The role of the $K_{\text{ATP}}$ channel in glucose homeostasis in health and disease: more than meets the islet

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ATP-sensitive potassium ($K_{\text{ATP}}$) channels are critical for the maintenance of glucose homeostasis. They are essential for glucose-stimulated insulin secretion from pancreatic $\beta$-cells, contribute to the mechanisms by which hypoglycaemia stimulates glucagon release from pancreatic $\alpha$-cells, and are involved in glucose uptake into skeletal muscle, glucose production and release from the liver, and feeding behaviour. Not surprisingly, loss- or gain-of-function mutations in $K_{\text{ATP}}$ channel genes have profound effects, giving rise to congenital hyperinsulinaemia and neonatal diabetes respectively. This symposium review focuses on our current understanding of the role of the $K_{\text{ATP}}$ channel in glucose homeostasis in health and disease.

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Introduction

Claude Bernard once wrote, ‘All the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of the internal environment which make a free and independent life possible’ Bernard (1879). This necessity for stability is particularly true of the blood glucose concentration. If it drops below 1–2 mM, the brain is deprived of its main energy source, causing rapid loss of consciousness. On the other hand, long-term elevation (>7 mM) of blood glucose is also dangerous for it leads to the complications of diabetes – neuropathy, retinopathy, peripheral neuropathy and cardiovascular disease. Thus it is imperative that plasma glucose levels are controlled within narrow limits.

It is well known that the $K_{\text{ATP}}$ channel plays a critical role in glucose homeostasis by regulating insulin secretion. What is less widely appreciated is that it also makes important contributions to other mechanisms controlling plasma glucose levels, all of which may be affected if $K_{\text{ATP}}$ channel function is impaired. For example, $K_{\text{ATP}}$ channels modulate glucose uptake into skeletal muscle, contribute to the central control of hepatic glucose output and appetite, and facilitate the counter-regulatory response to hypoglycaemia both centrally and peripherally by increasing the release of hormones such as glucagon. Perturbation of all these pathways – not just insulin secretion – may be expected in mice and men carrying $K_{\text{ATP}}$ channel mutations. Here, we review the role of the...
The \( \mathrm{K}_{\text{ATP}} \) channel is a metabolic sensor

The \( \mathrm{K}_{\text{ATP}} \) channel is a large macromolecular complex in which four inwardly rectifying potassium channel (Kir6.x) subunits form a central pore surrounded by four regulatory sulphonylurea receptor (SUR) subunits (Clement et al. 1997; Mikhailov et al. 2005). Kir6.x comes in two isoforms, Kir6.1 and Kir6.2, but in this review we confine our discussion to Kir6.2 channels. There are three SUR isoforms that confer distinct nucleotide and drug sensitivities: SUR2A, found in heart and skeletal muscle; SUR2B, found in smooth muscle and many neurones; and SUR1, which is widely expressed in neuroendocrine cells (including β-cells) and neurones.

Physiologically, the \( \mathrm{K}_{\text{ATP}} \) channel serves as a metabolic sensor, coupling cellular metabolism to electrical activity in a wide range of tissues. Opening of \( \mathrm{K}_{\text{ATP}} \) channels under conditions of low metabolism leads to membrane hyperpolarization and switches off cellular functions (Fig. 1A). Conversely, \( \mathrm{K}_{\text{ATP}} \) channels close when metabolism increases, producing a membrane depolarization that leads to cellular responses such as hormonal secretion, neurotransmitter release and contraction (Fig. 1B). Metabolic sensitivity varies between \( \mathrm{K}_{\text{ATP}} \) channels: cardiac and skeletal \( \mathrm{K}_{\text{ATP}} \) channels open only when metabolic stress is severe (as in ischaemia) while β-cell and neuronal channels open when plasma glucose levels fall.

Changes in the intracellular concentrations of adenine nucleotides mediate the metabolic regulation of channel activity. ATP closes the channel by binding to Kir6.2 while Mg-nucleotide binding/hydrolysis at the nucleotide-binding domains of SUR stimulates channel opening. The balance between these stimulatory and inhibitory effects determines the level of channel activity. In addition, channel activity is regulated by lipids, such as PIP\(_2\) and PIP\(_3\), which increase the channel open probability and reduce its inhibition by ATP (Baukrowitz & Fakler, 2000). \( \mathrm{K}_{\text{ATP}} \) channels are also the target of therapeutic drugs. Sulphonylureas (e.g. glibenclamide) have been used to treat type 2 diabetes for more than 50 years (Gribble & Reimann, 2003). They bind to SUR and close the \( \mathrm{K}_{\text{ATP}} \) channel, thereby depolarizing the cell and stimulating insulin release. Conversely, K-channel openers (diazoxide, pinacidil), stimulate \( \mathrm{K}_{\text{ATP}} \) channel activity by interacting with SUR.

Role of the \( \mathrm{K}_{\text{ATP}} \) channel in glucose homeostasis

Secretion of insulin and glucagon. The role of the \( \mathrm{K}_{\text{ATP}} \) channel in stimulus–secretion coupling in pancreatic β-cells is well established (Ashcroft et al. 1984; Ashcroft, 2007). When plasma glucose levels fall, metabolic inhibition opens \( \mathrm{K}_{\text{ATP}} \) channels, suppressing electrical activity and insulin release. Conversely, increased metabolism closes \( \mathrm{K}_{\text{ATP}} \) channels leading to membrane depolarization, opening of voltage-gated \( \mathrm{Ca}^{2+} \) channels, \( \mathrm{Ca}^{2+} \) influx and insulin secretion. \( \mathrm{K}_{\text{ATP}} \) channel closure also enables the amplifying effects of glucose and other secretagogues, such as the incretins GLP-1 and GIP (Henquin, 2009). The latter are secreted, from L-cells and K-cells, respectively, in response to the presence of nutrients in the gut lumen. Interestingly, although L- and
K-cells possess K\(_{ATP}\) channels it appears that these channels do not play a significant physiological role in incretin release (Parker et al. 2010); thus incretin release is not expected to be modified by K\(_{ATP}\) channel mutations.

Hypoglycaemia precipitates the release of counter-regulatory hormones such as glucagon and catecholamines, and K\(_{ATP}\) channels also appear to be important in this response. It has been proposed that glucose inhibits glucagon secretion from pancreatic \(\alpha\)-cells via both direct and indirect (paracrine) mechanisms (Gromada et al. 2007). The former mechanism has been attributed to insulin and zinc ions, which activate K\(_{ATP}\) channels, hyperpolarizing the \(\alpha\)-cells and inhibiting electrical activity and glucagon release (Franklin et al. 2005). The latter involves a direct inhibitory action of glucose on K\(_{ATP}\) channels in \(\alpha\)-cells (MacDonald et al. 2007).

The ability of glucose to stimulate \(\beta\)-cells but inhibit \(\alpha\)-cell secretion via K\(_{ATP}\) channel closure can be explained by the different complements of voltage-gated ion channels in these cells. Because \(\alpha\)-cells possess fewer K\(_{ATP}\) channels, the K\(_{ATP}\) current is small even in the absence of glucose. The membrane potential therefore exceeds the threshold for action potential firing, stimulating Ca\(^{2+}\) influx and glucagon release. A rise in extracellular glucose increases K\(_{ATP}\)-channel closure, further depolarizing the cell. This leads to inactivation of the voltage-gated channels (e.g. TTX-sensitive Na\(^+\) channels) that support electrical activity and so induces a depolarization block that suppresses glucagon secretion. Clearly, these proposed mechanisms (direct and indirect) predict opposite effects on the \(\alpha\)-cell membrane potential: thus the issue of precisely how glucose regulates glucagon release is not yet fully resolved (Gromada et al. 2007).

The counter-regulatory response to glucose also involves neuronally mediated mechanisms of glucagon release as described below.

**Glucose uptake into skeletal muscle.** Insulin stimulates the uptake of glucose into muscle, fat and liver, where it is stored: it is subsequently released when plasma glucose levels fall. Both uptake and release are modulated by K\(_{ATP}\) channels (composed of Kir6.2 and SUR2A subunits). When either Kir6.2 or SUR2A is genetically deleted, glucose uptake by skeletal muscle is enhanced, suggesting that K\(_{ATP}\) channel closure enhances, and opening decreases, glucose uptake (Chutkow et al. 2001; Miki et al. 2002). This explains the ability of sulphonylurea drugs to stimulate muscle glucose uptake (Wang et al. 1989). The mechanism by which K\(_{ATP}\) channel activity modifies glucose uptake is not resolved but unlike insulin does not seem to involve insulin receptor substrate and phosphatidylinositol 3-kinase signalling (Minami et al. 2003). Nor does it appear to involve the insulin-independent AMPK-dependent pathway (Minami et al. 2003).

**Neuronally mediated mechanisms.** It was Claude Bernard who first postulated that the brain controls peripheral glucose metabolism, in 1855 (Bernard, 1855). We now know that his hypothesis was correct and that neuronal K\(_{ATP}\) channels play an important role in glucose homeostasis (Miki & Seino, 2005). For example, hypothalamic K\(_{ATP}\) channels regulate hepatic glucose output as evidenced by the fact that stereotactic infusion of diazoxide into the hypothalamus inhibits hepatic glucose production and, conversely, that SUR1 knock-out mice show increased glucose production (Pocai et al. 2005). Furthermore, insulin suppresses hepatic glucose output by activating K\(_{ATP}\) channels in agouti-related peptide (AgRP)-expressing neurones of the arcuate nucleus of the hypothalamus (Konner et al. 2007).

K\(_{ATP}\) channels render the electrical activity of many types of neurone sensitive to the ambient glucose level and thereby influence glucose homeostasis in a variety of ways. Reduced extracellular glucose causes opening of K\(_{ATP}\) channels in glucose-sensitive neurones of the ventromedial hypothalamus, triggering glucagon secretion and the counter-regulatory response to hypoglycaemia (Miki et al. 2001). This is mediated via activation of the autonomic nervous system leading to release of catecholamines such as adrenaline, which is a powerful stimulator of glucagon secretion (Gromada et al. 2007).

Pro-opiomelanocortin (POMC)-expressing neurones in the arcuate nucleus are crucially important for feeding and their stimulation leads to anorexigenic behaviour, which influences blood glucose levels. K\(_{ATP}\) channel activation sufficient to abolish electrical activity of these neurones leads to hyperphagia and increased body weight (Plum et al. 2006). Partial activation, which reduces but does not abolish electrical activity, prevents glucose sensing and leads to impaired glucose tolerance (Parton et al. 2007).

**Loss-of-function K\(_{ATP}\) channel mutations cause hyperinsulinism.**

Congenital hyperinsulinism (HI) is characterised by continuous and unregulated insulin secretion despite very low plasma glucose levels (De Leon & Stanley, 2007). Patients usually present shortly after birth with persistent hypoglycaemia that requires immediate treatment to avoid brain damage. In most cases, therapy involves a partial pancreatectomy. Infants are also large for gestational age due to stimulation of fetal growth by the excess insulin. K\(_{ATP}\) channel mutations are the most common cause of HI: >150 have been found in SUR1 (ABCC8) and 24 in Kir6.2 (KCNJ11) (Flanagan et al. 2009). Most mutations
are recessive, suggesting that 50% $K_{ATP}$ channel function is sufficient to prevent hypersecretion of insulin. A few dominant mutations have been identified which are less severe and often responsive to diazoxide (Huopio et al. 2000; Pinney et al. 2008).

All HI mutations lead to a marked reduction in the whole-cell $K_{ATP}$ current, even at low glucose. Consequently, the $\beta$ -cell membrane is permanently depolarised, producing continuous calcium influx and insulin secretion (Fig. 2A). Mechanistically, mutations can be divided into those that lead to a total, or near-total, loss of channels in the plasma membrane (Class I), those that impair the ability of Mg-nucleotides to stimulate channel activity (Class II), and those that decrease the intrinsic (unliganded) channel open probability (Class III). Functional analysis of their effects has provided novel insights into channel structure–function properties, recently revealing, for example, that Kir6.2 contains a di-acidic endoplasmic reticulum exit signal ($^{280}$DLE$^{282}$) (Taneja et al. 2009) and identifying residues involved in gating or channel activation by PIP$_2$ (e.g. F55, Lin et al. 2008; T294, Shimomura et al. 2009).

Although mouse models of HI have provided valuable information about the mechanism of insulin secretion, they do not fully recapitulate the human disease phenotype, as hypoglycaemia is transient in mice (Miki & Seino, 2005). The reason for this difference is poorly understood. Except for insulin secretion, few other $K_{ATP}$-dependent processes involved in glucose homeostasis have been studied in detail in HI. The glucagon counter-regulatory response is impaired in HI (Hussain et al. 2005), but the mechanism has not been established.

The effects of HI mutations on the central control of glucose homeostasis is a fascinating issue but is difficult to assess as it is hard to be certain that any changes observed are not a consequence of hypoglycaemia.

**Gain-of-function $K_{ATP}$ channel mutations cause neonatal diabetes**

Gain-of-function mutations in Kir6.2 or SUR1 cause neonatal diabetes (ND). Patients normally, but not exclusively, present within the first 6 months of life with severe hyperglycaemia. In many people the diabetes is permanent but in others it follows a remitting relapsing time course. Around 20% of patients also exhibit neurological problems, including mental and motor developmental delay, muscle hypotonia, and (occasionally) epilepsy (Hattersley & Ashcroft, 2005). This spectrum of symptoms is a consequence of the widespread tissue distribution of $K_{ATP}$ channels, which are found in muscle, heart and brain as well as the islet.

Over 40 different ND mutations have been described in Kir6.2 and a similar number in SUR1 (Flanagan et al. 2009). All Kir6.2 mutations cause dominant disease, but SUR1 mutations are genetically more heterogeneous, with homozygous, heterozygous and compound heterozygous mutations being described. Permanent diabetes is most commonly associated with Kir6.2 mutations and transient diabetes with SUR1 mutations. Fifteen Kir6.2 mutations (but only two in SUR1) cause neurological problems (Flanagan et al. 2009).

All Kir6.2 mutations causing ND impair channel inhibition by ATP (Gloyn et al. 2004; reviewed by Ashcroft,

![Figure 2. Role of $K_{ATP}$ channels in insulin secretory disorders](image-url)

**A Hyperinsulinism**

- Loss-of-function mutations in Kir6.2 or SUR1 lead to permanent $K_{ATP}$ channel closure independent of cell metabolism. Consequently, the $\beta$ -cell membrane is always depolarised, producing continuous calcium influx and insulin secretion.

**B Neonatal Diabetes**

- Gain-of-function mutations in Kir6.2 or SUR1 prevent $K_{ATP}$ channel closure when adenine nucleotide levels rise in response to metabolism. Consequently, the $\beta$ -cell membrane remains hyperpolarised even when blood glucose levels are high, preventing insulin secretion.
2007). Some act by increasing the intrinsic (unliganded) channel open probability ($P_o(0)$), which indirectly reduces ATP block: it remains unclear if they influence gating directly or via changes in PIP$_2$ binding. Some mutations cluster around the putative ATP-binding site and are likely to impair ATP binding. Others may alter ATP binding allosterically, or influence the mechanism by which occupancy of the ATP-binding site is transduced into changes in channel gating. There is also evidence that some Kir6.2 mutations enhance Mg-nucleotide activation

Figure 3. ATP sensitivity correlates with disease severity
Correlation between disease severity and the extent of unblocked K$_{ATP}$ current measured in inside-out patches at 3 mM MgATP for the wild-type channel (WT) and the indicated Kir6.2 (A) and SUR1 (B) mutations. Mean (± S.E.M.) is shown. Blue bars: neonatal diabetes alone. Green bars: diabetes with muscle hypotonia and developmental delay. Red bars: DEND syndrome (diabetes with muscle hypotonia, developmental delay and epilepsy).
(mediated via SUR1). Only a handful of SUR1 mutations have been studied in detail but their effects are equally complex, with some increasing MgATP activation and others increasing $P_o(0)$. A common theme, however, is that the severity of the clinical phenotype correlates reasonably well with the ability of MgATP to inhibit channel activity in inside-out patches (Fig. 3A and B).

Because ND mutations impair the ability of ATP to inhibit the channel, they all increase the whole-cell $K_{ATP}$ current. Consequently, the β-cell remains hyperpolarised even in the presence of glucose, preventing insulin secretion and causing diabetes (Fig. 2B). ND patients were originally treated with insulin injections but the discovery of the causal role of $K_{ATP}$ channels has enabled ∼90% of patients (>400 to date) to switch to sulphonylurea therapy (Pearson et al. 2006; Ashcroft, 2010). This results in a significant improvement in their clinical condition: fluctuations in glucose homeostasis are reduced and HbA1C levels fall, reducing the risk of diabetic complications (Zung et al. 2004; Pearson et al. 2006). In some patients the neurological problems also improve (Slingerland et al. 2006; Mlynarski et al. 2007; Shimomura et al. 2007; Koster et al. 2008; Slingerland et al. 2008). There is a good correlation between the efficacy of sulphonylureas at blocking whole-cell $K_{ATP}$ currents and the ability of the patient with the same mutation to respond to sulphonylurea therapy (Fig. 4).

It is very clear from mouse models of ND that increased activity of $K_{ATP}$ channels in the β-cell alone is sufficient to produce diabetes (Koster et al. 2000; Girard et al. 2009; Remedi et al. 2009). It is yet to be determined if other $K_{ATP}$ channel-dependent mechanisms of glucose homoeostasis are altered in ND patients (or in mouse models). For example, do they show decreased insulin sensitivity, and changes in glucagon secretion, hepatic glucose output or food intake? And are these corrected by sulphonylurea therapy?

**E23K and type 2 diabetes**

A common polymorphism in Kir6.2 (E23K) predisposes to type 2 diabetes (Gloyn et al. 2003). Although the increase in disease risk is small (odds ratio, 1.2), the population risk is highly significant because ∼60% of people carry at least one K allele. The E23K polymorphism is found in strong linkage disequilibrium with another variant, S1369A, in the adjacent SUR1 gene (i.e. E23 is always found in conjunction with S1369, and K23 with A1369). This means either variant could cause the increased disease risk.

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**Figure 4. Tolbutamide sensitivity correlates with clinical response**

Correlation between the tolbutamide sensitivity of recombinant $K_{ATP}$ channels carrying the indicated mutations and the ability of at least some patients with the same mutation to transfer to sulphonylurea therapy. Mean (± S.E.M.) percentage $K_{ATP}$ current inhibition by 0.5 mM tolbutamide for the wild-type channel (WT) and the indicated Kir6.2 mutations, measured in the presence of 3 mM azide. Transparent grey bar indicates the threshold level for transfer (65–72% block). Blue bars: neonatal diabetes alone. Green bars: diabetes with muscle hypotonia and developmental delay. Red bars: DEND syndrome (diabetes with muscle hypotonia, developmental delay and epilepsy).
While the genetics is clear, the functional effects of these variants both in vivo and in vitro are controversial. Both increases and decreases in the ATP sensitivity of Kir6.2/SUR1 channels have been reported when E23 is mutated to K23 (Schwanstecher et al. 2002; Riedel et al. 2003; Villareal et al. 2009). Others have argued that it is not the K23 variant that is causal but the A1369 variant in SUR1 (Hamming et al. 2009). It is possible that some of these differences relate to the clones (human/rodent) and the heterologous expression system used. Interestingly, however, the shifts in ATP sensitivity observed are similar to those found with some ND mutations, raising the question of why KK carriers have only a small increase in diabetes risk and not neonatal diabetes. Considerable variability has also been reported for the effects of the E23K polymorphism on insulin secretion and insulin sensitivity in humans. However, larger studies report a lower insulin concentration, significantly reduced insulin secretion and enhanced insulin sensitivity (Villareal et al. 2009). The former would be consistent with increased $\mathrm{K_{ATP}}$ currents in pancreatic β-cells. The origin of the enhanced insulin sensitivity is unknown (it cannot be due to enhanced $\mathrm{K_{ATP}}$ channel activity in muscle as this would be expected to have the opposite effect).

Conclusions

Studies of rodents and humans with impaired $\mathrm{K_{ATP}}$ channel function have produced valuable insights into the role of $\mathrm{K_{ATP}}$ channels in glucose homeostasis. Nevertheless, many questions still need to be answered. In particular, to what extent are pathways that are modulated by the $\mathrm{K_{ATP}}$ channel (other than insulin secretion) impaired in hyperinsulinism and neonatal diabetes and how are these affected by current therapies?

References


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