The Pharmacology of ATP-Sensitive K^+ Channels (K_{ATP})

Yiwen Li, Qadeer Aziz, and Andrew Tinker

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Abstract

ATP-sensitive K^+ channels (K_{ATP}) are inwardly-rectifying potassium channels, broadly expressed throughout the body. K_{ATP} is regulated by adenine nucleotides, characteristically being activated by falling ATP and rising ADP levels thus playing an important physiological role by coupling cellular metabolism with membrane excitability. The hetero-octameric channel complex is

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formed of 4 pore-forming inward rectifier Kir6.x subunits (Kir6.1 or Kir6.2) and 4 regulatory sulfonylurea receptor subunits (SUR1, SUR2A, or SUR2B). These subunits can associate in various tissue-specific combinations to form functional K_{ATP} channels with distinct electrophysiological and pharmacological properties. K_{ATP} channels play many important physiological roles and mutations in channel subunits can result in diseases such as disorders of insulin handling, cardiac arrhythmia, cardiomyopathy, and neurological abnormalities. The tissue-specific expression of K_{ATP} channel subunits coupled with their rich and diverse pharmacology makes K_{ATP} channels attractive therapeutic targets in the treatment of endocrine and cardiovascular diseases.

Keywords

Cardiac arrhythmia · Diabetes · K_{ATP} · Sulfonylureas · SUR

1 Introduction

ATP-sensitive K^+ channels (K_{ATP}) were first described in heart muscle in the early 1980s, where treatment with metabolic poisons or hypoxia evoked an outward K^+ current that was inhibited by ATP (Noma 1983). Since then, they have been described in a variety of other tissues, most prominently in the cardiovascular, endocrine, and nervous systems including in pancreatic β-cells (Ashcroft et al. 1984), neurones (Ashford et al. 1988), skeletal muscle (Spruce et al. 1985), smooth muscle (Aziz et al. 2014; Standen et al. 1989), and endothelium (Aziz et al. 2017; Li et al. 2020).

K_{ATP} channels open in response to changes in cellular metabolism, activated by a decline in intracellular ATP and/or an increase in ADP levels, and thus play an important functional role by linking cellular metabolism to membrane excitability. In addition to regulation by changes in the ATP/ADP ratio, K_{ATP} channels are also modulated by a number of cell signalling pathways. They have an established pharmacological profile and some compounds are in routine clinical use. K_{ATP} channels have a number of important physiological functions, especially in the cardiovascular and endocrine systems such as regulation of insulin release, cardioprotection, and control of blood pressure. Extensive reviews of K_{ATP} channel function have been already published (Tinker et al. 2014, 2018). In this chapter, we will briefly discuss the structure and regulation of K_{ATP} channels, their physiological roles and pathophysiology in human diseases, and their pharmacology with a focus on their therapeutic use.

2 The Structure and Regulation of K_{ATP} Channels

The K_{ATP} channel complex is constituted of four pore-forming subunits (Kir6.1 or Kir6.2) and four sulphonylurea receptor subunits (members of the ATP binding cassette family of proteins; SUR1, SUR2A, and SUR2B) to form an octameric

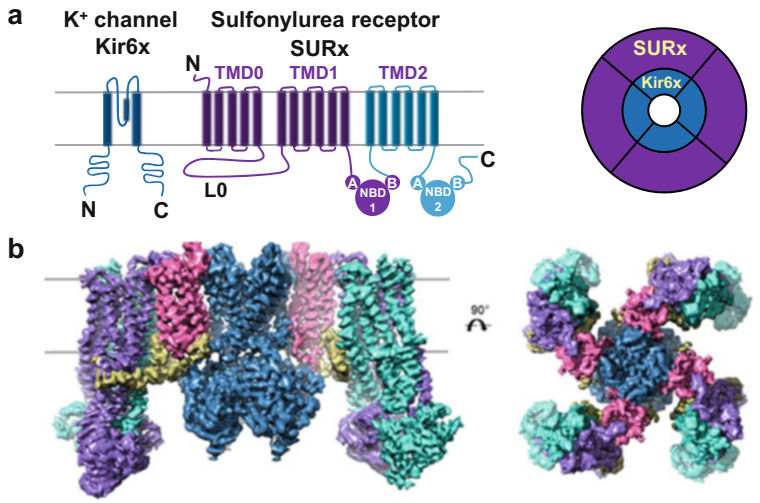


Fig. 1 Molecular composition of a K_{ATP} channel. (**a**) Four pore-forming Kir6.x subunits (belonging to the inward-rectifying K^+ channel family (Kir)) and four regulatory sulphonylurea receptor subunits (belonging to the ATP binding cassette (ABC) family of proteins) form a functional K_{ATP} channel. Kir6x consists of 2 transmembrane domains (M1 and M2), a pore-forming region (H5) with the K^+ selectivity sequence and intracellular N and C termini. SUR consists of 3 transmembrane domains (TMDs) composed of 5, 6, and 6 transmembrane segments, respectively. L0, the intracellular loop between TMD0 and TMD1, 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. (**b**) A side view (left) of the cryo-EM density map of the pancreatic K_{ATP} channel (3.63 Å resolution) and the extracellular view (right) of the channel. The position of the membrane is indicated by the grey bars. (This figure is reproduced with permission from Martin et al. 2017)

channel complex (Fig. 1). The association of a particular SUR with a specific Kir6.x subunit constitutes the K_{ATP} current in a specific tissue. The Kir6.x subunits are targets for inhibition by ATP and the SUR proteins for activation by MgADP.

The Kir6.x subunits have two transmembrane domains (M1 and M2), a pore-forming region (H5) with the K^+ selectivity sequence (GYG or GFG) and intracellular N and C termini (Tinker et al. 1996). SUR subunits consist of three transmembrane domains (TMD 0, 1, and 2) comprised of five, six, and six membrane spanning helices, respectively (Fig. 1).Each of these domains is connected by cytosolic linkers; N-terminus is extracellular while C-terminus resides intracellularly (Conti et al. 2001). Physical interaction with Kir6.1.x subunits is via the intracellular loop between TMD0 and TMD1, L0. Two nucleotide binding domains (NBD1 and NDB2), comprised of Walker A and B nucleotide binding motifs in the TMD1-TMD2 linker, and C-terminus provide the binding sites for magnesium-complexed adenine nucleotides.

K_{ATP} channels are highly selective for potassium ($P_{Na}/P_K \sim 0.01$) and display diverse unitary conductances in different tissues, for example, 70–90 pS in cardiac muscle, 55–75 pS in skeletal muscle, and 50–90 pS in pancreatic β-cells (Ashcroft

1988; Hibino et al. 2010; Quayle et al. 1997). However, smooth muscle K_{ATP} channels have unique properties; they have a lower (~35 pS) single-channel conductance and they absolutely require cytosolic nucleotide diphosphates being present in the solution to be active and this has led to the moniker "K_{NDP}" current in some of the literature (Beech et al. 1993). In addition, these channels are generally less sensitive to ATP inhibition than Kir6.2-containing channels (Beech et al. 1993; Cui et al. 2002). Furthermore, activation by ADP is dependent on the presence of magnesium, without which ADP inhibits the channels (Findlay 1987).

As well as direct regulation of K_{ATP} channels by ATP/ADP, other cell signalling pathways can also modulate channel activity. Membrane phosphoinositides, notably phosphatidylinositol 4,5-bisphosphate have been shown to antagonise ATP inhibition leading to opening of the K_{ATP} channels (Shyng and Nichols 1998). In vascular smooth muscle cells, K_{ATP} channels can be regulated by a number vasodilating (for example, adenosine and CGRP) and vasoconstricting (for example, angiotensin and endothelin) hormones. The binding of a vasodilator to a G_s-protein-coupled receptor leads to downstream activation of protein kinase A (PKA), direct phosphorylation of the K_{ATP} channel complex, leading to the opening of K_{ATP} channels, hyperpolarisation of the cell membrane and vasodilatation (Quinn et al. 2004; Shi et al. 2007). In contrast, vasoconstrictors act via $G_{q/11}$-protein-coupled receptors, leading to activation of protein kinase C (PKC), inhibition of K_{ATP} channels and membrane depolarisation, increased calcium entry and vasoconstriction (Aziz et al. 2012; Shi et al. 2008). The depletion of phosphatidylinositol (4,5) bisphosphate is another potential mediator after phospholipase C activation though this may not be critical with the vascular KATP channel (Quinn et al. 2003). In addition, PKC has been shown to modulate cardiac K_{ATP} channels (Light et al. 1996), and there is evidence of PKA-dependent modulation of the pancreatic K_{ATP} channel (Light et al. 2002).

3 The Pharmacological Properties of K_{ATP} Channels

K_{ATP} channels have a rich and well-developed pharmacology, with both activators and inhibitors existing. K_{ATP} channel openers (KCOs) and blockers (KCBs) have diverse chemical and structural properties (Tables 1 and 2). Importantly, from both research and therapeutic perspectives, there is a degree of channel subtype-specificity for some of these compounds allowing for some tissue-specific targeting.

3.1 K_{ATP} Channel Openers

Pharmacological compounds of diverse structures are able to potentiate K_{ATP} channel activity. These include benzothiadiazines (diazoxide), pyrimidine sulphates (minoxidil), pyridyl nitrates (nicorandil), benzopyrans (cromakalim), carbothiamides (aprikalim), and cyanoguanidines (pinacidil). Many of the KCOs show selectivity to different SUR subunits, for example, pinacidil, cromakalim, and

Table 1 Structure and pharmacology of KCOs acting on K_{ATP} channel

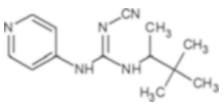
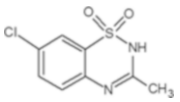
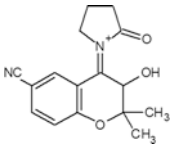
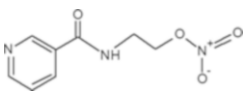
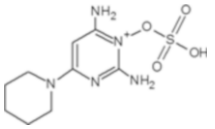
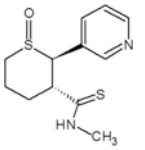
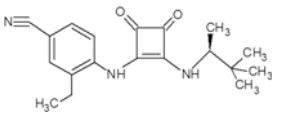
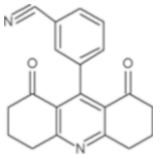
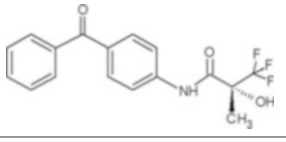
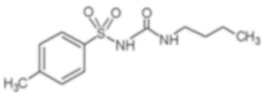
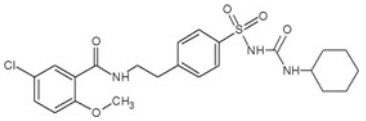
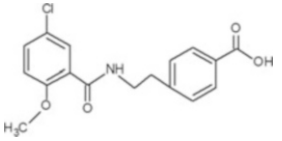
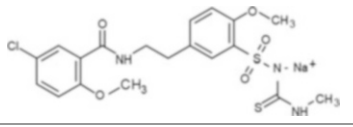
KCO (chemical class)	Chemical structure	Location of K_{ATP} channels	Same class drugs
First generation			
Pinacidil (cyanoguanidines)		Cardiomyocytes Smooth muscle	P-1075
Diazoxide (benzothiadiazines)		Cardiomyocytes Smooth muscle Pancreas Mitochondria	LN-5330
Cromakalim (benzopyrans)		Cardiomyocytes Smooth muscle	Levcromakallm Blmakallm Cellkallm Rilmakalim Y-27152
Nicorandil (pyridyl nitrates)		Cardiomyocytes	KRN-2391
Minoxidil (pyrimidine sulphate)		Cardiomyocytes	LP-805
Aprikalim (carbothiamides)		Cardiomyocytes Smooth muscle	MCC-134
Second generation			
WAY-151616 (cyclobutenediones)		Smooth muscle	WAY-133537
ZM-244085 (dihydropyridine)		Smooth muscle	ZD-0947
ZD-6169 (tertiary carbinols)		Smooth muscle	A-151892

Table 2 Structure and pharmacology of blockers acting on K_{ATP} channel

KCBs (chemical class)	Chemical structure	Location of K_{ATP} channels	Same class drugs
First generation			
Tolbutamide (sulfonylureas)		Pancreas	Chlorpropamide Acetohexamide Tolazamide
Second generation			
Glibenclamide (sulfonylureas)		Cardiomyocytes Smooth muscle Mitochondria Pancreas	Gliclazide glimepiride Glipizide
Third generation			
Meglitinide (benzoic acid derivatives)		Pancreas	Repaglinide Nateglinide Mitiglinide
HMR-1098 (sulfonylureas)		Cardiomyocytes	HMR-1883

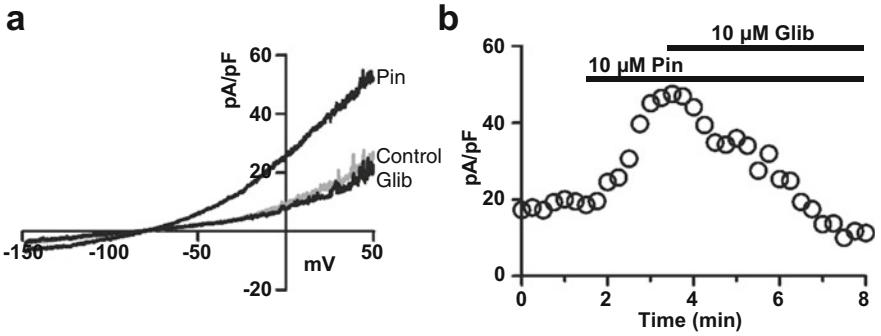


Fig. 2 The effects of pinacidil and glibenclamide on the K_{ATP} current in a murine aortic vascular smooth muscle cell. (**a**) Current Density-Voltage relationship in the presence of 10 μM pinacidil (Pin) and 10 μM glibenclamide (Glib). (**b**) Time course of the effects of pinacidil and glibenclamide at +40 mV. The data are from our own studies and these recordings are unpublished

nicorandil are selective for SUR2-containing channels, whereas diazoxide is more specific for SUR1-containing subunits but also activates SUR2B-containing channels (Giblin et al. 2002; Mannhold 2004); diazoxide has also been shown to activate SUR2A-containing channels under specific circumstances with high MgADP levels (D'hahan et al. 1999). Figure 2 shows activation of a K_{ATP} current by pinacidil in vascular smooth muscle cells.

The use of chimaeras between SURs and radioligand binding experiments has identified regions within TMD2, in particular the cytoplasmic linker between TM13 and TM14 and the last TM helices, TM16 and TM17, as important for pinacidil and cromakalim binding (Babenko et al. 2000; Moreau et al. 2000; Uhde et al. 1999). 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 (Babenko et al. 2000). The presence of more than one binding site on SUR for KCOs helps explain the structural diversity of KCOs.

KCOs were initially developed based on their ability to relax smooth muscle. However, studies using in vivo models showed differences in their physiological actions. For example, diazoxide was found to have both hypotensive and hyperglycaemic effects (RUBIN et al. 1962; Wolff 1964). Nicorandil, used in the treatment of angina, also acts on cardiac K_{ATP} channels thus potentially conferring cardioprotection (Horinaka 2011). Pinacidil, on the other hand, failed to reverse glibenclamide-induced hypoglycaemia in rats (Clapham et al. 1994), but shows a potent hypotensive effect in man (Carlsen et al. 1983; Ward et al. 1984).

KCOs have many potential therapeutic roles, including treatment of insulinomas with insulin hypersecretion, congenital hyperinsulinism, hypertension, myocardial ischaemia, congestive heart failure, bronchial asthma, urinary incontinence, and certain skeletal muscle myopathies (Hibino et al. 2010). Despite this, they have not been widely adopted in clinical practice because of side effects including profound hypotension, fluid retention, and others such as headache and flushing.

3.2 K_{ATP} Channel Blockers

3.2.1 Sulfonylureas

The hypoglycaemic action of sulfonylureas was inadvertently discovered in studies looking at their potential use as a treatment for typhoid fever. They work by inhibiting K_{ATP} channels in the pancreatic β-cell by binding to the SUR1 subunit, thus preventing K^+ efflux leading to the depolarisation of the β-cell membrane, opening of voltage-dependent calcium channels, increased Ca^{2+} influx, and subsequently insulin release. The first group of sulfonylureas such as tolbutamide and chlorpropamide has relatively low affinity for K_{ATP} channels. The early generations of sulfonylureas were initially used exclusively for treatment of type 2 diabetes mellitus; however, these compounds were also found to act on cardiac K_{ATP} channels with potential undesired cardiovascular side effects (Garratt et al. 1999). Subsequently, a more potent second generation (e.g. glibenclamide, gliclazide, and glipizide) was developed. The second generation drugs are relatively selective for the pancreatic channel and despite the potential for weight gain are still used in the treatment of type II diabetes mellitus. Advances in sulfonylurea chemistry led to the synthesis of a third generation of derivatives that show greater tissue selectivity. For example, HMR-1098 (Table 2) has a 400–800-fold selectivity for the cardiac K_{ATP} over the pancreatic K_{ATP} channel (Manning Fox et al. 2002).

There are differential effects of these agents between SUR1 and SUR2 containing channels. For example, glibenclamide and glimepiride show high-affinity block in both SUR1 and SUR2 containing channels whilst tolbutamide, gliclazide, and chlorpropamide have higher affinity for SUR1 (Gribble and Reimann 2003). In order to find the binding sites for these agents on SUR1 and SUR2, a chimeric approach was used and high-affinity inhibition was assayed (Ashfield et al. 1999). The last group of transmembrane domains, specifically the cytoplasmic loop between helices 15 and 16, was found to be important for binding (Ashfield et al. 1999). S1237 has been identified as a key amino acid residue for the binding of glibenclamide (Hansen et al. 2002) and introduction of serine at an equivalent residue in SUR2B led to an increase in the affinity of glibenclamide binding (Hambrock et al. 2001). Recent elucidation of the structure of SUR1 and Kir6.2 in complex using cryo-EM indicates that the binding site for glibenclamide might lie close to residues S1237, R1246, and R1300 but also that it might closely interact with residue Y230 in the linker between TMD0 and TMD1 (L0) (Ding et al. 2019; Martin et al. 2017) and R306 in TMD1 (Ding et al. 2019). Additional support for this model comes from biochemical studies. For example, glibenclamide binding is abolished with the deletion of TMD0 and L0 but not TMD0 alone. The L0 domain interlinks with Kir6.2 and, thus, is perfectly placed to regulate Kir6.2 gating. Finally, glibenclamide might prevent channel activation by altering the interaction between the NBDs preventing their alignment and dimerisation (Li et al. 2017; Martin et al. 2017). The cryo-EM structure showing drug–SUR interaction is shown in Fig. 3.

Physiologically, the actions of sulphonylureas can be affected by endogenous modulators such as MgADP. For example, in intact whole cell or in the presence of MgADP the action of tolbutamide is much more complete than in inside-out patches

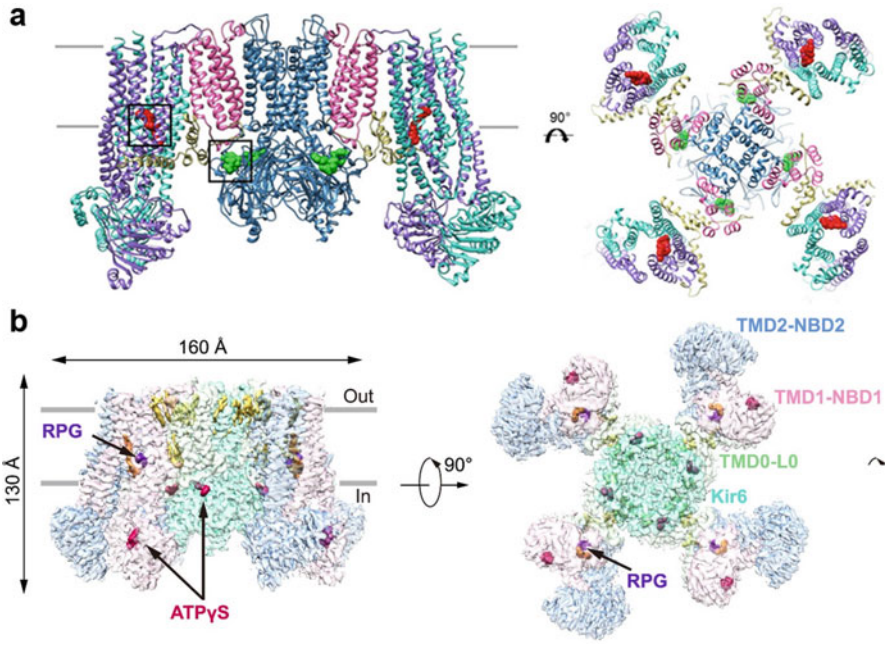


Fig. 3 The structure of the pancreatic K_{ATP} channel in complex with the K_{ATP} channel blockers glibenclamide and repaglinide. (**a**) A side view (left) of the model of the K_{ATP} channel in complex with ATP (green) and glibenclamide (red) and the model viewed from the extracellular side of membrane (right). (This figure is reproduced with permission from Martin et al. 2017). (**b**) Cryo-EM density map of the K_{ATP} channel in complex with repaglinide (RPG, purple) and ATPγS (red) viewed from the side (left) and intracellularly (right). (This figure was reproduced with permission from Ding et al. 2019)

where MgADP is absent (Gribble et al. 1997). This interaction with MgADP is not a feature of SUR2-containing channels and in fact sulphonylureas are less effective when MgADP concentrations are high (Reimann et al. 2003).

3.2.2 Nonsulphonylurea Drugs

Amongst the third generation of K_{ATP} blockers, a new chemical class of *nonsulphonylurea* drugs of benzoic acid derivatives was developed for the treatment of type 2 diabetes mellitus (Table 2). These include meglitinide, repaglinide, nateglinide, and mitiglinide. Benzoic acid derivatives are insulin secretagogues that bind primarily to pancreatic K_{ATP} channels, for example mitiglinide is highly tissue-specific and has a 1,000-fold greater affinity for pancreatic K_{ATP} channels over the cardiac and smooth muscle K_{ATP} channels (Reimann et al. 2001). Meglitinide and repaglinide show high-affinity block in both SUR1 and SUR2 containing channels whilst nateglinide does not exhibit high-affinity block with SUR2 (Gribble and Reimann 2003). A recent cryo-EM study has resolved the structure of the pancreatic K_{ATP} channel in complex with repaglinide (Ding et al. 2019). The images reveal that

repaglinide shares a region of the glibenclamide binding site in TMD2 (R1246 and R1300) for its carboxyl group but other parts of the structure bind to distinct regions of SUR. Specifically, residues in TMD1 including M441, L592, V596, F433, W430, L434, Y377, and I381 provide a suitable pocket for the hydrophobic portion of repaglinide. The positioning of the binding site between TMD1 and TMD2 inhibits NBD dimerisation preventing K_{ATP} channel activation (Fig. 3).

Other agents used clinically may exhibit their actions through K_{ATP} channels. For example, baclofen may exhibit its antidepressant-like effect through inhibition of K_{ATP} channels (Nazari et al. 2016). The anti-epilepsy drug carbamazepine can inhibit K_{ATP} channel activity by disrupting the response to MgADP (Zhou et al. 2014). Some drugs that display anticonvulsant properties such as the inotropic calcium sensitiser levosimendan (Gooshe et al. 2017), glycolytic inhibitor 2-deoxy-D-glucose (Yang et al. 2013), K^+-sparing diuretic triamterene (Shafaroodi et al. 2016), hypnotic agent zolpidem (Sheikhi et al. 2016), fatty acid caprylic acid (Socała et al. 2015), and gabapentin (Ortiz et al. 2010) could also exert their action through K_{ATP} channels.

3.2.3 K_{ATP} Channel Pore Blockers

Generic agents such as barium, tetraethylammonium, and 4-aminopyridine can also block K_{ATP} channels by directly occluding the pore (Ashcroft and Ashcroft 1990; Takano and Ashcroft 1996). In addition, derivatives from the cyanoguanidine K_{ATP} opener P1075 such as PNU-37883A, PNU-89692, PNU-97025E, PNU-99963, and PNU-9470 are also K_{ATP} channel blockers.

Of these, PNU-37883A has been extensively investigated and early studies suggested a potential for future therapeutic use. PNU-37883A is a morpholino-guanidine drug that has been shown to be selective for vascular smooth muscle K_{ATP} channels (Meisheri et al. 1993). Studies using different recombinantly expressed K_{ATP} channel subunit combinations showed a preference for Kir6.1-containing K_{ATP} channels (Kovalev et al. 2001; Surah-Narwal et al. 1999). Further investigations revealed a higher affinity for Kir6.1 over Kir6.2 and a chimeric approach found that the C-terminus of Kir6.1 was important for PNU binding (Kovalev et al. 2004). Specifically, residues 200–280 of Kir6.1 are critical for the inhibitory effect. Interestingly, the choice of SUR subunit complexing with Kir6.1 is also important for PNU potency. Thus, PNU is being more potent when Kir6.1 is partnered with SUR2B, as compared to Kir6.1-SUR1 complex, explaining the relative specificity of PNU-37883A for vascular smooth muscle channels (thought to be constituted of Kir6.1/SUR2B).

The early promise of PNU-37883A for therapeutic use has subsided, although it is not clear whether this is a result of off-target effects or lack of potency. Nevertheless, it is routinely used in the research environment to distinguish between Kir6.1 and Kir6.2-containing K_{ATP} channels.

4 The Physiology and Pathophysiology of K_{ATP} Channels

Defective K_{ATP} channel function because of mutations (both loss-of-function [LoF] mutations and gain-of- function [GoF] mutations) can lead to diseases in neurological, cardiac, and endocrine systems.

4.1 Pancreas

K_{ATP} channels in the pancreas, particularly in the β-cells, have been extensively studied. A combination of Kir6.2/SUR1 makes up the K_{ATP} channel population in the insulin-regulating β-cells and glucagon-secreting α-cells (Table 3). In pancreatic β-cells, K_{ATP} channels couple cellular metabolism to electrical activity in response to changes in blood glucose. When blood glucose is low, ATP production is reduced allowing K_{ATP} channels to open thus hyperpolarising the membrane and preventing an increase in intracellular Ca^{2+} and subsequent insulin release. At high blood glucose concentrations, ATP production increases leading to channel inhibition, an increase in intracellular Ca^{2+} and insulin release. In pancreatic α-cells, glucagon is released to promote the mobilisation of glucose, and this process is inhibited by increased blood glucose levels.

Congenital hyperinsulinism is a genetic disorder in which there are abnormally high levels of insulin secretion from pancreatic β-cells leading to hypoglycaemia. It typically occurs in infants and young children in approximately 1/25–50,000 births where, if left untreated, persistent hypoglycaemia increases the risk for serious complications such as breathing difficulties, seizures, intellectual disability, vision loss, brain damage, and coma. Congenital hyperinsulinism is caused by mutations that lead to an overall LoF of K_{ATP} channels and have been identified in both the *KCNJ11* (Kir6.2) and *ABCC8* (SUR1) genes. Loss of channel activity arises from loss of K_{ATP} channels at the membrane due to ER retention, production of non-functional proteins, impaired pore-opening, loss of MgADP sensitivity, and reduced sensitivity to metabolic inhibition and drug activation (Tinker et al. 2018).

Neonatal diabetes mellitus (NMD) is a rare form of diabetes that occurs within the first 6 months of life in approximately in 1/100,000 births (Rubio-Cabezas and Ellard 2013). Neonatal diabetes can be caused by mutations in *KCNJ11 and ABCC8 that lead to* ATP insensitivity and GoF (Babenko et al. 2006).

Type 2 diabetes mellitus is a common and lifelong condition where the body doesn't produce or respond to insulin, it is usually considered as a disease of peripheral insulin resistance, however, there is evidence that pancreatic β-cell mass is reduced leading to impaired insulin secretion. Type 2 diabetes is associated with variants in *KCNJ11* (Gloyn et al. 2003) and *ABCC8* (Hamming et al. 2009).

Table 3 Tissue-specific subunit composition and properties of K_{ATP} channels

Location		K_{ATP} subunits	Physiological function
Pancreas	α-cells	Kir6.2/SUR1	Regulation of glucagon secretion in response to changes in blood glucose
	β-cells	Kir6.2/SUR1	Regulation of insulin release in response to changes in metabolism
Enteroendocrine cells		Kir6.2/SUR1	Involved in the stimulus-secretion coupling of gut hormones such as GIP, GLP-1, and PYY
Skeletal muscle		Kir6.2/SUR2A/SUR1	Adaptation to strenuous exercise, regulation of glucose uptake and metabolism
Heart	Atria	Kir6.2/SUR1	Action potential repolarisation, adaptation to cell swelling
	Ventricle	Kir6.2/SUR2A	Protection against Ca^{2+} overload during hypoxia, adaptation response to stress
	Conduction system	Kir6.1/Kir6.2/SUR2B	Adaptation to stress, regulation of pacemaker activity
Smooth muscle	Endothelium	Kir6.1/Kir6.2/SUR2B	Vasodilation, blood pressure regulation
	Vascular smooth muscle	Kir6.2/SUR2B	Relaxation, contraction
	Non-vascular smooth muscle	Kir6.1/Kir6.2/SUR2B	Vasodilation, protective during ischaemia
Nervous system	Hypothalamus	Kir6.2/SUR1	Expressed in AgRP/NPY- and POMC-positive neurons, regulation of neuronal excitability in response to glucose
	Pituitary	Kir6.2/SUR2B/SUR1	Regulation of hormone secretion
	Substantia nigra	Kir6.2/SUR1	Neuroprotection from stress and against seizures, regulation of excitability, release of neurotransmitters such as dopamine, GABA, and glutamate in response to changes in metabolism, play a role in memory, locomotion and behaviour
	Dorsal root ganglion	Kir6.2/SUR1/SUR2	Suppression of hyperalgesia
	Glial cells	Kir6.1/Kir6.2/SUR1	Neuroprotective, potassium siphoning

4.2 Heart

A combination of SUR2A\Kir6.2 subunits underlie the cardiac K_{ATP} channel in ventricular myocytes, but other subunit combinations have been reported in atria and conduction tissues (Table 3). Under basal conditions, the K_{ATP} channels in cardiomyocytes are closed and contribute little to resting membrane potential or action potential repolarisation (Noma 1983). In pathological conditions associated

with hypoxia and ischaemia, cardiac K_{ATP} channels are activated leading to shortened action potential duration and attenuated/abolished contraction in myocytes (Lederer et al. 1989; Venkatesh et al. 1991). Similarly, K_{ATP} channels contribute to action potential duration and QT interval shortening in response to high-intensity exercise (Zingman et al. 2002).

Multiple mutations have been identified within K_{ATP} channel subunits that confer susceptibility to cardiac arrhythmia, cardiomyopathy, hypertrophy, and heart failure. Atrial fibrillation is the most common cardiac arrhythmia and can become persistent due to electrophysiological remodelling of the atria. A LoF missense mutation (T1547I) in *ABCC9* (SUR2) has been implicated in atrial fibrillation (Olson et al. 2007). Multiple mutations in *ABCC9* (SUR2), that impair nucleotide hydrolysis at NBD2, causing reduced function are associated with dilated cardiomyopathy (Bienengraeber et al. 2004). In addition, increased left ventricle size and heart failure are associated with the E23K variant in *KCNJ11* (Reyes et al. 2008, 2009). Whereas S422L GoF mutation in *KCNJ8* has been associated with Brugada syndrome, early repolarisation "J-wave" syndrome, atrial and ventricular fibrillation (Barajas-Martínez et al. 2012; Delaney et al. 2012; Haïssaguerre et al. 2009; Medeiros-Domingo et al. 2010). GoF (V734I and S1402C) mutations in *ABCC9* are thought to underlie Brugada and early repolarisation syndromes (Hu et al. 2014).

4.3 Cantu Syndrome

Cantu syndrome (CS) is a relatively new and rare syndrome, the hallmarks of which are hypertrichosis, abnormal facial features, and cardiomegaly (Cantú et al. 1982; Nichols et al. 2013). The features of CS vary among affected individuals and some patients also display other clinical features such as pericardial effusion, patent ductus arteriosus, conduction system abnormalities, pulmonary hypertension, and coarse lax skin (Scurr et al. 2011). Recently, the genetic basis of CS has been revealed showing the involvement of K_{ATP} channels. Specifically, missense mutations in *KCNJ8* and *ABCC9* have been identified. Using standard heterologous expression techniques, these mutations were shown to be GoF mutations leading to increased K_{ATP} channel activity (Cooper et al. 2015; Harakalova et al. 2012) as a result of reduced ATP-sensitivity and increased activation by MgADP (Cooper et al. 2015). The features of CS, particularly the cardiac abnormalities, have been replicated in murine models where both Kir6.1 and SUR2 GoF mutations have been transgenically introduced into a number of cardiovascular tissues (Levin et al. 2016).

4.4 Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is the sudden, unexpected, and unexplained death of an otherwise healthy baby, with most deaths occurring in the first 6 months of life. Although the exact cause of SIDS is unknown, LoF mutations in *KCNJ8* such

as the in-frame deletion E332del and missense mutation V346I have been associated (Tester et al. 2011).

4.5 Nervous System

K_{ATP} channels and currents are widely distributed in the nervous system (Table 3). In central and peripheral neurones, the channels are largely thought to be constituted of Kir6.2 (Sun et al. 2007), with the exception of glial cells, where the current is made up of Kir6.1/SUR1 (Eaton et al. 2002). Neuronal K_{ATP} channels exhibit various physiological functions, including modulation of neuronal excitability (Allen and Brown 2004), suppression of hyperalgesia (Zoga et al. 2010), control of locomotion and behaviour (Deacon et al. 2006), influencing nutrient sensing and satiety (Rother et al. 2008) and control of autonomic function and thus modulation of heart rate (Almond and Paterson 2000; Mohan and Paterson 2000).

Mutations in K_{ATP} channels that underlie congenital hyperinsulinism, neonatal diabetes, and Cantu syndrome all display varying degrees of neurological pathology, it is likely that the abnormalities in K_{ATP} channel expression in neurons are the main reason for this.

4.6 Pulmonary Circulation

Pulmonary arterial hypertension (PAH) is a rare but serious condition and can affect people of all ages. It is characterised by raised pulmonary artery pressure and increased pulmonary vascular resistance and can lead to right heart failure and death. Mutations in multiple genes have been implicated in the development of PAH. Alongside mutations in genes such as *BMPR2* (bone morphogenic protein receptor type 2), LoF mutations in K_{ATP} channels (as well as other K^+ channels) have also been identified (McClenaghan et al. 2019). Reduced K^+ channel activity causes vasoconstriction leading to an increase in blood pressure. Interestingly, patients with Cantu syndrome with GoF mutations in *ABCC9* and *KCNJ8* can also develop PAH, possibly due to systemic feedback involving the renin-angiotensin-aldosterone system (McClenaghan et al. 2019). KCOs such as iptakalim and diazoxide may have therapeutic potential as a treatment for pulmonary hypertension.

4.7 Current Therapeutic Uses of KCOs and Inhibitors of K_{ATP} Channel

K_{ATP} channel openers are only used as second line agents for the treatment of diseases such as stable angina and hypertension. Three KCOs are used in clinical practice; nicorandil (stable angina), diazoxide (hypertension, congenital hyperinsulinism in some patients), and minoxidil sulphate (hypertension and male pattern baldness). Iptakalim, a relatively new KCO thought to be specific for vascular

smooth muscle K_{ATP} channels, has shown promise in the treatment of mild to moderate essential hypertension and may also have therapeutic potential in the treatment of pulmonary hypertension (Sikka et al. 2012).

K_{ATP} channel inhibitors, the sulphonylureas, are still used in the treatment of type 2 diabetes in patients who are intolerant of metformin and in combination therapy, although the earlier generation of sulphonylureas are not recommended due to their possible inhibition of cardiac K_{ATP} channels. Sulphonylureas can lead to unwanted side effects including weight gain and also there is a risk of hypoglycaemia particularly in elderly patients (O'Hare et al. 2015).

The recent unmasking of the genetic basis of neonatal diabetes mellitus has revolutionised the management of the disease (Pearson et al. 2006). These patients were traditionally treated with insulin but the discovery that disease pathogenesis was due to over-activity of pancreatic K_{ATP} channels led to the use of sulphonylureas. The use of sulfonylureas normalised glucose homeostasis in many patients with normal responses of insulin release following a meal (Pearson et al. 2006). The presence of neurological symptoms requires higher doses and where the disease is due to mutations that do not affect ATP sensitivity the use of sulfonylureas may fail (Ashcroft et al. 2017; Babiker et al. 2016). Sulphonylurea treatment of the neurological deficits is not as effective as these deficits may have a developmental component (Koster et al. 2008; Shah et al. 2012; Slingerland et al. 2008). It is important that therapy with sulphonylureas is initiated as early as possible, as with time there is a decline in treatment efficacy (Babiker et al. 2016).

The characterisation of the genetic basis (GoF of K_{ATP} channels) of Cantu syndrome has given rise to the possibility of pharmacological intervention with sulphonylureas. Recent studies on murine models suggest that glibenclamide shows promising effects on the cardiovascular abnormalities that occur in CS such as reversing cardiac hypertrophy and increasing blood pressure (McClenaghan et al. 2020).

5 Conclusions

K_{ATP} channels are ubiquitously expressed in the body and have diverse functions in different tissue types. The physiological role of K_{ATP} channels is best described in the pancreatic β-cell, but recent work has also revealed their important pathophysiological roles in other cell types including cardiac, vascular, and nervous cells. K_{ATP} channels have a rich and diverse pharmacology that has the potential to be exploited to develop novel therapeutic agents for the treatment of various human diseases.

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