New insights into K_{ATP} channel mutations and neonatal diabetes mellitus

Tanadet Pipatpolkai[1,2], Samuel Usher[1], Phillip J. Stansfeld[2,3] and Frances M. Ashcroft[1†]

[1]Department of Physiology Anatomy and Genetics, Unviersity of Oxford, Oxford, UK

[2]Department of Biochemistry, University of Oxford, Oxford, UK

[3] School of Life Sciences & Department of Chemistry, University of Warwick, Coventry, UK.

[†]email: frances.ashcroft@dpag.ox.ac.uk

Abstract

The ATP-sensitive potassium (K_{ATP}) channel couples blood levels of glucose to insulin secretion from pancreatic β-cells. K_{ATP} channel closure triggers a cascade of events that results in insulin release. Metabolically generated changes in the intracellular concentrations of adenosine nucleotides are integral to this regulation, with ATP and ADP closing the channel and MgATP and MgADP increasing channel activity. Activating mutations in either of the two types of K_{ATP} channel subunit (Kir6.2 and SUR1) result in neonatal diabetes mellitus, whereas loss-of-function mutations cause hyperinsulinaemic hypoglycaemia of infancy. Sulphonylurea and glinide drugs, which bind to SUR1, close the channel through a pathway independent of ATP and are now the primary therapy for neonatal diabetes mellitus caused by K_{ATP} channel mutations. Insight into the molecular details of drug and nucleotide regulation of channel activity has been illuminated by cryo-electron microscopy structures that reveal the atomic-level organisation of the K_{ATP} channel complex. Here, we review how these structures aid our understanding of how the various mutations in Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) lead to a reduction in ATP inhibition and thereby neonatal diabetes mellitus. We also provide an update on known mutations and sulphonylurea therapy in neonatal diabetes mellitus.

[H1] Introduction

The ATP-sensitive potassium (K_{ATP}) channel has a central role in insulin secretion, because it couples the metabolism of the pancreatic β-cell to its electrical activity[1]. At sub-stimulatory glucose concentrations, the β-cell membrane potential is dominated by the K_{ATP} conductance, which holds the membrane at a hyperpolarised level. However, when blood levels of glucose rise, glucose is rapidly taken up by β-cells and metabolised to ATP, which binds to the K_{ATP} channel, causing it to close. As a result, the β-cell depolarises, leading to activation of voltage-gated calcium channels and an influx of calcium that triggers insulin granule release. The importance of the K_{ATP} channel in insulin secretion is exemplified by the fact that its mutation results in human disease. Loss-of-function mutations cause hyperinsulinaemic hypoglycaemia of infancy (BOX 1), which is characterised by persistent and unregulated insulin secretion and life-threatening hypoglycaemia. Conversely, gain-of-function mutations impair insulin secretion and produce neonatal diabetes mellitus, which is defined as diabetes mellitus that presents within the first 6 months of life[2]. Because the K_{ATP} channel is also expressed in the brain, patients with functionally severe mutations can also exhibit neurological symptoms in addition to neonatal diabetes mellitus, a condition known as DEND syndrome **[G]**. Sulphonylurea drugs, such as glibenclamide, stimulate insulin secretion by bypassing the metabolic steps and binding to and closing the channel directly. They have now replaced insulin as the therapy of choice for neonatal diabetes mellitus caused by K_{ATP} channel mutations.

Since 2017, cryo-electron microscopy **[G]** studies by several different groups have revealed the overall architecture of the K_{ATP} complex, and provided detailed information on the ATP and glibenclamide-binding sites[3-9]. Similarities and differences in these structures and their implications for nucleotide regulation have been reviewed elsewhere[10]. This Review considers how the various structures provide fresh insight into the mechanism of action of mutations that lead to neonatal diabetes mellitus, and briefly reviews work on the management this disease.

[H1] Architecture of the K_{ATP} channel

The β-cell K_{ATP} channel is a large (~900 kDa) macromolecular complex that comprises four pore-forming Kir6.2 (*KCNJ11*) subunits and four regulatory SUR1 (*ABCC8*) subunits. Kir6.2 is a typical inwardly rectifying K (Kir) channel that has two transmembrane segments linked by a pore loop, and intracellular N and C termini (Fig.1 a, b). The pore-helix contains the highly conserved selectivity filter TXGXG sequence in which the carbonyl backbones

coordinate the permeating K^+ ions. Kir6.2 possesses binding sites for both ATP and phosphatidylinositol-4,5-bisphosphate (PIP_2), which inhibit and activate the channel, respectively[11,12].

SUR1 belongs to the ABC superfamily of transporter proteins and is so-called because it binds sulphonylurea drugs[172]. Each SUR1 subunit contains three sets of transmembrane domains: TMD0, TMD1 and TMD2, where TMD1 and TMD2 form canonical ABC exporter domains (Fig.1 a, b). TMD0 and TMD1 are linked by a large cytosolic loop (the L0 or CL3 linker), which has a key role in channel gating. The cytoplasmic loops following TMD1 and TMD2 each contain a nucleotide-binding domain (NBD). These associate with one another in a head-to-tail dimer to form two cytoplasmic nucleotide-binding sites (NBSs) at the interface. Occupancy of NBS2 by MgADP enhances the channel open probability **[G]** [13].

The overall shape of the K_{ATP} channel complex was first identified at low resolution by electron microscopy[14]. Subsequent near-atomic resolution structures, solved by cryo-electron microscopy, have revealed the overall architecture of the complex, and provided information on the ATP, sulphonylurea and glinide binding sites[3-9]. Kir6.2 forms a central tetrameric pore resembling that of other mammalian Kir channels. The pore is surrounded by the four SUR1 subunits, each in complex with one Kir6.2. All but one structure (which adopts a 'quatrefoil' arrangement[6]) resemble a 'propeller' shape (Fig.1c). The 'quatrefoil' model, which probably represents a different state, shows a large conformational rotation of each SUR1 that markedly changes the interface between SUR1 and Kir6.2[6].

[H1] Nucleotide regulation of channel activity

The regulation of K_{ATP} activity by adenine nucleotides is central to its ability to regulate insulin secretion. This regulation is complex due to the existence of three distinct classes of ATP-binding site, one on each Kir6.2 subunit and two on each SUR1 subunit (making 12 sites in total)[3-9]. Expression of a C-terminally truncated Kir6.2 in the absence of SUR1 revealed that the inhibitory ATP-binding site lies on Kir6.2. The ability of Mg-nucleotides (such as MgATP and MgADP) to stimulate channel activity, on the other hand, resides with SUR1[15]. The balance between activation and inhibition of the K_{ATP} channel by adenine nucleotides determines the level of channel activity in the cell. Regulation by both Kir6.2 and SUR1 nucleotide-binding sites is essential for correct channel function. This point is illustrated by the fact that loss of ATP inhibition causes neonatal diabetes mellitus whereas lack of Mg-nucleotide activation leads to HI[2,16-18]. Severe gain-of-function mutations can also produce developmental delay and epilepsy due to the expression of Kir6.2/SUR1 channels in brain neurones[16].

[H1] Kir6.2 mutations

The ATP-binding site on Kir6.2 has been well characterised by electrophysiology, molecular modelling and cryo-electron microscopy. Functional studies have shown that inhibition of channel activity does not require Mg^{2+}, that ADP and AMP also inhibit the channel but with less potency than ATP, and that other purine and pyrimidine nucleotides (including guanosine triphosphate, inosine triphosphate and uridine triphosphate) are less effective than adenine nucleotides[11,19-21]. The addition of large groups (such as adenosine) to the γ phosphate of ATP does not impair channel inhibition, suggesting the terminal phosphate might be exposed[21]. Furthermore, ATP inhibition is enhanced if SUR1 is present. For example, the IC_{50} **[G]** for ATP inhibition of Kir6.2 expressed in the absence of SUR1 is ~100 μM, compared with 10 μM when SUR1 is also present[15].

The ATP-binding site on Kir6.2 lies at the interface between two Kir6.2 subunits and close to the L0 loop of SUR1 (Fig. 2a). In all structures determined to date, the ATP adopts an unusual conformation, with the phosphates curling back towards the adenine ring. As predicted[21], the γ-phosphate is exposed to the extracellular medium.

While the resolution of the cryo-electron microscopy density (~3.3–3.6Å) does not allow precise determination of atomic level ATP–protein interactions, when combined with functional studies it provides an accurate model of the ATP-binding site. Fig.2b highlights residues that interact with ATP[4]. The major part of the binding pocket is contributed by the C-terminus of one subunit, and comprises a beta-sheet containing residues K185 and I182 and a helical segment bearing residues Y330, F333 and G334. In addition, N48 and R50 from the N-terminus of the adjacent subunit interact with ATP. The α-phosphate of ATP is coordinated by the backbone nitrogen of K185, and the β-phosphates and γ-phosphates by the side chains of K185 and R50, respectively. Residues I182 and Y330 lie close to the ribose moiety, and the adenine ring interacts with N48, R50 and Y330. Mutations in all these residues give rise to neonatal diabetes mellitus and impair ATP inhibition (Table 1). The interaction between the NH_2 moiety at position 6 of the adenine ring and the backbone of N48 seems to be critical for selective nucleotide binding, as neither inosine triphosphate nor purine riboside-5'-O-triphsophate (which lack the critical NH_2) are effective at inhibiting the channel[21].

In addition, residues in the L0 linker of SUR1 either contribute directly to ATP binding, or lie in close proximity to it and stabilise the binding pocket. In a recent structure with bound

ATPγS, SUR1–K205 interacts with the α-phosphates and β-phosphates of ATP[8] (Fig.2c). Mutations at this position impair the channel ATP sensitivity[8,22], which might explain how SUR1 enhances ATP inhibition in the absence of Mg^{2+} [ref 15]. Furthermore, E203 in SUR1 interacts with Q52 in Kir6.2 and an engineered interaction between these residues results in channels with enhanced ATP sensitivity[22].

Multiple residues in Kir6.2 (>70) are known to cause neonatal diabetes mellitus (Fig.3; Table 1). These include all the residues that participate in ATP binding (see previous discussion) and others that lie in close proximity (such as H46, E51, Q52 and G53 in the N-terminus). Substitution of a negative charge at G334 (G344D) almost totally abolishes ATP inhibition, and causes a severe form of neonatal diabetes mellitus that is associated with neurological dysfunction[23]. Different mutations at R50 cause variable degrees of impairment of ATP sensitivity and disease severity, with R50Q causing transient neonatal diabetes mellitus and R50P giving rise to DEND syndrome[24]. The most commonly mutated residue in permanent neonatal diabetes mellitus is R201, but the structures show this residue does not interact with ATP. Instead, it is probably responsible for stabilising the backbones of F333 and V316, whilst also potentially forming cation-pi interactions with both F333 and F315. Its mutation would therefore destabilise the structure of this region, repositioning the sidechain of F333 and thereby impairing ATP binding.

Another class of neonatal diabetes mellitus mutations in Kir6.2 act by increasing the intrinsic open probability of the channel and/or the conformational relay by which ATP binding is translated into pore closure. These residues lie at the membrane interface within the slide helix that precedes TM1, in the lower part of TM2 (for example, W68 or V59M)[25-26], within the gating loops that reside below the mouth of the pore (T293)[27], and at the interface between subunits (for example, E322 and E292)[28-29] (Fig.3). Several of these mutations increase the intrinsic channel open probability and thereby indirectly also reduce the apparent affinity for ATP. The most common is V59M, which causes DEND syndrome[16,26]. Studies have shown an exponential relationship between the channel open probability and ATP inhibition, with a further dramatic fall in ATP sensitivity when the channel open probability exceeds ~0.8 [ref 173].

[H1] SUR1 mutations

The NBSs of SUR1 contribute to the nucleotide regulation of K_{ATP} channel activity. Each NBS consists of a canonical Walker A and B motif contributed by one NBD and the ABC signature motif of the other NBD (Fig.4a). The two binding sites are distinct, with NBS2

being a consensus site (capable of ATP hydrolysis) and NBS1 being a degenerate site (incapable of hydrolysis)[31]. It is proposed that occupancy of NBS2 by MgADP induces a conformational change that leads to closure of the NBS dimer (Fig.4b), and results in further conformational changes that produce opening of the Kir6.2 pore[174].

Initial approaches to determine Mg-nucleotide binding to SUR1 used photoaffinity labelling with azido-ATP [ref 31]. Subsequently, a method was developed to enable ATP binding to be studied at high temporal and spatial resolution in native membranes[32]. This technique involves measuring FRET **[G]** between a genetically engineered fluorescent amino acid (ANAP), placed close to the ATP-binding site, and fluorescent nucleotides (TNP–ATP and TNP–ADP). It was found that binding of both ATP and ADP to NBS2 is Mg^{2+}-independent, but that Mg^{2+} is required to trigger a conformational change in SUR1. Nucleotide dissociation was accelerated by the sulphonylurea tolbutamide (even in the presence of Mg^{2+}) and slowed by the K^+ channel opener diazoxide[32]. These findings are consistent with an activation model for K_{ATP} in which the NBDs of SUR1 dimerize in the presence of Mg^{2+}, preventing rapid nucleotide dissociation and triggering a conformational change that is communicated to the channel pore (Fig.4b)[32]. Sulphonylureas prevent this dimerization, as predicted from the structures[4,7,8], whereas K-channel openers stabilize it.

Numerous mutations associated with neonatal diabetes mellitus are found in SUR1 (Fig.5; Table 2), but in many cases their functional effects have not been studied. Although these mutations are found throughout the protein, two major clusters are evident, one in NBS2 and another in the L0 linker. There are three ways in which these SUR1 mutations could affect nucleotide regulation of Kir6.2: they might enhance MgADP stimulation[33,34], they might increase the intrinsic open probabability[35], or they might impair ATP binding at Kir6.2.

Functional studies support the idea that mutations in NBS2 that cause neonatal diabetes mellitus enhance occupancy by MgADP and/or stabilize the conformational change by which MgADP binding leads to an increase in the channel open probability[33-38]. In the β-cell, it is probable that the MgADP-bound state will be entered via hydrolysis of MgATP, which is present at much higher concentrations than MgADP. Thus, both the rate of ATP hydrolysis and the off-rate of MgADP will influence the duration of MgADP occupancy at NBS2. Functional analysis reveals the R826W mutation causes the ATPase cycle to linger in the post-hydrolytic MgADP.Pi-bound state (associated with channel activation) and that R1380 enhances the hydrolytic rate[34,36]. Increased MgADP activation partially compensates for ATP inhibition at Kir6.2, resulting in increased current at a given MgATP concentration.

A second hotspot of neonatal diabetes mellitus mutations is located on the L0 loop of SUR1 (19 mutations), and encompasses residues 206–215 (Fig.5; Table 2). Given that these residues lie in close proximity to the ATP-binding site on Kir6.2, they could help stabilise the binding pocket and their mutation might abrogate this interaction. It is also possible that many of these mutations also act by increasing the intrinsic channel open probability.

Very few SUR1 mutations cause DEND syndrome. An exception is F132L, which acts by increasing the channel open probability[35]. Interestingly, in the structures, SUR1–F132 is close to Kir6.2–G53 and Kir6.2–V59, which also cause DEND syndrome when mutated[35,39]. Quite how mutations elsewhere in SUR1 influence nucleotide regulation is unclear and requires further study.

[H1] Neonatal diabetes mellitus

In Europe, the incidence of neonatal diabetes mellitus varies between ~1 in 90,000 live births in Italy and Germany to 1 in 161,000 in Austria [40-45]. In populations with a high consanguinity rate, the prevalence can be even higher than this. For example, in north-west Saudi Arabia the incidence is ~1 in 20,000[46].

While mutations in many different genes result in neonatal diabetes mellitus, gain-of-function mutations in either Kir6.2 or SUR1 are the most common cause (~40% of cases, depending on the population)[40,42]. These mutations result in K_{ATP} channels that have reduced sensitivity to inhibition by ATP and thus remain open despite elevated blood levels of glucose. Consequently, insulin secretion is impaired, resulting in blood levels of glucose that are chronically elevated[106]. In some patients, the diabetes mellitus resolves within a few months or years, only for it to recur later in life (a condition referred to as transient neonatal diabetes mellitus)[41,47]. In other cases, the diabetes mellitus is permanent. Although the majority of cases present within the first 6 months of life, diabetes mellitus occasionally presents in the post-neonatal period[41,51]; it remains possible, however, that these individuals had transient neonatal diabetes mellitus that was undiagnosed in early life.

Around ~20–30% of patients have neurological symptoms[48], which include developmental delay, muscle hypotonia, autism and attention deficit hyperactivity disorder, as well as neonatal diabetes mellitus. This condition is known as intermediate (or incomplete) DEND syndrome. A few patients (<5%) have full DEND syndrome, in which the characteristics of intermediate DEND syndrome are also accompanied by epilepsy. The neurological features are a consequence of the fact that K_{ATP} channels are expressed in brain neurones[49,50].

There is a reasonably good correlation between the ability of a given mutation to reduce the ATP sensitivity of the channel and the clinical phenotype, with mutations that produce the greatest reduction in ATP inhibition causing DEND syndrome[17]. The reason only the most severe mutations produce dysfunction of the central nervous system is presumably because a greater increase in K_{ATP} channel activity is needed to influence electrical activity in neurones than in the β-cell.

Almost all patients with Kir6.2 mutations are heterozygous for the mutation. The exception is G324R, which causes neonatal diabetes mellitus in the homozygous, but not heterozygous, state[52]. The difference in ATP sensitivity between homozygous and heterozygous Kir6.2–G324R channels is remarkably small (IC_{50} of 38 μM and 30 μM, respectively) and not much greater than that of wild-type channels (20 μM)[52]. Thus, tiny changes in ATP sensitivity can cause neonatal diabetes mellitus. This finding is not surprising given that close to the threshold potential at which electrical activity is initiated, the β-cell membrane potential is exquisitely sensitive to the magnitude of the K_{ATP} current and a tiny decease in current will lead to action potential firing and thus insulin release[53].

Genome wide association studies have shown that a common variant in Kir6.2 (E23K) is associated with a small, but highly significant increase in the risk of type 2 diabetes mellitus (K allele, odds ratio 1.23, P = 0.000015; KK genotype odds ratio 1.65, P = 0.000002)[54]. Functional studies have also shown that in people with normal glucose tolerance, the 'at risk' lysine (K) allele is associated with a marked (40%) reduction in insulin secretion in response to an oral or intravenous glucose challenge[55]. Precisely how the K variant leads to impaired insulin release in later life has long been debated. The measured reduction in ATP sensitivity is small, often not statistically significantly different from wild-type and has not been replicated in all labs[52,55,56]. It has also been argued that the E23K mutation itself is not causal but rather a linked mutation in SUR1, A1369S [ref 56]. However, the tiny difference in ATP sensitivity between homozygous and heterozygous G324R channels suggests that a reduction in ATP sensitivity that predisposes to diabetes mellitus later in life can be hard to detect in electrophysiological experiments, except when very large sample sizes are used. It also explains why people with the K variant do not develop diabetes mellitus at birth — the reduction in ATP sensitivity contributed by this variant is too small. Whether they do so in later life might depend on their genetic background as well as environmental factors such as an obesogenic lifestyle.

[H1] Inhibition of the K_{ATP} channel

Sulphonylureas (for example, glibenclamide) and glinides (for example, repaglinide) are antidiabetic drugs that stimulate insulin secretion by inhibiting K_{ATP} channel activity. Analysis of cryo-electron microscopy structures obtained in the presence of glibenclamide or repaglinide indicate that sulphonylurea and glinide drugs bind within the same pocket, which lies within the transmembrane domains of SUR1 [ref 4,7,8,9]. Glibenclamide binding is coordinated by the inner helices of TMD1 (TMs 6, 7 and 8) and TMD2 (TM16), with which it forms both polar and electrostatic interactions. Both glibenclamide and repaglinide interact with two arginine residues — R1246 and R1300 [ref 4,7,8,9]. However, there are some subtle differences in the binding sites. For example, glibenclamide lies too close to S1238, which was previously shown to form part of the sulphonylurea binding site and accounts for the difference in drug affinity between SUR1 and SUR2 [ref 57]. This residue, however, does not contribute to repaglinide binding[8,9], as predicted from functional studies[58].

Sulphonylurea inhibition of the K_{ATP} channel is complex. The drug has a direct inhibitory effect on channel activity, which results in a maximal block of between 60–80% (depending on the specific sulphonylurea)[59]. In addition, sulphonylurea binding displaces bound MgATP at NBS2, promoting dissociation of the NBDs, which reduces channel activation by MgATP and/or MgADP and unmasks ATP inhibition at Kir6.2[32]. In practice, this means that neonatal diabetes mellitus mutations that strongly reduce the channel ATP sensitivity also reduce sulphonylurea inhibition. This finding explains why patients with the Kir6.2–G334D mutation do not respond to drug therapy[60]. A few mutations that cause neonatal diabetes mellitus (including Kir6.2–C166F and Kir6.2–I296L) dramatically decrease the time that the channel spends in a long closed state[61-63]. As sulphonylureas produce K_{ATP} channel inhibition by stabilizing this state[64], these mutations also greatly reduce sulphonylurea inhibition[26,60,65].

[H1] Sulphonylurea therapy

The discovery that many cases of neonatal diabetes mellitus are caused by mutations in Kir6.2 or SUR1 has transformed therapy for these patients. Previously treated by insulin injections, more than 90% of patients are now managed on oral sulphonylurea therapy[66-68], which greatly improves their quality of life and management of their disease. Glycaemic control is also markedly improved, reducing the risk of diabetic complications.

Of particular importance is that sulphonylurea therapy restores the insulin secretory response to food or an oral glucose challenge[66,68]. Incretins, such as GLP1, which are released in response to the presence of food in the gut, are effective stimulators of insulin

secretion[1]. However, they are only effective at glucose concentrations at which K_{ATP} channels are largely closed[69]. This is because they produce a small depolarising current that is only able to stimulate β-cell electrical activity when the K_{ATP} conductance is very low[70,71], and/or they amplify the effect of intracellular calcium on exocytosis (which depends on β-cell electrical activity)[1,71]. They can also cause a small reduction in the K_{ATP} current that, by itself, is insufficient to trigger electrical activity[72].

Sulphonylurea therapy in type 2 diabetes mellitus is often associated with hypoglycaemia and weight gain. However, there is no reported increase in hypoglycaemic episodes or body mass index in patients with neonatal diabetes mellitus who are treated with sulphonylureas, despite the high drug doses needed to control blood levels of glucose[68]. This implies that K_{ATP} channel closure induced by therapeutically effective sulphonylurea concentrations in patients with neonatal diabetes mellitus is sufficient to bring the β-cell membrane potential close to threshold, but is not enough to elicit electrical activity by itself. This is achieved in response to a meal by both incretins and any remaining sensitivity of the channel to metabolically generated ATP[106].

Not all patients with neonatal diabetes mellitus are able to transfer to sulphonylurea therapy. A successful outcome is determined both by the specific mutation and by the duration of diabetes mellitus[73]. As explained above, some K_{ATP} channel mutations can affect sulphonylurea efficacy. In addition, patients who commence sulphonylureas in the first few years after diagnosis are far more likely to successfully transfer than those who do so after diabetes mellitus of longer duration. Evidence from animal models suggests this is because chronic exposure to hyperglycaemia has deleterious effects on the β-cell: insulin content is reduced and mitochondrial metabolism impaired so that insufficient ATP is generated in response to a glucose stimulus[74-76]. These effects are reversible if the diabetes mellitus is of short duration, but high drug concentrations are needed when the disease duration is prolonged[75]. The fact that the sulphonylurea dose decreases with the duration of therapy in patients with neonatal diabetes mellitus[68] might be due to improved β-cell function and increased insulin content when good control of glycaemia is established. Preservation of β-cell function can also account for the fact that minimal dosing is needed in some patients when sulphonylurea treatment is initiated early[77].

In some individuals, the insulin dose can be reduced when sulphonylureas are introduced, but cannot be discontinued completely. It is recommended that both insulin and sulphonylurea are used to treat these patients[78]. In contrast to type 2 diabetes mellitus, where sulphonylurea failure is observed in ~44% of individuals after 5 years of treatment[79],

excellent glycaemic control remained after 10 years of sulphonylurea therapy in all patients with K_{ATP} mutations examined[68]. Thus, sulphonylureas remain the therapy of choice for this group of patients.

Neurological dysfunction is found in many patients with neonatal diabetes mellitus. During the past few years it has become evident that despite some initial improvement[68,80,81], central nervous system dysfunction persists with long-term sulphonylurea therapy. One possible explanation is that therapeutic drug concentrations are not reached in the brain because of active efflux across the blood–brain barrier[82]. Single photon emission computed tomography scans of the brain of patients with neonatal diabetes mellitus before and after glibenclamide therapy show changes in activity after ~6 months of therapy, but these are confined to the cerebellum[83]. Another possibility is that overactivity of K_{ATP} channels at an early developmental stage results in permanent neurological changes. It is noteworthy that for both glycaemic control and neurological function, the best outcome is achieved when drug therapy is commenced early. Further research in this area is clearly needed.

Pre-natal diagnosis is valuable for determining the optimal management of pregnant women with a K_{ATP} channel mutation because sulphonylureas can cross the placenta and cause macrosomia and neonatal hypoglycaemia in babies who do not carry the mutation[84]. On the other hand, a child with the same mutation might benefit from early exposure to the drug. Non-invasive pre-natal diagnosis has been successfully used to determine if the fetus carries a mutation in the K_{ATP} channel[85]. Sulphonylureas can also enter breast milk[84], which suggests breast feeding should be avoided if the child does not carry a K_{ATP} mutation.

[H1] Conclusions

The past few years have seen marked advances in our knowledge of the K_{ATP} channel and the relationship between channel structure and function. Atomic resolution structures have shown in considerable detail where ATP and antidiabetic drugs bind. With some exceptions, these structures have largely confirmed what was known of the nucleotide-binding sites from functional studies. By contrast, the sulphonylurea-binding and glinide-binding site was previously unidentified. What remains unclear is how nucleotide or drug binding is translated into changes in channel activity and how conformational changes in SUR1 lead to altered gating of the Kir6.2 pore. These questions can be expected to be a major focus of future studies.

In parallel, our understanding of how K_{ATP} channel mutations cause neonatal diabetes mellitus, and of sulphonylurea therapy in neonatal diabetes mellitus, has also progressed. Both structural and functional studies have illuminated how disease-causing mutations produce their functional effects. It is also now clear that patients can be managed for many years with no loss of glycaemic control[68], that hypoglycaemic episodes are rare[68] and that sulphonylureas can cross the placenta[84]. Functional studies in mouse models of neonatal diabetes mellitus suggest the reason older patients have a lower frequency of transfer to drug therapy than younger ones is due to adverse effects of chronic hyperglycaemia on β-cell function[74-76]. Future studies can be expected to address the mechanisms by which chronic hyperglycaemia impairs β-cell function and how this might be ameliorated, and determine if the progressive decline in β-cell function in type 2 diabetes mellitus has a similar aetiology.

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Author contributions

T.P., S.U., P.J.S. and F.M.A., researched data for manuscript and substantially contributed to discussion of content. F.M.A. wrote the manuscript and reviewed/edited the manuscript before submission.

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Fig. 1. Pipatpolkai et al

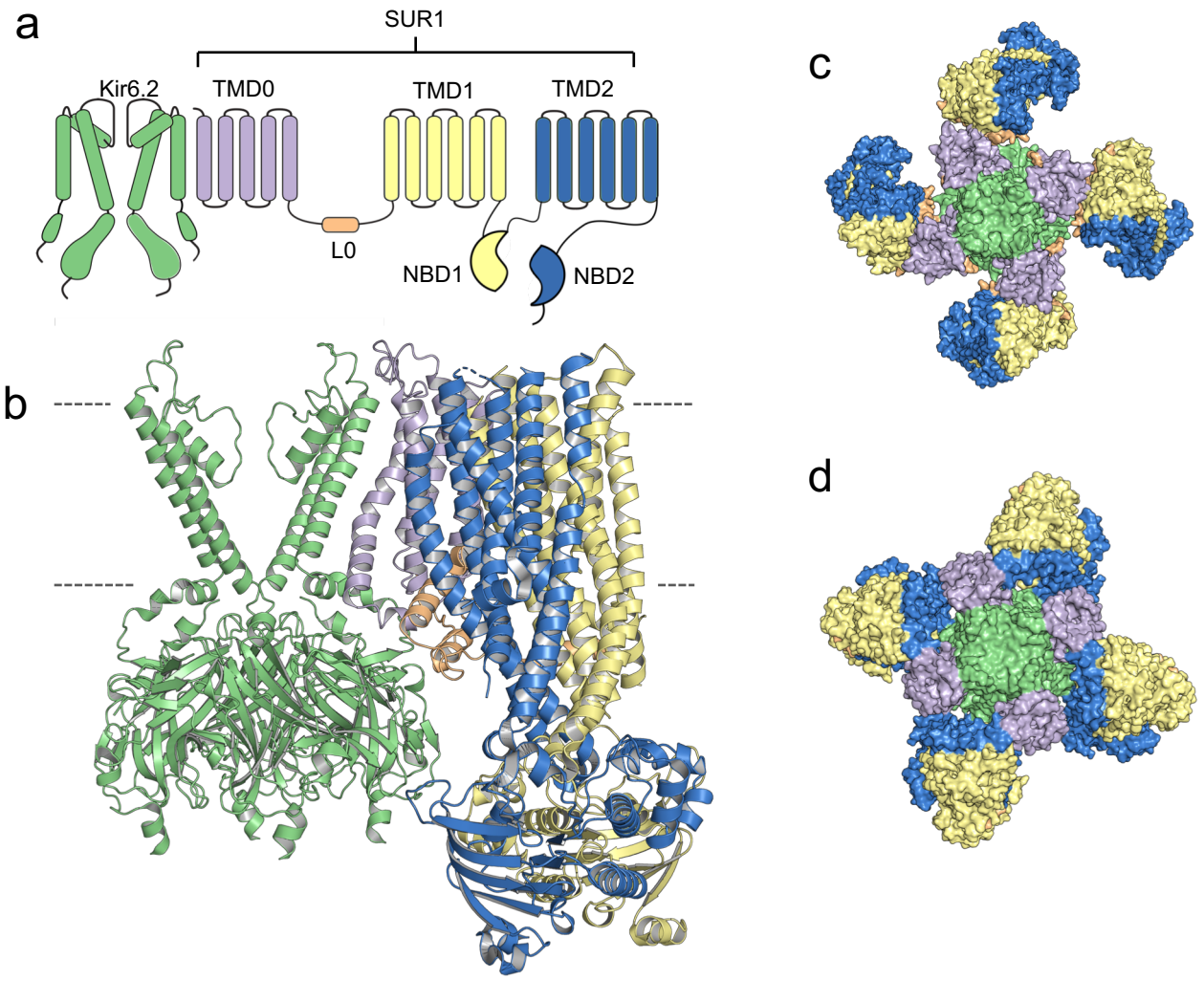


Fig. 2. Pipatpolkai et al

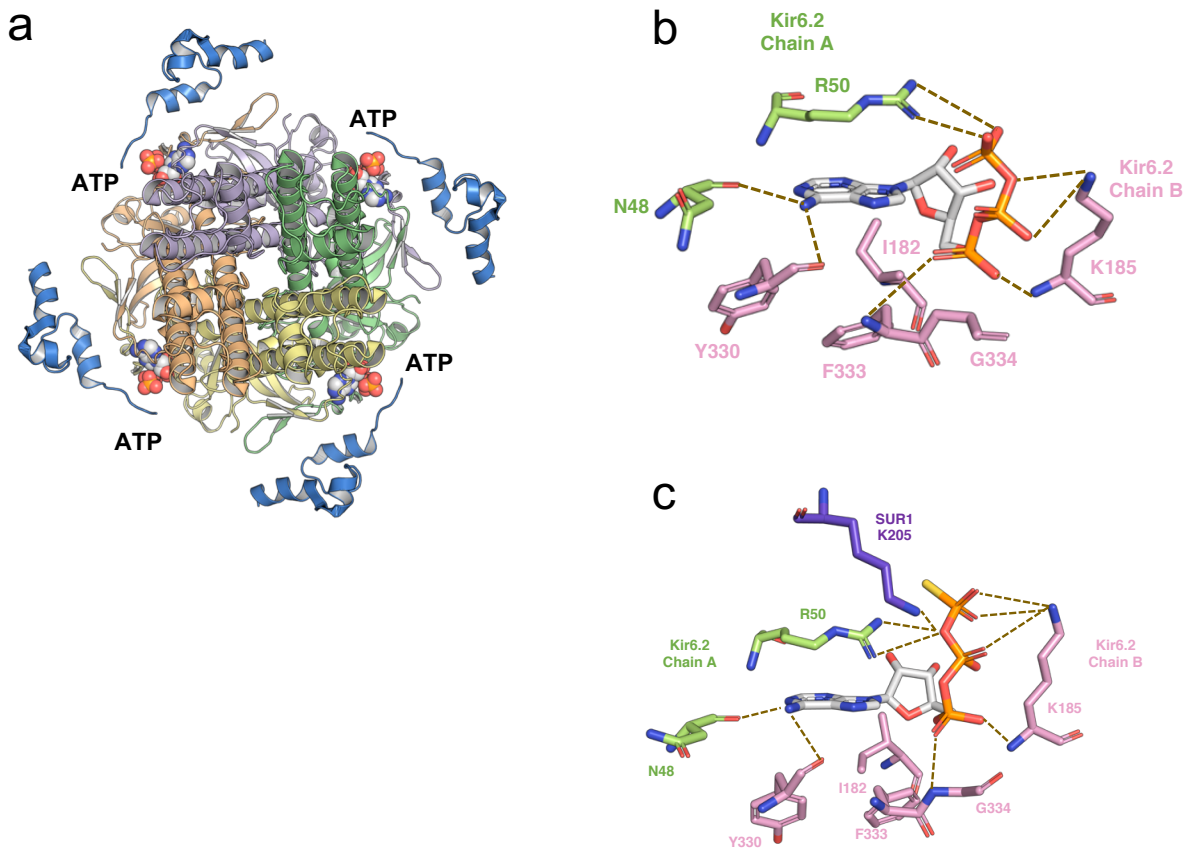


Fig. 3. Pipatpolkai et al

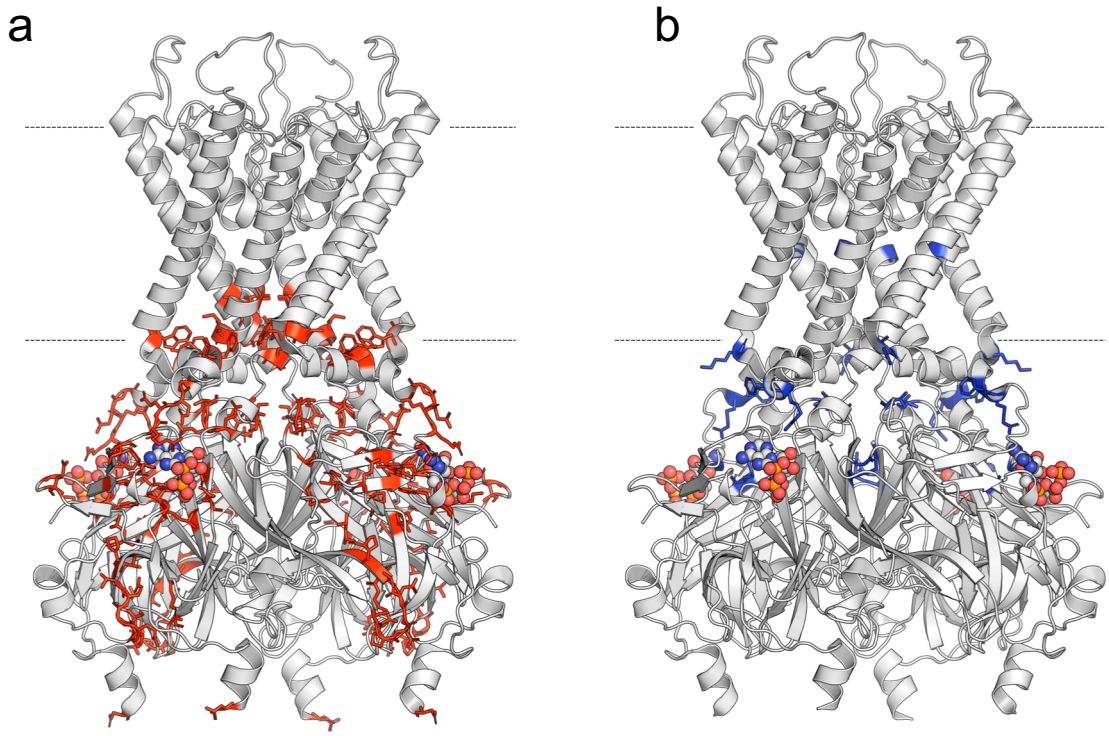


Fig. 4. Pipatpolkai et al

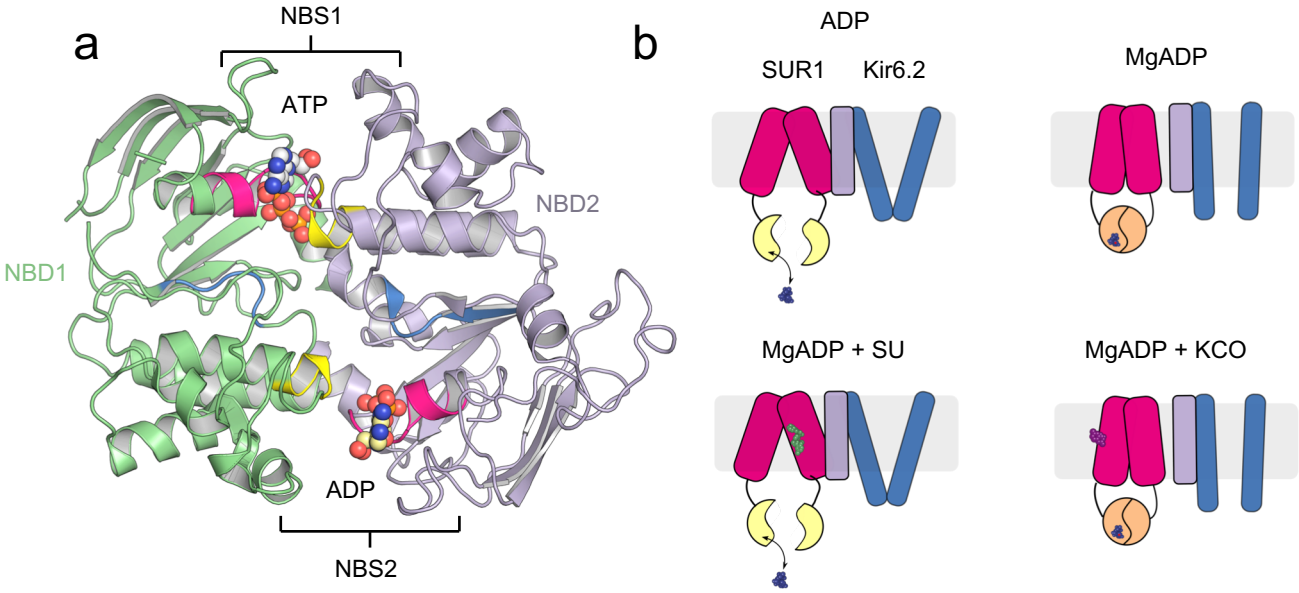
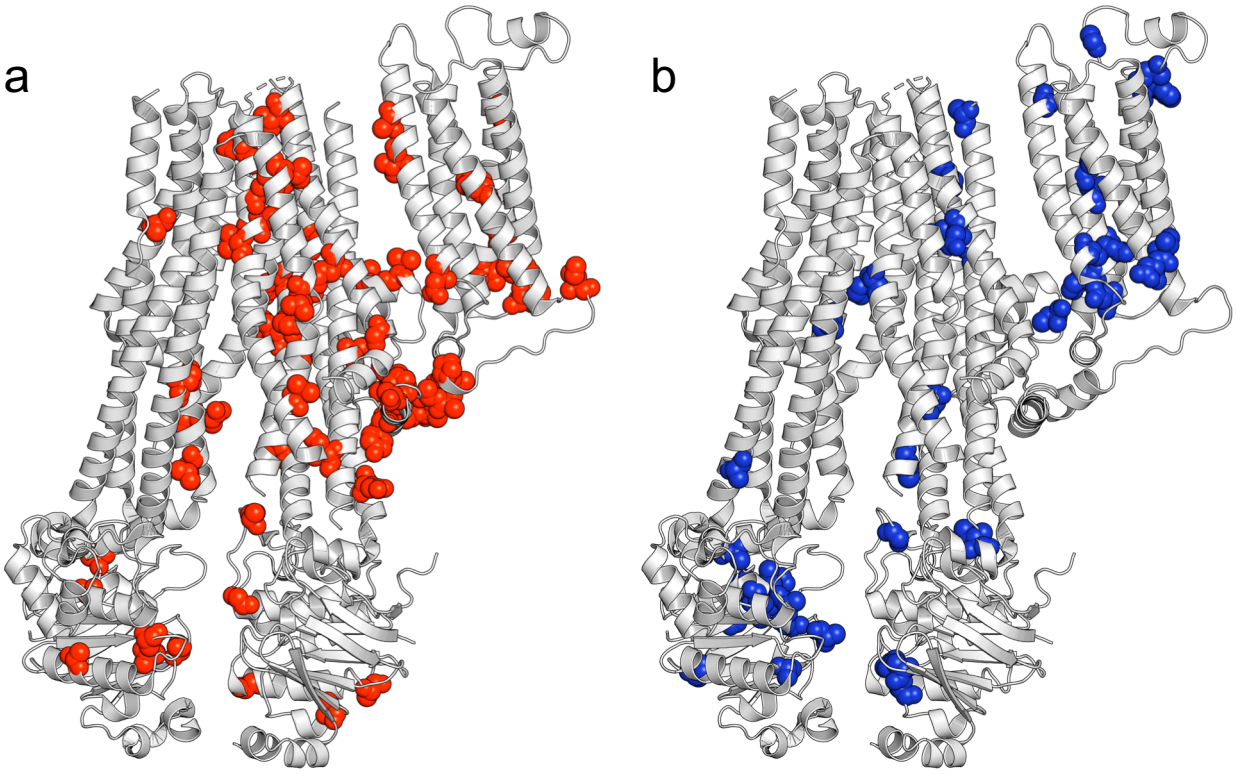


Fig. 5. Pipatpolkai et al



BOX 1: Mechanism of action of hyperinsulinaemic hypoglycaemia of infancy mutations

Given that gain-of-function mutations in K_{ATP} channel genes result in too little insulin secretion, and thus neonatal diabetes mellitus, it comes as no surprise that loss-of-function mutations in either *KCNJ11* or *ABCC8* lead to hypersecretion of insulin (congenital hyperinsulinism or HI)[2,18]. Hyperinsulinaemic hypoglycaemia of infancy mutations produce reduced K_{ATP} channel activity: consequently, the β-cell membrane is permanently depolarised and insulin is continuously released. The resulting low blood levels of glucose can cause irreversible brain damage if it is not promptly treated[86]. Although mutations in multiple genes can cause HI[2,18], the most commonly affected are *KCNJ11* and *ABCC8*.

Unlike neonatal diabetes mellitus, the functional effects of many K_{ATP} channel HI mutations remain to be investigated. Among those that have been studied, many result in the protein not being made or trafficked to the plasma membrane[87]. These mutations therefore do not offer insight into K_{ATP} channel gating or nucleotide regulation. Other HI mutations give rise to channels that traffic to the surface membrane and are briefly considered here. These mutant channels either have a low intrinsic open probability or are no longer activated by PIP_2 (via Kir6.2) or by MgATP and MgADP (via SUR1; Box figure 1). In Kir6.2, these residues lie in regions of the channel concerned with gating (for example, F55L[88], T294[27]) or around the putative PIP_2-binding site (for example, K67[89]). Molecular modelling studies suggest that K67 interacts with the phosphate group of PIP_2, which is consistent with functional studies that suggest the K67L mutation reduces PIP_2 binding[90]. Mutations at R301 are also proposed to act by destabilising the interaction of Kir6.2 with PIP_2[91]. Some HI mutations, located in SUR1, impair the mechanism by which Mg-nucleotides stimulate channel activity[13,37] but further research is needed to determine if they affect MgATP or MgADP binding, ATP hydrolysis or the conformational change that translates binding into channel opening.

Box 1 Figure. Location of Kir6.2 and SUR1 residues mutated in HI. a. Kir6.2 tetramer showing residues mutated in HI as blue sticks and ATP in CPK colours. Only mutations known to result in channels that are trafficked to surface membrane are shown. b. Single SUR1 subunit showing residues mutated in hyperinsulinism as blue spheres. Only mutations known to result in channels that are trafficked to surface membrane are shown.

Figure Legends

Figure 1: Structure of the K_{ATP} channel complex. a. Transmembrane topology of Kir6.2 and SUR1. For clarity, only a single SUR1 subunit and two opposing Kir6.2 subunits are shown. b. Side-view of the cryoEM structures of the Kir6.2 tetramer (green) and a single SUR1 subunit (PDB accession number 6BAA). SUR1 is colour-coded, with TMD0 in purple, L0 in orange, TMD1 in yellow and TMD2 in blue. The dashed line shows the approximate location of the membrane. c,d. Top view of the propeller (c) and quatrefoil (d) structures of the K_{ATP} channel complex (PDB accession numbers 6BAA and 63CO, respectively). Same colour code as in b. Panels adapted with permission from reference 10.

Figure 2. The inhibitory ATP-binding site. a. Top view of the K_{ATP} tetramer showing the four ATP-binding sites on Kir6.2. Each Kir6.2 subunit is shown in a different colour, residues 200–240 in L0 of SUR1 are in blue and ATP is in CPK colours. PDB accession number 6BAA. b. Close-up of the ATP-binding site, showing residues that participate in ATP binding. These are colour-coded according to the Kir6.2 subunit they come from. PDB accession number 6BAA. c. Close-up of the ATP-binding site, showing residues that participate in ATP binding, which are colour-coded according to the Kir6.2 subunit they come from. The structure was obtained in the presence of ATPγS. PDB accession number 6JB1.

Figure 3. Location of Kir6.2 residues mutated in neonatal diabetes mellitus. Kir6.2 tetramer showing residues mutated in neonatal diabetes mellitus as red sticks. ATP is shown as CPK spheres. The dashed line shows the approximate location of the membrane.

Figure 4. The nucleotide-binding sites on SUR1. a. The stimulatory nucleotide-binding sites on SUR1 are formed at the interface of NBD1 (green) and NBD2 (lilac). The Walker A motif is shown in magenta, the Walker B motif in blue and the ABC signature sequence in yellow. MgATP is shown bound to NBS1 and MgADP to NBS2. PDB accession number 6C3P. b. Schematic for activation of the K_{ATP} channel complex by Mg-nucleotides. *Top left*. In the absence of Mg^{2+}, ADP rapidly binds and unbinds to SUR1, but has no effect on channel activity. *Top right*. The presence of Mg^{2+} causes NBD dimerization, which induces a conformational change that leads to opening of the Kir6.2 pore. *Bottom Left*. Binding of sulphonylureas to SUR1 causes dimer dissociation and prevents MgADP stimulation. *Bottom Left*. Binding of K-channel openers to SUR1 stabilises the NBD dimer and supports MgADP stimulation. Figure adapted with permission from reference 32.

Figure 5. Location of SUR1 residues mutated in neonatal diabetes mellitus. Single SUR1 subunit showing residues mutated in neonatal diabetes mellitus as red spheres.

Table 1: Mutations in Kir6.2 associated with neonatal diabetes mellitus

Location in Kir6.2	Mutation	Phenotype	Po increase	ATP inhibition decrease	Transfer to SU therapy	Refs
NTD	L2P	NDM	-	-	-	92
NTD	S3C	PNDM	-	-	Yes	73
NTD	E23K and I337V	T2DM risk	-	-	-	54,93
NTD	R27H	Adult onset	-	Yes	Yes	93
NTD	A28–R32 deletion	PNDM	No	Yes	-	94
NTD	F33I	NDM	-	-	Yes	68
NTD	R34C	NDM	-	-	-	41
NTD	F35L	PNDM	Yes	Yes	-	95,96
NTD	F35V	PNDM	Yes	Yes	Yes	66,95
NTD	K39R	NDM	-	-	Yes	97
NTD	C42R	TNDM	Yes	Yes	Yes	73,98, 99
NTD	H46L	iDEND	-	Yes	Yes	73,100 ,101
NTD	H46R	NDM	-	-	-	102
NTD	H46Y	PNDM	No	Yes	Yes	29,40, 66,73
NTD	N48D	TNDM	-	Yes	-	29
NTD	N48I	PNDM	-	-	-	102
NTD	R50G	DEND	-	-	-	103,10 4
NTD	R50P	DEND and/or iDEND	No	Yes	Yes	24,73, 99,105
NTD	R50Q	TNDM and/or PNDM	-	Yes	Yes	24,66, 73,99, 103
NTD	E51A	PNDM	-	-	Yes	73
NTD	Q52R	DEND	Yes	Yes	Some	65,26, 73,106 ,107
NTD	Q52L	iDEND and/or PNDM	-	-	Yes	108
NTD	G53D	PNDM, iDEND and/or DEND	No	Yes	Yes	39,40, 73,99, 104,10

						9
NTD	G53N	PNDM	-	-	Yes	66,96
TM2	G53R	TNDM and/or iDEND	No	Yes	Yes	39,47, 73
NTD	G53S	TNDM	Yes	Yes	Some	39,47, 73
NTD	G53V	TNDM	-	-	-	104,11 0
Slide helix	V59A	DEND	-	-	Some	42,99, 111
Slide helix	V59G	DEND	Yes	Yes	-	26,106
Slide helix	V59M	iDEND	Yes	Yes	Some	26,65, 66,73, 99,106
Slide helix	F60Y	DEND	Yes	Yes	Yes	25,73
Slide helix	V64M	DEND	-	-	-	99
Slide helix	W68R	TNDM	Yes	Yes	Yes	73,112
Slide helix	W68L	PNDM	-	Yes	Yes	112,11 3
Slide helix	W68G	PNDM	-	Yes	Yes	112,11 3
Slide helix	W68C	PNDM	-	Yes	-	92,112
TM2	A161T	TNDM	-	-	Yes	73
TM2	L164P	PNDM	Yes	Yes	No	40,66, 73,114
TM2	C166F	DEND	Yes	Yes	-	61,62
TM2	C166Y	DEND	-	-	No	40,73
TM2	I167F	DEND	-	-	Yes	115
TM2	I167L	DEND	Yes	Yes	Yes	116
TM2	K170N	iDEND	-	-	Yes	73,104 ,105
TM2	K170R	PNDM	-	-	Yes	73,104 ,105
TM2	K170T	PNDM	No	Yes	Yes	28,40, 66,73
TM2	A174G	TNDM	-	-	-	103
CTD	E179A	NDM	-	-	-	41
CTD	I182T	PNDM	-	-	-	104
CTD	I182V	TNDM	-	Yes	-	47,104
CTD	K185Q	PNDM	-	Yes	Yes	104,11 7
CTD	K185T	NDM	-	-	Yes	73
CTD	H186D	PNDM	-	-	Yes	118

CTD	R192H	Adult onset	-	Yes	Yes	93
CTD	R201C	iDEND	No	Yes	Some	26,66, 73,106
CTD	R201G	PNDM	-	-	Yes	99
CTD	R201S	NDM	-	-	Yes	42,73
CTD	R201H	PNDM	No	Yes	Some	66,73, 96,106 ,107
CTD	R201L	PNDM	-	-	Yes	66,73
CTD	S225T + P226-P232 deletion	iDEND	Yes	Yes	Yes	119,12 0
CTD	E227L	TNDM, adult onset	-	Yes	Yes	121
CTD	E227K	TNDM and/or PNDM	Yes	Yes	Yes	29,73, 99
CTD	G228A	NDM	-	-	-	122
CTD	E229K	TNDM	Yes	Yes	Yes	29,73
CTD	V231L + G324R	NDM	-	-	-	102
CTD	L233F	NDM	-	-	Yes	73,123
CTD	V252A	TNDM and/or PNDM	-	Yes	-	29,104
CTD	V252G	iDEND	-	-	-	104
CTD	V252L	NDM	-	-	Yes	124
CTD	V252M	PNDM	-	-	Yes	73,104
CTD	P254Q	TNDM	-	-	-	125
CTD	V285I	TNDM	-	-	-	126
CTD	E292G	PNDM	-	Yes	-	29
CTD	T293N	iDEND and/or DEND	Yes	Yes	Yes	27,99
CTD	I296L	DEND	Yes	Yes	No	63,65, 66,73, 106
CTD	E322K	PNDM	No	Yes	Yes	28,66, 73,96
CTD	E322A + D352H	TNDM	-	-	Yes	127
CTD	G324R	TNDM	-	Yes	Yes	52
CTD	G324R + V231L	NDM	-	-	-	102

CTD	Y330C	PNDM	Yes	Yes	-	96,128,129
CTD	Y330S	PNDM	-	-	Yes	40,66,73
CTD	F333I	PNDM	No	Yes	Yes	73,128,129
CTD	F333L	PNDM	-	-	Yes	130
CTD	G334C	PNDM	-	-	Some	73,104
CTD	G334D	DEND	No	Yes	No	23,104
CTD	G334V	PNDM	-	Yes	Yes	78
CTD	I337V + E23K	T2D risk	-	-	-	54,93
CTD	D352H + E322A	PNDM	-	-	Yes	127
CTD	G366W	NDM	-	-	-	131

Mutations in Kir6.2 associated with neonatal diabetes mellitus. The effects on channel activity, determined from electrophysiology, are indicated where known. All mutations are dominant (heterozygous) except for G324R. NTD, N-terminal domain; CTD, C-terminal domain; TM2, transmembrane helix 2; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; NDM, neonatal diabetes mellitus; Po, open probability; Adult onset, adult onset diabetes; T2DM, type 2 diabetes mellitus; SU, sulphonylurea (a response to SU therapy is defined as patients who require no, or less, insulin when treated with SU); -, not tested or not known; Some, some patients transferred and others did not.

Table 2: Mutations in SUR1 associated with neonatal diabetes mellitus

Location in SUR1	Mutation	Phenotype	Po increase	MgATP inhibition decrease	SU therapy effective	Heterozygous or homozygous	Refs
TMD0	A30V	NDM	-	Yes	-	Compound heterozygous with G296R	132
TMD0	P45L	PNDM	-	-	Yes	Compound heterozygous with G1401R	133, 134
TMD0	I49F	DEND	-	-	Yes	het	135, 136
TMD0	N72S	PNDM	-	-	No	mosaic	133, 134, 137
TMD0	V84I	Adult onset	-	-	-	het	138
TMD0	V86A	PNDM	-	-	Yes	het	126, 133, 134
TMD0	V86G	PNDM	-	-	Yes	het	133, 134
TMD0	A90V	PNDM	-	-	-	het	103
TMD0	I93T	NDM	-	-	-	compound heterozygous with R826W	139
TMD0	E100K	Adult onset (MODY)	-	-	Yes	het	140
TMD0	F132L	DEND and/or iDEND	Yes	Yes	No	het	34,133,134
TMD0	F132V	PNDM	-	-	No	het	133, 134
TMD0	L135P	iDEND	-	-	-	het	141
TMD0	Y179X	PNDM	-	-	-	compound heterozygous with P207S	133
TMD0	I196N	PNDM	-	-	Yes	compound heterozygous with A1264V	99
CL3(L0)	P207S	PNDM	-	-	-	compound heterozygous with Y179X	133

CL3(L0)	E208K	TNDM	-	Yes	-	het	38,142
CL3(L0)	E208K	PNDM	-	-	Yes	compound heterozygous with Y263D	133, 134
CL3(L0)	D209N	PNDM	-	-	Yes	het	134
CL3(L0)	D209E	TNDM/PNDM	-	-	Yes	het	41,133,134,141
CL3(L0)	Q211K	PNDM	-	-	Yes	het	133, 134
CL3(L0)	D212I	TNDM[a]	-	-	Yes	het	41,134
CL3(L0)	D212N	TNDM	-	-	-	het	41
CL3(L0)	D212E	TNDM	-	-	-	het	143
CL3(L0)	D212Y	PNDM	-	Yes	Yes	het	126, 144
CL3(L0)	L213R	PNDM[a]	Yes	Yes	Yes	het	33,145
CL3(L0)	L213P	iDEND and/or DEND	-	-	Yes	het	42,146
CL3(L0)	G214R	Adult onset (MODY)	-	-	Yes	compound heterozygous with V222M	140
CL3(L0)	V215I	NDM	-	-	Yes	compound heterozygous with V607M	134
CL3(L0)	R216C	TNDM	-	-	-	het	99
CL3(L0)	V222M	Adult onset (MODY)	-	-	Yes	compound heterozygous with G214R	140
CL3(L0)	L225P	PNDM	No	Yes	Yes	het	38,133,134,147
CL3(L0)	T229N	PNDM	-	-	Yes	het	99
CL3(L0)	T229I	PNDM	-	Yes	Yes	compound heterozygous with V1523L	133, 134
CL3(L0)	T229I	TNDM	-	-	Yes	hom	134, 141

CL3(L0)	P254S	PNDM	-	Yes	-	hom	144
CL3(L0)	Y263D	PNDM	-	-	Yes	compound heterozygous with E208K	133, 134
CL3(L0)	A269D	NDM	-	-	-	het	142
TMD1	G296R	TNDM	-	Yes	-	het	132, 143
TMD1	G296R	TNDM	-	Yes	-	compound heterozygous with A30V	132
TMD1	R306H	NDM[a]	-	-	-	het	141
TMD1	V324M	TNDM/PNDM	-	Yes	-	het	38,41
	V324M	PNDM	-	-	Yes	compound heterozygous with W688R	42
TMD1	V324M	DEND	-	-	Yes	compound heterozygous with R1394L	136
TMD1	E350D	TNDM	-	-	-	het	148
TMD1	A355T	PNDM	-	-	Yes	het	42
TMD1	E382V	PNDM	-	-	Yes	hom	149
TMD1	E382K	PNDM	-	-	-	hom	133
TMD1	I395F	TNDM	-	-	No	het	150
TMD1	D424V	NDM	-	-	Yes	het	151
TMD1	C435R	TNDM[a]	-	-	-	het	33
TMD1	L438F	PNDM	-	-	-	compound heterozygous with M1290V	141
TMD1	L451P	NDM	-	-	-	het	41
TMD1	S459R	TNDM	-	-	-	het	43
TMD1	Q485R	MODY	-	-	Yes	het	140
TMD1	Q485H	PNDM[a]	-	-	-	het	122
TMD1	T488I	TNDM/PNDM	-	-	Yes	het	152
TMD1	S532G	TNDM	-	-	-	het	153
TMD1	F536L	NDM	-	-	-	het	102
TMD1	I544T	NDM	-	-	Yes	het	97
TMD1	F577L	PNDM	-	-	Yes	het	154
TMD1	L582V	TNDM	-	Yes	-	het	33,51
TMD1	I585T	TNDM	-	-	-	het	136
TMD1	V587G	iDEND	-	-	Yes	het	155
TMD1	T588I	TNDM	-	-	-	het	107

TMD1	V607M	PNDM/Adult onset (MODY)	-	-	-	het	99,156
TMD1	V607M	PNDM	-	-	Yes	compound heterozygous with V215I	134
TMD1	R653Q	TNDM[a]	-	n.s.	-	het	144
TMD1	W688R	PNDM	-	-	Yes	compound heterozygous with V324M	42
TMD1	E747X	PNDM[b]	-	-	Yes	hom	157
CL6 (NBD1)	H817R	PNDM	-	-	-	het	158
CL6 (NBD1)	R826W	TNDM/PNDM	No	Yes	Yes	het	34,41,134,142
CL6 (NBD1)	G832C	TNDM	-	-	Yes	het	99
CL6 (NBD1)	G833D	TNDM	-	-	-	het	149
CL6 (NBD1)	H863Y	NDM	-	-	Yes	het	159
CL6 (NBD1)	R878Q	TNDM	-	-	-	het	150
CL6 (NBD1)	D898V	NDM	-	-	Yes	het	160
CL6 (NBD1)	R993C	PNDM	-	n.s.	Yes	het	144
TMD2	H1024R	PNDM	-	-	Yes	hom	161
TMD2	H1024Y	TNDM	No	Yes	-	het	33,51
TMD2	F1068I	PNDM	-	-	Yes	hom	162
TMD2	N1123D	PNDM	-	-	-	het	103
TMD2	F1164L	iDEND	-	-	Yes	hom	149, 163
TMD2	Y1176C	TNDM	-	-	Yes	het	164
TMD2	F1177L	TNDM	-	-	-	het	99
TMD2	Q1179R	TNDM, Adult onset	-	Yes	Yes	het	165, 166
TMD2	F1182S	TNDM	-	-	-	het	167
TMD2	R1183Q	TNDM	-	-	-	het	33,41,14

							2
TMD2	R1183W	PNDM[a]	-	-	Yes	het	41,99,134
TMD2	A1185E	PNDM	-	-	-	hom	133
TMD2	P1199L	PNDM	-	Yes	Yes	het	99,168
TMD2	Q1225H	PNDM	-	n.s.	-	het	144
TMD2	N1245D	Adult onset (MODY)	-	-	Yes	het	140
TMD2	G1256S	TNDM	-	-	Yes	het	150
TMD2	A1264V	PNDM	-	-	Yes	compound heterozygous with I196N	99
TMD2	N1270-S1271 del	PNDM	-	-	Yes	het	169
TMD2	M1290V	PNDM	-	-	-	compound heterozygous with L438F	141
CL9 (NBD2)	R1314H	TNDM	-	-	Yes	het	141
CL9 (NBD2)	E1327K	PNDM	-	-	-	compound heterozygous with V1523A and T1043QfsX74	133
CL9 (NBD2)	R1380H	TNDM[a]/Adult onset (MODY)	-	-	Yes	het	41,140,142
CL9 (NBD2)	R1380C	TNDM	No	Yes	Yes	het	33, 36,41,99
CL9 (NBD2)	R1380S	NDM	-	-	-	het	102
CL9 (NBD2)	R1380L	TNDM[a]	-	-	Yes	het	134, 141
CL9 (NBD2)	F1393V	NDM	-	-	-	het	92
CL9 (NBD2)	R1394L	iDEND	-	-	Yes	compound heterozygous with V324M	136
CL9 (NBD2)	G1401R	PNDM	-	-	Yes	compound heterozygous with P45L	133, 134

CL9 (NBD2)	I1425V	PNDM	No	Yes	Yes	het	33
CL9 (NBD2)	A1458T	Adult onset (MODY)	-	-	Yes	het	170
CL9 (NBD2)	E1507G	TNDM	-	Yes	Yes	het	37,134
CL9 (NBD2)	E1507D	TNDM	-	Yes	-	het	37
CL9 (NBD2)	V1523A	PNDM	-	-	-	compound heterozygous with E1327K and T1043QfsX74	133
CL9 (NBD2)	V1523L	PNDM	-	Yes	Yes	compound heterozygous with T229I	133, 134
CL9 (NBD2)	V1523L	Adult onset (MODY)	-	-	Yes	het	140
CL9 (NBD2)	V1524M	PNDM	-	-	-	het	142
CL9 (NBD2)	A1537P	PNDM[a]	-	-	Yes	het	171

Mutations in SUR1 associated with neonatal diabetes mellitus. TMD0, TMD1 and TMD2 indicate transmembrane domains 0, 1 and 2. L0, intracellular loop 3. CL6 and CL9, intracellular loops 6 and 9 (which contain NBD1 and NBD2). The effects on channel activity, determined from electrophysiology, are indicated where known. A decrease in MgATP inhibition could be due to a reduction in ATP block at Kir6.2, or enhanced activation by SUR1. Heterozygous, homozygous and compound heterozygous mutations are indicated. Note that *ABCC8* loss-of-function mutations that cause hyperinsulinaemic hyperglycaemia at birth and diabetes in later life are not included. Mutations are numbered according to the *ABCC8* reference sequence NM_001287174.1. PNDM; permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; NDM, neonatal diabetes mellitus; Adult onset, adult onset diabetes (where this is classified as maturity-onset diabetes of the young (MODY) is indicated); Po, open probability; SU, sulphonylurea; -, not tested or not known. [a], indicates some patients show neurological features but were not diagnosed as either iDEND or DEND. [b], it is unclear how a loss-of-function mutation produces sulphonylurea-sensitive neonatal diabetes mellitus but the authors hypothesize that this mutation results in production of an alternative splice variant with reduced ATP sensitivity.

Key points

- K_{ATP} channels regulate insulin secretion from pancreatic β-cells by closing in response to metabolically generated ATP.
- Gain-of-function mutations in K_{ATP} channel subunits (Kir6.2 and SUR1) cause neonatal diabetes mellitus, whereas loss-of-function mutations cause hyperinsulinism of infancy.
- Most (~90%) patients with neonatal diabetes mellitus can be treated with sulphonylurea drugs, which inhibit the hyperactivated K_{ATP} channels.
- Atomic resolution structures of the K_{ATP} channel complex have identified the binding sites for nucleotides and sulphonylurea drugs and shed light on how disease-causing mutations produce their functional effects.
- Functional and clinical studies have elucidated why some patients can transfer to sulphonylurea therapy and others cannot.

Glossary

Channel open probability. A measure of the fraction of the total recording time that an ion channel spends in its open state. An open probability of 1 indicates the channel is permanently open, and an open probability of 0 indicates the channel is always closed.

Cryo-electron microscopy. An electron microscopy method in which samples are cooled to cryogenic temperatures and embedded in vitreous water. It is widely used as an alternative to X-ray crystallography for determining the atomic structure of molecules, including ion channels.

IC_{50}. Concentration (for example, of ATP) at which channel inhibition is half-maximal.

DEND syndrome. This syndrome is caused by K_{ATP} channel mutations that produce a severe reduction in channel sensitivity to ATP inhibition. It is characterised by permanent neonatal diabetes mellitus, epilepsy, motor and mental development delay, and can be accompanied by features such as attention deficit hyperactivity disorder.

FRET. Fluorescence-activated energy transfer describes the distance-dependent transfer of excitation energy from a fluorescent donor to a fluorescent acceptor that can be used for real-time imaging of the binding of a fluorescent ligand to a protein containing a fluorescent amino acid positioned close to the ligand-binding site.

ToC blurb

Gain-of-function mutations in K_{ATP} channel subunits cause neonatal diabetes mellitus. This Review discusses the mechanism of action of mutations that lead to neonatal diabetes mellitus and briefly reviews work on the management of this disease.