“Cardiac $K_{\text{ATP}}$”
A Family of Ion Channels

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Understanding the etiology of and development of appropriate treatment for myocardial ischemia and associated sudden cardiac death is a major goal of cardiovascular research. In a recent review,1 a compelling case is presented that sarcolemmal ATP-sensitive potassium ($K_{\text{ATP}}$) channels are an excellent target for antiarrhythmic therapy. Because opening of cardiac $K_{\text{ATP}}$ channels shortens the action potential and reduces the refractory period, its activation can establish an arrhythmogenic substrate, supporting reentry. Hence, inhibition of $K_{\text{ATP}}$ could be an ideal way to stop or even prevent arrhythmias: these channels tend to be closed under normal circumstances and to open only when cell metabolism is inhibited; therefore, any agents that inhibit $K_{\text{ATP}}$ activity should specifically target channels only during ischemia, leaving nons ischemic myocardium unaffected. On the other hand, activation of cardiac $K_{\text{ATP}}$ channels has consistently been shown to protect the heart from damage during ischemia by limiting Ca entry.2 Finding a way to balance these opposing effects on the heart before, during, and after an ischemic event remains an intractable issue. Until recently, efforts to manipulate cardiac $K_{\text{ATP}}$ have generally been conducted under a single underlying assumption, namely that cardiac $K_{\text{ATP}}$ channels are structurally and functionally the same throughout the heart. However, recent studies, including the new report of Bao and colleagues3 in this issue, reveal that “cardiac $K_{\text{ATP}}$” is not a single entity and is more accurately a collection of structurally distinct channels. The relative density of each one varies regionally in the heart, may differ between species, and may be under dynamic control.

$K_{\text{ATP}}$ channels are expressed in many different excitable tissues, where they couple cell energetic status with membrane excitability and function.4 In different tissues, $K_{\text{ATP}}$ channels exhibit different properties. This is well exemplified by comparing $K_{\text{ATP}}$ channel function in pancreatic β-cells, where activity changes as a function of blood glucose, to ventricular myocytes, where channel activity is basically insensitive to such a mild metabolic stimulus. Cell size, relative rates and mechanisms of ATP synthesis and hydrolysis, and membrane PIP$_2$ levels are all important cell-specific factors that contribute to determining the channel properties in vivo.5 However, the most important factor is probably the tissue-specific subunit channel composition. Cell-surface $K_{\text{ATP}}$ channels are octameric complexes of 4 pore-forming inward rectifier subunits (encoded by 2 genes: $KCNJ8$ [Kir6.1] and $KCNJ11$ [Kir6.2]) with 4 sulfonamide receptor subunits (also encoded by 2 genes: $ABCC8$ [SUR1] and $ABCC9$ [SUR2], with multiple natural splice variants).5 The Kir6.x subunits form the channel pore and the binding site for inhibitory ATP, whereas the SURx subunits provide the sites for regulation by MgADP, channel agonists (eg, diazoxide, pinacidil, and cromakalim), and antagonists (eg, glibenclamide). Different combinations of the subunits give rise to channels with markedly different physiological and pharmacological properties.

Based on transcript distribution, communoprecipitation studies, and similarities of pharmacology and function between recombinant native $K_{\text{ATP}}$ channels, it is evident that SUR1 and Kir6.2 form pancreatic β-cell $K_{\text{ATP}}$ channels. Compelling support for this conclusion has been obtained in SUR1+/− and Kir6.2−/− mice, both of which lack functional β-cell $K_{\text{ATP}}$, and in humans, in which the discovery of mutations in the SUR1 and Kir6.2 genes that cause hyperinsulinism or neonatal diabetes in humans consistent with impaired β-cell function.6 Using similar approaches, SUR2A (a major splice variant of the SUR2 gene) and Kir6.2 have been identified as components of the channel in ventricular myocytes, whereas SUR2B (another splice variant) and Kir6.1 were labeled as the smooth muscle isoforms. Again, these conclusions have been solidified by examining knockout mice,7,8 helping to establish the dogma that “cardiac $K_{\text{ATP}}$” is formed by SUR2A and Kir6.2.

However, there have been periodic observations that did not quite fit. For example, a whole field focused on mitochondrial $K_{\text{ATP}}$ channels originated in part because of the observation that the SUR1-selective agonist diazoxide can precondition cardiac tissue but is ineffective at opening channels composed of SUR2A and Kir6.2.9 Other studies consistently showed that all of the $K_{\text{ATP}}$ subunits are expressed in the heart, raising the possibility that combinations other than Kir6.2/SUR2A may generate sarcolemmal channels. Indeed, recent studies conclusively demonstrate that there is no single “cardiac $K_{\text{ATP}}$.” Our observation that sarcolemmal $K_{\text{ATP}}$ is essentially abolished in atrial myocytes but is unaffected in ventricular myocytes from SUR1−/− mice demonstrates that all $K_{\text{ATP}}$ channels in the heart are not the same.10 Now in this issue, Bao and colleagues provide
evidence that $K_{\text{ATP}}$ channels in the conduction cells are formed from yet another combination of subunits.\(^3\) Making clever use of a transgenic mouse model in which the cells of the cardiac conduction system are labeled, the group directly compared the biophysical fingerprint of sarcolemmal $K_{\text{ATP}}$ in ventricular myocytes and cells of the conduction system. Their analysis provides compelling support for the novel conclusion that $K_{\text{ATP}}$ in conduction cells is made up of SUR2B and a Kir6.1/Kir6.2 heteromeric pore complex.

Thus, it is now apparent that there are at least 3 (and maybe more) distinct sarcolemmal $K_{\text{ATP}}$ channels in the mouse heart—formed from SUR1+Kir6.2 (atrium), SUR2A+Kir6.2 (ventricle), and SUR2B+Kir6.1/Kir6.2 (conduction system). This realization raises a number of basic questions. (1) What factors determine the composition of the channel in a given cell? (2) What is the significance of the different $K_{\text{ATP}}$ channel composition for individual myocytes and for whole-heart function? (3) Are these novel combinations specific to the mouse or applicable to other species as well? The answers to these questions are not yet certain, but there are clues in the literature as to where to look and what we might find.

From studies in heterologous expression systems where SUR and Kir6 subunit expression can be controlled, it is apparent that all possible subunit combinations can and do occur. Posttranslational quality control mechanisms have been described that ensure the appropriate octameric composition of the channel,\(^{11,12}\) yet there is no evidence that these mechanisms discriminate between subunits. With this in mind, it is reasonable to conclude that specific transcription factors (or combinations of transcription factors) act to regulate the cell-specific transcription and translation of $K_{\text{ATP}}$ subunits and thus channel composition. In fact, this conclusion can be inferred from our study of atrial $K_{\text{ATP}}$, where SUR1 expression is greater in atrium than ventricle and vice versa for SUR2A. Similarly, Bao and colleagues demonstrate the enrichment of SUR2B and Kir6.1 mRNA, relative to the ventricle consistent with a central role for transcriptional control of $K_{\text{ATP}}$ composition.

There have been relatively few studies to examine the transcriptional regulation of $K_{\text{ATP}}$ subunits, and still relatively little is known about what specific factors might control $K_{\text{ATP}}$ structure. In probably the most extensive study of the topic, the observation that members of the forkhead transcription factor family and HIF-1α regulate the expression of some subunits (as well as metabolic enzymes)\(^{13,14}\) provides a good starting point for further investigating specific molecular pathways that determine cell-specific channel composition. Other regulatory factors might also be operative as well. For example, epigenetic factors such as DNA methylation and histone modification are increasingly recognized as important nongenetic pathways that may also dynamically regulate gene expression and cell phenotypes.\(^{15}\)

Because $K_{\text{ATP}}$ channels in different regions have different composition, it is likely that they will be operative under different conditions in vivo. In the same way that structurally similar Kv2.1 and Kv4.2 subunits exhibit unique rates of voltage-dependent inactivation that contribute differently to shaping an action potential,\(^{16}\) $K_{\text{ATP}}$ channels of different structure also open and close under unique physiological or pharmacological conditions and will contribute differently to cardiac excitability. For example, Bao et al show how shortening of the Purkinje action potential will be greater than that of the ventricular action potential at the same ATP/ADP ratio, given that SUR2B and Kir6.1 confer greater ADP sensitivity on the channel complex. Atrial $K_{\text{ATP}}$ channels, composed of SUR1 and Kir6.2, will have still different activation conditions. Therefore, in experiments to study the effects of $K_{\text{ATP}}$ activation, it is not sufficient to conclude that “cardiac $K_{\text{ATP}}$” channels are unaffected, solely based on direct measurement in the ventricle or in ventricular myocytes. In this light, it is worth revisiting some earlier studies to investigate whether a different conclusion might be reached. Last, it should be noted that $K_{\text{ATP}}$ composition may not be static, and there is evidence for postinfarction remodeling of $K_{\text{ATP}}$ composition.\(^{17}\) It is important to recognize that the key studies, which reveal regional heterogeneity of channel structure have all been carried out in mice. The availability of the mouse genetic models provides a signature benefit not readily available in other species. For example, further confirmation of the role of Kir6.1 in $K_{\text{ATP}}$ channels of the cardiac conduction system can come from examining Kir6.1\(^{-/-}\) animals. Additional support might be found in human disease, where loss-of-function mutations in the Kir6.1 or SUR2 genes may reveal specific conduction defects or cardiac dysfunction.\(^{18}\) Dissection of cell-specific $K_{\text{ATP}}$ structure relies principally on expression analysis and pharmacological assessment of channel activity. Using this approach, we have recently demonstrated in human heart that the strict distribution of atrial and ventricular $K_{\text{ATP}}$ channels might not be the same as in the mouse.\(^{19}\)

Perhaps no other channels in the heart engender more potential and promise than $K_{\text{ATP}}$ channels for breaking the link between myocardial ischemia and cardiac arrhythmia. Since the first report detailing the presence of $K_{\text{ATP}}$ in cardiac myocytes was published,\(^{20}\) the possibility that this channel (1) determines the electric behavior of the heart during ischemia and (2) might protect the heart has been well recognized. Nevertheless, efforts to exploit the “cardiac $K_{\text{ATP}}$” channel to ameliorate arrhythmia and moderate damage of the myocardium during ischemia have yet to mature. We conjecture one rationale for why this has been the case: studies such as that of Bao et al demonstrate that there is no such thing as a single cardiac $K_{\text{ATP}}$ channel. Rather, cardiac $K_{\text{ATP}}$ is more accurately a collection of structurally related but functionally distinct ion channels. With acceptance of this, we will now be better poised to understand how $K_{\text{ATP}}$ channel activation contributes to the pathology of the metabolically challenged heart and to learn how to harness its power to the benefit of patients with ischemic cardiovascular disease.

Disclosures

None.

References


**Key Words:** Editorials | atrial fibrillation | conduction | potassium channels or ion channels | ischemia | ventricular arrhythmia
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Circ Arrhythm Electrophysiol. 2011;4:796-798
doi: 10.1161/CIRCEP.111.968081

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/4/6/796

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