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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

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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.

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 cardio-protective 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 Langendorff-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].

3. Stress without distress: physiological role for K_{ATP} channels

While ischemic heart disease is the leading cause of morbidity and mortality [55], it does not per se explain the preservation of K_{ATP} channels through evolution. In the heart where the K_{ATP} channel has traditionally been recognized to provide metabolic protection against the insult of ischemia, recent experimental data support a wider interpretation of this channel as a guarantor of metabolic and ionic homeostasis to diverse stressors, appearing central to the cardiac participation in the general adaptation syndrome [16,55]. Selye originally introduced the concept, stress without distress, to describe the ability of an organism to confront and/or escape imposed threat, i.e. the “flight-or-fight” response, through the general adaptation syndrome [56]. Central to this universal response are physiologic alterations in bodily functions to achieve a superior level of performance necessary to cope with the demands of the imposed stress. The sustenance of this augmented performance requires there be safety mechanisms in place, such as the K_{ATP} channel, to ensure the maintenance of cellular and metabolic homeostasis such that the reaction to stress itself does not become harmful [56].

Acute exercise-stress, a common trigger of the general adaptation syndrome, provokes a systemic sympathetic stimulation that augments cardiac contractility, heart rate and thereby provides the necessary higher cardiac output. Mice lacking Kir6.2-containing K_{ATP} channels are unable to perform as well in acute treadmill exercise testing as age and sex matched wild-

type controls [16]. The delivery of this enhanced cardiac output imposes a significant metabolic load on the heart in large part due to the highly energy consuming calcium handling machinery. A compensatory increase in outward potassium current is normally activated to offset the resulting calcium influx thereby reducing energy-demanding myocardial calcium overload. As with ischemic challenge, hearts without K_{ATP} channels lack stress-induced cardiac action potential shortening upon adrenergic stress [16]. Indeed the loss of this regulator of membrane electrical stability under stress predisposed to cytosolic calcium overload in the Kir6.2-knockout associated with the development of progressive contractile dysfunction and death. On autopsy, contraction bands, pathognomonic of cytosolic calcium loading, were visible throughout the myocardium of the Kir6.2-knockout but not wild-type [16]. Thus, cardiac K_{ATP} channels, harnessing the ability to recognize alterations in the metabolic state of the cell and translate this information into changes in membrane excitability, provide the link necessary for maintaining myocardial well being in the face of stress-induced energy-demanding augmentation in performance.

4. Kir6.2-knockout predisposes to stress-induced ventricular tachycardia

Having established the critical link played by the metabolic sensing sarcolemmal K_{ATP} channels in adjusting membrane excitability to match the cellular energetic demands of imposed catecholamine stress, suggests the requirement of channel function in securing overall cardiac electrical stability [57]. Analogous to hearts with genetic and/or environmental compromise of repolarizing currents as observed in congenital or acquired long QT syndrome [58–60], adrenergic challenge was pro-arrhythmic in the K_{ATP} channel-deficient myocardium provoking early afterdepolarizations, triggered activity and ventricular dysrhythmia [57].

Deficits in repolarization reserve in the Kir6.2-knockout unmasked by sympathetic challenge evaluated in the isolated heart led to distorted action potential profiles with characteristic phase 3 early afterdepolarizations manifested as distinct humps in hearts lacking functional K_{ATP} channels with a high prevalence of early afterdepolarizations, unlike the wild-type which appropriately shortened action potential durations and maintained a smooth repolarization contour following catecholamine-stress without significant afterdepolarizations [57]. These afterdepolarizations in Kir6.2-knockout hearts induced triggered activity, disrupting regular rhythm and manifesting as a higher incidence of premature ventricular complexes than similarly challenged wild-type [57]. In the intact animal this predisposition to triggered activity and ventricular arrhythmia translated to an inherent risk for the development of QT prolongation and torsades de pointes ventricular tachycardia detected by telemetry [57,61]. Thus, under sympathomimetic stress K_{ATP} channels facilitate not just an appropriate functional response and maintenance of calcium homeostasis but also protect the myocardium from electrical instability. These studies underscore the central role for proper K_{ATP} channel activity in acute preservation of cardiac homeostasis, and further implicate K_{ATP} channel dysfunction as stress-induced long QT syndrome.

5. Functional K_{ATP} channels required for adaptive response to exercise

Chronic exercise training elicits an array of metabolic and cardiovascular responses that underlie fitness, a state of enhanced aerobic capacity associated with an improved long-term cardiovascular risk profile [62–64]. Yet, the molecular mechanisms that orchestrate the adaptive response to exercise and secure the wide-ranging gains of a regimented exercise program are poorly understood. Mice lacking K_{ATP} channels when challenged with a chronic collective aquatic training protocol manifested an impaired augmentation in exercise capacity and lacked metabolic improvement unlike the wild-type that became lighter, leaner and fitter [65]. Furthermore, the repetitive exercise-stress unmasked a survival disadvantage associated with cardiac damage in the Kir6.2-knockout, implicating the requirement of intact K_{ATP}

channel activity for achieving the physiologic benefits of exercise training without accumulating deficits [65].

Despite similar participation in swimming, displaying enhanced skeletal muscle aerobic capacity, measured by succinate dehydrogenase activity, lower resting heart rates, and superior performance on treadmill stress testing, the Kir6.2-knockout had less improvement in exercise capacity as measured by serial treadmill exercise testing compared to sex- and age-matched wild-type controls [65]. In those Kir6.2-knockout mice that completed the swimming protocol they manifested impaired cardiac contractile function with a significant reduction in left ventricular fractional shortening and an impaired cardiac output as measured by transthoracic echocardiography [65]. While in the absence of stress, mice lacking K_{ATP} channel activity had a normal survival, even the relatively modest stress imposed by the repetitive physical exertion of the swimming program induced a significant mortality in the Kir6.2-knockout mice with death occurring during or suddenly in the immediate post-exercise period, perhaps representing manifestation of stress-induced dysrhythmia, to which Kir6.2-knockout are predisposed [57]. Underlying the poor cardiac function, the Kir6.2-knockout hearts following swimming had heavier hearts and left ventricular mass and had pathologic evidence of myocyte damage with focal areas of contraction band necrosis, consistent with cytosolic calcium loading observed on both light and electron microscopy [65]. Kir6.2-knockout left ventricular tissue extracts from swum mice indicated an increased expression of myocyte-enhancing factor 2 (MEF2), a critical transcription factor that upon activation by a calcium-driven calmodulin kinase signaling pathway translocates to the nucleus where it initiates embryonic gene reprogramming and pathologic cardiac hypertrophy [65]. Indeed unlike swum wild-type animals, the Kir6.2-knockout had clear evidence of MEF2 nuclear localization on in situ immunostaining. Thus, with the findings in this study disruption of K_{ATP} channel activity in the setting of a chronic non-ischemic stress appears to render the myocardium vulnerable to both abnormal structural change and the development of cardiac dysfunction raising the question whether K_{ATP} channel dysfunction may be associated with the syndrome of heart failure.

6. K_{ATP} channel-mediated protection disrupted in heart failure

Myocardial structural remodeling with subsequent dysfunction in cellular processes is a hallmark of the syndrome of heart failure and ultimately progresses to a maladaptive state precipitating energetic, mechanical and electrical dysfunction [66]. The already compromised failing myocyte is faced with an array of metabolic insults of ischemia, hypoxia and adrenergic stress and an inability to tolerate this stress has the potential to exacerbate the abnormal cellular state and predispose to disease progression. Structural myocardial remodeling previously reported to affect K_{ATP} channel activity has the potential to disrupt homeostatic K_{ATP} channel-mediated cellular stress tolerance. In a model of heart failure, induced by transgenic expression of the cytokine tumor necrosis factor alpha (TNF α), it was recently demonstrated that while having no effect on the intrinsic biophysical properties of the cardiac K_{ATP} channel, the structural remodeling led to disruption of energetic signal-channel communication significantly disturbing the metabolic channel regulation [67]. This breakdown in intracellular signaling resulted in an inability of the K_{ATP} channel complex to appropriately recognize cellular distress and a failure to carry out its cellular homeostatic functions. When assessed in the excised patch mode, the intrinsic properties of K_{ATP} channels from myocytes isolated from either normal or failing hearts were indistinguishable suggesting that heart failure has no effect on the biophysical channel characteristics [67]. Yet, when analyzed in the cellular milieu of the failing myocyte, in the open-cell attached mode, recognition of the channels major metabolic ligand ATP was dramatically impaired [67]. This implicated a deficit in the cell proximal to the channel, i.e. in ATP production and/or in transmission of energetic signals to the channel site, as the source of channel dysregulation [67]. Indeed multiple bioenergetic disturbances have been observed, ranging from a reduced potential for ATP production by

mitochondria and a reduction in energetic stores to a significantly diminished creatine kinase flux and activity and culminating in an impaired regulation of K_{ATP} channels by the creatine phosphate/creatine kinase system [67]. These abnormalities in energy production and transfer compromised the ability of the K_{ATP} channel complex to match membrane responsiveness to metabolic changes under stress [67].

Cardiomyocytes from mice with heart failure failed to demonstrate either K_{ATP} channel activation in response to imposed cellular metabolic stress or hypoxia-induced shortening of the action potential duration, a K_{ATP} channel-mediated process [67]. Furthermore, analogous to hearts lacking K_{ATP} channels [16], cardiomyopathic hearts, tolerated sympathetic challenge poorly developing cytosolic calcium overload and contractile dysfunction [67]. Rescue of the cardiomyopathic hearts' vulnerability to stress was achieved through pharmacologic bypass of the deficit through the use of potassium channel openers [67]. By retaining intact intrinsic K_{ATP} channel properties direct therapeutic manipulation was feasible with K_{ATP} channel activation achieving improved cellular tolerance to catecholamine-stress challenge to levels equivalent to non-failing controls [68].

Thus, metabolic dysregulation of K_{ATP} channels created by the disease-induced structural remodeling appears to contribute to the dysfunction of heart failure. Moreover, in addition to their proven cardioprotective effects in ischemia and an emerging role in cardiac physiology under stress, potassium channel openers may have a role in attenuating myocardial stress-induced injury and ultimately disease progression in the setting of non-ischemic heart failure.

7. K_{ATP} channel mutations predispose to cardiomyopathy

Improper handling of myocardial calcium balance is the central contributor in the pathogenesis of cardiomyopathy with calcium recognized as a major elicitor of myocyte maladaptive remodeling that gradually progresses to contractile dysfunction and ultimately decompensates into congestive heart failure [68]. Until recently little was known about K_{ATP} channels in human heart disease, although mutations in channel subunits have been linked to metabolic disorders in other tissues [69–72]. Patients with heart failure and rhythm disturbances of unknown etiology were discovered to have mutations in *ABCC9*, the gene encoding the cardiac specific metabolism-sensing component of the K_{ATP} channel, the SUR2A protein [73]. The identified missense and frameshift mutations were mapped to domains bordering the catalytic ATPase pocket within SUR2A, but were not identified in healthy controls. These mutant SUR2A proteins reduced the intrinsic channel ATPase activity altering reaction kinetics, translating into dysfunctional channel phenotype with impaired metabolic signaling decoding and processing capabilities [73]. These data derived from genomic DNA scanning in patients with idiopathic dilated cardiomyopathy implicate a link between mutations in K_{ATP} channel genes and susceptibility for cardiac disease.

Further data with the Kir6.2-knockout exposed to hemodynamic load, due to either hypertension or transverse aortic constriction, further indicates that hearts deficient in functional K_{ATP} channels are susceptible to calcium-dependent maladaptive remodeling, progressing to congestive heart failure and death [74–76]. When placed in the context of the metabolic sensing deficit demonstrated with cardiac K_{ATP} channel mutations contributing to the development of cardiomyopathy [73], K_{ATP} channel dysfunction can be presented as a novel channelopathy in heart failure.

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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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