Calcium-dependent potassium channels in the heart: clarity and confusion

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This editorial refers to ‘Critical roles of a small conductance Ca\(^{2+}\)-activated K\(^+\) channel (SK3) in the repolarization process of atrial myocytes’ by X.-D. Zhang et al., doi:10.1093/cvr/cvt262 and ‘Overexpression of KCNN3 results in sudden cardiac death’ by S. Mahida et al., doi:10.1093/cvr/cvt269.

Small-conductance Ca\(^{2+}\)-activated K\(^+\) (SK) channels are widely expressed throughout the body. After initial dismissal of a functional role for SK channels in the heart,\(^1\) a series of elegant studies from the Chiamvimonvat laboratory rekindled interest,\(^2,3\) as did subsequent work suggesting that tachypaced rabbit pulmonary veins have enhanced SK channel trafficking to the cell membrane that accelerates repolarization.\(^6\) The field really got a boost from GWAS evidence, suggesting that variants in the KCNN3 gene encoding SK isoform 3 (SK3) channels are associated with the risk of atrial fibrillation (AF) in man.\(^5\)

Questions remain, however, about the functional role that SK currents play in cardiac electrophysiology. Recent studies of SK channels in native tissues have provided conflicting results. Two investigations using apamin to block SK currents showed increased action potential duration (APD) of atrial cells,\(^6,7\) while one did not observe an effect.\(^8\) Recent detailed studies with a novel selective SK channel blocker provide insight into this variability, by showing that the expression of SK current in the canine atrium is regionally determined and increased by AF-related remodelling, such that statistically non-significant APD effects of SK channel block are seen in control left-atrium, with larger statistically significant effects in pulmonary vein cardiomyocyte sleeves and still larger effects in the presence of AF-related remodelling.\(^7\)

There are also discrepant findings regarding the effects of SK blockade on atrial arrhythmias: several studies have shown clear anti-arrhythmic actions,\(^9-11\) while one paper reported pro-arrhythmic effects.\(^6\)

Experiments in genetically engineered mouse models have the potential to provide information about the functional importance of ion-channel subunits without the concerns about specificity that plague pharmacological studies. Li et al.\(^12\) took advantage of SK2 knockout mice to show a significant role of mice in murine atrial repolarization, as well as enhanced susceptibility of mice to AF induction.

In the present issue, two groups of investigators exploit genetically engineered mice to gain insights into the role of SK3 channels in cardiac electrical function.\(^13,14\) Both groups use SK3 overexpression to study effects on electrophysiology and survival; in addition, Zhang et al.\(^13\) use an inducible genetic knockdown system to suppress native SK-3 expression; the Zhang et al.\(^13\) study focuses primarily on atrial properties and the Mahida study on ventricular consequences.\(^14\)

Zhang et al.\(^13\) show that SK3 overexpression abbreviates atrial APD and facilitates AF induction, consistent with the majority of pharmacological studies of the role of atrial SK current.\(^10-11\) Genetic SK knockdown had inconsistent effects: APD was not significantly altered, pointing to no significant role of the SK3 subunit in repolarization; however, the apamin effect to prolong APD seen in wild-type and SK3 overexpressing mice was abolished by SK3 knockdown, suggesting a contribution.\(^13\) Zhang et al. found substantial premature mortality in SK3 overexpressing mice. The Mahida study complements and extends that of Zhang et al. Heart block and bradyarrhythmias were shown to occur in SK3 overexpressing mice at the time of premature death.\(^14\) While at 1 month SK3 overexpressing mice showed inducible atrial arrhythmias and a reduced AV nodal refractory period, at 3 months AV nodal refractoriness tended to be slightly prolonged. Moderate ventricular conduction slowing and increased ventricular APD dispersion were seen in 1-month mice, with enlargement and disorganization of the AV node at 5 months.

These studies clarify some questions but raise new ones about the functional role of SK subunits in the heart. At the atrial level, the findings support the idea that SK channels contribute to atrial repolarization and their loss of SK function promotes AF susceptibility. At the ventricular and AV nodal level, the results are quite thought provoking and challenging. Why does SK3 overexpression promote premature death? The simplest explanation of the observations is that SK3 overexpression causes conduction disturbances and bradyarrhythmic death. However, it is not clear why increasing repolarizing K\(^+\)-current should slow conduction. Furthermore, ventricular conduction slowing was modest and AV nodal function was not significantly affected. Could disturbed AV nodal structure have affected AV nodal function enough to cause high grade block and bradyarrhythmic death? AV nodal histology was examined in 5-month-old mice, whereas premature death began at 30 days. It would have been interesting to know what happened to AV node histology at an earlier time-point. The disrupted AV nodal histology is in itself quite interesting: could SK3 overexpression have produced this by disturbing function in some cell-type other than adult cardiomyocytes (e.g. fibroblasts, cardiomyocyte precursors, leucocytes, neural...
elements)? Finally, could bradycardia have been a result of the terminal event, rather than the cause? SK3 overexpression causes abnormal central control of respiration in mice\(^{15}\); could the deaths have been respiratory in origin, with bradycardia/AV block an agonal cardiac response? Clearly, we need to learn much more about the role of SK channel function in the cardiovascular system. As Alice said in Wonderland: ‘Curioser and curioser’!

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**References**