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# $K_{ATP}$ channels and cardiovascular disease: Suddenly a syndrome

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## Abstract

ATP-sensitive potassium ($K_{ATP}$ ) channels were first discovered in the heart 30 years ago[1]. Reconstitution of $K_{ATP}$ channel activity by coexpression of members of the pore-forming inward rectifier gene family (Kir6.1, *KCNJ8,* and Kir6.2 *KCNJ11*) with sulfonylurea receptors (SUR1, *ABCC8,* and SUR2, *ABCC9*) of the ABCC protein sub-family, has led to the elucidation of many details of channel gating and pore properties. In addition, the essential roles of Kir6.x and SURx subunits in generating cardiac and vascular $K_{ATP}$[2] and the detrimental consequences of genetic deletions or mutations in mice have been recognised[3]. However, despite this extensive body of knowledge, there has been a paucity of defined roles of $K_{ATP}$ subunits in human cardiovascular diseases, although there are reports of association of a single Kir6.1 variant with the J-wave syndrome in the electrocardiogram, and two isolated studies have reported association of loss of function mutations in SUR2 with atrial fibrillation and heart failure. Two new studies convincingly demonstrate that mutations in the SUR2 gene are associated with Cantu syndrome, a complex multi-organ disorder characterized by hypertrichosis, craniofacial dysmorphology, osteochondrodysplasia, patent ductus arteriosus, cardiomegaly, pericardial effusion, and lymphoedema. As we discuss, this realization of previously unconsidered consequences provides significant insight into the roles of the $K_{ATP}$ channel in the cardiovascular system and suggests novel therapeutic possibilities.

### Keywords

SUR2; Kir6.1; Kir6.2; Cantu; vasodilation; edema; arrhythmia

## $K_{ATP}$ channel structure and molecular regulation

Canonical $K_{ATP}$ channels are heterooctameric complexes of pore-forming Kir6 channel-forming subunits associated with regulatory SUR subunits, members of the ATP binding cassette (ABC) family of membrane proteins (Fig. 1). Two Kir6-encoding genes, *KCNJ8* (Kir6.1) and *KCNJ11* (Kir6.2)[4,5], and two SUR genes, ABCC8 (SUR1) and ABCC9 (SUR2)[5-7] encode mammalian $K_{ATP}$ subunits, but alternative RNA splicing can give rise to multiple SUR protein variants (e.g. SUR2A and SUR2B) that confer distinct physiological

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and pharmacological properties on the channel complex[8,9]. Interestingly (Fig. 1C), the genes for Kir6.2 and SUR1 are located next to each other on human chromosome 11p15.1[5] 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[7,10], implicating an evolutionary duplication. In heterologous expression systems, both Kir6.2 and SUR1 subunits co-assemble in a 4:4 stoichiometry[5] (Fig. 1A,B) to generate the functional $K_{ATP}$ channel[11-13]. Similarly, biochemical studies demonstrate that the SUR2 protein variants, SUR2A and SUR2B, can also coassemble with Kir6 subunits[4,14-16], presumably in a similar octameric arrangement.

Crystallographic studies of bacterial and eukaryotic Kir channels[17,18]] demonstrate a conserved architecture of Kir channels with two transmembrane helices (M1, M2) bridged by an extracellular loop that generates the narrow portion of the pore and controls ion selectivity (Fig. 1A). As with other ABCC family members, SURs contain two six-helix transmembrane domains, TMD1 and TMD2, but SURs also have an additional N-terminal TMD0 domain consisting of 5 transmembrane helices (Fig. 1A), critical for Kir6.x trafficking and gating[19]. SURs also contain one nucleotide binding fold (NBF1) between TMD1 and TMD2, and a second (NBF2) after TMD2 in the cytoplasmic loops (Fig. 1A). NBFs from bacterial ABC proteins crystallize as ‘head-to-tail’ dimers, and this is likely the functional arrangement between NBF1 and NBF2 in SUR (Fig. 1B)[20]. How the Kir6 and SUR subunits are physically connected remains unknown, but electron micrography and intersubunit FRET studies of complete $K_{ATP}$ complexes suggest an intimate packing of 4 SUR and 4 Kir6.x subunits[21,22] (Fig. 1A).

The key regulatory features of $K_{ATP}$ channels are rapid and reversible closure by cytoplasmic ATP, and activation by nucleotide tri- and diphosphates[20] (Fig. 1B). In the absence of other nucleotides, the free ATP concentration that causes half-maximal channel inhibition is in the micromolar range. Since cellular levels of cytosolic ATP concentration are in the millimolar range (1-5 mM) and change little with metabolism, [ATP] is probably always sufficient to almost fully inhibit channel activity. Channel activation then arises from the activating effects of Mg-nucleotides, particularly MgADP, on the SUR subunit[23]. Nucleotide regulation is probably the key molecular regulator of $K_{ATP}$ channel activities, although other second messenger systems and regulators[24] may be involved in control of channel activity and in causing channel-dependent pathologies.

## Cardiovascular tissue distribution of $K_{ATP}$ channel subunits

### Cardiac myocytes

Kir6.1 and Kir6.2, as well as SUR2A, SUR2B and SUR1, and additional potential splice variants of SUR1 and SUR2, are all expressed in the heart[4,25,26]. Given that any pair of SURx:Kir6.x tetramers can co-assemble when heterologously expressed[4,5], and that even within a single channel more than one SUR isoform or Kir6 isoform can coexist[27-32], determining the molecular makeup of the channel in specific cell types is a challenge. There is now good evidence that in mouse hearts, SUR1 and Kir6.2 are major constituents of the atrial myocyte sarcolemmal $K_{ATP}$, whereas SUR2A and Kir6.2 generate ventricular $K_{ATP}$[33,34]. However, in hearts of larger animals, including humans, both SUR1 and SUR2A subunits probably contribute to sarcolemmal channels in both atrial and ventricular myocytes[35] (Fig. 1D). The situation may be more complex in critical sub-regions of the heart, including nodal and conduction cells. $K_{ATP}$ channel currents have been detected throughout the pacemaking and conduction systems[36-38], but $K_{ATP}$ single channel conductances in rabbit SA node cells and mouse conduction cells may be smaller than in ventricular myocytes[36]. This suggests a possible role for Kir6.1 in generating the channel pore, yet sarcolemmal $K_{ATP}$ is abolished in Kir6.2$^{-/-}$ SA node cells[39] indicating a necessary

requirement for Kir6.2. The identity of the SUR component of $K_{ATP}$ in these tissues is unknown, although $K_{ATP}$ channels in these cell types do respond to the relatively SUR2-specific openers cromakalim and pinacidil, suggesting a major role for SUR2 in nodal $K_{ATP}$ channels[36-38].

### Smooth muscle myocytes

$K_{ATP}$ channel density is relatively low in vascular smooth muscle (VSM) compared to cardiac myocytes[40,41] and the biophysical and the pharmacological properties are quite variable, reflecting variable expression of $K_{ATP}$ subtypes in vascular beds[42-49]. There is considerable variation in reported single channel conductances[45,46,50-54], although low-conductance channels (unitary conductances from 20-50 pS) may represent the predominant $K_{ATP}$ channel subtype, with a more limited distribution of medium- and high conductance $K_{ATP}$ channels (50-70 pS and >200 pS, respectively)[55]. Importantly, and unlike classic $K_{ATP}$ channels of the heart[4,56] or pancreas[5,57], the predominant VSM $K_{ATP}$ conductances are inactive in isolated membrane patches, and require nucleotide diphosphates (ADP, UDP, GDP) in the presence of $Mg^{2+}$ to open, leading to their functional designation as 'nucleotide-dependent' $K^+$-channels, or $K_{NDP}$ channels[47,48,53]. Heterologously expressed Kir6.1/SUR2B channels recapitulate many of these biophysical properties of native VSM $K_{ATP}/K_{NDP}$[14,58-62]. 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 higher unitary conductance, reminiscent of Kir6.2/SUR2A-dependent $K_{ATP}$ channels[1,53,54,63]. Thus the Kir6.1/SUR2B channel may represent the predominant VSM $K_{ATP}$, but other subtypes are also likely to be expressed in specific vascular beds, separately or in combination with Kir6.1/SUR2B subunits[53] (Fig. 1D).

### Vascular endothelium

$K_{ATP}$ channels are also present in vascular endothelium[64] and, by regulating endothelial electrical activity, they may affect release of vasoactive agents that in turn modulate smooth muscle function. Activation by KCOs and inhibition by glibenclamide has been demonstrated in coronary endothelium[65] and in aortic endothelial cells[66,67]. The molecular composition of endothelial $K_{ATP}$ channels remains largely unknown, but the presence of Kir6.1, Kir6.2, and SUR2B mRNA in guinea pig[68] and in human coronary artery endothelial cells[65] suggests that all three subunits may be involved in channel generation in these cells.

### Mitochondrial $K_{ATP}$

A $K^+$-selective, small conductance channel was first identified in rat liver mitochondria[69], and reported to be reversibly inhibited by application of ATP, glibenclamide, and 4-aminopyridine (4-AP). These 'mito$K_{ATP}$' channels were inhibited by acyl-coA and activated by GTP, GDP and diazoxide[70,71]. The pharmacology of heterologously expressed SUR1/Kir6.1 complexes appears to most closely resemble such properties[72,73], yet 'mito$K_{ATP}$' function is apparently unaffected in both Kir6.1$^{-/-}$ and Kir6.2$^{-/-}$ animals[26,74] and efforts to determine whether specific SUR or Kir6 subunits are normally present in mitochondria have yielded inconsistent results[73,75-79].

Chutkow et al. generated a SUR2 'knockout' mouse in which the first nucleotide binding fold of SUR2 was disrupted by deletion of exons 12-16[80]. Experiments on these SUR2$^{-/-}$ mice revealed novel glibenclamide-insensitive channels in isolated sarcolemmal membrane patches, and antibodies raised against specific regions of the SUR2 protein suggested that the novel channels are formed of short SUR2 constructs that lack the first nucleotide binding fold (NBF1)[81,82]. Subsequent studies from the same group indicate that these proteins may be expressed in mitochondria[83], and that SUR2$^{-/-}$ mice are protected against myocardial infarction resulting from global ischemia (as we also reported for SUR1$^{-/-}$ mice[84]),

inconsistent with the generally accepted notion that opening of (SUR-dependent) sarcolemmal $K_{ATP}$ channels is a protective mechanism in ischemia. A later study from the group indicated that re-expression of full-length SUR2A improved recovery from ischemia[85], leading to the slightly convoluted argument that the improvement in the $SUR2^{-/-}$ animals over wild type is somehow the result of the short form SUR2 constructs. The possibility that these are increased in mitochondria might then explain improved mitochondrial energetics in these animals[86].

Lack of confirmed presence of canonical SUR or Kir6 subunits in mitochondria has led to alternative hypotheses regarding 'mito$K_{ATP}$' structure. In addition to opening $K_{ATP}$ channels, diazoxide may inhibit succinate dehydrogenase[87] and consistent with the idea that this key enzyme of both the Krebs cycle and electron transport chain might be a component of the 'mito$K_{ATP}$' channel, Ardehali and colleagues identified a macromolecular complex that recapitulated 'mito$K_{ATP}$' activity including diazoxide activation and 5-hydroxydecanoate inhibition[88,89]. The complex included succinate dehydrogenase, mitochondrial ATP-binding cassette protein-1 (mABC-1), ATP synthase, adenine nucleotide translocase, and phosphate carrier proteins, and it is not clear which component should be forming the channel pore, the reported records show only single channel activity over brief periods, and follow-up studies have not yet emerged.

Most recently, proteomic analysis of purified bovine mitochondrial inner membranes identified a short form (ROMK2) product of the KCNJ1 gene as containing an N-terminal mitochondrial targeting signal, and colocalization of a full-length epitope-tagged ROMK2 with mitochondrial ATP synthase β[90]. Additional experiments showed that tertiapin Q, a relatively specific ROMK blocker, inhibited functional assays of mitoK(ATP) activity in isolated mitochondria and inhibited the diazoxide-activated component of mitochondrial thallium uptake. While these studies await independent confirmation, they imply a role for ROMK2 (Kir1) subunits in generating the mito$K_{ATP}$ channel (Fig. 1D).

## $K_{ATP}$ and cardiovascular disease: The potential versus the genetic evidence

It has long been recognized that $K_{ATP}$ channels provide a very large potential ionic conductance in the surface membranes of cardiac myocytes, as well as vascular smooth muscle and endothelium, and perhaps in the mitochondrial inner membrane of many cells. Under normal metabolic conditions, cardiac sarcolemmal $K_{ATP}$ channels are predominantly closed, and they do not significantly contribute to cell excitability. However, these channels can open when exposed to a severe metabolic stress such as anoxia, metabolic inhibition or ischemia. In muscle cells, shortening the action potential reduces calcium entry and inhibits contractility[91], thereby reducing energy consumption, potentially protecting the cell. Such a preservation 'strategy' is of course self-limiting, since if too many myocytes stop contracting, the heart will stop pumping and the animal will die, but it has always been a reasonable, if unproven, notion that temporary protection of a small number of cells, or region of the heart, against the damage of Caoverload during ischemia, is likely to be operable.

In the vasculature, inhibition of $K^+$-channel activity will tend to cause depolarization of the membrane potential, activation of L-type voltage-sensitive $Ca^{2+}$-channels, $Ca^{2+}$-entry and vasoconstriction[92]. Conversely, activation of $K^+$-channels will lead to membrane *hyper*polarization, decrease in voltage-dependent $Ca^{2+}$-entry and vasodilation[92]. 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[93,94]. Endothelial cells lack voltage-dependent Ca channels and Ca entry through non-selective channels is enhanced at

hyperpolarized voltages, in contrast to 'excitable' cells[95,96]. Activation of $K_{ATP}$ channels will tend to hyperpolarize cells, leading to elevated $[Ca^{2+}]_i$, and elevated release of vasoactive agents, including EDHF and endothelin. Thus, gain- or loss-of $K^+$-channel activity in either smooth muscle or endothelium could have profound pro-relaxant or pro-constrictive effects respectively on smooth muscle tone, a point we return to below.

## Kir6 genes and disease

As discussed in detail below, genetic manipulation of $K_{ATP}$ genes in mice can result in dramatic cardiovascular pathologies, yet until recently there has been little evidence for human cardiovascular disease resulting from $K_{ATP}$ gene mutations (Table 1). *KCNJ11* encodes the predominant $K_{ATP}$ channel pore-forming subunit (Kir6.2) in both the pancreatic β-cell and in cardiac myocytes[97]. Gain- and loss-of function mutations in this gene are now very well understood to underlie neonatal diabetes and congenital hyperinsulinism, respectively[98], but there is no published evidence for any cardiac problems in these patients.

*KCNJ8* encodes Kir6.1, which is the main channel forming subunit expressed in smooth muscle and may also be expressed in some cardiac myocytes[97,99] (Fig. 1D). Several recent studies have reported a single mutation, S422L, in the Kir6.1 protein to be associated with the 'J-wave' phenomenon, characterized by abnormalities in the J-point of the ECG, and including Brugada syndrome (BrS) and early repolarization syndrome (ERS). First reported by Haissaguerre et al[100], J-point elevation in one patient with the S422L variant showed multiple (>100) recurrences of unresponsive ventricular fibrillation (VF), associated with accentuated early repolarization. Additional studies include that of Delaney et al[101] who reported two (out of 325) atrial fibrillation (AF) probands with early repolarization, that of Medeiros-Domingo et al[102], who reported one Brugada syndrome patient and one early repolarization syndrome patient carrying the same S422L variant out of 101 analyzed patients, and that of Barajas-Martinez et al., who reported 3 additional BrS and 1 ERS probands carrying the same variant[103]. The variant has not been identified in any control alleles. The latter two studies both reported enhanced channel activity for the S422L variant, arguing that gain-of-function in Kir6.1 channel activity is underlying the ERS and hence AF. Conversely, sequence analysis of DNA from necropsy tissue on 292 unrelated sudden infant death syndrome (SIDS) cases identified novel KCNJ8 variants in two individuals, an in-frame deletion (E332del) and a missense mutation (V346I), both in the distal C-terminus of Kir6.1. In this case, reduced channel activity was reported from recombinantly expressed mutant channels, leading the authors to conclude that loss-of-function mutations in Kir6.1may be one cause of SIDS[104], through as yet unexplained mechanisms.

## SUR genes and disease

*ABCC8* encodes SUR1, which is the predominant regulatory sulfonylurea receptor (SUR1) in the pancreatic β-cell and is also present in the heart, predominantly in atria in rodents[34], but potentially more widespread in humans[35]. Because of its involvement in the pancreatic $K_{ATP}$ channel, gain- and loss-of function mutations in this gene also underlie neonatal diabetes and congenital hyperinsulinism respectively, but again there is no report of cardiac problems in these patients[105-107]. *ABCC9* encodes the second SUR2 subunit, and this is likely to be the major SUR isoform in both cardiac and vascular muscle. There have been two reports of SUR2 loss of function mutations leading to cardiac disease, both from the group of Andre Terzic and colleagues[108,109] (Table 1). In each case, the mutations are present in the C-terminal exons and will lead to a disruption of the second nucleotide binding fold of SUR2A, and hence reduce nucleotide stimulation of channel activity, without affecting SUR2B. In the first report, the single patient with the mutation presented with long-standing atrial fibrillation originating in the vein of Marshall, with normal cardiac morphology and contractile features[109]. The patient was successfully treated by

radiofrequency ablation. In the second report, two individuals with two distinct mutations presented with heart failure due to idiopathic dilated cardiomyopathy[108]. There have been no subsequent reports of similar genetic defects in the intervening five years, and further evidence for causality of association of similar gene variants with disease in additional cases is lacking.

Two new papers reporting multiple different *ABCC9* mutations, all associated with Cantu syndrome, a distinctive multi-organ disease (Table 2), now provide a clear picture of associated outcomes, and open up multiple new avenues of investigation. The first study[110] involved genetic analysis of 14 individuals diagnosed with Cantu syndrome[111], and *ABCC9* coding mutations were identified in 11 of them. In six cases with no affected relatives, the mutations were *de novo.* Two families were also reported, one with an affected mother and two affected daughters, and one with an affected father and daughter, confirming that inheritance in this case is autosomal dominant. No analysis of recombinant channel function was made in this first study, but the conclusion that these mutations all lead to a gain-of channel function[112] is cemented by the second study[113], which identified *ABCC9* coding mutations in an additional 14 of 16 identified patients. In that study, recombinant expression of mutant channel proteins clearly demonstrated a reduced sensitivity to ATP inhibition in 3 example mutants which, as discussed below, will lead to enhanced $K_{ATP}$ channel activity wherever the channels are located.

## Cantu Syndrome: Multiple tissue symptoms

Cantu syndrome (MIM 239850), or hypertrichosis-osteochondrodysplasia-cardiomegaly syndrome, was first described in 1982[111]. Subsequent reports[112,114-121] have confirmed a constellation of features in ~30 patients (see Table 2). Congenital hypertrichosis is a constant feature, with thick scalp hair and excessive hair growth on the forehead, face, back and extremities. Generalized macrosomia is present in most cases, with large birth weights and lengths, although ultimate adult height is usually within the normal range. Macrocephaly is typically present at birth and usually persists. Multiple dysmorphic features (Table 2), including coarse facial appearance, skeletal abnormalities, and generalized osteopenia, as well as multiple additional clinical features have also been described. The cardiac features include cardiac enlargement, concentric hypertrophy of the ventricles, pulmonary hypertension and pericardial effusion. Yet, despite the enlargement of the heart with increased muscle mass, cardiac function is typically normal, with normal ventricular contractility on imaging studies[112]. Cardiac muscle biopsy in one patient showed mild myofibrillar disorganization but normal myofibers and mitochondria on electron microscopy, and in 2 other patients cardiac biopsy was reported as normal[112,122]. Pulmonary hypertension secondary to partial pulmonary venous obstruction has been reported in one case, and was associated with severe mitral valve regurgitation that spontaneously resolved[116]. Some patients have required pericardiocentesis and ultimately needed pericardial stripping to prevent reaccumulation of the pericardial effusion. A significant number of patients have had patent ductus arteriosus (PDA) requiring surgical closure, as well as bicuspid aortic valves with and without stenosis. Lymphedema involving the lower extremities may develop over time, and in one patient, lymphangiogram demonstrated dilated lymphatic vessels in the legs with delayed lymphatic drainage[123].

Diazoxide, minoxidil and other related drugs have been used since the 1960s to treat severe refractory hypertension. Multiple reports of side effects of these drugs also include pronounced hypertrichosis, pericardial effusions, and edema in treated patients[124] One report even noted coarsening of the facial features, reminiscent of Cantu syndrome, after 8 months treament with minoxidil[125]. It was subsequently recognized that one major action of minoxidil is opening of $K_{ATP}$ channels[97,126,127], and this led us to note the parallels between

the symptoms of minoxidil exposure and the features of Cantu syndrome, and to suggest the possibility that Cantu syndrome might be the result of K channel hyperactivity[112]. Teratogenic effects of minoxidil, including marked hypertrichosis, dysmorphic facial features and low blood pressure have been reported in the offspring of a minoxidil-treated mother[128]. In additional reported cases of minoxidil teratogenicity, one infant had transposition of the great vessels and pulmonary bicuspid valvular stenosis leading to neonatal death, and another infant had hypertrichosis that resolved over the first 3 months of life[129].

The two recent papers that describe specific mutations in the ABCC9 gene in a total of 25 of 31 Cantu syndrome patients[110,113], definitively link the gene defect to the syndrome. All reported patients had the typical Cantu syndrome phenotype (Table 2), but 6 of 31 patients had no identifiable ABCC9 mutation suggesting that additional gene defects may be involved. Previous studies of Cantu syndrome patients have provided no definitive explanation of the underlying cause of the various features, and even now the realization of SUR2 mutations as causal does not immediately provide explanations for all features. There is strong evidence discussed below, for a physiologically important role of SUR2 in vascular relaxation, such that persistence of the PDA in Cantu syndrome patients may be readily explained as a consequence of maintained vessel dilation following birth. Patency of the ductus arteriosus is controlled by many factors, the most important of which are relatively low fetal oxygen tension, prostaglandin [PGE2] and prostacyclin [PGI2]) in the fetus. After birth, the abrupt increase in oxygen tension and falling PGE2 and PGI2 levels lead to inhibition of voltage-gated K channels and contraction of the smooth muscle fibers in the ductus, resulting in wall thickening and lumen obliteration. Mechanisms of persistent PDA are not clear[130], but the enhancement of a K current in smooth muscle presents an obvious potential explanation in Cantu syndrome patients. Altered vascular tone may also underlie the edema and pericardial effusion, but the reason for cardiomegaly is not obvious. Cardiomegaly reported in most cases of Cantu Syndrome is due to increased myocardial mass (hypertrophy) with larger cardiac chambers but with normal systolic function, and this does not fit the diagnostic criteria of dilated or hypertrophic cardiomyopathy[131]. As we reported, cardiomegaly in two related Cantu syndrome cases has been associated with high output failure[112] and may well be a secondary response to reduced vascular tone[132]. Similarly, the reason for osteochondrodysplasia and facial dysmorphology is not obvious and the mechanism by which minoxidil causes hair growth has remained controversial[133]. It has been speculated that by opening vascular K channels and dilation of blood vessels, the supply of oxygen, blood and nutrients to the hair follicle is increased, which cause follicles in the telogen phase to shed and be replaced by new thicker hairs in a new anagen phase. However, there is also evidence that SUR2 isoforms are present in follicular dermal papillae[134] and while the new realization definitively ties the hair growth to an action on $K_{ATP}$ channels, it does not immediately prove where the action is.

## Cardiovascular disease and $K_{ATP}$ mutations: Insights from genetically modified animals

### Kir6.2 and SUR1 knockout animals exhibit complex cardiac phenotypes

Murine knockout models of each of the four $K_{ATP}$ channel genes have been generated and extensively analyzed. Knockout of Kir6.2 results in a loss of glucose-dependent insulin secretion, modeling features of hyperinsulinism in humans[135]. Knockout of SUR1 reiterates essentially the same phenotype as Kir6.2$^{-/-}$, and again the major effects are in the pancreas. Conversely (see next section), knockout of Kir6.1 or SUR2 leads to a vascular phenotype, presumably due to loss of $K_{ATP}$ channel activity in either vascular smooth muscle or endothelium[136,137].

Cardiac sarcolemmal $K_{ATP}$ channels are 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[138]. Accordingly, while Kir6.2 is the major cardiac Kir6 isoform, baseline ventricular action potential duration (APD) and contractile function are unaffected in isolated ventricular myocytes from Kir6.2$^{-/-}$ animals[74,139,140]. When metabolism is inhibited, the action potential can shorten markedly and contraction can be inhibited as a result of $K_{ATP}$ activation[91,141,142]. $K_{ATP}$ activation during ischemia is likely to be cardioprotective, since reduction of APD and 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 increases cellular ATP and energy stored as creatine phosphate[143]. AP shortening is absent in Kir6.2$^{-/-}$ hearts, and the time to contractile failure is prolonged but the time to onset of rigor contracture is reduced[74]. Diastolic $Ca^{2+}$ overload, myocardial damage, and increased mortality are also observed in isoproterenol challenged Kir6.2$^{-/-}$ myocytes[144]. In addition to highlighting the acute protective effect of $K_{ATP}$ activation, Kir6.2$^{-/-}$ animals show increased mortality and exaggerated hypertrophy in response to pressure overload[145,146], and to mineralocorticoid/salt challenge[147]. Together, these studies suggest that loss of $K_{ATP}$, by stopping the protective 'unloading' that $K_{ATP}$ activation leads to, should tend to cause Ca overload and perhaps hasten the transition to heart failure under stressed conditions. However, two further studies seem to contradict a cardioprotective role. In these studies, from independent groups, both SUR2- (SUR2$^{-/-}$) and SUR1-knockout (SUR1$^{-/-}$) mice were found to be more tolerant of global ischemia-reperfusion than control mice, with reduced infarct sizes[84,148]. Since the SUR2$^{-/-}$ mice have a marked reduction of ventricular sarcolemmal $K_{ATP}$ channels, the enhanced cardioprotection is opposite the expected phenotype (i.e. impaired protection). Cardioprotection in SUR2$^{-/-}$ mice might conceivably be due to the concomitant loss of the SUR2B component of vascular $K_{ATP}$ channels, but similar cardioprotection in SUR1$^{-/-}$ mice[84] could not be explained by such a mechanism.

As noted above, no cardiac problems have been reported for individuals with loss of function (LOF) or gain of function (GOF) mutations in Kir6.2 or SUR1, who suffer from profound pancreatic problems (hyperinsulinism or neonatal diabetes, respectively). In this regard, the lack of dramatic effects in both Kir6.2$^{-/-}$ and $K_{ATP}$ overactive hearts (see below) is consistent and, while it still does not answer the question of why this large potential conductance is present in the heart, it really does seem to tell us that change of sarcolemmal $K_{ATP}$ channels may not be so critical.

## Kir6.1/SUR2 knockouts highlight vascular roles

Mouse models in which the Kir6.1 and SUR2 genes have been 'knocked-out' highlight the critical role of these subunits in the cardiovascular system, particularly in the coronary circulation[26,137]. The cardiovascular phenotypes of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice are similar, and include baseline hypertension, coronary artery vasospasm and sudden cardiac death. Electrocardiograms from both animals show ST segment elevation and atrioventricular (AV) block, which may account for the sudden death. Importantly, SUR2$^{-/-}$ mice treated with the Ca channel blocker nifedipine 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[137]. Collectively, these $K_{ATP}$-null mice recapitulate clinical features of the human disorder of Prinzmetal (or variant) angina, but several studies have failed to demonstrate any association of human coronary vasospasm or hypertension with LOF mutations in Kir6.1 or SUR2[149,150], even though linkage analysis indicates that there are associated genes within the same locus as Kir6.1 and SUR2[151].

Kir6.1 transcripts are detected in heart, lung, brain, pancreas, and endothelium[152] and SUR2 transcripts are found in multiple tissues, including cardiac and skeletal muscle (SUR2A)[4,7], brain (SUR2A) and endothelium (SUR2B),[60]. Thus, the possibility exists that the cardiovascular phenotypes of Kir6.1$^{-/-}$ and SUR2$^{-/-}$ mice (or of Cantu syndrome patients), reflect loss (or gain) of $K_{ATP}$ in smooth muscle or other tissues[153]. 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[64,68,152], a similar phenotype to that observed in Kir6.1$^{-/-}$ mice[26]. 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[65]. 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. Transgenic restoration of VSM $K_{ATP}$ currents by specific expression of 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[154], providing further support for a potential role of non-VSM $K_{ATP}$ in regulation of vascular tone.

### Transgenic $K_{ATP}$ GOF models

Given that sarcolemmal $K_{ATP}$ channels are normally predominantly closed, we have long argued that gain-of-function mutations are as likely, if not more likely, to be key drivers of human disease as loss of function mutations[155]. To that end, we have generated multiple GOF mouse models. The first, modeling Kir6.2 GOF clearly revealed the potential for such GOF mutations to cause neonatal diabetes[156] and led to the subsequent demonstration that such mutations are indeed causal in human neonatal diabetes[157]. In parallel studies, we have explored the potential for Kir6.2 GOF action in the heart, with considerably less emergent clarity[158-160]. Although we introduce channels that are very ATP-insensitive, they still remain closed under all but extreme circumstances, and cause no overt malfunction, mirroring the human Kir6.2 GOF condition – neonatal diabetes with no cardiac phenotype[160]. Curiously, we find that in ventricular myocytes from these animals there is a dramatically enhanced Ca current,[158] which may be some compensatory response to an initial or local action potential shortening, and conceivably might be related to ‘high output’ heart failure that is seen in Cantu syndrome. These studies also reveal that overexpressing the SUR1 isoform the myocardium has an effect to prolong the PR interval[161], and that when Kir6.2 GOF is expressed together with SUR1, second and third degree AV block, progressing to ventricular and supra-ventricular arrhythmias and sudden death follows[161]. This is accompanied in some cases by cardiac hypertrophy and in the most extreme cases, causes cardiac malformation at the very earliest stages of embryonic cardiac development[162]. In recombinant channels, SUR1-dependent channels are more sensitive to metabolic activation than SUR2A-dependent channels[163], and we conclude that these pathologies are reflecting channel overactivity in some critical, but as yet unidentified, time-window or region of the heart. These results highlight that $K_{ATP}$ overactivity in heart muscle can certainly be structurally and functionally detrimental, and may be modeling some of the cardiac consequences of SUR2 overactivity in Cantu syndrome, although cardiac hypertrophy and failure in Cantu syndrome patients is not obviously accompanied by arrhythmias or other cellular defects.

Following the same rationale of exploring GOF models, we have embarked on generation of a series of Kir6.1 and SUR2 GOF transgenic animals. Expression of Kir6.1 gain-of-function mutants in smooth muscle leads to a reduction of systolic and diastolic blood pressures (Li, A., Koster, J.C., Knutsen, R. and C.G. Nichols, unpublished), paralleling the effects of

KCOs in human hypertensive patients. Conceivably, further study of these animals, as well as of SUR2 GOF transgenic animals will reveal additional features that model Cantu syndrome effects and permit testing of novel therapeutic approaches.

## Potential for therapeutic modulation of cardiovascular $K_{ATP}$ activity

There is tremendous potential for modulation of $K_{ATP}$ channel activity in general and more importantly perhaps, in a tissue-specific manner, since there is already a rich pharmacology, not only of channel inhibitors but also channel openers (KCOs). KCOs have been used in two major clinical settings: (1) to block insulin secretion in conditions of hyperinsulinema, and (2) as antihypertensives. So far, clinical use of sulfonylureas has been limited to treatment of type 2 diabetes, and there has been debate about negative cardiovascular effects.

Minoxidil is reportedly the most active KCO at causing human hair growth, hence its commercial use in topical hair restoration products[164,165], and as discussed above, it appears that most, if not all, of the effects of Cantu syndrome are replicated by high dose minoxidil, including hypertrichosis, facial dysmorphology, and pericardial effusion[128]. Such features have been reported for other KCOs; there is one report of pericardial effusion as a result of diazoxide therapy[166] and although not attributed to the drug by the authors, another reported case of a patient on diazoxide who suffered from a pericardial effusion[167]. Interestingly, a clinical trial for the use of nicorandil, as a SUR2A specific activator, in the setting of acute MI actually reported lower rates of pericardial effusion than in untreated patients[168].

Although there are certain dogmas in the literature regarding specificity of KCOs or inhibitors, careful binding analyses performed on cloned SURs have revealed complexities of binding and dependence on nucleotides which makes it difficult to predict ***in vivo*** efficacies at different SUR targets. In addition, it is very clear from intact cell and excised patch-clamp recordings that the ability of KCOs to activate $K_{ATP}$ channel currents, depends critically on the metabolic state of the intracellular milieu, making direct comparison between different studies difficult[169]. The ability of diverse KCOs to lower blood pressure is well recognized, leading to their clinical use in acute and refractory hypertensive settings. Sulfonylureas inhibit $K_{ATP}$ channels and have seen very widespread use as glucose lowering agents in the type 2 diabetes. There is a wide therapeutic range, and the main recognized side-effect is hypoglycemia, but there is a long-standing debate as to potential cardiovascular side-effects. $K_{ATP}$ channel inhibitory drugs have not reached clinical acceptance in the cardiovascular arena, the expectation being that blockade of cardiac $K_{ATP}$ channels may be detrimental in conditions of myocardial ischemia, during which these channels can open and are presumed protective as discussed above. This debate is still not resolved[170,171].

Given the new realization of the SUR2-dependent basis of Cantu syndrome, the opportunity immediately presents itself for the use of $K_{ATP}$ channel inhibitors as a potential ‘magic-bullet’ therapy, as they have proven in the treatment of Kir6.2- or SUR1-dependent neonatal diabetes[172]. It is generally accepted that most sulfonylureas are physiologically more potent inhibitors of SUR1-dependent $K_{ATP}$ than SUR2A-dependent channels, although there has been no careful comparison of effect on SUR1-versus SUR2B-dependent channels. There has been a long-standing dogma that the drug HMR1098 is a cardiac specific $K_{ATP}$ blocker[173-176], although several studies including our recent direct head-to-head comparison confirm that it is also a more effective blocker of SUR1-dependent than SUR2A-dependent $K_{ATP}$ channels[34,177,178]. Relative efficacies of HMR1098 versus sulfonylureas in specific physiological conditions may be important to understand, since it is conceivable that specific $K_{ATP}$ inhibitors may counteract the symptoms of Cantu syndrome, without significantly

affecting blood glucose control, a key issue if $K_{ATP}$ channel inhibition is to be a viable treatment for the disease.

## Further implications and future prospects

In spite of almost 30 years of research, we have remained 'largely in the dark regarding the true physiological determinants, and relevance of sarcolemmal $K_{ATP}$ activity'[179], until very recently. We now realize that the subunit make-up of sarcolemmal $K_{ATP}$ channels can be far more complex and labile than originally thought[16], and together with the existence of mito$K_{ATP}$, it may be reasonable to consider $K_{ATP}$ channels as a family of channels[180]. The details of the involvement of sarcolemmal versus mitochondrial $K_{ATP}$ channels in cardiovascular physiology and pathology remain unclear, but the growing association of Kir6.1 and SUR2 variants with specific electrical and contractile derangements and the new clear association with a complex syndrome firmly establish the importance of appropriate activity in normal function of the heart and vasculature. In addition to consideration of potential therapeutic implications of these new findings, we can also consider the broader mechanistic implications. As discussed above, key features of Cantu syndrome are consistent with activation of SUR2B-dependent $K_{ATP}$ channels in the vasculature, leading to vasorelaxation. In this case, the likely associated Kir channel subunit is Kir6.1 (Fig. 1D) and we might reasonably suggest that GOF mutations in Kir6.1 should also be associated with these, if not all, symptoms of Cantu syndrome, paralleling the similar neonatal diabetic phenotypes of Kir6.2 and SUR1 GOF mutations. A purported GOF Kir6.1 mutation is already associated with the J-wave syndrome[100-103], and this leads to a clear inconsistency: neither J-wave abnormalities nor other arrhythmias have been reported in Cantu syndrome patients, and none of the Cantu syndrome features have yet been reported for ERS patients. It remains conceivable that Cantu syndrome features are not due to enhanced cell membrane $K_{ATP}$ activity, but instead are the result of Kir6-independent – i.e. mitochondrial - SUR2 activity. Also unexplained thus far is how opposing effects of LOF mutations[108,109] versus GOF mutations[110,113] in SUR2 could give rise to myocardial electrical derangements in the former case, but vascular derangements in the second.

Finally, we should recognize that the monogenic disease-associated $K_{ATP}$ mutations, which cause relatively severe changes in channel function, are likely to represent only the 'tip of the iceberg' when it come to the disease-promoting effects of change in protein activity. Further studies of patients with some or all symptoms of Cantu syndrome will be facilitated by efforts to bring such patients together (www.cantusyndrome.org) and will no doubt reveal new mutations in the $K_{ATP}$ subunits and perhaps in proteins that regulate $K_{ATP}$ synthesis, trafficking, or location. We do not yet know which of the Cantu syndrome features are the most penetrant, and hence which of these features might appear in isolation, as the severity of the effect of a specific mutation is reduced. If one or other of the affected cardiovascular functions is the most sensitive to SUR2 GOF, then we may find far more cases of individuals with GOF variants linked to specific features such as PDA, pericardial effusion, and cardiomegaly with or without high output cardiac failure. It may require the detection of these patients with newer cardiac imaging modalities such as strain imaging to study the heterogeneity of myocardial fiber mass and orientation, or to detect abnormal electrical activation sequences at subclinical levels that may exist with SUR2 GOF mutations. We are only just beginning to recognize the cellular control mechanisms that regulate $K_{ATP}$ channel subunit synthesis, trafficking and degradation[181]. Any alterations in such mechanisms, whether genetic or environmentally based, may also give rise to disease phenotypes similar to those resulting from the mutations discussed above, and may ultimately benefit therapeutically from the unique pharmacology of the sulfonylurea receptors.

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## Non-standard abbreviations

| | |
|---|---|
| **$K_{ATP}$** | ATP-sensitive potassium channel |
| **ABC** | ATP-binding cassette family of proteins |
| **KCNJ** | Inward rectifier K channel gene family |
| **Kir1, Kir6** | Pore-forming subunits of KATP channels |
| **M1, M2** | transmembrane helices of Kir6 subunits |
| **TMD1, TMD2** | Transmembrane domains of SUR subunits |
| **NBF1, NBF2** | Nucelotide binding folds of SUR subunits |
| **FRET** | Fluorescence resonance energy transfer |
| **VSM** | Vascular smooth muscle |
| **mito$K_{ATP}$** | Mitochondrial KATP channel |
| **mABC-1** | mitochondrial ATP-binding cassette protein-1 |
| **ROMK** | protein product of the KCNJ1 gene |
| **BrS** | Brugada syndrome |
| **ERS** | Early repolarization syndrome |
| **AF** | Atrial fibrillation |
| **APD** | Action potential duration |
| **LOF** | Loss of function |
| **GOF** | Gain of function |
| **AV** | Atrioventricular |
| **KCO** | Potassium channel opener |

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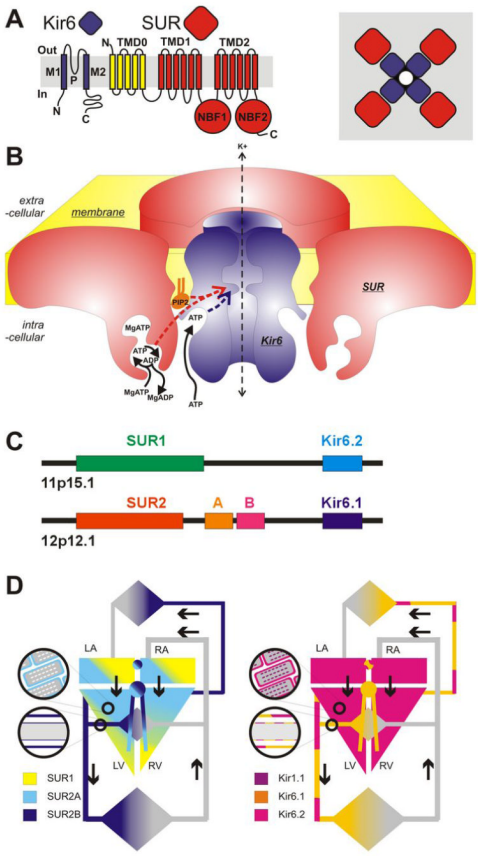


**Fig. 1.**

Cardiovascular $K_{ATP}$ channels (A) Kir6 subunits generate the channel pore, SUR subunits serve the regulatory role, each channel being a functional octamer of 4 Kir6 subunits and 4 SUR subunits. (B) The metabolically controlled gate of the channel is located at the cytoplasmic end of the inner cavity. ATP binds to Kir6 subunits and this provides the energetic push to channel closure. MgATP binds to the ATP-binding sites (ABSs) formed at the NBF1-NBF2 interface on SUR subunits. ATP hydrolysis results in a conformational 'activated' state that is transduced to 'over-ride' ATP inhibition. The 'activated state' persists through ADP dissociation, and can be maintained by ADP rebinding. In addition, PIP2 interaction at a site near the ATP inhibitory site also provides an energetic pull to open channels, and sulfonylureas (SU) or K channel openers (KCO), interacting with the SUR subunit within the membrane, respectively cause channel closure or opening. (C) Human $K_{ATP}$ gene structure. ABCC8 (SUR1) and KCNJ11 (Kir6.2) are immediately adjacent on chromosome 11p, whereas ABCC9 (SUR2) and KCNJ8 (Kir6.1) are immediately adjacent on chromosome 12. (D) $K_{ATP}$ channel subunit distribution in the cardiovascular system.

## Table 1

REPORTED ASSOCIATION OF DISEASE WITH $K_{ATP}$ CHANNEL MUTATIONS

| Gene | Clinical condition | Features | # of affected individuals | Refs |
|---|---|---|---|---|
| ***KCNJ8*** **(Kir6.1)** | J-wave syndrome | S422L mutation. Reportedly gain-offunction (GOF). Abnormalities in the Jpoint of the ECG, and including Brugada syndrome (BrS) and early repolarization syndrome (ERS), including VF and AF | 9 | 100-102 |
| | SIDS | In-frame deletion (E332del) and lossof-function mutation (V346I). through as yet unexplained mechanisms. | 2 | 104 |
| ***KCNJ11*** **(Kir6.2)** | Neonatal diabetes | Multiple GOF mutations cause inhibition of insulin secretion. No cardiovascular phenotype | >100 | 182 |
| | Type 2 diabetes | E23K variant, mild GOF, associated with T2DM, and potentially associated with HF | 30% Caucasians | 183-188 |
| | Congenital hyperinsulinism | LOF mutations cause hypersecretion of insulin. No cardiovascular phenotype | >10 | 98,182 |
| ***ABCC8*** **(SUR1)** | Neonatal diabetes | Multiple GOF mutations cause inhibition of insulin secretion. No cardiovascular phenotype | >100 | 182 |
| | Congenital hyperin | Multiple LOF mutations cause hypersecretion of insulin. No cardiovascular phenotype | >100 | 98,182 |
| *ABCC9 (SUR2)* | AF | Isolated case of LOF mutation assicated with AF originating in the vein of Marshal | 1 | 109 |
| | Idiopathic dilated cardiomyopathy | Two cases with distinct LOF mutations associated with heart failure due to idiopathic dilated cardiomyopathy | 2 | 108 |
| | Cantu syndrome | GOF mutations associated with complex multi-organ disease (See Table 2) | 25 | 110,113 |

**Table 2**

MAJOR CLINICAL FEATURES OF CANTU SYNDROME

| |
|---|
| **Neonatal Features** |
| Neonatal macrosomia |
| History of maternal polyhydramnios |
| Macrocephaly |
| Occasional slow postnatal growth and short stature later in life |
| **Craniofacial dysmorphology** |
| Coarse facial appearance (can be confused with a storage disoder) |
| Epicanthal folds |
| Broad nasal bridge |
| Anteverted nostrils |
| Long philtrum |
| Wide mouth with full lips |
| Macroglossia |
| High or narrow palate |
| Gingival hyperplasia |
| Anterior open bite |
| **Hair** |
| Congenital generalized hirsutism |
| Thick scalp hair |
| Thick and/or curly eyelashes |
| Excessive hair growth on forehead, face, back and limbs |
| **Cardiovascular** |
| Cardiomegaly |
| Concentric hypertrophy of the ventricles |
| Normal ventricular contractility |
| Pericardial effusion |
| Pulmonary hypertension |
| Partial pulmonary venous obstruction |
| Mitral valve regurgitation |
| Congenital anomalies |
| Patent ductus arteriosus |
| Bicuspid and/or stenotic aortic valve |
| **Skeletal abnormalities** |
| Thickened calvarium |
| Narrow shoulders and thorax |
| Pectus carinatum |
| Broad ribs |
| Platyspondyly and ovoid vertebral bodies |
| Hypoplastic ischium and pubic bones |
| Erlenmeyer-flask-like long bones with metaphyseal flaring |

| |
|---|
| Narrow obturator foramen |
| Coxa vara |
| Scoliosis |
| Osteopenia |
| Delayed bone age |
| Hypoplastic ischium and pubic bones |
| Erlenmeyer-flask-like long bones with metaphyseal flaring |
| Narrow obturator foramen |
| Coxa vara |
| Scoliosis |
| Osteopenia |
| Delayed bone age |
| **Skin and joints** |
| Loose and/or wrinkled skin, especially in neonates |
| Deep palmar and plantar creases |
| Persistent fingertip pads |
| Hyperextensibility of joints |
| **Lymphatic system** |
| Lymphedema, onset usually in adolescence or adulthood |
| **Gastrointestinal** |
| Pyloric stenosis |
| Increased risk for upper gastrointestinal bleeding |
| **Other reported features** |
| Immune dysfunction or recurrent infections |
| Umbilical hernia |
| Renal anomalies |
| Genital anomalies |