CONTEMPORARY REVIEW

Small-conductance Ca^{2+}-activated K^+ channels and cardiac arrhythmias

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Small-conductance Ca^{2+}-activated K^+ (SK, $K_{Ca}2$) channels are unique in that they are gated solely by changes in intracellular Ca^{2+} and, hence, function to integrate intracellular Ca^{2+} and membrane potentials on a beat-to-beat basis. Recent studies have provided evidence for the existence and functional significance of SK channels in the heart. Indeed, our knowledge of cardiac SK channels has been greatly expanded over the past decade. Interests in cardiac SK channels are further driven by recent studies suggesting the critical roles of SK channels in human atrial fibrillation, the SK channel as a possible novel therapeutic target in atrial arrhythmias, and upregulation of SK channels in heart failure in animal models and in human heart failure. However, there remain critical gaps in our knowledge. Specifically, blockade of SK channels in cardiac arrhythmias has been shown to be both antiarrhythmic and proarrhythmic. This contemporary review provides an overview of the literature on the role of cardiac SK channels in cardiac arrhythmias and serves as a discussion platform for the current clinical perspectives. At the translational level, development of SK channel blockers as a new therapeutic strategy in the treatment of atrial fibrillation and the possible proarrhythmic effects merit further considerations and investigations.

KEYWORDS Calcium-activated potassium channel; Small-conductance calcium-activated potassium channel (SK channel); Atrial arrhythmia; Atrial fibrillation; Heart failure; Antiarrhythmic drug; Proarrhythmia

ABBREVIATIONS **AERP** = atrial effective refractory period; **AF** = atrial fibrillation; **AP** = action potential; **APD** = action potential duration; **CaM** = calmodulin; **CK2** = casein kinase II; **EAD** = early afterdepolarization; **HF** = heart failure; **MLC2** = myosin light chain-2; **PP2A** = protein phosphatase 2A; **PSC** = pluripotent stem cell; **PV** = pulmonary vein; **SAN** = sinoatrial node; **SK** = small-conductance Ca^{2+}-activated K^+

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Introduction

Cardiac action potentials (APs) are shaped by the intricate interplay of inward Na^+, Ca^{2+}, and outward K^+ currents. Ca^{2+} influx through voltage-gated Ca^{2+} channels is critical not only for the initiation of cardiac excitation–contraction coupling but also for the activation of multiple downstream molecules to couple the function of the proteins with changes in membrane potentials, including Ca^{2+}-activated ion channels.

The initial study of Ca^{2+}-activated K^+ channels in the heart dating back to 1983 did not support the functional role of the channels in the heart.[1] However, Giles and Imaizumi[2] reported a few years later that Ca^{2+}-activated K^+ currents could be observed and were larger in atria than ventricles. There were no additional reports on the functional roles of Ca^{2+}-activated K^+ channels in the heart until a decade ago, when we reported the molecular identity and functional significance of small-conductance Ca^{2+}-activated K^+ (SK) channels in human and mouse hearts.[3] Since then, our knowledge of cardiac SK channels has greatly expanded over the past decade. Studies by our group and others have provided evidence substantiating the important roles of SK channels in the heart.[4–15] Indeed, interests in cardiac SK channels are further fueled by recent studies suggesting the critical roles of SK channels in human atrial fibrillation (AF),[16,17] the SK channel as a possible novel therapeutic target in atrial arrhythmias,[18–20] and upregulation of SK channels in heart failure (HF) in animal models[10,11] and human HF[21] (Figure 1). However, major gaps remain in our knowledge. Conflicting studies have been reported regarding the existence of SK channels in the heart.[22] Moreover, blockade of SK channels in cardiac arrhythmias has been shown to be both antiarrhythmic[18–20] and proarrhythmic[23–25] in various models (Figure 1). This review provides an

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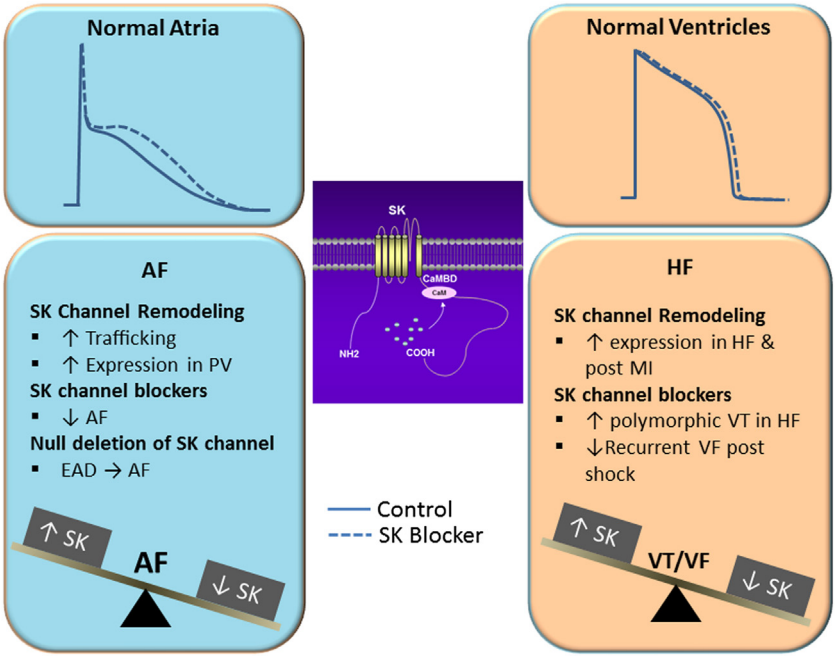

Figure 1 Functional roles of SK channels in normal and diseased hearts. Distinct roles of SK channels in atria and ventricles are depicted together with remodeling in atrial fibrillation (AF), heart failure (HF), and postmyocardial infarction MI (post MI). EAD = early afterdepolarization; PV = pulmonary vein; VF = ventricular fibrillation; VT = ventricular tachycardia.

overview of the literature over the past decade on the role of cardiac SK channels in electrophysiology, molecular interactions, and cardiogenesis and serves as a discussion platform for the current clinical perspectives.

Identification and functional expression of SK channels in the heart

SK channels are gated solely by intracellular Ca^{2+} and, hence, provide a critical link between changes in intracellular Ca^{2+} and membrane potentials. The discovery of SK channels started more than 70 years ago when convulsions in mice were observed after injection of bee venom.[26,27] The active neurotoxin in bee venom is apamin, a remarkably specific blocker of SK channels.[28,29] The highly selective blockade by apamin is the signature of SK channels that enables verification of the molecular identity of SK channels in mammalian brain.[30] The family of SK channels consists of 3 members with differential sensitivity to apamin: SK1 (or $K_{Ca}2.1$ encoded by the *KCNN1* gene) with the least sensitivity (EC_{50} for hSK1 ~10 nM); SK2 (or $K_{Ca}2.2$ encoded by the *KCNN2* gene) with the highest sensitivity (EC_{50} ~40 pM); and SK3 (or $K_{Ca}2.3$ encoded by the *KCNN3* gene) with intermediate sensitivity (EC_{50} ~1 nM).[27] They have a relatively small single channel conductance (~10 pS in symmetric K^+) and are activated by submicromolar concentrations of intracellular Ca^{2+} ions (apparent K_d ~0.5 μM). They are highly conserved among mammalian species and are identified in many organisms, including *Drosophila*.[27] Functional SK channels assemble to form homomeric[30] or heteromeric[5,31] tetramers. An intermediate-conductance Ca^{2+}-activated K^+ channel (IK or SK4 encoded by the *KCNN4* gene) that is structurally and functionally similar to the SK channel is classified to the same gene family.[27,32]

SK channels were first identified in brain[30,32] and were later described in a variety of tissues, including smooth muscle, endothelia, epithelia, and blood cells.[32] SK4 expression is restricted to nonneuronal tissues such as muscle, epithelia, and blood cells.[32,33] Our laboratory demonstrated that all 3 isoforms of SK channels are expressed in mouse and human cardiomyocytes.[3,4] Since then, expression of SK1 and SK3 in human heart tissues[34] and SK2 and SK3 in rabbit pulmonary veins (PVs) has also been reported.[7] The existence of SK currents in the heart was further supported by the findings of apamin-sensitive currents in rabbit PV[7,9] and ventricular myocytes,[10,11] human atrial myocytes,[12,13] and rat ventricular myocytes.[14] Recently, the presence of SK currents has also been demonstrated in canine PV and left atrial myocytes using the SK-specific current blocker NS8593.[15] Moreover, SK channels have been identified in pacemaking cells, including mouse atrioventricular nodal cells[35] and rabbit sinoatrial nodal (SAN) cells.[9] SK currents show an inward rectification profile that may result from pore block by intracellular divalent cations at positive membrane potential or may be mediated by intrinsic charged residues in the sixth transmembrane domain.[27] Apamin-sensitive SK currents in atrial myocytes show the inward-rectifier feature reminiscent of the hetero-expressed SK currents.[3,30,36]

Cardiac SK channel interactome

Ion channels do not exist and function in isolation. Instead they form part of multiprotein complexes that interact with extracellular matrix and cytosolic proteins.[37–39] The composition