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The diabetic β -cell: hyperstimulated vs. hyperexcited

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Abstract

Hyperglycaemia has multiple effects on β -cells, some clearly prosecretory, including hyperplasia and elevated insulin content, but eventually, a ‘glucotoxic’ effect which leads to pancreatic β -cell dysfunction, reduced β -cell mass and insulin deficiency, is an important part of diabetes pathophysiology. Myriad underlying cellular and molecular processes could lead to such dysfunction. High glucose will stimulate glycolysis and oxidative phosphorylation, which will in turn increase β -cell membrane excitability through K_{ATP} channel closure. Chronic hyperexcitability will then lead to persistently elevated $[Ca^{2+}]_i$, a key trigger to insulin secretion. Thus, at least a part of the consequence of ‘hyperstimulation’ by glucose has been suggested to be a result of ‘hyperexcitability’ and chronically elevated $[Ca^{2+}]_i$. This link is lost when the [glucose], K_{ATP} -channel activity link is broken, either pharmacologically or genetically. In isolated islets, such studies reveal that hyperexcitability causes a largely reversible chronic loss of insulin content, but *in vivo* chronic hyperexcitability *per se* does not lead to β -cell death or loss of insulin content. On the other hand, chronic inexcitability *in vivo* leads to systemic diabetes and consequential β -cell death, even while $[Ca^{2+}]_i$ remains low.

Keywords

apoptosis; diabetes; excitability; function; glucose; glucotoxicity; insulin; islets; K_{ATP} ; membrane; mice; neonatal

Effects of Hyperglycaemia on Islet Function: Glucose Stimulation and Excitation are Normally Tightly Linked

The normal pancreatic β -cell responds to acutely elevated blood glucose with uptake through glucose transporters, conversion to glucose-6-phosphate by glucokinase and metabolism to generate ATP. A rise in cytoplasmic $[ATP] : [ADP]$ leads to ATP-sensitive potassium (K_{ATP}) channel closure at the plasma membrane, which in turn results in membrane depolarization, opening of voltage-dependent Ca^{2+} and voltage-gated K^+ channels [1–4]. Calcium entry through Ca^{2+} channels results in increased intracellular calcium concentration ($[Ca^{2+}]_i$), which, in turn, triggers insulin exocytosis [5,6]. In response to a chronic rise of glucose *in vivo*, normal pancreatic islets generate a compensatory increase in insulin secretion and β -cell mass [7], which may in part be the result of elevated $[Ca^{2+}]_i$ [8–10].

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Chronic hyperglycaemia also clearly can lead to ‘glucotoxic’ pancreatic β -cell dysfunction, including reduced β -cell mass and loss of insulin content [11]. One potential mechanism is mitochondrial production of reactive oxygen species as well as the process of increased glycosylation and the formation of advanced glycation end products [12]. There is also the concept of ‘ β -cell exhaustion’, that is chronic stimulation of metabolism, excitation and insulin secretion cannot be sustained by the β -cell and there is evidence that insulin depletion is an important part of the reduced or absent insulin response to glucose seen after chronic hyperglycaemia *in vivo* and elevated glucose *in vitro*. Inhibiting insulin secretion by the K_{ATP} channel opener (KCO), diazoxide [13], during continuous hyperglycaemia typically improves insulin secretion when tested after the withdrawal of the blocking agent [12], an effect that correlates with restoration of cellular insulin content. ‘ β -cell exhaustion’ could also induce endoplasmic reticulum stress, and some markers of ER stress are induced by elevated glucose [14]. Since chronically elevated $[Ca^{2+}]_i$ can have detrimental effects on cell survival and physiology through numerous mechanisms [15] and chronic hyperglycaemia will lead to long-term increases in cytosolic Ca^{2+} that may be proapoptotic and induce β -cell dysfunction [12,16].

In the normal pancreatic β -cell, glucose metabolism thus leads to insulin secretion via coupling to electrical excitation [17]. In diabetes, this link will normally be maintained, such that ‘hyperstimulation’, that is exposure to elevated glucose, will be coupled to electrical ‘hyperexcitation’ (figure 1) and chronically elevated $[Ca]_i$, such that detrimental consequences cannot be causally separated. However, by removing the K_{ATP} channel sensitivity to metabolic state, this link can be broken and the effects of hyperstimulation of metabolism and hyperexcitation can be separated.

Glucose Stimulation and Electrical Stimulation are Coupled Through the K_{ATP} Channel

The pancreatic K_{ATP} channel is a unique hetero-octameric complex of two separate proteins: the sulphonylurea receptor (SUR1) subunit and the pore-forming (Kir6.2) subunit [18]. Nucleotide regulation of K_{ATP} channels is unique among K^+ channels: the channel is rapidly and reversibly inhibited by binding of cytoplasmic adenosine nucleotides and exhibits complex activation by nucleotide tri- and diphosphates [18,19]. Inhibition results from ATP binding to the Kir6.2 subunit, whereas Mg ADP activates the K_{ATP} channel by binding to the SUR subunit [20], which is also the site of action of pharmacological channel openers and blockers [21–23]. Sulphonylureas (SUs), such as tolbutamide and glibenclamide (glyburide) inhibit K_{ATP} channel activity, causing membrane depolarization and triggering of insulin secretion. These drugs therefore can uncouple metabolism from electrical activity and are widely used to treat type-2 diabetes, stimulate insulin secretion independently of the metabolic state of the β -cell. Conversely, KCOs, such as diazoxide, activate K_{ATP} channels, thereby electrically silencing the cell at elevated [glucose], and inhibiting insulin secretion [18]. As discussed below, the ability to pharmacologically uncouple metabolism from electrical activity, either by SUs (making the cell electrically active at any [glucose]) or diazoxide (making the cell electrically silent at any [glucose]) together with the ability to genetically manipulate excitability by knockout or transgenic mutation of the K_{ATP} channels to render them ATP insensitive have provided dramatic new insights to the question of hyperstimulation vs. hyperexcitation and to the chronic consequences for β -cell function.

In Vivo Consequences of Genetically Uncoupled Metabolism-Excitation

Following the cloning of K_{ATP} channel subunits, genetic manipulation in mice, both by classical knockout approaches and transgenic approaches, based on understanding of how to manipulate ATP sensitivity and activity by key mutations, have permitted the *in vivo* study

of islet function after uncoupling metabolism from excitability. As schematized in figure 1, normal islets are not excited at 'non-stimulatory' [glucose], and only excited at stimulatory [glucose]. Islets lacking K_{ATP} channels (e.g. $SUR1^{-/-}$ and $Kir6.2^{-/-}$) will be chronically excited, even when metabolism is not stimulated (pink). Conversely, islets with ATP-insensitive K_{ATP} subunits (e.g. $Kir6.2[\Delta N30]$) will be inexcitable, even when metabolism is stimulated (blue).

Uncoupled by Chronic Hyperexcitability

$Kir6.2^{-/-}$ and $SUR1^{-/-}$ mice [24–26] as well as mice expressing dominant-negative $Kir6.2$ mutant transgenes in β -cells ($Kir6.2[AAA]$ [27] or $Kir6.2[G132S]$ [28]) have been generated. $Kir6.2^{-/-}$, $SUR1^{-/-}$, and $Kir6.2[G132S]$ mice show the same complex, unexpected, phenotype. Completely lacking any β -cell K_{ATP} channels [24–26], the islets in these mice are all hyperexcited, with chronically elevated $[Ca^{2+}]_i$, as expected. These animals reportedly show the expected transient hyperinsulinemia and hypoglycaemia as neonates, but islets from adult $SUR1^{-/-}$ or $Kir6.2^{-/-}$ mice show a dramatic loss of insulin secretion at all [glucose] [24–26]. In $Kir6.2[G132S]$ mice, loss of β -cell mass was reported [28], although hyperglycaemia was apparently spontaneously improved and insulin content even increased in older mice [29]. In our experience, both $SUR1^{-/-}$ and $Kir6.2^{-/-}$ exhibit normal islet morphology and insulin content throughout adulthood [30].

β -Cell-specific $Kir6.2[AAA]$ dominant-negative mice lose K_{ATP} channel activity in only ~70% β -cells. With ~30% residual K_{ATP} conductance, metabolism-excitation is not completely uncoupled and excitation and insulin secretion are only left-shifted relative to normal [27] (figure 1) in these animals, which exhibit elevated circulating insulin levels that persists through adulthood [27]. Heterozygous $Kir6.2^{+/-}$ and $SUR1^{+/-}$ mice, with ~60% reduction in K_{ATP} density in every cell, show a similar phenotype [30]. These animals show no tendency for insulin secretion to be suppressed, and they again maintain essentially normal insulin content and islet morphology through adulthood.

Thus, $Kir6.2^{-/-}$ and $SUR1^{-/-}$ mice (100% reduction in K_{ATP} density) are glucose-intolerant, but heterozygous $Kir6.2^{+/-}$ and $SUR1^{+/-}$ mice, as well as $Kir6.2[AAA]$ mice all show enhanced glucose-tolerance and increased glucose-stimulated insulin secretion (GSIS) [30]. In all these models, there is marked ($SUR1^{-/-}$, $Kir6.2^{-/-}$) or relative hyperexcitation ($Kir6.2^{+/-}$, $SUR1^{+/-}$, $Kir6.2[AAA]$), but in each case, there is minimal evidence of cell death or ER stress, and there is no chronic loss of insulin content or marked changes in islet morphology. This argues that *in vivo*, chronic excitation and chronically elevated $[Ca^{2+}]_i$ are not *per se* detrimental to the β -cell and do not affect β -cell survival.

There is, however, a dramatic reduction of insulin secretion in the most severely hyperexcited ($SUR1^{-/-}$, $Kir6.2^{-/-}$, $Kir6.2[G132S]$) models [24–26]. We have proposed an 'inverse U' model to explain this secondary response to enhanced excitability [31], in which excessive hyperexcitability drives β -cells to insulin secretory failure without cell death [17]; mice with genetically reduced K_{ATP} channel activity shows hyperinsulinism, but mice with complete loss of K_{ATP} (K_{ATP} knockout mice) progress 'over the top' to the unexpected insulin undersecretory phenotype. Importantly, this phenotype was reiterated by chronic pharmacologic block of K_{ATP} *in vivo*, in mice implanted with slow-release SU (glibenclamide) pellets [32]. Pellet-implanted wild-type mice became progressively and consistently glucose-intolerant, with greatly reduced insulin secretion in response to glucose, such that after only 1 week of treatment, these mice were as glucose intolerant as adult K_{ATP} knockout mice, and freshly isolated islets from these glibenclamide-implanted animals showed as marked a reduction of secretory capacity as K_{ATP} knockout islets. Strikingly, however, secretory capacity was fully restored in islets isolated from pellet-implanted mice

within hours of drug washout *ex vivo* [32]. These results show that chronic glibenclamide treatment causes loss of insulin secretory capacity due to β -cell hyperexcitability, but further reveal the rapid reversibility of this secretory failure, again arguing against β -cell apoptosis or other cell death being induced by hyperexcitation [32].

Uncoupled by Chronic Inexcitability

The link between metabolism and excitation is also removed by making K_{ATP} channel activity insensitive to the inhibitory effects of ATP (figure 1). In this case, islets can be metabolically hyperstimulated but are actually underexcited. Site-directed mutagenesis studies on cloned K_{ATP} channels revealed that many mutations can significantly reduce or even abolish ATP inhibition [18]. Truncations of 10–30 amino acids from the Kir6.2 N-terminus, as well as point mutations throughout the N- and C-terminal regions of Kir6.2 all significantly decrease ATP sensitivity [33]. *In vivo*, such mutations will result in ‘overactive’ β -cell channels and will be expected to markedly decrease excitability, and hence suppress GSIS. Confirming this prediction, mice expressing mutant K_{ATP} channels with reduced ATP sensitivity only in pancreatic β -cells (Kir6.2[Δ N2-30]) developed severe neonatal diabetes mellitus (NDM) and died within days of birth [34]. This study predicted the subsequent demonstration that similar ATP insensitive gain-of-function (GOF) mutations in Kir6.2 and SUR1 are common causes of transient (TNDM) and permanent (PNDM) human neonatal diabetes [35,36]. We and others have now engineered second generation, inducible K_{ATP} GOF transgenic mice under Cre-recombinase control [37,38]. Both rat insulin promoter (Rip-Cre)- [39] and tamoxifen-inducible Pdx1PBCre^{ERTM} [40] (Pdx-Cre)-driven transgenes lead to severe glucose-intolerance, around weaning (Rip-Cre), or within 2 weeks after tamoxifen injection (Pdx-Cre) and progress to severe diabetes [37,38].

Inexcitability removes the trigger to insulin secretion, and so primary diabetes is expected in these animals. However, they also reveal dramatic secondary consequences that are not trivially predicted. The animals show growth retardation and dramatic reduction of insulin content, accompanied by profound loss of β -cell mass over time [37]. The question arises: are these secondary effects a consequence of the inexcitability or of the resultant hyperglycaemia? Importantly, syngeneic islet transplantation or chronic treatment with glibenclamide, initiated prior to tamoxifen induction, not only prevented the development of diabetes but also maintained both pancreatic islet architecture and β -cell mass [37]. This argues quite strongly that the secondary consequences are due to the systemic hyperglycaemia, and therefore represent ‘glucotoxic’ effects of ‘hyperstimulation’ of metabolism, but without ‘hyperexcitation’, and $[Ca^{2+}]_i$ remains low at all [glucose], whether the animals are diabetic or protected from diabetes by syngeneic transplant [41].

Thus, in this case, we can clearly ascribe the detrimental effects of glucose ‘hyperstimulation’ to mechanisms that are restricted to upstream of electrical excitation, $[Ca^{2+}]_i$ and insulin secretion. A clue to potential mechanisms is provided by analysis of $[Ca^{2+}]_i$ in these islets [38,41]. Elevated $[Ca^{2+}]_i$ enhances Ca^{2+} uptake into the mitochondria, which can stimulate oxidative phosphorylation and ATP synthesis via activation of several dehydrogenases [42,43]. Endogenous islets from K_{ATP} -GOF mice that were protected from hyperglycaemia by transplant with normal islets showed a small increase in NAD(P)H at intermediate glucose levels between 6–10 mM [41], consistent with a loss of Ca^{2+} -dependent activation of the respiratory chain [44], which otherwise occurs in normal islets at intermediate and higher glucose levels. However, as discussed below, further altered metabolism and mitochondrial function is found secondary to systemic diabetes, and these may also be important contributors to secondary changes in islet function.

Ex Vivo Consequences of Genetically Uncoupled Metabolism-Excitation

The above studies show that *in vivo*, hyperstimulation of metabolism and hyperexcitability can be uncoupled genetically, and the primary driver of β -cell dysfunction is then glucotoxicity via direct effects of glucose, or by stimulation of metabolism, without chronic toxic effects of hyperexcitability, elevated $[Ca^{2+}]_i$ or insulin hypersecretion. However, these studies do not rule out a modulatory effect of excitability on a primary glucotoxic action through metabolism. Many studies have showed that isolated islets exposed to hyperglycaemia exhibit negative consequences, some of which can be delayed or avoided by inhibition of secretion via inhibition of excitation. Islets incubated in high glucose in the presence of diazoxide have preserved insulin content, supporting the hypothesis that rest from hyperexcitability and chronically elevated $[Ca^{2+}]_i$ is protective against insulin depletion and perhaps against Ca^{2+} -dependent apoptosis [14,45–47]. Human islets exposed to chronic high glucose *in vitro* have been reported to exhibit elevated basal Ca^{2+} and loss of glucose-induced rise in cytosolic $[Ca^{2+}]_i$, effects that were again reversed by diazoxide [48].

Such *in vitro* studies show an electrical excitability-dependent loss of β -cell insulin content in high glucose, which is rapidly restored after exposure to non-stimulatory glucose, suggesting β -cell ‘exhaustion’ with a physical depletion of the insulin stores, but not glucotoxicity and β -cell death. We have compared the responses of isolated islets from WT, K_{ATP} -GOF and K_{ATP} knockout (KO) mice to incubation in high or low glucose, to directly assess the role of β -cell excitability in the islet response to hyperglycaemia, without the interference of systemic changes associated with hyperglycaemia *in vivo*. Isolated islets were cultured in low (5 mM) vs. high (30 mM) glucose media. Within a few days, WT islets lost significant insulin content in high glucose but not in low glucose conditions. Only a small decrease was observed in K_{ATP} -GOF islets in either high or low glucose conditions, but there was significant loss of insulin content in both low and high glucose, in K_{ATP} -KO islets (Z. Wang, C. G. Nichols and M. S. Remedi, unpublished results). Over 10 days, there was no change in islet survival in any groups. Notably, the decrease in insulin content in WT islets was recoverable when high glucose was replaced with low glucose, over 3 days. These data lead us to conclude that: *in vitro*, (i) hyperglycaemia decreases islet insulin content, but does not change islet survival over 10 days; (ii) insulin content in response to hyperglycaemia correlates with β -cell excitability, suggesting that (iii) it is a direct, reversible, result of hyperstimulation and hypersecretion. Thus, reduced membrane excitability protects against loss of insulin content *in vitro* and argues against an acute role of inexcitability and low $[Ca^{2+}]_i$ in β -cell death.

As discussed above, a marked reduction of insulin content, β -cell mass and insulin mRNA clearly develops *in vivo* in the islets with reduced membrane excitability in diabetic K_{ATP} -GOF mice [37,38], a result of chronic systemic diabetes, similar to what is observed in other rodent diabetic models [49–56]. The lack of reduction in β -cell mass in K_{ATP} -GOF islets chronically incubated in high glucose *in vitro* is also consistent with other islet studies [16,52,57]. Conversely, islets with genetically or chronically pharmacologically increased membrane excitability and $[Ca^{2+}]_i$ show preserved insulin content *in vivo* [24–27,32]. These results thus argue against hyperexcitability and high $[Ca^{2+}]_i$ *per se* as being causal in loss of insulin content or β -cell death [12,16,58].

Human Diseases of Uncoupled Metabolism-Excitation: Recapitulation of – and Implications from – Mouse Models

In humans, loss-of-function (LOF) mutations in K_{ATP} genes are major causes of congenital hyperinsulinism (HI) [59–62]. While heterozygous $Kir6.2^{+/-}$ and $SUR1^{+/-}$ mice, with ~60% reduction in K_{ATP} density in every β -cell, show a similar phenotype [30], $Kir6.2^{-/-}$ and

SUR^{-/-} mice (both with 100% reduction in K_{ATP} density) are actually glucose-intolerant. Even though complete lack of K_{ATP} activity has been reported in β -cells from some HI patients [63], the phenotype of many HI mutations would suggest that K_{ATP} is not always completely absent [60,64–66], and both active K_{ATP} channels and diazoxide sensitivity have been detected in some patients [67,68]. The progress of HI can be complex and, although surgical removal of the overactive pancreatic tissue may result in diabetes, it is also observed that some non-surgically treated patients spontaneously cross-over to diabetes anyway [60,69,70]. Our apparent recapitulation of this complex phenotype in mice with variable loss of K_{ATP} channels suggests that similar mechanisms may be operating in mice and humans. It is now also clear that GOF mutations in Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) are common causes of human TNDM and PNDM [35,36]. This finding has led to improved control of blood sugars, as well as dramatic lifestyle improvements, since therapy can be switched from insulin injections to oral SUs, in the presence of which intact incretin responses lead to quasi-physiological insulin secretion patterns [71]. Although the majority of NDM has been successfully treated with SU, the ability to transfer from insulin to SU seems to be negatively correlated with the severity and the duration of the disease [71]. We have shown that prolonged hyperglycaemia gradually leads to islet disappearance and loss of insulin content in K_{ATP}-GOF mice, as secondary consequences of the systemic diabetes. These consequences were abrogated by tight glucose control from disease onset, whether by transplantation of normal islets or by SU treatment at the disease onset [37,72]. We also showed that if SU therapy is initiated after severe diabetes has developed; the treatment is ineffective, because of the already marked loss of insulin content [37].

These experiments raise the question of how reversible is the loss of insulin content in untreated animals and perhaps in humans with long standing NDM. In NDM patients on SUs, there is typically a reduction in SU dose requirement with time after transfer to SU therapy that is correlated with improved control of blood sugar levels [71]. We showed that severely diabetic K_{ATP}-GOF mice show a secondary increase in glucose metabolism at non-stimulatory glucose [41] while normoglycemic (glibenclamide-treated) K_{ATP}-GOF mice compensate with an increase in the peripheral insulin sensitivity [72]. We also find that while insulin content is greatly depressed in islets from animals that have become diabetic after disease induction, it is apparently restored in islets from such animals within 1 month after normalization of blood sugar levels by aggressive insulin treatment (Z. Wang, C.G. Nichols and M.S. Remedi, unpublished results). This result is significant for two reasons. Firstly, it suggests that even after long-standing diabetes has led to secondary loss of β -cell insulin content in NDM patients, tight glycaemic control may in fact restore normal endogenous β -cell insulin content, which would then presumably restore or enhance SU sensitivity. In this context, this result argues that whatever the ‘glucotoxic’ effects that lead to β -cell ‘damage’ in these non-excited islets, it is still reversible. It is important to note that in this scenario, removal of the ‘hyperstimulation’ of hyperglycaemia rests the β -cells from hyperstimulation of metabolism, but the islets are inexcitable throughout, and hence there is no involvement of ‘rest’ from hyperexcitation or hypersecretion.

β -Cell Exhaustion and Hyperexcitability?

There has been much interest in the notion that β -cells become ‘exhausted’ because of the excess demands of secretion induced by hyperglycaemia in the diabetic state and that exogenous insulin treatment leads to ‘ β -cell rest’ in type-2 diabetes, which permits restoration of β -cell function [73,74]. Alvarsson et al. [75] directly compared relief by insulin vs. diazoxide in newly diagnosed (and only mildly hyperglycemic) type-2 diabetic patients. Glucose control was similar during the first 2 years of the study, but with better endogenous insulin secretion in the insulin-treated group, although after 4 years, this difference disappeared and C-peptide responses were similarly reduced in both groups [76],

indicating that in human type-2 diabetes, a prolonged beneficial effect is present. Similarly, a 3-month diazoxide treatment period delayed the decline of endogenous insulin secretion in patients with adult [77] and childhood [78] onset type-1 diabetes. In contrast, no beneficial effect was seen in a study in type-2 diabetic patients who received only oral treatment, presumably because the inhibitory effect of diazoxide on endogenous insulin secretion was not compensated by exogenous insulin [79]. In normal islets, either insulin or diazoxide therapy will cause reduced secretion from the endogenous islets. As discussed, K_{ATP} -GOF mice transplanted with normal islets under the kidney capsule show avoidance of systemic diabetes and K_{ATP} -GOF mice with long-standing diabetes show normalization of blood glucose by chronic insulin treatment, accompanied by restoration of insulin content and SU drug responsiveness. Essentially, these islets from K_{ATP} -GOF mice are primarily resting in terms of excitability, $[Ca^{2+}]_i$ and insulin secretion. Our results therefore point to rest from hyperstimulation of metabolism, or from some other action of hyperglycaemia upstream of hyperexcitability, as the key mechanism of the recovery.

The Role of Excitability in Glucose ‘Hyperstimulation’: Conclusions and Implications

There is much evidence that a ‘glucotoxic’ effect, which leads to pancreatic β -cell dysfunction, reduced β -cell mass and insulin deficiency, is an important part of diabetes pathology. In the diabetic state, the notion of β -cell ‘hyperstimulation’ as a result of the ambient hyperglycaemia, leading to β -cell ‘exhaustion’, is often invoked. Glucose hyperstimulation will normally lead to hyperstimulated metabolism, inhibited K_{ATP} , elevated $[Ca^{2+}]_i$ and hyperstimulated secretion. Thus, at least a part of the consequence of ‘hyperstimulation’ by glucose has been suggested to be linked to ‘hyperexcitability’, chronically elevated $[Ca^{2+}]_i$, and chronic hypersecretion. This link is lost when the [glucose]- K_{ATP} channel activity link is broken, either pharmacologically or genetically. Animal experiments reveal that hyperexcitability *per se* does not lead to β -cell death *in vivo*. Conversely, even in chronically underexcited, non-secreting, islets, systemic diabetes leads to dramatic loss of β -cell insulin content, which may be reversible following lowering of blood glucose. These results matched by findings in the equivalent human conditions of congenital HI and neonatal diabetes, thus point to the diabetic ‘glucotoxic’ effect as being a result of hyperstimulation of metabolism, not of excitation and secretion. They thus suggest that rest from hyperstimulation of metabolism, or from some other action of hyperglycaemia upstream of hyperexcitability, may be the key mechanism in the recovery resulting from insulin-driven ‘ β -cell rest’. Such a mechanism may also be key to the beneficial effects of insulin therapy in type-2 diabetes, and it may be that more emphasis should be placed on the idea of rest from metabolic stimulation than the idea of rest from secretion.

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Figure 1.

Dependence of islet excitation and intracellular $[Ca^{2+}]$ on stimulatory [glucose]. In the normal wild type (WT) pancreatic β -cell, elevated [glucose] leads to insulin secretion via coupling to electrical excitation. By removing the K_{ATP} channel sensitivity to metabolic state, this link can be broken and the effects of hyperstimulation of metabolism and hyperexcitation can be separated. Islets lacking K_{ATP} channels (e.g. $SUR1^{-/-}$ and $Kir6.2^{-/-}$) will be chronically excited, even when metabolism is not stimulated (pink). Conversely, islets with ATP-insensitive K_{ATP} subunits (e.g. $Kir6.2[\Delta N30]$) will be inexcitable, even when metabolism is stimulated (blue).