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Focused issue on K_{ATP} channels

Cardiac K_{ATP} channels in health and disease

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Abstract

ATP-sensitive potassium (K_{ATP}) channels are evolutionarily conserved plasma-membrane protein complexes, widely represented in tissue beds with high metabolic activity. There, they are formed through physical association of the inwardly rectifying potassium channel pore, most typically Kir6.2, and the regulatory sulfonylurea receptor subunit, an ATP-binding cassette protein. Energetic signals, received via tight integration with cellular metabolic pathways, are processed by the sulfonylurea receptor subunit that in turn gates the nucleotide sensitivity of the channel pore thereby controlling membrane potential dependent cellular functions. Recent findings, elicited from genetic disruption of channel proteins, have established in vivo the requirement of intact K_{ATP} channels in the proper function of cardiac muscle under stress. In the heart, where K_{ATP} channels were originally discovered, channel ablation compromises cardioprotection under ischemic insult. New data implicate the requirement of intact K_{ATP} channels for the cardiac adaptive response to acute stress. K_{ATP} channels have been further implicated in the adaptive cardiac response to chronic (patho)physiologic hemodynamic load, with K_{ATP} channel deficiency affecting structural remodeling, rendering the heart vulnerable to calcium-dependent maladaptation and predisposing to heart failure. These findings are underscored by the identification in humans that defective K_{ATP} channels induced by mutations in *ABCC9*, the gene encoding the cardiac sulfonylurea receptor subunit, confer susceptibility to dilated cardiomyopathy. Thus, in parallel with the developed understanding of the molecular identity and mode of action of K_{ATP} channels since their discovery, there is now an expanded understanding of their critical significance in the cardiac stress response in health and disease.

Keywords: ATP-sensitive K^+ channel; Kir6.2; SUR2A; Ischemia; Flight-or-fight; Heart failure; Stress; Calcium

1. Introduction

Located throughout the body in metabolically active tissues, the evolutionarily conserved ATP-sensitive potassium (K_{ATP}) channels were first discovered in the cardiac sarcolemma where they are expressed in high density [1–5]. Formed through the heteromultimerization of an inwardly rectifying pore-forming K^+-conducting subunit and the regulatory sulfonylurea receptor, an ATPase-harboring ATP-binding cassette protein, K_{ATP} channels harness energetic decoding capabilities [6–14] and provide a high-fidelity feedback mechanism capable of adjusting cellular excitability to match demand [15,16]. In this way, energetic signals of cellular distress, received via tight integration with cellular metabolic pathways, are processed by the regulatory module to gate the nucleotide responsiveness of the K_{ATP} channel pore controlling cardiac action potential duration and associated cellular functions under stress [2,13,17–19]. Since their identification, much has been learnt of their molecular composition, biophysical properties, integration with cellular metabolic pathways and regulation of membrane-dependent cellular functions. Most recently the functional significance of these membrane metabolic sensors and effectors of cytoprotection under stress has been further established, identifying the K_{ATP} channel as a critical endogenous element for cardiac adaptation in the ischemic myocardium, in the "flight-or-fight" response and in heart failure. Highlighting the role of sarcolemmal K_{ATP} channels in health and disease is the focus of this current review.

Abbreviations : K_{ATP} channel, ATP-sensitive potassium channel ; Kir6.2-knockout, Kir6.2 gene knockout mouse ; MEF2, myocyte enhancer factor 2 ; SUR, sulfonylurea receptor.

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Central steps in advancing the understanding of this field were the cloning of members of the inwardly rectifying K^+ channel family (Kir6.1 and Kir6.2) and the sulfonylurea receptor isoforms (SUR1, SUR2A and SUR2B) [6,7,20–22], and the evidence suggesting that the cardiac K_{ATP} channel is a hetero-octameric complex composed of four pairs of these two distinct subunits [23–25]. Reconstitution experiments suggested that the cardiac K_{ATP} channel is derived from the union of the Kir6.2 and SUR2A subunits [8,26]. The subsequent development of Kir6x isoform-specific knockout animals [27–29] and their phenotyping confirmed that in the heart the pore-forming subunit of the sarcolemmal K_{ATP} channel is encoded by *KCNJ11* and that of the vascular, including the coronary, by *KCNJ8*, the Kir6.2 and Kir6.1 genes, respectively [29–31]. Studies in SUR2 knockout complement these findings with the demonstration that the SUR2 isoform is needed to form cardiac K_{ATP} channel function [32].

2. K_{ATP} channels: myocardial protectors against ischemia

K_{ATP} channels were recognized early on to serve a cardioprotective role in ischemia with K_{ATP} channel-mediated shortening of the cardiac action potential controlling calcium influx into the cytosol [1,4]. The classic clinical indicator for acute transmural myocardial injury, ST-segment elevation on surface electrocardiography, is the key feature that determines whether an emergent revascularization therapy is indicated in the presence of acute myocardial infarction [33]. Indeed, sarcolemmal K_{ATP} channel activation was found responsible for the electrical current that underlies the characteristic ST-segment elevation of transmural ischemic injury [30]. In a series of experiments with the Kir6.2-knockout mouse, transmural anterior myocardial infarction was induced by ligation of the left coronary artery and the absence of significant and sustained ST-segment change was noted [30]. This was in contrast to the wild-type that demonstrated prompt and readily visible ST-segment elevation following ischemic injury induced by arterial ligation [30]. There are indications that this experimental premise holds true in clinical medicine. Patients with diabetes mellitus presenting with acute myocardial infarction demonstrate an attenuated magnitude of ST-segment elevation when taking sulfonylureas, which are established inhibitors of K_{ATP} channel activity, resulting in a failure to meet criteria for emergent revascularization therapy and, as a consequence, inappropriate withholding of proven beneficial therapy [34]. Thus, K_{ATP} channel activity in the setting of ischemia appears to have a diagnostic implication of major clinical significance.

Moreover, K_{ATP} channel activity has been implicated in the endogenous mechanism by which exposure of the heart to brief periods of ischemia preceding a sustained ischemic insult, leads to a significant reduction in subsequent infarct size, coined ischemic preconditioning [35–37]. Analogous to ischemic preconditioning, pharmacologic activation of the channel through the use of potassium channel openers appear to have cardioprotective capabilities in single cells, as well as in intact animal and human hearts subjected to ischemic challenge [38–42].

While such therapies have the potential for diverse subcellular actions including positive effects on mitochondrial function [43,44], experiments in transgenic animals have identified the critical importance of intact sarcolemmal K_{ATP} channel function in cardioprotection, ischemic preconditioning and potassium channel opener-induced protection underscoring the integral role of this plasma-membrane metabolic sensor in the coordinated cytoprotective network within the cardiomyocyte [45–48]. Both ischemic and pharmacologic preconditioning is abolished in the absence of Kir6.2-containing K_{ATP} channels [45,48]. In vivo, a preconditioning protocol of three cycles of transient ischemia and short reperfusion attenuates the ischemic damage conferred to the wild-type heart by sustained ischemic insult, halving infarct size, but no protection in hearts lacking K_{ATP} channels [45,47]. Cardiac K_{ATP} channel current induced by metabolic challenge was confirmed to be absent in Kir6.2-deficient cardiomyocytes as did stress-induced action potential shortening [45,49]. Furthermore a series of in vitro experiments in Lagendorff-perfused hearts demonstrated that during global stop-flow ischemia the Kir6.2-knockout hearts had higher increases in left ventricular end diastolic pressure and worse contractile recovery [50]. Hence absence of sarcolemmal K_{ATP} channel activity has striking negative effects on cardiac relaxation and contractility under acute ischemic stress. In parallel experiments using sensitive measures of the cardiac bioenergetic state with ^{18}O-assisted ^{32}P-NMR spectroscopy [51], knockout of Kir6.2 negated the protection afforded by ischemic preconditioning on myocardial energy generation, transfer and utilization, while having no effect on baseline energetic state [47]. Total ATP turnover, a global parameter of myocardial energetic dynamics, failed to increase in the ischemic-preconditioned K_{ATP} channel knockout as opposed to that seen in the wild-type, correlating with the failure of preconditioned hearts lacking K_{ATP} channels to functionally recover [47]. The maintenance of energetic stability in the myocardium is a complex process requiring synchronized ATP generation and utilization accomplished through energetic phosphotransfer relay systems transferring energy from sites of production to sites of utilization and promptly removing end products from sites of utilization [52]. In this regard, in wild-type but not Kir6.2-knockout ischemic hearts preconditioning preserved creatine kinase phosphotransfer, the major energy transfer pathway in the heart [47]. This disruption formed the basis of the reduction in energetic production and/or consumption that contributed to the observed contractile dysfunction [45,47]. Thus, genetic ablation of the metabolic sensing K_{ATP} channel disrupts an integrated homeostatic mechanism required in maintaining energetic myocardial stability under ischemic stress. Those finding in transgenic animals confirm the observation of potential deleterious outcomes associated with use of sulfonylurea medication in the setting of acute cardiac infarction [53,54].