Small-conductance Ca\(^{2+}\)-activated K\(^{+}\) channels: insights into their roles in cardiovascular disease

Mingxia Gu\(^1\), Yanrong Zhu\(^1\), Xiaorong Yin\(^2\) and Dai-Min Zhang\(^1\)

Abstract
Life-threatening malignant arrhythmias in pathophysiological conditions can increase the mortality and morbidity of patients with cardiovascular diseases. Cardiac electrical activity depends on the coordinated propagation of excitatory stimuli and the generation of action potentials in cardiomyocytes. Action potential formation results from the opening and closing of ion channels. Recent studies have indicated that small-conductance calcium-activated potassium (SK) channels play a critical role in cardiac repolarization in pathophysiological but not normal physiological conditions. The aim of this review is to describe the role of SK channels in healthy and diseased hearts, to suggest cardiovascular pathophysiologic targets for intervention, and to discuss studies of agents that target SK channels for the treatment of cardiovascular diseases.

Introduction
The repolarization phase during an action potential (AP) is prone to aberrant excitation in cardiac electrophysiology activity. Regarding the AP duration (APD), outward currents that constitute the late repolarization phase of the AP are crucial for understanding the etiology of arrhythmias. Recent studies have provided evidence for the existence and functional significance of small-conductance Ca\(^{2+}\)-activated K\(^{+}\) (SK) channels in the heart. SK channels, which are gated solely by intracellular Ca\(^{2+}\), contribute markedly to the late phase of cardiac repolarization; hence, these channels provide a critical link between changes in intracellular Ca\(^{2+}\) levels and membrane potentials. Alteration of the intracellular Ca\(^{2+}\) concentration in certain pathologic conditions may produce profound changes in the AP profiles via these Ca\(^{2+}\)-dependent channels. Although SK channels are relative newcomers in the field of cardiac electrophysiology, our knowledge of cardiac SK channels has expanded greatly over the past decade, particularly concerning the clinical relevance of SK channel mutation in many cardiac diseases, such as atrial fibrillation (AF), heart failure (HF), hypertension, and ischemia reperfusion injury. In this review, we summarize the known mutations of SK channels and potential therapeutic targets in pathophysiological states.

Identification of SK channels in the heart
Researchers first reported SK channels in the central nervous system 70 years ago\(^1\). These channels are stable macromolecular complexes of ion-pore-forming subunits and calmodulin, protein kinase CK2, and protein phosphatase 2A that regulate somatic excitability in central neurons, affecting learning and memory\(^2\)–\(^4\). SK channels also play an important role in other tissues, such as the endothelium, intestine, and urinary bladder\(^5\),\(^6\).

Xu et al.\(^7\) first demonstrated SK channels in human and murine hearts in 2003. This report represented the first
The increase in intracellular Ca\(^{2+}\) evoked by AP firing decays slowly, allowing SK channel activation to generate a long-lasting hyperpolarization, termed the slow after hyperpolarization. This spike frequency adaptation protects the cell from the deleterious effects of continuous tetanic activity. In the heart, the current contributes markedly to the late phase of cardiac repolarization. It is conceivable that alterations in intracellular Ca\(^{2+}\) levels under certain pathologic conditions could produce profound changes in the AP profiles via this Ca\(^{2+}\)-dependent channel.

Recently, SK channels were identified in the mitochondrial inner membrane; these provided protective effects against acute ischemia reperfusion injury by reducing intracellular levels of reactive oxygen species and decreasing oxidation of reactive cysteine in ryanodine receptors (RyRs), which ultimately led to the stabilization of RyR-mediated Ca\(^{2+}\) release\(^8\).

**Structure and function of SK channels in the heart**

The International Union of Pharmacology has now grouped all Ca\(^{2+}\)-activated K\(^{+}\) channels into one gene family\(^9,10\), including large conductance Ca\(^{2+}\)- and voltage-activated K\(^{+}\) (BK) channels, intermediate conductance Ca\(^{2+}\)-activated K\(^{+}\) channels (IK), and small-conductance Ca\(^{2+}\)-activated K\(^{+}\) (SK) channels, which are sensitive to apamin. SK channels consist of six transmembrane regions (TMs) and a single pore loop, with four subunits around a central pore. Both N-termini and C-termini are oriented toward the cytoplasm. The hypothesis that Ca\(^{2+}\)-activated K\(^{+}\) channels link free intracellular Ca\(^{2+}\) to the opening of K\(^{+}\) channels is long-standing, and could explain several effects of free cytosolic Ca\(^{2+}\) on TM currents. SK channels have no charged amino acids in the fourth TM domain, which is usually an important component of a voltage sensor. The activity of BK channels is induced both by Ca\(^{2+}\) and voltage, whereas SK channels and IK channels are activated and deactivated solely as a consequence of Ca\(^{2+}\) binding or release.

SK channel gating depends on the interplay between the pore-forming α subunits and Ca\(^{2+}\)-binding protein calmodulin (CaM)\(^11,12\) (Fig. 1). The most important mechanism underlying SK channel activation is the conformation of the four calmodulin molecules, each potentially binding two calcium ions to activate the channel\(^13\). CaM binds to a high conserved CaM-binding domain (CaMBD) residing within the C-terminus of the SK channels, located immediately distal to the sixth transmembrane segment. CaM is a cytoplasmic calcium sensor that interacts with the cardiac RyR, a large Ca\(^{2+}\) channel complex that mediates Ca\(^{2+}\) efflux from the sarcoplasmic reticulum (SR) to activate cardiac muscle contraction\(^14,15\). CaM is not only essential for Ca\(^{2+}\) sensitivity but also critical for trafficking of SK channels. CaM is able to bind and activate its target proteins in both Ca\(^{2+}\)-replete and Ca\(^{2+}\)-depleted forms. CaM mutants can affect the interaction of CaM with target proteins\(^16\). CaM mutations have been reported to be associated with catecholaminergic polymorphic ventricular tachycardia and congenital long QT syndrome, associated with recurrent cardiac arrest\(^17,18\).

Apamin, a highly selective SK channel blocker, does not affect human cardiac Na\(^{+}\), L-type Ca\(^{2+}\), or major K\(^{+}\) currents\(^20\). The family of SK channels consists of three members that exhibit differential sensitivity to apamin: SK1 (also known as KCNQ1, encoded by the KCNQ1 gene), which has the least sensitivity (EC\(_{50}\) for hSK 1–10 nM), SK2 (also known as KCNQ2, encoded by the KCNQ2 gene), which has the highest sensitivity (EC\(_{50}\) ~40 pM), and SK3 (also known as KCNQ3, encoded by the KCNQ3 gene), which has intermediate sensitivity (EC\(_{50}\) ~1 nM) (Table 1).

In a normal heart, SK1 and SK2 are expressed predominantly in the atria, and SK3 is expressed in both the atria and ventricles\(^21\). Yu et al. found that KCNQ2 variants were adjunctive markers for risk stratification in patients susceptible to sudden cardiac death (SCD)\(^22,23\). Mahida et al.\(^24\) recently reported that overexpression of the KCNQ3 gene, which encodes SK3 in mice, resulted in SCD and atrial arrhythmias. Moreover, KCNQ3 is one of the few genes directly linked to clinical AF, indicating that SK channels are important in human atria\(^25\).
In the functional regulation of cardiomyocytes, SK channels include homomeric and heteromeric SK channel α subunits, CaM, α-actinin2, filamin A, and MLC2. SK2 channels directly interact with α-actinin2 and MLC2 via their C-termini and with filamin A via their N-termini. New insights into the regulation controlling the repolarization of the atrial myocytes have demonstrated that α-actinin2 facilitates the recycling of SK2 channels from both early and late endosomes, while filamin A likely assists in the recycling of SK2 channels from recycling endosomes.

### Roles of SK channels in cardiac repolarization

Cardiac APs are shaped by the intricate interplay of inward Na⁺ and Ca²⁺ and outward K⁺ currents. Ca²⁺ influx changes the membrane potential, including Ca²⁺-activated ion channels. SK channels are coupled to L-type Ca²⁺ channels, and Ca²⁺ influx through L-type Ca²⁺ channels can directly activate SK channels. Terentyev et al. reported that SR Ca²⁺ release is also necessary for SK channel activation. Ca²⁺-induced Ca²⁺ release also triggers the activation of SK channels. SK channels are activated during the systolic phase when the level of Ca²⁺ increases; the activation of SK channels repolarizes cardiomyocytes and shortens the APD. A longer APD leads to a longer Ca²⁺ wave and enhances the activation of SK channels, which helps shorten the APD. This mechanism forms a negative feedback system and helps prevent excessive prolongation of AP. The differences in AP shape between atria and ventricles are mainly due to the atrial-selective occurrence of potassium channels, which provide a potential target for atrial-selective anti-arrhythmic therapy. SK2 knockout mice demonstrate atrial APD prolongation, with no significant changes in the ventricles of the same animal.

Prior studies have shown that SK currents are upregulated in pathogenic conditions, while SK current blockade may be proarrhythmic. This suggests that upregulation of SK channels is a physiological response to reduced repolarization reserve and that SK current blockade may be arrhythmogenic in certain clinical conditions.

### Atrial fibrillation

Atrial fibrillation is associated with an increased risk of cerebrovascular stroke and other pathologies, including impaired quality of life, increased hospitalization rates, stroke incidence, and increased medical costs. The pathophysiology of AF centers around four general types of disturbances that promote ectopic firing and reentrant mechanisms: (1) ion channel dysfunction, (2) Ca²⁺-handling abnormalities, (3) structural remodeling, and (4) autonomic neural dysregulation. Current therapies for AF reduce the risk of stroke (antiaggregation) and tachycardia-induced cardiomyopathy (rate or rhythm control).

In patients with persistent and chronic AF, shortening of the AP is a major hallmark of electrical remodeling. The first indication that SK channels might play a role in AF was reported in 2007 by Ozgen et al., 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 APs due to increased SK channels. Ca²⁺ influx changes the membrane potential and impacts the SK channel function and their role in promoting AF. APD shortening and prolongation may similarly facilitate atrial arrhythmia.

Quantitative real-time PCR analyses showed higher transcript levels of SK2 and SK3 than the SK1 subtype in human atrial tissue. The expression level of SK2 and SK3 decreased in chronic AF compared with sinus rhythm patients. In streptozotocin-induced diabetic mice, the expression levels of SK2 and SK3 isoforms were downregulated by 85% and 92%, respectively, whereas that of SK1 was unchanged. These findings suggest SK channel-associated electrical remodeling in diabetic atria that may promote arrhythmogenesis. Similar findings have been previously reported. However, other groups have reported contradictory results in right atrial myocytes from patients with chronic AF and paroxysmal AF. Both up and downregulation of SK currents have been observed in AF patients. We speculate that the expression levels of SK channels depend on the duration of AF. An initial upregulation of SK expression might be followed by downregulation during long-lasting AF, as the atria undergo extensive structural and electrical remodeling.

In humans, genome-wide association studies of single AF patients have identified a significant association between AF and intronic regions of KCNN3 (SK3) on chromosome 1q21 (rs13376333). Overexpression of KCNN3 in mice causes an increased risk of sudden death associated with brady-arrhythmias and heart blockade, likely due to atrioventricular (AV) node dysfunction. SK channel inhibition can exert an anti-arrhythmic action by the direct block of SK channels, which results in increased APD90, an extended effective refractory period (ERP), and

### Table 1: Pharmacological characterization of SK channels

| Subunit | Isoform | Gene | Apamin (EC₅₀) |
|---------|---------|------|--------------|
| SK1     | KCa2.1  | KCNN1| 1–10 nM      |
| SK2     | KCa2.2  | KCNN2| ~40 pM       |
| SK3     | KCa2.3  | KCNN3| ~1 nM        |

The family of SK channels consists of three members that exhibit differential sensitivity to apamin: SK1 (also known as KCa2.1, encoded by the KCNN1 gene), which has the least sensitivity (EC₅₀ for hSK ~1 nM), SK2 (also known as KCa2.2, encoded by the KCNN2 gene), which has the highest sensitivity (EC₅₀ ~40 pM), and SK3 (also known as KCa2.3, encoded by the KCNN3 gene), which has intermediate sensitivity (EC₅₀ ~1 nM).
the indirect inhibition of Na\(^+\) channels due to the depolarization of resting membrane potential (RMP), causing a reduction in upstroke velocity and further prolongation of the ERP and post-repolarization refractoriness. SK channel inhibition might therefore constitute an intriguing anti-arrhythmic therapeutic target for patients with recent onset AF before SK channel expression is strongly downregulated due to intensive remodeling.

**Cardiac ischemic disease**

The SK channel current was upregulated in patients with acute myocardial infarction (AMI) or chronic MI\(^46\). Apamin prolonged the APD to a greater extent in chronic MI rabbit ventricles than in control rabbit ventricles, and the effects of APD prolongation were magnified by a rapid heart rate. In addition to chronic MI, Stowe et al.\(^47\) showed that the activation of SK channels protected hearts against acute ischemia reperfusion injury, and SK channel blockers antagonized this protection. However, the activation of SK channels might also contribute to the development of ventricular tachyarrhythmia during AMI.

**Chronic heart failure**

The mechanisms underlying tachyarrhythmia in HF are complex, involving anatomic remodeling, an impaired conduction system, ion channel alteration, Ca\(^{2+}\) homeostasis, changes in neurohumoral signaling, and genetic factors\(^35\). Under normal physiological conditions, the general consensus is that SK channels play a minor role in ventricular tissue. However, this might be different under pathophysiological conditions, such as HF or AMI. Chen and colleagues\(^48\) found that cardiac SK channels in a rabbit model of tachycardia-induced HF. In this model, they demonstrated that SK channels were upregulated in failing rabbit ventricles. Consistent with previous findings, their studies demonstrated that inhibition of SK channels had minimal effects in non-failing rabbit ventricles. However, in failing rabbit ventricles, apamin prolonged APD at fast and slow heart rates but not at intermediate heart rates. The APD prolongation was reported to be anti-arrhythmic at fast heart rates but proarrhythmic at slow heart rates.

Chua et al.\(^49\) discovered that the upregulation of apamin-sensitive SK channels in failing hearts was responsible for post-shock APD shortening. Apamin prolongs the APD, increases the incidence of early after depolarizations and induces torsades de pointes ventricular tachyarrhythmia in failing hearts\(^33\). These results showed that apamin had minimal effects on the APD in normal ventricles. However, a significant prolongation of the APD occurred in failing ventricles\(^49\). Bonilla et al.\(^50\) and Ni et al.\(^51\) confirmed these observations and further demonstrated that apamin significantly prolonged the APD in failing human and canine ventricular cardiomyocytes, which was associated with increased expression of SK channel proteins in failing ventricles.

The inhibition of SK channels in ex vivo or in vivo models with a normal sinus rate appears to be anti-arrhythmic; however, SK channel inhibition has been found to be proarrhythmic in AV-block SK-knockout models, isolated left atrial models, or isolated cardiomyocytes paced at slow rates, especially in failing hearts. Therefore, in contrast to the prolongation of the APD in normal atrial myocytes, SK blockade did not affect APDs in either human or canine failing atrial cells. SK channel inhibition for atrial arrhythmias could be ineffective in patients with HF; moreover, it may have proarrhythmic effects in failing ventricles\(^15\).

**Hypertension**

Aldosterone plays a key role in regulating blood pressure. Primary hyper-aldosteronism, caused by autonomous overproduction of aldosterone, is the most common form of endocrine-induced hypertension, with an incidence of ~10% among hypertensive patients. Yang et al.\(^52\) found that apamin decreased membrane voltage, increased intracellular Ca\(^{2+}\) levels, and increased aldosterone secretion in a dose-dependent manner from human adrenocortical H295R cells. In contrast, 1-ethyl-2-benzimidazolinone, an agonist of SK channels, antagonized the actions of apamin and decreased aldosterone secretion. SK channel activity negatively regulates aldosterone secretion in human adrenocortical cells. Apamin-mediated blockade and the silencing of SK2 channel gene expression evokes equivalent changes in the expression of steroidogenic enzymes and regulatory proteins, notably increasing the mRNA expression levels of STAR and CYP11B2, which control the early and late rate-limiting steps of aldosterone biosynthesis, respectively\(^52\).

**Diabetes mellitus**

The most striking feature of cardiac myocytes is their AP profile, showing long APDs with plateaus of sustained depolarization prior to repolarization. The prolongation of the atrial AP is associated with an increased incidence of atrial arrhythmias.

Epidemiological studies have indicated an association between DM and a subsequent risk of AF. Individuals with DM present with an increased risk of subsequent AF compared to unaffected individuals, but the underlying mechanism remains unclear. Spontaneous atrial arrhythmia is more prevalent in diabetic atria due to prolongation of APDs. To the best of our knowledge, activation of SK channels has been suggested to contribute to repolarization of the AP in atrial myocytes. Inactivation of SK channels results in the prolongation of the atrial AP, which is associated with an increased incidence of atrial arrhythmias.
Diabetes mellitus is known to be associated with increased oxidative stress. These activated signal transductions induce changes in gene expression and functions of ion channels. A recent study showed that the protein expression levels of the SK2 channel and SK3 channel in streptozotocin-induced diabetic mice were downregulated by 85% and 92%, respectively. The effects of DM on SK channel protein expression were mimicked in cultures of HL-1 cells with high glucose and exposure to H2O2 and were abrogated by treatment with the antioxidant Tiron. Increased oxidative stress in DM causes SK channel downregulation through post-translational modifications, resulting in SK channel-associated electrical remodeling in diabetic atria, which may promote arrhythmogenesis.

**Mutation of SK channels**

SK channels allow repolarization currents responsible for after-hypopolarization of neurons in the central nervous system. Recent studies have indicated that the existence of SK channels in atrial myocytes is responsible for atrial repolarization. The genetic basis of ventricular tachyarrhythmias and SCD remains unclear. In normal ventricular myocytes, SK channels are expressed at very low or undetectable levels, whereas upregulation of SK channels in HF is responsible for post-shock APD shortening and recurrent spontaneous ventricular fibrillation. Therefore, the role of SK channel upregulation or downregulation in ventricular arrhythmia is complex. Yu et al. elucidated a significant association between KCNN2 (SK2 channels) variants and clinically significant ventricular tachyarrhythmias. These findings indicated that KCNN2 variants may serve as adjunctive markers for risk stratification in patients susceptible to SCD.

**Future perspectives**

There is a consensus that ventricular SK channels play a minor role in normal physiological conditions; the data are more controversial in pathophysiological conditions, such as HF and AMI. Recently, researchers have found that SK channel inhibition of atrial arrhythmias may be ineffective in patients with HF; moreover, it potentiates the risk of proarrhythmic effects in the failing ventricles. Hsueh et al. reported that the proarrhythmic mechanisms of SK channel blockade might be due to prolonged APD and more pronounced APD heterogeneity. These studies suggest that SK channel blockade might be both proarrhythmic and anti-arrhythmic in the atria, depending on the experimental models and study protocols. Currently, the precise mechanisms underlying SK channel functions in normal and disease states remain unknown. The regulation of Ca2+ via atrial and ventricular SK channels might be different; however, this hypothesis is currently speculative.

SK channel modulation may represent an ideal approach for managing atrial tachyarrhythmia because the ion channel blocking effects on ventricular cardiomyocytes are reportedly minimal. These observations have led to significant enthusiasm for developing SK channel blockers to manage atrial arrhythmias. In addition to apamin, other compounds also inhibit SK channels, including tamapin, UCL-1684, UCL-1848, NS8593, d-tubocurarine, and dequalinium. Recently, N-(pyridin-2-yl)-4-(pyridin-2-yl) thiazol-2-amine (ICA), a SK channel inhibitor, was demonstrated to have anti-arrhythmic effects. ICA prevented electrical induced runs of AF in isolated right atria and induced atrial post-repolarization refractoriness and depolarized RMPs. Moreover, ICA (1–10 µM) was found to slow conduction velocity.

A synergistic effect in AF treatment was identified by combining low concentrations of SK and Na+ channel blockers. Recent evidence indicates that SK channels constitute a new target for treatment of AF. Diness et al. found that both vernakalant and AP14145, a novel SK channel inhibitor, significantly prolonged atrial refractoriness and reduced AF duration without affecting ventricular refractoriness or blood pressure in pigs subjected to 7 days of atrial tachypacing. Preliminary evidence suggests that increased SK currents in patients with paroxysmal AF were inhibited by treatment with the peptide apamin. This was associated with a fourfold increase in AP prolongation. These results suggest that SK channel blockers may serve as potential anti-AF drugs.

Therefore, SK channel blockers represent a new therapeutic strategy for treating AF, although the possible proarrhythmic effects merit additional consideration and investigation.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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