K_{ATP} Channels and the Metabolic Regulation of Insulin Secretion in Health and Disease: The 2022 Banting Medal for Scientific Achievement Award Lecture

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Diabetes is characterized by elevation of plasma glucose due to an insufficiency of the hormone insulin and is associated with both inadequate insulin secretion and impaired insulin action. The Banting Medal for Scientific Achievement Commemorates the work of Sir Frederick Banting, a member of the team that first used insulin to treat a patient with diabetes almost exactly one hundred years ago on 11 January 1922. This article is based on my Banting lecture of 2022 and concerns the mechanism of glucose-stimulated insulin secretion from pancreatic β-cells, with an emphasis on the metabolic regulation of the K_{ATP} channel. This channel plays a central role in insulin release. Its closure in response to metabolically generated changes in the intracellular concentrations of ATP and MgADP stimulates β-cell electrical activity and insulin granule exocytosis. Activating mutations in K_{ATP} channel genes that impair the ability of the channel to respond to ATP give rise to neonatal diabetes. Impaired K_{ATP} channel regulation may also play a role in type 2 diabetes. I conjecture that K_{ATP} channel closure in response to glucose is reduced because of impaired glucose metabolism, which fails to generate a sufficient increase in ATP. Consequently, glucose-stimulated β-cell electrical activity is less. As ATP is also required for insulin granule exocytosis, both reduced exocytosis and less β-cell electrical activity may contribute to the reduction in insulin secretion. I emphasize that what follows is not a definitive review of the topic but a personal account of the contribution of my team to the field that is based on my Banting lecture.

When I entered the field, in 1984, it was known that glucose was taken up and metabolized by the β-cell and that this led to membrane depolarization, the opening of voltage-gated calcium channels, electrical activity, calcium influx, and insulin secretion. What was unclear was what served as the link between glucose metabolism and membrane depolarization (Fig. 1*A*).

Previous work from several laboratories had suggested that a glucose-stimulated reduction in membrane potassium flux was responsible for triggering β-cell electrical activity (1). We therefore used the newly invented patch-clamp technique to search for a potassium channel closed by glucose metabolism. It was essential to use cell-attached membrane patches as, with this configuration, metabolism is not disturbed, and any effect of bath-applied glucose must be mediated via an intracellular route. What we found was a potassium channel that was active in the absence of glucose and that was closed by glucose metabolism (2). At almost the same time, Dan Cook and Nick Hales (3) found a similar channel in β-cells that was blocked by application of ATP to the intracellular surface of an excised membrane patch. Within a couple of years, Patrik Rorsman and Gerd Trube had shown the two channels were identical (4) and that the channel could be blocked by the sulfonylurea drugs used to treat type 2 diabetes, thus solving a long-standing question as to how these drugs act (5).

METABOLIC REGULATION OF THE K_{ATP} CHANNEL

It is now well established that the glucose- and ATP-sensitive potassium (K_{ATP}) channel plays a central role in insulin secretion and that glucose regulates channel activity via metabolically induced changes in intracellular adenine nucleotide concentrations (6) (Fig. 1*B* and *C*). Initially, there was some resistance to the idea that ATP could act as an intracellular second messenger. This was not helped by the fact that the channel is so sensitive to ATP inhibition that it was hard to

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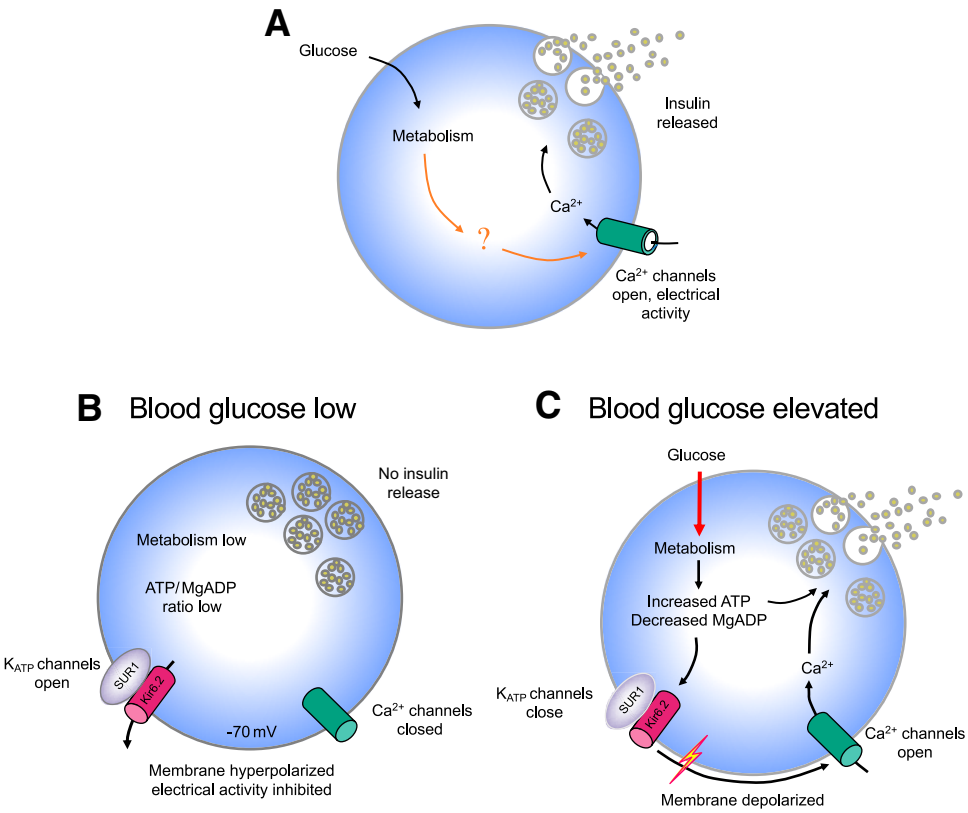

Figure 1—Metabolic regulation of the K_{ATP} channel is a key step in insulin secretion. *A*: Prior to 1984, it was known that glucose metabolism by the pancreatic β-cell was essential for glucose-stimulated insulin secretion and that this somehow led to membrane depolarization, calcium-dependent electrical activity, and insulin release. *B* and *C*: By 1985, the missing link had been identified as the K_{ATP} channel, which was closed by metabolically generated changes in ATP and MgADP. At low (substimulatory) blood glucose levels, the channel was open and the β-cell was electrically silent (*B*), whereas when glucose was elevated to stimulatory concentrations the channel closed, leading to membrane depolarization, electrical activity, calcium influx, and insulin release (*C*).

understand how it could be open in a living cell, and yet it clearly was. However, the issue was resolved when it was discovered that channel activity is increased by MgADP (7,8) and that the ATP sensitivity is also reduced by the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) (9). The current model of stimulus–secretion coupling in the β-cell thus postulates that at substimulatory blood glucose concentrations, intracellular ATP levels are relatively low and MgADP levels are relatively high, so K_{ATP} channels are open. The resulting potassium efflux holds the β-cell membrane hyperpolarized and switches off electrical activity, calcium influx, and insulin release. Conversely, when blood glucose levels rise, glucose metabolism increases the relative amount of ATP and decreases that of MgADP (abbreviated here as an increase in the ATP-to-ADP ratio). This closes the K_{ATP} channels, thereby producing a membrane depolarization that opens voltage-gated calcium channels and triggers electrical activity, calcium influx, and insulin secretion. The ATP that closes the K_{ATP} channel has long been assumed to be mitochondrial in origin, but recent data suggest it may be partly, or wholly, produced in glycolysis by pyruvate kinase associated with the K_{ATP} channel (10).

The K_{ATP} channel thus serves as a metabolic sensor, coupling β-cell metabolism to insulin secretion. Because the K_{ATP} channel plays such a central role in insulin secretion, its impaired metabolic regulation can be expected to cause diabetes. As explained below, this can result either because of mutations in the channel that render it insensitive to ATP, as in neonatal diabetes, or because of impaired metabolism, which fails to generate enough ATP to close the channel and which is what I hypothesize happens in type 2 diabetes (Fig. 2).

NUCLEOTIDE REGULATION OF THE K_{ATP} CHANNEL

The central role of the K_{ATP} channel in insulin secretion immediately suggested that a gain-of-function mutation in the protein would cause diabetes. Thus, it became imperative to clone the β-cell K_{ATP} channel. This was not straightforward, because, as it later turned out, it is a large octameric complex composed of two different types of subunit with 4:4 stoichiometry (Fig. 3*A* and *B*). A member of the inwardly rectifying K^+ channel family, Kir6.2, serves as a tetrameric pore (11,12). Each Kir6.2 subunit is associated with a much larger regulatory subunit, the

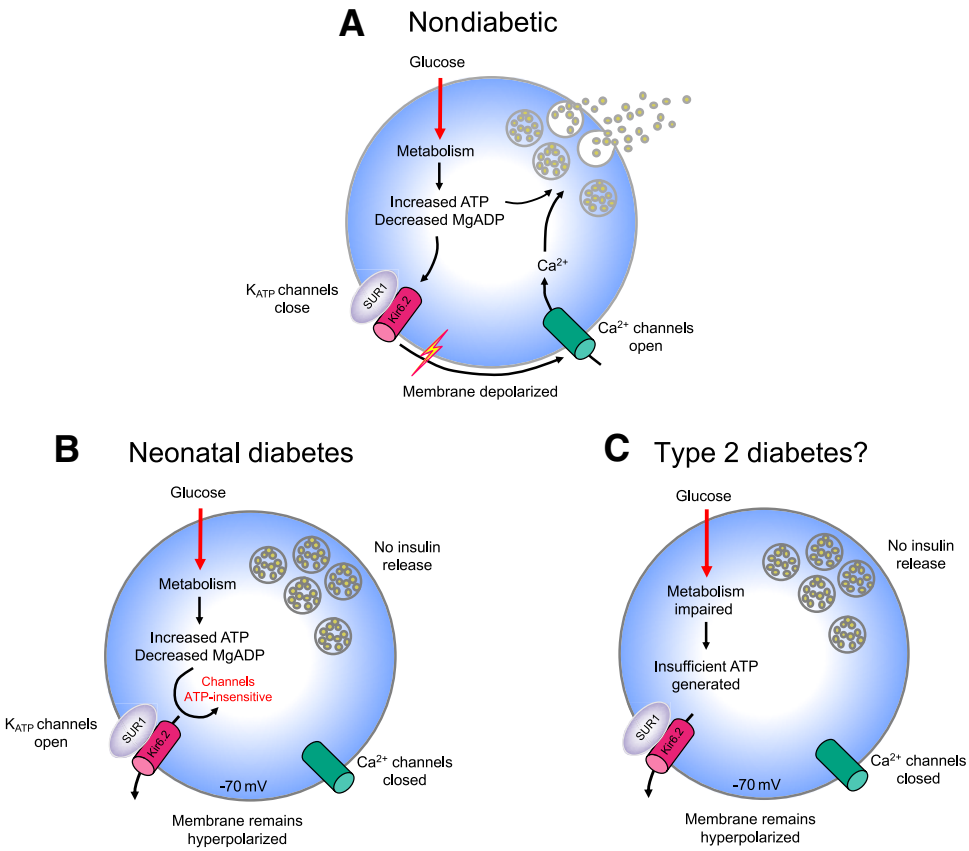

Figure 2—The K_{ATP} channel influences insulin secretion under both physiological conditions and in diabetes. *A*: In nondiabetic β-cells, glucose metabolism closes K_{ATP} channels and elicits insulin secretion. *B*: Activating mutations in K_{ATP} channel genes that impair the ability of the channel to respond to ATP give rise to neonatal diabetes by preventing membrane depolarization. *C*: In type 2 diabetes, glucose metabolism is reduced, leading to less ATP generation, which is expected to impair K_{ATP} channel closure and insulin secretion.

sulfonylurea receptor SUR1, so called because it binds the sulfonylurea drugs used to treat type 2 diabetes (13). The structure of the β-cell K_{ATP} channel complex has been determined in both the open and closed states (14–16) and in the presence of bound ATP, MgADP, or sulfonylureas (14–17) by cryogenic electron microscopy. These structures reveal in considerable detail how ligands interact with the channel to regulate channel activity (reviewed in Driggers and Shyng [18]).

Intracellular nucleotides interact with both Kir6.2 and SUR1 subunits (Fig. 3). Binding of ATP (and, to a lesser extent, ADP) to Kir6.2 in a Mg-independent fashion causes channel inhibition (19). There are four ATP-binding sites in the Kir6.2 tetramer, one per subunit. These lie just below the plasma membrane, at the interface between the N terminus of one subunit and the C terminus of its neighbor. Residues in SUR1 also contribute to the ATP-binding site (14), thus explaining why SUR1 enhances the ATP sensitivity of Kir6.2 (19). Interaction of MgADP (or MgATP) with the two nucleotide-binding sites of SUR1 stimulates channel activity (19,20), with MgADP being the more potent (21). Precisely how binding of Mg-nucleotides leads to opening of the Kir6.2 pore is still unclear, but some mechanistic insights are offered by structural and functional studies (18,22).

K_{ATP} CHANNEL MUTATIONS CAUSE NEONATAL DIABETES

Once the K_{ATP} channel had been cloned, we looked for mutations associated with diabetes. Although we identified a common variant in Kir6.2 (E23K), we were unable to detect an association with type 2 diabetes (23). Nevertheless, this polymorphism was subsequently found to predispose to type 2 diabetes in better-powered studies (24). However, we quickly realized we were studying the wrong population. Type 2 diabetes typically presents later in life, whereas a severe pathogenic mutation would be expected to manifest its effects at birth. Subsequently, Andrew Hattersley and his team at the University of Exeter screened patients with neonatal diabetes for K_{ATP} channel mutations, and I shall never forget the day he and Anna Gloyn informed me they had identified a mutation in Kir6.2 and invited us to study its functional effects (25). Finding that the mutation caused a reduction in the ATP sensitivity of the K_{ATP} channel but did not

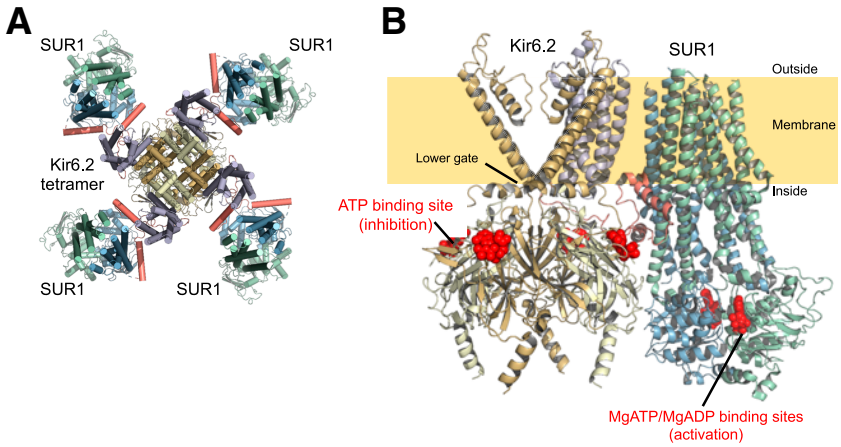

Figure 3—Structure of the K_{ATP} channel complex determined by cryoelectron microscopy. *A*: Top view showing the central pore formed from four Kir6.2 subunits (olive) and four SUR1 subunits. SUR1 is color coded with transmembrane domains (TMs) 1–5, shown in gray; TMs 6–11, shown in blue; and TMs 12–17, shown in green. The cytoplasmic loop between TMs 1–5 and TMs 6–11 is shown in orange. The Protein Data Bank accession number is 6BAA. *B*: Side view showing two Kir6.2 subunits and a single SUR1 subunit. The color code is the same as that for *A*. ATP and ADP molecules are shown in red. The Protein Data Bank accession number is 6C3P. Adapted with permission from Dr. Michael Puljung.

prevent its inhibition by the sulfonylurea tolbutamide was another red-letter day.

We now know that approximately 50% of neonatal diabetes cases are due to an activating mutation in either Kir6.2 (*KCNJ11*) or SUR1 (*ABCC8*). Almost all Kir6.2 mutations cause dominant disease (25–29), but SUR1 mutations are genetically more heterogeneous, with homozygous, heterozygous, compound heterozygous, and uniparental disomy mutations all having been described (29–33). Most mutations arise spontaneously. These mutations are very rare—about 1 in 200,000 live births. Birth weights are low because of reduced fetal insulin secretion. Patients with neonatal diabetes normally, but not exclusively, present within the first 6 months of life with severe hyperglycemia and often ketoacidosis. In many people the diabetes is permanent, but in others it is transient and follows a relapsing-remitting time course (27). Some patients with mutations that usually cause transient neonatal diabetes are not diagnosed with diabetes until early adult life (34), when it is often misdiagnosed as type 1 diabetes or type 2 diabetes. There are also a few mutations that appear to present only in early adult life and may represent an intermediate between neonatal diabetes and type 2 diabetes. These are usually also misdiagnosed as type 1 or type 2 diabetes.

In addition to neonatal diabetes, around 20% of patients have serious neurological impairments, such as mental and motor developmental delay and muscle hypotonia (28), and about 3% of patients have neonatal diabetes plus a more severe neurological phenotype, which includes developmental delay and epilepsy that begins in infancy (28). These conditions are known as intermediate DEND (iDEND) syndrome and DEND syndrome, respectively (DEND stands for developmental delay, epilepsy and neonatal diabetes). Both syndromes are more common with mutations that cause a large reduction in ATP sensitivity (such as Kir6.2-V59M, which causes iDEND syndrome), but mild psychological symptoms have also been reported for other, less functionally severe, mutations.

All neonatal diabetes mutations result in an increase in K_{ATP} channel activity, but their mechanism of action differs. Many Kir6.2 mutations are clustered around the ATP-binding site or are found in regions of the channel involved in its opening and closing (gating) (29). Some directly inhibit ATP binding (35), whereas others act by increasing the channel open probability, which indirectly reduces ATP sensitivity (26). Mutations in SUR1 are found throughout the protein and increase the ability of MgADP to activate the channel (30) or act by enhancing the channel open probability (31). All neonatal diabetes mutations impair the ability of glucose (via changes in ATP and MgADP) to reduce K_{ATP} channel activity and thereby stimulate insulin secretion.

A SPECTRUM OF DISEASE SEVERITY

It is now clear that there is a spectrum of disease severity and a clear genotype–phenotype relationship. Kir6.2 mutations that strongly reduce ATP inhibition are associated with the more severe forms of the disease such as DEND syndrome, while those that produce a smaller reduction in ATP sensitivity cause iDEND syndrome or permanent or transient neonatal diabetes (28).

Even a tiny reduction in ATP sensitivity can be sufficient to cause neonatal diabetes (36). It may also predispose to type 2 diabetes, as is the case for the common E23K polymorphism in Kir6.2 (24). About 40% of people carry at least one K allele at residue 23, and although the individual effect size is small, the enhanced risk of diabetes is highly significant (24). The change in ATP sensitivity produced by the E23K mutation is extremely tiny (37) and cannot always be detected by heterologous expression,

raising the question of if it really is responsible for increasing the risk of type 2 diabetes or if a linked variant in SUR1 is to blame (38). To address this question, we generated a mouse carrying the E23K mutation in the endogenous Kir6.2 gene (39). Mice homozygous for the KK variant were more glucose intolerant than those with the EE variant and secreted less insulin at a threshold level of 7 mmol/L glucose. Thus, the dose-response curve for insulin secretion is shifted to higher glucose concentrations, explaining the impaired glucose tolerance of the KK mice and the enhanced diabetes risk in human carriers. This does not, of course, exclude the possibility that the linked SUR1 variant (S1369A) also has an effect on insulin secretion.

The reason why tiny changes in ATP sensitivity have such a significant effect on insulin secretion is because the resting potential of the pancreatic β-cell is almost exclusively determined by the activity of the K_{ATP} channel. When most K_{ATP} channels are closed, the membrane resistance is very high, and consequently a tiny change in channel activity (i.e. current) will cause a large change in membrane potential that can switch the β-cell from electrical silence (and no insulin secretion) to electrical activity and insulin release (40). This property ensures that insulin release is exquisitely sensitive to small fluctuations in blood glucose.

EXTRAPANCREATIC EFFECTS OF NEONATAL DIABETES MUTATIONS

K_{ATP} channels are present in more than just β-cells. They are also found in various endocrine cells and multiple types of brain neurons (where, as in β-cells, they comprise Kir6.2 and SUR1 subunits), as well as in heart and skeletal muscle (which express Kir6.2/SUR2A channels). Gain-of-function K_{ATP} mutations are therefore expected to reduce the electrical excitability of all these cell types. However, in general, only the most functionally severe mutations give rise to the neurological symptoms found in iDEND and DEND patients. This may be because neurons and β-cells differ in their metabolism or possess a different complement of ion channels that regulate their membrane potential. The β-cell is unusual in that the resting potential is dominated by the activity of the K_{ATP} channel and that channel activity is sensitive to changes in extracellular glucose.

Although Kir6.2 also forms the pore of the cardiac K_{ATP} channel, no obvious cardiac problems have been documented in patients with gain-of-function Kir6.2 mutations. Likewise, no cardiac abnormalities are found in mice expressing an activating Kir6.2 mutation specifically in cardiac and skeletal muscle (41). These mice also show no deficit in skeletal muscle strength, arguing the muscle hypotonia of iDEND patients is neurological in origin (42). The fortunate lack of cardiac and skeletal muscle deficits is due to the different compositions of the K_{ATP} channels in these tissues (Kir6.2/SUR2A rather than Kir6.2/SUR1). The SUR2A subunit confers less sensitivity to Mg-nucleotide activation, even for the mutant channels (42).

IMPLICATIONS FOR THERAPY

The discovery that neonatal diabetes was caused by K_{ATP} channel mutations had implications for therapy. Patients with neonatal diabetes presented with all the features of severe insulin deficiency, with hyperglycemia, ketoacidosis, and low or absent C-peptide. Consequently, they were treated with insulin, and it was assumed they would require it all their lives. However, our studies with the Hattersley team (25–28) suggested the reason for the lack of insulin secretion in these patients was that their β-cells were simply switched off due to the increase in K_{ATP} channel activity. This suggested it might be possible to bypass the metabolic steps in stimulus–secretion coupling using sulfonylurea drugs, which bind directly to the K_{ATP} channel and induce it to close. These drugs had been used for many years to treat type 2 diabetes and could be tested immediately. Electrophysiological studies revealed that most mutant channels could still be closed by sulfonylureas (25,26,43,44). This also proved to be the case in patients (43,44). Indeed, their HbA_{1c} level decreased following transfer to sulfonylurea therapy (43), and fluctuations in blood glucose levels were reduced (45). Importantly, insulin secretion in sulfonylurea-treated neonatal diabetes patients is meal dependent. This is because drug-induced K_{ATP} channel closure has a permissive effect on the actions of gut incretins such as glucagon-like peptide 1 (GLP-1), enabling them to stimulate insulin secretion (43).

More than 90% of patients with neonatal diabetes caused by K_{ATP} channel mutations have now been transferred to drug therapy, and both their clinical condition and their quality of life have improved (43–48). Furthermore, unlike type 2 diabetes, there is no evidence of sulfonylurea failure even after >10 years of therapy (46,47). Hypoglycemia is rare, despite the very high drug doses patients require to stabilize their blood glucose. This is probably because sulfonylureas are unable to completely close the mutant K_{ATP} channels (49).

Sulfonylureas do not fully correct the neurological problems experienced by patients with iDEND/DEND syndrome, although small improvements are possible, especially if the drug is given immediately after diagnosis (48,50). Mouse studies suggest this is because sulfonylureas are rapidly pumped out of the brain and never reach a therapeutic concentration (51).

DOES TYPE 2 DIABETES INVOLVE IMPAIRED K_{ATP} CHANNEL REGULATION?

For patients with activating K_{ATP} channel mutations, sulfonylurea therapy has been transformative. However, neonatal diabetes is a rare disease. The vast majority of patients with diabetes have type 2 diabetes. This is a progressive disorder that starts with impaired glucose tolerance and progresses to diabetes as β-cells gradually fail. By the time patients are diagnosed, it is estimated only 50% of β-cell function remains (52). The fact that it is more difficult for older patients with neonatal diabetes to transfer to

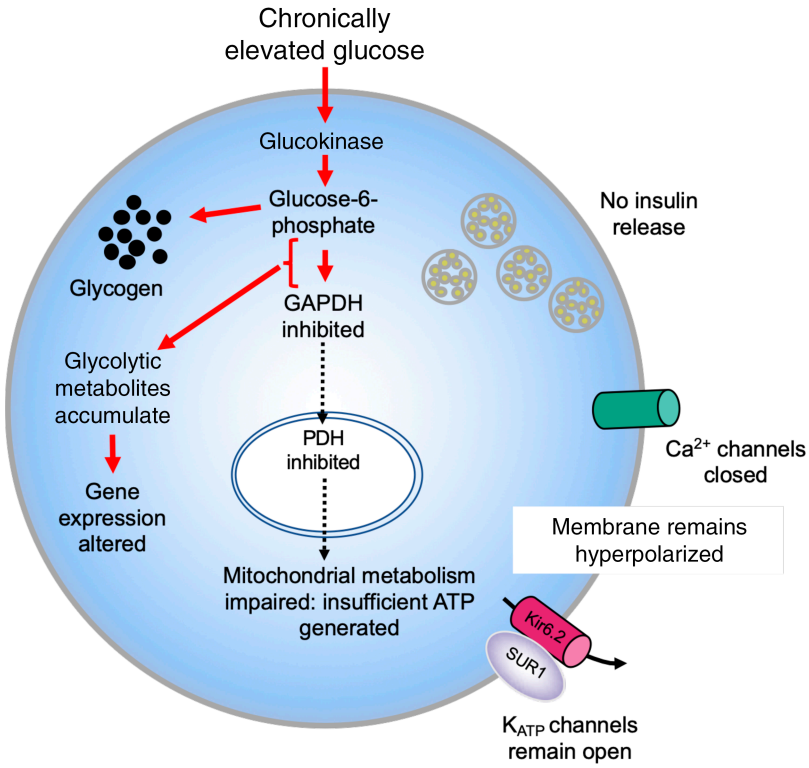

Figure 4— Cartoon illustrating metabolism in a β-cell exposed to chronic hyperglycemic or type 2 diabetes. Glucose uptake is increased due to the elevated extracellular glucose concentration. This leads to increased glucose-6-phosphate, which is channeled into glycogen as the activity of both GAPDH and PDH are inhibited. Accumulation of metabolites upstream of GAPDH cause changes in gene expression that downregulate the expression of multiple genes, including insulin genes and genes involved in insulin granule processing, exocytosis, and mitochondrial metabolism. Because metabolism is reduced, glucose-dependent changes in the ATP-to-ADP ratio and K_{ATP} channel activity are expected to be reduced, leading to impaired insulin secretion. Likewise, exocytosis may be decreased, as this also requires ATP.

sulfonylurea therapy (44) suggests that β-cell function also declines with disease duration in neonatal diabetes. This does not necessarily mean there is a loss of β-cells; indeed, while β-cell number may decline in type 2 diabetes, it does not do so enough to explain the impaired insulin release.

One potential driver of β-cell decline in type 2 diabetes is chronic hyperglycemia. It is well established that culture of β-cell lines at high glucose concentrations leads to impaired insulin secretion (53–56), and culture of human islets at just 8 mmol/L glucose decreases both stimulated insulin secretion and insulin content (57). To understand how chronic hyperglycemia affects the β-cell, we generated a mouse model of inducible diabetes (βV59M mice) (58). These mice express an inducible gain-of-function K_{ATP} channel mutation found in neonatal diabetes (Kir6.2-V59M), specifically in their pancreatic β-cells. Induction of the transgene leads to β-cell hyperpolarization, inhibition of insulin secretion, and an immediate rise in blood glucose (to >20 mmol/L) (58). The mice are hyperglycemic and hypoinsulinemic but not dyslipidemic, obese, or insulin resistant. Consequently, the effects of chronic hyperglycemia can be studied in isolation.

Within 2 weeks of diabetes induction, there was a dramatic reduction in insulin content. This was not primarily due to loss of β-cells but rather to a lack of insulin granules and downregulation of insulin gene expression. Similar β-cell degranulation has been observed in other diabetic mouse models (59) and in islets from donors with type 2 diabetes (60,61). Thus, β-cell loss in type 2 diabetes may be overestimated if assessed by insulin staining.

Diabetic βV59M β-cells accumulated large amounts of glycogen (62,63). Glycogen particles have also been detected in human diabetic islets, even those isolated from donors with good glycemic control (63). Glycogen is not normally present in β-cells, because the role of the β-cell is to detect changes in blood glucose concentration, which would not be possible if glycogen stores were to maintain β-cell metabolism when extracellular blood glucose falls. The increase in glycogen content therefore suggests that chronic hyperglycemia impairs metabolism in diabetic β-cells.

Accumulating evidence supports this idea. Using a combination of transcriptomics, proteomics, and metabolomics, we found significant dysregulation of the major metabolic pathways in islets from diabetic βV59M mice (55,56). Multiple genes and proteins involved in glycolysis and gluconeogenesis were upregulated, whereas almost all those involved in the tricarboxylic acid cycle and the electron transport chain were downregulated. This led to a reduction in both glycolytic and oxidative glucose metabolism, with glucose-induced increases in NAD(P)H, oxygen

consumption, and the ATP-to-ADP ratio all being impaired. Two key metabolic bottlenecks were identified (56). First, pyruvate dehydrogenase was largely inhibited due to upregulation of pyruvate dehydrogenase kinase 1; this will restrict entry into the tricarboxylic acid cycle and reduce mitochondrial metabolism. Second, GAPDH activity was dramatically suppressed, which will decrease glycolysis. A similar bottleneck in metabolism at GAPDH has been detected in stem cell–derived β-cells, which also show reduced glucose-stimulated insulin secretion (64).

A progressive decline in β-cell metabolism may be expected to lead to a gradual increase in K_{ATP} channel activity and thus to reduced insulin secretion (6) (Fig. 4), although whether such an increase in channel activity occurs has not been established. It is important to point out that impaired metabolism not only affects expression of metabolic genes but also causes a dramatic decrease in insulin gene expression and reductions in multiple genes involved in insulin processing and granule exocytosis (55). The latter finding, along with reduced ATP and MgADP levels, may help explain why exocytosis is compromised in β-cells from donors with type 2 diabetes (65).

Although glycolytic enzymes are upregulated, the excess glucose entering the β-cell cannot be metabolized to lactate, as β-cells have low levels of lactate dehydrogenase and lack the lactate transporter MCT1 (55,66,67). Furthermore, glycolytic flux is reduced due to the marked GAPDH inhibition (56). This leads to pooling of upstream metabolites and results in glucose-6-phosphate being channeled into glycogen (Fig. 4). It is possible that utilization of glycogen stores explains the elevated basal insulin secretion of diabetic islets, but this requires investigation.

There is a growing body of evidence suggesting that it is not glucose itself but a glycolytic metabolite that causes the hyperglycemia-induced changes in gene expression. First, mannoheptulose, which inhibits the first step in glucose metabolism (glucose phosphorylation by glucokinase), prevents the effects of chronic hyperglycemia, indicating these are not caused by glucose but by a downstream metabolite (53,56). Second, chronic culture at high pyruvate concentrations did not recapitulate the effects of chronic hyperglycemia, indicating the metabolite lies upstream of pyruvate (54,56). Third, GAPDH activity is markedly downregulated in diabetes, and chronic inhibition of GADPH in INS-1 cells cultured with a low concentration of glucose mimicked the effects of chronic hyperglycemia on metabolic gene expression (56). This argues that one or more of the glycolytic metabolites lying between glucokinase and GAPDH are responsible for orchestrating the gene changes that underlie the decline in β-cell metabolism caused by chronic hyperglycemia.

Multiple genome-wide association studies have indicated that variation in numerous genetic regions alters diabetes risk (68), but it has always been difficult to understand why diabetes develops later in life. I favor the idea that this is because chronic hyperglycemia drives a progressive decline in β-cell function (Fig. 5). I propose that a number of factors such as a genetic predisposition, in combination with stressors such as insulin resistance, age, or pregnancy, cause a small increase in blood glucose. This produces mild glucose intolerance, which may persist for many years. Over time, however, the elevated blood glucose drives accumulating changes in gene and protein expression that eventually impair β-cell metabolism and reduce insulin secretion further. This will exacerbate the hyperglycemia, raising blood glucose even higher and thereby initiating a vicious spiral that accelerates exponentially and culminates in frank diabetes (Fig. 5). Preventing this vicious spiral might slow β-cell decline and help reduce the complications of diabetes caused by chronic hyperglycemia that have such devastating effects on patients' lives.

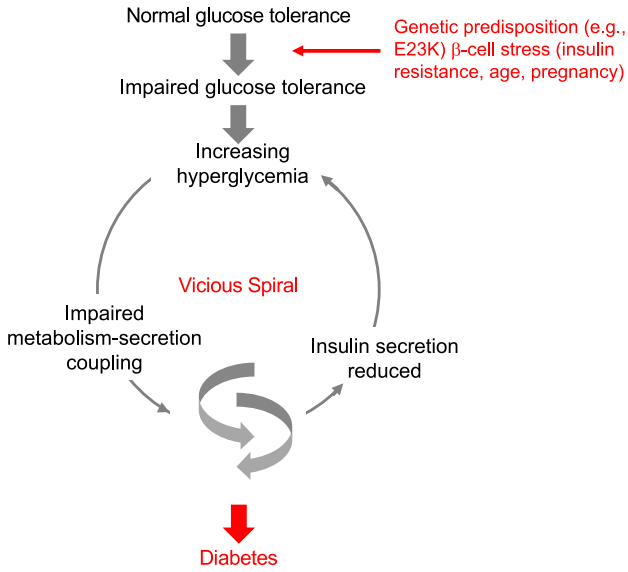

Figure 5—Schematic suggesting how a small rise in plasma glucose may lead to a progressive decline in β-cell function.

CAN THE INEXORABLE DECLINE IN β-CELL FUNCTION BE HALTED OR REVERSED?

β-Cells remain viable for many years after the onset of diabetes, as evidenced by the ability of numerous patients with neonatal diabetes to transfer to drug therapy even after many years of insulin therapy (44). Furthermore, reversal of diabetes in diabetic βV59M mice was associated with restoration of normal gene expression and insulin content (58). Very low calorie diets and bariatric surgery also can reverse type 2 diabetes, at least for diabetes of short duration (69,70). While the mechanisms by which they do so are still debated, all these therapies reduce plasma glucose levels, which is likely to improve β-cell function.

However, many people find caloric restriction difficult, so alternative strategies are needed. Our studies, and those of others, suggest that one way to halt β-cell decline would be to reduce glycolytic flux by partial inhibition of glucokinase

(53,56,71–74). This would prevent the buildup of downstream signaling metabolites that lead to the changes in gene expression that drive β-cell functional decline. Glucokinase may be a good target, as it is confined to β-cells, the liver, a few neurons, and some endocrine cells. Indeed, partial inhibition of glucokinase with mannoheptulose prevents all the changes in INS-1 cells (56) and restores insulin secretion in diabetic mouse islets (75). There is also accumulating evidence that partial glucokinase knockdown both in vitro and in vivo can help preserve and restore β-cell function in diabetic mice (72–74). Most importantly, perhaps, patients with heterozygous inactivating glucokinase mutations require no therapy, their diabetes does not progress, and, despite lifelong mild hyperglycemia, their incidence of diabetes complications is similar to that of people without diabetes (76,77). It seems possible that people with heterozygous glucokinase mutations are protected from progressive β-cell decline because the mutation prevents the vicious spiral of hyperglycemia leading to impaired insulin release and thus to greater hyperglycemia. Taken together, these data not only suggest that partial glucokinase inhibition may be beneficial in diabetes but also help explain why glucokinase activators have been largely unsuccessful at preserving β-cell function: they exacerbated the metabolic effects of chronic hyperglycemia.

FINAL THOUGHTS

In summary, the K_{ATP} channel seems to play a key role in both neonatal diabetes and type 2 diabetes (Fig. 2). In the former case, activating mutations in either Kir6.2 or SUR1 impair the ability of ATP and ADP to close the channel so that glucose fails to cause membrane depolarization and insulin secretion. I postulate that, in type 2 diabetes, K_{ATP} channel closure in response to glucose is reduced because impaired glucose metabolism fails to generate a sufficient increase in the ATP-to-ADP ratio. Impaired metabolism will also affect downstream events in stimulus–secretion coupling, such as granule mobilization and exocytosis. Further investigation is now needed to determine if metabolism is impaired in β-cells isolated from donors with type 2 diabetes, if this leads to a reduction in β-cell electrical activity, and if this can be prevented or reversed by partial reduction of glycolytic flux.

Numerous questions remain as to how impaired β-cell mitochondrial metabolism in type 2 diabetes mediates its effect on insulin secretion. Is this primarily via changes in K_{ATP} channel activity (it is still uncertain if β-cells are depolarized or hyperpolarized in diabetes)? Is K_{ATP} channel activity regulated by mitochondrially generated ATP, by ATP at the plasma membrane, or both? There are also many other unsolved mysteries. We now know that it is possible to reverse type 2 diabetes, at least temporarily and for diabetes of short duration, but the underlying mechanism is still unclear. To what extent is chronic hyperglycemia a driver of β-cell decline? How much do elevated plasma lipids contribute? How do glycolytic metabolites mediate their effect on gene expression? What are the relative contributions of reduced insulin content, decreased metabolism, and lower autophagy to impaired β-cell function in type 2 diabetes? Most importantly, how closely do the properties of isolated human islets recapitulate those of rodent islets or β-cell lines, or of human islets in vivo? It is a truly exciting time for diabetes research, and I look forward to seeing the answers to these questions in the future.

The Banting lecture is an opportunity for reflection, and when I think back on my scientific life, I am reminded of Lord Carnarvon's words when he peered through the hole into Tutankhamen's tomb: "I see many wonderful things!" As a scientist, I have been privileged to have seen many wonderful things, but perhaps none more marvelous than the improvement in the lives of families with neonatal diabetes.

Acknowledgments. I thank the many generations of talented PhD students and postdoctoral fellows I have been privileged to work with. They have been a source of constant inspiration and delight, and this award is as much their award as mine. I am also indebted to my wonderful mentors and collaborators. I particularly wish to thank Steve Ashcroft (University of Oxford) for introducing me to the β-cell and teaching me about metabolism, Patrik Rorsman (University of Oxford) for many years of friendship, scientific inspiration, and generous collaboration, and Andrew Hattersley (University of Exeter) for inviting me to participate in a life-enhancing collaboration on neonatal diabetes. Thank you, dear friends. I also thank the patients with neonatal diabetes and their families for their friendship and willingness to participate in research. I never expected to see our studies have an impact on people's lives in my own lifetime, and it has been an immense privilege that this has happened. Finally, I have been fortunate not only to have worked with many wonderful people but to have been part of an inspirational and supportive diabetes community. I thank all my colleagues for stimulating discussions.

As the list of references is limited and this review is based on my Banting lecture, I have focused on my own laboratory's contributions rather than providing a comprehensive review of the literature. I apologize for the many omissions of others' work.

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