ATP-sensitive potassium channels and their physiological and pathophysiological roles

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Running Head: ATP-sensitive potassium channels

Abstract

ATP sensitive potassium channels (K_{ATP}) are so named because they open as cellular ATP levels fall. This leads to membrane hyperpolarisation and thus links cellular metabolism to membrane excitability. They also respond to MgADP and are regulated by a number of cell signalling pathways. They have a rich and diverse pharmacology with a number of agents acting as specific inhibitors and activators. K_{ATP} channels are formed of pore-forming subunits, Kir6.1 and Kir6.2, and a large auxiliary subunit, the sulphonylurea receptor (SUR1, SUR2A and SUR2B). The Kir6.0 subunits are a member of the inwardly rectifying family of potassium channels and the sulphonylurea receptor is part of the ATP binding cassette family of proteins. Four SURs and four Kir6.x form an octameric channel complex and the association of a particular SUR with a specific Kir6.x subunit constitutes the K_{ATP} current in a particular tissue. A combination of mutagenesis work combined with structural studies has identified how these channels work as molecular machines. They have a variety of physiological roles including controlling the release of insulin from pancreatic β cells and regulating blood vessel tone and blood pressure. Furthermore, mutations in the genes underlie human diseases such as congenital diabetes and hyperinsulinism. Additionally, opening of these channels is protective in a number of pathological conditions such as myocardial ischaemia and stroke.

Didactic Synopsis

Major teaching points

- ATP-sensitive potassium channels (K_{ATP}) are widely distributed and characteristically are activated by falling cellular ATP levels.
- K_{ATP} channels link membrane excitability to cellular metabolism.
- K_{ATP} channels have a rich and diverse pharmacology with specific inhibitors such as glibenclamide and openers such as diazoxide.
- The channel is an octamer formed of four inwardly rectifying potassium channels of the Kir6.0 family and four sulphonylurea receptor subunits, a member of the ATP binding cassette family of proteins.
- Extensive mutagenesis experiments and recent structural studies have defined many aspects of how the channel works as a molecular machine.
- K_{ATP} channels are key to the release of insulin from pancreatic β cells.
- K_{ATP} channels in the heart are involved in adaptation to exercise and cellular protection and in vascular smooth muscle controlling vascular tone and blood pressure.
- K_{ATP} channels are present in the brain and may be involved in neuroprotection and nutrient sensing.
- Mutations in K_{ATP} channel subunits can result in human disease and includes disorders of insulin handling, cardiac arrhythmia, cardiomyopathy and neurological abnormalities.

Introduction

Potassium conductances in cell membranes ~~play an important role~~ are important in determining membrane potential and in excitable cells in shaping repetitive firing and action potential characteristics. Opening potassium channels hyperpolarises the membrane potential towards the potassium equilibrium potential and can lead to repolarisation of an action potential. A number of families of potassium channel are distinguished by their electrophysiological properties with even greater molecular diversity underpinning these functional attributes (182; 251; 455).

One such family of potassium channel are the ATP-sensitive potassium (K_{ATP}) channels. The fundamental property of K_{ATP} channels is that they open in response to metabolic challenge, specifically a fall in ATP and\or a rise in ADP. They are widely found in a number of tissues. They have been described in cardiac myocytes (391; 544), pancreatic β cells (9; 88; 446), skeletal muscle (498), neurones (18; 154), smooth muscle (38; 500), the kidney (234) and epithelial cells (296; 297). They thus link cellular metabolism to membrane excitability. In one of the early reviews before the molecular identity of the channels was determined a number of different families were distinguished based on ATP sensitivity (15). In this review we consider only those channels constituted of Kir6.0 subunits with the exception of the mitochondrial K_{ATP} channel. For example, it is now known that in kidney tubules, where the channels are sensitive to ATP inhibition, albeit to mM ~~ATP~~ concentrations, the pore-forming subunits are likely constituted of Kir1.0 subunits (223).

Biophysical and physiological properties

The K_{ATP} channel is considered to be a member of the inwardly rectifying family of potassium channels. Inward rectification refers to the fact that this class of channel passes more inward current at potentials negative to the potassium equilibrium potential whilst less

current is passed at membrane potentials positive to that. Thus the driving force for the current is determined by the difference between the membrane potential and the potassium equilibrium potential and not simply the membrane potential as with voltage-gated potassium channels (192). However, the degree of rectification can vary substantially and is relatively weak for K_{ATP} channels compared to other members of the inward rectifier family such as those responsible for the cardiac current, I_{K1}. Thus, in single channel studies from inside-out patches in ~140 mM symmetrical potassium concentration the single-channel conductance is ohmic with a conductance of 50-80 pS (88; 391; 446). In contrast, in cell-attached patches there is significant inward rectification largely accounted for by voltage-dependent block by magnesium ions (142; 143). Figure 1 shows some typical single-channel recordings of K_{ATP} channels. Lower values reported in some papers have asymmetric potassium concentrations often with one or both concentrations significantly lower than the above. The channel is highly selective for potassium over sodium ions with a permeability ratio of P_{Na}/P_K~0.01 (499). Like all potassium channels, ion conduction is likely best modelled using multi-ion conduction models which entail multiple potassium ions binding within the pore and ion-to-ion repulsion ensuring high transport rates and selective binding (222; 421; 499). Indeed, we now have crystal structures of a number of potassium channels which identify multiple potassium ion binding sites and reveal how selectivity over the smaller sodium ion is achieved (see below). Models of ion conduction now use molecular dynamics simulations with these actual structures.

Opening of an inward rectifier potassium channel is largely thought to influence the resting membrane potential buffering it close to the potassium equilibrium potential. However in cells with a high intrinsic potassium permeability the major effects may be on repolarisation. In addition, K_{ATP} channels are weak inward rectifiers and Kir6.1 containing channel complexes may actually have a degree of outward rectification even in whole cell

recording with relatively physiological solutions (20; 22).

The direct response of the channel to adenine nucleotides can be assessed best in inside-out patches and subsequent measurement of the change in open probability with bath perfusion, equivalent to the cytosol, of different nucleotide containing solutions. Channel activity is inhibited by ATP with a K_i in the range of 10-500 μM with a Hill coefficient between 1 and 2 (11; 88; 256; 446; 499). There are variations according to the tissue and exact recording conditions with pancreatic channels being more sensitive than cardiac ones (11; 256). The inhibitory effect is not reliant on magnesium ions and ATP can be substituted with non-hydrolysable derivatives (10; 547). Furthermore adenine dinucleotides can inhibit channel activity in magnesium free solutions (144). In early single-channel formulations of gating kinetics at least a single open and two closed states were necessary to describe the open and closed time distributions. The channel conforms to "bursting" behaviour with bursts of opening separated by long closed intervals (446; 499). ATP promotes channel inhibition by decreasing the number of opening per burst, shortening the length of the burst, increasing the length of closed times and decreasing the open time (499). The main feature affecting open probability is the increase in long closed times. ADP is able to relieve the inhibition of K_{ATP} channels by ATP. The action is distinct from that of ATP inhibition as it requires MgADP (144; 303). More recent gating models have attempted to integrate key features revealed from cloning and functional work into more structurally realistic schemes. For example, an allosteric model has been proposed based on the tetrameric pore structure with four ATP binding sites (129; 130).

These properties apply to most of the well-studied and known K_{ATP} channel populations. However, smooth muscle K_{ATP} channels have unique properties. Specifically, the single-channel conductance is lower at ~35 pS and there is an absolute dependence for activity on cytosolic nucleotide diphosphates being present in the solution and this has led to

the channel being designated a "K_{NDP}" current in some of the literature (38). Furthermore, these channels are generally less sensitive to ATP inhibition (38; 101).

Rundown of K_{ATP} channels was noted even in the earliest publications. This refers to a steady decrease in channel activity in excised patches or whole-cell recordings. The channel activity can be refreshed to some extent by exposure to low μM concentrations of MgATP (145; 394). In early studies this was attributed to direct protein kinase regulation of the channel. However it is now known that channel activity is absolutely dependent on the provision of the anionic phospholipid phosphatidylinositol (4,5) bisphosphate (PIP_2) for activity (37; 132; 220; 484).

The pharmacology of K_{ATP} channels

K_{ATP} channels have a diverse pharmacology with both inhibitors and activators of the channel described. In addition, therapeutic agents often developed with another target or use in mind can have off-target effects on K_{ATP} channels. Figure 2 summarises the structures of some select drugs that modulate K_{ATP} channels. Table 1 summarises the properties of key potassium channel openers and inhibitors.

Sulphonylureas and related agents

The hypoglycaemic effects of sulphonylureas were discovered by chance when investigating their potential antibacterial action against typhoid fever. Since then a number of derivatives have been synthesised (Figure 2 and Table 1). They act by inhibiting K_{ATP} channels present in the pancreatic β cell leading to the depolarization ~~of pancreatic β cells~~ and increase in intracellular calcium levels resulting in the release of insulin (185).

A number of developments were made in generating sulphonylureas or sulphonylurea-related agents. In the first generation they have relatively low affinity and include drugs such

as tolbutamide and chlorpropamide. The second group have a higher affinity and include agents such as glibenclamide, glipizide and gliclazide. Finally, a new generation of agent have emerged, the "glinides" including meglitinide and repaglinide and these resemble the non-sulphonyurea component of glibenclamide. The affinity of the pancreatic K_{ATP} channel for glibenclamide is high enough ~~so~~ that equilibrium radioligand-binding studies can be performed (389).

Although the main target of these drugs is the pancreatic K_{ATP} channel, earlier sulphonylureas also interact with cardiac channels and may lead to undesired cardiovascular side effects such as increased cardiovascular mortality in patients with type II diabetes (170). Recent developments in sulphonylurea chemistry have led to the synthesis of new derivatives that show tissue-specific selectivity. For example, the sulphonylurea HMR-1098 shows 400-800 fold selectivity for the cardiac K_{ATP} over the pancreatic K_{ATP} channel (338). In comparison, the benzoic acid derivative insulin secretagogue mitiglinide has a 1000 fold greater affinity for the pancreatic over the cardiac and smooth muscle K_{ATP} channels (430).

Two novel but selective non-sulphonylurea K_{ATP} channel inhibitors are the compounds PNU99963 and PNU37883A. They were initially developed as potentially selective agents for the vascular channel. PNU99963 is a cyanoguanidine similar to pinacidil whilst the PNU37883A is a morpholinoguanidine (233; 278; 350). In the initial characterisation of these agents it was shown that PNU99963 and PNU37886A inhibited dilation of blood vessels induced by various potassium channel openers (233; 278; 350). Electrophysiological studies showed PNU37883A at low micromolar concentrations inhibited K_{ATP} currents in single vascular smooth muscle cells but not currents in cardiac and skeletal myocytes (568). Subsequent molecular studies revealed that PNU99963 interacted with high nanomolar affinity with the sulphonylurea receptor whilst PNU37883A was a direct pore-blocker and showed some selectivity to Kir6.1-containing channel complexes (100; 289).

Potassium Channel Openers

Pharmacophores of widely different structures are able to activate K_{ATP} channels and lead to hyperpolarization and reduced electrical activity. These include; diazoxide (benzothiadiazines), minoxidil (pyrimidine sulfate), nicorandil (pyridyl nitrates), cromakalim (benzopyrans), aprikalim (carbothiamides) and pinacidil (cyanoguanidines) (Figure 2) (337). Initially these drugs were developed on the basis of their ability to relax smooth muscle in low (up to 20 mM) but not high (>50 mM) potassium containing external media and ~~the ability~~ to stimulate potassium flux (89; 419). A comprehensive study was performed to compare their capacity to dilate smooth muscle in various tissue types. The conclusions were that diazoxide has lower dilator potency in comparison to rilmakalim in aorta, coronary artery and trachea, and nicorandil shows higher tissue selectivity to aorta than trachea (337).

Differences in the pharmacological properties of the K_{ATP} openers were also observed in clinical settings and in *in-vivo* studies using animal models. Diazoxide was found to be a hypotensive agent, to promote hyperglycaemia (450; 576) and have a cardioprotective effect through its anti-ischaemic properties (169; 564). Nicorandil, used to treat patients with angina, has a dual pharmacological effect acting both as a cardiac K_{ATP} channel opener and at the same time being a nicotinamide nitrate derivative as a NO donor (226; 295; 514). In contrast, pinacidil fails to reverse glibenclamide-induced hypoglycaemia in rats (78) but shows a potent hypotensive effect in man (53; 63; 369; 565).

Radioligand-binding has allowed the study of the molecular interaction of potassium channel openers with the K_{ATP} channel providing further information on the differences in their binding sites and tissue-specific selectivity. Examples include an analogue of pinacidil ([3H] P 1075), which can be radiolabelled (52). [3H] P 1075 binds with high affinity to cardiac K_{ATP} but not to pancreatic K_{ATP} and its binding is inhibited by glibenclamide (137;

551). These observations were consistent with normoglycaemia on the administration of pinacidil in the intact animal. The detailed pharmacology of potassium channel openers acting on the K_{ATP} channel are summarised in Table 1.

Miscellaneous agents

K_{ATP} channels like many other potassium channels are blocked by the generic agents barium, tetraethylammonium and 4-amino-pyridine (15; 516). They most likely act by directly occluding the pore. A number of clinically used drugs may actually exert some of their therapeutic effects through K_{ATP} channel modulation. For example baclofen is a muscle relaxant primarily used to treat spasticity in multiple sclerosis and stroke. It also has an antidepressant effect. In mice, co-administration of low doses of glibenclamide with baclofen showed a synergistic antidepressant-like effect in the forced swimming test and a low dose of cromakalim inhibited these effects suggesting that baclofen has an antidepressant action through its inhibition on K_{ATP} channels (376). The anticonvulsant drug carbamazepine used for treating epilepsy can inhibit K_{ATP} channel activity by disrupting the response to MgADP (613). Moreover, a number of drugs that display anticonvulsant properties in animal models may exert their effects through K_{ATP} channels. Examples include the inotropic calcium sensitizers levosimendan (183), glycolytic inhibitor 2-deoxy-D-glucose (594), K^+-sparing diuretic riamterene (594), hypnotic agent zolpidem (469) and fatty acid caprylic acid (472) though the mechanisms are complex and mostly seem to be indirect in nature. Another interesting example is the anticonvulsant and analgesic gabapentin which decreases [3H]-noradrenaline release from rat hippocampal and human neocortical slices. This effect can be mimicked by pinacidil, and antagonized by glibenclamide and suggests an involvement of K_{ATP} channels. As a drug to treat nerve pain, using an inflammatory pain model in diabetic rat, glibenclamide blocked the gabapentin-induced antinociception (492). Other classes of

drug may also be able to inhibit K_{ATP} channels such as phenformin but not metformin (21). Rosiglitazone may also have an off target inhibitory effect which shows selectivity for the vascular channel and acts through the pore-forming subunit (601; 602).

Cloning and isoform distribution

The inwardly-rectifying family of potassium channels were cloned using expression cloning techniques (223; 293) and this then led to additional homology based approaches and the description of a substantial gene family and multiple members in various subfamilies (386). The Kir subunits have two transmembrane domains with an intracellular N and C-terminus and assemble as a tetramer. An H5 segment intercalates into the membrane and contains a consensus motif (GYG or GFG) responsible for potassium selectivity (535). However when expressed alone none of the isolated cDNAs robustly recapitulated the properties of K_{ATP} channels. Using classic protein purification based on sulphonylurea binding activity, a second and distinct class of protein was isolated namely the sulphonylurea receptor (SUR) (1). The breakthrough then came when SUR1 was coexpressed with Kir6.2 and this led to currents that recapitulated many of the properties of the native pancreatic β cell K_{ATP} channel (241; 454). Further cloning efforts revealed two isoforms of Kir6.0 (Kir6.1 and Kir6.2) and two SURs (SUR1 and SUR2 with two splice variants SUR2A and SUR2B) (240; 247; 587) (Inagaki et al., 1996; Isomoto et al., 1996; Yamada et al., 1997). SUR is a member of the superfamily of ATP binding cassette (ABC) proteins and is related to the subfamily which includes multidrug resistant-related proteins (219; 539). They are classified into the ABCC family and have seventeen transmembrane segments grouped into three domains comprised of five (TMD0), six (TMD1) and six (TMD2) membrane spanning helices respectively. The N-terminus is extracellular, each of these domains are connected by cytosolic linkers and then an intracellular C-terminus (87). Another distinctive feature is the

presence of nucleotide binding domains (NBD) with Walker A and Walker B motifs in the TMD1-TMD2 linker and C-terminus. These domains generally bind and hydrolyse adenine nucleotides and in multidrug resistant-related proteins enable the active transport of drugs and other molecules out of the cell (318). The genes encoding SUR1 and Kir6.2, and SUR2 and Kir6.1 are adjacent to one another on 11p15.1 and 12p12.1, respectively in the human genome (76; 242). Kir6.1 (KCNJ8, gene ID: 3764) has five exons, Kir6.2 (KCNJ11, gene ID: 3767) has three exons, SUR1 (ABCC8, gene ID: 6833) has 39 exons and SUR2 (ABCC9, gene ID: 10060) has 42 exons. Alternative splicing is best established for SUR2 which generates two variants SUR2A and SUR2B differing in the sequence of the terminal C-terminus (240). Other splice variants in SUR1 and SUR2 have been proposed but their importance isn't clearly established (131; 196; 417). Four Kir6.0 subunits and four SUR subunits come together in a hetero-octamer to form the basic channel complex (83; 487). Figure 3 shows a cartoon and schematic of K_{ATP} channel assembly.

The properties of the current are determined by the assembly of a particular SUR with a Kir6.0 subunit. So for example, the channel present in pancreatic β cells is almost certainly constituted of SUR1\Kir6.2. This generates a channel with a single-channel conductance of 70 pS, a K_i for ATP inhibition in the 10-30 μM range and inhibition by tolbutamide (1; 12; 377; 454). In contrast, Kir6.1\SUR2B may underlie the K_{ATP} current in many smooth muscles and this leads to a single channel conductance of 35 pS, an absolute requirement for adenine nucleotides for activation and activation by levcromakalim (101; 587).

The octameric structure means that heteromultimeric populations might occur, combining different Kir subunits and different SUR subunits. In heterologous expression systems the co-assembly of Kir6.1 and Kir6.2 can be readily demonstrated (99). Furthermore, it might also occur in native tissues such as endothelial cells, some smooth muscles and the cardiac conduction system (31; 525; 600). In contrast we and others have been unable to

conclusively demonstrate heteromultimeric populations of SUR subunits (172; 542) whilst other laboratories have data demonstrating this might be a possibility (70). In practice this is likely to be less of an issue as the expression of SURs is more tissue-specific and co-expression of different subunits in the same cell is more limited. Secondly, the composition of the channels may show subtle but important anatomic variations. Indeed, single neurons within a defined brain region may have specific expression of different SUR subunits which leads to differences in metabolic sensitivity (319).

K_{ATP} channel trafficking, assembly and association with auxiliary proteins

The discovery that co-expression of two subunits was necessary to fully reconstitute the channel and that expression of the Kir6.0 alone did not lead to substantive currents led to the question of why this occurred. The two possibilities are that the subunits are present at the plasma membrane but functionally inactive or alternatively the assembly of SUR with the Kir6.0 subunit is necessary for the channel complex to traffic through the secretory pathway. The first clue to the answer to this question came with studies showing that truncation of the C-terminus of Kir6.2 by 36 amino acids led to the expression of an ATP-sensitive potassium selective current with the characteristic single channel conductance of ~ 70 pS (548). Co-expression of SUR was necessary to endow the channel with sulphonylurea and diazoxide sensitivity and activation by MgADP (548). Other investigators then identified an RKR motif in both Kir6.0 ~~subunits~~ and SUR subunits that behaved as an endoplasmic retention\retrieval signal (605). The mutual masking of these signals between each Kir6.0 and SUR subunit is thought to allow only mature octameric channels to progress through the secretory pathway and enter the plasma membrane. The arginine based retention\retrieval motif recognises coat protein I complexes and this vesicle population is involved in retrograde transport from the golgi to the endoplasmic reticulum (604). Furthermore, this interaction is antagonised by

interaction with 14-3-3 proteins and also by phosphorylation by protein kinase A (7; 218).

A second and related question raised by the cloning work was which domains were responsible for the assembly of the K_{ATP} channel complex? In the inward rectifier family it seems the M2 transmembrane domain and proximal C-terminus are important with contributions from the N-terminus (535; 546; 579). Furthermore, essentially all regions in inward rectifiers have been implicated in the interaction with SUR (173; 465). Finally it appears the TMD0 region is important for the assembly of SUR with the Kir6.0 subunits (66). Many of these studies were subsequently supported by the solution of the recent crystal structures as discussed below.

In addition to the obligatory co-assembly of SUR and Kir6.0 subunits, it is also apparent that K_{ATP} channels may assemble with other auxiliary proteins. In the first studies investigators focused on specific proteins and were able to show interaction of K_{ATP} channels with adenylate cyclase (64), creatinine kinase (95), lactate dehydrogenase (94), various glycolytic enzymes (115; 225), syntaxin-1A (409), exchange proteins directly activated by cAMP (402) and Ankyrin (282). In more recent work using modern proteomic techniques and co-purification strategies a number of proteins were isolated from cell lines of heart tissue, endothelial cells, pancreatic β cells and the brain (277). A bioinformatics analysis revealed enrichment of proteins involved in metabolic processes, in particular glycolysis, but also fatty acid metabolism particularly in the heart and in proteins involved in endocytic and membrane trafficking (277). Specifically for the proteins involved in trafficking association was shown with cytoskeletal proteins (non-muscle myosins, F-actin capping proteins, dynein etc) and endosomal trafficking checkpoints (various ras related proteins and ADP ribosylation factors etc) (277). It is interesting that these interactions may explain some functional observations. For example, it is known that K_{ATP} channels in ventricular myocytes are preferentially modulated by ATP derived from glycolysis (566). Furthermore, the pancreatic βcell K_{ATP}

channel is subject to endocytosis and this leads to changes in the membrane current-density (336). Finally, drugs that disrupt the cytoskeleton can change the functional behaviour of K_{ATP} channels (164).

K_{ATP} channels as molecular machines

This topic can be viewed at a number of different levels of sophistication. Initially the questions of conduction, gating and drug binding were approached using biophysical models. However after the cloning of potassium channel genes, numerous studies were undertaken in which single amino acids were mutated or domains were swapped between different channels using standard molecular techniques. The mutated and\or chimaeric channels and subunits were then expressed in heterologous expression systems such as *xenopus laevis* occytes or mammalian cell lines and studied using two-electrode voltage-clamp and patch-clamp. The functional consequences could then be interpreted in an attempt to define binding sites. Ultimately these experiments would be optimally complemented by high resolution structural information. Recently, this aspiration has culminated in three land mark publications (305; 310; 342) and these have superseded lower resolution structures (353). Figure 4 and 5 show structures obtained in these studies. Most work has focussed on pancreatic (SUR1) and cardiac (SUR2A) channels with Kir6.2 constituting the pore-forming subunit.

Ion conduction

Kir6.1 and Kir6.2 contain a GFG motif in the H5 domain which is a recognised variant of the classic K^+ channel selectivity sequence GYG (212). Whilst there have been only a few direct studies of ion permeation in K_{ATP} channels it seems likely it will follow the general principles developed from the study of other potassium channels using mutagenesis and structural studies. In particular the latter has been revolutionary in developing our

understanding (118; 298). The technical breakthrough, allowing the production of large quantities of protein in bacteria suitable for protein purification and crystallisation, came from the use of prokaryotic ion channels. In the crystal structures of KcsA and KirBac1.1 the channel contains a number of binding sites for potassium. The ion is complexed by the backbone carbonyl groups of the amino acids of the potassium channel signature sequence (VGYG) acting to replace the water molecules that the potassium ion would normally complex with if it were in solution. The structure is rigid and will not accommodate the smaller sodium ion in an energetically favourable position (118; 298) and this steric factor accounts for the exquisite potassium selectivity. Furthermore in the KcsA structure four helix dipoles further stabilise potassium ions in the central channel cavity. The KcsA channel likely represents an open conformation whilst the KirBac1.1 structure is closed. In the latter the pore is closed shut on the cytosolic side by hydrophobic residues (phenylalanine 146 in KirBac1.1) at the end of the second transmembrane segment also labelled as the inner helix in the crystal structures. The crystal structure of the pancreatic K_{ATP} (Kir6.2\SUR1) channel has been solved to 5 to 6 angstrom resolution (305; 310; 342). The structure of Kir6.2 closely resembles that of KcsA and the structure of the eukaryotic Kir3.2 (570). The pore is closed at the cytoplasmic face by the inner helices and outer helices forming a critical constriction (305; 310; 342; 570). Thus the mechanism of potassium selectivity and pore gating are likely to be broadly similar to that in other potassium channels.

Although K_{ATP} channels do not show pronounced inward rectification, it is instructive to look at the molecular basis for why this is the case. Inward rectification arises from voltage-dependent block by cytosolic magnesium and cellular polyamines i.e. as the membrane voltage becomes more depolarised these species are increasingly driven into the pore but are unable to permeate and this leads to occlusion of ion flow (329; 330; 385). The block by polyamines is extremely high affinity and practically it is very difficult to “wash

off" these molecules even when recording in inside-out patches. This accounts for what was previously ascribed to be an "intrinsic" gate. Site-directed mutagenesis revealed that acidic amino acids such as aspartate and glutamate in the second transmembrane segment and the proximal C-terminus act as two potential key binding sites (140; 329; 332; 501; 596). In the crystal structure these acidic amino acids form two rings of negative charge, one within the membrane and the other in a C-terminal cytosolic extension of the transmembrane domains (298). K_{ATP} channels show little sensitivity to polyamines (588) and this is likely accounted for by not having acidic residues in homologous positions to those in the strong inward rectifiers. For example, in Kir6.2 the M2 transmembrane residue is a neutrally charged asparagine and not a negatively charged aspartic acid.

Inhibition by ATP

The central defining property of K_{ATP} channels is the inhibition of channel gating by cytosolic ATP. This property is determined by residues in the pore-forming Kir6.0 subunit and was revealed using a C-terminal deletion mutant of Kir6.2 that was able to express at the plasma membrane ~~of the cell~~ in the absence of the sulphonylurea receptor (see above) (548). In inside-out patches the mutant had an IC_{50} (the concentration at which activity is inhibited by 50%) for inhibition by ATP of ~100 μM. However the sulphonylurea receptor is not without some role as expression with SUR1 decreases the IC_{50} to ~ 10 μM indicative of an allosteric effect (548). Co-expression of Kir6.2 with SUR2 does not result in this change in IC_{50}. Generally Kir6.1 is not thought to be as ATP-sensitive though it can be shown under specific experimental conditions (24; 101). Furthermore, both Kir6.1 and Kir6.2 containing channels are activated by metabolic challenge (134). Site-directed mutagenesis in the C-terminal deleted Kir6.2 was then used to define key residues influencing K_{ATP} channel inhibition by ATP and thus delineating a potential binding site. A series of such studies

implicated R50, C166, I167, T171, I182, K185, R201 and G334 amongst others (5; 254; 431; 540). A key feature is that these mutations do not significantly perturb the gating model (86; 541). For example, it is possible that mutations could modify gating without affecting ATP binding but in functional assays the ability of ATP to inhibit the channel could still be impaired (86; 541). In the crystal structure the residues R38, R50 and K185 form a cluster of positively charged amino acids unique to the Kir6.0 family and in a pocket that could accommodate the adenosine ring of ATP (310). However in this crystal structure the Kir6.2\SUR1 octamer was crystallised in the absence of ATP. In contrast, in the other crystallographic studies ATP was included in the solution. In this case ATP is adjacent to K185 and a pocket is defined by the interface of adjacent N and C domains in Kir6.2 which includes I182, L205, Y330, F333, and G334 from the same subunit, and R50 from the other subunit (342). In the second structure (305), this is resolved even more clearly. ATP lies in a horseshoe shape in a pocket defined by 182-185 (IFSK) and 332-335 (KFGN) in one subunit whilst residues N48 and R50 from the neighbouring subunit making two hydrogen bonds with the adenine base of ATP (Figure 5). The channel complex was seen to bind four molecules of ATP and this is compatible with Hill coefficients of more than one when describing the dose-response curve for channel inhibition by ATP (5; 130). Binding of a single ATP to one subunit is sufficient to close the channel (554).

Activation by MgADP

In contrast to ATP inhibition, activation by ADP is dependent on the provision of magnesium. In its absence ADP leads to inhibition probably acting via the ATP inhibitory site on Kir6.2. In contrast in the presence of a SUR the channel complex becomes sensitive to activation by MgADP and specifically is determined by residues in the nucleotide binding domains (NBD) (187; 483). NBDs in other ABC transporters adopt a two lobed structure with

the larger one containing the Walker A and Walker B motifs followed by aspartate ("D") and histidine ("H") loop residues. The smaller lobe is an α-helical domain and comprises the ABC transporter signature sequence (usually LSGGQ) and a "Q-loop". Characteristically the larger lobe of NBD1 interacts with the smaller lobe of NBD2 to form a functional unit capable of hydrolysing adenine nucleotides. A second functional unit is formed by the large lobe of NBD2 and small lobe of NBD1. The Walker A motif contains a lysine that is critical for beta and gamma phosphate binding of ATP. The Walker B motif has a conserved aspartate amino acid that complexes magnesium ions and is central to nucleotide hydrolysis. The ABC signature sequence is part of a helix-dipole important for positioning ATP in the catalytic site (521; 555). There are functional and now structural data that the NBDs in SURs are asymmetric in the closed conformation.

The first critical evidence for the involvement of NBDs in activation of the channel complex by MgADP was that mutagenesis of key residues such as lysines and others in the Walker A, linker and Walker B motifs abolished or altered stimulation by MgADP (187; 483). However the NBDs are asymmetrical in functional behaviour and seem to differ in whether they bind and\or hydrolyse MgATP. Biochemical studies support the proposition that NBD1 binds ATP without Mg^{2+} with slow hydrolysis whilst NBD2 binds and hydrolyses MgATP rapidly (42; 112; 550). The post and pre-hydrolytic states in the NBDs can be mimicked by using vanadate and beryllium in electrophysiological experiments and support the notion that MgATP hydrolysis at NBD2 is needed for increases in channel activity in Kir6.2\SUR2A complexes (615). However in excised patch-clamp recordings, MgADP clearly stimulates the channel and this implies that nucleotide hydrolysis is not a prerequisite for channel modulation. In addition, there are only a few reports of direct hydrolysis by SUR NBDs and if it were necessary for channel gating this would violate microscopic reversibility (42; 344). Furthermore, non-hydrolysable ATP derivatives may lead to conformational changes in the

NBDs (400). It is also a general feature of ABC transporters that dimerization of the NBDs in the fashion detailed above is necessary for ATP hydrolysis to occur (318). The NBDs in SUR however are asymmetric in terms of their primary sequence with a degenerate Walker B motif in NBD1 and a degenerate ABC signature sequence in NBD2 (555). In the crystal structures the NBDs are clearly separate and asymmetric in relative position (310; 342). However this is a closed channel configuration co-crystallised in the presence of glibenclamide and it is possible that the NBDs might align and dimerise in an open configuration. Thus it is possible that whilst SURs may retain the ability to hydrolyse nucleotides it is not central to activation. However the adoption of the post-hydrolytic and MgADP bound state in NBD2 in a dimeric NBD structure is crucial for activation. It is however possible that the hydrolytic properties of the SUR subunit might be crucial for other functions though, for example, no clear transport ligand has been identified.

New light has been shed on these issues with the very recent publication of a high resolution structure of the pancreatic K_{ATP} channel co-crystallised with magnesium nucleotides and PIP_2 (305). They distinguished two forms: a propeller like overall structure similar to those studied previously and a new quatrefoil shape. Crucially in the latter structure nucleotides were bound to SUR1 and reveal a canonical ABC transporter like structure with transmembrane segments 9 and 10 from NBD1 and transmembrane segments 15 and 16 from NBD2 reaching across to interact with the other half NBD. The NBDs form head to tail dimers with the signature 'LSGGQ' motif in NBD1 disengaged from the bound MgADP leading to an open consensus ATPase site whilst the signature sequence in NBD2 is mutated to 'FSQGQ' directly contacting ATP and leads to a closed and degenerate ATPase site. The presence of ADP in one NBD site and ATP in another is a unique feature for an ABC transporter. The authors suggest that the ADP binding consensus site is an ADP sensor without a hydrolysis cycle during gating. In another structural feature, the lasso motif in

SUR1 is disengaged from the ATP binding site and C-terminal domain on Kir6.2 in the quatrefoil but not in the propeller structure. The significance of this for gating however is not clear.

Pharmacological Inhibitors

Once the K_{ATP} channels were cloned a priority for mutagenesis work was to determine the likely binding sites for sulphonylureas. Given that SUR1 was initially cloned by the use of high affinity binding and protein purification, it was clear that this subunit was the major binding site (1). However, in studies with tolbutamide in *Xenopus laevis* oocyte membrane patches expressing Kir6.2\SUR1, the dose-response curve for inhibition was best described by two independent binding sites. The curve was biphasic with a high affinity and low affinity site respectively (188). This is a feature of other sulphonylureas and related compounds (184; 185; 203). The high affinity component corresponds to the binding site on SUR and the low affinity site to one on the pore forming Kir6.2 subunit (16; 188). Furthermore, there are differential effects of these agents between SUR1 and SUR2 containing channels. Thus glibenclamide, glimepiride, repaglinide and meglitinide show high affinity block in both SUR1 and SUR2 containing channels whilst tolbutamide, gliclazide, chlorpropamide and nateglinide do not exhibit high affinity block with SUR2 (185). This observation drove an approach in which chimaeras were constructed between SUR1 and SUR2 and high affinity tolbutamide inhibition was assayed (16). The results indicated that the last group of transmembrane domains was important specifically the cytoplasmic loop between helices 15 and 16 in SUR1 (16). Subsequent studies isolated S1237 as being the key amino acid residue (203) and introduction of serine at an equivalent residue in SUR2B led to an increase in the affinity of glibenclamide binding (195). The cryo-EM structures are not clear as regards glibenclamide binding and will need higher resolution structures to

unambiguously identify it. In the structure where glibenclamide is present, it might lie close to the S1237 residue but also that it might interact with the linker between TMD0 and TMD1 ("L0") specifically residue Y230 (342). There is some support from biochemical work for such a model (354; 574). For example deletion of TMD0 and L0 but not TMD0 led to an abolition of glibenclamide binding. The L0 domain interdigitates with Kir6.2 and thus would be optimally placed to regulate Kir6.2 gating. Finally, the structural studies suggest that glibenclamide might distort the relationship between the NBDs preventing alignment, dimerisation and consequent channel activation (310; 342).

At the physiological level there are also interactions between MgADP and sulphonylurea block. In inside-out patches tolbutamide acting at the high affinity site only leads to partial but not complete channel block in SUR1 containing channels. However in intact whole cells or in the presence of MgADP the action of tolbutamide is much more complete (188). This is a general feature of sulphonylureas and related compounds (185). This interaction with MgADP is not a feature of SUR2 containing channels and in fact they are less effective when MgADP concentrations are high (427).

Pharmacological Openers

As discussed above there are a wide variety of pharmacophores that can activate K_{ATP} channels. Nicorandil, pinacidil and cromakalim are selective for SUR2 containing channels whilst diazoxide is probably more specific for SUR1 containing subunits though it does activate SUR2B (172; 337). Diazoxide can activate SUR2A and cardiac channels under specific circumstances with high cellular MgADP (104). Studies using chimaeric approaches and binding studies have identified regions within TMD2 in particular the cytoplasmic linker between TM13 and TM14 and the last TM helices, TM16 and TM17, as responsible for the activation by pinacidil and cromakalim (25; 367; 551). The binding site for diazoxide is less

well mapped though it is known that binding is nucleotide-dependent and occurs between TM6 to TM11 and NBD1 (25). The presence of more than one binding site on SUR for potassium channel openers may help rationalise the observed structural diversity of potassium channel openers. The binding sites are separate between that of the sulphonylureas and the potassium channel openers though there is some interaction which is likely to be allosteric in nature (195; 327). The pharmacological topology of drug-SUR interaction is summarised in Figure 6. It is worth noting that this has largely been determined from site-directed mutagenesis and chimaeric studies and the contribution of structural studies using cryo electron microscopy is currently modest.

Principles of assembly determined from structural studies

The cryo-EM structures have unambiguously delineated the key regions for the assembly and interaction of SUR1 with Kir6.2 in the closed channel configuration (310; 342) (and see Figure 4). Four SUR1 subunits are arranged peripherally to the pore-forming tetramer of Kir6.2. The complex is 125 angstroms in height, 200 angstroms wide and shaped like a propeller blade (Figure 4). The TMD0 and linker L0 contact the N-terminus of Kir6.2 and also the proximal C-terminus close to the putative PIP_2 and ATP binding site (see below). This is the primary point of contact and essentially TMD0-L0 is sandwiched between Kir6.2 and TMD1 and TMD2 of SUR1. At the other interface between TMD0-L0 and TMD1-TMD2 of SUR1 there is a so called “lasso” motif bound onto transmembrane segments M7, M15 and M16. Both of the cryo-EM structures are in a closed conformation however it is possible to speculate about sequences of events that might occur to gate the pore into an open state. MgADP binding for example could dimerise the NBDs and in other ABC transporters this results in motions of M6 and M7 in TMD1 and M15 and M16 in NBD2 relative to one another. This in turn is transmitted to the lasso and L0 linker which results in clockwise

rotation of the proximal C-terminal domain of Kir6.2 opening the pore (310; 342).

The regulation of K_{ATP} channels

Metabolism and pH

The direct regulation of K_{ATP} channels by intracellular nucleotides has already been discussed. It is worth noting that in cardiac cells it seems that K_{ATP} channels preferentially sense ATP derived from glycolysis (567). This is supported by more recent observations of direct association of glycolytic enzymes with the K_{ATP} channel complex as discussed above (225). However cardiac cells also possess well developed phosphotransfer networks, using adenylate kinase and creatinine kinase, allowing mitochondrial energy homeostasis to be sensed and relayed to channels in the sarcolemma (64; 124). In contrast, in pancreatic beta cells mitochondrial oxidative metabolism is essential for K_{ATP} channel regulation by ATP (120; 214).

Intracellular acidification is an activator of K_{ATP} channels such as may occur with cellular anaerobic metabolism (111; 563; 583). The exact molecular basis for this effect is not clear though it involves an antagonism of ATP inhibition (581) and residues T71 and His-175 in the Kir6.2 subunit (98; 584). The latter residue is a good candidate for a direct pH sensor as it could readily be titratable by protons. In studies examining natively expressed K_{ATP} channels, the cardiac channel seems less sensitive to changes in intracellular pH than the skeletal muscle channel (111; 290; 303).

Regulation by phosphatidylinositol (4, 5) bisphosphate (PIP_2)

An emerging theme in ion channel research has been the dependency of channel activity on the presence of PIP_2 and perhaps other anionic phospholipids in the plasma

membrane (220; 221). PIP_2 is a relatively minor lipid component of the plasma membrane making up less than 0.5% of total lipid composition (102; 560). Run-down could often be ameliorated by the provision of ATP or ATP-generating systems. The key observation was that ~~this~~ rundown in inside-out patches was reversed by the addition of PIP_2 (either in lipid vesicles or as a water soluble derivative). This was also the case with the application of other anionic phospholipids but this was more variable and dependent on the specific channel being studied. This fundamental lipid dependency was observed for a number of channels and transporters and specifically with Kir6.2 containing K_{ATP} channels (132; 220; 484). Furthermore, with K_{ATP} channels the addition of increasing concentrations of PIP_2 profoundly antagonised ATP inhibition (37; 484). This suggests that ATP inhibition and metabolic regulation might be subject to dynamic regulation within the cell. The Kir6.0 subunit determines the PIP_2 sensitivity and there have been mutagenesis studies that have identified key positively charged residues in the slide helix. In particular basic residues in the C-terminus (regions 176-222 and 301-314) have been identified as being important (485). The binding site for PIP_2 in the cryo-EM structures was not particularly well resolved. However a binding pocket was better determined in other inward rectifier potassium channels (204; 570). It consisted of an interface between the transmembrane domain which confers non-specific lipid binding through hydrophobic acyl chains in PIP_2 and the cytoplasmic domain which generates a specific phosphatidylinositol-binding region. The latter site is also contributed to by amino acid residues from the N-terminus. The effects of PIP_2 are through direct binding. For example, it is possible to bind the C-terminus of Kir6.0 channels to phospholipid arrays and the ion channel activity of other inward rectifiers such as Kir2.0 channels can be reconstituted into PIP_2 containing lipid vesicles (103; 422). Interestingly, in the binding assays the Kir6.0 channel domain is able to bind a wider array of phosphatidylinositol species and there are some indications that this might have functional significance in terms of

regulation of K_{ATP} channel activity for phosphatidylinositol (4) phosphate (437).

PIP_2 is an important substrate for a number of signalling enzymes including phospholipase C and phosphatidylinositol (3) phosphate kinase. One key question is whether PIP_2 can act as a signalling molecule in its own right or whether cellular PIP_2 depletion is ever sufficient to inhibit channels. Such regulatory phenomena can be demonstrated after heterologous expression of various components in cell lines and *Xenopus laevis* oocytes however these approaches lead to high and often non-physiological levels of expression. The critical point is what happens in native cells. There are studies examining phospholipase C activation via muscarinic receptors in neurones and these have revealed that PIP_2 levels can fall by up to 60-70% (96; 572). However the remaining fraction is protected from depletion and once the agonist is removed the levels of PIP_2 recover rapidly (generally within a minute). Ion channels regulated by PIP_2 show a wide range of apparent affinities (441). Indeed in the Kir6.0 family, Kir6.1 has a higher affinity than Kir6.2 and this may account for why these channel complexes are less sensitive to ATP (422). The best evidence for PIP_2 acting as a true second messenger in signalling is the muscarinic receptor-mediated inhibition of the M-current (Kv7.0 channels) (56; 608). It is notable that these channels have low affinity PIP_2 binding and the channel activity is exquisitely sensitive to changes in cellular PIP_2 (291; 438). In many other channels including K_{ATP} channels such strong evidence is not evident and the jury is out on the potential signalling significance of the lipid regulation. In intracellular vesicles and organelles there are much lower amounts of PIP_2. Thus one idea is that the PIP_2 sensitivity of the majority of ion channels leads to them being closed in intracellular compartments. This would minimise ionic fluxes and water movement across these membranes (221).

Regulation by other lipids

Other lipid species in particular fatty acids and metabolites are able to modulate K_{ATP} channel function. Fatty acids can also be metabolised by oxidation to acetyl CoA derivatives and independent of entering the citric acid cycle can modulate K_{ATP} channel function (321). These can directly activate K_{ATP} channels and seem to do so using the same binding site and mechanisms as PIP_2 (339; 464). The effects are more pronounced on cardiac than pancreatic channels though both are regulated to some degree (51; 159). Furthermore oleate is able to activate K_{ATP} channels in hypothalamic neurones: an effect that is independent of metabolism (105).

Regulation by protein kinases

Vascular smooth muscle cells

It is clear that in vascular smooth muscle phosphorylation of K_{ATP} channels is important in physiological function. It has been known for many years that vasodilators can activate K_{ATP} channels with subsequent membrane hyperpolarisation, decreased calcium entry and relaxation of vascular smooth muscle (420). This occurs through the classic signalling pathway where binding of an agonist to a G-protein coupled receptor activates the stimulatory G-protein (46; 174). This then leads to production of cAMP by adenylate cyclase and the activation of protein kinase A. Adenosine released from metabolically challenged tissue can bind to the adenosine receptor G-protein coupled receptors A2A and perhaps A2B (107; 109; 281). Calcitonin gene-related peptide is present in sensory nerve endings and leads to vasodilatation when it binds to the calcitonin receptor-like receptor which complexes with a receptor activity-modifying protein to form the mature receptor in vascular smooth muscle (34; 378; 569). Vasoactive intestinal polypeptide is another example of a vasodilator that is released from peripheral nerves and binds to its cognate receptor probably VIPR2 (597).

Vascular smooth muscle cells contain α1 and β2 receptors and thus norepinephrine released from nerve endings will cause vasoconstriction whilst increases in circulating epinephrine will activate β2 receptors and cause relaxation (61; 227; 518). The response to exercise in an individual tissue is viewed as an interaction between a local signal, indicating metabolic demand, that can override the nervous signal mediated by sympathetic innervation. Finally endothelial mediators such as prostacyclin can activate their relevant GPCR in smooth muscle and this is particularly important in the pulmonary circulation (250; 463). It is worth emphasising that the activation of K_{ATP} channels is not the sole mechanism by which these vasodilators act and for example in some vascular beds the effects are only partially inhibited by sulphonylureas (280).

Protein kinase A acts by directly phosphorylating the channel complex. On the SUR2B complex T633, S1387 and S1465 are important whilst on Kir6.1 S385 is involved (423; 477). The phosphorylation sites on SUR2B are in and around the NBDs and it is plausible they promote MgADP binding and channel activation. It is also conceivable that the sequential phosphorylation of increasing numbers of these residues allows a graded increase in open probability and response with increasing strength of upstream signal (423).

In contrast vasoconstrictors can inhibit the K_{ATP} channel and this leads to membrane depolarisation, increased calcium entry and vasoconstriction (420). The vasoconstrictors include endothelin-I, an endothelial mediator, circulating angiotensin II, norepinephrine from sympathetic nerve endings and histamine released from mast cells (50; 210; 292; 361). The binding of relevant agonists to their cognate G-protein coupled receptors leads to the activation of the $G_{q\backslash 11}$ family of G-proteins and then activation of phospholipase C beta (45). This in turn leads to the production of diacylglycerol and inositol trisphosphate from PIP_2. The former activates protein kinase C and the later mobilises Ca^{2+} from intracellular stores (41). It seems that protein kinase C is the important mediator. The vascular channel binds

PIP_2 with high affinity and it functions more like a cofactor necessary for channel activity than a signalling mediator (422). Where detailed measurements have been performed it seems likely that there is only ever modest depletion of PIP_2 in native cells after receptor activation (375; 572). Electrophysiological studies support the involvement of calcium independent isoforms of protein kinase C and specifically the epsilon isoform (210). The inhibitory effect is dependent on phosphorylation of a cluster of serine residues in the distal C-terminus of the Kir6.1 subunit (S354, S379, S385, S391 and S397) (476). The Kir6.2\SUR2B channel complex can also be regulated by PKC but in this case the effect is calcium dependent and a single residue S372 is key (23). Whilst it is clear that PKC can directly inhibit channel opening it also seems that it can promote channel internalisation perhaps via caveolae (23; 253). The modulation of K_{ATP} via PKC may contribute to vasoconstrictor action but it is clear that other potassium channels can be inhibited such as voltage-gated potassium channels (211; 424). In addition, IP_3 mediated calcium release will directly promote vascular smooth muscle contraction.

There a number of ways the contractile response via K_{ATP} channels can be amplified. Agonist bound angiotensin receptor (AT-1) activates PKC via the Gq\11 family of heterotrimeric G-proteins but in smooth muscle it also couples to inhibitory G-proteins. This has the effect of inhibiting adenylate cyclase and down regulating basal PKA activity and vasodilatation (210). Phosphatases are important in reversing the action of protein kinases. Calcineurin (also known as PP2B) is a calcium dependent phosphatase and it can inhibit K_{ATP} channels in vascular smooth muscle (573). It is likely it does this through reversing PKA-mediated phosphorylation (398). As vasoconstrictors promote calcium mobilisation, this will reverse PKA-mediated channel phosphorylation through the activation of calcineurin. Exchange proteins activated by cAMP represent a PKA independent signalling pathway. The emergence of good pharmacological tools to separate the two systems has implicated them in

a number of cellular signalling events (308). Activation of exchange proteins by cAMP inhibits smooth muscle K_{ATP} channels via Ca^{2+} mobilisation and subsequent activation of calcineurin (418).

Caveolae are cholesterol rich vesicles and are involved in native smooth muscle in compartmentalising both PKA and PKC mediated signalling. Thus adenylate cyclase and Kir6.1 localise in caveolae as determined by sucrose gradient separation and electron microscopy (457). Cholesterol depletion, which disrupts caveolae formation, attenuates PKA mediated signalling (457). Protein kinase C epsilon translocates to caveolae on angiotensin II receptor activation (456). The PKA-mediated activation of K_{ATP} channels in vascular smooth muscle cells might also be enabled by A-kinase anchoring proteins (209). Use of a peptide which inhibits PKA binding to A-kinase anchoring proteins led to attenuation of K_{ATP} channel activation in whole-cell recordings (209). The regulation of vascular smooth muscle K_{ATP} channels by protein kinases is summarised in Figure 7.

Cardiac myocytes

Protein kinase C is thought to be a critical mediator in various cardioprotective phenomena. For example, ischaemic preconditioning describes the phenomena where short periods of ischaemia, prior to a more damaging insult, protects the heart and reduces infarct size (598). This can be mimicked by phorbol esters, diacylglycerol analogues and receptor activation of receptors coupled to the Gq\11 family of G-protein and the protective response is inhibited by PKC inhibitors (323; 325; 326; 496). Ischaemic preconditioning could also be mirrored by potassium channel openers and prevented by sulphonylureas (495). Initially it was proposed that this involved the sarcolemmal K_{ATP} channel but the focus quickly shifted to the mitochondrial channel (see below).

Thus protein kinase C modulation of cardiac K_{ATP} channels was highly topical

~~initially~~ as an avenue for investigation. Indeed, as was expected, investigators were able to show activation of the cardiac channel by PKC. For example, perfusion of a catalytic subunit of PKC in inside-out patches increased open probability three-fold and this was inhibited by PKC inhibitors. The effect was rendered irreversible if phosphatase activity was blocked using okadaic acid (316). However the position is now known to be more complex. The prevailing level of ATP is thought to be important: thus the channel is activated by PKC under conditions of high ATP and inhibited in the presence of low ATP when channel activity is high (313; 316). The level of intracellular Ca^{2+} is also influential and in conditions where physiological levels of Ca^{2+} prevail there is a biphasic effect with activation followed by a slower inhibition due to channel internalisation (229). This complex behaviour is determined by the Kir6.2 subunit and thus would be expected to be observed with channels in the heart and pancreas. This is in contrast to Kir6.1-containing complexes which seem to be universally inhibited by PKC. The specifics of regulation of cardiac and skeletal myocyte K_{ATP} channels through PKA has been little studied though it is plausible it is important during exercise (see below).

Pancreatic cells and other tissues

A wide range of hormones including incretins, growth factors and neurotransmitters can regulate glucose-stimulated insulin release in pancreatic β cells. Two incretin hormones have been heavily studied, glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, and it is known that both promote insulin release (166; 347). Glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide are agonists at G-protein coupled receptors and are coupled to the stimulatory G-protein. In addition there are GPCRs such as GPR40 that sense free fatty acids and also amplify insulin signalling (366). In contrast the free fatty acid receptors couple to the $G_{q\backslash 11}$ family of G-proteins and thus activate PKC and

mobilise Ca^{2+} from intracellular stores. Drugs acting on these pathways are already being developed and taken into clinical trials (366).

Thus PKA-dependent modulation of the pancreatic K_{ATP} channel and the cloned equivalent has an important and emerging physiological context. In pancreatic β cells isolated from SUR1 knockout mice, glucagon-like peptide 1 was able to elevate cAMP but did not cause insulin release implicating K_{ATP} channels in incretin action (481). In this physiological setting it would be expected that PKA-mediated signalling should inhibit K_{ATP} channel currents thus promoting insulin release. However using the cloned subunits SUR1 and Kir6.2 and examining regulation in a heterologous expression system, PKA-mediated phosphorylation led to increased currents. Furthermore, important residues were identified that were homologous to those established to be important in SUR2B and Kir6.1 (181; 317; 423). Further studies revealed, rather like the actions of PKC, that the exact conditions used were important. Thus with 0.2 mM ADP the phosphorylation mediated by the PKA catalytic subunit was inhibitory whilst with 0.5 mM it was stimulatory (315). The S1488 residue in SUR1 was identified as being involved (315). There are also data, as for the vascular channel, implicating a non-PKA dependent pathway acting via cAMP and exchange proteins activated by cAMP (262; 263). It is important to note that incretins affect multiple other events in β cell signalling and the K_{ATP} channel likely plays only a contributory role. For example, glucagon-like peptide 1 can also modulate TRPM channels (478) and PKA may modulate the insulin vesicle secretory apparatus.

Insulin exocytosis is mediated by soluble N-ethylmaleimide-sensible factor attachment protein receptors (SNAREs). In β cells these include plasma membrane associated syntaxyn-1A and SNAP25/23, and granule membrane associated vesicle-associated membrane protein and synaptobrevin. These two sets of proteins interact and govern docking and fusion of insulin containing vesicles with the plasma membrane (272). K_{ATP} channels

interact with syntaxin-1A via the NBDs of SUR1 and the interaction inhibits channel opening. Syntaxin-1A also influences the trafficking of K_{ATP} channels with a decrease in protein expression of syntaxin-1A leading to reduced surface expression of Kir6.2\SUR1 (68; 384; 409).

Leptin is a satiety hormone secreted by adipocytes and its absence leads to obesity. Leptin can inhibit insulin secretion by increasing the surface expression and activity of pancreatic K_{ATP} channels (224). The activation of the AMP-activated protein kinase by leptin may be central to the regulation of trafficking (406; 407) though there are also data showing that phosphoinositide 3 kinase may also be involved (585).

Modulation by gasotransmitters

Nitric oxide is an important endothelial mediator and diffuses into smooth muscle where it activates guanylate cyclase increasing cGMP and activating protein kinase G. There is no clear consensus on whether PKG can directly activate K_{ATP} channels. For example, in cardiac ventricular myocytes activation of K_{ATP} channel currents has been seen (198; 199). However nitric oxide may predominantly affect non-potassium channel dependent pathways and if it does activate potassium channels there is most evidence for the activation of large conductance Ca^{2+}-activated K^+ channels (458; 610). Nitric oxide can also directly nitrosylate proteins and some of its effects on potassium channels may occur because of this (49; 373). Endothelial K_{ATP} channels can potentially modulate calcium entry and this would promote release of NO. Much less is known of the regulation of endothelial channels but they seem to be constituted of Kir6.1\SUR2B and can be activated via Gs- coupled adenosine receptors (20).

It is clear there are more gaseous endothelial mediators than simply nitric oxide. The endothelium also generates carbon monoxide and H_2S. Carbon monoxide activates guanylate

cyclase in a manner analogous to nitric oxide (373) and K_{ATP} channels do not seem to be prominently involved. H_2S is synthesised largely by cystathionine γ-lyase and the deletion of the gene encoding the enzyme results in hypertension in mice (593). In this case activation of vascular smooth muscle K_{ATP} channels is thought to be involved and occurs through S-sulphydration of cysteine residues (71; 372). In particular the SUR2B subunit appears to be the main target on residues C24 and C1455 (266). The regulation of K_{ATP} channels may extend more widely than just the vasculature including into non-vascular smooth muscle and neurones (67; 139).

Mechanosensitivity of K_{ATP} channels

It has been known for some time that K_{ATP} channels seem to be directly sensitive to mechanical stretch. This is an important idea as it could potentially couple workload and contraction with channel activation independent of changes in adenine nucleotides. In rat atrial myocytes, the application of a hypotonic solution increased K_{ATP} channel activity in perforated patch whole-cell recordings (553). The channel seems to directly respond to membrane deformation such as would be generated by suction on the pipette in inside-out patch recordings (231). However this bilayer tension can be regulated by the actin cytoskeleton (231). This sensitivity was dependent on the SUR subunit and in particular nucleotide handling in NBD2 (135): specifically mutation of a residue (K1337) abolished the effect.

Studying K_{ATP} channel function: an overview

A number of different approaches have given major insight into the integrated function of K_{ATP} channels in physiology. There is a long standing use of small molecule inhibitors and activators and in this regard K_{ATP} channels have a rich and well understood

pharmacology (see above). Once the channel subunits were cloned this opened up engineering a variety of murine models of increasing sophistication including transgenic overexpression, global genetic deletion and conditional gene deletion and expression using cre\loxP approaches. Finally modern genetics and genomics has implicated K_{ATP} channels in human endocrine, cardiac and neurological disease and given important insights that complement the animal work. Table 2 summarises details of the various genetically modified mouse models that have been developed.

Physiological and pathophysiological function of K_{ATP} channels

Species conservation

Comparative genomics can be valuable in suggesting functional specialisation within the animal kingdom and identifying by homology domains key for core channel function. In general investigators will focus on traditional model organisms. In the invertebrate *Drosophila melaganostar* there are three inwardly rectifying channel subunits each with a GFG motif in the consensus sequence (117). A potential sulphonylurea like subunit also exists however the two proteins are expressed in different regions and there are no data on K_{ATP} like currents being present in native cells (374). Thus mature K_{ATP} currents may be a unique specialisation of vertebrates. In the lower vertebrate zebrafish (*Danio rerio*) subunits homologous to Kir6.1 and Kir6.2 are present but in addition there is another member of the family, Kir6.3, present in the genome (606). Two sulphonylurea subunits also exist and there is co-expression of these with Kir6.3 in the brain and heart (606). Expression of the zebrafish Kir6.3 with mammalian SUR1 in heterologous expression systems led to K_{ATP} like currents, however, currents in native cells were not examined and function was not further explored. However it is known that lizards, frogs and other fish have K_{ATP} like currents in cardiac cells

(403; 404). In a recent study K_{ATP} currents have been found in zebrafish islet βcells and modulation of channel activity leads to changes in glucose homeostasis illustrating conservation of function between lower and higher vertebrates (128).

K_{ATP} channels in the endocrine tissues

K_{ATP} channels play a key role in nutrient-sensing. The classical paradigm is in the pancreatic βcell where they are central in glucose-stimulated insulin release. However more recently it has also become apparent that similar K_{ATP} channels may have a physiological role in glucagon release from αcells in the pancreas and are also present in various enteroendocrine cells in the gut. Furthermore, nutrient-sensing is also important for regulating feeding behaviour and K_{ATP} channels in the central nervous system may be involved in this process. The major channel populations in endocrine tissues are summarised in Table 3.

Insulin release and pancreatic β cells

Pancreatic β-cells in the islets of Langerhans synthesise, store, and secrete insulin so that the fasting blood glucose level is kept within a narrow range of 3.5–5.5 mM. Insulin promotes glucose uptake into skeletal muscle, the liver and adipose tissue and switches off glucose production by metabolic processes such as glycogenolysis. K_{ATP} channels are essential in the tightly regulated process that couples the blood glucose concentration to the secretion of insulin ("stimulus-secretion coupling"). Pancreatic β cells are excitable and respond to increases in glucose with membrane depolarisation and action potential firing (442; 443). It is essential that glucose is metabolised to pyruvate and enters into mitochondrial oxidative metabolism which leads to changes in the cellular ATP concentration (214). K_{ATP} channels constituted of SUR1 and Kir6.2 are the main glucose-sensitive

conductance in the pancreatic β cell and control electrical activity. In the absence of glucose the resting membrane potential is ~-70 mV. If exposed to 6 mM glucose the cell depolarises due to a 70% reduction in the K_{ATP} conductance and this triggers action potential firing above a threshold of -60 mV (442). These effects can be mimicked by the use of drugs such as tolbutamide. The action potential is driven by a variety of calcium channels (L, R and T types) and repolarisation by calcium-activated potassium channels (442). The repetitive action potential firing leads to calcium entry and oscillations resulting in insulin vesicle exocytosis. There are species differences with mouse islets needing higher glucose concentrations than human beta cells to trigger action potential firing and insulin release. This is likely underpinned by significantly lower K_{ATP} current density in human beta cells together with differences in glucose transporter expression (442; 443). A cartoon shown in Figure 8 illustrates the process of stimulus secretion coupling in pancreatic βcells.

The use of genetically modified mice has generally supported the key involvement of βcell K_{ATP} channels in insulin secretion however there are some qualifications. In pancreatic islets that have expression of gain of function mutations in K_{ATP} channel subunits there is impaired insulin release and resultant diabetes mellitus (176; 288; 432; 433). However, in SUR1 and Kir6.2 global knockout mice and loss of function mutations, hyperinsulinism and hypoglycaemia are a highly variable finding (232; 355; 467; 480). In fact the opposite is often true in that there is impaired insulin secretion and βcell loss ultimately resulting in diabetes. In congenital hyperinsulinism in man, due to loss of function mutations in KCNJ11 and ABCC8, patients may be predisposed to developing diabetes mellitus later in life. ~~(and see below).~~ It seems K_{ATP} channels are important for βcell survival and that the mouse is more predisposed to βcell loss resulting from K_{ATP} channel inactivation. A variety of hormones and neurotransmitters can modulate insulin release from pancreatic βcells and this is discussed in the section above.

K_{ATP} channels in pancreatic α cells

Glucagon is released from pancreatic α cells and promotes the mobilisation of glucose. Glucagon release is inhibited by increase in blood glucose. Paradoxically K_{ATP} channels may also be involved in stimulus-secretion coupling in these cells (444). K_{ATP} channels are inhibited by the rise in blood glucose and this leads to membrane depolarisation. The key difference is that pancreatic alpha cells fire action potentials at normal blood glucose concentrations leading to the constitutive release of glucagon. Membrane depolarisation leads to an increase in action potential frequency but a reduction in amplitude. The latter is central and results in less calcium entry via P\Q calcium channels. Glucagon secretion is strongly dependent on calcium entry via P\Q calcium channels and thus secretion is reduced (444).

Gut-derived hormone release

Glucagon-like peptide-1 is released from the gut and acts as an incretin to increase insulin release from the pancreas (see above). It is one of a number of gut-derived hormones, which also includes glucose-dependent insulinotropic polypeptide, released from different enteroendocrine cell populations in response to a variety of dietary cues (fasting, carbohydrates, protein, fats etc) (186). Glucagon-like peptide-1 is released from L-cells and glucose-dependent insulinotropic polypeptide from K cells (186). In an interesting study, a reporter mouse was developed that enabled the isolation and study of this cell population. The release of glucagon-like peptide 1 is sensitive to glucose in the intestine and stimulus secretion coupling involves calcium entry and K_{ATP} channels (429). However the mechanisms may not be as clear as with glucose-sensing in pancreatic βcells and may involve a variety of specialised G-protein coupled receptors recognising the dietary components and their breakdown products (186).

K_{ATP} channels in the heart

The cardiac action potential is shaped by a large number of ionic conductances and the exact morphology varies between different chambers and within the conduction system (534). The calcium entry that occurs during the plateau of the action potential is central to calcium-induced calcium release and excitation-contraction coupling (146). Under resting conditions however K_{ATP} channels seem to contribute little to resting membrane potential or action potential repolarisation.

The classic composition of the cardiac K_{ATP} channel is thought to be Kir6.2\SUR2A and this is largely derived from studies in the ventricle. In fact K_{ATP} currents are widely distributed including the atria and conduction tissues and there may be some nuances in subunit expression. In the His-Purkinje system heteromultimers of Kir6.1 and Kir6.2 exist together with SUR2A (31; 600). Furthermore, in murine atrial cardiac myocytes there is good evidence that K_{ATP} is formed by Kir6.2\SUR1 however in human atrial myocytes it is Kir6.2\SUR2A (136; 149). The major channel populations in striated muscle are summarised in Table 4.

Physiological function

Relatively large K_{ATP} currents can be observed when cardiac myocytes are metabolically challenged but not under resting conditions (391). Action potential duration and contractile function in the Kir6.2 knockout mice are also normal in the basal resting physiological state (511). This raises the question of what is the exact physiological role of the channel. The study of murine models with global genetic deletion of Kir6.2 has pointed to some interesting possibilities. In an exercise treadmill stress test the Kir6.2 knockout mice had significantly lower tolerance to high intensity running (616). Furthermore when

challenged with isoprenaline they showed impaired contractile function, failure of action potential shortening and the development of arrhythmia and myocardial necrosis (616). Thus, despite the caveats of using a mouse with global genetic deletion, this suggests the cardiac channel is involved in adaptation to the stresses of a sympathetic "fear and flight" response. Additionally, exercise may have more chronic effects leading to an increase in K_{ATP} channel subunit expression (617). This would promote physiological adaptation to high intensity exercise.

Hypoxia and ischaemia

Classically the activation of cardiac K_{ATP} channels occurs under pathological conditions associated with hypoxia and ischemia. Such stressors substantially shorten the action potential duration and can attenuate or even abolish contraction (304; 557). Whilst it is difficult to envisage that these responses evolved to deal with pathological challenges, the opening of K_{ATP} channels is likely to enhance myocyte survival and the field of cardioprotection is discussed further below. It is intriguing that K_{ATP} channels are localised at the neck of the t-tubule and activation could locally and preferentially inhibit t-tubule depolarisation impairing calcium induced calcium release and excitation-contraction coupling (285).

Cardiac excitability

The action potential and QT interval on the ECG shorten with exercise. It is generally thought that increased magnitude of the slow component of the delayed rectifier potassium current are responsible for counteracting and overriding the increase in inward voltage-dependent calcium currents that will occur with increased sympathetic drive during exertion (40; 459). This occurs through current accumulation at higher heart rates and direct protein

kinase A phosphorylation of the channel (343; 503). However given the known properties of cardiac K_{ATP} channels it is plausible that these channels may also contribute to action potential shortening during exercise. Deviations of the ST segment from the isoelectric point occur during cardiac ischaemia and infarction and suggest spatial differences in repolarisation are occurring. These variations in ECG morphology occurring during cardiac ischaemia are reduced by glibenclamide and mimicked in the absence of ischaemia by potassium channel openers. This pharmacology is consistent with K_{ATP} channel activation underlying these features (294). In support of this hypothesis, mice with global genetic deletion of Kir6.2 do not develop ST segment elevation in response to ischaemic episodes (311). However, SUR2 null mice do show ischaemia-provoked ST segment elevation so there may be additional mechanisms operative under some circumstances (74).

Cell volume regulation

The regulation of cell volume is important to the normal physiological function of the cell and if cell swelling is excessive membrane rupture and cell death will occur. It is known that K_{ATP} channels can be activated in atrial myocytes when the cells swell (453). In Kir6.2 knockout mice K_{ATP} currents were not activated by cell swelling and atrial natriuretic peptide release was significantly higher suggesting that K_{ATP} channel activation limited the release of the hormone. The Kir6.2 knockout mice also showed exaggerated atrial natriuretic peptide release with systemic volume loading (453). In separate studies, when myocytes are challenged with a mild hypo-osmotic shock or with a hyperkalaemic cardioplegic solution, they swell and myocardial contractility is impaired (363; 415). The addition of diazoxide ameliorates this process as does the transgenic expression of a gain of function Kir6.1 mutant (213). Thus it would seem that activation of K_{ATP} channels prevents excessive cell swelling and myocardial contractile failure. However some results from Kir6.2 knockout mice and

with K_{ATP} channel inhibitors are contradictory and do not support this hypothesis (362; 468). To some extent these contradictions can be resolved by proposing that activation of Kir6.1\SUR1, but not of Kir6.2\SUR2A, is the specific channel population modulating cell adaptation to swelling. The effects on cell swelling might also contribute to cardioprotection (474).

K_{ATP} channels in skeletal muscle

It was originally assumed that Kir6.2 and SUR2A underlie K_{ATP} currents in skeletal muscle and this view was reinforced by studies on mice with global genetic deletion of the genes (75). However the picture may be more intricate than this. K_{ATP} current-density is higher in fast twitch skeletal muscle and this is accompanied by higher SUR1 expression than in other muscle fibre types (542). As in cardiac muscle the channel is closed and contributes little to the electrophysiological properties of skeletal muscle at rest (236). The precise physiological role of the current is not clearly defined. The properties of channels in striated muscle are summarised in Table 4.

Muscle fatigue

Characteristically there is a decline in force with repetitive and prolonged muscle use; a process known as fatigue. K_{ATP} channels are not involved directly in the initial decline of force with repetitive use however, after fatigue has developed, they help preserve a hyperpolarised membrane potential and prevent a rise in resting tension (77; 180). Furthermore, in Kir6.2 knockout mice the recovery of muscle tension after excessive muscle use is impaired (77; 180). The channel is also involved in preventing muscle damage after excessive exercise. Mice with global genetic deletion of Kir6.2 develop significant myofibre damage after swimming or treadmill exercise and the cellular mechanisms may be similar to

those in analogous studies with cardiac muscle (260; 528). This adaptation to strenuous exercise is one potentially good candidate for the physiological function of the channel in skeletal muscle.

Glucose uptake

Skeletal muscle K_{ATP} channels have been associated with regulation of glucose uptake. Sulphonylureas have been known to improve blood glucose control independent of their effects on pancreatic insulin release (110; 440). Specifically they enhance uptake of glucose into skeletal muscle and this is supported by studies on Kir6.2 and SUR2 knockout mice (75; 356; 545). Analogously increased activity of the channel during exercise might decrease glucose uptake and promote the use of alternative energetic substrates.

Skeletal muscle metabolism

K_{ATP} channels in skeletal muscle may be involved more broadly in regulating metabolism. Even at low workloads K_{ATP} channel opening was observed and the absence of the channel led to increased heat production (614). Furthermore, these mice have a lean body phenotype with reduced glycogen and fat stores (2). They were also resistant to weight gain from high fat feeding but had impaired endurance due to inefficient muscle substrate metabolism. Absence of K_{ATP} channels also promoted the release of musclin, a peptide similar the natriuretic peptides that promotes mitochondrial biogenesis in muscle (488; 506).

K_{ATP} channels in the vasculature

As discussed above the channel present in the vascular smooth muscle has distinct properties namely a lower single channel conductance (~30-35 pS compared to 70-80 pS), is less prominently regulated by ATP and channel activity is absolutely dependent on the

provision of intracellular dinucleotides (a "K_{NDP}" current) (38; 79; 420). These properties, summarised in Table 5, correspond closely to that of the Kir6.1\SUR2B combination and this is likely to generate the "K_{NDP}" current in smooth muscle (22; 101; 358; 587). In vascular smooth muscle cells from mice with genetic deletion of Kir6.1 and SUR2, K_{ATP} currents are no longer present, whereas similar smooth muscle cells from Kir6.2 knockout mice show a similar current-density of K_{ATP} currents when compared to littermate control (511). This may not be universally the case and there are some indications for example in portal vein that Kir6.2 may be expressed together with Kir6.1 and SUR2B (85). Interestingly, endothelial cells also express an ATP-sensitive potassium current (273; 274; 462) and this has been less studied. SUR2B is expressed in the endothelium and there is a study in human endothelial cells showing a heteromeric population of Kir6.1 and Kir6.2 (600).

Blood pressure control

K_{ATP} currents are widely expressed in a number of vascular beds and throughout the vascular tree (379). This observation and the fact of clear regulation of vascular smooth muscle K_{ATP} currents by vasodilators and vasoconstrictors (see above) support the potential role for the channel in blood pressure control. Smooth muscle cell contraction is promoted by the entry of Ca^{2+} through L-type calcium channels in the sarcolemma and K_{ATP} channels by influencing membrane potential can promote vasodilatation and vasoconstriction. The exact effects observed will depend on whether there is tonic activity of the channel and this may not be the case in all vascular beds. It is known for example that the perfusion of glibenclamide into the coronary vascular bed increases coronary perfusion pressure (405; 426). Figure 7 shows the regulation of K_{ATP} channels in vascular smooth muscle cells by cell signalling and how the channels could potentially be involved in blood pressure regulation.

The best evidence for the role of vascular K_{ATP} channels in blood pressure control

comes from the study of genetically modified mice. SUR2 and Kir6.1 global knockout mice have significantly elevated blood pressure (74; 358). A mouse with conditional deletion of Kir6.1 in vascular smooth muscle cells is also hypertensive though it is intermediate in magnitude between the global Kir6.1 knockout and littermate controls (22). Furthermore, vasodilators such as calcitonin gene-related peptide no longer hyperpolarise vascular smooth muscle cells and the application of the agonist no longer increases potassium currents in whole-cell recordings in the mice with genetic modification (22). Finally, mice with a gain of function mutation rendering Kir6.1 ATP-insensitive are hypotensive when this subunit is transgenically expressed in vascular smooth muscle (309).

Vascular reactivity

Mice with global genetic deletion of Kir6.1 and SUR2 have more complex phenotypes than simply hypertension (74; 358). The two lines of mice are prone to dying suddenly and this has been attributed to coronary artery spasm in a syndrome equivalent to that of severe human Prinzmetal angina. It was proposed that the absence of the K_{ATP} channel in vascular smooth muscle in the coronary arteries predisposed them to vasoconstriction. However this simple hypothesis may only be part of the explanation. On the background of the SUR2 knockout mouse, Kakkar et al transgenically overexpressed SUR2B selectively in smooth muscle (257). The K_{ATP} current was fully reconstituted in the coronary arteries but vasospasm still occurred. Furthermore, a mouse with conditional deletion of Kir6.1 in smooth muscle ~~in contrast~~ did not have evidence of coronary artery spasm even after the administration of ergonovine (22). A key corollary of this study is that smooth muscle deletion of Kir6.1 does not fully recapitulate the phenotype and suggests the important influence of K_{ATP} currents constituted of Kir6.1 in other tissues.

In hypertensive animal models there is remodelling of K_{ATP} channels in vascular beds

leading to functionally impaired and fewer K_{ATP} channels (47; 515). The membrane potential of vascular smooth muscle cells is more depolarised in hypertension. In addition, potassium channel openers have little effect on membrane potential compared to normotensive animals (515).

Endothelial K_{ATP} channel

Increases in potassium currents can influence endothelial function by hyperpolarising the membrane potential. In contrast to smooth muscle cells, hyperpolarisation promotes calcium entry and leads to the release of vasoactive mediators (390). Endothelial cells may also express an ATP-sensitive K^+ current (273; 274; 462), activation of which can increase intracellular calcium (167; 302; 562) and important mediators such as adenosine may modulate K_{ATP} channels in the endothelium as a component of their physiological action (299). Calcium is central to many endothelial functions such as mediator release and angiogenesis (69). Kir6.1 is thought to make a significant contribution to the current but is perhaps not the sole subunit underlying it (600). Furthermore, the expression of a dominant negative K_{ATP} channel construct selectively in endothelial cells increased endothelin-1 release (335). We have recently completed a study in which we selectively deleted Kir6.1 in endothelial cells using cre\loxP technology. This genetic manipulation abolishes K_{ATP} currents in endothelial cells and pinacidil-induced calcium entry (20). These mice also showed impaired reactivity to hypoxia in the coronary circulation resulting in increased cardiac damage during ischaemia-reperfusion (20). The effects were potentially mediated by adenosine receptor activation in endothelial cells leading to the activation of K_{ATP} channels. Iptakalim, a K_{ATP} channel opener, has been developed as an anti-hypertensive agent (489) and has also been shown to increase NO release and NOS activity and to inhibit endothelin release in aortic endothelial cells (167).

K_{ATP} channels in non-vascular smooth muscle

K_{ATP} channels are ubiquitously expressed in non-vascular smooth muscles and these include throughout the gastrointestinal tract (207; 255), bladder (155), uterus (328), urethra (524) and the respiratory airways (258). The currents are similar in properties to those of vascular smooth muscle and there is substantial evidence for the expression of Kir6.1 and SUR2B (255; 524). There may be some variations in specific smooth muscles. For example, in the urethra there is evidence for expression of Kir6.2 and of heteromultimer formation (525) and both pore-forming subunits may also be expressed in the colonic smooth muscle (536).

In general less is known of the physiological role of these channels in these varied organ systems and they have been little studied in the various genetically modified mouse lines. The application of K_{ATP} channel openers and inhibitors often causes relaxation and contraction respectively of the smooth muscle and thus it is clear these currents are of sufficient density to have the potential to significantly modify organ function (284; 371; 523). There is also the potential for drug development to treat conditions such as asthma or bladder instability.

K_{ATP} channels in the central and peripheral nervous system

K_{ATP} channels are ubiquitously distributed in central and peripheral neurones and in glial cells (507). In glia the main current is probably made up of SUR1 and Kir6.1 (125; 532) though there is also evidence for Kir6.2 expression in some limited glial populations (612). The current is activated by diazoxide as might be expected from the SUR1 expression. In neurones the most common molecular composition appears to be Kir6.2\SUR1 however in some brain regions and even between individual neurones different SURs can be expressed

(194; 270; 271). In an interesting study, using single-cell expression analysis the individual genetic makeup of SUR subunits within a cell was correlated with the exact electrophysiological phenotype and this defined the metabolic sensitivity of the respective neuron (319). The major channel populations in the nervous system are summarised in Table 6.

Neuronal excitability

K_{ATP} channels may contribute to modulating neuronal excitability even in the absence of hypoxia (3; 194). Even moderate levels of neuronal spiking can lead to a significant metabolic challenge for the neuron and a consequent fall in cellular ATP levels. The activation of K_{ATP} current will hyperpolarise the membrane potential and this limits action potential spiking. Single channel cell-attached recordings show an increase of K_{ATP} channel activity after a burst of action potentials and this is attenuated if energy consumption is reduced by inhibiting the sodium-potassium ATPase transporter (520).

Pain

K_{ATP} channels are present in dorsal root ganglion neurones and experimental studies support a role in suppressing hyperalgesia (618). Kir6.2, SUR1 and SUR2 are expressed in these neurones and severing of the nerve leads to hyperalgesia. This is accompanied by decreased subunit expression and reduced K_{ATP} current levels. Interestingly K_{ATP} channel subunits and currents are widely distributed in soma, axons and in Schwann cells (276; 618). The loss of K_{ATP} currents promotes hyperexcitability and facilitates neuronal firing. In injured dorsal root ganglion cells calcium signalling is impaired. In normal neurones, K_{ATP} currents are enhanced by increases in intracellular calcium in a process that is sensitive to calcium-calmodulin dependent protein kinase inhibitor (275). In contrast in axotomised neurones

calcium had no effect on K_{ATP} currents and this correlated with the degree of hyperalgesia. Thus K_{ATP} channels may be a drug target in the treatment of neuropathic pain.

Locomotion and Behaviour

K_{ATP} channels may be involved in locomotion and behaviour. Using a broad battery of behavioural tests revealed that Kir6.2 knockout mice have reduced activity and impaired co-ordination (113). Normal mice characteristically actively explore new environments especially if this is associated with reward. Dopaminergic neurones in the midbrain are critical for integrating this behaviour and it is associated with increased burst firing in these neuronal populations. In Kir6.2 knockout mice this behaviour does not occur and neuronal firing is also reduced. Furthermore injection of an adeno-associated virus expressing a dominant-negative construct for Kir6.2 bilaterally into the relevant dopaminergic neurones led to a similar phenotype as in the global Kir6.2 knockout mouse (461). Kir6.2 knockout mice also have impairment in working memory as they age which was thought to be a direct result of the loss of currents in the hippocampus and not secondary to systemic metabolic abnormalities (73).

Nutrient sensing and satiety

It is now appreciated that the hypothalamus can influence hepatic glucose production through nervous innervation of the liver. Furthermore, the neurones in the hypothalamus can respond directly to glucose and to key hormones such as insulin and leptin (449; 493). This is a complex area and a number of details remain unclear. The two main neuronal populations mediating these effects are agouti-related peptide (AgRP)/neuropeptide Y (NPY)- and proopiomelanocortin (POMC)-expressing neurons of the mediobasal hypothalamus (17; 265; 449). K_{ATP} channels are key in both cell types to integrating the response to glucose (449).

Thus in POMC neurones physiological changes in blood and cerebrospinal fluid glucose can directly regulate neuronal excitability and firing pattern. Glucose causes changes in cellular ATP which is dependent on glucokinase and subsequent mitochondrial metabolism: analogous to the mechanisms of metabolite sensing present in the pancreatic βcell (264). In addition, AMP-activated protein kinase may also act as a direct glucose sensor influencing cellular energetics and ATP levels (80). The net result is an increase in efferent signal from the hypothalamus and this leads to less glucose mobilisation from the liver. Insulin signalling in AgRP/NPY neurones seems key to the effects of insulin on hepatic glucose production (449). In addition to the well-known transcriptional effects, insulin receptor activation can also entrain effects on cellular excitability. Insulin and other important metabolic hormones such as leptin lead to activation of PI-3 kinase and the production of PIP_3 and may represent a critical signalling node for K_{ATP} channel activation in hypothalamic neurones (206; 449). This then activates K_{ATP} channels by promoting cytoskeletal changes and also through direct lipid modulation of ATP sensitivity (360; 441; 484; 494). This results in membrane hyperpolarisation and reduced neuronal output. The net effect of this is to supress hepatic gluconeogenesis via IL-6 dependent changes in gene transcription (449). Leptin is also able to modulate these neuronal populations but probably also via K_{ATP} channel independent mechanisms.

Glial function

Glia cells have a range of functions but one role pertinent to potassium channels is potassium siphoning. Inwardly rectifying potassium channels form the main potassium conductance of glial cells and set the resting membrane potential (60). These channels are key in allowing glia and astrocytes in particular to siphon potassium from areas of high neuronal activity and high extracellular concentration to areas of lower concentration. Kir4.1 is central

to this but the opening of K_{ATP} channels may form some kind of reserve under metabolically challenging conditions (60; 396).

Peripheral nerve function

K_{ATP} channels are also present in peripheral nerves and specifically appear to have a role in controlling autonomic function. For example, inhibition using glibenclamide led to potentiation of the heart effect of both vagal and sympathetic nerve stimulation likely through presynaptic rather than direct cardiac action (4; 365).

K_{ATP} channels and immune function

Sepsis can impose a substantial load on the cardiovascular system and at its most lethal can engender shock often with a high mortality. There have been a number of contradictory studies of the role of K_{ATP} channels in sepsis. Initially, it was proposed that excessive K_{ATP} channel activation occurs in septic shock leading to hypotension which could be reversed by sulphonylureas (346). Other studies support this increase of activity in the vasculature in sepsis but also suggest certain changes in pharmacology namely the lack of effect of sulphonylureas. Only direct pore blockers were able to inhibit activity (392). Furthermore, the expression of Kir6.1 is regulated via Toll-like receptors and nuclear factor kappa-light-chain-enhancer of activated B cells and the increase in expression of the current is postulated to underlie the poor response to vasoconstrictors with overwhelming sepsis (475). However, subsequent studies on mice and flies with global genetic deletion of Kir6.1 revealed that they have a substantial survival disadvantage in models of septic shock (97; 261). The precise mechanism has not been elucidated but a poor response to increased metabolic demand in the coronary circulation is one idea.

K_{ATP} channels may be involved more broadly in immune function. Thus hydrogen

sulphide promotes neutrophil migration into tissues and this response is sensitive to K_{ATP} channel inhibitors (106). The exact mechanism was not defined but it was mediated via mechanisms involving chemokine receptor expression on the neutrophil and given some of these assays were *in-vitro* in nature a direct role of K_{ATP} channels in neutrophil biology cannot be excluded. A second mechanism is endothelial injury promoting the release of mediators and a consequent inflammatory response (141). As we have discussed above K_{ATP} channel may well be a component in that response. K_{ATP} channels within the cellular milieu can also modulate the inflammatory response. Thus in Drosophila infection by a cardiotropic virus is promoted by K_{ATP} channel knockout and inhibited by treatment with a K_{ATP} channel opener (126). Nicorandil can prevent monocyte to macrophage transition and promotes an anti-inflammatory macrophage phenotype (607). Thus in summary, K_{ATP} channels may be involved in inflammatory responses through classic actions in cardiac and vascular tissues however there are also indications that they may have direct actions in modulating immune cell biology. This is an area for future research.

Mitochondrial K_{ATP} channels

There has been considerable interest in whether a K_{ATP} channel is resident in mitochondrial membranes ("mitoK_{ATP}") (244; 410). The earliest study directly recorded channel activity using patch-clamp in the mitochondrial inner membrane by fusing rat live mitochondria to form giant mitoplasts. They measured a 10 pS single channel conductance for a potassium-selective conductance. Critically single channel open probability was reduced by ATP and glibenclamide (244). Later work focussed on cardiac tissues and specifically tried to define a distinctive pharmacology for the mitochondrial channel over that of the sarcolemmal channel. On the basis of more indirect measurements of mitochondrial function, specifically mitochondrial swelling induced by water accompanying the K^+ flux, it was

proposed that 5-hydoxydecanoate was a specific inhibitor and mitoK_{ATP} was activated by diazoxide unlike the sarcolemmal channel (189). However this pharmacology may not be so clear cut (104; 312) and it is notable the number of publications that have made use of this pharmacology as an argument for involvement of mitoK_{ATP} in various protective phenomena (598).

These questions and ambiguities could be resolved by the cloning of the relevant channel subunits. Initially Kir6.1 was suggested as a candidate (324; 510) however this relied on the use of antibodies that may be recognising unrelated mitochondrial proteins (157). A proteomic study isolated succinate dehydrogenase, mitochondrial ATP-binding cassette protein 1, phosphate carrier, adenine nucleotide translocator, and ATP synthase as a complex (8). However none of these proteins is a recognised sulphonylurea like subunit or inwardly rectifying potassium channel subunit. It is becoming clear that 5-hyroxydecanoate and diazoxide also have direct interactions with the components of the mitochondrial respiratory chain (108; 202). However one more recent study is potentially plausible (156). In bovine hearts an inward rectifier subunit (Kir1.2) was isolated from inner mitochondrial membranes. Kir1.2 is a member of the "ROMK" family originally expression cloned from kidney and these channels do show some intrinsic ATP sensitivity (223). Furthermore, short SUR2 variants may localise to mitochondria (131). Finally in *C elegans,* deletion of all three inward rectifier genes did not affect potassium flux across mitochondria or hypoxic preconditioning (575).

In summary, it is clear that drugs traditionally affecting K_{ATP} channels can change mitochondrial function however whether these observations definitively indicate the existence of a K_{ATP} channel can be contested. The ambiguities would be much clarified by the isolation and *in-vivo* validation of a channel subunit encoding mitoK_{ATP}.

Other tissues

There are reports of K_{ATP} channels in joint tissues such as articular chondrocytes and also in bone cells such as osteoclasts (249; 364). Interestingly, nicorandil inhibits osteoclast differentiation: an effect that is dependent both on its ability to act as an NO donor and also to activate K_{ATP} channels (249). K_{ATP} channel subunits are also expressed in the hair follicle and may be involved in regulating the follicle growth cycle (482).

K_{ATP} channels in disease

Human disease can be directly caused by defects in ion channel function particularly neurological, cardiac and endocrine disease. This occurs most commonly as a result of a mutation in an ion channel gene or subunit that occurs either spontaneously or is inherited in a Mendelian fashion within a family. The resultant mutant channels may then not be transcribed or if the protein is produced the channel may not reach the plasma membrane. Finally, if mutant channels do reach the plasma membrane they may then fail to gate or conduct properly or more rarely have enhanced function ("gain of function mutations"). These different mechanisms are summarised in Figure 9. "Channelopathies" can also be acquired in nature for example because of the production of auto-antibodies to channels such as with myasthenia gravis and the muscle endplate acetylcholine receptor. These conditions can give substantial insight into the physiological function of ion channels in man. Secondly, ion channels may be implicated in the genetic architecture of human traits in large scale genome wide association studies (370). Furthermore, ion channels may play a role in complex pathophysiological mechanisms and appropriate pharmacological intervention may ameliorate or reverse disease progression. K_{ATP} channels have been implicated in a range of human pathologies and this is discussed below. Table 7 summarises the association of mutations or genomic variants in K_{ATP} channels with human diseases or traits.

Congenital Hyperinsulinism

Congenital hyperinsulinism describes a disease in which there are inappropriate and high levels of insulin secretion from pancreatic βcells. This leads to low blood glucose and can result in loss of consciousness and neurological damage if left untreated. The disease can present at any time, even into adulthood, but the more severe forms present in the neonate and young child. It occurs in 1 to 50,000 births but is much higher in areas of the middle-east with high levels of consanguinity (122; 381). There are a variety of genetic causes including a abnormalities in a number of metabolic enzymes, such as glutamate dehydrogenase and glucokinase, but those presenting early in life are generally due to mutations in *ABCC8* (SUR1) and *KCNJ11*(Kir6.2) (123; 381; 531). Morphologically a number of different patterns of disease are seen. In diffuse disease, which is the commonest, all pancreatic βcells are affected but the islet histology is normal. In general patients have a recessive inheritance pattern with homozygous or compound heterozygous mutations in the K_{ATP} channel genes (259; 383; 592). In focal disease one or more areas of the pancreas are affected and the cells in these regions are histologically abnormal. The genetics of this disease are more complex with a paternally inherited mutation in *ABCC8* or *KCNJ11* and the loss of a corresponding maternal allele (558). Furthermore, the imbalanced imprinting in the focal areas results in the expression of genes which promote islet cell hyperplasia (insulin-like growth factor 2 and various tumour suppressor genes) (158). Though rarer than the diffuse pattern it still constitutes up to 30-40% of cases and is an important differential in the diagnosis as surgical resection can be curative. Finally there is an atypical histological pattern that does not fit into either of the above (381).

In congenital hyperinsulinism a large number of mutations have been described through-out the *ABCC8* and *KCNJ11* genes (123; 383; 531; 538). In general the mutations are

missense leading to a loss of channel function and this can occur in two ways. Figure 10 illustrates the disease pathogenesis. The first is that the channels no longer reach the plasma membrane due to defects in cellular trafficking (65; 471; 519; 592). They may be retained in the endoplasmic reticulum and\or retrieved from the golgi apparatus where they are likely recognised as abnormal and degraded by the proteasome. Alternatively, they may be rapidly endocytosed on reaching the plasma membrane and degraded in lysosomes (336). In a second class of mutation, the SUR1 subunit is delivered to the plasma membrane but the ability of the channel complex to be stimulated by MgADP is impaired (486). This results in membrane resident but inhibited K_{ATP} channels that no longer respond to metabolism in the normal way. These mechanisms have been elucidated generally in heterologous expression systems but have also been confirmed in patient derived samples obtained after pancreatectomy (123; 259). In addition, studies of patient-derived pancreatectomy samples also showed that βcells were depolarised and calcium overloaded.

The disease can be treated using diazoxide but this is only successful in a proportion of cases. In focal disease, the lesion or lesions can be surgically removed resulting in cure. In severe diffuse disease, partial pancreatectomy is ultimately necessary and may in later life lead to diabetes mellitus (502). There has been preclinical interest in whether trafficking deficient mutants can be rescued and trafficked to the plasma membrane using various pharmacological agents. There have been cellular studies showing that diazoxide and sulphonylureas can act as chemical chaperones resulting in improved delivery of channels to the plasma membrane (408; 591; 592). Whilst there are obvious practical issues with using sulphonyureas it suggests it is possible to find pharmacophores that can perform this function. For example recent studies have suggested that carbamazepine can act in this fashion (341). The recent clinical success of mutation-specific therapy in cystic fibrosis also means that other channelopathies may be amenable to similar approaches (425; 561).

The majority of congenital hyperinsulinism is autosomal recessive in inheritance. Interestingly however autosomal dominant disease is described and is generally milder often presenting later and is well managed by medical therapy especially diazoxide (235; 268; 413). It appears that the majority of these mutations have impaired function: an effect that is dominant in the assembled octamers. Some dominant mutations do not respond to medical therapy and these appear to be a dominant negative trafficking deficit (380). Furthermore there are some indications that these patients may develop diabetes mellitus in later life (235). It is thought the excess calcium entry ultimately leads to pancreatic β cell apoptosis as in mice (see above).

Neonatal Diabetes Mellitus

Neonatal diabetes mellitus is generally defined as diabetes mellitus occurring within the first six months of life though this has recently been extended by some investigators to nine months (451; 452). Type 1 diabetes is very rare in this age group and these patients have a unique genetic aetiology. A large number of genes have been implicated in causing the disease and these are involved in beta cell function, insulin release, pancreatic development and beta cell death (451). The three most commonly affected genes are *KCNJ11*, *INS* which encodes the proinsulin protein and *ABCC8* (451). The discussion will be confined to disease causing genes in the pancreatic K_{ATP} channel subunits. The disease is rare occurring in 1 to 100,000 of births (451).

Mutations in *KCNJ11* and *ABCC8* generally occur de-novo in outbred populations and are heterozygotic (178; 451; 533). There are spectrums of presentation from transient neonatal diabetes, and permanent neonatal diabetes through to much severer syndromes involving neurological manifestations which make up about 20% of cases (152; 177). These include developmental delay, autism and epilepsy (developmental delay, epilepsy and

neonatal diabetes; DEND syndrome) and in some patients the epilepsy is absent (intermediate DEND; iDEND syndrome) (177; 451). In addition motor delay, ataxia, anxiety and attention deficit hyperactivity disorder can also be features of the neurological disease. SUR1 and Kir6.2 constitute a large population of widely distributed neuronal channels and thus it is not surprising that the central nervous system is involved (82). A murine model has been developed in which it was possible to selectively express the V59M Kir6.2 mutation in a variety of tissues using various tissue selective cre recombinases and these models offer insight into human disease pathogenesis. Expression of V59M Kir6.2 in the pancreas leads to impaired insulin release and diabetes (176). Furthermore, it seems that the muscle weakness is related to expression of mutant K_{ATP} channels in the central nervous system and not in muscle myocytes (81; 82). The expression of V59M Kir6.2 in the central nervous system as well as muscle weakness also leads to reduced anxiety (301). Interestingly, it appears that "neonatal diabetes" can present later in life due to K_{ATP} channel mutations either around adolescence or during pregnancy (152). In *KCNJ11* the mutations often cluster on select residues particularly R201 and V59 whilst they are more widely distributed in *ABCC8* (13). When the mutations are expressed in heterologous expression systems they lead to channels that have a "gain of function" phenotype and that are, to varying extents, insensitive to ATP inhibition (26; 175; 178). Figure 10 illustrates the disease pathogenesis. The severity of phenotype correlates with the degree of ATP insensitivity: DEND mutations lead to a severe loss of ATP inhibition whilst in neonatal diabetes the impairment can be modest (13). In this regard, a recessive KCNJ11 mutation has been described (G324R) which in the homozygous form leads to transient neonatal diabetes mellitus whilst the parents as heterozygous carriers show no evidence of impaired glucose homeostasis (556). When the mutation is expressed in heterologous expression systems the IC_{50} for channel inhibition is only modestly shifted from 30 μM to 38 μM with the mutant (556). It is interesting that even with KCNJ11 mutations

there is little evidence for cardiac or muscle disease that is independent of nervous innervation (81). Indeed in expression studies with SUR2A, KCNJ11 mutations do not affect ATP sensitivity to the same degree (517).

The discovery of the genetic basis of this disease has led to a revolution in the management of the patients and is a genuine example of precision medicine (411). Traditionally these patients were treated with insulin but the discovery of the over-activity of pancreatic K_{ATP} channels as central in the disease pathogenesis led to the use of sulphonylureas. The responses were dramatic with glucose homeostasis becoming normalised in many patients with normal responses of insulin release following eating due to preservation of the response of pancreatic β cells to incretins (411). High doses are necessary particularly when neurological disease is present and with severe disease and ATP-insensitive mutants the use of sulphonylureas may fail (13; 27). The neurological deficits are often only partially ameliorated by sulphonylurea treatment as their origins may, to a degree, be developmental (13; 39; 138; 286; 470; 490). Another interesting feature is that in contrast to type II diabetes mellitus, where with time sulphonylurea therapy fails, in neonatal diabetes the opposite occurs with a reduction in dose often necessary (237). However it is important to begin therapy as early as possible, as with time there is a decline in the success of sulphonylureas in neonatal diabetes (27). Expression of V59M Kir6.2 in the murine model above in the endocrine pancreas leads to additional morphological changes with glycogen accumulation in islets suggesting that high glucose can itself lead to βcell damage (55; 433). These morphological changes can be reversed by restoration of a normal blood glucose. The study of these naturally occurring mutations has also supported the molecular models of sulphonylurea action. Sulphonylureas inhibit MgADP activation and binding but this does not lead to complete closure and the antagonism is partial with a maximum of 70-80% inhibition (416). In intact cells the remaining inhibition is postulated to arise from MgADP now being

able to act as an inhibitor of Kir6.2 in the presence of sulphonylureas. However if the mechanism of ATP inhibition by the mutant Kir6.2 subunit is severely attenuated then sulphonylureas may lead to incomplete block (416). This may account for why therapy for very severe forms of neonatal diabetes, with or without the neurological sequelae, is less effective.

Type 2 diabetes and genome wide association studies

Type 2 diabetes is usually thought of as a disease of peripheral insulin resistance however ~~it is clear that~~ pancreatic βcell mass is reduced and insulin secretion impaired. In addition to the role of K_{ATP} channels in Mendelian diseases of blood glucose homeostasis, genome wide association studies in type 2 diabetes have implicated loci in and around the *ABCC8-KCNJ11* genes in addition to numerous other associations (171). In general the exact mechanism by which such genomic changes result in changes in β cell physiology are not clear. It is complicated by the fact that the tag single nucleotide polymorphism is often in linkage disequilibrium with a number of other variants any of which may be causative. However in the case of the K_{ATP} channel complex there is a coding variant (E23K) in KCNJ11 that drives the association (179). The E23K mutant when expressed in heterologous expression systems leads to modest reductions in ATP sensitivity (197; 559). Furthermore, it is interesting that the E23K mutation is in linkage disequilibrium with another coding mutation in ABCC8 (S1369A) and co-expression of the two variants may potentiate the functional phenotype (197). The E23K mutant channels are also more susceptible to activation by long chain fatty acyl CoA species (436).

Cardiac Arrhythmia

A variety of different arrhythmic mechanisms can be distinguished including re-entry,

abnormal automaticity and abnormal electrical events such as early and delayed after-depolarisations (146). In guinea pig ventricular myocytes action potential duration (APD) was reduced by as much as 50% when as little as 0.7% of the maximum K_{ATP} conductance was active (387) and the opening of K_{ATP} channels leads to foreshortened repolarisation and QT interval on the surface ECG (165; 294). In turn this gives a reduced effective refractory period, which in principle can predispose to re-entrant circuits and a pro-fibrillatory state. Pro-fibrillatory effects of K_{ATP} openers have been shown in numerous animal models and a major factor in this is likely to involve heterogeneous dispersion of action potential duration both in an interventricular, and intraventricular manner between layers of the myocardium (72; 116; 163; 549; 577; 578). The corollary is that blocking K_{ATP} channels would be anti-arrhythmic. Studies in rat and canine models have looked at ventricular fibrillatory potential in the context of ischaemia and shown that this is reduced in the presence of K_{ATP} blocking drugs (44; 267; 578). This has been replicated in a Langendorff-perfused explanted cardiomyopathic human heart model (133).

Studies have also investigated arrhythmia inducibility in atrial preparations. In a rat model β-adrenergic induced metabolic stress caused reduced intracellular ATP concentration and led to inducible atrial tachyarrhythmia that was reversed with glibenclamide (279). In a murine model with salt-induced hypertension, atrial K_{ATP} channel upregulation was seen coinciding with a shortened effective refractory period and increased atrial arrhythmia inducibility (300). In human hearts obtained at transplantation, potassium channel openers were seen to increase atrial arrhythmia inducibility that was then terminated with a K_{ATP} inhibitor (133). Interestingly, in clinical trials with nicorandil there was no increased arrhythmic risk (529). Atrial electrophysiology remodels as a consequence of atrial fibrillation (571) but conflicting evidence exists for remodelling of K_{ATP} current in human chronic AF. Two studies have looked at differences in K_{ATP} current density in isolated right

atrial appendage myocytes between sinus rhythm and chronic AF patients and showed opposing results (28; 580).

The significance of an early repolarisation pattern ("J wave") on the ECG is controversial. For example, it is commonly observed in healthy males and athletes but in other circumstances it may presage something more malignant and the early repolarisation pattern ("J wave syndromes") may predispose individuals to ventricular fibrillation and sudden death (6). A rare variant in KCNJ8 (S422L) has been associated with prominent early repolarisation and ventricular fibrillation (193). Other groups subsequently described similar findings with the same mutation (32; 349). In functional studies in heterologous expression systems this mutation led to an increase in current-density when the mutant Kir6.1 subunit was expressed with a SUR caused by a decrease in ATP sensitivity (32; 193; 349). ABCC9 mutations have also been reported in Brugada syndrome and these too led to gain of function phenotypes in expression systems (228). Sudden infant death syndrome has also been reported to be associated with mutations in KCNJ8. An in frame deletion E332del and a missense mutation V346I have been associated with this condition and both led to some loss of K_{ATP} channel function in heterologous expression systems (527). It is worth bearing in mind that the ExAc project is discovering a large number of missense mutations present in the population at large and has resulted in re-interpretation of the pathogenicity of missense mutations in a number of diseases (269).

Whilst K_{ATP} channel opening might lead to an increased likelihood of re-entry, in the case of abnormal automaticity or triggered activity it is also possible that hyperpolarisation of the membrane will lead to the arrhythmia being extinguished. Thus in isolated Purkinje fibre preparations K_{ATP} channel opening slows spontaneous firing rate and suppresses automaticity (239) whilst hypoxia-induced spontaneous cycle length prolongation was blunted in Kir6.2 knockout mice suggesting a role in sinus node automaticity (161). Pinacidil has been shown

to abolish early and delayed after-depolarisations (497). Indeed, nicorandil can abolish transmural dispersion of repolarisation and triggered activity in canine long QT models (479) and when given intravenously, has been shown to abolish EADs and ventricular fibrillation in a patient with long QT syndrome (460). Loss of K_{ATP} channel function has also been shown to promote triggered activity: for example, Kir6.2 knockout mice developed early afterdepolarisations after isoproterenol challenge (322). A similar mechanism was proposed in a patient with lone atrial fibrillation emanating from the vein of Marshall who was found to have a missense mutation in the *ABCC9* gene encoding the SUR2A subunit (397). Thus the exact role of K_{ATP} channels in arrhythmia is complex and dependent on the substrate.

Heart failure, hypertrophy and cardiomyopathy

Adult cardiac cells do not divide and respond to a prolonged increase in workload with cell hypertrophy. This can be physiological as occurs with exercise training but can also be the response to cardiac disease such as in hypertension and heart failure (84). The pathological hypertrophy can contribute significantly to the disease pathobiology. Aortic banding is a commonly used approach to generate hypertrophy in animal models and in Kir6.2 knockout mice it leads to increased hypertrophy compared to littermate controls (589). However, the interpretation of these results is complicated by the paradoxical observation that this also occurs in mice with transgenic overexpression of SUR1 (230). The suggestion is that the SUR1 transgenic mouse also has disrupted cardiac sarcolemmal currents (230). Hypertrophy also occurs following myocardial infarction and Kir6.1 expression has been shown to be increased around the infarct border zone (246). Furthermore, this increase in Kir6.1 expression correlated with increased angiotensin II and tumour necrosis factor α expression (245; 246). In contrast Kir6.2 expression decreased. The cells also become responsive to diazoxide and have significantly upregulated K_{ATP} currents. Although under

resting conditions the action potential duration is prolonged, after the application of diazoxide it significantly shortens (246). Similar observations have been made in human samples (136). Cardiomegaly is also a feature of the Cantu syndrome (see below).

There are also some indications that K_{ATP} channels might lead to rare forms of heart muscle disease. A group of patients with dilated cardiomyopathy were subjected to sequencing of the K_{ATP} channel genes. A missense mutation A1513T and a frameshift mutation leading to a premature stop codon at Leu1524 were discovered in ABCC9. In functional studies these mutations impaired nucleotide hydrolysis at NBD2 (43). We have already discussed the non-synonymous polymorphism in Kir6.2 which generates a coding change (E23K) in relation to predisposition to type II diabetes mellitus. It is interesting that this polymorphism is also associated with increased left ventricular size in hypertensive patients and is also over-represented in heat failure patients (434; 435). Furthermore, homozygous carriers have reduced exercise capacity with an attenuated heart rate response and lower maximal oxygen consumption (434).

Cardioprotection

Cardioprotection is a broad term which includes protection from cardiac ischaemia, ischaemia-reperfusion injury and phenomena such as early and late preconditioning (599). K_{ATP} channels have a long history of being implicated in these various processes. These include as both an initiator and\or a downstream effector of the response whether present in cardiac sarcolemmal or mitochondrial membranes (153; 598). For example, ischaemic preconditioning was eliminated in Kir6.2 global knockout mice and diazoxide was no longer able to mimic ischaemic preconditioning (190; 512; 513). It is thought that the action potential shortening due to K_{ATP} channel opening leads to reduced calcium entry and attenuated contractile function as illustrated in Figure 11 ~~and also discussed above~~ (304; 557).

The net effect is to reduce the energy demands on the cell and prevent calcium overload both of which, if unchecked, would lead to cell death. Thus K_{ATP} inhibitors prevent the action potential shortening whilst potassium channel openers potentiate the effect preserving cellular ATP levels (348; 557). In the Kir6.2 knockout mouse there was a failure of action potential shortening and prolonged contractile dysfunction (513). Application of potassium channel openers also reduced the amount of calcium entering the cell during reperfusion: a possible central event in ischaemia-reperfusion injury. Transgenic mice, with over-expression of SUR2A in cardiac myocytes, have increased cardiac K_{ATP} currents and this protects the cardiac myocytes from subsequent ischaemic challenge (119). There may even be a reservoir of K_{ATP} channels that can translocate from intracellular sites to the plasma membrane under conditions of metabolic strain (30; 58). Recent studies have shown that eps15 homology domain-containing protein 2 increases K_{ATP} channel trafficking and currents by inhibiting endocytosis. Furthermore expression of a dominant-negative mutant sensitised increased cardiac damage to ischaemia (595). Latest observations also suggest that activation of Kir6.2-containing channel complexes occurs relatively late during ischaemic challenge in ventricular myocytes and other channels perhaps even those containing Kir6.1 subunits might also be important in the initial phase (54). It is also worth remembering that vascular K_{ATP} channels can have a significant influence on cardiac protection. Ischaemia-reperfusion injury was significantly increased in mice with both endothelial and smooth muscle deletion of Kir6.1 (20).

Thus the comprehensive available data using pharmacological agents and molecular approaches do indicate a potential role for K_{ATP} channels in a variety of cardioprotective processes. A host of second messengers and receptor pathways have been invoked either upstream or downstream of the channels and these include protein kinase C, adenosine receptors and reactive oxygen species to name but a few. However recent trends have

focussed on new pathways including opening of the mitochondrial permeability transition pore and various protein kinases including protein kinase B and janus kinase pathways (191; 447). It is not yet clear how these new paradigms integrate with the body of older literature to give a coherent view of these processes. Furthermore, the critical issue is whether cardioprotection can be used to benefit patients in common clinical scenarios. Human tissue preconditions in the same way that animal hearts do and thus this may be potentially feasible (495). Preconditioning can also be evoked remotely for example by repeatedly inflating a blood pressure cuff and this is much easier to use safely in patients in the hospital setting (331). K_{ATP} channels have a role in the effect and it likely resembles the phenomena invoked by local ischaemia though the full transduction pathway is not clear (35; 331; 345). However clinical trials have so far failed to show benefit: for example, remote ischaemic preconditioning was disappointingly unable to improve outcomes in the well-controlled setting of cardiac surgery (208; 352). The cardioprotection field is currently under a cloud as the best path to realising clinical benefit is not clear.

Cantu syndrome

Cantu syndrome is a very rare disease characterised by hypertrichosis, abnormal facial features with similarities to that occurring in acromegaly, macrosomia, skeletal abnormalities and an enlarged heart (62; 439; 448). A number of other clinical features have been noted to occur in some individuals and these include pericardial effusion, patent ductus arteriosus, conduction system abnormalities, pulmonary hypertension and coarse lax skin (466). The genetic basis of the disease was initially obscure though sporadic autosomal dominant mutations were suspected. The advance came from the use of exonic sequencing in parent patient trios and led to the discovery of novel missense mutations in *ABCC9* (205; 552). Subsequently a few missense mutations were also described in *KCNJ8* (57; 91). Using

standard heterologous expression techniques these mutations were expressed and shown to lead to increased K_{ATP} channel activity (92; 205). This occurs in two ways: the first is to impair inhibition to ATP and the second to increase activation by MgADP (92). A murine model has been developed in which Kir6.1 gain of function mutations can be transgenically expressed in various tissues and this can replicate features of the disease (306). However, this approach allows such mutant channels to be expressed ectopically where they may not under normal circumstances be expressed and does not replicate possible developmental aspects of the disease. In both Cantu syndrome and neonatal diabetes there is an argument for making true knock-in models to phenocopy the disease especially as this is easier now with CRISPR\cas9 technologies. As in neonatal diabetes sulphonylureas may significantly influence the course of the adult disease though they may not be effective in every case (90). To date there are no clinical data on the efficacy of this approach. One intriguing feature is that the clinical phonotype seems to be equivalent in *ABCC9* and *KCNJ8* mutation carriers. *ABCC9* mutations would be thought to influence both Kir6.1 and Kir6.2 channel populations. This suggests that Kir6.1 might have a wider role in tissue physiology than is commonly appreciated and particularly during development.

K_{ATP} channels and neurological disease

The K_{ATP} channel mutations that underlie congenital hyperinsulinism, neonatal diabetes and the Cantu syndrome can all have varying degrees of neurological pathology. It seems that these are due to primary abnormalities associated with K_{ATP} channel expression in neurones and not simply a secondary consequence of metabolic changes. Thus K_{ATP} channels can directly influence brain function in man but the he exploitation of this for wider neurological disease is very much at an experimental stage.

There has been interest in the involvement of K_{ATP} channels in neuroprotection and

stroke (217). The arguments are similar to those invoked for cardioprotection in that hyperpolarisation leads to neuronal silencing thus reducing metabolic demands. In addition the hyperpolarisation prevents the terminal depolarisation and large rise in intracellular calcium that is a prelude to neuronal death. A number of studies have shown such effects in several different neuronal populations (160; 168; 590). In CA1 hippocampal neurones five minutes of hypoxia induces hyperpolarisation whilst in the same neurones from Kir6.2 knockout mice there is a rapid depolarisation (509). Furthermore middle cerebral artery occlusion resulted in greater brain injury in an *in-vivo* model in mice lacking Kir6.2 compared to control mice (508). Finally, transgenic mice overexpressing Kir6.2 in the forebrain were resistant to ischaemic injury due to neuronal silencing (216).

Neurones vary in their sensitivity to damage by anoxia. For example dorsal vagal neurones are highly resistant and this is attributed to prominent expression of K_{ATP} channel currents (29). However this is not a universal phenomenon and there has been focus on dopaminergic neurones in the substantia nigra given their relevance for Parkinson's disease. In an interesting study the behaviour of ventral tegmental neurones with those in the substantia nigra was compared. The neurones in the substantia nigra were particularly susceptible to toxins known to lead to dopaminergic neuronal death and Parkinson's disease. The application of these known toxins provoked K_{ATP} channel firing and cell death in the substantia nigra but not in the ventral tegmental area. The cell death and degeneration was prevented in the Kir6.2 knockout mouse (320).

Neuronal K_{ATP} channel also seem to be important in determining seizure threshold. Kir6.2 knockout mice are predisposed to hypoxia induced seizures and this was thought to arise from abnormal excitability of substantia nigral neurones in the genetically modified mice (586). In addition, mice transgenically overexpressing SUR1 in the forebrain were resistant to kainic acid induced seizures (215).

The current clinical use of drugs modulating K_{ATP} channels

Sulphonylureas are still used in the treatment of type II diabetes however they can lead to counterproductive weight gain and also a risk of hypoglycaemia particularly in the elderly (393). In addition, it is recommended that the newer classes of sulphonylurea and related agents are used because of the potential for drugs such as glibenclamide to inhibit K_{ATP} channels in cardiac cells. The more modern trend is to use metformin instead though suphonylureas still have a place in those intolerant of metformin and in combination therapy (393). In addition to fewer problems with weight gain there is also evidence that metformin is associated with a lower risk of dementia (399).

Nicorandil is used as a second line agent for the treatment of stable angina with β adrenoreceptor blockers and calcium channel antagonists the agents of choice. Nicorandil can also be used in combination treatment with these drugs however if more than two drugs fail to control symptoms some form of coronary revascularisation is generally recommended. The drug has been associated with gastrointestinal and skin ulceration and this has limited its use (200). Nicorandil has been tested in clinical trials to see if it can prevent acute coronary syndromes in patients with stable angina (529). There was some evidence of efficacy and also in a subsequent meta-analysis (333). However in the UK nicorandil is not recommended for secondary prevention after myocardial infarction (https://www.nice.org.uk/guidance/cg172).

Very high levels of blood pressure represent a medical emergency and need urgent pharmacological intervention. Diazoxide and minoxidil are potent anti-hypertensives and can be used in these situations. However they are second line drugs with labetolol and nicardipine preferred in modern clinical practice (412). Monoxidil is also known to promote hypertrichosis and this has been exploited as a topical preparation for male pattern baldness (395). Hair follicles express K_{ATP} channel subunits but it is unclear what the mechanism is

with direct effects on the follicle growth cycle or increases in blood flow being plausible (482). It is interesting that hypertrichosis is a feature of Cantu syndrome and suggests there is a direct effect of K_{ATP} channel in the hair follicle.

Conclusions

K_{ATP} channels are potassium channels that are directly sensitive to cell metabolism. They are complex molecular machines constituted of an octamer of four sulphonylurea receptors and four Kir6.0 inward rectifier potassium channel subunits. The channels are widely distributed in a number of tissues and differential functional and pharmacological properties are accounted for by distinct subunit expression. The combination of structure function studies and recent high resolution structural information, means we understand in much greater molecular detail how the channels select for potassium and respond to ATP, MgADP, PIP_2 and various pharmacological agents. The use of pharmacology, genetically engineered murine strains and the study of human disease have supported a number of physiological and pathological roles for K_{ATP} channels. The best characterised are K_{ATP} channels in pancreatic β cells that are central in supporting stimulus secretion coupling between blood glucose and insulin secretion. Furthermore, glibenclamide and derivatives are used to treat type II diabetes mellitus and mutations in SUR1 and Kir6.2 can result in congenital hyperinsulinism and diabetes. However the physiological role of K_{ATP} channels is broader and includes regulation of muscle excitability and contraction, neuronal excitability and vascular and non-vascular smooth muscle contractility. K_{ATP} channels are also involved in cellular protection in a number of tissues and there may be ways of harnessing this for use in human disease.

It is likely that further definition of molecular function, such as nucleotide regulation and K_{ATP} channel drug interactions, will come through additional structural studies and this

may help develop new therapeutic approaches. The trafficking and regulation of the channel are still poorly defined particularly in native cells. Proteomic techniques are likely to reveal novel interactions and give clues to similarities and differences in different tissues. The use of increasingly sophisticated genetically modified mouse lines such as those that allow temporal and tissue-specific deletion is likely to further refine our integrated understanding of K_{ATP} channel function in the whole organism. Modern human genomics including genome wide association studies in various physiological and disease traits, and exome and genome wide sequencing technologies are likely to further reveal the role of these channels and associated pathways in human disease. Furthermore, the transcriptional control of expression in development and disease are little investigated and again modern epigenetic techniques could have an impact in this area.

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Tables

Table 1 - Pharmacology of drugs acting on K_{ATP} channels

	Drug	Chemical class	Type of K_{ATP} channel	Mechanism of action	Drugs of same class
KCOs	*First Generation*				
	Pinacidil	Cyanoguanidines	Cardiac K_{ATP}, Smooth muscle K_{ATP}	↓ Sensitivity to ATP ↑ K_{ATP} opening	P-1075, PNU-99963, PNU-9470
	Diazoxide	Benzothiadiazines	Cardiac K_{ATP}, Smooth muscle K_{ATP}, Mitochondrial K_{ATP}, Pancreatic K_{ATP}	Require ADP for activity	LN-5330
	Cromakalim	Benzopyrans	Cardiac K_{ATP}, Smooth muscle K_{ATP}	↓ Sensitivity to ATP ↑ K_{ATP} opening	Levcromakalim, Blmakalim, Cellkalim, Rilmakalim, Y-27152
	Nicorandil	Pyridyl Nitrates	Cardiac K_{ATP}	Require ADP for activity Exhibit nitrate-like effect	KRN-2391
	Minoxidil	Pyrimidine Sulfate	Cardiac K_{ATP}	ND	LP-805
	Aprikalim	Carbothiamides	Cardiac K_{ATP}	ND	MCC-134
	Second Generation				
	WAY-151616	Cyclobutenediones	Smooth muscle K_{ATP}	ND	WAY-133537
	ZM-244085	Dihydropyridine	Smooth muscle K_{ATP}	ND	ZD-0947
	ZD-6169	Tertiary carbinols	Smooth muscle K_{ATP}	ND	A-151892
Inhibitors	*First Generation*				
	Tolbutamide	Sulfonylureas	Pancreatic K_{ATP}	Binding with lower affinity	Chlorpropamide, Acetohexamide, Tolazamide
	Second Generation				
	Glibenclamide	Sulfonylureas	Cardiac K_{ATP}, Smooth muscle K_{ATP}, Mitochondrial K_{ATP}, Pancreatic K_{ATP}	Binding with higher affinity	Glipizide, Glimepiride, Glipizide
	Third generation				
	Meglitinide	Benzoic acid derivatives	Pancreatic K_{ATP}	Nonsulfonylurea insulin secretagogues Binding with lower affinity	Repaglinide, Nateglinide, Mitiglinide
	HMR-1098	Sulfonylureas	Cardiac K_{ATP}	Binding with higher affinity	HMR-1883

Table 2 – A summary of genetically modified mouse models used in investigating the biology of K_{ATP} channels

Mouse Genotype	Functional effect on K_{ATP}	Premature Death	Blood Pressure Effects	Cardiac Effects	Mouse Phenotype	References
Whole animal						
Kir6.1-/-	Loss of current in vascular smooth muscle	Yes	Increased	Yes	Coronary artery vasospasm, hypertension, heart block and premature death	(22; 309; 358)
Kir6.2-/-	Loss of current in striated muscle and β-cells	No	No	Yes	Defective glucose-induced insulin secretion. Loss of current in ventricular myocytes. Action potential shortening and depressed cardiac contractility in response to KCOs. Enhanced glucose uptake in skeletal muscle. Impaired glucagon secretion. Impaired exercise tolerance with muscle damage and arrhythmia under stress. No neuroprotection after seizure.	(322; 355; 357; 511-513; 528; 586; 616)
Kir6.2 Y12X ENU mutagenesis	Loss of current in pancreatic β-cells	ND	ND	ND	Impaired insulin secretion and no hypoglycaemia	(232)
SUR1-/-	Loss of current in atrial cardiomyocytes and β-cells	No	No	ND	Glucose intolerance and impaired insulin secretion. Protected against ischemic insult.	(127; 149; 467; 481)
SUR1 E1506K knock-in	Loss of current in pancreatic β-cells	ND	ND	ND	Initially hyperinsulinism but later followed by reduced β cell insulin content and diabetes mellitus	(480)
SUR2-/-	Loss of current in smooth, cardiac and skeletal muscles	Yes	Increased	Yes	Coronary artery vasospasm, hypertension, heart block and premature death. Increased glucose uptake in skeletal muscle. Impaired exercise tolerance and skeletal muscle myopathy. Resistant to cardiovascular stress.	(74; 75; 504; 505)
Smooth muscle						
sm22α cre-Kir6.1 (flx, flx)	Loss of current in vascular smooth muscle	No	Increased	No	Hypertension	(22)
sm22α-SUR2B/SUR2-/-	SM-specific expression of SUR2B in SUR2 KO	Yes	ND	Yes	Coronary artery vasospasm, hypertension, heart block and premature death	(257)

	mice					
smMHC-Kir6.1-AAA	Dominant-negative suppression of Kir6.1 in smooth muscle	No	Increased	No	Hypertension	(309)
smMHC-Kir6.1[G343D]	Gain of function in smooth muscle	No	Decreased	No	Hypotension, reduced blood vessel contractility	(309)
smMHC-Kir6.1[G343D,Q53R]	Gain of function in smooth muscle	No	Decreased	No	Hypotension, reduced blood vessel contractility	(309)
Endothelium						
Tie2 cre, Tg STOP Kir6.1-AAA	Dominant-negative suppression of Kir6.1 in endothelium	No	No	Yes	Coronary vasospasm. Increased coronary perfusion pressure	(335)
Tie2 cre -Kir6.1 (flx, flx)	Loss of current in endothelium	No	No	No	Protective against ischemia-reperfusion damage	(20)
Cardiac Tissue						
CMV-SUR2A	Increased expression in Cardiac muscle	No	ND	ND	Resistant to hypoxia, ischemia and ischemia-reperfusion injury	(119)
αMHC-Kir6.1[G343D]-AAA	Increased expression in Cardiac muscle	No	ND	Yes	Decreased ATP sensitivity, AV nodal abnormalities, Increased tolerance to cardioplegic stress	(213; 307)
α-MHC cre, Tg STOP Kir6.1-AAA	Dominant-negative suppression of Kir6.1 in cardiac muscle	No	ND	Yes	Loss of current in ventricular myocytes, Increased heart rate, Prolonged APD, Compromised exercise tolerance.	(537)
α-MHC cre, Tg STOP Kir6.2-AAA	Dominant-negative suppression of Kir6.1 in cardiac muscle	No	ND	Yes	Loss of current in ventricular myocytes. Prolonged APD	(537)
α-MHC-FLAG-SUR1	Overexpression in cardiac muscle	Yes	ND	No	PR Prolongation. Reduced K_{ATP} conductance	(151)
α-MHC-Kir6.2[ΔN2-30,K185Q]	Overexpression in cardiac muscle	Yes	ND	Yes	Increased incidence of AV block. Reduced K_{ATP} conductance. Prolonged APD	(147; 287)
α-MHC-FLAG-SUR1/ α-MHC-Kir6.2[ΔN2-30,K185Q	Overexpression in cardiac muscle	Yes	ND	Yes	PR Prolongation, Ventricular tachycardia, AV block, Atrial fibrillation, atrial flutter	(150)
α-MHC-FLAG-SUR2A	Overexpression in	No	ND	No	Reduced K_{ATP} current-density	(151)

	cardiac muscle					
Mck-cre, Rosa26STOP Kir6.2 V59M	Gain of function in muscle cells	No	ND	No	Impaired ATP sensitivity of channels in skeletal and cardiac muscle. No discernible phenotype	(81)
Pancreas						
Rip-cre, Rosa26STOP Kir6.2 V59M	Gain of function in pancreatic islets	ND	ND	ND	Reduced insulin secretion and diabetes mellitus	(176)
Rip-Kir6.1[G343D]	Gain of function in pancreatic islets	No	ND	ND	Glucose intolerance	(432)
Rip-Kir6.1[G343D,Q53R]	Gain of function in pancreatic islets	No	ND	ND	Reduced plasma insulin and severe diabetes mellitus	(432)
Neuronal						
CMK-SUR1	Increased expression in forebrain	No	ND	ND	Protective against seizures and neuronal damage	(215)
Nestin-cre, Rosa26STOP Kir6.2 V59M	Gain of function in central neurones	ND	ND	ND	Muscle weakness and reduced anxiety	(82; 301)

Table 3 – Summary of the properties of K_{ATP} channel populations in the pancreas and gut

Location	Subunit Composition	Conductance (pS)	ATP IC_{50} (μM)	Physiological Function	Refs
α-cells	Kir6.2\SUR1	45-70	17	Regulation of glucagon secretion in response changes in blood glucose	(36; 48; 445; 609)
β-cells	Kir6.2\SUR1	70-80	15-160	Regulation of insulin release in response to changes in metabolism	(14; 241; 243) (359)
Enteroendocrine cells	Kir6.2\SUR1	ND	ND	Involved the stimulus-secretion coupling of gut hormones such as GIP, GLP-1 and PYY	(334; 388; 428)

GIP - gluco-insulinotropic peptide, GLP-1 - glucagon-like peptide-1, PYY - peptide tyrosine tyrosine

Table 4 – Summary of the properties of the major K_{ATP} channel populations in striated muscle

Location	Subunit Composition	Conductance (pS)	ATP IC_{50} (μM)	Physiological Function	Refs
Atria	Kir6.2\SUR1	52-90	39-100	Action potential repolarisation. Adaptation to cell swelling	(33; 149; 248; 553; 619)
Ventricles	Kir6.2\SUR2A	70-90	10-100	Protection against Ca^{2+} overload during hypoxia, Adaptation response to stress	(31; 148; 240; 391; 526)
Conduction System	Kir6.1\Kir6.2\ SUR2B	52-60	16-120	Adaptation to stress, regulation of pacemaker activity	(31; 162; 201; 314)
Skeletal Muscle	Kir6.2\SUR2A Kir6.2\SUR1	60-71	13-123	Adaptation to strenuous exercise and prevention of muscle fibre damage during exercise. Regulation of glucose uptake and metabolism.	(22; 74; 75; 351; 356; 358; 420; 488; 528; 543; 545; 587; 614)

Table 5 – Summary of the properties of the major K_{ATP} channel populations in smooth muscle

Location	Subunit Composition	Conductance (pS)	ATP IC_{50} (μM)	Physiological Function	Refs
Endothelium	Kir6.1\Kir6.2\ SUR2B	25-40 and 150	ND	Protective during ischemia	(20; 252; 273; 274; 335; 600)
Vascular Smooth Muscle	Kir6.1\SUR2B	15-50	29-200	Vasodilation Blood pressure regulation	(22; 74; 358; 420; 587)
Non-vascular Smooth Muscle	Kir6.1\Kir6.2\ SUR2B	18-80		Relaxation/Contraction	(284; 522)

Table 6 – Summary of the K_{ATP} channel expression profile and function in the central and peripheral nervous systems.

Location	Subunit Composition	Conductance (pS)	ATP IC_{50} (μM)	Physiological Function	Refs
Hypothalamus	Kir6.2\SUR1	13-86, 149	ND	Expressed in AgRP/NPY- and POMC-positive neurons. Regulation of neuronal excitability in response to glucose. Activity regulated by insulin and leptin.	(238; 414; 493)
Pituitary	Kir6.2\SUR2B Kir6.2\SUR1	74	30	Regulation of hormone secretion	(59; 582)
Substantia Nigra	Kir6.2\SUR1	77	12	Neuroprotection from stress and against seizures, Regulation of excitability, Release of neurotransmitters such as dopamine, GABA and glutamate in response to changes metabolism. Play a role in memory, locomotion and behaviour	(19; 121; 283; 461; 473; 586)
Dorsal Root Ganglion	Kir6.2\SUR1\ SUR2	72-78	ND	Suppression of hyperalgesia.	(275; 618)
Glial Cells	Kir6.1\Kir6.2\ SUR1	ND	ND	Neuroprotective Potassium siphoning	(532; 603; 611)

AgRP/NPY-agouti-related peptide/neuropeptide Y, POMC-proopiomelanocortin

Table 7 – A summary of human diseases associated with mutations in K_{ATP} channel subunits.

Gene	Clinical Condition	Mechanisms of disease	Reference
KCNJ8	Cantu Syndrome	Missense non-synonymous variant V65M, functional characteristics not confirmed	(57)
	Sudden Infant Death Syndrome	In frame deletion E332del and missense mutation V346I each cause loss of function and have been associated with this condition	(527)
	Brugada syndrome, Early repolarisation ("J wave") syndrome, atrial and ventricular fibrillation	S422L GOF has been associated with these conditions	(32; 114; 193; 349)
KCNJ11	Congenital Hyperinsulinism	Recessive mutations leading to loss of K_{ATP} channels at the membrane and ER retention eg. H259R	(340)
		Recessive mutations producing non-functional protein eg. Y12X, L147P	(382; 530)
		Dominant mutation causing impaired pore-opening e.g. in-frame deletion I284del	(268; 380)
	Neonatal Diabetes	Missense mutations causing ATP insensitivity and GOF eg. E227K, E229K	(175; 177; 556)
		In-frame deletion Kir6.2-28Δ32 causing ATP insensitivity and GOF	(93)
	Type 2 Diabetes	E23K mutant causing modest ATP insensitivity and GOF	(179)
	Increased LV size and Heart Failure	E23K mutant appears over-represented in heart failure patients	(434; 435)
ABCC8	Congenital Hyperinsulinism	Recessive mutations leading to loss of K_{ATP} channels at the membrane and ER retention e.g. F1388del	(65; 471; 519; 592)
		Recessive mutations causing loss of MgADP and drug sensitivity despite membrane resident channels e.g. T1139M,	(486)

		R1215Q	
		Dominant mutations causing reduced sensitivity to metabolic inhibition and drug activation eg. V187D, E1506K	(235; 268; 401)
	Neonatal Diabetes	Missense mutations causing ATP insensitivity and GOF eg. L213R, I1424V	(26)
	Type 2 Diabetes	S1369A variant when co-expressed with KCNJ11 E23K variant causes ATP insensitivity and GOF	(197)
ABCC9	Cantu Syndrome	Missense mutations leading to reduced ATP sensitivity or increased MgADP activation and GOF eg. P432L, A478V, C1043Y	(92; 205; 552)
	Dilated Cardiomyopathy	Missense mutation A1513T or frameshift mutation and stop codon introduction at L1524 - both impair nucleotide hydrolysis at NBF2 causing reduced function and associated with DCM patients	(43)
	Atrial Fibrillation	Missense mutation T1547I leading to loss of function and implicated in AF initiating from the Vein of Marshall	(397)
	Brugada and Early Repolarisation Syndromes	V734I and S1402C GOF mutations implicated	(228)
	Coronary spasm and Myocardial Infarction	Association with V734I mutation which causes both reduced ATP inhibition and reduced MgNDP activation when mutant co-expressed with SUR2B	(491)

Figure Legends

Figure 1 – Recordings of single K_{ATP} channels. Cell-attached single channel recordings of Kir6.2\SUR2B channels expressed in HEK293 cells. Co-expression of Kir6.2\SUR2B forms a channel with a single channel conductance of ~70 pS.

Figure 1 Teaching points: Ion channels have an open and closed conformation and when open pass a current with a characteristic conductance. The figure illustrates such high resolution single channel recordings of K_{ATP} channels using the patch-clamp recording technique.

Figure 2 – The structure of drugs acting on K_{ATP} channels.

Figure 2 Teaching points: K_{ATP} channels have a rich pharmacology with a variety of pharmacophores able to selectively inhibit or activate the currents.

Figure 3 – A cartoon of the molecular composition of a K_{ATP} channel. K_{ATP} channels are formed from four pore-forming Kir6.x subunits and four regulatory sulphonylurea receptor subunits. Kir6x is a member of the inward-rectifying K^+ channel family (Kir) with 2 transmembrane domains (M1 and M2), a pore-forming region (H5) with the K^+ selectivity sequence and intracellular N and C termini. SUR belongs to the ATP binding cassette (ABC) family of proteins. SUR consists of 3 transmembrane domains (TMDs) composed of 5, 6 and 6 transmembrane segments respectively. The intracellular loop between TMD0 and TMD1, L0 provides the physical interaction with Kir6x. Two nucleotide binding domains (NBD1 and

NDB2) comprised of Walker A and B nucleotide binding motifs provide the binding sites for magnesium complexed adenine nucleotides.

Figure 3 Teaching points: We understand the molecular composition of K_{ATP} channels. They are composed of four inwardly rectifying potassium channel subunits (Kir6.1 and Kir6.2) and four sulphonylurea receptors (SUR1, SUR2A and SUR2B) which are a member of the large family of ATP binding cassette proteins. ATP inhibits the channel by binding to the channel pore forming subunit whilst MgADP, sulphonylureas and potassium channel openers act on the sulphonylurea receptors. The channels in different tissues have different properties and this is accounted for by selective expression of different Kir6.0 subunits and different SURs.

Figure 4 – The high resolution structure of the pancreatic K_{ATP} channel. A. The linear sequence of Kir6.2 and SUR1 proteins. The various critical domains are coloured and the same scheme is used in the other panels. The numbers indicate amino acid residues defining the regions. B. A side view of the cryo-EM density map of the K_{ATP} channel (3.6 Å resolution). The position of the membrane is indicated by the gray bars. C. An extracellular view of the complex. D. A model of the K_{ATP} channel complex with various ligands as indicated (ATP is green and glibenclamide is red). E. The model viewed from the extracellular side of membrane. This figure is reproduced from the recent study (342).

Figure 4 Teaching points: One of the major advances has been the determination of crystal structures of K_{ATP} channels using cryo EM. These have revealed their characteristic structural features and given insight into how glibenclamide might bind and inhibit the channel.

Figure 5 – The ATP binding pocket in Kir6.2 determined in the quatrefoil form. A. An EM

density of the Kir6.2 tetramer with ATP molecules shown in yellow. B. A ribbon representation of Kir6.2 with two pore domains shown with important structural elements indicated. The ATP molecule is again shown in yellow. C The ATP binding site with residues contacting the yellow ATP as indicated. The The N-terminus from the neighbouring subunit interacts with the purine base of ATP. Dashed lines indicate hydrogen bonds. D. The EM density of the ATP molecule is outlined with a blue mesh and illustrates a horseshoe-shaped conformation. This figure is reproduced from the recent study (305).

Figure 5 Teaching points: The defining feature of K_{ATP} channels is their sensitivity to nucleotide levels and ATP in particular thus enabling them to link cellular metabolism and membrane potential. The crystal structures show in exquisite molecular detail how ATP binds to the Kir6.2 subunit.

Figure 6 - Proposed sites of action of K_{ATP} openers and inhibitors. The above schematics demonstrate the pharmaco-topology with respect to the different sulphonylurea receptor subtypes. The colour of the various segments of each SUR demonstrates broadly the homology between the subtypes. SUR2A and SUR2B (red) share almost 100% homology and that which is different from SUR1 (blue). However, the terminal 42 amino acids of the C terminus of SUR2A and SUR2B differ, and in fact this segment in SUR1 shares almost 100% homology with that in SUR2B as depicted by the colour coding in blue. Openers and their sites of action are depicted in green and inhibitors black. Capital letters denotes binding with high affinity and lower case with lower affinity. The action of diazoxide on SUR2A is shown in darker green given the fact that this interaction requires the presence of a high concentration of MgADP, and this probably results allosterically due to the differing terminal 42 amino acids at the C terminus of SUR2A (368).

Figure 6 Teaching points: The drugs that work on K_{ATP} channels show some tissue selectivity accounted for by differential Kir6.0 and SUR expression.

Figure 7 – The regulation of vascular smooth muscle K_{ATP} channels. Activation or inhibition of K_{ATP} channels in the vascular smooth muscle cell determines its membrane potential. Vasoactive factors that activate K_{ATP} channels either directly or indirectly cause membrane hyperpolarisation, closure of voltage-dependent calcium channels, reduced intracellular Ca^{2+} and dilation. Conversely factors that inhibit K_{ATP} channels cause depolarisation of the cell membrane leading to opening of voltage-dependent calcium channels, increased intracellular Ca^{2+} and contraction. Left, Dilation of VSM as a result of K_{ATP} channel activation initiated by vasodilators such as adrenaline, adenosine, calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) via the G-protein (Gs)/Adenylate Cyclase (AC)/Protein Kinase A (PKA) signalling pathway. Hypoxia, ischemia and metabolic stress indirectly activate K_{ATP} channels by inhibiting oxidative phosphorylation and therefore decreasing the ATP/ADP ratio. Right, endogenous mediators such as noradrenaline, angiotensin II, endothelin-1 and histamine inhibit K_{ATP} channels via the G-protein (Gi, q)/PKC signalling pathway leading to VSM contraction.

Figure 7 Teaching points: K_{ATP} channels are critically involved in many physiological processes. In vascular smooth muscle cells they significantly influence vascular smooth tone and both vasodilators and vasoconstrictors can modulate activity through direct protein phosphorylation of the channel subunits.

Figure 8 – A cartoon of stimulus-secretion coupling in pancreatic β cells. K_{ATP} channels couple cellular metabolism to electrical activity. When blood glucose is low, ATP production is reduced allowing K_{ATP} channels to open thus hyperpolarising the membrane and preventing an increase intracellular Ca^{2+} and subsequent insulin release. When there is a high blood glucose concentration, ATP production increases leading to channel inhibition, an increase in intracellular Ca^{2+} and insulin release.

Figure 8 Teaching points: K_{ATP} channels are critically involved in many physiological processes. The best described are their role in stimulus secretion coupling in the pancreas. Increases in blood glucose are tightly coupled to ATP production in pancreatic beta resulting in channel inhibition, membrane depolarisation and entry of calcium which promotes the release of insulin vesicles.

Figure 9 - Disease mechanisms in hereditary channelopathies. The route to delivery of fully and normally functioning ion channels at the cell membrane can be halted or disturbed at various checkpoints. Mutations can lead to: (1) Defective transcription or translation such that channel proteins are merely not synthesised at all. (2) Aberrant folding of channel proteins into their tertiary and quaternary structures that is recognised by chaperone proteins in the endoplasmic reticulum and leads to their degradation and failure to exit the endoplasmic reticulum. (3) Further quality control in the golgi complex where channels can still be recognised as faulty and retro-translocated back to the endoplasmic reticulum or assigned for degradation. (4) Defective cycling to and from the membrane through exo- and endocytosis. (5) Channels that pass through all the checkpoints and are delivered to the membrane but which display abnormal gating and/or kinetics, or abnormal responses to modulatory pathways.

Figure 9 Teaching points: An emerging theme has been the involvement of ion channels in human disease known as "channelopathies". For example, defects in K_{ATP} channels lead to disorders of insulin handling through gain and loss of function mutations. This can occur through many different mechanisms and not simply changes in the activity of the channel at the plasma membrane. Differences in channel trafficking through the secretory pathway and in endocytosis may also be involved.

Figure 10 – The pathogenesis of hereditary hyperinsulinism and diabetes due to mutations in K_{ATP} channels. Loss of function mutations leads to excessive insulin release and hypoglycaemia. In contrast, gain of function mutation affect ATP sensitivity and impair insulin release from pancreatic beta cells resulting in diabetes.

Figure 10 Teaching points: The critical role of role of K_{ATP} channels in insulin release is reinforced by human hereditary diseases of both excessive and reduced insulin release which result from mutations in the genes underlying subunits of K_{ATP} channels.

Figure 11 - Protective role of K_{ATP} channels in cardiomyocytes. Activation of K_{ATP} channels by protein kinase C or metabolic insults such as ischemia and/or hypoxia stabilises the membrane potential, leads to shortening of the action potential duration and reduces the influx of calcium through voltage dependent calcium channels. This attenuates calcium-induced calcium release from the sarcoplasmic reticulum which reduces contractility, prevents calcium overload and decreases ATP demand.

Figure 11 Teaching points: K_{ATP} channels in the heart and elsewhere are protective to the cell. One of the main ideas in the heart is that this limits calcium entry and release reducing muscle contraction, calcium overload and ATP demand.

Cross-References to Comprehensive Physiology

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619. **Zunkler BJ, Henning B, Ott T, Hildebrandt AG and Fleck E**. Effects of tolbutamide on ATP-sensitive K+ channels from human right atrial cardiac myocytes. *Pharmacol Toxicol* 80: 69-75, 1997.

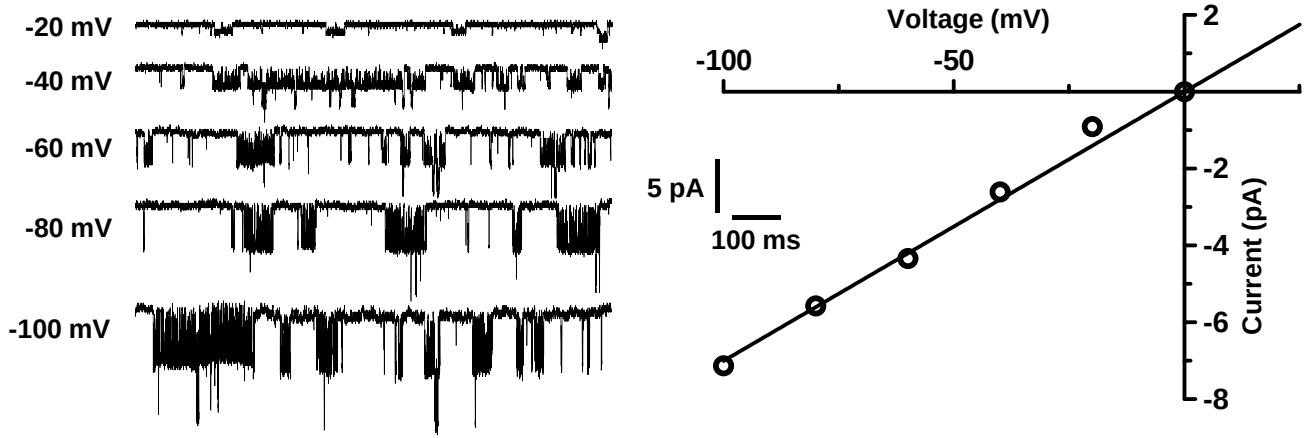
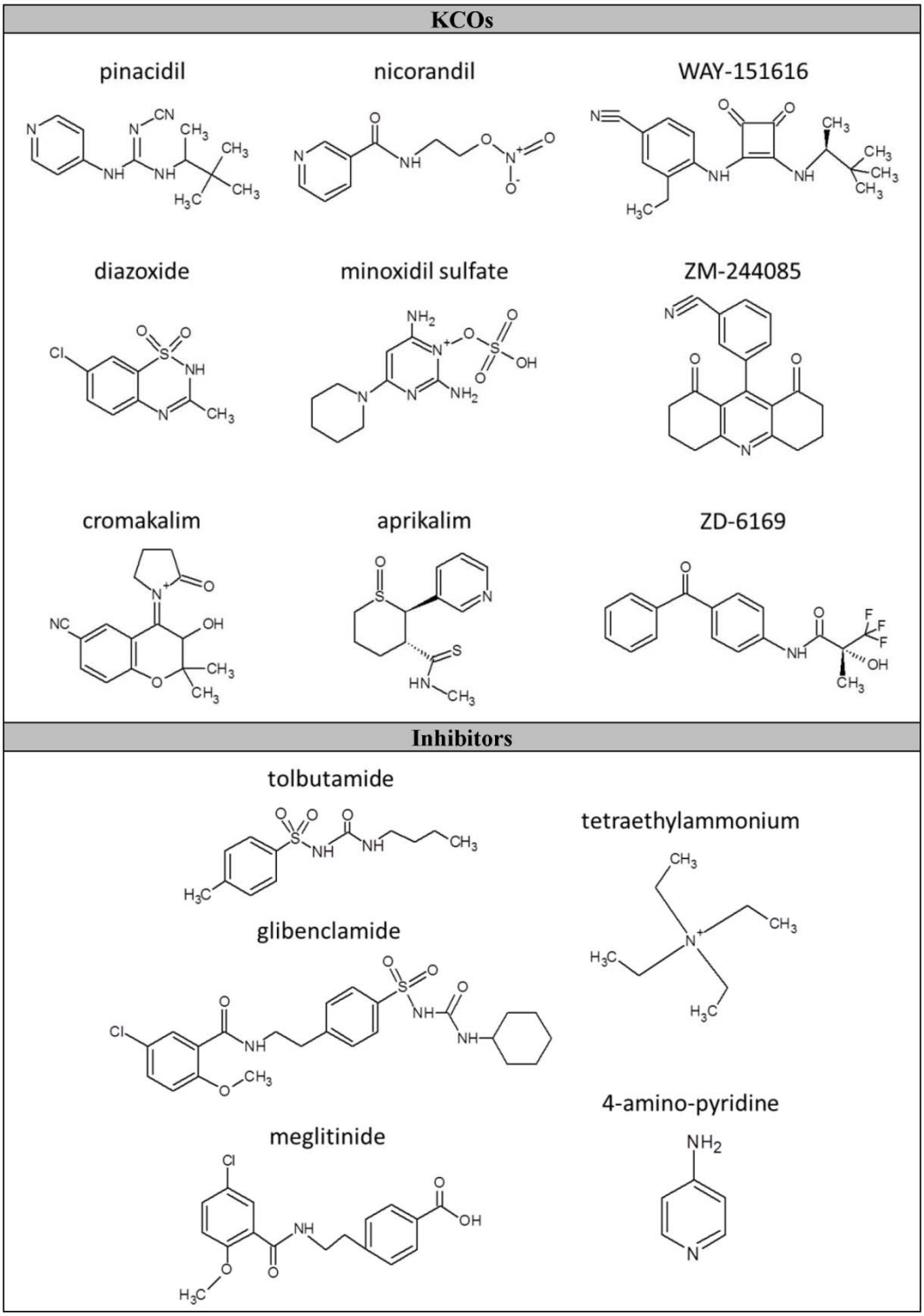

-20 mV
-40 mV
-60 mV
-80 mV
-100 mV
Voltage (mV)
-100
-50
2
-2
-4
-6
-8
Current (pA)
5 pA
100 ms

Figure 1

Figure 2


KCOs
pinacidil
nicorandil
WAY-151616
diazoxide
minoxidil sulfate
ZM-244085
cromakalim
aprikalim
ZD-6169
Inhibitors
tolbutamide
tetraethylammonium
glibenclamide
4-amino-pyridine
meglitinide

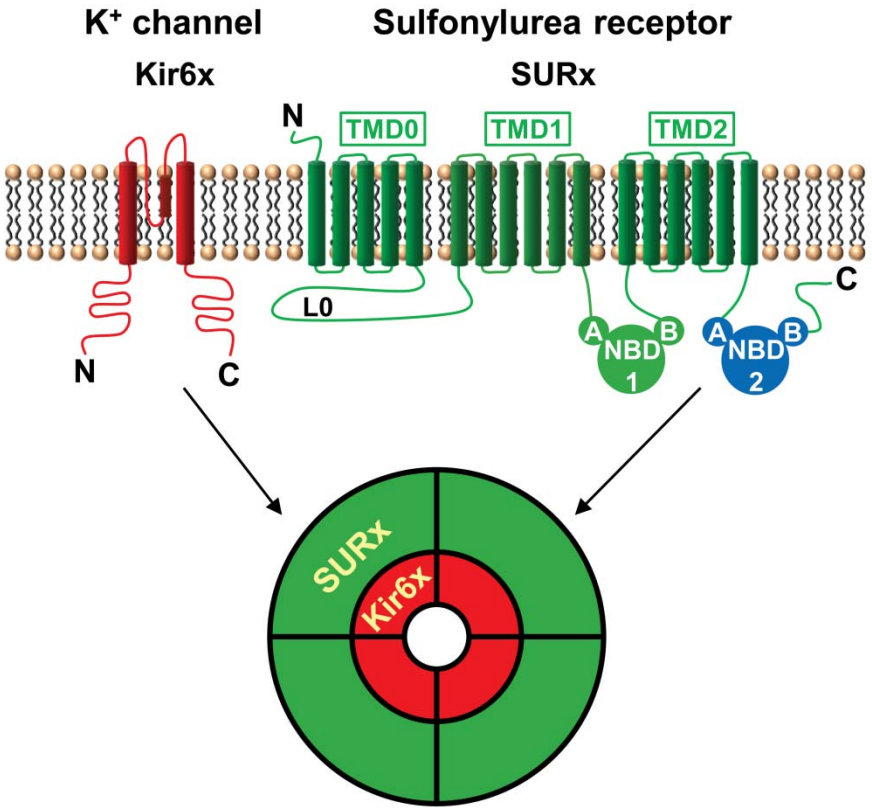

K+ channel
Kir6x
Sulfonylurea receptor
SURx
N
TMD0
TMD1
TMD2
L0
C
N
C
A
NBD
B
1
A
NBD
B
2
SURx
Kir6x

Figure 3

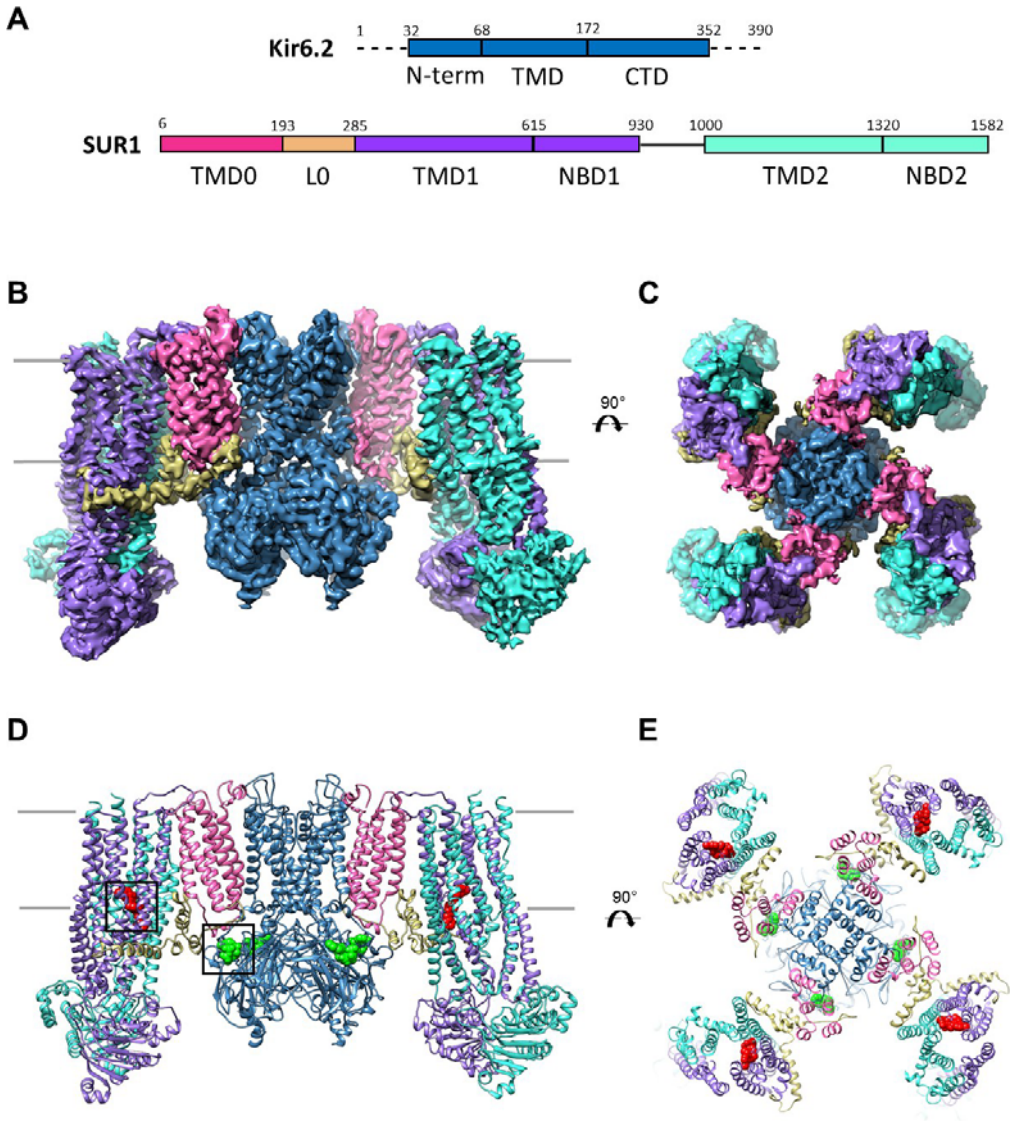

A
Kir6.2
1
32
68
172
352
390
N-term
TMD
CTD
SUR1
6
193
285
615
930
1000
1320
1582
TMD0
L0
TMD1
NBD1
TMD2
NBD2
B
C
90°
D
E
90°

Figure 4

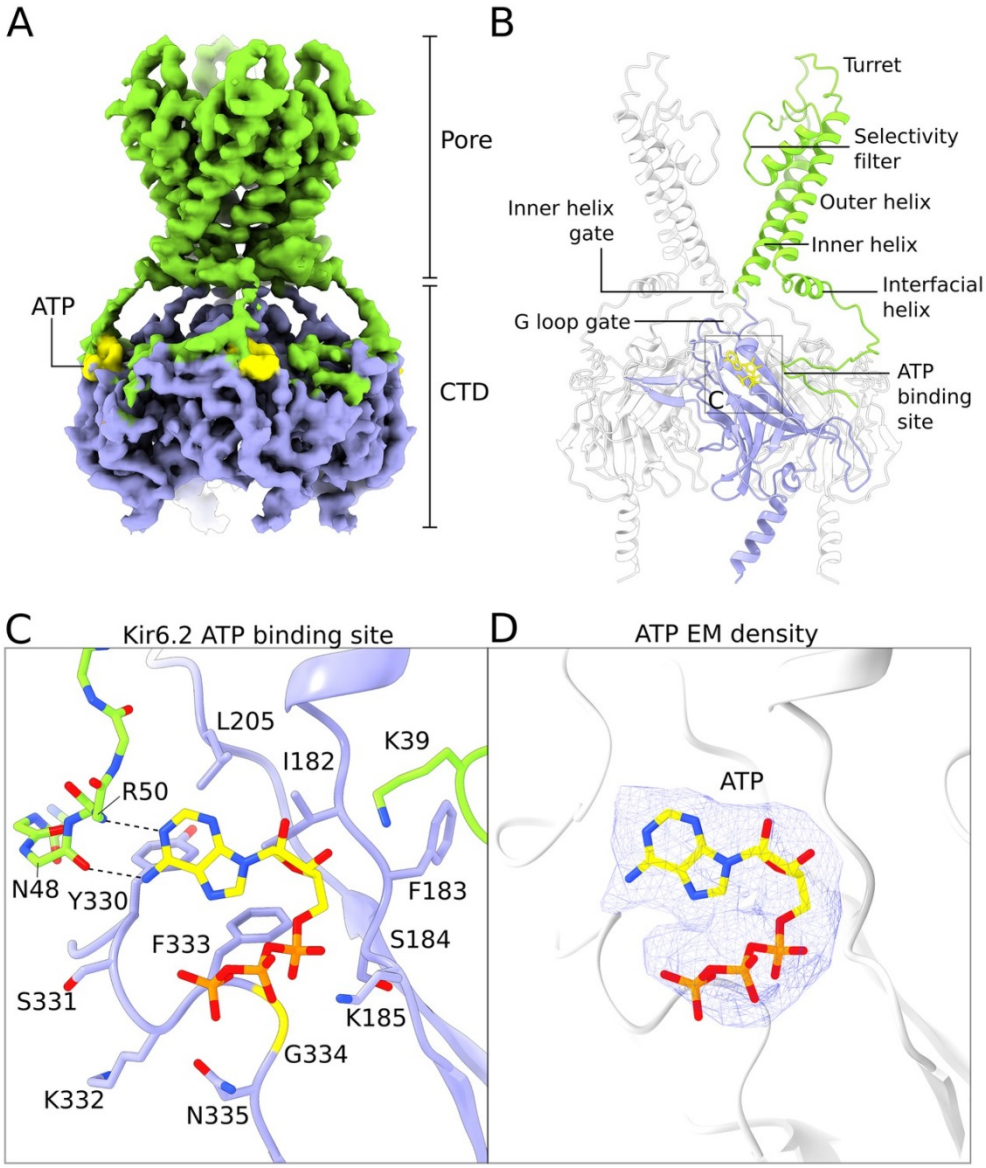

A
Pore
ATP
CTD
B
Turret
Selectivity filter
Outer helix
Inner helix gate
Inner helix
Interfacial helix
G loop gate
ATP binding site
C
C
Kir6.2 ATP binding site
L205
K39
I182
R50
N48
Y330
F183
F333
S184
S331
K185
G334
K332
N335
D
ATP EM density
ATP

Figure 5

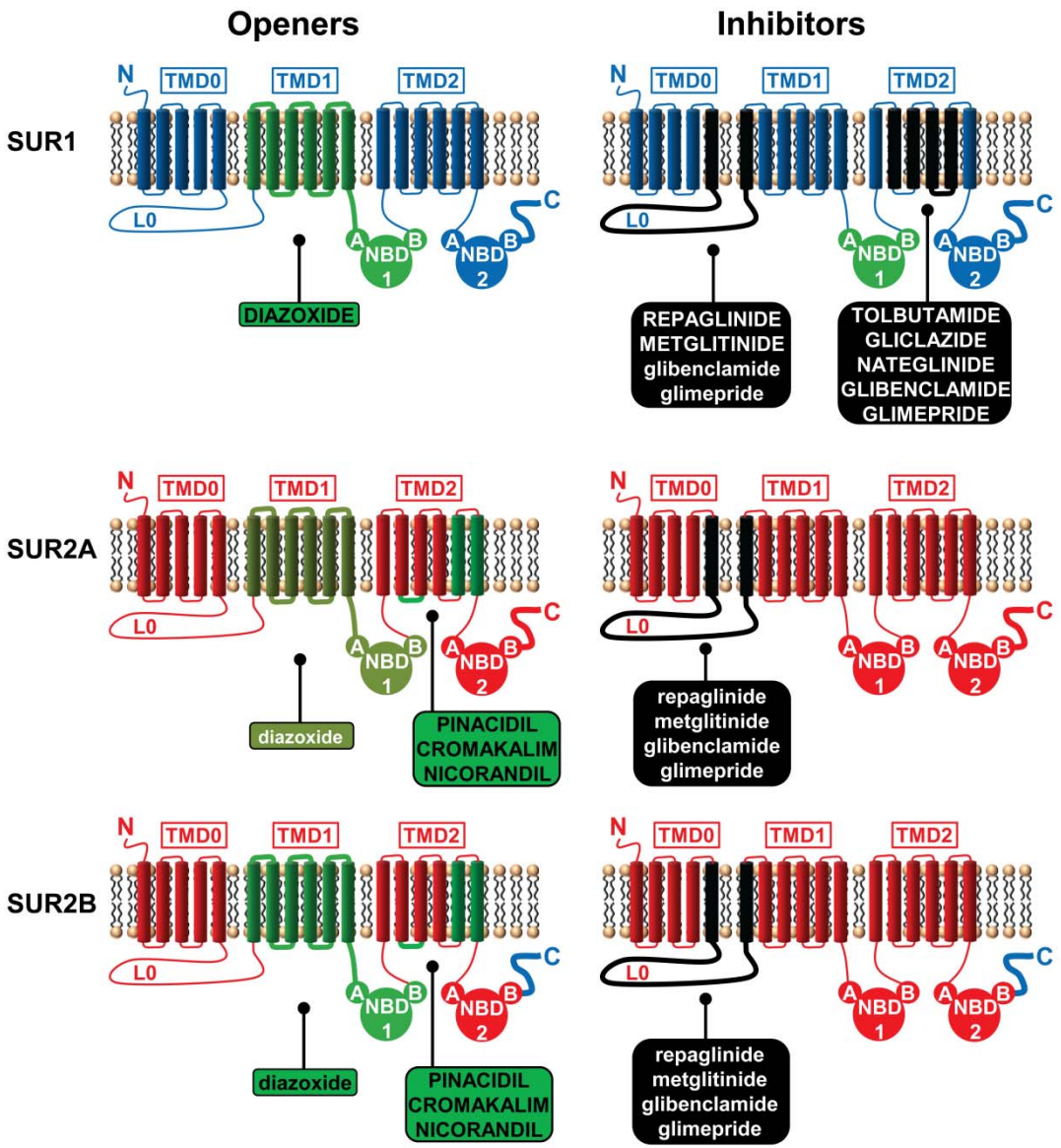

Openers
Inhibitors
SUR1
SUR2A
SUR2B
N
TMD0
TMD1
TMD2
L0
A
NBD
B
1
2
C
DIAZOXIDE
REPAGLINIDE
METGLITINIDE
glibenclamide
glimepride
TOLBUTAMIDE
GLICLAZIDE
NATEGLINIDE
GLIBENCLAMIDE
GLIMEPRIDE
diazoxide
PINACIDIL
CROMAKALIM
NICORANDIL
repaglinide
metglitinide
glibenclamide
glimepride

Figure 6

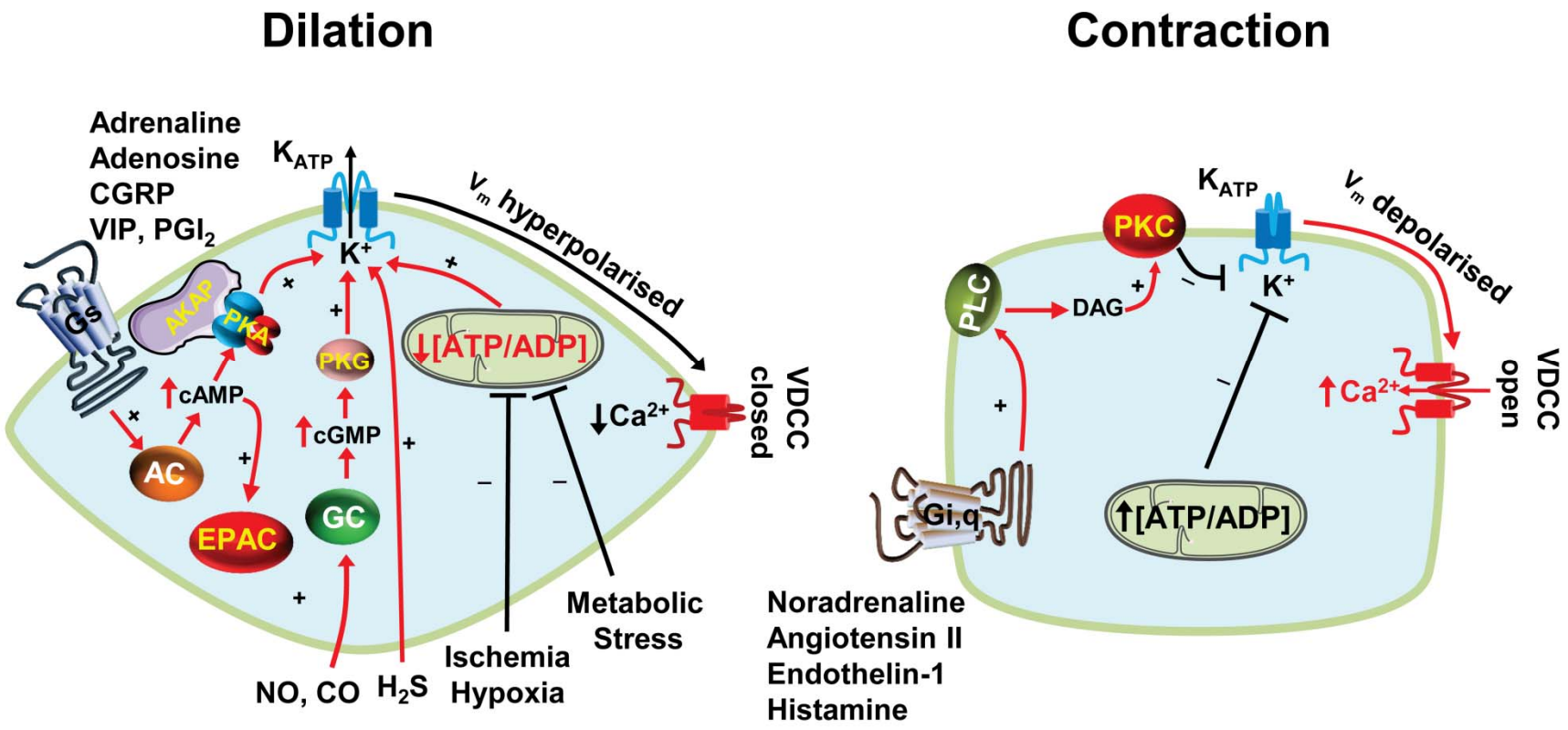

Dilation
Contraction
Adrenaline
Adenosine
CGRP
VIP, PGI2
KATP
K+
Vm hyperpolarised
Gs
AKAP
PKA
PKG
↓[ATP/ADP]
↓Ca2+
VDCC closed
cAMP
cGMP
AC
GC
EPAC
NO, CO
H2S
Ischemia
Hypoxia
Metabolic Stress
PKC
PLC
DAG
Gi,q
↑[ATP/ADP]
↑Ca2+
VDCC open
Vm depolarised
Noradrenaline
Angiotensin II
Endothelin-1
Histamine

Figure 7

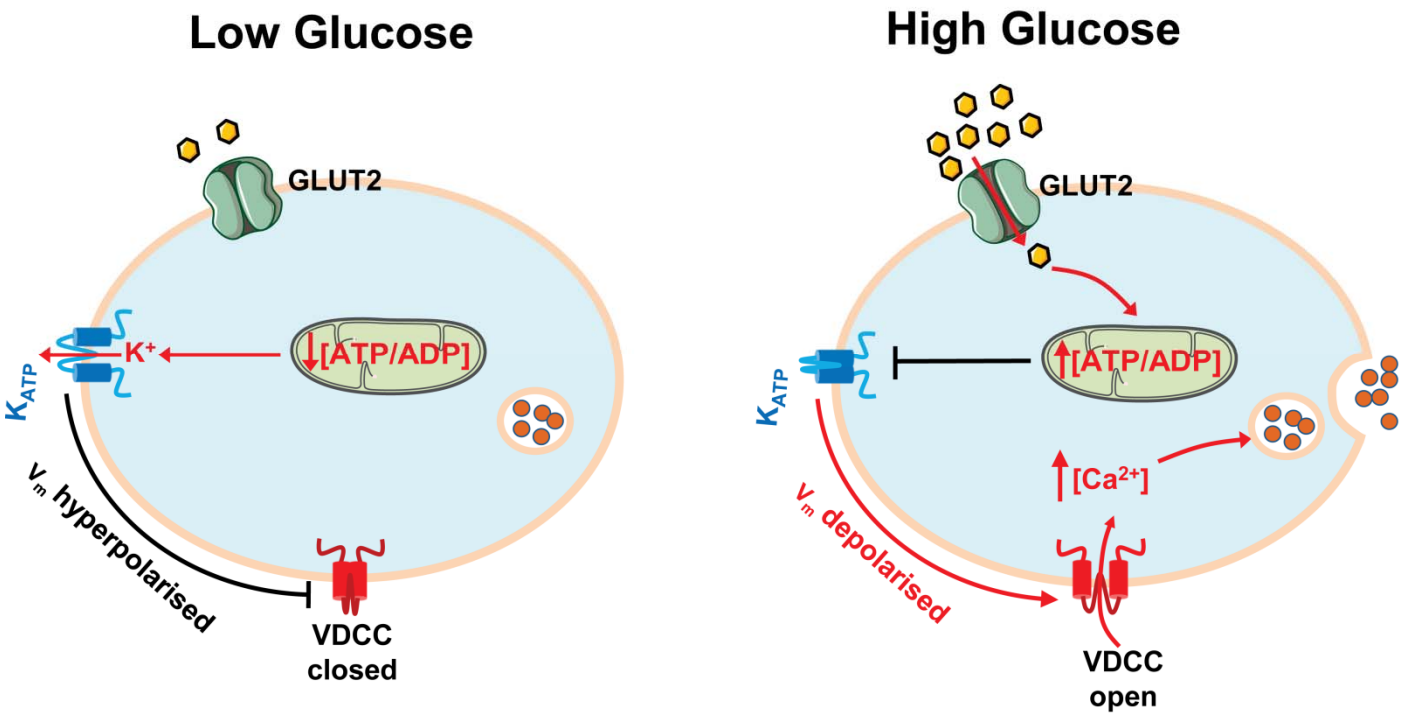

Low Glucose
GLUT2
K+
↓[ATP/ADP]
KATP
Vm hyperpolarised
VDCC
closed
High Glucose
GLUT2
↑[ATP/ADP]
KATP
↑[Ca2+]
Vm depolarised
VDCC
open

Figure 8

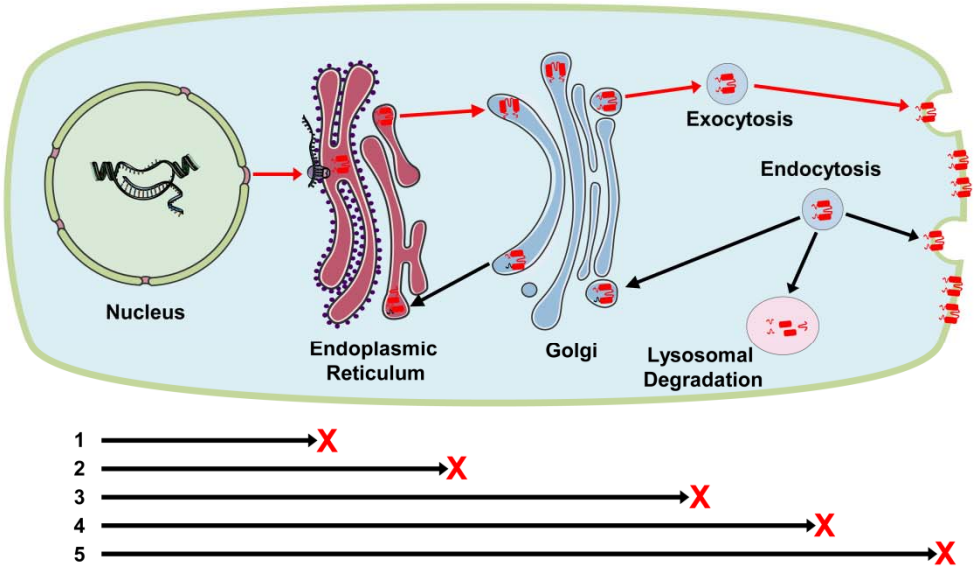

Nucleus
Endoplasmic Reticulum
Golgi
Exocytosis
Endocytosis
Lysosomal Degradation
1
2
3
4
5

Figure 9

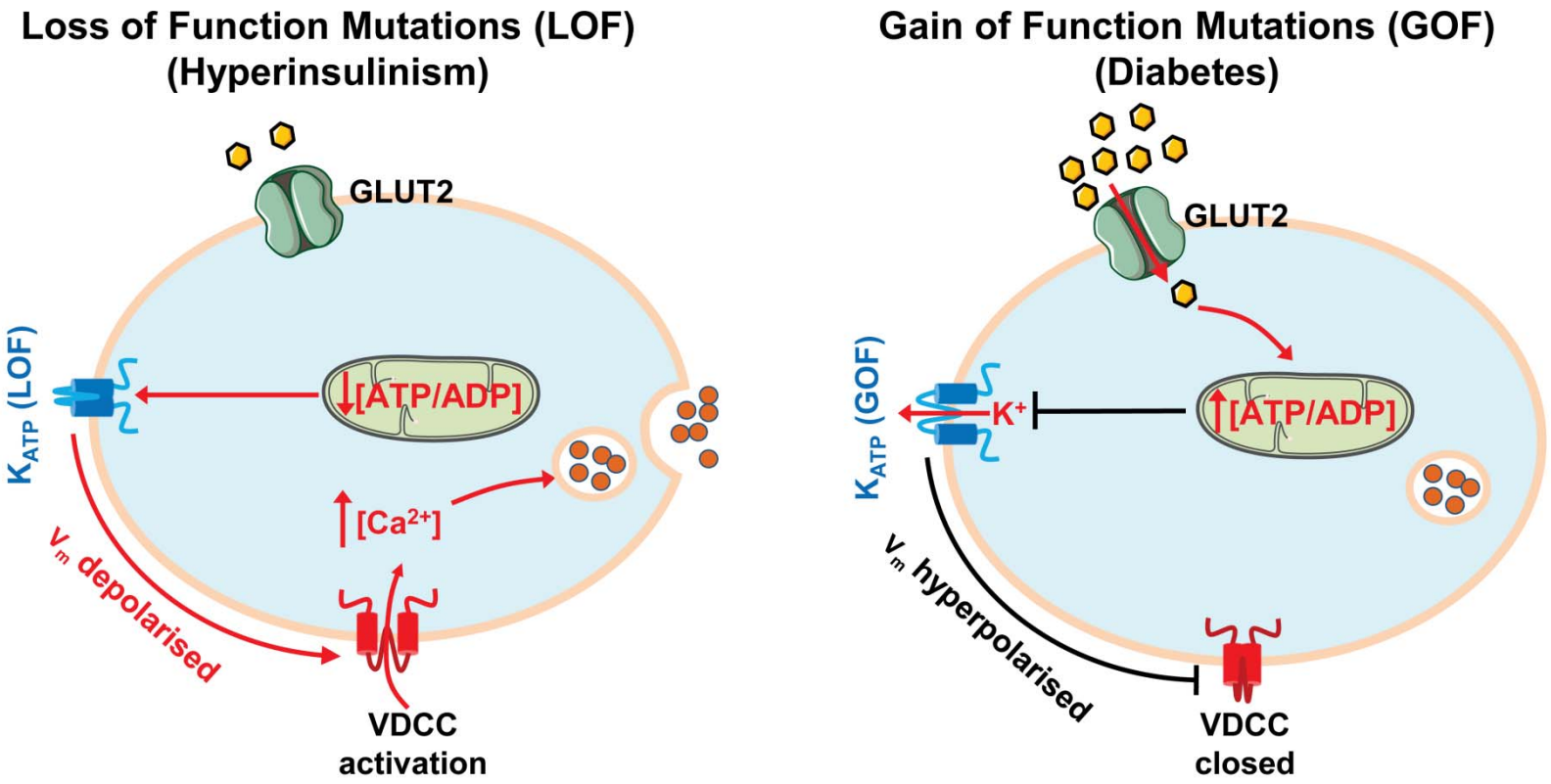

Loss of Function Mutations (LOF)
(Hyperinsulinism)
GLUT2
K_{ATP} (LOF)
↓[ATP/ADP]
↑[Ca^{2+}]
V_m depolarised
VDCC
activation
Gain of Function Mutations (GOF)
(Diabetes)
GLUT2
K_{ATP} (GOF)
K^+
↑[ATP/ADP]
V_m hyperpolarised
VDCC
closed

Figure 10

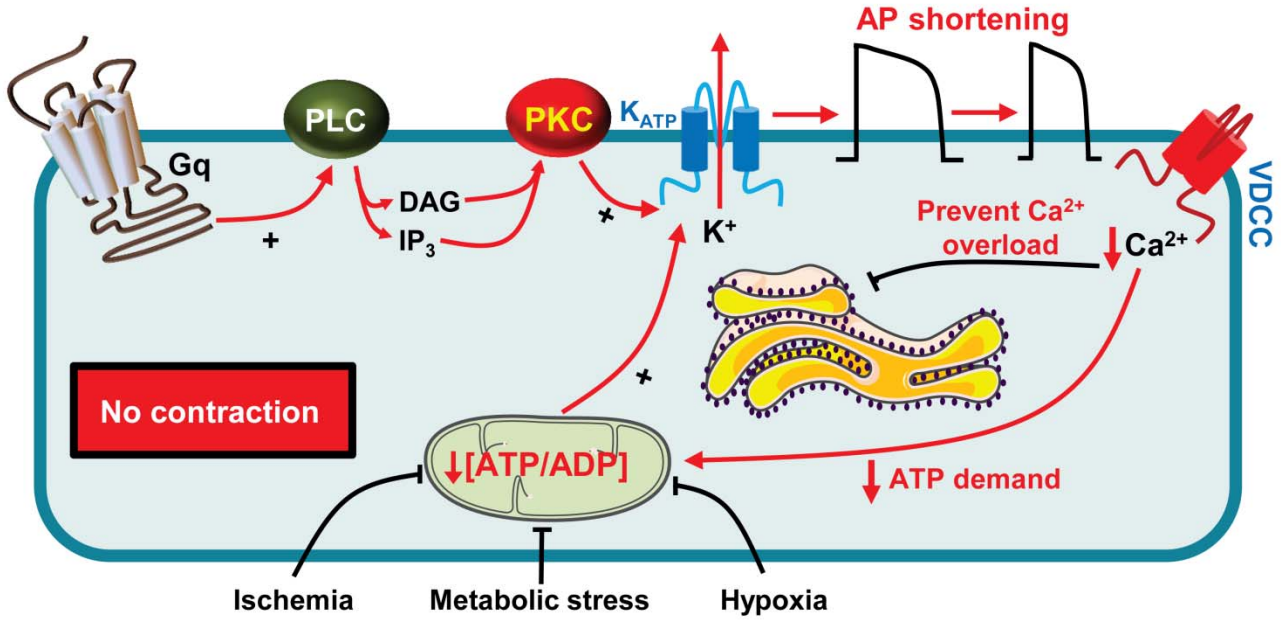

AP shortening
PLC
PKC
K_{ATP}
Gq
DAG
IP_3
+
+
K^+
Prevent Ca^{2+} overload
Ca^{2+}
VDCC
No contraction
+
↓[ATP/ADP]
↓ ATP demand
Ischemia
Metabolic stress
Hypoxia

Figure 11