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SYMPOSIUM REVIEW

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

James S. McTaggart, Rebecca H. Clark, and Frances M. Ashcroft

Henry Wellcome Centre for Gene Function, Department of Physiology, Anatomy and Genetics, and OXION Centre for Ion Channel Studies, Sherrington Building, Parks Road, Oxford OX1 3PT, UK

ATP-sensitive potassium (K_{ATP}) channels are critical for the maintenance of glucose homeostasis. They are essential for glucose-stimulated insulin secretion from pancreatic β-cells, contribute to the mechanisms by which hypoglycaemia stimulates glucagon release from pancreatic α-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_{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_{ATP} channel in glucose homeostasis in health and disease.

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Corresponding author F. M. Ashcroft: Henry Wellcome Centre for Gene Function, Department of Physiology, Anatomy and Genetics, and OXION Centre for Ion Channel Studies, Sherrington Building, Parks Road, Oxford OX1 3PT, UK. Email: frances.ashcroft@dpag.ox.ac.uk

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_{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_{ATP} channel function is impaired. For example, K_{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_{ATP} channel mutations. Here, we review the role of the

Frances Ashcroft is the GlaxoSmithKline Royal Society Research Professor at the University of Oxford. She was fortunate enough to do a post-doc with Peter Stanfield at Leicester who provided much-needed training in electrophysiology and persuaded her that potassium channels are far more interesting than calcium channels. **Rebecca Clark and James McTaggart** are both doing PhDs in Frances's laboratory, looking at mouse models of neonatal diabetes.

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K_{ATP} channel in glucose homeostasis in health and disease and demonstrate its central importance.

The K_{ATP} channel is a metabolic sensor

The K_{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 K_{ATP} channel serves as a metabolic sensor, coupling cellular metabolism to electrical activity in a wide range of tissues. Opening of K_{ATP} channels under conditions of low metabolism leads to membrane hyperpolarization and switches off cellular functions (Fig. 1*A*). Conversely, K_{ATP} channels close when metabolism increases, producing a membrane depolarization that leads to cellular responses such as hormonal secretion, neurotransmitter release and contraction (Fig. 1*B*). Metabolic sensitivity varies between K_{ATP} channels: cardiac and skeletal K_{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). K_{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 K_{ATP} channel, thereby depolarizing the cell and stimulating insulin release. Conversely, K-channel openers (diazoxide, pinacidil), stimulate K_{ATP} channel activity by interacting with SUR.

Role of the K_{ATP} channel in glucose homeostasis

Secretion of insulin and glucagon. The role of the K_{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 K_{ATP} channels, suppressing electrical activity and insulin release. Conversely, increased metabolism closes K_{ATP} channels leading to membrane depolarization, opening of voltage-gated Ca^{2+} channels, Ca^{2+} influx and insulin secretion. K_{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

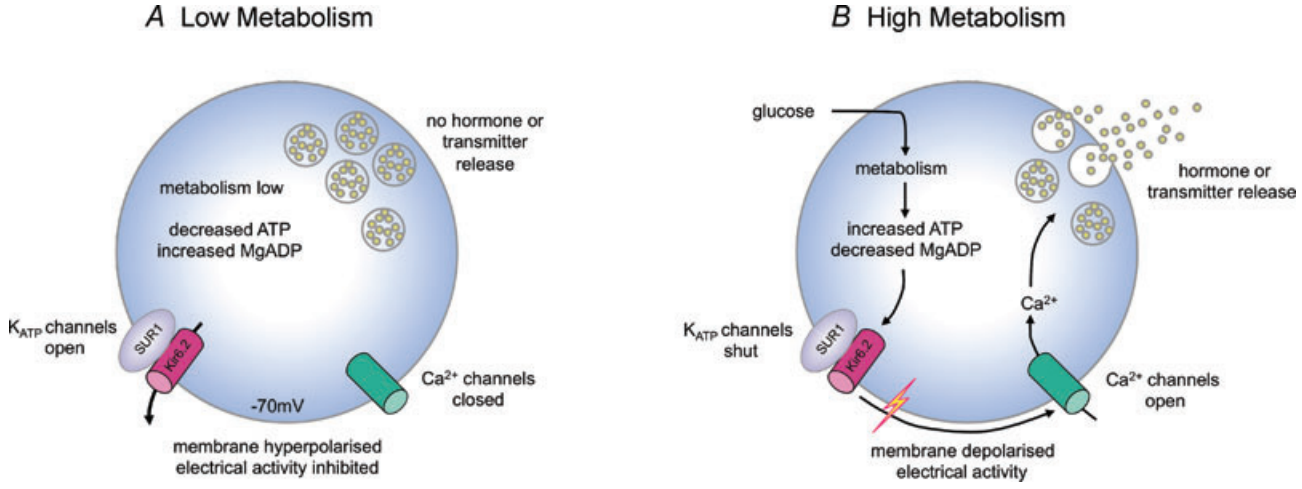

Figure 1. K_{ATP} channels couple metabolism to electrical activity
A, K_{ATP} channels are open when metabolism is low, due to low ATP and elevated MgADP concentrations. Their activity generates a hyperpolarised membrane potential that prevents electrical activity. *B*, When metabolism increases, ATP rises and MgADP falls, closing K_{ATP} channels. This triggers membrane depolarization and electrical activity, which in turn stimulates cell functions such as contraction, transmitter release and hormone secretion.

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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 α-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 α-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 α-cells (MacDonald *et al.* 2007).

The ability of glucose to stimulate β-cells but *inhibit* α-cell secretion via K_{ATP} channel closure can be explained by the different complements of voltage-gated ion channels in these cells. Because α-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 α-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

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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 β-cell membrane is permanently depolarised, producing continuous calcium influx and insulin secretion (Fig. 2*A*). 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,

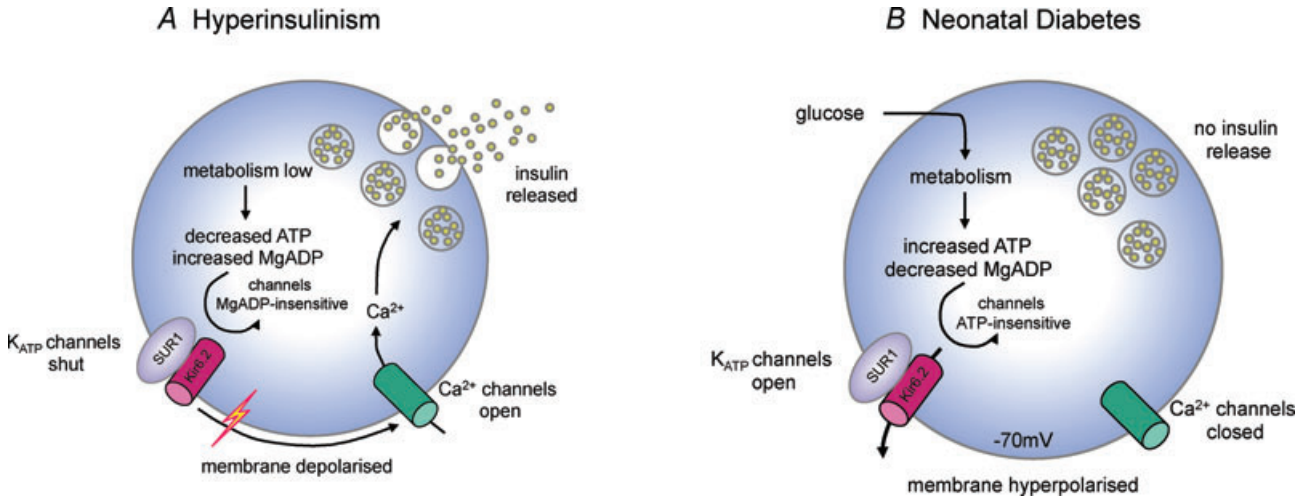

Figure 2. Role of K_{ATP} channels in insulin secretory disorders
A, Loss-of-function mutations in Kir6.2 or SUR1 lead to permanent K_{ATP} channel closure independent of cell metabolism. Consequently, the β-cell membrane is always depolarised, producing continuous calcium influx and insulin secretion. *B*, 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 β-cell membrane remains hyperpolarised even when blood glucose levels are high, preventing insulin secretion.

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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

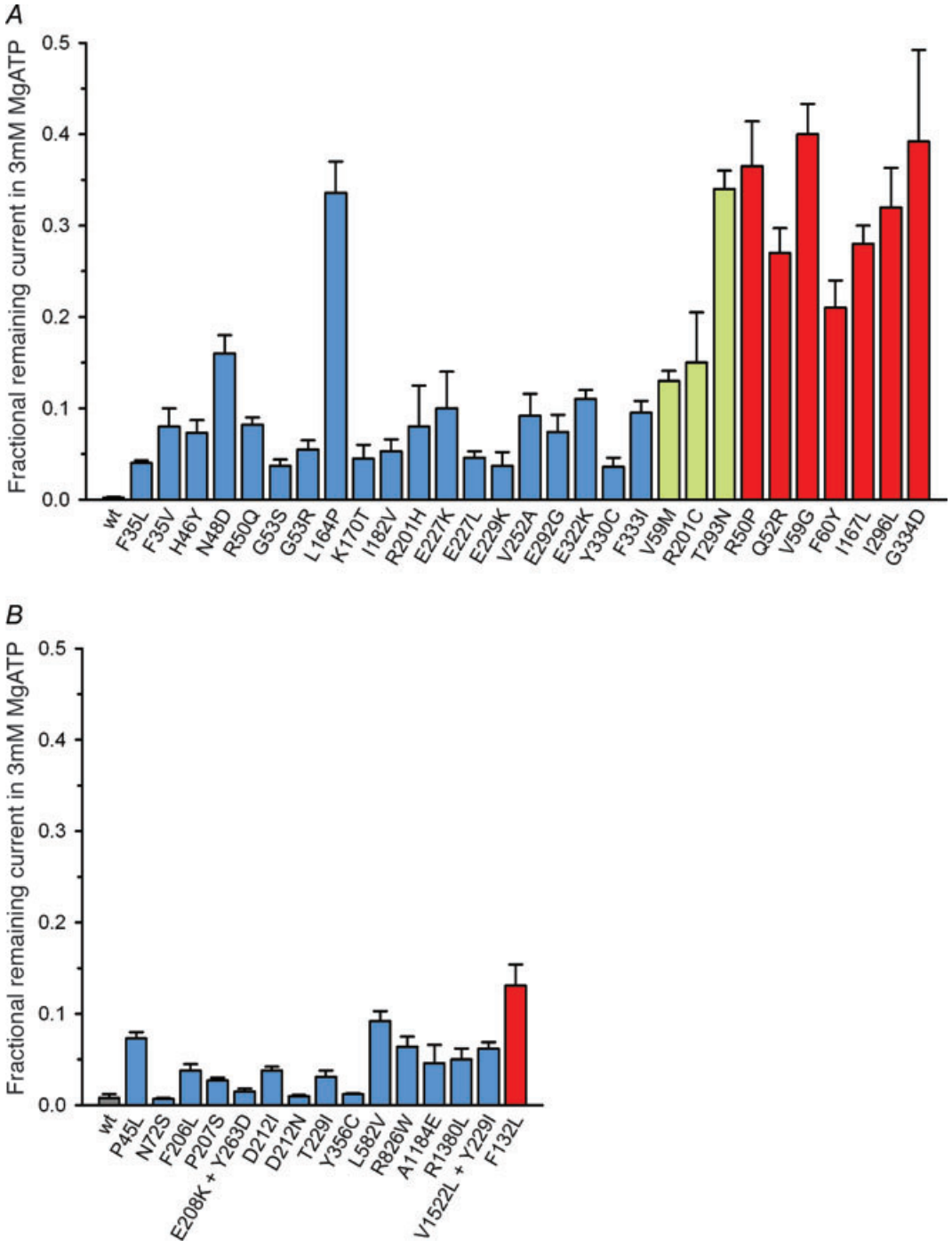

Figure 3. ATP sensitivity correlates with disease severity
Correlation between disease severity and the extent of unblocked K_{ATP} current measured in inside-out patches at 3 mM MgATP for the wild-type channel (WT) and the indicated Kir6.2 (*A*) and SUR1 (*B*) mutations. Mean (± S.E.M.) is shown. Blue 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).

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(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. 3*A* 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. 2*B*). 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 homeostasis 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.

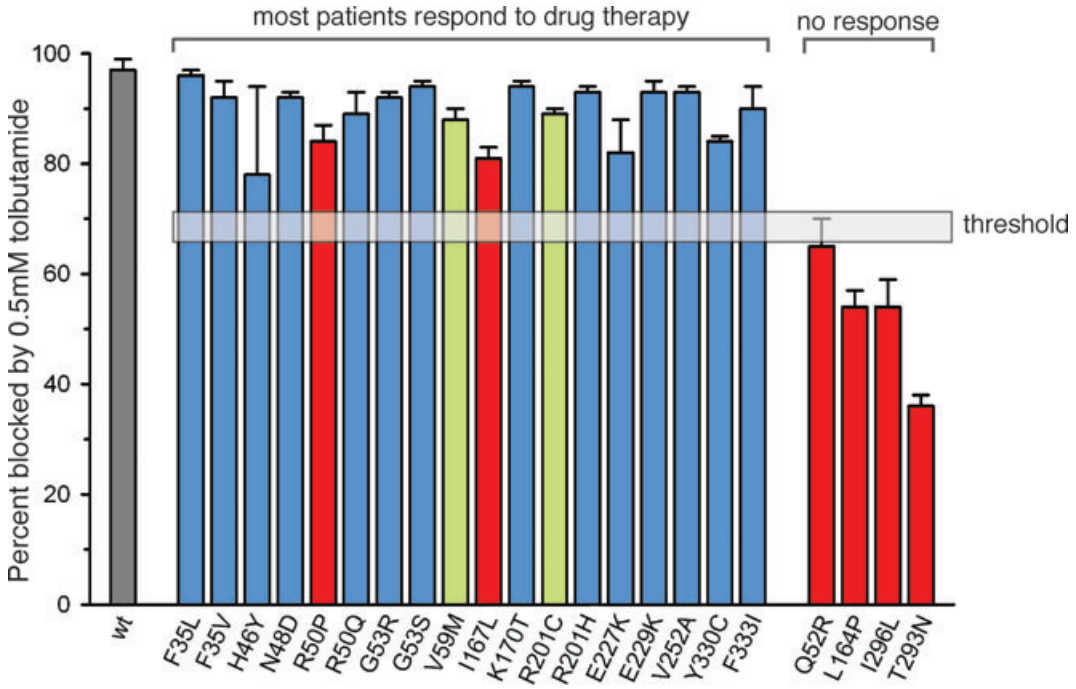

Figure 4. Tolbutamide sensitivity correlates with clinical response
Correlation between the tolbutamide sensitivity of recombinant K_{ATP} channels carrying the indicated mutations and the ability of at least some patients with the same mutation to transfer to sulphonylurea therapy. Mean (± S.E.M.) percentage 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).

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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 in Kir6.2 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 K_{ATP} currents in pancreatic β-cells. The origin of the enhanced insulin sensitivity is unknown (it cannot be due to enhanced K_{ATP} channel activity in muscle as this would be expected to have the opposite effect).

Conclusions

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

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