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K_{ATP} channels and islet hormone secretion: new insights and controversies

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Abstract

ATP-sensitive potassium channels (K_{ATP} channels) link cell metabolism to electrical activity by controlling the cell membrane potential. They participate in many physiological processes but have a particularly important role in systemic glucose homeostasis by regulating hormone secretion from pancreatic islet cells. Glucose-induced closure of K_{ATP} channels is crucial for insulin secretion. Emerging data suggest that K_{ATP} channels also play a key part in glucagon secretion, although precisely how they do so remains controversial. This Review highlights the role of K_{ATP} channels in insulin and glucagon secretion. We discuss how K_{ATP} channels might contribute not only to the initiation of insulin release but also to the graded stimulation of insulin secretion that occurs with increasing glucose concentrations. The various hypotheses concerning the role of K_{ATP} channels in glucagon release are also reviewed. Furthermore, we illustrate how mutations in K_{ATP} channel genes can cause hyposecretion or hypersecretion of insulin, as in neonatal diabetes mellitus and congenital hyperinsulinism, and how defective metabolic regulation of the channel may underlie the hypoinsulinaemia and the hyperglucagonaemia that characterize type 2 diabetes mellitus. Finally, we outline how sulphonylureas, which inhibit K_{ATP} channels, stimulate insulin secretion in patients with neonatal diabetes mellitus or type 2 diabetes mellitus, and suggest their potential use to target the glucagon secretory defects found in diabetes mellitus.

Introduction

Whether you indulge in a large slice of chocolate cake or decide to fast for the day, the pancreatic islets of Langerhans ensure that the swings in your blood sugar level are not large. Each islet contains several types of endocrine cells, which have opposing roles in glucose homeostasis. Insulin, the only hormone to lower blood glucose concentration, is secreted by the β cells, which make up >60% of the islet: it stimulates glucose uptake and

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storage in liver, muscle and adipose tissue. Insufficient insulin secretion results in elevated blood glucose levels, a hallmark of diabetes mellitus. The α cells release glucagon, the body's principal plasma-glucose-elevating hormone. By increasing hepatic glucose production, glucagon prevents hypoglycaemia during fasting and exercise and provides glucose to brain and active muscles. Somatostatin, released from δ cells, inhibits both insulin and glucagon secretion.

Hormone secretion from all three cell types is triggered by action potential firing that leads to the influx of calcium ions (Ca^{2+}) through voltage-gated Ca^{2+} channels and a rise in the intracellular Ca^{2+} concentration that activates secretory granule exocytosis. In β cells and δ cells, glucose metabolism elicits electrical activity and hormone secretion by closing ATP-sensitive potassium channels (K_{ATP} channels).^{1–4} Paradoxically, K_{ATP} channel closure seems to have the opposite effect in α cells, where genetic or pharmacological inactivation of the channel is associated with inhibition of secretion.^{5,6} This Review provides an introduction to the differing role of K_{ATP} channels in insulin and glucagon secretion and considers how defective K_{ATP} channel activity causes the hormonal abnormalities associated with diseases such as diabetes mellitus and hyperinsulinism.

Regulation of electrical activity

The K_{ATP} channel consists of four pore-forming Kir6.x sub-units and four regulatory sulphonylurea receptor (SUR) subunits,² which in islet cells constitute Kir6.2 (encoded by *KCNJ11*) and SUR1 (encoded by *ABCC8*).^{7–9} The hallmark of the K_{ATP} channel is its inhibition by intracellular ATP, which binds to Kir6.2 to cause channel closure.¹⁰ Conversely, interaction of intracellular MgATP (the active form of ATP) and MgADP with SUR1 stimulates channel opening.^{11–13} Modulation by adenine nucleotides means that K_{ATP} channel activity is, in turn, regulated by cell metabolism. The fact that magnesium ions (Mg^{2+}) are not required for ATP (or ADP) binding to Kir6.2 but are needed for binding to SUR1 reflects the different structure of the binding sites on these proteins; this property can also be used experimentally to distinguish between nucleotide effects on Kir6.2 and SUR1. Drug binding to SUR1 also regulates channel activity: K_{ATP} channel openers, such as diazoxide, stimulate channel opening whereas sulphonylurea drugs, such as tolbutamide and glibenclamide, induce channel closure.^{14–16}

K_{ATP} channels link metabolism to cellular electrical activity by regulating the membrane potential. Gating of the K_{ATP} channel is both voltage-independent and time-independent, so that K_{ATP} channel activity results in an ATP-gated leak current.¹⁷ The effect of this leak current on the electrical activity of the cell depends on the relative magnitudes of the K_{ATP} current and other, depolarizing membrane currents. When the K_{ATP} current dominates, the membrane will hyperpolarize, switching off electrical activity. Conversely, if inward currents dominate—as is the case when K_{ATP} channels are almost completely closed—membrane depolarization occurs. If this depolarization is sufficient, electrical activity will be initiated.¹⁸ It is important to recognize that when the electrical resistance of the membrane is very high—as when most K_{ATP} channels are shut—even a tiny change in current can have a large effect on the membrane potential.

Role of the K_{ATP} channel in β cells

The K_{ATP} channel is essential for glucose-stimulated insulin secretion.¹ At glucose concentrations that do not stimulate insulin secretion, the ambient level of intracellular ATP ensures that K_{ATP} channel activity is high enough to keep the membrane hyperpolarized, preventing electrical activity and insulin secretion (Figure 1). K_{ATP} channel closure in response to metabolically generated ATP reduces the K_{ATP} current so that background inward currents now make a greater contribution to the membrane potential. As a consequence, the membrane depolarizes and electrical activity is initiated if this depolarization exceeds the threshold for initiation of action potential firing—which in β cells lies between -60 mV and -50 mV.¹⁹

High-threshold voltage-gated Ca^{2+} channels activate during the action potentials, and the associated Ca^{2+} influx triggers Ca^{2+} -dependent exocytosis of insulin granules. L-type Ca^{2+} channels underlie the action potential in rodent β cells,²⁰ but in humans P/Q-type Ca^{2+} channels are functionally more important.²¹ Unlike mouse β cells, human β cells also have a prominent T-type Ca^{2+} current that activates at voltages as negative as -60 mV and a voltage-gated Na^+ current.²¹ These differences, together with the smaller K_{ATP} current (10% of that in mouse β cells), may explain why electrical activity and insulin secretion from human β cells are triggered at lower glucose concentrations than those from mouse β cells.²²

At glucose concentrations between ~ 6 mM and 20 mM, electrical activity in mouse β cells consists of characteristic bursts of action potentials (lasting 5–15 s), which are superimposed on depolarized plateaux and separated by repolarized electrically silent intervals (5–20 s),^{23,24} as shown schematically in Figure 1. The duration of the bursts increases, and the interburst interval decreases, with increasing glucose concentration and eventually culminates in continuous electrical activity. β cells from other species also generate bursts, but these are less regular than those seen in the mouse, and different ion channels probably contribute to their generation. Although the bursts were first described ~ 45 years ago,^{25–28} their origin still remains a matter of debate. Thus, they have variously been attributed to oscillations in K_{ATP} channel activity,^{29,30} opening of small-conductance Ca^{2+} -activated K^+ channels,³¹ periodic activation of depolarizing currents,³² Ca^{2+} channel inactivation³³ or cell–cell coupling.^{19,34}

Many of the early patch-clamp studies of β cells were performed on isolated cells maintained in tissue culture, in which the rapid oscillatory electrical activity characteristic of β cells in freshly isolated intact islets²³ is either absent and electrical activity is continuous, or it occurs on a timescale 10–20 times slower than that in intact islets.^{31,35} This finding suggests that β -cell isolation could lead to changes in channel density, channel regulation and/or cell–cell coupling. When the integrity of the islet is maintained, and electrical activity is recorded from β cells lying within the islet, normal bursting activity is recorded (Figure 1c). The various patch-clamp configurations, and how they can be used to study ion channel function, are illustrated in Figure 2.

Perforated patch measurements (which preserve cellular metabolism, Figure 2e) from β cells within intact islets reveal that each glucose-induced burst is associated with the gradual development of an outward current (termed K_{slow}),^{36,37} which is produced by activation of Ca^{2+} -activated K^+ channels (50%) and reactivation of K_{ATP} channels (50%).²⁹ This current arises because Ca^{2+} influx through L-type Ca^{2+} channels, which open during the β -cell action potential, increases intracellular Ca^{2+} and thereby activates Ca^{2+} -activated K^+ channels. It also leads to increased ATP consumption by Ca^{2+} -ATPases, and a fall in intracellular ATP levels,^{38–40} which partially reopens K_{ATP} channels closed by glucose metabolism. When K_{slow} has increased sufficiently to overcome the depolarizing influence of other ion channels, the burst terminates. Cessation of electrical activity results in a fall in intracellular Ca^{2+} levels, restoration of cellular ATP levels and thus closure of both Ca^{2+} -activated K^+ -channels and K_{ATP} channels. As a result, the membrane depolarizes, triggering a second burst.¹⁹

The progressive lengthening of the bursts observed as glucose levels increase results from the reduced activation of K_{ATP} channels during electrical activity. This decline in K_{ATP} channel activity has been attributed to increased ATP generation (as a result of increased glucose metabolism), which enables more efficient buffering of ATP consumption by Ca^{2+} -ATPases and further elevates the submembrane ATP concentration.¹⁹ Thus, K_{ATP} channel closure not only initiates electrical activity, but oscillations in the reactivation and closure of K_{ATP} channels shape the bursting behaviour of the β cell and underlie the graded increase in insulin secretion observed as glucose levels are elevated. This model also explains how sulphonylureas, which close K_{ATP} channels, convert oscillatory electrical activity into continuous action potential firing.⁴¹

Sulphonylureas have been used for almost 60 years to treat type 2 diabetes mellitus (T2DM) because of their ability to close K_{ATP} channels and stimulate electrical activity and insulin secretion.^{15,42} These drugs act as partial antagonists, producing a maximum block of only ~60% if studied in excised membrane patches (Figure 2b) in the absence of intracellular Mg-nucleotides.⁴³ When studied under whole-cell conditions (Figure 2d), however, they fully block channel activity.¹⁴ This is because sulphonylureas prevent channel activation by Mg-nucleotides that are present in the cell, but not (unless added) in the solution that perfuses the intracellular surface of an excised inside-out patch. As ATP inhibition of the channel is no longer antagonized by Mg-nucleotide activation, channel inhibition is enhanced.^{44,45} This complicated mechanism of drug action has an important consequence: it predicts that mutations that substantially decrease ATP inhibition will also reduce the maximal extent of sulphonylurea block of the whole-cell K_{ATP} current. It may also explain why some patients with severe activating K_{ATP} channel mutations (see below) cannot be treated with sulphonylureas.⁴⁶

Role of the K_{ATP} channel in α cells

Glucagon is released from α cells in response to a fall in the blood glucose concentration or an increase in circulating levels of amino acids, fatty acids, hormones and neurotransmitters.^{47,48} Precisely how glucose regulates glucagon release remains controversial. At the heart of the debate is whether secretion is primarily controlled by an intrinsic mechanism (as in

the β cell), or by an extrinsic mechanism that involves paracrine factors (such as hormones, metabolites and ions) released from neighbouring β cells or δ cells in response to changes in plasma glucose levels,⁴⁷ or even from innervating nerve terminals.⁴⁹ These hypotheses are not, of course, mutually exclusive. Furthermore, whatever mechanism(s) are involved, studies on islets from mice lacking K_{ATP} channels indicate that K_{ATP} channels have a key role.^{5,6,50} What is in question is whether regulation of K_{ATP} channel activity directly controls glucagon secretion (as it does insulin release) or if channel activity has an indirect, permissive role by setting the stage for other mechanisms that operate via changes in membrane conductance.

Candidates for a glucose-dependent extrinsic regulator of glucagon release include insulin,⁵¹ zinc⁵² and GABA,⁵³ all of which are released from β cells when blood glucose levels rise and have been shown to inhibit α -cell electrical activity and glucagon secretion in isolated islets.⁵⁴ Zinc, an activator of K_{ATP} channels,⁵⁵ co-crystallizes with insulin and is co-released in response to glucose. However, it seems that zinc is not a physiological regulator of glucagon release, because mice lacking zinc in their insulin granules (owing to a β -cell-specific knockout of the zinc transporter ZnT8) show no defect in glucagon secretion.⁵⁶ Somatostatin, released from δ cells in response to glucose elevation, may also contribute to the inhibitory action of glucose on glucagon secretion, as glucagon secretion in islets isolated from mice lacking somatostatin is enhanced and no longer regulated by glucose.^{57,58} Nevertheless, it remains possible that loss of somatostatin, or indeed ZnT8, may lead to compensatory changes that mask the normal physiological function of these proteins.

The fact that in both human and rodent islets, glucagon secretion is maximally inhibited by glucose concentrations with no or little stimulatory effect on insulin secretion⁵⁹ and that glucose remains capable of inhibiting glucagon secretion in isolated islets (that is, when innervation has been severed)⁶⁰ suggests that α cells do indeed possess an intrinsic glucose-sensing mechanism. The nature of this regulation remains obscure, but modulation of α -cell electrical activity is an obvious candidate.

Unlike β cells, α cells are electrically active in the absence of glucose (Figure 3).^{61–64} This difference reflects the fact that the whole-cell K_{ATP} conductance measured in metabolically intact α cells exposed to glucose-free solution is much less than that in β cells (1–10%).^{65,66} However, the maximal K_{ATP} conductance (measured in the absence of intracellular ATP) is as high, or higher, in α cells than in β cells.^{67,68} The half-maximal concentration of MgATP required to inhibit the K_{ATP} current in β cells dialysed with MgATP is much higher (about sevenfold) than that observed in inside-out patches,⁶⁹ probably due to intracellular generation of MgADP. Interestingly, it requires less ATP to block whole-cell K_{ATP} currents in α cells than in β cells,⁷⁰ which may account for the smaller K_{ATP} currents observed in metabolically intact α cells than β cells.

Whatever the reason that the K_{ATP} conductance in α cells exposed to low glucose concentrations is less than that in β cells, it ensures that the membrane is sufficiently depolarized for action potential firing to occur in the absence of glucose. The paradox is why further closure of K_{ATP} channels should reduce glucagon secretion but increase insulin release: surprisingly, tolbutamide inhibits glucagon secretion yet activates insulin release.⁶⁰

Tolbutamide also results in α -cell membrane depolarization, a reduction in the peak amplitude of the action potential and, in some cases, even cessation of electrical activity. Our group have postulated that depolarization results in voltage-dependent inactivation of inward currents—most importantly sodium ion (Na^+) currents—involved in action potential firing.^{60,71} This idea is supported by the fact that the Na^+ -channel blocker tetrodotoxin, which mimics the effect of tolbutamide on peak action potential amplitude, also inhibits glucagon release. Importantly, the reduction in action potential amplitude is expected to reduce Ca^{2+} entry through P/Q-type Ca^{2+} channels and thereby decrease glucagon release. From the voltage-dependence of exocytosis, it can be predicted that a 10–15 mV reduction in action potential peak voltage will produce a ~80% decrease in exocytosis.⁷²

A key question is whether glucose exerts a tolbutamide-like effect on K_{ATP} channel activity and action potential firing. The fact that glucose inhibition of glucagon secretion is antagonized by low concentrations of diazoxide suggests this may be the case.⁶⁰ Indeed, a small (10%) glucose-induced reduction in K_{ATP} channel activity has been observed in isolated rat α cells.⁷³ Puzzlingly, in stark contrast to what is observed in intact islets, glucose stimulates electrical activity and secretion in isolated α cells. This difference may be because the whole-cell K_{ATP} conductance is greater in isolated α cells (0.45 nS/pF)⁷³ than in α cells within intact islets (0.02 nS/pF; P. Rorsman, unpublished work). A possible explanation for this difference is that the loss of surrounding β cells may induce changes in α -cell gene expression, as was observed following β -cell destruction.⁷⁴

A novel mechanism for extrinsic regulation of glucagon release has been proposed by Li *et al.* based on the finding that γ -hydroxybutyrate (GHB) is released from β cells in response to glucose metabolism and that GHB release is required for glucose-induced inhibition of glucagon release.⁷⁵ Both the α -cell receptor for GHB and the molecular mechanism by which GHB prevents glucagon secretion are unknown, but an intriguing possibility is that GHB blocks K_{ATP} channels, either directly or indirectly.

Role of the K_{ATP} channel in exocytosis

Both Kir6.2 and SUR1 are found at high density in dense-core secretory granules of pancreatic β cells, α cells and δ cells^{76–79} but their role there is unclear and the type of dense-core granule involved is controversial. Several studies have provided evidence that SUR1 and Kir6.2 localize to the insulin secretory granules in β -cells.^{76–78} However, others have argued that K_{ATP} channel subunits are confined to non-insulin-containing dense-core granules.⁷⁹

Why K_{ATP} channels are present in the granules is also unknown. Possibly, it might provide a route for trafficking K_{ATP} channels to or from the plasma membrane. Evidence also exists that K_{ATP} channels have a role in exocytosis. This idea is suggested by the fact that SUR1 binds to the exocytosis-regulating protein EPAC2.⁸⁰ EPAC2 mediates the incretin effects of hormones such as glucagon-like peptide 1 (GLP-1), and these effects are absent or reduced in mice lacking SUR1.^{81,82} One hypothesis suggests that by enhancing the ATP-sensitivity of K_{ATP} channels, EPAC2 facilitates K_{ATP} channel closure and membrane depolarization in response to incretins (such as GLP-1).⁸³ Another idea is that SUR1 serves as a scaffold

protein for EPAC2 and other proteins involved in exocytosis. Interactions of SUR1 with various exocytotic proteins, such as syntaxin-1A84 and the Ca^{2+} sensor piccolo80 have also been reported but their functional significance is not yet established.

In addition to the well-documented ability of sulphonylureas to close K_{ATP} channels (and so trigger islet-cell secretion), these drugs potentiate Ca^{2+} -evoked exocytosis in both β cells⁸⁵ and α cells⁸⁶ by a mechanism that is downstream of K_{ATP} channel closure. However, K_{ATP} channels are not involved, as sulphonylureas still stimulate exocytosis in β cells from mice lacking SUR1.⁸¹ Although these findings have been contested,⁸⁷ it has been discovered in the past few years that sulphonylureas bind directly to EPAC2.⁸⁸ The extent to which this mechanism of drug action is of therapeutic significance remains unclear and, in any case, is dependent on sulphonylurea-induced membrane depolarization and Ca^{2+} entry.

Effects of K_{ATP} channel mutations

Neonatal diabetes mellitus

Gain-of-function mutations in the genes encoding either Kir6.2 (*KCNJ11*) or SUR1 (*ABCC8*) cause neonatal diabetes mellitus (NDM), a rare monogenic form of diabetes mellitus that usually presents within the first 6–9 months of life.^{89–92} The disease may be permanent or follow a remitting–relapsing time course. The reduced insulin secretion causes not only diabetes mellitus but also intrauterine growth retardation and a low birth weight. Because K_{ATP} channels are expressed in multiple tissues, around 20% of patients also exhibit neurological symptoms, such as mental and motor developmental delay, muscle hypotonia, hyperactivity and, in rare cases, epilepsy.⁹⁰ Expression of a human NDM mutation (Kir6.2-Val59Met) in mice indicates that hypotonia results from impaired neuronal regulation of muscles, not from enhanced K_{ATP} channel activity in skeletal muscle.⁹³

Multiple mutations in Kir6.2 and SUR1 that cause NDM have been studied biophysically.^{46,94–98} All increase the K_{ATP} current, either by reducing the ability of ATP to block the channel or by enhancing Mg-nucleotide stimulation. The increased K_{ATP} current prevents β -cell depolarization in response to glucose metabolism and impairs insulin secretion. Mice in which activating K_{ATP} channel mutations are expressed specifically in the β cell show severe loss of glucose-induced insulin secretion and diabetes mellitus.^{99–101} However, sulphonylureas, which close the open K_{ATP} channels, remain effective secretagogues. In general, those mutations that produce the greatest reduction in ATP sensitivity are associated with the most severe clinical phenotype.⁹⁵

The effect of Kir6.2 and SUR1 mutations on glucagon secretion has received less attention. Nevertheless, one might predict that the effect would resemble that of diazoxide;⁶⁰ in other words, severe mutations that cause a large increase in K_{ATP} conductance would be expected to inhibit glucagon secretion whereas those that produce a small increase in K_{ATP} current would stimulate glucagon release (Figure 4b,c).

Prior to the discovery that K_{ATP} channel mutations could cause NDM, all patients with NDM were treated with insulin. Now, >90% of patients with NDM have switched to sulphonylurea therapy,^{102,103} which substantially improves their glucose homeostasis and

reduces the risk of diabetic complications.^{102,104} Interestingly, patients with NDM usually require a much higher sulphonylurea dose (relative to body weight) than patients with T2DM. A lower sensitivity of the mutant K_{ATP} channel to sulphonylureas,^{46,99} or a higher open probability at ambient glucose levels, may contribute to the need for a higher dose. The sulphonylurea dose required also often declines with time after the onset of therapy, which suggests that β -cell mass or function may gradually improve when glucose homeostasis and/or normal K_{ATP} channel activity is restored. Fascinatingly, in a subset of mice expressing a β -cell-specific activating K_{ATP} channel mutation, early sulphonylurea treatment led to permanent remission of diabetes mellitus.¹⁰⁵ To what extent this might be the case in humans is unknown. Sulphonylurea therapy might also restore normal function of glucagon-secreting α cells by bringing the K_{ATP} -channel activity in α cells into a range in which paracrine factors and circulating hormones become operational.

Congenital hyperinsulinism

Loss-of-function mutations in Kir6.2 or SUR1 result in congenital hyperinsulinism (HI), which is characterized by persistent and unregulated insulin secretion despite low blood glucose levels.^{92,106–109} The disease usually presents soon after birth as life-threatening hypoglycaemia. Strong suppression of glucagon secretion and of counter-regulation during hypoglycaemia also occur.¹¹⁰

Histologically, HI may be diffuse or focal. In diffuse HI, β cells in all islets are affected, whereas in focal HI, affected islets are confined to a small region of the pancreas. Focal HI usually occurs when the patient carries a recessive mutation in the paternal allele and locally loses the (normal) maternal allele by somatic deletion. Focal HI is treated by identification of the affected region of the pancreas using ^{18}F -dihydroxyphenylalanine PET (^{18}F -DOPA PET) scanning, followed by its surgical excision, and this treatment results in a cure.^{111,112} Diffuse HI is usually inherited recessively, but dominant mutations, which cause a less severe phenotype, have also been identified.¹⁰⁸ The disease is sometimes treatable by K_{ATP} channel openers, such as diazoxide, but most cases require near total pancreatectomy. Interestingly, patients with dominant HI who do not undergo pancreatectomy may develop diabetes mellitus in later life.^{108,109}

Patch-clamp studies have shown that β cells obtained from resected pancreases of patients with congenital HI have few or no functional K_{ATP} channels,¹¹³ This may be due to lack of K_{ATP} channels in the plasma membrane (by affecting protein expression, maturation, assembly or trafficking) or the loss of Mg-nucleotide activation. The resulting reduction in K_{ATP} channel activity explains why β cells are depolarized and show increased intracellular calcium and insulin secretion, even at low glucose levels. Glucose elevation is able to cause a further modest increase in insulin secretion,¹¹⁴ presumably via its effect on metabolic amplifying pathways that lie downstream of K_{ATP} channel closure.¹¹⁵

A major puzzle in studies of congenital HI is why mouse models do not recapitulate the human disease, even when the identical mutation is involved.¹¹⁶ In mice, loss of Kir6.2 or SUR1 does not cause sustained hypoglycaemia—rather, blood glucose levels normalize within a few days of birth, and in later life animals develop glucose intolerance.^{117,118} In addition, whereas heterozygous *Kcnj11* and *Abcc8* knockout mice do show mild HI and

improved glucose tolerance,¹¹⁹ except for a few rare dominant mutations in humans, most people with heterozygous mutations are nonsymptomatic. Why these differences occur is still unclear.

Insulin secretion from islets isolated from patients with congenital HI and mice lacking SUR1 also shows some differences.¹¹⁴ A further complication is that freshly isolated islets from mice lacking SUR1 behave differently from those that have been cultured overnight.¹²⁰ It is also important to remember that mouse and human islets are not identical. In contrast to human islets, mouse islets are densely innervated.¹²¹ Furthermore, adrenaline stimulates glucagon secretion (by binding to β -receptors¹²²) in mouse islets, but (if anything) inhibits glucagon secretion in human islets.⁵⁹ As a consequence of these differences, the counter-regulatory response is much weaker in humans than in mice, which might contribute to the differences in mice and humans with HI.

Role of the K_{ATP} channel in T2DM

T2DM is far more prevalent than NDM and a worldwide scourge. It currently afflicts 335 million people and the number increases hourly.¹ T2DM is a bihormonal disorder that involves both insufficient insulin secretion and defective glucagon secretion. Glucagon secretion is increased at high plasma glucose concentrations (exacerbating the consequences of impaired insulin secretion) and is inadequate at low plasma glucose levels (potentially resulting in fatal hypoglycaemia).¹²³ Oversecretion of glucagon contributes considerably to the hyperglycaemia in patients with T2DM, and suppression of glucagon secretion by administration of somatostatin leads to a marked reduction in the insulin required to maintain euglycaemia.¹²⁴ The report that mice in which the glucagon receptor has been genetically inactivated remain normoglycaemic even after complete chemical destruction of the β cells, whereas wild-type mice become strongly hyperglycaemic, highlights the role of glucagon as a causal factor in diabetic hyperglycaemia.¹²⁵ Interestingly, both under physiological and diabetic conditions, very few α cells (only ~2%) are needed to prevent major counter-regulatory deregulation.¹²⁶

T2DM has a strong genetic component, but disease risk is also enhanced by factors such as age, pregnancy and obesity.¹ Multiple genes are probably involved, which may differ between individuals. One of the first to be associated with increased T2DM risk was a common polymorphism (Glu23Lys) in the Kir6.2-encoding gene (*KCNJ11*).^{127,128} Subsequently, this variant was shown to be in strong linkage disequilibrium with another variant, Ser1369Ala, in the adjacent SUR1-encoding gene (*ABCC8*), such that >95% of people who are homomeric for Kir6.2-Lys23 also carry two copies of SUR1-Ala1369. Thus, either variant could cause the increased disease risk. Although the increase in individual risk is small (OR 1.2), the population risk is highly significant, because 58% of people carry at least one Kir6.2-Lys23 allele.¹²⁸

How the 'at-risk' variant(s) predisposes to T2DM is not fully resolved. In clinical studies, the Kir6.2-Lys23 variant has been shown to reduce glucose-induced suppression of glucagon secretion whilst not affecting insulin secretion.¹²⁹ At the molecular level, the effects of the mutation(s) on K_{ATP} channel function are subtle and vary between laboratories. For

example, increases, decreases and no change in ATP sensitivity have been documented for the Kir6.2-Lys23 variant.^{130–132} Studies combining both polymorphisms reveal that the Kir6.2-Lys23/SUR1-Ala1369 variant shows a very small reduction in the ATP concentration causing half-maximal inhibition (IC_{50}) of K_{ATP} channel activity.¹³³ This may be because the SUR1-Ala1369 variant enhances the ATPase activity of nucleotide binding site 2 of SUR1 and leads to increased nucleotide activation of the channel by Mg-nucleotides.¹³⁴ However, although there is a difference in IC_{50} , at higher (presumably more physiological) ATP concentrations, no difference in channel inhibition exists between ‘low-risk’ and ‘at-risk’ channels.¹³⁴ Thus, how the Kir6.2-Lys23/SUR1-Ala1369 variant increases the risk of T2DM is not immediately clear.

A further complication is that T2DM is (usually) a disease of later life. This fact is generally attributed to a gradual decline in β -cell function or mass, which is postulated to occur with age in all individuals but only progresses to overt T2DM in people who initially have compromised β -cell function. Clinical evidence indeed suggests a progressive age-dependent decline in β -cell function.¹³⁵ Although longitudinal studies on isolated human islets are impossible (for obvious reasons), evidence exists that islets from organ donors with T2DM exhibit reduced glucose metabolism and glucose-induced insulin secretion.¹³⁶ Fascinatingly, restoration of glucose metabolism by pharmacological activators of glucokinase restores glucose metabolism and insulin secretion in these islets.¹³⁶ Thus, impaired glucose metabolism may be a feature of T2DM. If so, this would decrease glucose-induced K_{ATP} channel closure and, particularly if combined with a lower K_{ATP} channel ATP sensitivity, might compromise β -cell function. Importantly, even small changes in K_{ATP} channel activity can have dramatic effects on β -cell and α -cell electrical activity

Sulphonylureas, by closing K_{ATP} channels, are expected to normalize Ca^{2+} entry in β cells from patients with T2DM. However, if a metabolic defect exists, sulphonylureas will not fully restore insulin secretion because glucose metabolites are also required for downstream steps in insulin release (subsequent to K_{ATP} channel closure). By contrast, metabolism is not predicted to be impaired in patients with NDM caused by K_{ATP} channel mutations. This difference may explain why sulphonylureas continue to work in NDM, but—despite being initially effective—eventually fail in T2DM (secondary failure).¹³⁷

Conclusions

K_{ATP} channel closure has a dual role in the regulation of pancreatic hormone release. Depending on the relative magnitudes of the resting K_{ATP} current and other currents in the cell, it can either stimulate (insulin) or inhibit (glucagon) secretion. Dysregulation of this mechanism might underlie the reciprocal changes in insulin secretion and glucagon secretion found in T2DM. Gain-of-function mutations cause a spectrum of diabetes syndromes that range in severity from NDM to T2DM; conversely, loss-of-function mutations cause HI. Defects in islet cell metabolism may also be expected to affect glucose homeostasis via changes in K_{ATP} channel activity, and several studies suggest that it may contribute to impaired hormone secretion in both NDM^{138,139} and T2DM. Future work should be directed at investigating the role of impaired K_{ATP} channel regulation in T2DM, and its effect on both insulin and glucagon secretion. Available data also suggest it might be worth

exploring the potential of sulphonylureas for the treatment of the impaired glucagon secretion found in both type 1 diabetes mellitus and T2DM.

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Key points

- Closure of ATP-sensitive potassium channels (K_{ATP} channels) stimulates insulin secretion but inhibits glucagon release
- The role of K_{ATP} channels in insulin secretion is well understood, but precisely how glucose inhibits glucagon release remains controversial
- Activating mutations in K_{ATP} channel genes cause neonatal diabetes mellitus, whereas loss-of-function mutations cause congenital hyperinsulinism
- Both insufficient insulin secretion and dysregulation of glucagon release contribute to impaired glucose homeostasis in type 2 diabetes mellitus (T2DM)
- A common K_{ATP} channel haplotype predisposes to T2DM
- An age-dependent decline in metabolism may also contribute to T2DM via mechanisms that are both dependent on, and independent of, K_{ATP} channels

Review criteria

This Review was based on the authors' personal collection of publications concerning K_{ATP} -channels, insulin secretion and glucagon release. All papers cited were English-language, full-text papers.

Figure 1. K_{ATP} channel modulation of β -cell electrical activity.

Insulin secretion is **a** | inhibited at low glucose concentrations and **b** | stimulated at high glucose levels. **c** | Schematic illustrating the changes in membrane potential (V), intracellular Ca^{2+} ($[Ca^{2+}]_i$), cytosolic $[ATP]_i/[ADP]_i$ ratio and whole-cell K_{ATP} current produced by increasing glucose concentrations. At 5 mM glucose, K_{ATP} channels are active because of the low $[ATP]_i/[ADP]_i$ ratio, which keeps the membrane hyperpolarized and prevents electrical activity. At 10 mM glucose, via stimulation of glucose metabolism, the $[ATP]_i/[ADP]_i$ ratio increases, resulting in a reduced K_{ATP} current. When K_{ATP} channel activity is

sufficiently low, the membrane depolarizes initiating electrical activity and Ca^{2+} influx. Elevation of $[\text{Ca}^{2+}]_i$ activates ATP-consuming Ca^{2+} -pumps, causing a fall in the $[\text{ATP}]_i/[\text{ADP}]_i$ ratio, reactivation of K_{ATP} channels, membrane repolarization and temporary termination of electrical activity. Elevated $[\text{Ca}^{2+}]_i$ also opens Ca^{2+} -activated K^+ -channels, which contributes to the membrane repolarization (not shown). In the hyperpolarized state, Ca^{2+} influx ceases, $[\text{Ca}^{2+}]_i$ returns to basal, ATP consumption falls, the $[\text{ATP}]_i/[\text{ADP}]_i$ ratio is restored, K_{ATP} and Ca^{2+} -activated K^+ channels close and electrical activity is reinitiated. Horizontal lines indicate the fall in ATP ($[\text{ATP}]_i/[\text{ADP}]_i$) needed to activate K_{ATP} channels to the level (K_{ATP} channel activity) required to initiate repolarization of the burst. Thus, the oscillations in the $[\text{ATP}]_i/[\text{ADP}]_i$ are phase shifted (θ) with respect to changes in intracellular Ca^{2+} , K_{ATP} channel activity and action potential firing (vertical lines). At 20 mM glucose, ATP production is high enough to compensate for the increased ATP consumption. Consequently, the $[\text{ATP}]_i/[\text{ADP}]_i$ ratio is maintained at a sufficiently high level to keep K_{ATP} channels closed, resulting in continuous electrical activity. Abbreviation: K_{ATP} channels, ATP-sensitive potassium channels.

Figure 2. Patch clamping enables the activity of one or more ion channels to be recorded from single cells or isolated membrane patches with high precision.

a | In the cell-attached configuration, the patch electrode is sealed to the surface of an intact cell, allowing channel activity in the patch of membrane under the electrode tip to be studied under physiological conditions. If the pipette is withdrawn from the cell surface, an excised membrane patch is produced, spanning the pipette tip, which has its **b** | intracellular surface (inside-out patch), or **c** | extracellular surface (outside-out patch) exposed to the bath solution. Inside-out patches are used to test the effects of intracellular modulators on channel

activity (for example, ATP). The whole-cell configuration measures the summed activity of the many ion channels in the membrane of the whole cell. **d** | The standard whole-cell method is obtained by forming a cell-attached patch and then destroying the patch membrane with strong suction to gain electrical access to the cell interior. The intracellular solution then dialyses with that in the patch (so, for example, ATP is lost or the intracellular solution can be manipulated). **e** | The perforated patch method preserves cellular metabolism and intracellular second messenger systems by using a pore-forming antibiotic (such as amphotericin B) to provide electrical access to the cell interior. Parts a to e adapted from *Prog. Biophys. Mol. Biol.*, **54** (2), Ashcroft, F. M. & Rorsman, P. Electrophysiology of the pancreatic β -cell, 87143, ©1989, with permission from Elsevier.

Figure 3. K_{ATP} channel modulation of α -cell electrical activity.

a | Glucagon secretion is stimulated at low glucose levels and **b** | inhibited at high glucose levels. **c** | Schematic illustrating the changes in membrane potential (V), whole-cell K_{ATP} current and glucagon secretion produced by increasing glucose levels from 1 mM to 6 mM or by hyperactivation of the K_{ATP} channel using the K_{ATP} -channel activator diazoxide (far left). K_{ATP} channels are under strong tonic inhibition (99%) at low glucose levels, so that the membrane is depolarized sufficiently to elicit electrical activity, which consists of large-amplitude action potentials. Electrical activity is associated with activation of voltage-gated

Na⁺ channels and voltage-gated Ca²⁺ channels, and Ca²⁺ influx through the latter triggers glucagon secretion. Increasing glucose levels to 6 mM closes K_{ATP} channels completely, further depolarizing the membrane. As in β cells, membrane depolarization increases action potential frequency. However, it also reduces α-cell spike amplitude, due to inactivation of voltage-gated Na⁺ channels, which leads to less activation of the P/Q-type Ca²⁺ channels linked to exocytosis and thus to reduced glucagon secretion. Abbreviation: K_{ATP} channels, ATP-sensitive potassium channels.

Figure 4. Relationship between K_{ATP} channel activity and hormone release.

a | Sigmoidal relationship between β -cell K_{ATP} channel activity and insulin release. The green circle indicates channel activity at normal glycaemic levels in humans ($\sim 4\text{--}5\text{ mM}$), where insulin secretion is slightly stimulated. Hyperglycaemia decreases K_{ATP} channel activity and stimulates insulin secretion. Hypoglycaemia increases K_{ATP} channel activity and inhibits insulin release. **b** | Bell-shaped relationship between α -cell K_{ATP} channel activity and glucagon release. Hyperglycaemia decreases K_{ATP} channel activity and inhibits glucagon secretion. Hypoglycaemia increases K_{ATP} channel activity and stimulates glucagon release. **c** | In β cells from patients with type 2 diabetes mellitus (T2DM), K_{ATP} channel activity is enhanced (either because of impaired metabolism or activating K_{ATP} channel variants or mutations). Hypoglycaemia suppresses insulin secretion further. Hyperglycaemia increases insulin secretion but not as much as in nondiabetic β cells. Closure of K_{ATP} channels by sulphonylureas (SU) reduces channel activity at normal glycaemic levels and so boosts insulin secretion in both normoglycaemia and hypoglycaemia. The pink circle shows that in neonatal diabetes mellitus (NDM) K_{ATP} channel activity is so much enhanced that insulin secretion is abolished. The orange circle shows that in congenital hyperinsulinism (HI) there is little or no K_{ATP} channel activity, which causes persistent insulin secretion. **d** | In α cells from patients with T2DM, K_{ATP} channel activity is enhanced. Because of the bell-shaped relationship, reduced K_{ATP} channel activity in response to hyperglycaemia leads to

increased glucagon secretion whereas hypoglycaemia causes reduced glucagon secretion. The orange circle illustrates the situation in severe HI and the pink circle in NDM. Abbreviation: K_{ATP} channels, ATP-sensitive potassium channels.