Review
Neonatal Diabetes and the K\textsubscript{ATP} Channel: From Mutation to Therapy

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Activating mutations in one of the two subunits of the ATP-sensitive potassium (K\textsubscript{ATP}) channel cause neonatal diabetes (ND). This may be either transient or permanent and, in approximately 20\% of patients, is associated with neurodevelopmental delay. In most patients, switching from insulin to oral sulfonylurea therapy improves glycemic control and ameliorates some of the neurological disabilities. Here, we review how K\textsubscript{ATP} channel mutations lead to the varied clinical phenotype, how sulfonylureas exert their therapeutic effects, and why their efficacy varies with individual mutations.

Introduction
ND (see Glossary) is a rare disorder with a prevalence of around 1 in 100 000–200 000 live births. 1 in 1001 in 100 It is characterized by diabetes that usually presents within the first 6 months of life. ND is caused by mutations in several different genes but those in the genes encoding the pore-forming (Kir6.2, KCNJ11) and regulatory (SUR1, ABCC8) subunits of the K\textsubscript{ATP} channel are the most common (~50\% of cases) and are the focus of this review.

The K\textsubscript{ATP} channel plays a key role in insulin release from pancreatic beta cells because it links cell metabolism to electrical activity [1]. It does so by regulating the beta cell resting membrane potential. At low glucose levels, channel activity is high, which hyperpolarizes the beta cell and switches off electrical activity and insulin secretion [1]. Elevation of extracellular glucose increases glucose uptake and metabolism and stimulates ATP production at the expense of ADP. These nucleotide changes result in closure of the K\textsubscript{ATP} channel, triggering membrane depolarization, opening of voltage-gated calcium channels, calcium influx, and insulin release. Decreased K\textsubscript{ATP} channel activity not only initiates insulin secretion; its further closure also contributes to the graded increase in action potential firing and insulin secretion at glucose concentrations above threshold [2].

Activating mutations in either Kir6.2 or SUR1 that reduce the ability of metabolically generated ATP to close the channel prevent glucose-induced electrical activity and insulin release, resulting in ND [3–5]. However, most mutant channels can be closed by sulfonylurea drugs, such as glibenclamide (glyburide) [6]. These are now the treatment of choice for ND, because they improve the patient’s clinical condition and quality of life, and reduce medical costs [7,8].

In this review, we provide an overview of recent advances in our understanding of the molecular mechanisms underlying K\textsubscript{ATP} channel ND, and its treatment with sulfonylureas.

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**Activating K\textsubscript{ATP} Channel Mutations Cause ND**

The K\textsubscript{ATP} channel is a large octameric complex comprising a central Kir6.2 tetramer, surrounded by four SUR1 subunits, as can be seen in the recent 6-Å resolution cryo-electron microscopy (EM) structure [9,10] (Figure 1). Activating mutations in the K\textsubscript{ATP} channel produce a range of phenotypes that correlate with the extent of reduction in channel ATP sensitivity [4,11]. At one end of the spectrum are mutations that cause a small decrease in ATP inhibition. These produce permanent (PNDM) or transient ND (TNDM) [3,4,12,13], lead to diabetes in young adult life [14–16], or enhance the risk of type 2 diabetes mellitus (T2DM) [17]. At the other end of the spectrum are mutations that render the channel highly insensitive to ATP and cause neurological complications in addition to diabetes [4,18]. Thus, the greater the decrease in channel ATP sensitivity, the more severe the clinical phenotype.

Most ND mutations occur spontaneously. Kir6.2 mutations are almost all heterozygous and most frequently occur at residues R201 and V59 [11], whereas SUR1 mutations are genetically more heterogeneous [11,19]. Although diabetes usually develops within 6 months after birth, it is now clear that some patients, including those with intermediate developmental delay and ND (DEND) syndrome [20,21], gestational diabetes, adult-onset diabetes [14–16], or PNDM [22] may present significantly later in life. Why diabetes does not occur immediately after birth in all patients remains something of a puzzle.

All ND mutations reduce the ability of ATP to cause channel closure. However, mechanistically, they act in a variety of ways. They may impair ATP binding at Kir6.2 or the way in which ATP binding is translated into pore closure [23–25]. They may enhance MgADP activation at SUR1 by increasing the affinity of the nucleotide-binding domains (NBDs) for nucleotides [26]. In addition, mutations in either Kir6.2 or SUR1 may increase the unliganded channel open probability, which leads to a decrease in both ATP and sulfonylurea block [18,27].

**Sulfonylurea Therapy in ND**

Sulfonylureas bind to SUR1 and induce K\textsubscript{ATP} channel closure, thereby triggering membrane depolarization, electrical activity, calcium influx, and insulin release. They have been used for >50 years to treat T2DM [6], and are now the therapy of choice for K\textsubscript{ATP} channel-dependent ND [7,28]. Higher drug concentrations are often needed in patients with ND than in those with T2DM: the usual dose for an adult with T2DM is 0.08–0.25 mg/kg/day, whereas patients with
ND, on average, require 0.5 mg/kg [29]. Patients with functionally severe mutations may need even higher doses to ameliorate their neurological complications; up to 2.3 mg/kg/day has been used [29,30]. The greater drug dose required by patients with ND may be attributed to the increased K\textsubscript{ATP} channel activity and, in some cases, a reduced sensitivity of the mutant channel to sulfonylureas. Patients with SUR1 mutations often require a lower drug dose compared with those with Kir6.2 mutations, consistent with the fact that SUR1 mutations have less functional impact. Most patients with ND have been treated with glibenclamide, although a few have been treated with other sulfonylureas, such as glitazide [7].

Sulfonylurea therapy has considerable therapeutic benefits. First, the marked fluctuations in blood glucose characteristic of insulin therapy are absent [31,32]. Second, control of glucose homeostasis dramatically improves, as indicated by a lower HbA1c level [7]. Consequently, it is expected that patients will be less likely to develop diabetic complications. Third, despite the improved glucose control, there is no change in incidence of hypoglycemic events [6] and reports of hypoglycemic events are rare [28]. Finally, sulfonylurea therapy is far easier for the patient (or carer) to manage. Despite the high doses needed to treat ND, sulphonylureas have few side effects (apart from potential hypoglycemia). Transient gastric problems (e.g., diarrhea or abdominal pain) may occur, but generally quickly resolve [28,33]. Staining of tooth enamel by glibenclamide has also been reported, usually in patients who chew their tablets before swallowing [33,34].

The ability of most patients with ND to transfer to sulfonylurea therapy implies they retain significant numbers of beta cells, often despite many years of diabetes. This is consistent with post-mortem EM studies of the pancreas from patients with ND [35,36]. However, islets were smaller and reduced in number, and the percentage of cells staining for insulin was decreased. Similar features are found in mouse models of ND [37–40]. It is likely they result from poor glucose homeostasis.

In marked contrast to T2DM, where sulfonylureas eventually fail to control glycemia, a common feature of sulfonylurea therapy in ND is that the drug dose declines with time after transfer from insulin [6]. This may reflect a time-dependent improvement in beta cell function and/or mass, because glycemias is better controlled by sulfonylureas. Support for this idea comes from studies of an inducible mouse model of diabetes, where diabetes of longer duration required higher glibenclamide doses to achieve euglycemia [38]. This arises because hyperglycemia causes marked downregulation of insulin content, numerous changes in gene expression, and impaired beta cell metabolism [37–40]. Many (but not all) of these changes are prevented or reversed by restoration of euglycemia [38]. A time-dependent improvement in beta cell mass and/or function may explain why drug dose declines with time in many patients with ND.

**Insights into the Molecular Mechanism of Sulfonylurea Action**

Sulfonylureas interact with two sites on the K\textsubscript{ATP} channel, a high-affinity site on SUR1 and a low-affinity site on Kir6.2 [6,41], but only the former is of therapeutic importance. The location of the sulfonylurea-binding site on SUR1 is still unknown, but mutagenesis studies indicate that it involves residues in the third and eighth cytosolic loops. These regions come into close apposition in the recent 6-Å cryoEM structure of the K\textsubscript{ATP} channel [9,10], suggesting a possible site for the sulfonylurea-binding pocket (Figure 1B).

It is important to recognize that sulfonylureas act as partial antagonists at the high-affinity site, and that K\textsubscript{ATP} channels with sulfonylurea bound to SUR1 are still able to open, albeit with lower open probability [42]. As a consequence, high-affinity inhibition is not complete, but reaches a maximum of approximately 50–80%, producing a pedestal in the concentration-response curve when studied in excised inside-out membrane patches [41,43]. Surprisingly, however,
channel inhibition by sulfonylureas is complete when studied in intact cells, using the whole-cell configuration [43]. Resolution of this paradox comes from the finding that sulfonylurea block is modulated by intracellular adenine nucleotides [41,43]. This arises from a combination of a mutual antagonism between sulfonylurea binding and MgATP nucleotide binding at the NBDs of SUR1, and the complex effects of nucleotides on the K\textsubscript{ATP} channel.

Mg\textsuperscript{2+} nucleotides both inhibit and stimulate K\textsubscript{ATP} channel activity by interaction with Kir6.2 and SUR1, respectively [1] (Figure 2A). Thus, channel activity is governed by the relative intensity of these two effects. Inhibition can be studied in isolation by expressing Kir6.2 in the absence of SUR1. Conversely, activation can be isolated by expressing SUR1 with an ATP-insensitive Kir6.2 mutant [44]. This reveals that sulfonylureas impair both nucleotide binding to SUR1 and its transduction into channel activation, as exemplified by a decrease in both the EC\textsubscript{50} for activation and its maximal amplitude [43]. Consequently, channel activation is markedly decreased by sulfonylureas. Therefore, in wild-type channels, nucleotide inhibition predominates and this adds to the sulfonylurea block to produce almost complete channel inhibition at physiological nucleotide levels (Figure 2B).

Sulfonylurea inhibition (or, more correctly, apparent inhibition) will therefore be influenced by the extent of ATP block at Kir6.2. It will be less for channels with mutations that reduce ATP inhibition (Figure 2C,D), leading to a pedestal of unblocked current whose magnitude varies with the ATP sensitivity of the channel [45,46]. This probably explains why sulfonylureas are ineffective in patients with ND who carry mutations that give rise to channels that are very ATP insensitive [24].

The fact that sulfonylurea inhibition is incomplete for channels containing severe ND mutations (due to their impaired ATP sensitivity), explains why patients with these mutations are less

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**Figure 2.** Schematic Showing How Nucleotides and Sulfonylureas Interact with SUR1. In wild-type channels, MgATP stimulates channel activity at SUR1 and inhibits it at Kir6.2. Thus, channel activity is a balance between these inhibitory and stimulatory effects (A). Sulfonylureas both block channel activity directly (by a maximum of 50–80%) and prevent MgATP activation (B). Consequently, ATP inhibition is no longer counteracted by MgATP activation. Thus, ATP and sulfonylurea block now summate to produce complete channel inhibition (B). Channels with mutations that reduce ATP block (e.g., G334D) are activated, but not blocked, by MgATP (C). Sulfonylureas still both block channel activity and prevent MgATP activation (D). However, the overall block of channel activity is less than for wildtype channels because of lack of ATP block at Kir6.2.
susceptible to severe hypoglycemia [8]. Given that channel activity is never completely abolished [46], maximal insulin secretion will be limited. However, patients with mutations that only produce a mild reduction in ATP sensitivity can be expected to have channels that are completely blocked by sulfonylureas and, therefore, may experience hypoglycemia if they take too much drug.

In addition to inhibition of the $K_{ATP}$ channel, certain sulfonylureas (such as glibenclamide and tolbutamide, but, interestingly, not glipizide) stimulate insulin secretion via an interaction with Epac2 [47,48]. Therefore, it appears possible that Epac2 mediates the reported effects of sulfonylureas on beta cell exocytosis [49]. However, it is important to emphasize that $K_{ATP}$ channel inhibition is a prerequisite for sulfonylurea-stimulated insulin secretion, in order to elevate intracellular calcium.

Why Is Glucose Homeostasis Better on Sulfonylurea Therapy?

Wild-type $K_{ATP}$ channels are largely blocked at resting blood glucose concentrations (5–7 mM) [50,51], so that the beta cell sits poised on the cusp of secretion and only a small reduction in channel activity is needed to trigger electrical activity and insulin secretion. In patients with ND, it appears likely that circulating sulfonylures close the $K_{ATP}$ channel to a similar extent, sufficient to maintain blood glucose at resting levels, but not enough to cause hypoglycemia.

Transfer to sulfonylurea therapy restores meal-stimulated insulin release [7] and decreases fluctuations in blood glucose [31,32]. Restoration of the beta cell incretin response and the amplifying effects of glucose likely contribute to these important effects. Incretins are released in response to the presence of food in the gut and exert a stimulatory effect on insulin secretion, reducing the excursion in blood glucose. However, both incretins (e.g., GLP-1) and paracrine hormones (e.g., glucagon) only potentiate insulin secretion induced by glucose. They do not initiate insulin release because they are only effective once intracellular calcium has been elevated by glucose-stimulated $K_{ATP}$ channel closure [3]. Therefore, they are ineffective in patients with insulin-treated ND, but become effective following transfer to sulfonylureas [7]. Likewise, the amplifying effects of glucose on insulin secretion [52] will only be enabled following $K_{ATP}$ channel closure and membrane depolarization.

It is well recognized that the ability of sulfonylureas to enhance insulin secretion in patients with T2DM rapidly wanes. By contrast, to date, patients with ND have not shown secondary failure to sulfonylureas, although many have been treated for at least 8–10 years [53]. This argues that the origin of the beta cell defect in T2DM is not the same as in ND.

Given that their diabetes is so well controlled, some patients with ND elect to remain on drug therapy when pregnant. Good glycemic control is important for both mother and fetus. However, glibenclamide can cross the placenta and, as a consequence, fetuses who do not carry a ND mutation may require early delivery, and develop fetal macrosomia and/or postnatal hyperinsulinemic hypoglycemia [54–56]. Thus, sulfonylurea therapy should be avoided (at least during the third trimester) if prenatal genetic testing has not been performed or if the fetus is found not to carry the mutation. Non-invasive prenatal genetic testing in the offspring of a father with ND has been successfully performed [57]. By contrast, if the fetus does carry the mutation, sulfonylureas may be beneficial, because they can be expected to prevent the low birth weight [7,19], caused by reduced fetal insulin secretion in utero that is characteristic of ND neonates.

Why Do Some Patients Not Respond to Sulfonylureas?

Not all patients respond to sulfonylurea therapy. Whether they do so depends on the specific mutation they possess and the duration of their diabetes.
Some mutations cause a marked increase in channel activity in the absence of nucleotide [18]: this produces a marked decrease in sulfonylurea inhibition [58]. Other mutations do not alter channel gating but produce a dramatic reduction in ATP block at Kir6.2 [24], and thereby decrease sulfonylurea block (as described above). All patients with these mutations fail to transfer [59] and it is unlikely that they would be able to transition even if the drug dose were greatly increased.

There are also several mutations for which some patients transferred and others failed to do so, despite taking an adequate dose of sulfonylureas [33,59]. This appears to be related to the duration of diabetes. Almost all individuals who started taking sulfonylureas during the first 5 years after diabetes diagnosis transferred successfully, whereas only 65% of those over the age of 18 were able to do so [59]. This emphasizes the need to implement sulfonylurea therapy as early as possible.

One explanation for the better outcome when sulfonylureas are started early is that the patient’s beta cells have been exposed to chronic hyperglycemia for a shorter time. Mouse models of ND reveal that chronic hyperglycemia markedly impairs beta cell function and reduces beta cell mass [37–40]. Nevertheless, even when the patient fails to transfer fully, it is recommended they continue sulfonylureas (as well as insulin) because of the improvement in glycemic control and neurological function this can provide.

Why Is ND Sometimes Transient?
In some patients with ND, diabetes is transient, remitting within a few months or years of birth [4,11,12]. Why diabetes remits is unclear. One possibility is that it reflects a reduced insulin demand or improved beta cell function at the time of remission. Why many TNDM patients subsequently relapse also remains unknown, but might, in part, result from the increase in insulin resistance that normally develops at puberty [60,61].

Interestingly, approximately 30% of mice expressing an activating K$_{ATP}$ channel mutation that were treated with glibenclamide at disease onset for just 6 days, were subsequently able to maintain euglycemia without drug therapy [62]. Quite why this happens is unclear. Because the mutation was targeted specifically to the beta cell, one possible explanation is that new beta cells are generated (subsequent to gene induction) from progenitor cells. As these will lack the mutant K$_{ATP}$ channel, they will be essentially normal (provided hyperglycemia is prevented). Thus, a gradual increase in the number of beta cells lacking the mutation might underlie the improved glucose control. Lineage tracking could determine if this idea is correct.

That early glibenclamide therapy can ‘cure’ human ND appears unlikely. It has been reported that aggressive glibenclamide therapy immediately following diagnosis can cause diabetes remission, with patients subsequently requiring no drug or a subtherapeutic dose [63,64]. However, because of their young age, it is difficult to know whether these individuals are in fact patients with TNDM who have remitted but not yet relapsed. Nevertheless, this is an interesting area that deserves further study.

It is worth noting that, because ND may be transient, iatrogenic hyperglycemia may occur if sulfonylurea therapy is not discontinued.

**ND Mutations Can Cause Neurological Problems**
K$_{ATP}$ channels (Kir6.2/SUR1) are not confined to beta cells; they are found in many other tissues, including muscle and brain. This accounts for the fact that approximately 20% of patients with ND have profound neurological deficits. These include delayed motor and mental development, attention deficit, hyperactivity, autism, aggression, intellectual disability, and (occasionally)
seizures [4,65,66]. Hand–eye coordination is also impaired [67]. This spectrum of disorders is known as iDEND syndrome. In 3% of cases, epilepsy is also present (DEND syndrome). In general, these features are confined to patients with the most functionally severe mutations and are mainly (but not invariably [68]) associated with mutations in Kir6.2. The motor and behavioral problems are usually ameliorated by sulfonylurea therapy, in some cases markedly so [65,69], and seizures may cease [13,30]. However, the neurological problems often persist or are only partially improved [65,66,70]. The motor problems of patients with iDEND/DEND are recapitulated in mice expressing an activating KATP channel mutation specifically in their neurones (nV59M mice), but no effect was seen when the same mutation was expressed in muscle [71]. Furthermore, muscle function tests were normal in patients with ND [65] and gliclazide (which acts on neuronal but not muscle KATP channels [6]) enhanced motor function [25]. This argues that the motor deficit is neuronal in origin. This reflects, at least in part, impaired cerebellar activity, because nV59M mice show decreased electrical activity in their cerebellar Purkinje cells [72] and SPECT scanning suggests that patients with iDEND also have reduced cerebellar activity [73]. Interestingly, the latter is improved by glibenclamide, which accords with the improved motor function observed after transfer to sulfonylurea therapy in patients with iDEND.

Anxiety disorders, attention deficit hyperactivity disorder (ADHD), and autism are frequently observed in patients with iDEND (especially those with the V59M mutation) [66]. Similarly, nV59M mice show hyperactivity and increased exploratory behavior [72,74]. However, in contrast to patients with iDEND, nV59M mice show reduced anxiety [74]. Why this is the case is unclear, but it is worth noting that it is difficult to disentangle effects on anxiety and locomotor activity in mice. Interestingly, nV59M mice also exhibit reduced sensitivity to common inhalation anaesthetics, such as isofluorane [75], but whether this happens in humans is unknown.

The failure of sulfonylureas to fully reverse the neurological deficits of patients with iDEND may result from a failure of the drug to reach a therapeutic concentration in the brain. In rats, sulfonylureas are rapidly pumped out of the brain [75]. Whether other drugs that inhibit KATP channels (e.g., carmazepine [76]) might be more effective remains to be tested. Given that KATP channel activation appears to decrease inhibitory tone, drugs that decrease GABA uptake or prolong its action might also be worth exploring.

An alternative explanation for the poor effects of sulfonylureas on cognitive function is that KATP channel overactivity in the developing brain produces irreversible structural effects. Although gross changes in brain anatomy are not observed, it is possible that the enhanced KATP current prevents synaptic connections from forming correctly. Because the brain continues to develop after birth, this may explain why early treatment affords the best outcome, with some patients carrying severe mutations who were treated at diagnosis meeting their developmental milestones, at least initially [13,69].

There are several reports that some patients with SUR1 mutations that cause transient ND also have neurological symptoms [5,77,78]. By contrast, this is not observed in patients with transient ND due to Kir6.2 mutations. This is clearly an area where more research is necessary. If the neurological symptoms are confirmed to be a consequence of the SUR1 mutation, it would suggest that SUR1 may have an additional role in the brain, distinct from its ability to modulate the KATP channel. In beta cells, SUR1 is also found in the insulin granule (where its role remains to be defined) [79] and has been proposed to act as a scaffold for exocytotic proteins in beta cells [80]. This raises the question of whether SUR1 serves a similar function at the neuronal synapse.

**Why Do ND Mutations Not Cause Cardiac Problems?**

Surprisingly, despite the fact that Kir6.2 forms the pore of both beta cell and cardiac KATP channels, there are no reported cardiac effects in patients with ND. Similarly, mice in which an
activating Kir6.2 mutation is expressed in the heart (cV59M mice) show no cardiac defects [71]. This is probably because most cardiac $K_{\text{ATP}}$ channels contain $\text{SUR2A}$ rather than SUR1 subunits. The Kir6.2/SUR2A channel shows a markedly lower sensitivity to activation when cytosolic ATP falls [72,81]. Why this is the case is not fully established. In isolated membrane patches, ATP inhibits (and MgADP activates) Kir6.2/SUR2A and Kir6.2/SUR1 channels to similar extents [72]. However, MgADP markedly reduces the inhibitory effect of ATP on Kir6.2/SUR1, but not on Kir6.2/SUR2A [72,82]. This probably explains the different metabolic sensitivities of beta cell and cardiac $K_{\text{ATP}}$ channels, and protects patients with ND from deleterious cardiac effects.

This interpretation rests on the assumption that cardiac $K_{\text{ATP}}$ channels are primarily composed of $\text{SUR2A}$, not SUR1, subunits. Interestingly, SUR1 is expressed in mouse atrial myocytes [83], and its activation contributes to action potential shortening during metabolic inhibition [84]. However, no change in heart rate is seen in cV59M mice [71]. Furthermore, the functional importance of SUR1 in the human heart remains unclear, and the lack of obvious changes in cardiac function in patients with ND suggests that its contribution is small.

**Does ND Offer Insight into T2DM Etiology?**

Given that activating $K_{\text{ATP}}$ mutations cause ND, can mutations that produce a lesser decrease in ATP sensitivity cause diabetes in later life? The answer appears to be yes.

First, mutations in SUR1 are associated with adult-onset diabetes, with some patients exhibiting glucose intolerance, some having clinical features of maturity-onset diabetes of the young (MODY), and others being diagnosed with T2DM [14–16,85,86]. In a few cases, functional studies [85] or the existence of an ND relative (or other patient) carrying the same mutation [12,15,16,86], confirmed that the mutation was pathogenic. Similarly, $\text{KCNJ11}$ mutations can cause young-onset diabetes or gestational diabetes [87,88]. However, the frequency of such cases is low.

Second, a common variant in Kir6.2 (E23K) is associated with a 40% reduction in glucose-stimulated insulin secretion in people with normal glucose tolerance [89], and a slightly increased risk of T2DM [17]. The effects on $K_{\text{ATP}}$ channel function are somewhat controversial, but most studies have found a (very) small decrease in ATP inhibition [89,90]. Others have suggested that it is a polymorphism in SUR1 (A1369S), linked to Kir6.2-E23K, that accounts for the lower ATP sensitivity [91]. Whichever subunit is involved, the crucial question is whether the reduction in ATP sensitivity is sufficient to increase diabetes risk. This is not easy to address, given that the increased disease risk only achieves significance in population studies comprising thousands of subjects [17]. It is clearly not possible to perform functional experiments on this scale.

However, some insight into the puzzle is offered by a recessive Kir6.2 mutation (G324R) that causes TNDM. The difference in ATP sensitivity between heterozygous and homozygous Kir6.2-G324R channels is tiny ($IC_{50}$ of 30 µM versus 38 µM) yet the homozygous proband

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**Box 1. Small Changes in $K_{\text{ATP}}$ Current Markedly Impact Insulin Secretion**

It is important to appreciate that, because the $K_{\text{ATP}}$ channel dominates the beta cell membrane potential, its closure causes a large increase in the input resistance of the membrane. Ohm’s law dictates that, when the membrane resistance is high, tiny changes in current will lead to marked changes in membrane potential. One should also bear in mind that, below the threshold for electrical activity, there will be no insulin secretion. Above it, insulin release will be initiated. Thus, even a tiny change in $K_{\text{ATP}}$ current may suffice to make the difference between electrical silence and action potential firing (depending on the input resistance and the membrane potential). This explains why tiny changes in $K_{\text{ATP}}$ current (or ATP sensitivity), which can be very hard to measure, can markedly affect insulin secretion.
had TNDM, while his heterozygous parents were unaffected [92]. Furthermore, the ATP sensitivity of heterozygous Kir6.2-G324R channels was less than that of homozygous Kir6.2-E23K channels (IC50 ~20 μM) [89,90,92]. This suggests that the heterozygous Kir6.2-G324R parents may have an increased risk of T2DM in later life. It also demonstrates that tiny differences in ATP sensitivity can markedly impact insulin secretion (Box 1).

Concluding Remarks and Future Perspectives

ND provides a paradigm for how understanding the pathophysiology of a disease can improve therapy for affected patients. It is an excellent example of pharmacogenomics, illuminating the beneficial effects of tailoring therapy to a patient’s individual genetic make-up. Functional studies have revealed why some mutations produce a more severe clinical phenotype and why some patients respond to drug therapy whereas others do not. Conversely, ND has provided novel insights into the physiological role of the KATP channel. Nevertheless, many questions remain (see Outstanding Questions). We still lack an understanding of precisely how nucleotides and drugs regulate channel activity, how chronic hyperglycaemia impairs beta cell mass and/or function, why diabetes is transient is some patients, and what causes the neurological deficits. Answers to these questions will illuminate our understanding not only of neonatal diabetes, but also of its far more common relative, T2DM. They will also provide fresh insight into the role of the KATP channel in tissues other than the beta cell.

Acknowledgments

The research from our laboratory described here was funded by the Wellcome Trust (grant no. 089795), the European Research Council (ERC, grant no. 332620), and the Royal Society, F.M.A. holds a Royal Society/Wolfson Merit Award and an ERC Advanced Investigatorship.

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Outstanding Questions

What is the atomic (high-resolution) structure of the KATP channel complex?

How does nucleotide interaction with the NBDS of SUR1 regulate the gating of the Kir6.2 pore?

Why does diabetes remit in TNDM and why does it then relapse?

Why does hyperglycaemia decrease beta cell mass and function, and is this fully reversed by good glucose control? For how high and how long must glucose be elevated to cause irreversible beta cell damage?

What causes the neurological complications in iDEND/DEND syndrome and how can these best be managed?
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