylating CaM. CK2 decreases the Ca^{2+} sensitivity of closed SK channels, while PP2A increases the Ca^{2+} sensitivity of open SK channels [9]. Increased expression of PP2A and decreased co-localization of CK2 with SK2 may be the underlying mechanism of increased sensitivity of apamin-sensitive K^+ current to intracellular Ca^{2+} in HF, as shown in a volume-overload HF rat model [55].

Various mechanisms of SK channel regulation may have clinical significance with respect to SK channel pathology seen in certain disease states. For example, upregulation of SK channels in ventricular myocytes in cardiac hypertrophy has been shown to result from phosphorylation by both calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase A (PKA) [28, 56]. In addition, microRNA (miRNA) also plays a role in cardiac SK channels regulation. MicroRNA 499 (miR-499) is upregulated in atrial tissue from patients with permanent AF, resulting in increased binding to the KCNN3 gene and downregulation of SK2 channel expression [26].

5. SK channels in heart disease

5.1 Atrial fibrillation

5.1.1 Overview

Atrial fibrillation (AF), a condition characterized by rapid and disorganized atrial activation, is the most common cardiac arrhythmia with a prevalence of 1–2% among the general population [57]. A variety of risk factors have been linked to the

development of AF, such as age, male sex, obesity, hypertension, heart failure, structural heart disease (valvulopathy, CHF, MI), diabetes, hyperthyroidism, and family history [58]. Of these factors, age and sex carry the highest risk: males have a 1.5–2× greater chance of developing AF than females, and individuals between ages 40–55 carry a lifetime risk of 22–26% [59].

AF is classified into several categories based on the duration of the AF episode(s). These include paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF [60]. The term "lone AF" remains a diagnosis of exclusion and has been used to describe AF in younger patients without a prior history of structural heart disease or cardiovascular risk factors [61]. The specific molecular and electrophysiological mechanisms that underly AF are highly complex and remain poorly understood. Nonetheless, most current conceptual frameworks of the pathogenesis of AF involve a combination of structural remodeling, electrical remodeling, and autonomic remodeling that generate atrial reentry circuits, rotors (localized electrical spiral waves), and ectopic impulse generation [57].

Regarding electrical remodeling, a variety of altered ionic currents can be seen in AF, including increased activity of LTCC, increased activity of inward rectifier potassium channels (KiR), and decreased function of gap junctions [62–65]. Excessive LTCC activity may trigger excessive cardiomyocyte SR Ca^{2+} release via RyR activation, leading to hyperexcitability. Excessive KiR activity may alter atrial myocyte resting potential and phase 3 activation, resulting in reduced atrial refractoriness. Gap junction defects may slow atrial conduction velocity, which when combined with atrial myocyte hyperexcitability and decreased refractoriness favors reentry, ectopic foci, and initiation of AF.

Structural remodeling in AF largely involves fibrosis and atrial dilation. Atrial fibrosis may be due to several factors such as aging, myocardial infarction, volume overload, or aberrant renin-angiotensin-aldosterone system (RAAS) activity [66–70]. Proliferation of fibroblasts and extracellular matrix in fibrotic atria may create barriers to electrical conduction that interfere with cardiomyocyte electrical coupling, creating conduction abnormalities and variable action potential durations that predispose to ectopic activity and reentrant circuits [71, 72]. In addition, larger atria have increased odds of developing reentrant circuits [73]. Finally, autonomic remodeling in AF involves increased sympathetic or parasympathetic tone in the atria that influences atrial tachypacing [74–77].

5.1.2 SK channels and AF heritability

The heritability of AF has been widely studied over the past two decades, and lone AF appears to have a greater heritable component than structural AF [78]. Recent genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) that are associated with increased risk of AF. Some examples include rs2200733 on chromosome 4q25, rs2106261 on chromosome 16q22, rs10824026 on chromosome 10q22, and rs7394190 on chromosome 10q22 [61, 78, 79]. Overall, GWAS studies of AF atrial tissue have found mutations in genes coding for ion channels, gap junction connexin proteins, nuclear membrane components, calcium homeostasis, and cardio-genesis [80].

Potassium channel gene mutations are of special interest in AF because of the important role of potassium channels in maintaining the resting membrane potential and facilitating repolarization after generation of the action potential. For example, gain of function mutations have been found in KCNQ1 (the alpha subunit of the

inward rectifier cardiac potassium channel Kv7.1), KCNH2 (voltage gated potassium channel Kv11.1), KCND3 (alpha subunit of the voltage-gated potassium channel Kv4.3), KCNJ2 (inward rectifying potassium channel Kir2.1), and KCNA5 (voltage-gated potassium channel Kv1.5) [81–85]. All of these changes lead to increased inward potassium currents in atrial myocytes, which may shorten APD, QT intervals, and the effective refractory periods. In 2010, Ellinor et al. in their GWAS discovered a novel AF susceptibility locus on chromosome 1q21 among Caucasian individuals. The most significant SNP at this locus, rs13376333, can be found in the intron between the first and second exon of KCNN3, which encodes the SK3 channel [61]. Rs13376333 is strongly associated with lone AF, bearing an odds ratio of 1.56 ($P = 6.3 \times 10^{-12}$). The association of rs13376333 with more typical forms of AF is also significant, albeit weaker (OR = 1.13, P = 0.006) [61].

Similar results have been reported by several other labs using genomic data from identical or different ethnic groups. Indeed, Chang et al. report significant associations between rs13376333 and risk of lone (OR 3.02) and structural (OR 2.18) AF among a Taiwanese cohort, with even stronger odds ratios than those reported by Ellinor et al. [86]. Among a Han Chinese cohort, Luo et al. found that the frequency of rs13376333 at KCNN3 was significantly higher in lone AF than in controls, although there were no significant differences in rs13376333 frequency between total AF patients and controls [87]. Curiously, an earlier study by Li et al. failed to produce a significant association between rs13376333 and AF among Han Chinese AF individuals [88]. It is possible that different ethnic demographic groups may exhibit different risk propensities with respect to SNPs, which would imply contribution of some form of gene-environment interplay that either diminishes or enhances genetic effects. Given the complexity of AF as a disease process, this is a very likely scenario and requires further investigations involving larger sample sizes and different demographic groups. Besides rs13376333, another SNP at KCNN3, rs1131820, has also been associated with increased risk of lone AF in individuals of Danish ethnicity, with an OR of 2.85 [89].

In addition to KCNN3, a weak association of AF with KCNN2 has also been discovered in a Han Chinese cohort, at the SNP rs13184658 [90]. How variations in KCNN alleles specifically affect the risk of AF remains unclear. A recent study revealed that rs13376333 is associated with increased mRNA expression of KCNN3 in human atrial tissue [91]. In addition, given that most other potassium channel mutations observed in AF are gain of function mutations, perhaps the SK channel SNPs follow the same trend. Further study of the KCNN3 locus could help reveal pathways underlying the association between KCNN3 and AF, with the potential of developing novel treatments of AF that target KCNN3.

5.1.3 SK expression and electrophysiology in AF

At the mRNA and protein levels, there is mixed evidence about whether SK channels are over or under-expressed in atrial remodeling in human and animal models of AF. Ozgen et al. first reported that SK channels are associated with initiation of atrial remodeling. Using a burst-paced rabbit atrium, they showed that SK2 mRNA and protein levels were upregulated in the region of the left atrium where the pulmonary veins empty; this suggests that SK channels have a role in burst-pacing induced APD shortening [34]. Likewise, Qi et al. reported upregulation of SK1 and SK2 protein induced by atrial tachypacing in dog PVs and left atrial cells; SK2 mRNA expression was also increased, although no significant changes in SK1 mRNA were observed, suggesting that overexpression of SK1 may be the result of posttranslational

modifications or altered membrane trafficking of SK1 channels [23]. In dopamine tautomerase-deficient mice induced to exhibit AF by apamin administration, Tsai et al. observed increased protein and mRNA levels of SK1 and SK3 in mouse right atrial tissue [92].

These results seem to contradict other studies that reported decreased expression of SK channels in human and animal AF. Darkow et al. found decreased expression of KCNN2 (SK2) mRNA in atrial tissue of patients with AF when compared with healthy controls [25]. Similarly, transcripts of KCNN1–3 were downregulated in paroxysmal AF and chronic AF patients at a similar level [93]. Rahm et al. also examined KCNN mRNA expression in a pig model of atrial tachypacing-induced AF with reduced left ventricular function and found decreased expression of KCNN2 and KCNN3 with normal levels of KCNN1 [93]. Furthermore, Fan et al. report decreased mRNA and protein levels of SK1, SK2, and SK3 in atrial appendage tissue from humans with chronic AF [32]. Another study of atrial tissue from chronic AF patients by Yu et al. replicated these results with respect to SK1 and SK2 mRNA and protein expression, although no differences were observed in SK3 expression at either level [27]. Finally, Skisbye et al. observed reduced SK2 and SK3 expression in chronic AF human atrial tissue, with no changes in SK1 expression [7]. The research findings of the up/down regulation of SK channels in AF were summarized in **Table 2**.

Ozgen et al. first discovered that burst pacing induced increased SK2 channel trafficking to the cell membrane and increased SK currents in rabbit pulmonary veins [34]. In their dog model, Qi et al. found that atrial tachypacing enhanced SK currents and single-channel open probabilities [23]. In contrast, Yu et al. reported decreased SK currents in right and left atrial appendage tissue from patients with chronic AF, alongside decreased SK1 and SK2 mRNA and protein levels (discussed earlier) [27]. Another possible mechanism of increased SK currents in AF is enhanced activity of

Species	Model	Up/down regulation of SK channels	Reference
Rabbit	Burst-paced rabbit atrium	SK2 mRNA and protein levels were upregulated in the left atrium	[34]
Dog	Atrial tachypacing in dog pulmonary veins and left atrial cells	Upregulation of SK1 and SK2 protein; upregulated SK2 mRNA expression	[23]
Mouse	Induced AF in dopamine tautomerase-deficient mice	Increased protein and mRNA levels of SK1 and SK3 in right atrial tissue	[92]
Pig	Atrial tachypacing-induced AF with reduced left ventricular function	Decreased expression of KCNN2 and KCNN3 with normal levels of KCNN1	[93]
Human	Patients with AF	Decreased expression of SK2 mRNA in atrial tissue	[25]
	Paroxysmal AF and chronic AF patients	Transcripts of KCNN1–3 were downregulated	[93]
	Atrial appendage tissue from chronic AF patients	Decreased mRNA and protein levels of SK1, SK2, and SK3	[32]
	Atrial tissue from chronic AF patients	Decreased mRNA and protein levels of SK1, SK2; no difference in SK3 expression levels	[27]
	Atrial tissue from chronic AF patients	Reduced SK2 and SK3 expression; no changes in SK1 expression	[7]

Table 2.
Up/down regulation of SK channels in atrial fibrillation (AF).

CaMKII, which is required for SK channel calcium-dependent activation. CaMKII exhibited significantly increased expression alongside, increased intracellular calcium levels in human AF tissue studied by Fan et al. [32].

Approached from a different angle, a mouse model of SK3 overexpression also showed considerable shortening of APD and increased SK channel currents in atrial myocytes [44]. Likewise, mice engineered to overexpress SK2 channels displayed significant atrioventricular nodal dysfunction, manifesting as increased firing frequency, and shortening of spontaneous action potential, while SK2 ablation eliminated these effects [36]. Furthermore, SK2 knockout mouse models studied by Li et al. exhibited the opposite effects: significant prolongation of atrial myocyte APD among homozygous and heterozygous mutants, with homozygous mutants having an increased susceptibility to AF [94].

Inconsistencies regarding observed SK channel expression and activity in AF across different studies might be due to a variety of factors including the specific method of AF induction, differences in atrial tissue characteristics among different species of animal models, patient population demographic differences, and different stages or durations of AF. It is also possible that SK channels are initially upregulated in AF before being downregulated due to atrial remodeling. There are several reported mechanisms by which SK channels are regulated in AF, including histone deacetylase related epigenetic mechanisms [95], miRNA [26], and CaMKII [32].

5.1.4 Pharmacologic modulation of SK channels in AF

Pharmacologic studies of SK channel modulation provide additional insights into the role of SK channels in AF, although the results are complicated. First, the IK antagonist HMR1556 preserved hemodynamic stability in pigs induced by atrial burst pacing to express persistent AF [96]. At time of sacrifice, HMR1556 treated pigs also exhibited significantly higher left ventricular ejection fraction than untreated pigs, along with significantly longer right atrial APD [96]. Next, application of the SK channel inhibitor apamin increased spontaneous action potential generation in isolated rabbit PVs while decreasing spontaneous activity and prolonging APD in sinoatrial nodal myocytes [35]. However, in isolated canine left atrial tissue, apamin treatment significantly increased APD heterogeneity and proved to be pro-arrythmogenic [24].

The SK channel inhibitor NS8593 increased APD and effective refractory in right atrial appendage tissue of patients with AF [7]. Identical results were found by Qi et al. in a dog model of AF [23]. Haugaard et al. and Burashnikov et al. examined the effects of NS8593, along with another SK channel inhibitor (UCL1684), in human and equine atrial myocytes, and verified the ability of both inhibitors to reduce AF inducibility or terminate induced AF [97, 98]. However, conflicting results were found by Fenner et al. in their horse model of tachypacing-induced persistent AF [99]. There, delayed right atrial conduction after NS8593 treatment actually increased AF complexity through increased anisotropy and electrical dissociation [99]. Meanwhile, the left atrium exhibited no change at all in AF complexity, and neither left nor right atrium ultimately resulted in cardioversion [99].

Moving on, treatment with SK2 inhibitor AP30663 in atrially tachypaced live AF pigs resulted in conversion to sinus rhythm, increased right atrial effective refractory periods, and prevented reinduction of AF [100]. Additional studies using whole-cell and inside-out patch clamp recordings of guinea-pig heart tissue confirmed a right-shift of the calcium-activation curve of SK2 channels in the presence of AP30663, with

concentration-dependent prolongation of atrial refractoriness and minor effects of QT prolongation [91].

Finally, Saljic et al. tested the use of an antisense oligonucleotide GapmeR in rats and showed that GapmeR downregulates SK3 protein expression in the heart and provides protection against AF [101]. Though targeting the expression level of SK channel seems promising, Darkow et al., showed that that SK3 was upregulated in ventricular tissue in heart failure patients, suggesting that SK channels are not likely to be an atria-selective target as previously expected [25].

In a recent study, Gatta et al. conducted a detailed examination of the effects of SK channel inhibitor AP14145 on goat hearts induced to AF after 30 days of burst-pacing stimulation delivered by pericardial electrodes implanted above the left atria [102]. The authors found that AP14145 produced dose-dependent prolongation of AF cycle length and increased the effective refractory period of atrial impulses [102]. Interestingly, atrial conduction velocity in AF following AP14145 treatment remained unchanged until the final seconds before AF termination, where sudden organization of fibrillatory conduction occurred prior to AF cardioversion [102].

Most animal models of AF discussed up to this point involve AF induction via simple electrode-delivered burst-pacing to atrial tissue. However, other approaches also exist. For example, Yan et al. studied an atrial stretch-induced rabbit AF model [103]. As discussed earlier, atrial enlargement increases the risk of AF by shortening atrial effective refractory periods. Hence the authors of this study placed an inflatable balloon into their rabbit heart left atria to mechanically dilate atria to various sizes. Sustained AF was induced by brief delivery of burst pacing to dilated atria that produced rapid irregular atrial rhythms. For the experimental group, the SK inhibitor ICA was applied to rabbit hearts before atrial stretch and burst pacing. Final analyses showed that ICA pretreatment significantly attenuated stretch-induced atrial effective refractory period and reduced overall AF inducibility and duration when compared with untreated hearts [103]. Another alternative approach was taken by Celotto et al., who focused on the role of autonomic dysfunction in AF pathogenesis [104]. Using human atrial cell and tissue models, the authors induced AF via high dose acetylcholine administration, which shortened atrial APD [104]. SK channel blockade was able to partially revert APD shortening due to acetylcholine, while a combination of SK blockade and the adrenergic agonist isoproterenol were able to completely reverse APD shortening back to pre-AF baseline [104].

How SK channel inhibitors compare to current mainstay antiarrhythmic medications is another important question with significant clinical implications. Two studies by Kirchhoff et al. provides some insights into this issue [105, 106].

In one study, Kirchhoff et al. explored the effect of combining SK channel inhibition via ICA and voltage-gated sodium channel inhibition on AF in atrial-burst pacing induced AF guinea pigs [105]. Ultimately, AF combining ICA with normally subefficacious concentrations of flecainide or ranolazine (sodium channel blockers) reduced AF duration [105].

Next, Kirchhoff et al. examined the effect of the SK inhibitor ICA on AF in an atrial burst-pacing guinea pig model when used alongside amiodarone or dofetilide, two major class III antiarrhythmics. The authors found that combining ICA with either dofetilite or amiodarone reduced AF duration at normally sub-optimal concentrations of all three drugs if used individually [106]. In addition, ICA combined with a standard therapeutic dose of dofetilide prevented QT prolongation that is often seen with dofetilide monotherapy [106]. Overall, both studies suggest that combining SK channel inhibitors with traditional antiarrhythmics may provide a useful synergistic

benefit that allows for reducing doses of traditional antiarrhythmics. This in turn may help mitigate against adverse effects of high-dose antiarrhythmics (e.g. long QT, VA).

Note that when all available evidence (pharmacologic, omic, and knockout studies) is considered together, over and underactivity of SK channels both appear to increase likelihood of developing AF. Perhaps discrepancies between different studies are the result of differences in experimental techniques or different species. Alternatively, a two-fold mechanism may drive SK pathology in AF. On one hand, gradually increasing potassium currents due to increased insertion or presence of SK channel in cell membranes may contribute to the observed accelerated actional potential refractory periods and steady progression of APD shortening. On the other hand, action potential prolongation due to diminished potassium currents in the absence of SK channel activity may increase likelihood of generating early afterdepolarizations that may evolve into ectopic foci or reentry circuits. If correct, this proposal implies that seeking to modulate SK channel activity in AF is not a simple matter of complete pharmacologic blockade or complete potentiation. Rather, the objective would be restoring balance towards a homeostatic level of SK channel activity. Further research is required to define the precise pathophysiology of altered SK channel activity in AF to better guide development and protocols for new therapeutic tactics.

5.2 SK channels in ventricular arrhythmias and heart failure

Ventricular arrhythmias (VA) are abnormal heart rhythms that include premature ventricular complexes (PVC), non-sustained ventricular tachycardia (VT), accelerated idioventricular rhythm, and sustained VT or ventricular fibrillation (VF). VT and VF in particular may cause sudden cardiac death (SCD) [107]. Ventricular arrhythmias can be seen in patients with structurally normal hearts, but malignant ventricular arrhythmias usually occur in patients with underlying structural heart disease including HF, ischemic cardiomyopathy, and nonischemic cardiomyopathy [107, 108].

In the normal heart, SK1 channels are expressed at a higher level in atria versus in ventricles, while SK2 and SK3 are expressed at a similar level in both chambers [14, 25]. Normally, apamin-sensitive currents are more prominent in atria than ventricles [12, 14]. However, under certain pathological conditions such as HF and chronic MI, SK currents are upregulated in ventricles, suggesting that SK channels play an important role in ventricular repolarization and VA in pathologic hearts [39, 40].

In healthy ventricles, apamin does not alter APD [14, 22]. Under pathological conditions such as HF, chronic MI, cardiac hypertrophy, and hypokalemia, SK channel blockers prolong APD in ventricles as shown in human and animal models [29, 39, 40, 105, 109]. In acute MI, however, the results are mixed. Some studies show that SK channel blockade prolongs APD in rat acute MI models [110, 111], but a recent study using a porcine model of acute MI showed no significant effect of APD alteration by SK blockade [112]. In the studies that showed prolonged APD by SK blockade in pathologic ventricles, the effects could be either antiarrhythmic or proarrhythmic, probably due to different baseline heart rhythms in the specific animal models used for the studies [18].

Antiarrhythmic effects of SK blockade may occur through attenuation of APD shortening and reduction of repolarization heterogeneity in pathologic hearts [112]. Indeed, Chua et al. were the first to show proarrhythmic effects of SK channels in the ventricles. They showed that HF heterogeneously increased the SK channel's sensitivity to intracellular Ca^{2+} and upregulated SK currents, which led to APD shortening and

recurrent spontaneous VF in a rabbit model of tachycardia-induced HF [39]. In this scenario, the rapid heart rate in heart failure caused APD shortening, and excessive APD shortening was arrhythmogenic. APD shortening led to increased intracellular Ca^{2+}, which activated SK currents and further shortened APD, resulting in late phase 3 early afterdepolarization and recurrent spontaneous VF [39]. The antiarrhythmic effects of SK blockers in the ventricles have also been demonstrated in human HF [29], in rabbits with chronic MI [40], in rats with acute MI [110, 111], in rats with cardiac hypertrophy [113, 114], and in hypokalemic guinea pig heart [100].

Chen et al. reported that SK channels are proarrhythmic and play a role in inducing J wave syndrome (JWS). They showed that concurrent activation of SK currents and inhibition of Na^+ currents shortened APD and induced JWS and SVF in rabbit hearts. SK channel blockade in this rabbit model was antiarrhythmic—JWS was reduced and SVF was abolished, suggesting that SK current activation contributed to the development JWS and SVF in rabbit ventricles [109]. A recent study showed that colocalization of LTCC and SK channels in ventricular myocytes activates SK currents, which then promote phase 2 reentry and T-wave alternans, leading to JWS and VA [115].

Although SK blockers have potential antiarrhythmic benefits in the management of ventricular arrhythmias, blocking SK channels may carry significant proarrhythmic risk in patients with underlying heart disease such as HF, MI, and cardiac hypertrophy, based on animal model studies [116–118]. Blocking SK channels might reduce the repolarization reserve in patients, trigger early after depolarizations (EADs), increase risk of developing torsade's de pointes (TdP) and induce fatal arrhythmia [18, 112, 116]. In addition, SK blockers might be proarrhythmic in hypokalemic hearts. Chan et al. reported that hypokalemia activates SK channels, shortening APD and maintaining the repolarization reserve at late activation sites. In their rabbit model of hypokalemic ventricles, apamin was proarrhythmic by prolonging APD at late activation sites and inducing VF [119].

In addition, Wan et al. showed that SK blockade might even interfere with ventricular automaticity in normal ventricles [120]. Although SK channels do not participate in repolarization in healthy ventricles, SK currents and SK2 protein are prominent in Purkinje cells in normal rabbit ventricles [42]. Wan et al. reported that apamin accelerated ventricular escape rhythms from the Purkinje fibers, enhanced ventricular automaticity and led to VT in normal rabbit ventricles [120].

To summarize, the heterogenous activation of SK channels is proarrhythmic and contributes to the development of ventricular arrythmia in diseased hearts. SK blockers such as apamin have some antiarrhythmic benefits, but also carry significant proarrhythmic risks, thus limiting the practical use of SK blockers for managing ventricular arrythmia. Furthermore, SK channels are widely expressed in the human body including in the nervous system, so blocking SK channels may have undesired off-target effects. Alternatively, drugs that target the signaling pathway of SK channels might have antiarrhythmic effects without directly blocking the channel. Given that increased intracellular Ca^{2+} triggers the upregulation of SK channel in pathologic ventricles, drugs that affect the interactions of SK channel and intracellular Ca^{2+} might have antiarrhythmic or proarrhythmic effects. For example, β-blockers, a known treatment for ventricular arrhythmias, downregulate SK1 and SK3 expression, the SK channel's sensitivity to Ca^{2+}, and the SK current density as shown in a volume-overload rat model [121]. Kamada et al. showed that β- adrenoreceptor stimulation activated SK channels via CaMKII activity in hypertrophied rat hearts, which might contribute to the antiarrhythmic effects of β-blockers [122]. Finally, recent studies

showed that sex differences existed with respect to ventricular SK channel activation in response to autonomic stimulation [109, 123], which might have important clinical implications for drug efficacy and safety.

5.3 SK channels and ischemia/reperfusion

During cell ischemia and hypoxia, the altered redox state leads to excess reactive oxygen species (ROS) production which overwhelms the ROS scavenger system, causing mitochondrial Ca^{2+} overload that results in cell apoptosis and necrosis [124]. Given that mitochondria are important in ROS production, ion channels present on the mitochondrial membranes could contribute to the regulation of homeostasis by regulating ROS production during ischemia [124]. In 2013, Stowe et al. discovered that SK channels were located in the guinea pig cardiac IMM, and that SK channel opening had a protective effect during ischemia [37]. In their study, the SK and IK channel opener DCEB resulted in decreased infarct size, reduced superoxide (O_2^-) and mitochondrial Ca^{2+} levels, and more normal NADH and FAD levels. The protective effects were reduced when TBAP, a dismutator of O_2^- was added, suggesting that the benefits of channel openers were related to ROS production [37].

Later on, in a separate study, Stowe et al. also showed that SK channel opening improved contractility and reduced infarct size during ischemia/reperfusion (IR) [125]. In their guinea pig heart model of global IR injury, the SK channel opener DCEB improved contractile function, while SK antagonists worsened contractility and increased infarct size. Furthermore, in cardiac mitochondria after IR, combined SK channel and large conductance Ca^{2+}-activated K^+ (BK) channel agonists improved respiratory control index and Ca^{2+} retention capacity, while the combined antagonists worsened Ca^{2+} retention capacity [125]. Once again, these results show that SK channel plays a role in regulating homeostasis of mitochondria and reducing cell damage during IR.

In 2017, Yang et al., showed that SK3 channels were located in the mitochondria of guinea pig, rat and human ventricular myocytes. They reported that SK channel agonists were protective against IR injury while SK antagonists worsened IR injury. Overexpression of SK3.1 specifically increased Ca^{2+}-activated K^+ uptake in mouse atrial tumor cells and protected the cells from hypoxia/reoxygenation injury. Consistently, silencing SK3.1 channel expression exacerbated cell injury and death [38]. Hence the authors conclude that the protective effect of SK channels during IR suggests their role in reducing oxidative stress resulting from mitochondrial Ca^{2+} overload [38].

In addition, in hypertrophic hearts, mitochondrial SK channels also appear to have protective benefits by decreasing mitochondrial ROS production as shown in a rat model [126]. Kim et al., reported that SK channel enhancers reversed the oxidation of RyRs, improved RyR function and stabilized SR Ca^{2+} release, leading to the protective effects of SK channels in hypertrophic heart [126]. To summarize, mitochondrial SK channel have important protective effects during cardiac cell ischemia, hypoxia and hypertrophy by regulating Ca^{2+} homeostasis and ROS production in the mitochondria.

6. Conclusion

It is increasingly evident that SK channels have important roles in myocardial physiology and pathophysiology. While different studies report different expression

levels of various SK channel isoforms in atrial vs. ventricular tissue, all SK channel isoforms present in the heart are necessary for promoting atrial and ventricular repolarization following myocardial impulse generation. The high calcium sensitivity of SK channels, mediated by channel-bound calmodulin and modulated by important regulators such CK2 and PP2A, renders them crucial for feedback control of myocardial contractility and prevention of runaway excitation. In the context of arrythmias, SK channel polymorphisms confer increased risk of atrial fibrillation, and both hyper- and hypoactivity of SK channels along with aberrant SK channel expression likely contribute to automaticity, re-entry circuits, and ectopic pacemaker activity that drives atrial and ventricular tachyarrythmias; these effects are exacerbated in the context of underlying heart disease, such as congestive heart failure. Furthermore, SK channel activity appears to have a protective effect in mitigating oxidative stress during ischemia, with particular significance given to myocardial mitochondrial SK channels.

Pharmacologic studies of SK channel inhibition or activation show promise for treating many animal models of arrythmias and ischemia-reperfusion, although results are still not consistent across different models and different protocols; hence additional research will be required prior to clinical trials of SK channel antagonists in humans. In the future, more research on SK channel pathology using human atrial or ventricular tissue will also be necessary to complement and verify cellular/molecular findings from animal models. Likewise, the specific mechanisms behind altered SK channel expression in many of the diseases discussed in this chapter remain murky and must be elucidated to better characterize specific aspects of pathology at play.

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