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Mouse Models of β-cell K_{ATP} Channel Dysfunction

Melissa F Brereton and **Frances M Ashcroft**
Henry Wellcome Centre for Gene Function, Department of Physiology, Anatomy and Genetics, and OXION Centre for Ion Channel Studies, Sherrington Building, Parks Road, Oxford OX1 3PT, UK

Abstract

ATP-sensitive K^+ (K_{ATP}) channels in pancreatic β-cells couple glucose metabolism to insulin secretion. Reduced K_{ATP} channel activity produces excessive insulin release and hyperinsulinism whereas increased K_{ATP} channel activity leads to lower insulin secretion and diabetes. Paradoxically, mice with genetic deletion of K_{ATP} channels, or loss-of-function mutations, are only transiently hypoglycaemic during the neonatal period and often display reduced glucose-stimulated insulin secretion subsequently. Mice with K_{ATP} channel gain-of-function mutations are hyperglycaemic and have impaired glucose-stimulated insulin secretion, a phenotype that accurately mimics human diabetes. This review discusses how mice expressing altered K_{ATP} channels have provided valuable insight into β-cell function.

Introduction

Blood glucose homeostasis is essential: too little glucose rapidly results in brain damage whereas elevation of blood glucose for an extended period leads to the complications of uncontrolled diabetes - retinopathy, nephropathy, and micro- and macro-vascular disease. Insulin is the only hormone capable of reducing blood glucose, which is why its impaired secretion can lead to diabetes (too little secretion) or hyperinsulinism (too much release). The mechanisms controlling insulin secretion from pancreatic β-cells are well understood and lessons from over 20 years of molecular, structural and whole animal studies have highlighted the essential role of the ATP-sensitive K^+ (K_{ATP}) channel. In this review, we discuss the physiological and pathophysiological roles of K_{ATP} channels in controlling β-cell function in health and disease. Focusing specifically on animal models of K_{ATP} channels, we highlight how their study has advanced our understanding of β-cell dysfunction in metabolic disease.

Physiological role of K_{ATP} channels in β-cells

K_{ATP} channels link changes in circulating blood glucose to alterations in β-cell activity and insulin secretion. They are large macromolecular complexes composed of four Kir6.2 subunits, which form a central K^+-selective pore, and four regulatory sulphonylurea (SUR) subunits, which modify and regulate the channel's properties. In β-cells, the K_{ATP} channel is

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composed of Kir6.2 and SUR1 isoforms [1,2]. Its activity is regulated by intracellular adenine nucleotides, being inhibited by binding of ATP to Kir6.2 and stimulated by MgATP/MgADP interaction with the nucleotide-binding domains of SUR1 [3,4]: the balance between these competing actions determines the level of K_{ATP} channel activity.

Electrophysiology studies in isolated pancreatic β-cells have demonstrated that increased glucose metabolism, elicited by a rise in blood glucose, promotes intracellular ATP formation and closure of K_{ATP} channels [5] (Figure 1A). The resulting membrane depolarisation opens voltage-gated Ca^{2+} channels, thereby permitting Ca^{2+} influx and exocytosis of insulin granules. Conversely, K_{ATP} channels open when metabolism falls in response to reduced blood glucose, which hyperpolarises the β-cell membrane potential and prevents electrical activity and insulin secretion (Figure 1B). Channel activity is also inhibited by sulphonylurea (SU) drugs, which bypass metabolic regulation and stimulate insulin secretion directly [6]: they are widely used to treat type 2 diabetes mellitus (T2DM).

Pathophysiological role of K_{ATP} channels in β-cells

Given the crucial role K_{ATP} channels play in controlling insulin secretion, it is not surprising that diseases characterised by excessively high, or low, circulating glucose are associated with altered K_{ATP} channel expression and/or function. Below, we highlight three diseases where K_{ATP} channel dysfunction is a common factor.

Congenital Hyperinsulinism

Loss of K_{ATP} channel activity leads to congenital hyperinsulinaemia (CHI), which is characterised by continuous and unregulated insulin secretion in response to low blood glucose levels [7–9]. It affects around 1 in 50,000 live births and patients present early in life with hypoglycaemia. If left untreated, it can cause brain damage. Over 100 loss-of-function mutations in Kir6.2 and SUR1 have been associated with CHI. Some affect the expression, maturation, assembly or trafficking of the K_{ATP} channel, resulting in a lower channel density. Others prevent the ability of MgADP/MgATP to stimulate channel activity. All mutations lead to a loss of K_{ATP} channel activity that causes permanent depolarisation of the β-cell membrane and excessive insulin secretion (Figure 2A).

Patients with mutations that cause mild CHI can sometimes be treated by diet or oral administration of the K_{ATP} channel activator, diazoxide [10]; this implies K_{ATP} channels are present in their β-cells but that they fail to open when blood glucose levels fall. Patients with functionally more severe CHI mutations (that prevent the channel from reaching the plasma membrane), fail to respond to diazoxide therapy and are usually treated by sub-total pancreatectomy. In individuals with embryonic loss of heterozygosity, leading to focal homozygous expression of a paternally derived mutation, the lesion can often be revealed by 18-fluoro L-3,4-dihydroxyphenylalanine (^{18}F(DOPA) positron emission tomography (PET) scanning and its surgical removal can result in a cure [11]. In diffuse CHI, where up to 80% of the pancreas may require removal, patients are at increased risk of subsequently developing diabetes. Alternative methods to treat these patients would be valuable. Although most diffuse CHI mutations are inherited recessively, a few are inherited in a dominant

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fashion. Some dominant mutations cause mild CHI that does not require pancreatectomy and may even predispose to type 2 diabetes in later life [12,13].

Neonatal Diabetes

Neonatal diabetes (ND) is characterised by severe hyperglycaemia within the first six months of life. It can be caused by mutations in a number of genes, including those encoding Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) [8,14,15]. Gain-of-function mutations render the K_{ATP} channel inappropriately active and its failure to close in response to glucose metabolism means that insulin secretion is prevented, even when blood glucose is elevated (Figure 2B). Prior to the discovery that ND can be caused by K_{ATP} channel mutations, patients required daily insulin injections to maintain normoglycaemia. Now ~90% of ND patients diagnosed with K_{ATP} channel mutations have transferred to oral SU drugs, which block the K_{ATP} channel and thereby stimulate insulin secretion [16].

Some ND mutations, with severe functional effects, lead to diabetes that is accompanied by neurological problems such as developmental delay, epilepsy and muscle hypotonia [14,17]. This condition, termed DEND syndrome, affects ~3% of patients; rather more (~20%) show developmental delay but not epilepsy and are said to have intermediate DEND syndrome. Electrophysiology studies of ND mutant channels expressed in a heterologous system reveal a correlation between the magnitude of K_{ATP} current at physiologically relevant ATP concentrations and the clinical phenotype: the larger the current, the more severe the disease [18]. It is now clear that the neurological phenotype is not a secondary consequence of hyperglycaemia, but due to expression of the mutant K_{ATP} channel in neurones [19].

Type 2 Diabetes Mellitus (T2DM)

T2DM is also characterised by reduced β-cell function and reduced glucose-dependent insulin secretion [20]. It develops in later life and is extremely common, affecting 336 million people worldwide. T2DM has multiple aetiologies and is also influenced by environmental and lifestyle factors, such as age and obesity. Genetic polymorphisms that predispose to T2DM occur in a large number of genes. Of relevance here, however, is that two common variants in the K_{ATP} channel genes *KCNJ11* (Kir6.2-E23K) and *ABCC8* (SUR1-S1369A) which are in strong linkage disequilibrium (i.e. individuals carry both variants) predispose to T2DM [21,22]. In heterologous studies, the K23/A1369 variant causes a mild decrease in channel inhibition by ATP, but which variant is the more important remains controversial [23,24] and how these variants lead to diabetes in later life is unclear. Mouse models may help answer these questions.

T2DM is initially managed with diet and lifestyle modifications. As the disease progresses, pharmacological intervention is required and patients may switch first to oral SU therapy and subsequently to insulin. Why SU therapy eventually fails in T2DM but not ND, and why hypoglycaemia is less common in ND patients, is still unclear. Potentially, animal models may help resolve this puzzle.

Mouse models of β-cell K_{ATP} channel function

Why use mouse models to study metabolic disease?

The use of the mouse as a model system to study the molecular mechanisms of human disease is well established. Its many advantages include the fact that the mouse is mammalian, has a short life cycle, and the full genomic sequence of the C57BL/6J strain is available. Furthermore, such is the elegance of the molecular biology techniques used to generate genetically modified mice that a single nucleotide base pair can be changed and its effect studied in a specific cell type and/or at a defined time-point during the mouse's life.

Mouse models have been employed for both *in vivo* and *in vitro* studies of metabolic disorders including diabetes. The latter is especially useful, as access to human islets, and diabetic islets in particular, is limited. However, like any animal model, extrapolation of findings in a diabetic mouse to human diabetes has to be made with caution. The difference in size and circadian rhythm between the two species can influence metabolism and hormone secretion, and differences in islet architecture and the ion channels that underlie action potential firing in β-cells are also evident [25,26]. Despite these potential caveats, however, mouse models have proven valuable for elucidating the molecular mechanisms underlying β-cell dysfunction in diabetes and, to a lesser extent, CHI.

K_{ATP} Channel Loss-of-function Mouse Models: ß-cell Hyperexcitability

Mouse models of CHI have been generated by genetic deletion of Kir6.2 ($Kir6.2^{-/-}$) and SUR1 ($SUR1^{-/-}$) or loss-of-function mutations in these genes (Figure 3, Table 1). Unexpectedly, however, these models do not fully recapitulate the human phenotype.

$Kir6.2^{-/-}$ mice showed transient neonatal hypoglycaemia but subsequently became normoglycaemic, normoinsulinaemic and displayed mild glucose intolerance (Table 1) [27,28]. A similar phenotype was observed in mice expressing the human CHI homozygous mutation Kir6.2-Y12X (Table 1) [29]. In $Kir6.2^{-/-}$ mice there was a marked reduction in insulin secretion both *in vivo* and *in vitro* following glucose, arginine or GIP stimulation, despite enhanced insulin sensitivity [27,28,30,31]. Although K_{ATP} currents were absent, leading to spontaneous electrical activity at low glucose, there was only a modest increase in basal intracellular $[Ca^{2+}]_i$ and insulin secretion from freshly isolated islets [31]. However, when cultured overnight, islets exhibited increased basal $[Ca^{2+}]_i$ [27,31], and restored glucose-stimulated insulin secretion [31].

$SUR1^{-/-}$ mice were hypoglycaemic on the first day of life, but subsequently became normoglycaemic and showed impaired glucose tolerance [32,33]. Like $Kir6.2^{-/-}$ mice, freshly isolated islets showed impaired insulin secretion [32,34], but following overnight culture, resting $[Ca^{2+}]_i$ and basal insulin secretion were elevated, and glucose-stimulated insulin release was greater than in control islets [34,35]. Unlike $Kir6.2^{-/-}$ mice [30], $SUR1^{-/-}$ mice showed impaired GLP-1-mediated insulin secretion, despite normal cAMP levels [36]. This may reflect the fact that SUR1 interacts with Epac2, which mediates the PKA-independent effect of cAMP on exocytosis [37]: perhaps SUR1 serves as a scaffold protein to anchor Epac2 in the correct location. The reduced GLP-1 response may account for the impaired oral glucose tolerance [33] and lack of post-prandial hypoglycaemia [32]. In

contrast to Kir6.2$^{-/-}$ mice, insulin sensitivity was normal [32]: this is expected because skeletal muscle K_{ATP} channels are composed of Kir6.2/SUR2 subunits rather than Kir6.2/SUR1 subunits [18].

Why Kir6.2$^{-/-}$ or SUR1$^{-/-}$ mice fail to show a hypoglycaemic/hyperinsulinaemic phenotype is unclear. No evidence for β-cell loss has been reported for these mice [27,28,30,32]. It has been proposed that hyperexcitability drives the β-cell into secretory failure [38]. Others have suggested that an inhibitory signal constrains release *in vivo* [35], or a reduced incretin response may also contribute [30,33,36].

Interestingly, heterozygous knockout of K_{ATP} channels in β-cells (Kir6.2$^{+/-}$, SUR1$^{+/-}$; 60-70% reduction in functional channels) resulted in hyperinsulinaemia, enhanced glucose tolerance and increased glucose-stimulated insulin secretion, despite no change in islet size or composition (Table 1) [28]. A similar result was observed for mice expressing a dominant negative transgene (Kir6.2-AAA residues 156-158), selectively in ~70% of β-cells [28,39,40]. However, Kir6.2$^{+/-}$, SUR1$^{+/-}$ and Kir6.2-AAA mice do not perfectly mimic human CHI as they are normoglycaemic (Table 1).

K_{ATP} Channel Gain-of-function Mouse Models: ß-cell Hypoexcitability

A mouse model of enhanced K_{ATP} channel activity was first described by Nichols and colleagues [39] (Figure 3, Table 1). Expression of Kir6.2 with an N-terminal truncation of 30 amino acids (Kir6.2-ΔN30), resulted in a 7-fold reduction in ATP inhibition. Transgenic mice with this mutation were severely hyperglycaemic and hypoinsulinaemic, and died within 5 days of birth. No abnormalities in islet size and distribution were observed but there was a decrease in insulin-positive β-cells and an increase in glucagon-positive α-cells, as seen in islets from patients with T2DM [41]. Addition of a point mutation at residue 185 (Kir6.2-ΔN30,K185Q) and targeted expression of the Kir6.2-ΔN30,K185Q transgene to β-cells in adult life using Cre-lox technology, also resulted in hyperglycaemia and undetectable levels of circulating insulin, due to impaired glucose-stimulated insulin secretion [42]. This was attributed to a failure of glucose to elevate intracellular calcium, as a result of the K_{ATP} channel hyperactivity [43].

A second mouse model of ND has also been generated that expresses a human Kir6.2 mutation (V59M) under the control of the endogenous ROSA26 promoter: this drives relatively weak expression and mimics the heterozygous state observed in ND patients [44] (Figure 3, Table 1). Kir6.2-V59M mice were hyperglycaemic, hyperinsulinaemic and hyperglucagonaemic by 5 weeks of age. Insulin content and β-cell area were reduced and islet architecture affected [44], as also seen in Kir6.2-ΔN30,K185Q mice [42], and β-cell proliferation decreased [45].

In islets isolated from Kir6.2-V59M mice, addition of the sulphonylurea tolbutamide to block K_{ATP} channels restored glucose-stimulated insulin secretion and normal Ca^{2+} dynamics [44]. This suggests that the mutant β-cells retain their capacity to produce and secrete insulin confirming the defect lies in K_{ATP} closure and explaining why ND patients respond to SU therapy. Further evidence for this idea comes from the fact that transplantation of normal islets under the kidney capsule, or administration of SUs in the

form of a subcutaneous pellet prior to gene induction, prevented the development of hyperglycaemia, hypoinsulinaemia and loss of islet insulin content and β-cell architecture in Kir6.2-ΔN30,K185Q mice [42]. This has important implications for ND patients as it highlights the need for rapid transfer to SUs following diagnosis. No mice expressing K_{ATP} channels with a gain-of-function SUR1 mutation have yet been reported.

The Future: K_{ATP} Channels, β-cells and Disease

Collectively, these mouse models highlight the importance of K_{ATP} channel activity for regulating β-cell function and insulin secretion. They have also been helpful in understanding the molecular mechanisms that underlie altered insulin secretion in ND caused by gain-of-function K_{ATP} channel mutations. Furthermore, they serve as a valuable tool for exploring how SU treatment may prevent or reverse disease progression in ND patients. Potentially, mice expressing gain-of-function K_{ATP} channel mutations selectively in pancreatic β-cells may also be used to explore the effects of hypoinsulinaemia/hyperglycaemia on both pancreatic function and extra-pancreatic tissues. Their advantages over other models of T2DM are that they exhibit a known genetic defect that is confined to the β-cell, and that can be reversed by SU or insulin therapy. Models of CHI have been less successful as they fail to recapitulate human CHI and illustrate the point that it is wise to confirm all data obtained from mouse models in humans, wherever possible. Nevertheless, they too have provided valuable insight into β-cell function.

Despite significant progress gained from studies of mouse models in recent years, much remains to be done. It will be interesting, for example, to determine the effects of β-cell specific knockout models and SUR1 gain-of-function mutations. No doubt, they will provide further insight into β-cell function as well as human disease.

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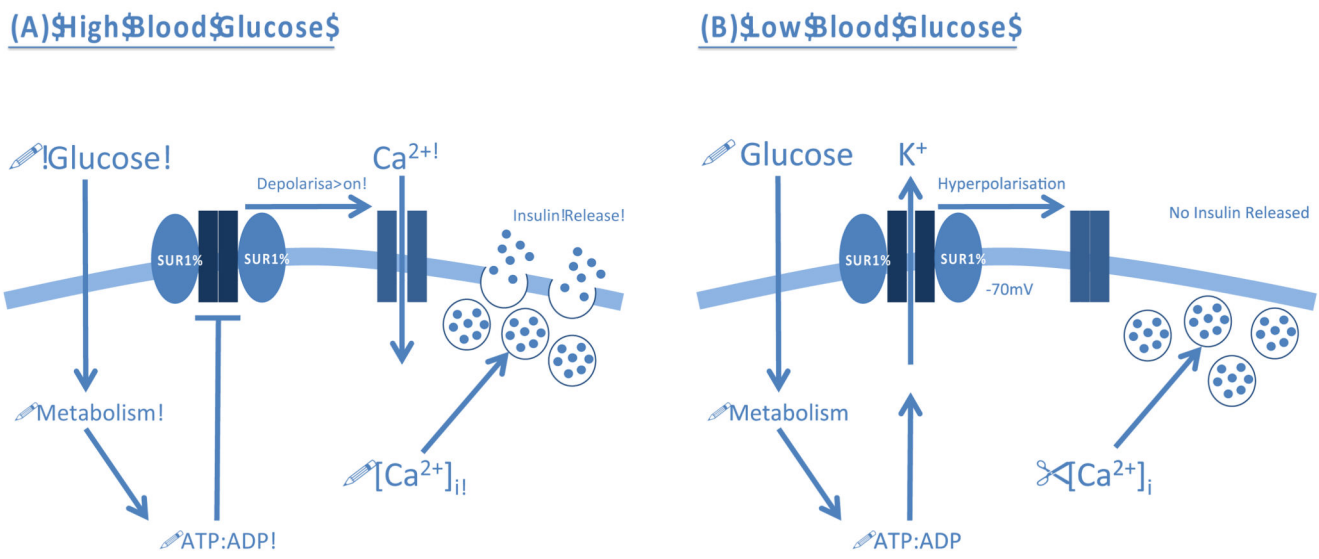

Figure 1. Physiological role of ATP-sensitive K^+ Channels (K_{ATP}) in controlling glucose-stimulated insulin secretion from pancreatic β-cells.

(A) A rise in blood glucose increases β-cell metabolism. The resulting increase in intracellular ATP (and fall in MgADP) promotes closure of K_{ATP} channels and membrane depolarisation. This triggers opening of voltage-gated Ca^{2+} channels (VGCCs), Ca^{2+} influx and exocytosis of insulin granules. **(B)** A decrease in blood glucose reduces metabolism and the ATP:ADP ratio within the β-cell. This opens the K_{ATP} channel and hyperpolarises the membrane, preventing VGCC opening. Thus, no insulin is released.

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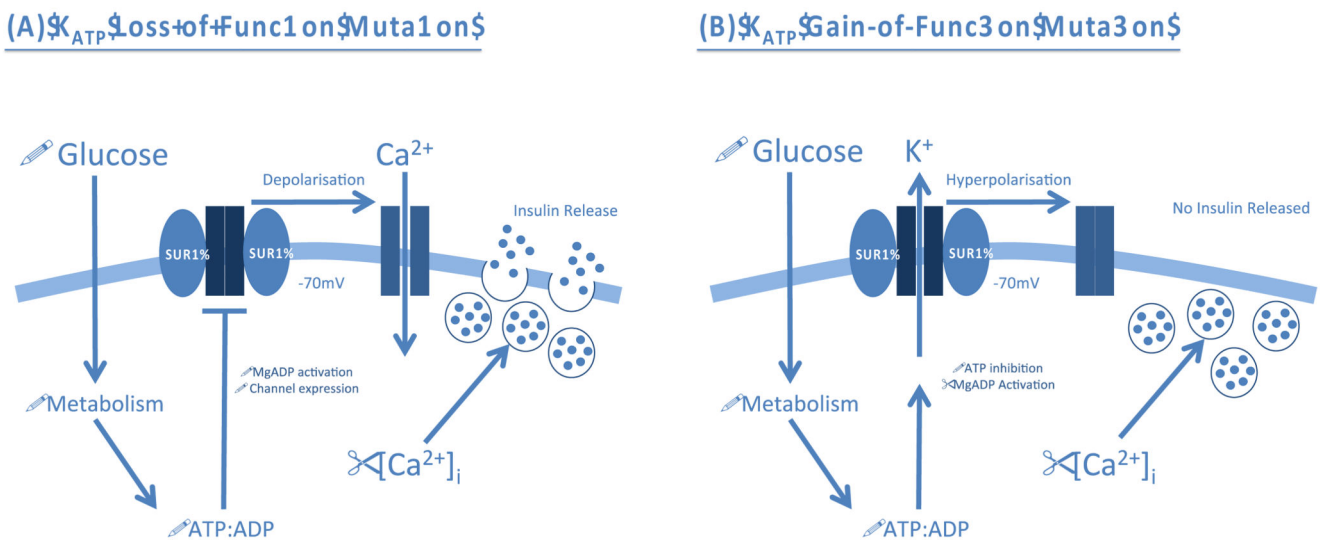

Figure 2. Pathophysiological role of β-cell ATP-sensitive K^+ Channels (K_{ATP}) in disease.

(A) K_{ATP} channel loss-of-function mutations impair MgADP activation or reduce channel expression. This results in permanent depolarisation of the β-cell membrane and opening of voltage-gated Ca^{2+} channels (VGCCs). The subsequent Ca^{2+} influx promotes exocytosis of insulin granules even when blood glucose and metabolism are low. **(B)** K_{ATP} channel gain-of-function mutations increase the sensitivity of the channel to ATP inhibition, or enhance activation by MgADP, rendering the channel inappropriately open. The resulting hyperpolarisation of the β-cell membrane prevents VGCC opening and Ca^{2+} influx. Therefore, insulin secretion is prevented even when blood glucose is elevated.

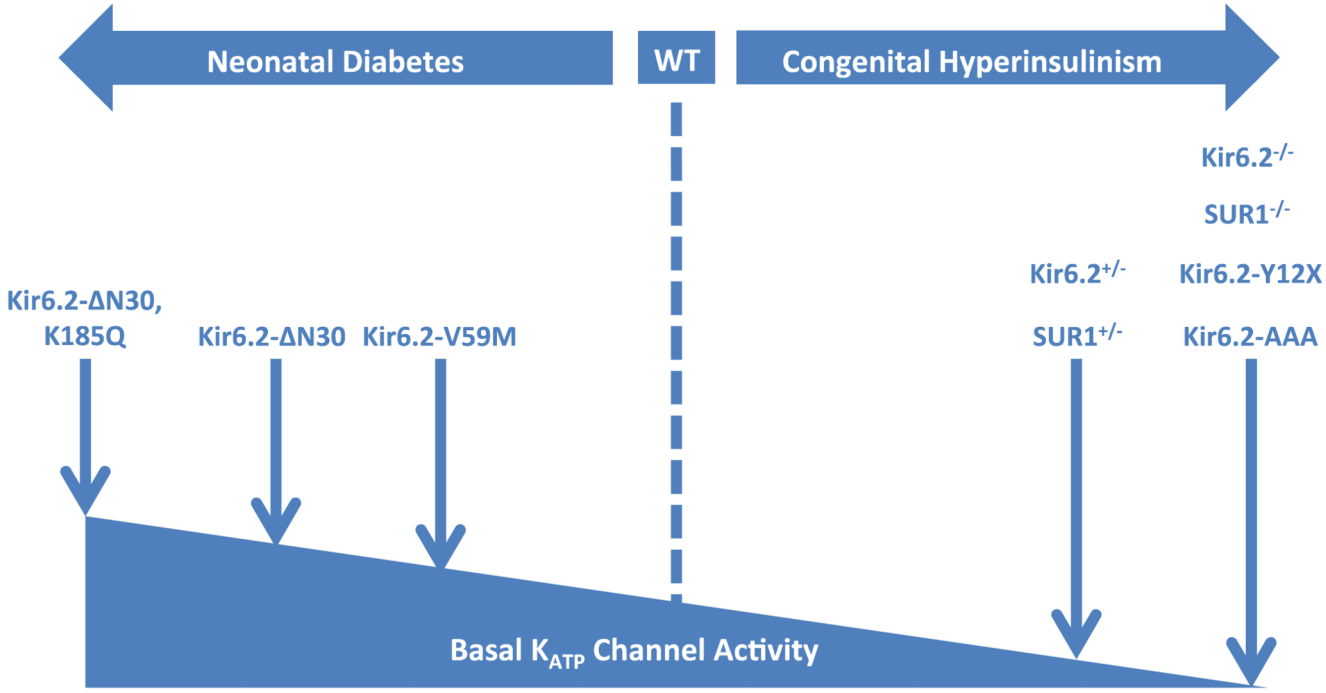

Figure 3. Mouse models of β-cell K_{ATP} channel insulin secretory disorders.

An increase in basal K_{ATP} channel activity reduces insulin secretion and leads to neonatal diabetes. Mouse models of increased K_{ATP} channel activity display hyperglycaemia and hypoinsulinaemia: they include those with Kir6.2-V59M, Kir6.2-ΔN30, and Kir6.2-ΔN30,K185Q mutations. Reduced basal K_{ATP} channel activity results in congenital hyperinsulinism. Mouse models with partial deletion ($Kir6.2^{+/-}$, $SUR^{+/-}$) or ablated channel expression / function ($Kir6.2^{-/-}$, $SUR^{-/-}$, Kir6.2-Y12X, Kir6.2-AAA) have been generated but do not fully recapitulate the human disease.

Table 1

Mouse models of β-cell K_{ATP} channel insulin secretory disorders: Phenotype description.

K_{ATP} Channel Loss-of-Function				
Mutation	**K_{ATP} Effect**	**Phenotype**		**Reference**
$SUR1^{-/-}$	Global SUR1 deletion from birth	β-cells	- Depolarised membrane potential in low glucose - Spontaneous action potentials - Increased basal $[Ca^{2+}]_i$ observed following overnight culture - No change in Ca^{2+} sensitivity of exocytotic machinery	[32–37]
		Isolated islets	- No tolbutamide or glucose-stimulated increase in $[Ca^{2+}]_i$ or insulin secretion in fresh islets - Increased glucose-stimulated insulin secretion observed in islets following overnight culture - Intact amino acid and ACh-stimulated insulin secretion - Impaired GIP, GLP-1, and cAMP-stimulated insulin secretion (despite normal cAMP levels) - Absent diazoxide-mediated decrease in $[Ca^{2+}]_i$ and insulin secretion	
		Islet histology	- No change in insulin or somatostatin staining - α-cell infiltration into centre of islet - No evidence of apoptosis	
		In vivo	- Hypoglycaemic at birth - Hyperinsulinaemic at birth - Postprandial normoglycaemia and normoinsulinaemia in adulthood - Fasting hypoglycaemia and hyperinsulinaemia in adulthood - Mild glucose intolerance in adulthood - Absent glucose or GLP-1-stimulated insulin secretion - Unaltered insulin sensitivity	
$Kir6.2^{-/-}$	Global Kir6.2 deletion from birth	β-cells	- K_{ATP} currents absent - Depolarised membrane potential and electrical excitability in low glucose - Increased $[Ca^{2+}]_i$ observed β-cells following overnight culture - Absent glucose or tolbutamide-stimulated $[Ca^{2+}]_i$ increase - Retained ACh and K+-stimulated $[Ca^{2+}]_i$ increase	[27–28, 30–31]
		Isolated islets	- Reduced glibenclamide-sensitive $^{86}Rb^+$ efflux - Absent glucose and tolbutamide-stimulated insulin secretion - Increased glucose-stimulated insulin secretion observed in islets following overnight culture - Retained ACh, K^+ and GLP-1-stimulated insulin secretion - Impaired arginine and GIP-stimulated insulin secretion	

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K_{ATP} Channel Loss-of-Function				
Mutation	**K_{ATP} Effect**	**Phenotype**		**Reference**
		Islet histology	- α-cell infiltration into centre of islet	
		In vivo	- Transient hypoglycaemia at birth - Normoglycaemia and normoinsulinaemia in adulthood - Mild glucose intolerance in adulthood - Impaired glucose, arginine and GIP-stimulated insulin secretion - Retained GLP-1 stimulated insulin secretion - Enhanced insulin sensitivity	