Published in final edited form as:
Physiol Rev. 2010 July ; 90(3): 799–829. doi:10.1152/physrev.00027.2009.

Muscle K_{ATP} Channels: Recent Insights to Energy Sensing and Myoprotection

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Abstract

ATP-sensitive (K_{ATP}) channels are present in the surface and internal membranes of cardiac, skeletal and smooth muscle cell, and provide a unique feedback between muscle cell metabolism and electrical activity. In so doing, they can play an important role in the control of contractility, particularly when cellular energetics are compromised, protecting the tissue against calcium overload and fiber damage, but the cost of this protection may be enhanced arrhythmic activity. Generated as complexes of Kir6.1 or Kir6.2 pore-forming subunits with regulatory sulfonylurea receptor subunits, SUR1 or SUR2, the differential assembly of K_{ATP} channels in different tissues gives rise to tissue-specific physiological and pharmacological regulation, and hence to the tissue-specific pharmacological control of contractility. The last ten years have provided insights to the regulation and role of muscle K_{ATP} channels, in large part driven by studies of mice in which the protein determinants of channel activity have been deleted or modified. As yet, few human diseases have been correlated with altered muscle K_{ATP} activity, but genetically modified animals give important insights to likely pathological roles of aberrant channel activity in different muscle types.

A. INTRODUCTION

It is now a quarter century since Akinori Noma (305) first described ATP-sensitive K^+-currents in cardiac myocytes. In the intervening years, details of the signature inhibition of K_{ATP} by ATP, activation by MgADP, and pharmacological modulation by inhibitory sulfonylureas, and potassium channel opening (KCO) drugs, have been clarified, and are described in earlier reviews (13, 295, 299, 385). The cloning of genes encoding the underlying subunits, in the mid 1990's (2, 56, 168, 171) led to a detailed molecular dissection of channel function and regulation, and insights to the tissue-specific nature and regulation of these channels. Here we review these advances in understanding of the molecular structure and physiological function of cardiac, skeletal and smooth muscle K_{ATP}, with a particular focus on the insights that have been gained over the last ten years, driven in large part by the generation of knockout mouse models for each of the K_{ATP} genes (*KCNJ8*, *KCNJ11*, *ABCC8*, *ABCC9*) (55, 275, 360, 362) and transgenic mice with altered K_{ATP} function (114, 219, 260). These studies have pointed to muscle-specific roles of K_{ATP}

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channels, including ischemic protection in the heart, protection against fiber damage in skeletal muscle, and control of vasomotor tone in smooth muscle. Unlike the pancreatic β-cell, where human disorders clarify the physiological role of K_{ATP} in glucose-dependent insulin secretion (126, 221, 379), no consistent picture has yet emerged of human myopathic disease resulting from altered K_{ATP} activity. However, there are compelling findings and correlations that implicate not only an important physiologic role for K_{ATP}, but potential pathophysiologic roles in disease states.

Molecular basis of K_{ATP} channel activity

K_{ATP} channels are heterooctameric complexes of pore-forming Kir channel subunits together with members of the ATP binding cassette (ABC) family of membrane proteins (Fig. 1). Two genes, *KCNJ8* (Kir6.1) and *KCNJ11* (Kir6.2) encode K_{ATP} pore-forming subunits (167, 168), while two SUR genes, *A*BCC8 *(SUR1) and ABCC9* (SUR2), generate regulatory subunits (2, 56, 168). Alternative RNA splicing gives rise to several SUR protein variants (e.g. SUR2A and SUR2B) that confer distinct physiological and pharmacological properties on the channel complex (53, 365). Interestingly (Fig. 1D), the genes for Kir6.2 and SUR1 are located next to each other on human chromosome 11p15.1 (168) suggesting an as yet unconsidered co-regulation at the gene level. In addition, the genes for Kir6.1 and SUR2 are also adjacent to one another on chromosome 12p12.1 (56, 170), implicating an evolutionary duplication event. In order to recapitulate K_{ATP} channel activity in a heterologous expression system, both Kir6 and SUR subunits must be co-expressed (168), and biophysical and biochemical studies show that Kir6.2 and SUR1 subunits combine in a 4:4 stoichiometry (Fig. 1) to generate the functional K_{ATP} channel (60, 169, 373). Similarly, biochemical studies demonstrate that the SUR2 protein variants, SUR2A and SUR2B, can also coassemble with Kir6 subunits (20, 167, 311, 442), presumably in a similar octameric arrangement.

The Kir6 subunit—Kir6.1 and Kir6.2 are typical inward rectifier channel proteins consisting of two transmembrane helical domains, TM1 and TM2, and cytoplasmic N- and C-termini (Fig. 1C). The two transmembrane helices and pore domain of Kir6.1 and Kir6.2 (Fig. 1C) share significant structural similarity to the pore-forming S5–S6 membrane segment of voltage-gated K^+ channels. Both Kir subunits contain a highly conserved sequence of residues called the K^+ channel signature sequence (TVGY/FG) (152), that confers K^+ selectivity and is found throughout the K^+ channel family. While the same general pore structure is predicted for both Kir6.1 and Kir6.2, the two subunits exhibit distinct single channel conductances of ~35 and ~80 pS, respectively in 150 mM K^+ solutions (167, 168, 178, 216, 442), conferred by specific residues in the TM1-TM2 regions (341).

The signature property of K_{ATP} is inhibition by intracellular ATP with ATP-binding occurring on the Kir6 subunit (92, 239, 374, 410, 411). Heterologously expressed K_{ATP} channels comprised of Kir6.2 plus SUR1 or SUR2A close in the presence of ATP with an average $K_{1/2}$ for inhibition of ~10 μM (298). Although initially reported to be insensitive to ATP (442), Kir6.1-containing channels have since been shown to exhibit ATP inhibition comparable to Kir6.2 (18, 356). Both non-hydrolyzable ATP analogues and ATP inhibit K_{ATP} channels, confirming that inhibition is not a consequence of phosphorylation, but of direct binding to the channel (110, 197, 237). In the absence of Mg^{2+}, ADP also blocks channel activity (197, 237, 305), albeit with lower affinity, suggesting that electrostatic interactions with the phosphate moieties on the ATP molecule, particulary the γ-phosphate, are important for binding (187).

Following the publication of the structure of the tetrameric cytoplasmic domains of eukaryotic Kir3.1 (304), and of the full length bacterial homolog KirBac1.1 (231), modeling of the tetrameric Kir6 pore revealed that three-dimensional folding brings several residues in the cytoplasmic N-and C-termini together (R50, R201, G334, II82) to form a binding pocket for ATP (Fig. 1C) (8, 103, 188, 342, 406), for a total of four binding sites per channel (i.e. each Kir subunit in the tetrameric pore binds one molecule of ATP) (8, 103, 136, 406). In addition, the N-terminus contains an amphipathic "interfacial" or "slide" helix, predicted to lie parallel to the inner surface of the lipid membrane (Fig. 1A, C) (102). This "slide" helix is physically coupled to the cytoplasmic end of the pore and may provide the physical link between ATP binding and the gate of the channel, which is likely to be located at the crossing point of the inner helix bundle (230, 231, 321, 343). More detailed homology models of Kir6.2 continue to follow the appearance of more refined bacterial channel structures (KirBac3.1) and eukaryotic channel cytoplasmic domains (Kir3.1, Kir2.1) (230, 231, 273, 304, 321). Mikhailov et al. have successfully purified a Kir6.2/SUR1 complex and provided a low-resolution structure using single-particle electron microscopy (273), but direct crystallographic analysis of the K_{ATP} channel pore structure has thus far been unattainable.

The SUR subunit—In the absence of Mg^{2+}, nucleotides inhibit K_{ATP} channel activity, but in the presence of Mg^{2+}, both ATP and ADP stimulate channel activity (95, 160, 196, 237), through interaction with the SUR subunit (132, 303, 372). The unifying structural feature of all ABC proteins are the cytoplasmic nucleotide binding folds, NBF1 and NBF2, comprised of Walker A and Walker B nucleotide-binding motifs and other conserved sequences (154) (Fig. 1C). The NBF domains contain the binding sites for Mg^{2+}-adenosine nucleotides that serve to stimulate K_{ATP} function (48, 264). In the ABC superfamily, the transmembrane domains (TMD1,2) each comprised of 6 transmembrane helices typically carry out transmembrane transport function. However, SUR1 and SUR2 are atypical in that no such transport function has been identified, and these subunits contain an additional transmembrane domain at the N-terminus, TMD0, that is joined to TMD1 by a cytoplasmic linker L0 (Fig. 1). Physical interaction between the cytoplasmic N-terminus of Kir6.2 and the TMD0 domain of SUR, including the cytoplasmic L0 linker, is demonstrated to be important in regulation of Kir6.2 gating by SUR (19).

In bacterial ABC proteins, dimerization of NBFs is favoured by the presence of nucleotides, and ATP hydrolysis requires co-operative interactions of the two NBFs (233, 380), leading to the hypothesis that the nucleotide-bound dimer is the catalytically active species. By analogy, it is suggested that Mg^{2+}-dependent ATP hydrolysis at the dimeric SUR NBFs provides the 'power stroke' that overcomes the inhibitory effect of ATP on Kir6. The Mg^{2+} dependence of α^{32}P- and γ^{32}P-azido-ATP labelling of SUR NBFs suggests that SUR NBFs also hydrolyse ATP (266, 412). Trapping of channels in the activated state by vanadate (a transition-state analogue that mimics a post-hydrolytic, ADP-bound state) and in an inactivated state by beryllium fluoride (a transition-state analogue that mimics the pre-hydrolytic, ATP-bound state) (460) further support the hypothesis that ATP hydrolysis underlies channel activation in intact cells, where ATP concentrations will always be at millimolar levels, even when metabolism is substantially inhibited (98). However, direct measurements of nucleotide hydrolysis by SUR NBFs are sparse (37, 263, 273, 460), and SUR-NBF mutations analogous to those that have drastic effects on ATP hydrolysis in bacterial NBFs have only modest effects on SUR-mediated hydrolysis (37). In membrane patch-clamp experiments, channel activation by exogenous MgADP is much more effective than activation by MgATP, and the same 'hydrolysis' mutations lead to decreased MgADP stimulation of K_{ATP} channels (37, 132, 372, 462). Why MgADP should so strongly activate the channel in excised patches if a hydrolytic cycle is required for activation is unclear. This would require that the 'activated' state resulting from hydrolysis persists after MgADP

dissociation, at least long enough for rebinding of exogenous MgADP to maintain the state. Just how reasonable this notion is has not been addressed and it remains conceivable that hydrolysis, if it occurs, is an epiphenomenon and that preferential binding of MgADP at the second nucleotide binding site is actually the physiological activator of the channel.

Additional subunits of K_{ATP} and macromolecular complexes—In addition to different gene products, SUR splicing may also be important in determining channel function (53, 142, 350, 365). Expression of SUR1 splice variants with deletions of TM16/17 (133), in NBF1 (142) and in NBF2 (350) have been reported in the heart. Alternative splicing of SUR2 exons 14 and 17, leading to deletion of segments of NBF1 are also expressed in the heart (53). The functional significance of these variants is not known, although channels containing SUR2A Δexon17 are reportedly less sensitive to ATP inhibition (53). In addition, the recent identification of short-form or partial SUR2 gene products (328) has arisen from studies of the $SUR2^{-/-}$ mouse. The targeting construct used in the generation of these animals contained a replacement of exons 12–16, coding for regions of NBF1 (55). Naturally transcribed short-form SUR2 subunits lacking the NBF1 domain have been identified using antibodies raised against distal parts of the protein (329, 388) and are reported to coassemble with Kir6.1 and Kir6.2 to form glibenclamide-insensitive, ATP-sensitive, currents in ventricular myocytes (328). A further recent study provides evidence that these short forms are present in mitochondria, and therefore may actually be a component of 'mitoK_{ATP}' (449).

While the coassembly of Kir6x and SURx are sufficient to reiterate hallmark properties of K_{ATP} channels, additional proteins may also contribute to a macromolecular channel complex and fine-tune channel function. Recent studies have implicated an elaborate β-cell K_{ATP} channel macromolecular structure (318, 368), and there is mounting evidence that metabolic enzymes, including adenylate kinase (AK) (49), creatine kinase (CK) (73) and lactate dehydrogenase (LDH) (71), can physically associate with, and regulate, the cardiac K_{ATP} channel complex. Formation of a multi-protein complex (Fig. 2) that includes both phosphotransfer and glycolytic enzymes (89, 191) may explain early studies of the native sarcolemmal channel, in which direct application of glycolytic substrates to excised membrane patches inhibited K_{ATP} channel activity (426, 427). Recent studies further demonstrate the importance of a local phosphotransfer network in regulating K_{ATP} channel activity (363): by amplifying small changes in cytoplasmic ATP concentration, adenylate kinase and creatine kinase may play an integral role in regulating the nucleotide concentration in the localized membrane environment (Fig. 2), thereby regulating the K_{ATP} response to metabolic events. In the cell, glycolysis can oscillate periodically, driven by feedback loops in regulation of key glycolytic enzymes by free ADP and other metabolites (155, 309, 444). Several studies have shown that when the capacity to buffer cellular ATP and ADP levels is suppressed by metabolic inhibition, oscillations in glycolysis can cause concurrent oscillations in ventricular action potential duration, due to oscillatory activation of K_{ATP} (9, 309, 310, 444), which may promote arrhythmias during acute metabolic stresses, such as myocardial ischemia.

Modulation by cellular lipids, metabolites and protein kinases—Nucleotide regulation is the signature property of K_{ATP}, although other regulatory ligands modulate channel activity through direct interaction with the Kir6 subunit, the SUR subunit or both. Membrane phospholipids, phosphoinositides, in particular (e.g. phosphatidylinosital-4,5-bisphosphate (PIP_2), potently stimulate K_{ATP} activity by binding the Kir6.2 subunit (29, 107, 344, 375, 439). Application of PIP_2 directly to the intracellular side of excised membrane patches leads to significant increase in K_{ATP} channel activity and restores channel activity after channel 'run-down' (107, 156). Conversely, treatment of a patch with phospholipase C (PLC), to hydrolyze PIP_2, reduces channel activity (107, 156). Similarly,

receptor–mediated activation of phospholipase C (PLC) modulates K_{ATP} activity in recombinant cell systems where receptor and channel proteins are overexpressed (29, 438), although direct support for a dynamic regulation in native muscle cells is lacking. Importantly, there exists a negative coupling between PIP_2 activation and ATP sensitivity of K_{ATP} channels such that as PIP_2 increases, channel open probability increases and ATP-sensitivity decreases (103). Physiologically, this means that ATP sensitivity is not a fixed parameter, and may change dynamically with changes in membrane composition. Residues involved in PIP_2 binding and activation overlap with the ATP binding site on Kir6.2, consistent with their competitive effects observed in binding assays (103, 258, 344). The activation of channels by PIP_2 requires the presence of both the headgroup and the phospholipid tail, since the cleavage products of PIP_2 hydrolysis (IP_3 and di-acyl glycerol), have little effect on channel activity. The negative charge of the head group is also critical, since phosphatidyl serine (net negative charge) can activate K_{ATP} but phosphatidyl choline (net positive charge) cannot (107). Consistent with an electrostatic interaction between the negatively charged head group and a region of the Kir6.2 protein close to the membrane, a number of positively charged amino acid residues in the slide helix region directly interact with PIP_2 in the membrane (79, 80, 358, 374). While PIP_2 interaction with Kir6.1 has been less extensively studied, Kir6.1 channels are activated by PIP_2 (335), suggesting conservation of the fundamental determinants of phospholipid binding and gating (164, 347, 455).

Long chain acyl-coA molecules (LC-CoA), intermediates of β-oxidation of fatty acids, have also been shown to modulate K_{ATP} channel activity in an analogous manner to membrane phosphoinositides (249). The same residues on Kir6.2 that mediate PIP_2 activation, also contribute to the stimulatory effect of LC-CoA (262, 358), suggesting that Kir6.2 is the major site of LC-CoA action. The effect of LC-CoA on ATP sensitivity is greater in ventricular myocytes than in pancreatic β-cells (43, 44, 117, 235), and the degree of acyl-coA activation increases with chain length for cardiac ventricular channels, while in pancreatic β-cells medium chain fatty acyl moieties seem to be less effective. PIP_2 and lipid modulation of ATP sensitivity is a very powerful modulator of channel activity, and changes of lipids in pathophysiological conditions may be an important regulator. Since cardiac ventricular K_{ATP} is predominantly SUR2A-dependent, whereas the pancreatic K_{ATP} is predominantly SUR1-dependent (see below), the distinct effects of acyl-coA on cardiac ventricular and pancreatic channels suggest that there is also a role for differential SUR involvement in determining the activation properties of the lipid metabolites, although this needs further work and the implications remain unclear.

Acidic intracellular pH stimulates K_{ATP} channel activity (87, 88, 440), and intracellular acidification concomitant with anaerobic metabolism provides another potential physiological stimulus of K_{ATP} activity. The mechanistic basis of pH regulation is still not completely established, although there is a general consensus that protons act to decrease sensitivity to inhibitory ATP. Mutagenesis studies of recombinant Kir6.2 subunit have revealed two amino acids (Thr71 and His175) that appear to be critical determinants of pH sensing (76, 437), but it remains unclear whether these residues are directly protonated and how they regulate the effect of pH on ATP-dependent gating.

Agonist-dependent, protein kinase A (PKA) phosphorylation is an important regulator of smooth muscle K_{ATP} channels and of pancreatic K_{ATP}, although the importance of channel phosphorylation is not entirely clear in striated muscle. The Kir6.2 subunit has two consensus PKA phosphorylation sites (33) which when phosphorylated increase channel open probability (33, 247). In human SUR1, a unique, constitutively phosphorylated PKA site acts to both increase the surface expression of the channel and decrease channel open probability, although this residue is not conserved in rodent SUR1 (33). The specific effects

of PKA on Kir6.2/SUR2A combinations have not been examined, and it is unknown whether the potential PKA sites of SUR2A are phosphorylated and what effect, if any, this might have on channel activity in striated muscle, where these subunits are predominant. In contrast, the physiological role of PKA-dependent activation of K_{ATP} channels in vascular smooth muscle is now established, and phosphorylation of both Kir6.1 and SUR2B appear to be critical in regulating channel activity, and hence vascular tone (see section D).

Protein kinase C has mixed actions on native ventricular K_{ATP} channels, inhibiting at low micromolar ATP concentrations (242), but activating at high ATP concentrations (246), through phosphorylation of highly conserved T180 residue in the Kir6.2 subunit (243). Chronic PKC activation also stimulates the retrieval of Kir6.2 from the surface membrane through a dynamin-dependent mechanism (162). Kir6.1/SUR2B channels are inhibited (335) by acute PKC treatment, due to phosphorylation of residues in Kir6.1 (see section D), whereas Kir6.2/SUR2B channel activity is reportedly unaffected by PKC (366, 402), highlighting the specificity of K_{ATP} channel subunit combinations in physiological regulation.

Structural basis of K_{ATP} pharmacology—The SUR subunit also determines the sensitivity of the channel to a huge range of pharmacological K_{ATP} channel openers (KCOs) and blockers (2, 17, 21, 22, 37, 82, 139, 282, 292, 413). All SUR isoforms are inhibited by the sulfonylurea glibenclamide, with sulfonylurea inhibition being dependent on nucleotide concentrations, and hence on metabolic state (223, 339). SUR1 is typically more sensitive to sulfonylureas than SUR2 (131), a difference that has been exploited with SUR1/2 chimeric constructs to implicate a binding site for tolbutamide in TMD2 of SUR1 (17, 22). Mutation of residue S1237 in SUR1 to tyrosine, the analogous residue in SUR2, reduces the affinity for tolbutamide and gliblenclamide (17), while the reverse mutation (Y1206S in SUR2) increases affinity (141). The SUR subunits confer also sensitivity to KCO's such as diazoxide, cromakalim, and pinacidil (298). Diazoxide is an effective activator of SUR1 and SUR2B, but not SUR2A, whereas pinacidil and cromakalim are effective activators of SUR2A and SUR2B, but not SUR1 (112, 333), highlighting the potential for tissue specificity, which remains an important pharmaceutical strategy (15). The channel openers typically contain one or more nitrogen-substituted aromatic rings, and include derivatives of cyanogaunidines (e.g. pinacidil), benzopyrans (e.g. cromakalim), but also many others, and a common pharmacophore has proven elusive (61, 261). Regions important for KCO action are spread throughout the SUR subunits, and include TMD1 and NBD1 for diazoxide (21), and TMD2 for cromakalim and pinacidil (140, 282, 413). These openers all require the presence of hydrolysable ATP (90, 140, 359), which suggests that they act to stabilize or enhance ATP hydrolysis at the NBFs.

B. K_{ATP} IN CARDIAC MUSCLE

Under normal physiological conditions, voltage-gated K^+ channels and I_{K1}, the strong inward rectifier current, provide the major repolarizing current and stabilize the cardiac resting potential (297), while K_{ATP} channels seem to play little or no role in regulating heart rhythm or contraction, despite the fact that they are the most densely expressed K^+ channel and if fully activated can lead to complete cessation of cardiac electrical activity and contractile failure (237, 238). Recent studies, taking advantage of genetically altered mice, are providing unique insight into the molecular mechanisms of cardioprotection and surprising revelations about the molecular basis of K_{ATP} channel activity.

Cardiac muscle K_{ATP} structure

Ventricular sarcolemmal K_{ATP} structure—Several splice variants of SUR1 and SUR2, as well as Kir6.1 and Kir6.2, are expressed in the heart (147, 167, 276, 284, 285).

Given that any pair of SURx:Kir6.x tetramers can co-assemble when heterologously expressed (167, 168), and that even within a single channel more than one SUR isotype or Kir6 isotype can coexist (50, 51, 77, 218, 325, 431), determining the molecular makeup of the channel in different tissues has been challenging. A number of observations support the conclusion that K_{ATP} channels in ventricular myocytes are composed primarily of SUR2A and Kir6.2 subunits. First, SUR1 mRNA is relatively low in the heart, whereas SUR2 is abundant (168). Second, while both SUR2A and SUR2B splice variants are expressed in the heart, only the properties of recombinant Kir6.2/SUR2A channels closely match those of the native ventricular myocyte channel (20, 167), with high sensitivity to pinacidil and cromakalim, and insensitivity to diazoxide. Kir6.2 and SUR2A physically interact *in vitro* to form functional channels (255), and, most significantly, K_{ATP} channel activity is essentially absent in hearts of either Kir6.2$^{-/-}$ mice (391) or SUR2$^{-/-}$ mice (55) (Table 1), providing unequivocal evidence that Kir6.2 and SUR2A are at least essential components of the K_{ATP} channel in ventricular sarcolemma. Expression of dominant-negative Kir6.1 subunits can inhibit K_{ATP} currents in ventricular myocytes (361, 405, 414), although this could be due to heterologous assembly with endogenous Kir6.2 subunits during channel turnover, and K_{ATP} current in ventricular myocytes is apparnetly unaffected in Kir6.1$^{-/-}$ mice, further arguing against a role for Kir6.1 in native sarcolemmal K_{ATP} (276).

SUR1 and SUR2 subunits can also coassemble within the same channel complex (50, 51, 431), and both SUR1 mRNA and protein have been detected in the hearts of various species (177, 284, 285, 322, 350, 381, 450). K_{ATP} channel activity is unaffected in ventricular myocytes from SUR1$^{-/-}$ mice (100, 112), yet antisense oligonucleotides specifically directed at SUR1 markedly reduce rat neonatal ventricular K_{ATP} current density (450). It is important to recognize that the molecular architecture need not be static and may change in response to metabolism or other signals. For example, hypoxia increases SUR2A subunit expression in cultured rat heart H9C2 cells (72), and SUR1 expression and diazoxide-sensitive current are both increased in infarcted heart regions (177). In addition, Kir6.1 mRNA expression is significantly elevated following myocardial ischemia or hypoxia, raising the possibility that Kir6.1 protein may be upregulated in myocytes in response to stress (177, 271). At this juncture, whether the increase in Kir6.1 in the heart during cardiac disease reflects increased expression specifically in cardiac myocyte or other cell types remains uncertain.

Atrial sarcolemmal K_{ATP} structure—Comparatively few studies have examined the biophysical and pharmacological properties of K_{ATP} channel in atrial myocytes but the work that has been done suggests that the structure of atrial and ventricular K_{ATP} are distinct. We have recently demonstrated that SUR1 protein is present in wild type mouse atrial myocytes and that K_{ATP} currents are undetectable in atrial myocytes from SUR1$^{-/-}$ mice (112), providing unequivocal evidence for an essential role of SUR1 in the atrial sarcolemmal K_{ATP} channel in mice (Table 1). In agreement with this conclusion, native atrial K_{ATP} is more sensitive to diazoxide than pinacidil, similar to recombinant SUR1/Kir6.2, while the ventricular channel exhibits the opposite specificity (112, 127), similar to recombinant SUR2A/Kir6.2. Although genetic proof by knockout of specific subunits is not possible in other species, there is some evidence for chamber-specific K_{ATP} pharmacology in other species. For instance, K_{ATP} channels in neonatal rat atrial myocytes are significantly more sensitive to activation by metabolic inhibition and diazoxide than are ventricular K_{ATP} channels, as would be expected for SUR1-containing channels (26, 324). The functional implication of disparate structure of atrial and ventricular K_{ATP} is unclear, but conceivably, SUR1-based channels are necessary for an atrial specific function, such as coupling atrial stretch with the secretion of atrial natriuretic peptide (186, 206, 348, 441). Interestingly, atrial K_{ATP} channels have been reported to be activated by stretch (214, 326, 416), although

the data is sparse, and the finding that atrial Kir3.4 channels are also stretch-sensitive (173) may provide an alternative explanation.

Nodal and Purkinje cell K_{ATP} structure—K_{ATP} channel currents have been detected in sino-atrial (SA) node (143), atrio-ventricular (AV) node (198), and Purkinje fiber cells (245), although the molecular structure in these specialized conducting cells has not been extensively tested. The observed K_{ATP} single channel conductance in rabbit SA node cells is reported to be smaller than that in ventricular myocytes (52 versus 80 pS) (143), which may suggest a role for Kir6.1 in the channel, but sarcolemmal K_{ATP} is abolished in Kir6.2$^{-/-}$ SA node cells (Table 1) indicating a requirement for the Kir6.2 pore-forming subunit (119). The AV node and Purkinje cells from Kir6.2$^{-/-}$ animals have not been similarly studied. Additionally, the identity of the SUR component is uncertain, although the channels in these cell types do respond to the relatively SUR2A-specific opener cromakalim, suggesting a major role for SUR2A in nodal K_{ATP} channels (143, 198, 245).

The molecular basis of 'mitoK_{ATP}'—The major focus of this review is on sarcolemmal membrane K_{ATP} channels, but it is necessary to also consider the mitochondrial K_{ATP} ('mitoK_{ATP}') channel that has also been significantly implicated in cardiac pathophysiology. A K^+-selective, small conductance channel was first identified in fused giant mitoplasts from rat liver mitochondria (174), and reported to be reversibly inhibited by application of ATP, glibenclamide, and 4-aminopyridine (4-AP). Further examination revealed a number of properties that distinguish these 'mitoK_{ATP}' from sarcolemmal K_{ATP} channels. First, 'mitoK_{ATP}' channels are reportedly inhibited by acyl-coA and activated by GTP and GDP when ATP is also present, and second, 'mitoK_{ATP}' channels reconstituted into liposomes exhibited increased diazoxide sensitivity relative to reconstituted Kir6.2/SUR2A channels (123, 319). Collectively, these observations implicate an ATP-sensitive K^+ conductance in the mitochondria that is distinct from sarcolemmal channels.

The pharmacology of heterologously expressed SUR1/Kir6.1 complexes appears to most closely resemble the reported 'mitoK_{ATP}' properties (161, 252), most particularly in being sensitivie to activation by diazoxide. However, studies to date indicate that 'mitoK_{ATP}' channel activity is unaffected in Kir6.1$^{-/-}$ and Kir6.2$^{-/-}$ animals (276, 393), arguing that neither of these gene products form the channel. Other biochemical and physiological efforts to determine whether specific SUR or Kir6 subunits are normally present in mitochondria have yielded inconsistent results (81, 116, 161, 232, 378, 390, 459). This may in part reflect the difficulty of isolating pure mitochondria. Contamination of mitochondrial preparations with sarcolemmal proteins could yield erroneous results, particularly given the abundance of K_{ATP} channels in the sarcolemma. In addition, the biochemical and molecular analysis may be hindered by lack of specific antibodies for K_{ATP} subunits. For example, a recent study by Foster, et al. (116), which analyzed the proteins precipitated by anti-Kir6.1 antibodies from mitochondrial extracts, found that no Kir6.1 protein was detectable by mass spectrometry. Instead, NADH flavoprotein I and mitochondrial isocitrate dehydrogenase were detected in high abundance indicating non-specificity of the antibodies. As discussed further below, short-form SUR2 subunits lacking the NBF1 domain have been identified in cardiac cells (328), and specifically localized to mitochondria (449), using antibodies raised against distal parts of the protein (329, 388). Although further studies are needed, these short forms may actually be a component of 'mitoK_{ATP}' (449).

Lack of confirmed presence of canonical SUR or Kir6 subunits in mitochondria has led to alternative hypotheses regarding 'mitoK_{ATP}' structure. Diazoxide, an activator of 'mitoK_{ATP}', has been shown to inhibit succinate dehydrogenase (145). Consistent with the idea that this key enzyme of both the Krebs cycle and electron transport chain might be a component of the 'mitoK_{ATP}' channel, Ardehali and colleagues identified a macromolecular

complex by co-immunoprecipitation that included succinate dehydrogenase, mitochondrial ATP-binding cassette protein-1 (mABC-1), ATP synthase, adenine nucleotide translocase, and phosphate carrier proteins, that recapitulated 'mitoK_{ATP}' activity including diazoxide activation and 5-hydroxydecanoate inhibition (10, 11). In this case, it is not clear which component should be forming the channel pore, although given the chloride channel function of the ABC protein CFTR (31), conceivably the mABC could form the pore, but the reported records show only single channel activity over brief periods, and follow-up studies have not yet emerged.

There is now a large body of work on the pathophysiological involvement of 'mitoK_{ATP}' in cardiac pathophysiology and the phenomenon of preconditioning (144, 308). The above discussion reflects our own skepticism regarding the nature of the 'mitoK_{ATP}', but since the interpretations of such studies lean heavily on the attendant pharmacology, the finding that diazoxide-sensitive K_{ATP} channels are present in the sarcolemma, as well as the reconfirmation that 5-hydroxydecanoate can inhibit sarcolemmal K_{ATP} channels (241), warrants at the least a careful reassessment of the interpretations.

Regulation of cardiac K_{ATP} function and implications for heart function

The multi-level regulation by membrane phospholipids (PIP_2), fatty acids (LC-Acyl-CoA), protein kinases (PKA, PKC), pH, and intracellular nucleotides (ATP, MgADP) ensures complexity of metabolic sensing by K_{ATP} channels (Fig. 2). ATP inhibits native channel activity in excised atrial or ventricular membrane patches with an average $K_{1/2}$ of approximately 50–100 μM (110, 237, 305, 306). Several studies have demonstrated that when channels are opened by metabolic inhibition, injection of ATP into the cytosol closes channels, implicating the fall in [ATP] as a contributor to channel opening under these extreme conditions (238, 306, 395). Nevertheless, ATP probably never falls below millimolar levels in a living tissue (97), and the activating effect of Mg^{2+}-bound nucleotide diphosphates will be important physiologically (237) so it is probably most appropriate to consider both the fall in ATP and accompanying rise in ADP as the major physiological regulatory parameters (Fig. 2).

Additional cytoplasmic compartmentation may modify the nucleotide-sensitivity *in vivo*. In open-cell-attached patch-clamp experiments, where the cytoplasmic milieu is largely intact, channel activity is apparently less sensitive to global changes in ATP, presumably as a result of the phosphotransfer enzymes and ATP buffering capacity (300). Compartmentalization of ATP may also be important; there is a close functional co-localization of the K_{ATP} channel and the Na-K-ATPase, such that changes in Na-K-ATP-ase activity can result in very local changes in ATP levels that are sensed by the K_{ATP} channel (148, 193, 327).

The role of intracellular pH, membrane phospholipids, channel phosphorylation and fatty acyl-coA in the regulation of native K_{ATP} channels in cardiac muscle are less well understood. Although recombinant Kir6.2/SUR2A channels are sensitive to a fall in intracellular pH (76, 437) as can occur during myocardial ischemia (418), native cardiac K_{ATP} channels are resistant to intracellular acidification by as much as 1 pH unit (75, 225, 237) and insensitive to lactate (237). Adenosine, a metabolite released from metabolically challenged myocytes, stimulates K_{ATP} channel activity in ventricular myocytes (179, 207) through a G-protein signaling cascade. PKC-dependent cardiac preconditioning by adenosine (see below) indicates an important role for adenosine-mediated K_{ATP} channel activity *in vivo*, but it remains unclear whether sarcolemmal or mitochondrial K_{ATP} or both are direct targets (63, 251, 355).

Importantly, intracellular elements other than ATP must act to keep cardiac K_{ATP} channels closed under normal conditions in order to prevent AP shortening and to maintain

contractility. This is made quite clear by studies of transgenic mice that express ATP-insensitive Kir6.2 subunits in the heart, such that sarcolemmal channels are ~100 fold less sensitive to inhibition by intracellular ATP (111, 219). In these animals, K_{ATP} channels remain largely closed and the action potential is not shortened under normal conditions. Conversely, expression of similar ATP-insensitive Kir6.2 transgenes in pancreatic β-cells suppresses electrical activity and can completely shut down insulin secretion (125, 220, 340). Experimental studies (212, 302, 428) have consistently demonstrated that activation of only 1% of the total sarcolemmal K_{ATP} population is sufficient to shorten the action potential by 50%, and significantly reduce contractility. Computer models of the action potential, in which K_{ATP} activity is controlled only by ATP/ADP ratios (300, 364), indicate that this would happen at low millimolar ATP and micromolar ADP levels in hearts with normal K_{ATP} channels, and that in hearts expressing the above ATP-insensitive transgenes, dramatic AP shortening should occur at any physiological ATP levels. It thus appears that additional factors are acting to keep these channels closed in cardiac myocytes. What combination of regulatory factors that control K_{ATP} channel opening in cardiac myocytes remains a key question.

K_{ATP} in physiology and pathophysiology of cardiac muscle: Insight from genetically modified mice

Ischemia-Reperfusion and Myocardial Infarction in K_{ATP} null mice—

Sarcolemmal K_{ATP} channels seem to be predominantly closed and do not contribute significantly to the process of excitation-contraction coupling in physiological conditions (except perhaps under adrenergic stimulation, see below), since application of sulfonylureas generally has little or no effect on the cardiac action potential (105), and ventricular action potential duration (APD) and contractile function are unaffected in isolated ventricular myocytes from Kir6.2$^{-/-}$ animals (Table 1) (240, 391, 393). However, when metabolism is inhibited chemically, or with profound anoxia, the action potential shortens dramatically and contraction fails as a result of K_{ATP} activation (66, 238, 419), both effects being absent when K_{ATP} channels are ablated either by gene knockout of Kir6.2 (393) or treatment with a K_{ATP} channel blocker (153, 419).

Activation of K_{ATP} during ischemia is likely to be cardioprotective *in vivo*, since reduction of the APD and reduction of contraction may preserve ATP stores that would otherwise be consumed during the contractile cycle. In support of this idea, treatment with the K_{ATP} opener pinacidil during ischemia increased the levels of cellular ATP and energy stored as creatine phosphate (269), and in Kir6.2$^{-/-}$ hearts, the time to contractile failure is prolonged but the time to onset of contracture, which likely reflects the depletion of ATP (301), is reduced (393). In addition to preservation of ATP, K_{ATP} activation can reduce excessive Ca^{2+} entry and its destructive sequellae, including arrhythmia, contractile dysfunction and cell death (36). Increase in intracellular Ca^{2+} in response to metabolic inhibition-reperfusion is exacerbated in both cardiac myocytes from Kir6.2$^{-/-}$ animals relative to wild type myocytes, and in untransfected COS-7 cells (relative to cells expressing recombinant K_{ATP} channels) (24, 30, 189, 190). The increase in Ca^{2+} during metabolic inhibition-reperfusion is correlated with cell death and membrane depolarization, and is significantly blunted by activation of K_{ATP} channels (23, 24, 189, 190). Ca^{2+} entry by reverse-mode Na+-Ca^{2+} exchanger activity is a major contributor to Ca^{2+} overload during ischemia-reperfusion (357) and, by reducing membrane depolarization, it is reasonable to predict that K_{ATP} activation will minimize reverse-mode exchanger activity (23). Diastolic Ca^{2+} overload, myocardial damage, and increased mortality are also observed in isoproterenol challenged Kir6.2$^{-/-}$ myocytes (461). In this case, the L-type Ca channel inhibitor verapamil, blocks the increased mortality and is consistent with the model that K_{ATP}-dependent hyperpolarization also suppresses Ca^{2+} entry through voltage dependent Ca^{2+} channels in

wild type animals. Finally, evidence of 'contractile dysfunctions' in skeletal muscle in the absence of K_{ATP} (57, 58) gives further support to the conclusion that a major function of K_{ATP} activation during metabolic stress is to reduce Ca^{2+} entry by minimizing cell depolarization.

Although there is a generally accepted consensus that activation of K_{ATP} within ventricular myocytes will be protective, there are some unexplained and unexpected findings that may require adaptation of the current model. For example, $SUR1^{-/-}$ mice actually exhibit reduced infarct size and greater functional recovery following ischemia-reperfusion than WT mice (100). As discussed above, SUR1 is not normally a major component of mouse ventricular K_{ATP} channel (100, 112, 127), suggesting that extra-ventricular K_{ATP} channels, perhaps in neurons or in atria, contribute to increased infarct size through an as yet to be defined mechanism. Similarly, infarct size resulting from global ischemia is reduced in $SUR2^{-/-}$ mice when compared to WT mice (387). Since K_{ATP} channel activity in ventricular myocytes is essentially absent in $SUR2^{-/-}$ mice, an extra-ventricular origin of protection is again postulated. Because $SUR2^{-/-}$ mice also lack vascular smooth muscle K_{ATP}, it is intriguing to speculate that persistant coronary vasospasm in these mice might generate a kind of preconditioning that helps protect the heart (see section D). Consistent with this notion, the Ca channel blocker nifedipine reversed the cardioprotection evident in $SUR2^{-/-}$ mice (387), potentially by blocking spontaneous vasospasm.

Cardiac K_{ATP} channels and arrhythmia—Common ECG findings during myocardial ischemia are a peaked T wave and elevation or depression of the ST-segment, reflecting dispersion of repolarization. Consistent with activation of sarcolemmal K_{ATP} underlying these features of the ECG during ischemia, both are blocked by the sulfonylureas glibenclamide and HMR1098 (40, 217, 229), and the K_{ATP} channel opener pinacidil induces ST-segment elevation in the absence of ischemia (229). Moreover, ischemia-induced changes in the ECG that are reminiscent of ST-elevation are absent in $Kir6.2^{-/-}$ mice (Table 1) (240), arguing strongly that K_{ATP} channel activation causes ST-segment elevation. It should be pointed out, however, that ST-segment elevation also occurs in SUR2−/− mice (see below) (54). This is surprising, since the absence of SUR2A leads to loss of ventricular K_{ATP}, and suggests that it may be the absence of SUR2 in vascular smooth muscle cells or elsewhere that is responsible.

Arrhythmias frequently accompany myocardial ischemia and reperfusion. Increased potassium conductance can stabilize the resting membrane potential, which may suppress ectopic pacemaker activity, but because K_{ATP} channel activation also accelerates repolarization, shortening of the QT-interval and reduced refractory period may actually predispose the heart to re-entrant arrhythmias. Most studies (39, 52, 66, 369, 436), but not all (369), indicate that pharmacological activation of K_{ATP} promotes ventricular tachycardia and fibrillation, while channel blockers during ischemia-reperfusion generally decrease the incidence of sustained tachycardia and ventricular fibrillation (205, 436), but again not in all studies (369). Pharmacological treatments used to tease out the effects of K_{ATP} channels on cardiac rhythm have thus yielded equivocal results but in general, K_{ATP} activation should probably be considered pro-arrhythmic in the setting of ischemia.

Cardiac hypertrophy and heart failure in K_{ATP} null mice—In response to a chronic stress such as hypertension, the complex pathological phenomena of cardiac hypertrophy and heart failure ensue. There is typically a progression of the heart from a compensated state characterized by myocardial growth and maintained cardiac output (i.e. cardiac hypertrophy), to a decompensated state in which cardiac contractility is depressed (i.e. dilated cardiomyopathy). Elevated intracellular Ca^{2+} is a key component in the development of cardiac hypertrophy (433); activation of the calcineurin-NFAT signal transduction

cascade by Ca^{2+} drives the expression of hypertrophy genes. By virtue of their responsivity to changes in energy supply and their ability to regulate APD, Ca^{2+} entry and contraction, K_{ATP} channels should tend to abrogate the disease process. Kir6.2$^{-/-}$ animals do exhibit increased mortality and exaggerated hypertrophy in response to both pressure overload (163, 443), and to mineralocorticoid/salt challenge (202). Moreover, elevated intracellular Ca^{2+} and increased calcineurin-NFAT activation are evident in Kir6.2$^{-/-}$ myocytes compared with WT following stress, consistent with the greater degree of hypertrophy (202, 443). Cardiac function is also dramatically impaired in Kir6.2$^{-/-}$ animals following hypertensive stress (i.e TAC, mineralocorticoid/DOCA salt treatment): APD (443) and QT interval (202) are prolonged, indicating that K_{ATP} may normally act to normalize the APD. Progression to congestive heart failure also appears to be more rapid in the absence of K_{ATP} channels. Both animals with trans-aortic constriction (TAC) and Kir6.2$^{-/-}$ animals treated with mineralocorticoid/DOCA salt exhibit increased pulmonary congestion and reduced fractional shortening (202, 443), Taken together these data suggest that K_{ATP} may normally impede the myocardial death that is associated with the transition from hypertrophy to overt heart failure (91), such that in the absence of K_{ATP}, heart failure is accelerated.

Importantly, K_{ATP} channels respond differently to metabolic signals in the hypertrophied or failing heart as compared to the normal heart. K_{ATP} channels are less sensitive to inhibitory ATP in hypertrophied or heart failure myocytes (47, 224, 452) and in a transgenic TNFα mouse model of heart failure, K_{ATP} channels responded poorly to metabolic inhibition (159) suggesting impaired metabolic control of channel activity. Reduced creatine kinase flux, a feature of the hypertrophic and failing heart (172), is observed in transgenic TNFα mouse model (159), and in open-cell attached patches, K_{ATP} channels are less responsive to creatine phosphate (159), suggesting that disruption of this phosphate shuttling pathway impairs ATP generation and hence channel activity in the TNFα mouse model. Consistent with the hypothesis that impaired metabolic sensing by K_{ATP} can affect the progression of heart failure, mutations (F1524S and A1513T) within the SUR2 gene locus that reduce the catalytic activity of NBF2, and should therefore reduce physiological activation of the channel, are associated with human dilated cardiomyopathy (38).

Finally, altered K_{ATP} channels may also contribute to the metabolic phenotype of the failing heart. In a pressure overload model of heart failure, reduced K_{ATP} channel activity impairs expression of the transcription coactivator PGC-1α (163), which controls expression of a number of metabolic enzymes (109). A recent proteomic comparison of wild-type and Kir6.2$^{-/-}$ animals reveals a K_{ATP}-dependent subproteome (i.e. proteins that are differentially expressed in WT and Kir6.2$^{-/-}$ myocardium), ~60% of which consists of proteins directly related to cellular metabolism (12, 463). These early studies suggest that feedback from K_{ATP} activity to metabolism may turn out to be an important process in the chronic cardiac response to altered demands, and associated disease processes.

Ischemic preconditioning and cardiac K_{ATP} channels—Because K_{ATP} channel activation can minimize the cell damage that results from ischemic or metabolic challenge, substantial effort has been devoted to exploiting the K_{ATP} channel either pharmacologically or physiologically to improve cardiac function in disease states. Paradoxically, “preconditioning” of the heart by brief ischemic periods improves the recovery of contractile function and reduces the infarct size that results from a subsequent prolonged metabolic insult (290). That this effect can be blocked by glibenclamide, has generated much interest in the cardioprotective role of K_{ATP} channels (134). Preconditioning of the heart can be mimicked by a number of humoral factors, including adenosine (248, 445) and acetylcholine (447). Blockade of adenosine-(445) and acetylcholine-induced preconditioning (447) with the K_{ATP} channel blocker glibenclamide, coupled with the observation that the cardioprotective effects can be reproduced with K_{ATP} channel openers (448) seemingly

confirms a role for K_{ATP} channels in preconditioning. However, a number of subsequent observations suggest an internal site of action in the mitochondria, leading to an ongoing debate over the distinct roles of sarcolemmal K_{ATP} and 'mitoK_{ATP}' in protection from ischemia.

The first line of evidence that questioned a role for sarcolemmal K_{ATP} channels in preconditioning was that cardioprotection by K_{ATP} channel openers bimakalim, cromakalim or pinacidil did not require shortening of the cardiac APD (138, 446). An additional line of argument arose from the observation that the channel opener diazoxide mimics ischemic preconditioning (122). Because diazoxide is relatively ineffective at opening ventricular sarcolemmal K_{ATP} channels, but effective in stimulating 'mitoK_{ATP}' activity, the latter became a primary candidate cardioprotective factor. Finally, 5-hydroxydecanoic acid (5-HD), reported to block 'mitoK_{ATP}' (although initially described as a sarcolemmal K_{ATP} blocker (307)) effectively abolishes ischemic preconditioning (253). These observations have been central to the argument that 'mitoK_{ATP}', and not sarcolemmal K_{ATP}, plays the major role in ischemic preconditioning.

However, one key assumption, that diazoxide is a specific opener for 'mitoK_{ATP}' and does not act on the sarcolemmal K_{ATP} is incorrect: diazoxide has been shown to open sarcolemmal K_{ATP} channels in ventricular myocytes at high concentrations (122) or when ADP concentrations are elevated (83) and it is now clear that sarcolemmal K_{ATP} channels in the mouse atrium are exclusively diazoxide sensitive (112, 127). In light of these findings, the experimental conditions in preconditioning studies should be carefully re-examined to ensure that diazoxide is not activating sarcolemmal channels in the ventricle. Diazoxide has also been shown to inhibit succinate dehydrogenase (145), a key enzyme in both the electron transport chain and citric acid cycle and F_1F_0 ATPase function (67, 69), raising the possibility that diazoxide speeds ATP depletion during ischemia, providing cardioprotection by indirectly activating sarcolemmal K_{ATP} channels.

Similarly, the idea that 5-HD is a specific blocker of 'mitoK_{ATP}' channels must also be carefully evaluated. An increase in flavoprotein oxidation occurs as a result of mitochondrial uncoupling and 5-HD blocks the increase in flavoprotein oxidation during ischemia (161, 252). This finding, coupled with observations that 5-HD failed to block cromakalim-induced sarcolemmal K_{ATP} activation and resultant APD shortening (268), has led to the assertion that 5-HD is a'mitoK_{ATP}' specific blocker. However, 5-HD was initially described as a blocker of sarcolemmal K_{ATP} channels in guinea-pig ventricular myocytes (307), and has also been shown to both reduce extracellular K^+ accumulation and to block APD shortening in the ischemic heart (283), all consistent with blockade of sarcolemmal K_{ATP} channels (349).

While there is certainly much work required to sort out the molecular details of ischemic preconditioning, it is important to note that both ischemic- and diazoxide-induced preconditioning are abolished in hearts from Kir6.2$^{-/-}$ animals (392, 393) as well as in hearts with transgenic overexpression of ATP-insensitive Kir6.2 subunits (337)(Table 1). Because the prevailing data indicate that Kir6.2 is not a subunit of 'mitoK_{ATP}' (see above), these findings provide further challenge to the primacy of 'mitoK_{ATP}' in preconditioning, and argue that Kir6.2, and thus the sarcolemmal K_{ATP} channel, is a critical player in cardiac preconditioning.

Catecholamine challenge and exercise in K_{ATP} null mice—Most studies of K_{ATP} channel regulation *in vivo* have focused on severe metabolic events (e.g. global ischemia or complete metabolic inhibition), but none have clearly identified the normal physiologic events, or minimal metabolic stress, that cause channel opening. During exercise or

catecholamine (eg. isoproterenol)-stimulation, increases in heart rate and contractility support the metabolic demands of skeletal muscle. Kir6.2$^{-/-}$ mice exhibit reduced tolerance to treadmill stress and impaired survival in response to isoproterenol-treatment (Table 1), suggesting that cardiac K_{ATP} normally activated during vigorous exercise, and that it is required to support the increased workload (461). The signal driving K_{ATP} activation under these conditions could be decreased ATP, and elevated ADP or agonist-dependent channel phosphorylation. The deleterious phenotype of the Kir6.2$^{-/-}$ animals seems to result from two major outcomes. First, isoproterenol-induced action potential shortening, is absent in the Kir6.2$^{-/-}$ heart, implicating K_{ATP} channels as key regulators of exercise- or stress-induced action potential shortening (461). Second, histological evidence of contraction bands, indicative of Ca^{2+} overload, in hearts from isoproterenol-treated Kir6.2$^{-/-}$ mice are consistent with enhanced Ca^{2+} entry, and Ca^{2+} channel blockade with verapamil improves survival of Kir6.2$^{-/-}$ mice during isoproterenol treatment (461). Evidence of focal myocardial necrosis, ventricular hypertrophy and increased mortality in Kir6.2$^{-/-}$ mice subjected to a four week swim training regimen (203) corroborates the idea that exercise-induced activation of K_{ATP} is a physiologically important cardioprotective mechanism.

SUR2$^{-/-}$ animals do exhibit reduced exercise (both treadmill and swim training) capacity (388), similar to Kir6.2$^{-/-}$ animals (203). Importantly, however, no exercise-induced decrement in cardiac function is reported in SUR2$^{-/-}$ mice (388). Isoproterenol challenge does not affect survival and actually ameliorates the arrhythmias that accompany spontaneous coronary vasospasm in SUR2$^{-/-}$ animals (388), with no ST-segment depression that is characteristic in the isoproterenol response of wild type mice. It is thus not entirely clear that it is the lack of cardiac KATP function that underlies the reduced exercise capacity in these animal models. Additional non-cardiac benefits of exercise training which might contribute to increased exercise tolerance include a decrease in body weight and in fasting blood glucose. Interestingly these features are observed in both wild-type mice and SUR2$^{-/-}$ mice, but are absent in Kir6.2$^{-/-}$ animals (203) (Table 1). Since the latter additionally lack K_{ATP} in the pancreas, altered pancreatic function may be the primary factor in this case, and might ultimately underlie the exercise-induced cardiac dysfunction in Kir6.2$^{-/-}$ animals.

C. K_{ATP} IN SKELETAL MUSCLE

K_{ATP} channels are also among the most densely expressed K^+ channels in the skeletal muscle sarcolemma (382, 383). Our understanding of the physiological role of the skeletal muscle channel has lagged behind that of its cardiac counterpart and some counterintuitive observations using pharmacological agents to modulate skeletal K_{ATP} activity were initially hard to reconcile. Nevertheless, recent studies of genetically altered mice reveal the important myoprotective role of sarcolemmal K_{ATP} in skeletal muscle physiology.

Molecular structure and regulation of skeletal muscle K_{ATP}

Higher levels of SUR2 expression than SUR1 in skeletal muscle (167, 168), together with observations that cromakalim and pinacidil (SUR2-selective openers) (4, 331), typically stimulate skeletal muscle K_{ATP} channels better than diazoxide (SUR1- or SUR2B-selective opener) (28, 35, 424) have led to the general assumption that skeletal muscle K_{ATP} channels are formed of Kir6.2 plus SUR2A subunits. The conclusion is further supported by loss of K_{ATP} activity in skeletal muscles from Kir6.2$^{-/-}$ (274) and SUR2$^{-/-}$ (55) animals. However, more recent studies reveal that, as in the heart, skeletal muscle K_{ATP} channel structure is more heterogeneous. Using a combination of electrophysiological and mRNA expression analyses, a recent study provided evidence that K_{ATP} channel density and channel composition vary in different types of skeletal muscle (407): K_{ATP} channel density is higher in fast-twitch fibers than in slow type and this is correlated with an increased

expression of the Kir6.2 subunit. In addition, SUR1 expression is significantly higher in fast-twitch muscles, and these K_{ATP} channels exhibit a characteristic diazoxide-sensitivity, indicative of a functional role for SUR1. Thus, as in cardiac muscle (112), it appears that while Kir6.2 is the predominant Kir6x isoform, both SUR1 and SUR2A are likely to play a role in the generation of functional channels, depending on the fiber type.

As in cardiac muscle, skeletal muscle K_{ATP} channels remain predominantly closed at rest and do not contribute to electrical activity unless the muscle is stressed (165). Consistent with this idea, glibenclamide treatment has no effect on muscle excitability or contractility under normal resting conditions (265). Channel regulation by intracellular ATP and MgADP is similar to that in cardiac muscle (3, 382, 383, 420), and metabolic inhibition similarly leads to activation of K_{ATP} channels in the intact myocyte (5). Adenosine, which is released from metabolically compromised muscle, also stimulates skeletal muscle K_{ATP} as it does in cardiac K_{ATP} (27). One notable distinction between cardiac and skeletal muscle K_{ATP} channels is their regulation by intracellular pH. Cardiac channels are relatively insensitive to decreases in pH (75, 225, 237), while intracellular acidification is a potent activator of skeletal muscle K_{ATP} (87, 88, 384).

K_{ATP} in physiology and pathophysiology of skeletal muscle: Insight from genetically modified mice

Fatigue and exercise in K_{ATP} null mice—Muscle fatigue is the decline in force production during prolonged and repetitive stimulation and many biochemical mechanisms have been proposed to contribute to the fatigue process (6). One possible mechanism is that activation of K_{ATP} channels, in response to reduction of ATP/ADP ratios, might underlie a decrease in action potential duration and hence twitch force. Consistent with this idea, application of cromakalim or pinacidil opens K_{ATP} channels in skeletal muscle and accelerates the force failure in anoxic or fatiguing conditions (128, 129, 265, 430). However, glibenclamide, which will block K_{ATP} channels activity does not slow the decline of force during fatigue, instead, glibenclamide has no effect or may even accelerate the decline in tetanic force during fatigue, similar to channel openers (68, 244, 265, 415). Thus, paradoxically, both openers and blockers of K_{ATP} can accelerate skeletal muscle fatigue.

Myographic examination of muscles from Kir6.2$^{-/-}$ and SUR2$^{-/-}$ animals has helped to resolve this paradox. These studies reveal that the initial decline in force during fatigue is not typically associated with K_{ATP} activation directly (hence glibenclamide does not slow fatigue development in wild type skeletal muscle), but the activation of K_{ATP} channels after fatigue has developed still helps to preserve a polarized membrane potential, protecting against voltage-dependent Ca entry and rise of (non-stimulated) tension that is observed in Kir6.2$^{-/-}$ muscles (129) or glibenclamide-treated wild type muscles (265), that are exposed to fatiguing stimuli (57, 58, 128, 130). This model accounts for the observation that the rate and extent of post-fatigue recovery is decreased in both Kir6.2$^{-/-}$ (57, 128, 129) and glibenclamide treated muscle (130). Finally, the observation that there is extensive fiber damage in Kir6.2$^{-/-}$ (203, 400) subjected to treadmill or swim training protocols reinforces the conclusion that K_{ATP} channel activation is a physiologically relevant myoprotective mechanism *in vivo*, even though K_{ATP} activation does not itself underlie the gradual loss of contractile activity in fatigue.

It remains to be seen whether these same phenotypes are found in SUR2$^{-/-}$ mice, which also lack sarcolemmal K_{ATP} but initial studies suggest that this will be the case: extensive fiber damage, as in Kir6.2$^{-/-}$ mice, is observed in trained SUR2$^{-/-}$ mice (388). It is not clear whether mitoK_{ATP} channels have a role in myoprotection. As in the heart, skeletal muscle can be preconditioned by ischemia or adenosine and again this process has been linked to mitoK_{ATP} (286, 287, 314, 315), but detailed studies of skeletal muscle preconditioning have

yet to be carried out on K_{ATP} null mice, and these will be necessary to confirm a role for 'mitoK_{ATP}'.

Glucose uptake in K_{ATP} null mice—A potentially interesting, but poorly understood, role of skeletal muscle K_{ATP} is regulation of glucose uptake. It has been recognized for some time that treatment with sulfonylureas improves glucose homeostasis, independent of its effect on insulin secretion, by improving peripheral insulin sensitivity (86, 346, 386). Skeletal muscle is a major site for insulin-stimulated glucose uptake and sulfonylureas can enhance insulin-stimulated and basal glucose uptake into isolated skeletal muscle or L6 myotubes (330, 409, 423). The conclusion that blockade of skeletal muscle K_{ATP} channels increases basal or insulin-dependent glucose uptake is supported by studies of K_{ATP}-deficient Kir6.2$^{-/-}$ and SUR2$^{-/-}$ animals (Table 1) (55, 274). In these mice there is enhanced glucose uptake, consistent with an inhibitory effect of skeletal muscle K_{ATP} activity on glucose uptake. It remains unclear precisely how K_{ATP} regulates glucose uptake, but appears to be independent of the classical IRS-1/PI3-K signaling pathway (277).

A negative relationship between K_{ATP} channel activity and glucose uptake potentially provides a negative feedback from electrical activity to the metabolic state of the cell and its substrate usage. It is intriguing to speculate that with increased K_{ATP} channel activity (e.g. as will occur with K_{ATP} mutations associated with neonatal diabetes (298)), not only will insulin secretion from β–cells be reduced, but glucose uptake into skeletal muscle may also be limited, thereby exacerbating the hyperglycemic phenotype. Similarly, we may also speculate that in obesity an accumulation of fatty acyl coA intermediates, by activating K_{ATP} (249), will exacerbate insulin resistance (422).

D. K_{ATP} CHANNELS IN SMOOTH MUSCLE

Multiple K^+-channel types control electrical activity of the smooth muscle cell, including members of *i*) the voltage-dependent K^+-channel family (K_v); *ii*) large-conductance Ca^{2+}-activated K^+-channels (BK_{Ca}); *iii*) two-pore domain K^+-channel (K_2P); and *iv*) inward rectifier K^+-channels (K_{ir}), including the ATP-sensitive K^+-channels (K_{ATP}) (182, 213, 295, 425). The membrane potential of the smooth muscle myocyte (approximately-50 mV at rest in arteries and arterioles) is determined primarily by the K^+-conductance which, in turn, controls diameter of the blood vessels and, thereby, the vascular tone. According to the paradigm, inhibition of K^+-channel activity will cause depolarization of the membrane potential, activation of L-type voltage-sensitive Ca^{2+}-channels, Ca^{2+}-entry and vasoconstriction (295), although, unlike cardiac and skeletal muscle, most smooth muscle cells do not generate action potentials (157, 158). Conversely, activation of K^+-channels, because of the K^+ electrochemical gradient, will lead to K^+-efflux, membrane *hyper*polarization, decrease in voltage-dependent Ca^{2+}-entry and vasodilation (295). The relationship between membrane potential and Ca^{2+}-influx is especially steep in smooth muscle, with membrane depolarization or hyperpolarization of only a few millivolts causing several fold increases or decreases in $[Ca^{2+}]_i$ respectively (294, 296). Thus, modulation of membrane potential by both metabolic and humoral vasoactivators that act on K^+-channels can have profound effects on smooth muscle tone. The primary focus of this section is on the role of K_{ATP} in maintaining and regulating vessel tone in the prototypical smooth muscle, the vascular smooth muscle (VSM), and the possible cardiovascular consequences of altered VSM K_{ATP}.

Vascular smooth muscle K_{ATP} structure

Deciphering the molecular composition of the K_{ATP} subtypes in VSM has proven challenging. This is due to a number of factors, including the low density of K_{ATP} expression in the vasculature (~300 K_{ATP} channels/cell in VSM versus ~50,000 channels/

cell in cardiac myocytes) (84, 300); the experimental difficulties in isolating and analyzing the electrophysiological properties of vascular smooth muscle cells (295, 312), and, most notably, the complex and variable biophysical and pharmacological properties of native VSM K_{ATP}, which likely reflect differential expression of multiple K_{ATP} subtypes in vascular beds (e.g. cororany arteries coexpress K_{ATP} subtypes with varying conductances) (32, 41, 78, 195, 201, 281, 313, 385). Early studies on native VSM K_{ATP} from various sources demonstrated considerable variations in single channel conductances, even after accounting for different experimental conditions (65, 120, 280, 281, 313, 421, 456). Low-conductance channels (unitary conductances from 20–50 pS) represent the predominant K_{ATP} channel subtype; whereas medium- and high conductance K_{ATP} channels exhibit a more limited distribution in the vasculature (50–70 pS and >200 pS, respectively) (64). Adding to the molecular complexity, K_{ATP} channels from coronary arteries are reported to exhibit multiple sub-conductance states (313). Unlike classic K_{ATP} channels of the heart (1, 167) and pancreas (16, 168), the predominant VSM K_{ATP} subtype is inactive in isolated membrane patches, and requires nucleoside diphosphates (ADP, UDP, GDP) in the presence of Mg^{2+} to open, leading to their functional designation as 'nucleoside-dependent' K^+-channels, or K_{NDP} channels (32, 195, 456)

Heterologously expressed Kir6.1/SUR2B channels recapitulate many of the salient biophysical properties of the native VSM K_{ATP}/K_{NDP} including: *i*) a lack of spontaneous channel activity upon membrane patch excision; *ii*) an obligatory requirement for di-, and triphosphate nucleosides in the presence of Mg^{2+} for activity; *iii*) a high sensitivity to the potassium channel openers (KCOs), pinacidil and nicorandil, and to the inhibitory sulfonylurea, glibenclamide; *iv*) a low unitary conductance of ~33 pS (145 mM external $[K^+]$); and *v*) a complex regulation by ATP in which *micro*molar $[MgATP]_i$ activates the channel; whereas, *milli*molar $[ATP]_i$ inhibits channel activity (18, 108, 171, 178, 356, 442). Electrophysiological studies of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice confirm an essential requirement for both Kir6.1 and SUR2 subunits in formation of VSM K_{ATP}: in aortic smooth muscle isolated from Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice pinacidil- and glibenclamide-sensitive K_{ATP} currents are absent, whereas normal K_{ATP} currents are observed in smooth muscle myocytes from both Kir6.2$^{-/-}$ mice (54, 276, 391).

Again, however, the conclusion that the Kir6.1/SUR2B heteromultimer exclusively forms the ATP-sensitive K^+-channel in VSM, requires qualification. In addition to variations in the reported unitary conductances, a subpopulation of VSM K_{ATP} in portal vein exhibits spontaneous activity in excised membrane patches, and displays high sensitivity to inhibitory ATP ($K_{1/2\ ATP}$ = ~20 μM), and a unitary conductance (49 pS in external K^+ 60 mM) that is reminiscent of the cardiac K_{ATP} channel (Kir6.2/SUR2A) (65, 305, 408, 456). Thus it is reasonable to conclude based on the current dataset that while the Kir6.1/SUR2B channel represents the predominant VSM K_{ATP}, other subtypes are also likely to be expressed in specific vascular beds, separately or in combination with Kir6.1/SUR2B subunits (456), and contribute to overall contractility. As discussed below, the VSM K_{ATP} represents a clinically important target in the pharmacological control of vascular disease and diversity of subunit makeup provides scope for vascular bed-specific agents. Diazoxide, an activator of SUR2B-containing channels (267), has long been recognized as a potent hypotensive agent in treatment of both acute (7, 401, 417), and pregnancy-induced hypertension (257), and understanding the molecular diversity and differential expression of K_{ATP} subtypes will be important in further refining pharmacological approaches to target specific vascular beds and to treat hypertensive disorders (e.g. angina, hypertension, asthma)

Regulation of VSM K_{ATP} and implications for vascular tone

K_{ATP} channels are tonically active in many vascular beds, including the coronary (94, 96, 166, 351), and mesenteric circulation (121, 293), and hence play a role in establishing basal

tone in these vessels. This conclusion is based on the potent property of glibenclamide to depolarize and constrict isolated arteries (96, 121, 293, 351) and to increase coronary vascular resistance in perfused vascular beds under resting conditions *in vivo* (94, 175). Inhibition of the VSM K_{ATP} channel will cause membrane depolarization, a sustained rise in intracellular [Ca^{2+}] (through both Ca^{2+} influx and Ca^{2+} release from intracellular stores), a decrease in arteriole diameter and increase in vascular resistance (280, 281, 421). Conversely, activation of K_{ATP} channels leads to a lowering of intracellular Ca^{2+} levels, an increase in arteriole diameter and a decrease in vascular resistance (385, 435). Not surprisingly, the VSM K_{ATP} represents an important mediator in the vascular response of various pharmacological and endogenous factors (45).

Effects of endogenous vasodilators and vasoconstrictors on VSM K_{ATP}— Vasoactive factors modulate VSM K_{ATP} currents through activation of serine/threonine protein kinase pathways, including cAMP-dependent protein kinase A (PKA), Ca^{2+}- and phospholipid-dependent protein kinase C (PKC) (45), and possibly the cGMP-dependent protein kinase G (PKG) (334). Adenosine, released from cardiac myocytes during hypoxia/ischemia, was the first vasoactive factor shown to directly activate VSM K_{ATP} and to cause vasodilation through adenosine (A_2) receptor activation (34, 84, 85, 181, 210, 211, 272). Other endogenous vasodilators of note (Fig. 3) include the calcitonin-generated peptide (CGRP) released from sensory nerve endings (279, 293, 332, 429), β-adrenoreceptor agonists (208, 278, 291), vasoactive intestinal peptide (VIP) released from perivascular nerves, as well as nitric oxide (NO) (288) and the eicosanoid, prostacyclin (PGI_2), both released from endothelial cells (183, 234)(Fig. 3). Vasodilators that bind to G-protein (Gs)-coupled receptors (e.g. adenosine (A_2) receptor) activate intracellular adenylate cyclase (AC) leading to elevated cAMP levels, increased PKA activity, and direct phosphorylation and activation of the SUR2B-containing channel complex (336, 367). PKA-mediated phosphorylation of SUR2B occurs at three key residues (Thr633, Ser1387, and Ser1465) in the nucleotide-binding folds (NBF1, NBF2) and these modifications are postulated to enhance binding of stimulatory MgADP to the NBFs (336, 367). Biochemical studies on isolated basilar (brain) and coronary arterial smooth muscle utilizing membrane permanent cAMP analogues and PKA-specific modulators confirm a central role of the PKA-K_{ATP} axis in mediating the effect of endogenous vasodilators (208, 332, 429), although the physiologic action of vasoactive factors is complex and involves additional K_{ATP}-independent pathways. For example, vasorelaxation of basilar and mesenteric arterial smooth muscle by CGRP is only partially reversed by glibenclamide (~12–60% of the total current is glibenclamide-insensitive) (209, 259, 293, 332), and a separate study reports virtually no effect of glibenclamide on CGRP-induced vasodilation in coronary arteries (194). Nitric oxide (NO), which mediates its effect through the cGMP-PKG signaling pathway may cause activation of K_{ATP} in multicellular or intact systems (226, 288), although direct application of NO-donors to smooth muscle cells has no obvious effect (334), and direct evidence for phosphorylation of K_{ATP} by PKG is lacking.

Conversely, endogenous vasoconstrictors act, in part, by inhibiting K_{ATP} currents via the PKC signaling pathway (Fig. 3), as evidenced by the ability of vasoconstrictors to reduce pre-activated K_{ATP} currents, but not in the presence of PKC inhibitors (64). Vasoconstrictor agonists that target VSM K_{ATP} to promote contraction include the neurotransmitter serotonin (5-HT) (42, 211), the renal-derived angiotensin-II (150, 227, 280), endothelin-I from endothelium (124, 281, 288, 316, 317), and pro-inflammatory histamine released from mast cells (42, 211), among others (Fig. 3). Binding of vasoconstrictors to the G-protein coupled receptor subtypes, G_i or G_q, activates the PKC-ε isoform (150, 192, 352). In turn, PKCε-mediated phosphorylation of a serine-rich motif in the C-terminus of Kir6.1 (S354, S379, S385, S391, and S397) results in both decreased frequency of channel openings (366) and a caveolin-dependent internalization of the Kir6.1/SUR2B channel complex from the

plasma membrane (185, 353). The net effect of PKC-mediated decrease in K_{ATP} current (Fig. 3) is membrane depolarization and vasoconstriction (65, 335, 366, 402).

Notably, the inhibitory action of angiotensin-II on VSM K_{ATP} involves not only activation of PKC signaling, but also suppression of steady-state PKA activity (150), implying a potential crosstalk between the positive (PKA) and negative (PKC) branches of the protein kinase signaling pathways in net regulation of VSM K_{ATP} (Fig. 3). Finally, alternative signaling pathways can potentially regulate VSM K_{ATP} activity and thereby, modulate vascular tone. For example, the Ca^{2+}-dependent phosphatase type 2B (PP-2B), also known as calcineurin, inhibits K_{ATP} in isolated aortic smooth muscle under conditions of elevated intracellular Ca^{2+} (434). The exact mechanism of PP-2B action is unclear, but may involve dephosphorylation of PKA-mediated phosphorylation sites on the channel (228, 457). In addition, K_{ATP} in the retinal microvasculature is sensitive to the redox state of the cell, with oxidants from polyamine catabolism increasing K_{ATP} activity, and causing local vasodilation (176).

It is of course important to note that the integrated activity of all K^+-channels types (K_v, BK_{Ca}, K_{ir}) ultimately establishes the membrane potential of smooth muscle cells and, hence, the contractile state. Since the activity of other K^+-channels is modulated by endogenous vasoactive factors through PK-signaling pathways (e.g. Kv currents are inhibited by endothelin-I and angiotensin-II (PKC) (151, 213, 370), whereas BK_{Ca} channels are activated by NO (PKG) (345) and bradykinin (PKC) (118)), the net effect of PK modulation on VSM electrical activity will be complex.

Adenosine triphosphate; a passive or dynamic regulator of VSM K_{ATP} activity?—The hallmark of the archetypal K_{ATP} channel is inhibition by ATP and stimulation by MgADP through direct interactions with the Kir6.X and SUR subunits, respectively (298). With respect to the VSM K_{ATP}, intracellular nucleotides are clearly important in establishing the magnitude of K_{ATP}/K_{NDP} currents, since induction of hypoxia activates K_{ATP} currents and induces a pronounced vasodilatation of coronary arteries (85, 338, 394). The hypoxic effect is presumably a consequence of a lowered ATP/ADP ratio in the myocyte, and not necessarily secondary to release of vasoactive adenosine from the damaged cardiac tissue (85). Moreover, inhibition of metabolism with metabolic poisons (e.g dinitrophenol, cyanide and deoxyglucose), which lowers the ATP/ADP ratio, also activates whole-cell K_{ATP} currents in various smooth muscle cell-types as well as in transfected cells expressing reconstituted Kir6.1/SUR2B (32, 70, 85, 108, 376, 454).

Nevertheless, it remains unclear what the adenosine nucleotide levels are in the VSM myocyte and whether cellular metabolism changes sufficiently to dynamically regulate VSM K_{ATP} activity under physiological condition. We may speculate that ambient ATP and ADP levels establish a tonic level of VSM K_{ATP} activity upon which vasoactive factors act (295). In this way, the K_{ATP} channel will determine the basal tone by providing a steady ‘brake’ on contractility, the strength of which is determined by the ambient ATP/ADP levels (Fig. 3) (108). Vasodilators and vasoconstrictors will then act to either increase or decrease the strength of the K_{ATP} ‘brake’, and hence the contractile state. The net contractility at any time will therefore be a summation of both vasodilatator and vasoconstrictor inputs. In metabolically inhibited states, such as hypoxia or ischemia, a fall in the intracellular ATP/ADP ratio will cause a resetting of the K_{ATP} ‘brake’ to favor vasodilatation (this pathology would apply to renal (256), cerebral (46, 338), and pulmonary arteries (432) where K_{ATP} may not contribute to the basal tone but rather, the channel may serve a protective role by opening to promote vasodilation during severe hypoxia (59, 394, 432)). Thus, while the ambient [ATP]/[ADP] ratio may establish a background level of K_{ATP} activity, it may be the

vasoactive cues that dynamically regulate the magnitude of VSM K_{ATP} and, hence, the contractile state.

K_{ATP} in physiology and pathophysiology of vascular smooth muscle: Insight from genetically modified mice

Hypertension in K_{ATP} null mice—Mouse models in which the Kir6.1 and SUR2 genes have been 'knocked-out' highlight the critical role of K_{ATP} in the cardiovascular system, particulary in the coronary circulation (54, 276). The cardiovascular phenotypes of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice are similar (Table 1) and include baseline hypertension, coronary artery vasospasm and sudden cardiac death, with 50% of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice reportedly dying by approximately 6 and 27 weeks of age, respectively. Electrocardiograms from both animals show marked ST segment elevation and atrioventricular (AV) block, and which may account for the sudden death. Importantly, SUR2$^{-/-}$ mice treated with nifedipine (which inhibits the voltage-sensitive Ca^{2+}-currents downstream of K_{ATP}) exhibit a reduction in coronary artery vasospasm, implicating abnormally elevated $[Ca^{2+}]_i$ due to loss of hyperpolarizing K_{ATP} current as causal in the hypercontractility (54). Collectively, these K_{ATP}-null mice recapitulate the clinical features of the human disorder of Prinzmetal (or variant) angina, and predict that loss-of-function mutations in the VSM K_{ATP} may be disease-causing in humans (see below).

Vascular response to sepsis in K_{ATP} null mice—During infection, the normal host immune response includes cytokine-induced systemic inflammation, or sepsis (62, 389). To meet the increased energetic demands during septic shock, the cardiovascular system responds through coronary artery vasodilatation to increase coronary circulation and oxygen delivery to the heart. The altered response of Kir6.1$^{-/-}$ mice to induced endotoxemia (204) implicates the VSM K_{ATP} in this adaptive vascular response. When immuno-stimulated with the endotoxin lipopolysaccharide (LPS)(Table 1), Kir6.1$^{-/-}$ mice show a marked and persistent ST elevation (indicative of myocardial ischemic injury) a decrease in cardiac performance, and increased mortality, indicating that loss of VSM K_{ATP} predisposes Kir6.1$^{-/-}$ mice to a significant survival disadvantage. Importantly, administration of the K_{ATP} opener pinacidil (236) improves survivability in endotoxin-treated wild-type mice presumably by increasing coronary circulation, but has no effect on the survival rate in Kir6.1$^{-/-}$ mice.

A recent, unbiased screen of randomly ethyl-N-nitrosourea (ENU)-mutagenized mice for increased susceptibility to immunostimulatory agents has independently confirmed this critical role of Kir6.1 in mediating the vascular response to metabolic stress (74). Mutagenized mice with a loss-of-function mutation in Kir6.1 were identified based on their decreased survivability when challenged with mouse cytomegalovirus (MCMV) infection (74). In this same study, specific suppression of the SUR ortholog in Drosophila melanogaster by RNA interference similarly causes hypersensitivity to viral infection (74). It is intriguing to speculate that the baseline coronary vasospasm and sudden cardiac death in the initial studies of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice (54, 276) may also reflect an impaired adaptive response; in this case, to metabolic stress in the course of normal pathogen exposure.

Role of extra-smooth muscle K_{ATP} in the control of vascular tone—While the hypertensive phenotype of both Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice seemingly underscores the critical role of the VSM K_{ATP} in controlling vascular tone, particularly in the coronary arteries and arterioles, this conclusion requires qualification. In addition to smooth muscle, Kir6.1 transcripts are detected in heart, lung, brain, pancreas, and endothelium (451). Similarly, RNA transcripts for the SUR2 gene (*ABCC9*), which encodes the SUR2A and

SUR2B splice variants, are found in multiple tissues, including cardiac and skeletal muscle (SUR2A) (56, 167), brain (SUR2A) and endothelium (SUR2B), (178). Thus, the possibility exists that the cardiovascular phenotypes of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice reflect loss of K_{ATP} in both smooth muscle and non-smooth muscle tissues (124). A role for non-smooth muscle K_{ATP} in cardiovascular homeostasis is supported by the finding that targeted suppression of endothelial K_{ATP} (Kir6.1/SUR2B) by transgenesis results in an increase in coronary perfusion pressure and a decrease in coronary blood flow (184, 270, 451), a similar phenotype to that observed in Kir6.1$^{-/-}$ mice (276). Interestingly, release of the vasoconstrictor endothelin-1 is *increased* by transgenic suppression of endothelial K_{ATP}, potentially implicating an elevated level of circulating endothelin-1 as causal in the vasoconstriction. These studies raise the possibility of K_{ATP}-dependent paracrine signaling between endothelial cells and overlying vascular smooth myocytes, with the endothelial K_{ATP} regulating the release of endothelin-1, which then acts to inhibit the VSM K_{ATP}. At present, the mechanism by which endothelial K_{ATP} inhibits endothelin-1 release is unknown, although immunolocalization of the endothelial K_{ATP} (Kir6.1) to intracellular organelles may indicate a role in the exocytotic machinery on endothelin-containing vesicles (260).

Further support for a potential role of non-VSM K_{ATP} in regulation of vascular tone comes from additional mouse studies. Transgenic restoration of VSM K_{ATP} currents by specifically expressing the SUR2B isoform in VSM of SUR2$^{-/-}$ mice, does not resolve the coronary artery vasospasm, atrioventricular (AV) heart block, or sudden cardiac death exhibited by SUR2$^{-/-}$ animals (199). Although this result suggests the importance of a smooth muscle-extrinsic process, the conclusion must be tempered by inability to confirm the extent of the restored K_{ATP} activity, particularly in the microcirculation.

Taken together, the transgenic mouse studies implicate VSM K_{ATP} (Kir6.1/SUR2) as central in control of vascular tone, although K_{ATP} in other cells types, such as the brain and endothelium, may also contribute. Generation of additional mouse models of altered K_{ATP} in specific tissues will further help to define the interaction of non-vascular with vascular K_{ATP} in regulating vascular tone.

Cardiovascular disease and VSM K_{ATP}: Where are the K_{ATP} mutations?

Mutations in the pancreatic β-cell K_{ATP} channel (both the Kir6.2 and SUR1 subunits) underlie insulin secretory disorders in mice and humans (222). Heterozygous, activating mutations suppress glucose-induced insulin secretion from theβ-cell and give rise to neonatal diabetes, whereas inactivating mutations result in unregulated secretion and underlie the corollary disorder of congenital hyperinsulinism (CHI) (14, 135). This realization has led to a significant improvement in therapy options to treat insulin secretory disorders secondary to β-cell K_{ATP} mutations (320, 323). Given the high sequence and structural homology between Kir6.1 and Kir6.2 (75% amino acid identity), and assuming similar mutation rates at the respective gene loci (Kir6.2 on *11p15.1* (168) and Kir6.1 on *12p12* (104)), it is reasonable to predict that homologous mutations in Kir6.1 will occur naturally and cause pathology in humans. Specifically, based on the coronary artery hypertension and coronary vasospasm described for Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice (54, 276), loss-of function VSM K_{ATP} is predicted to underlie a Prinzmetal angina or similar phenotype in humans. Two recent genetic screens of Italian and Japanese cohorts diagnosed with impaired coronary vasoreactivity and coronary spastic angina (CSA), respectively, have failed to uncover associated Kir6.1 mutations (101, 404). However, the impact of the studies was limited due to the small sample size in each case (n=18–19 patients) and failure to screen SUR2 (*ABCC8*) for associated variants. The Kir6.1 and SUR2 genes are located on human chromosome 12p (104), and chromosome 12p recombination has been shown to underlie autosomal-dominant hypertension (25) and postural *hypo*tension is linked to

chromosome 12 (146). Again however, our recent analysis of Kir6.1 and SUR2 genes in a cohort of such patients failed to reveal any associate variants (99).

Nevertheless, there is increasing biochemical and genetic evidence linking the Kir6.1 and SUR2B isoforms with cardiovascular abnormalities, including *i*) association of a Kir6.1 variant (S422L) with ventricular fibrillation with prominent early depolarization (137), *ii*) a growth hormone-induced *hypo*tension is associated with upregulation of Kir6.1 and SUR2B transcript levels in rat aorta (403), *iii*) both Kir6.1 and SUR2B protein expression is reduced in aortas from obese hypertensive (106) and spontaneously hypertensive rats (41), which may contribute to the hypercontractility. Comprehensive assessment of VSM K_{ATP} as a risk or causal factor in cardiovascular disease will require both larger control-based studies with increasing power, as well as additional animal models of K_{ATP}-induced vascular disease in order to identify potentially affected cohorts.

K_{ATP} in visceral smooth muscle

K_{ATP} channels are also expressed in a variety of visceral (non-vascular) smooth muscle tissues, including gallbladder (458), stomach (180), esophagus (149), bladder (115), intestine (215), and uterus (254, 354). Although less well studied, the biophysical properties and physiology of visceral K_{ATP} generally parallel those of VSM K_{ATP}. As in the vasculature there is significant heterogeneity of K_{ATP} expression, with the predominant non-vascular K_{ATP} subtyperecapitulating the salient properties of the K_{NDP} channel, including a low unitary conductance (~40 pS), a requirement for NDPs for activation, and similar sensitivity to KCOs (pinacidil and diazoxide) (192, 215, 377, 397, 398, 453). In addition to Kir6.1 and SUR2B, urethral myocytes express the Kir6.2 and SUR1 isoforms (453), and there is evidence for heteromeric assembly of Kir6.1 with the Kir6.2 in a $(Kir6.1)_3$-$(Kir6.2)_1$ arrangement with channels exhibiting intermediate channel behavior (399). Colonic smooth muscle actually expresses Kir6.2 and SUR2B mRNA with no evidence for Kir6.1 transcript expression. A role for K_{ATP} in regulating basal tone in visceral smooth muscle is evidenced by the ability of glibenclamide to increase tone and cause depolarization in multiple tissues including trachea (289), airway (200), and urethra (396). Surprisingly, perhaps, there are no reports of non-vascular smooth muscle dysfunction (e.g. altered myometrial contractility during parturition, or nutrition deficits due to impaired gastrointestinal function) in either $Kir6.1^{-/-}$ or $SUR2^{-/-}$ mice (54, 276). Whether the lack of a phenotype reflects compensatory K^+-channel expression in non-vascular smooth muscle, or more subtle physiological consequences of K_{ATP} ablation, remains unclear.

Acknowledgments

In reviewing this broad topic of K_{ATP} in muscle, we have tried to comprehensively acknowledge recent advances, and to draw attention to major earlier studies, and to point to relevant earlier reviews. We would like to acknowledge the support of the National Institutes of Health (grants HL45742 and HL95010 to CGN), and American Heart Association (grant-in-aid to JCK), which have supported our own efforts in this field.

Prior to final acceptance of this manuscript, our co-author, colleague and friend, Joseph C. “Bo” Koster passed away, suddenly, unexpectedly and prematurely. In this final collaborative review effort, we wish to acknowledge his contribution to our lives, both professional and personal. Through his kindness, humor, and wisdom, Bo enriched our lives every day and he will be sorely missed.

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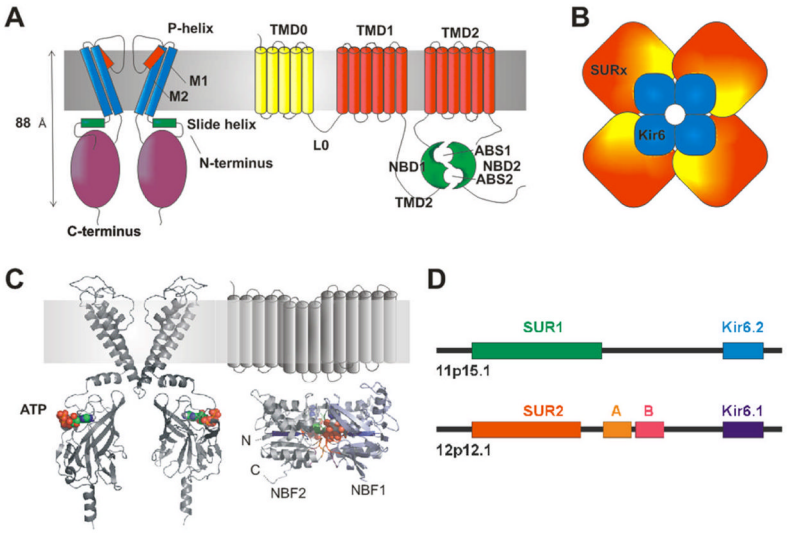

Fig. 1. The structural basis of K_{ATP} channel activity

(A) K_{ATP} channels are formed from Kir6 (left) and SUR (right) subunits. Kir6 consists of a tetrameric arrangement of subunits, each consisting of two transmembrane helioces (M1, M2) a pore-forming region (including the p-helix and selectivity fitler) and cytoplasmic N-temrinus (including the amphipathic slide helix) and C-terminus. SUR consists of the TM0 and L0 regions that interact with and mosulate gating of Kir6, followed by two additional 6-helix TM regions, each followed by a nucleotide binding fold (NBF). The two nucleotide binding folds come together to generate two nucleotide interacting sites at their interface. (B) The K_{ATP} channel is an octameric structure of Kir6 and SUR subunits. (C) Kir6 and SUR can be modeled on the structure of other prokaryotic and eukaryotic proteins. Such structures predict one ATP binding site at each of the Kir6 interfaces, and Mg-nucleotide binding sites in the dimeric NBF structures of SUR. (D) Human SUR and Kir6 gene structures indicate that each pair are located adjacent to each other on two chromosomes.

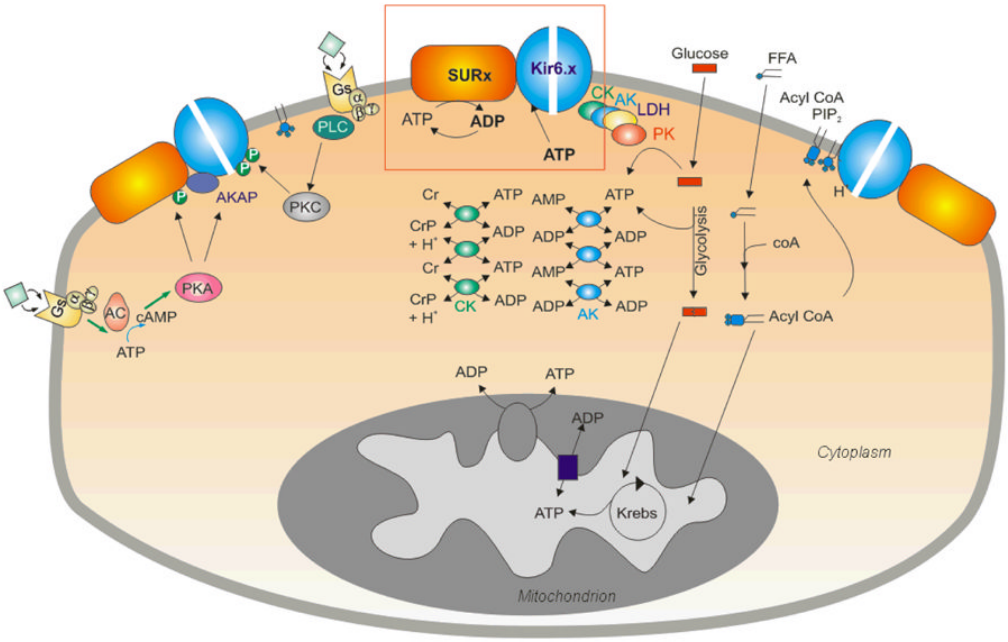

Fig. 2. Complexities of K_{ATP} channel regulation in striated muscle

The balance of ATP synthesis and usage, reflected by ATP and ADP levels, is the major direct determinant of channel activity (red box). Metabolic enzymes, including adenylate kinase (AK), creatine kinase (CK), and lactate dehydrogenase (LDH) in the cytoplasm and physically associated with the channel may serve to amplify metabolic changes, or locally buffer and control ATP/ADP levels, thereby fine tuning channel activity. Non-nucleotide ligands, including PIP2, acyl-coA and H^+ may also play a key role. PIP_2 and acyl CoAs have powerful stimulatory effects that are antagonistic to ATP inhibition. In addition, hormone receptor activation can lead to protein phosphorylation (P) with both stimulatory and inhibitory effects on the channel. However, none of these molecules acts in isolation and the resultant K_{ATP} channel activity is an integrated response to a myriad of interrelated metabolic signals.

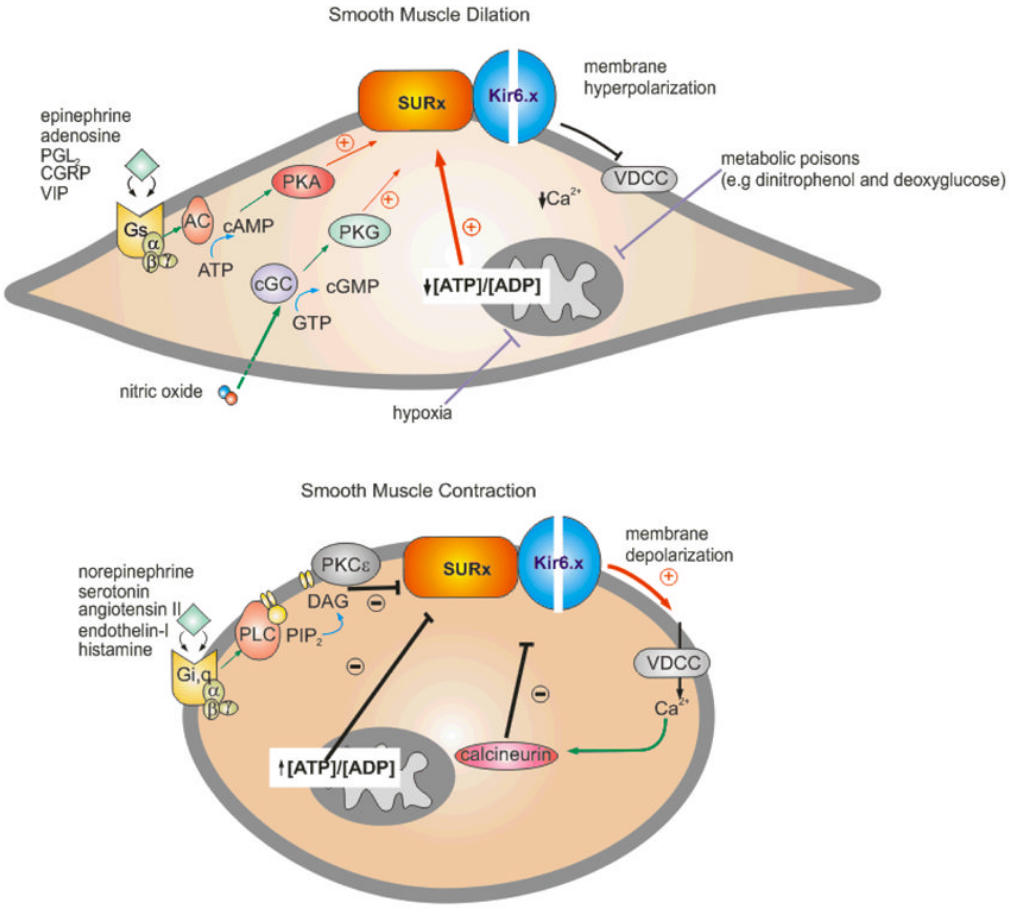

Fig. 3. Signaling pathways involved in regulation and modulation of the smooth muscle K_{ATP} channel

The K_{ATP} channel determines, in part, the membrane potential of the smooth muscle cell and, hence, the contractile state. Vasoactive factors that inhibit K_{ATP} activity cause membrane depolarization, activation of voltage-dependent Ca^{2+}-channels (VDCC), a rise in intracellular [Ca^{2+}] and smooth muscle contraction. Conversely, factors that activate K_{ATP} prevent the depolarization-dependent rise in [Ca^{2+}] and promote smooth muscle dilation. **(A)** Endogenous vasodilators, including epinephrine, adenosine, prostacyclin (PGI_2), calcitonin-generated peptide (CGRP), and the vasoactive intestinal peptide (VIP), stimulate K_{ATP} activity through the classic G-protein (Gs)/adenylate cyclase (AC)/protein kinase A (PKA) signaling pathway. Serine/threonine phosphorylation at several key residue in SUR2B (Thr633, Ser1387, and Ser1465) is thought to underlie channel activation. Conversely, nitric oxide activates K_{ATP} through the protein kinase G (PKG) signaling pathway. Hypoxia and metabolic poisons (dinitrophenol and deoxygluxose) indirectly activate K_{ATP} by suppressing oxidative phosphorylation, resulting in a decrease in the ATP/ADP levels. The K+-channel opener drugs (KCOs) (eg. pinacidil and diazoxide) promote their anti-hypertensive effects by opening vascular smooth K_{ATP} channels via interaction with the SUR2B subunit. **(B)** Vasoconstrictor agonists that target VSM K_{ATP} to promote contraction include the neurotransmitter serotonin (5-HT), angiotensin-II, endothelin-I, and the pro-inflammatory histamine. Binding of vasoconstrictors to the G-protein receptor subtypes, Gi or Gq, indirectly activates the PKC-ε isoform. In turn, PKCε-mediated phosphorylation of a serine-rich motif in the C-terminus of Kir6.1 results in a decrease in the frequency of channel openings. Ca^{2+}-activated calcineurin (phosphatase type 2B) inhibits

VSM K_{ATP} although the mechanism is unclear. Sulfonylurea compounds (e.g glibenclamide) induce vasoconstriction by binding to the SUR2B subunit causing K_{ATP} channel closure.

Table 1

Genotype-Phenotype Correlation in Genetically-Modified Mice with Altered K_{ATP} channel Function

Mouse genotype	K_{ATP} function	Early Death	Coronary spasm	Hypertension	Heart rate	Arhythmias	Major phenotypes	Citation
Whole-animal								
Kir6.2$^{-/-}$	Loss-of-function in striated muscle, neurons and β-cell	No	No	↔	↔	No	Insulin secretion impaired, Impaired cardiac and skeletal muscle stress response. Increased glucose uptake in sk. muscle, Increased exercise-induced fiber damage	(240, 250, 274, 275, 391, 392, 393, 400, 461)
Kir6.1$^{-/-}$	Loss-of-function in vascular smooth muscle	Yes	Yes	↔	↔	Yes	Coronary-vasospasm and premature death	(276)
SUR2$^{-/-}$	Loss-of-function in all muscle	Yes	Yes	↑	↔	Yes	Coronary-vasospasm and premature death, resistant to ischemia-reperfusion damage. Increased glucose uptake in sk. Muscle.	(54, 55)
SUR1$^{-/-}$	Loss-of-function in atrial muscle, neurons, and β-cell	No	No	↔	n.d.	No	Insulin secretion impaired, Loss of atrial K_{ATP} channels, Resistant to ischemia-reperfusion damage	(112, 371)
CMV-SUR2A	Gain-of-function in cardiac muscle	No	No	n.d.	n.d.	n.d.	Resistant to ischemic damage	(93)
Cardiac-specific transgene								
αMHC-Kir6.2[ΔN30,K185Q]	Reduced ATP-sensitivity and current density in cardiac muscle	No	n.d.	n.d.	↓	No	Remodeling of E-C coupling, ↑ I_{Ca}, ischemic preconditioning abolished	(111, 219)
αMHC-FLAG-SUR1	Reduced current density in heart	No	n.d.	n.d.	n.d.	Yes	PR prolongation	(113, 114)
αMHC-FLAG-SUR2A	Reduced current density in heart	No	n.d.	n.d.	n.d.	No	No significant physiological effect	(114)
αMHC-Kir6.2[ΔN30, K185Q] × αMHC-FLAG-SUR1	Reduced ATP-sensitivity and current density in cardiac muscle	Yes	n.d.	n.d.	n.d	Yes	Constellation of arrhythmias and premature death	(113)
αMHC- Kir6.2[ΔN30, K185Q] × αMHC-FLAG-SUR2A	Reduced ATP-sensitivity and current density in cardiac muscle	No	n.d.	n.d.	n.d	No	No significant physiological effect	(113)
αMHC-Kir6.1-AAA	Dominant-negative suppression in cardiac muscle	Yes	n.d.	n.d.	↑	No	APD prolongation, Premature death	(405)

Mouse genotype	K_{ATP} function	Early Death	Coronary spasm	Hypertension	Heart rate	Arhythmias	Major phenotypes	Citation
αMHC-Kir6.2-AAA	Dominant-negative suppression in cardiac muscle	Yes	n.d.	n.d.	↔	No	APD prolongation, Premature death	(405)
Vascular-specific transgene								
SM22-SUR2B/*SUR2*$^{-/-}$	Smooth muscle-restored expression in *SUR2*−/− mice	Yes	Yes	n.d.	↔	Yes	Coronary-vasospasm and premature death	(199)
Tek-Kir6.1-AAA	Dominant-negative suppression of endothelial K_{ATP}	No	Yes	n.d.	n.d.	n.d.		(260)