

Metabolic regulation of insulin secretion in health and disease

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Despite the current media focus, Covid-19 is not the only current pandemic. There is also a global pandemic of diabetes. It is caused by an insufficiency of the hormone insulin, which lowers blood glucose levels. Here we highlight recent work that addresses the question of how insulin is normally secreted from the β -cells of the pancreas and what goes wrong with this process in diabetes. We focus on the metabolic regulation of the ATP-sensitive potassium channel, an ATP-gated membrane pore that regulates insulin secretion. We show that when this pore is shut, insulin is released, and when it is open, insulin release is prevented. As may be expected, genetic mutations that impair the ability of ATP to close the channel cause neonatal diabetes. We also consider if a failure of β -cell metabolism to generate enough ATP to close the channel may lead to the progressive decline in β -cell function in type 2 diabetes.

Insulin regulates the blood glucose level

The year 2021 marks 100 years since the discovery of insulin, a hormone that plays a key role in glucose homeostasis. It revolutionized therapy for diabetes and is a triumph of modern medical research. We often forget that prior to insulin's discovery, diabetes was a death sentence. Now, patients can have a normal lifespan. But as Banting said in his Nobel lecture, "insulin is not a cure – it is a treatment that keeps people alive" and if we are to prevent the long-term complications of the disease we need to understand how insulin is normally secreted and what goes wrong with this process in diabetes.

It is essential that the blood glucose is kept within narrow limits. In non-diabetic individuals, the fasting blood glucose level is around 4–5 mM. If it drops below ~1–2mM the brain is starved of fuel, causing cognitive impairment and death within just a few minutes. On the other hand, elevation of blood glucose, as in diabetes, is also dangerous. If untreated, it results in excessive urination (as glucose spills over into the urine dragging water with it osmotically) and a switch from glucose to fat metabolism that results in accumulation of ketoacids, coma and death. Chronic elevation, even at levels that do not cause ketogenesis, as may occur in diabetic patients treated with insulin, results in a range of complications, including an increased risk of heart disease, kidney disease, blindness, nerve damage and limb amputation.

Insulin ensures that blood glucose elevations after a meal are small and transient. It is released from the β -cells of the pancreatic islets and stimulates the uptake of glucose into muscle, liver and fat, thereby restoring blood glucose to its resting level. In its absence these tissues cannot take up glucose, hence diabetes has been

referred to as starvation in the midst of plenty. Insulin is of particular importance because it is the only hormone that can lower blood glucose concentration: in contrast, many hormones can elevate blood glucose. Why this is the case is likely because too much insulin is quickly lethal, as blood glucose drops precipitously (indeed, insulin has been employed as a murder weapon). Thus a paucity of blood glucose has been a far more important evolutionary driver than an excess.

Diabetes is a metabolic disease that results from an insufficiency of insulin for the body's needs, which results in chronically elevated blood glucose levels. The International Diabetes Federation estimated 463 million people worldwide had the disease in 2019 and that is expected to rise to around 700 million by 2045. Many types of diabetes are recognized, but in all cases insulin secretion is deficient. In type 1 diabetes the β -cells die from an autoimmune attack. By contrast, in type 2 diabetes (the most common variety: >90% of cases), and in some rare genetic forms of diabetes, the β -cells are present but simply fail to secrete insulin in response to a rise in blood glucose. Much research has focused on understanding why this is the case. A widespread view is that the main defect lies in metabolism–secretion coupling in the β -cell.

Glucose metabolism regulates insulin secretion

The β -cell acts as a glucose sensor, adjusting its insulin output according to ambient changes in blood glucose. Numerous studies have shown that glucose must be metabolised in order to stimulate secretion, and that mitochondrial metabolism is essential. The consensus

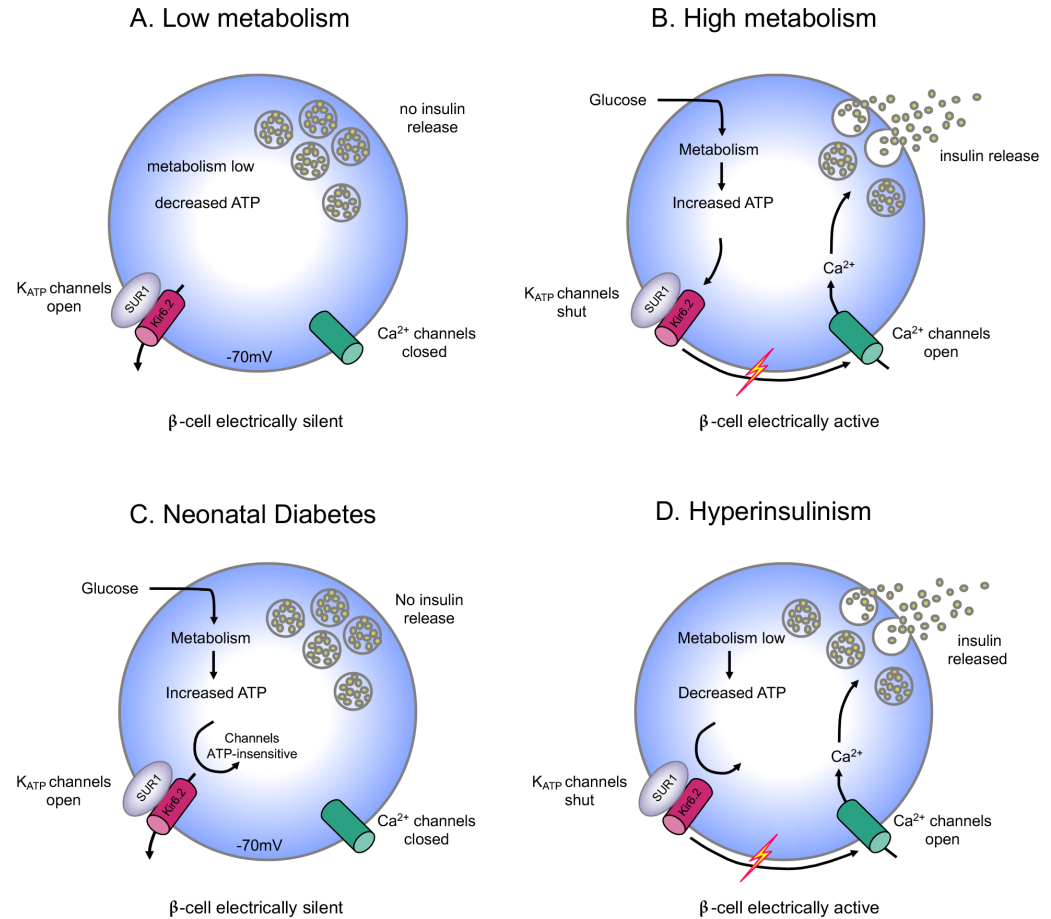


Figure 1. (a) K_{ATP} channels are open when metabolism is low, due to low ATP and elevated MgADP concentrations. Their activity prevents electrical activity and insulin secretion. (b) When glucose rises, its metabolism by the β -cell increases elevating ATP, which closes K_{ATP} channels. This triggers electrical activity, which opens calcium channels allowing calcium to enter the cell and stimulate insulin secretion. (c) Neonatal diabetes. Gain-of-function mutations in Kir6.2 or SUR1 prevent K_{ATP} channel closure when ATP levels rise in response to metabolism. Consequently, the β -cell membrane is electrically inactive, switching off insulin secretion. (d) Congenital hyperinsulinism. Loss-of-function mutations in Kir6.2 or SUR1 lead to permanent K_{ATP} channel closure independent of cell metabolism. Consequently, the β -cell is permanently electrically active, causing continuous calcium influx and insulin secretion. Adapted from McTaggart et al (2010).

view is that the sugar is metabolised via glycolysis, the TCA cycle and oxidative phosphorylation in the mitochondria to produce ATP. ATP is best known as the energy currency of the cell but in the β -cell it also has a second (and rather unusual) function – it serves as a metabolic second messenger, coupling changes in glucose metabolism to the electrical activity of the plasma membrane. In turn, the degree of electrical activity determines the rate of insulin secretion. ATP controls the electrical activity of the β -cell via a plasmalemmal ion channel known as the ATP-sensitive potassium (K_{ATP}) channel, so called because K^+ flux through the channel pore is inhibited by ATP. At low blood glucose levels, when ATP levels are lower, the K_{ATP} channel is open, which renders the β -cell electrically silent (Figure 1A). However, when blood glucose increases, cytosolic ATP

also rises and binds to the K_{ATP} channel causing it to close. This results in β -cell electrical activity which triggers a chain of events that culminates in exocytosis of insulin granules (Figure 1B). The K_{ATP} channel is thus the link between β -cell metabolism and membrane events that lead to insulin release.

Metabolism in β -cells has several unusual properties. First, in many cells, excess glucose that enters the cell is stored (e.g., as glycogen) and used to maintain metabolism and intracellular ATP when extracellular glucose levels fall. This is incompatible with the role of the β -cell as a glucose sensor – instead, β -cell ATP levels vary with extracellular glucose and glycogen is not normally stored. Second, in β -cells, almost all of the glucose entering glycolysis proceeds into the TCA cycle. Little is metabolized to lactate because expression of

lactate dehydrogenase is low. Furthermore, expression of the monocarboxylate transporter MCT1, which regulates lactate and pyruvate flux across the cell membrane, is also suppressed. This ensures that circulating lactate and pyruvate during exercise do not trigger insulin secretion and lower blood glucose (thus reducing exercise capacity). The importance of this metabolic anomaly is shown by the fact that a mutation in the MCT1 promoter which causes its expression in β -cells is associated with exercise-induced hypoglycaemia.

Likewise, the crucial role of the K_{ATP} channel – and its metabolic regulation by ATP – in insulin secretion is demonstrated by the fact that mutations in K_{ATP} channel genes cause insulin secretory disorders (Figure 1C,D). Loss-of-function mutations result in permanent closure of the K_{ATP} channel at all glucose concentrations and persistent and unregulated insulin secretion, a disorder known as congenital hyperinsulinism (CHI). Patients have very low blood glucose soon after birth and if not rapidly treated may suffer brain damage. In the most severe cases the only treatment is partial resection of the pancreas but some milder cases can be treated with K channel openers (such as diazoxide); or even diet – in this case eating chocolate is to be encouraged!

Neonatal diabetes

Gain-of-function mutations cause neonatal diabetes, a rare inherited form of diabetes that is characterised by marked hyperglycaemia within the first 6 months of life. About 50% of cases are due to mutations in the K_{ATP} channel genes. These mutations all act by reducing the ability of MgATP to close the channel. This prevents insulin release and accounts for the diabetes of the patient. It was originally assumed that neonatal diabetes patients had an unusually early onset form of type 1 diabetes and they were therefore treated by insulin injections as it was thought that they had no functional β -cells. However, the discovery that their diabetes was caused by K_{ATP} channel mutations suggested this might not be the case and that the reason for their lack of insulin secretion was instead because their β -cells were essentially switched off – their K_{ATP} channels failed to close in response to glucose. What was needed was a drug that could bypass the metabolic steps and close the channel directly. Happily there was one readily available. Sulphonylurea drugs bind to and close K_{ATP} channels and have been used for over 50 years to stimulate insulin secretion in type 2 diabetes. When they were tested, it was found that most mutant K_{ATP} channels could also be closed by sulphonylureas. Importantly, they also facilitated insulin secretion in most neonatal diabetes patients. More than 90% of neonatal diabetes patients with K_{ATP} channel mutations have now transferred to

drug therapy and both their clinical condition and their quality of life improve. Interestingly, blood glucose levels are even better controlled by sulphonylureas than by insulin, showing a lower fasting level and less excursions after a meal; patients also have meal-stimulated insulin release. It appears that in many patients the drug returns K_{ATP} channel activity to the level normally seen for fasting blood glucose concentrations, allowing agents that normally amplify insulin secretion (like gut hormones) to be effective.

However, neonatal diabetes is a very rare disease. The vast majority of diabetes patients have type 2 diabetes. Could it be that the impaired metabolic regulation of the K_{ATP} channel is also involved in this disease?

Type 2 diabetes

Type 2 diabetes is associated with both impaired insulin release and impaired insulin action (insulin resistance) in extra-pancreatic tissues. Insulin resistance is exacerbated by obesity, and the marked increase in diabetes in the last 50 years is largely driven by a rise in obesity. However, it is clear that obesity is not the primary cause of type 2 diabetes, for not all obese people have the disease. Rather evidence indicates the primary cause of type 2 diabetes is impaired insulin secretion. Type 2 diabetes is a progressive disease that starts with impaired glucose tolerance and progresses to diabetes as β -cells gradually fail. By the time patients are diagnosed they have already lost 50% of their β -cell function. A key question therefore is why do the β -cells stop working?

The available evidence suggests that it is increased blood glucose levels (rather than elevated lipid) that leads to the gradual loss of β -cell function. Although diabetes patients take drugs, or insulin, to help control their blood glucose levels, it is not possible to do so perfectly (due to the risk of hypoglycaemia). Thus their fasting and fed blood glucose levels are inevitably somewhat elevated. Chronically high blood glucose leads to a dramatic loss of insulin content per β -cell and strongly impairs β -cell mitochondrial metabolism and ATP production. It has also been shown that ATP can leak out of diabetic β -cells through a large channel known as VDAC, which is normally located in the mitochondrial membrane, but in diabetes is misdirected to the surface membrane. This leaves the diabetic β -cell drained of energy and with insufficient ATP to close the K_{ATP} channel. In the long run, the number of β -cells per islet also decreases, although not by enough to solely account for the reduction in insulin secretion. Together, however, all these effects lead to a reduction in glucose-stimulated insulin secretion. Our studies suggest that this drives diabetes progression by progressively impairing β -cell function (Figure 2). We suggest that

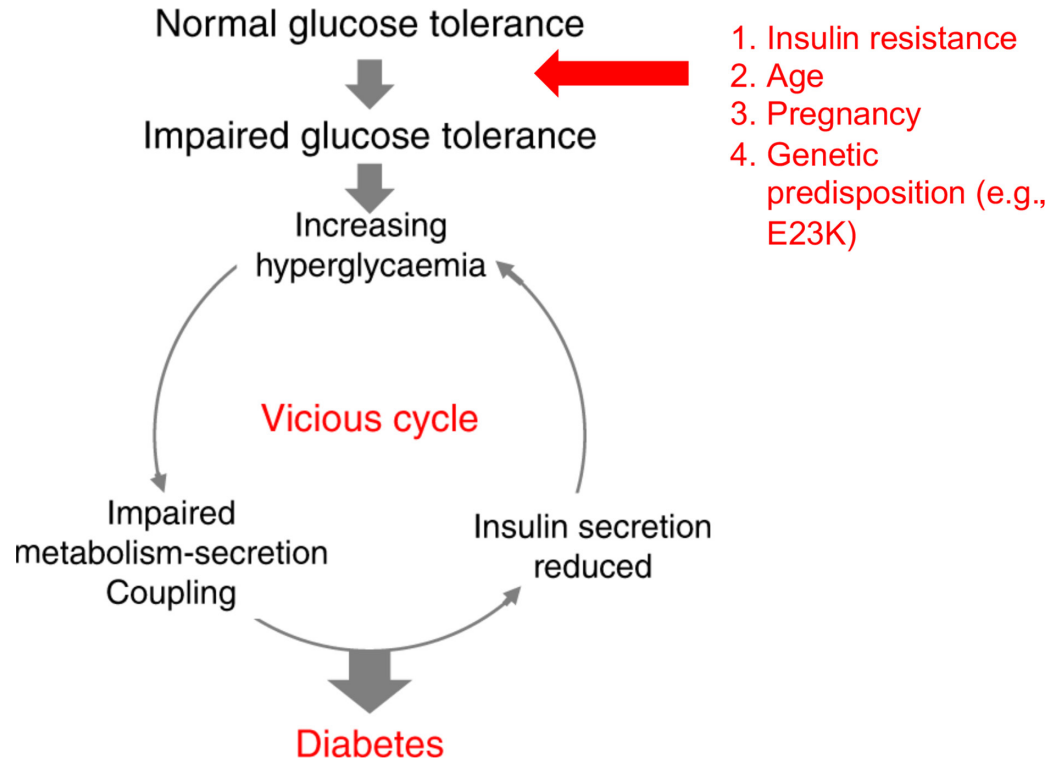


Figure 2. Schematic showing how impaired glucose tolerance can be triggered by one or more different causes. The resulting small rise in blood glucose can then precipitate a vicious cycle in which hyperglycaemia impairs insulin secretion increasing hyperglycaemia further. Eventually this culminates in diabetes. Adapted from Haythorne et al (2019) under CC-BY 4.0 license.

a number of factors such as a genetic predisposition, age, pregnancy, or insulin resistance due to obesity may cause a small rise in blood glucose, producing mild glucose intolerance. The problem is that this causes gene changes that impair β -cell metabolism and thereby ATP production, which prevents K_{ATP} channel closure and reduces insulin secretion further. This will exacerbate the hyperglycaemia raising blood glucose even more and producing a vicious cycle that underlies the progression to overt diabetes.

A key question is whether returning blood glucose levels to normal levels can restore β -cell function. The ability of most neonatal diabetes patients to transfer to sulphonylurea therapy suggests this is the case. However, this happens far more readily in younger patients, who

have had diabetes for less long. Type 2 diabetes can also be reversed in some patients by a very low calorie diet but again this is easier in people who have had diabetes for less time. Thus it seems that long-term diabetes may cause irreversible changes in β -cell function.

It is therefore important to find out how to slow the progression of glucose intolerance to type 2 diabetes. This is given even greater urgency by the current Covid-19 pandemic, because people who catch coronavirus are at a greater risk of severe symptoms if they have diabetes. However, if we are to slow diabetes progression, we first need to understand how chronic hyperglycaemia reduces insulin content and β -cell metabolism. This is currently a mystery and is the focus of on-going research both in our laboratory and in many others. ■

Further reading

- <https://www.ibiology.org/speakers/frances-ashcroft/>. Two talks that cover some of the same ground as this article but in more detail.
- <https://www.diabetesgenes.org>. A website explaining the different types of monogenic diabetes.
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