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Channeling dysglycemia: ion channel variations perturbing glucose homeostasis

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Abstract

Maintaining blood glucose homeostasis is a complex process dependent on pancreatic islet hormone secretion. Hormone secretion from islets is coupled to calcium entry, which results from regenerative islet cell electrical activity. Therefore, the ionic mechanisms that regulate calcium entry into islet cells are critical to maintaining normal glucose homeostasis. Genome wide association studies have identified single nucleotide polymorphisms, including five located in or near ion channel or associated subunit genes, which show association with human diseases characterized by dysglycemia. This review focuses on polymorphisms and mutations in ion channel genes that are associated with perturbations in human glucose homeostasis and discusses their potential roles in modulating pancreatic islet hormone secretion.

Ion channels are key regulators of glucose homeostasis

Glucose sensitive cells of the pancreatic islet respond to deviations in blood glucose, with corresponding changes in transmembrane ion flux that, in turn, regulate the secretion of metabolic hormones [1–3]. High blood glucose (hyperglycemia) stimulates islet β -cell calcium entry causing insulin secretion, whereas low blood glucose (hypoglycemia) stimulates islet α -cell calcium entry resulting in glucagon secretion [1, 3–6]. Islet cell calcium influx occurs through voltage-dependent calcium channels (VDCCs), which are regulated by glucose-induced changes in membrane potential [3–5, 7]. The membrane potential of islet cells is modulated by the orchestrated activities of potassium, sodium, chloride, and calcium channels; these ion channels are, therefore, key regulators of islet cell hormone secretion [5, 8, 9]. As the number of Genome-Wide Association Studies (GWAS) is growing, it is becoming apparent that heritable mutations or polymorphisms in genes encoding ion channels can lead to dysregulation of islet hormone secretion and metabolic disease [10–19]. This review describes ion channel gene polymorphisms and mutations that are associated with perturbations in human glucose homeostasis and examines how they might cause dysglycemia.

K_{ATP} channels and endocrine disorders

ATP-sensitive potassium (K_{ATP}) channels are metabolic sensors that couple glucose metabolism to cell excitability [20–22]. The K_{ATP} channel complex is an octameric assembly of four pore-forming Kir6.X (Kir6.1 or Kir6.2) subunits and four regulatory

nucleotide-binding sulfonylurea receptor (SUR) subunits (SUR1, SUR2A or SUR2B) (Figure 1c, Table 1)[20–22]. In glucose sensitive cells of the pancreatic islet, K_{ATP} channels are primarily comprised of the Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) genes [20–22]. The K_{ATP} channel is sensitive to intracellular levels of ADP and ATP nucleotides; ATP inhibits the channel, via the Kir6.x subunits, whereas MgATP or MgADP stimulate the channel via the SUR subunits [21, 22]. Under high glucose conditions an increase in the ATP/ADP ratio inhibits K_{ATP} channels, whereas a decrease in this ratio during low glucose conditions leads to K_{ATP} channel activation [20, 21]. K_{ATP} channel activity influences the islet plasma membrane potential, causing membrane hyperpolarization under low glucose conditions and membrane depolarization under high glucose conditions [1, 8, 23]. Depolarization of the islet membrane activates many ion channels including VDCCs, voltage-gated sodium (Na_V) channels, and potassium channels, whereas, hyperpolarization inactivates these channels [1, 3, 8, 23]. Islet cell calcium entry and hormone secretion are precisely modulated by changes in the membrane potential, thus, K_{ATP} channels play a pivotal role in coupling metabolic state and islet hormone secretion [20–22]. Therefore, mutations and polymorphisms of K_{ATP} subunit genes that perturb K_{ATP} channel function might affect glucose homeostasis and result in conditions of dysglycemia.

Neonatal diabetes

The reduced glucose-stimulated insulin secretion (GSIS) observed in neonatal diabetic patients with mutations in K_{ATP} channel subunits, underscores the importance of K_{ATP} channels in glucose sensing [10, 12]. Two monogenic neonatal diabetic conditions that arise from K_{ATP} channel subunit gene mutations are permanent neonatal diabetes mellitus (PNDM) and transient neonatal diabetes mellitus (TNDM) [11–13]. Both forms of the disease typically present with severe hyperglycemia within the first six months of life [11, 13]. Although the majority of TNDM cases result from an imprinting defect that does not involve K_{ATP} channels, mutations in K_{ATP} genes also cause TNDM [11, 13]. To date, at least 13 mutations in the Kir6.2 (*KCNJ11*) subunit and 15 mutations in the SUR1 (*ABCC8*) subunit have been identified in patients with TNDM [11, 22] and more than 61 *KCNJ11* mutations and 27 *ABCC8* mutations are known to cause PNDM (Figure 1 and 2, Table 1) [12, 13]. K_{ATP} channels carrying these mutations exhibit a gain-of-function (GOF) due to a loss of regulatory inhibition by ATP [10, 21]. Thus, in TNDM or PNDM patients, glucose stimulation fails to evoke β -cell membrane excitability and insulin secretion, leaving blood glucose levels elevated (Figures 1 and 2, Tables 1 and 2) [10, 21]. Fortunately, many of these mutant channels retain sensitivity to inhibitory sulfonylurea derivatives, which interact with SUR1 to induce channel closure (BOX 1) [24, 25]. Sulfonylurea treatment of diabetics with K_{ATP} GOF mutations often results in a recovery of GSIS. Thus, oral sulfonylureas have replaced insulin injections for the majority of patients with neonatal diabetes caused by K_{ATP} mutations (Box 1) [10].

Some neonatal diabetic patients also show evidence of severe nervous system impairment. Two mutations in the *ABCC8* gene and more than 15 mutations in *KCNJ11* have been associated with a syndrome characterized by developmental delay, epilepsy, and neonatal diabetes (DEND) [12, 26]. The resulting K_{ATP} channels exhibit greater GOF properties than those causing PNDM or TNDM [27]. Since Kir6.2 and SUR1 are expressed in the nervous system, it is possible that overactive K_{ATP} channels in neurons may explain some of the clinical manifestations of DEND syndrome [28, 29]. However, diabetes in DEND patients is primarily caused by a significant reduction of β -cell GSIS similar to TNDM and PNDM [12, 26]. Therefore, insulin injections or oral sulfonylureas are utilized to treat the diabetes phenotype of DEND syndrome (Box1) [26].

Studies of the K_{ATP} channels causing PNDM, TNDM and DEND reveal insights into the molecular and biophysical mechanisms underlying neonatal diabetes [12, 30]. Four general

GOF mechanisms have been described to date: 1) Increased open probability of K_{ATP} channels which reduces the ability of ATP to inhibit channel activity (Figure 2) [31]; 2) Decreased affinity of ATP for the K_{ATP} channel [32]; 3) Increased Mg-nucleotide activation of K_{ATP} channels (due to SUR1 nucleotide binding domain (NBD) mutations) [33]; and 4) Defective transduction between ATP binding and channel closure [27] (Figure 1 and 2, Table 1). Many of the mutations which cause K_{ATP} channel GOF reside in protein domains that regulate channel function (Figures 1 and 2, Tables 1 and 2) and these include: 1) the Kir6.2 ATP binding domain [34]; 2) the SUR1 Mg-ATP and MgADP NBDs [35]; 3) the SUR1 ATPase domain [21]; 4) Kir6.2 (Q52 and V59) and SUR1 gating domains (F132) [36, 37]; and 5) domains that transduce nucleotide binding to Kir6.2 channel opening (such as the cytoplasmic loop L0 between transmembrane domains TMD0 and TMD1 of SUR1) [33, 38]. Future analysis of additional K_{ATP} GOF mutations will enhance our understanding of how the K_{ATP} channel complex is regulated by glucose.

Hyperinsulinemia

Mutations in K_{ATP} subunit genes that result in a loss of channel function lead to hyperinsulinemia of infancy (HI) [21, 39]. Over 150 mutations in *ABCC8* and more than 25 mutations in *KCNJ11* are known to cause HI, and new mutations continue to be identified (Figures 1 and 2, Tables 1 and 2) [12]. Most cases of persistent HI are caused by autosomal recessive K_{ATP} mutations, whereas autosomal dominant transmission of HI occurs with only 24 *ABCC8* mutations and 3 *KCNJ11* mutations [40, 41]. Patients with HI caused by recessive K_{ATP} mutations tend to present with greater plasma insulin levels earlier in life than patients with dominant K_{ATP} mutations [40, 41]. In contrast to the β -cell membrane hyperpolarization caused by GOF mutations, loss of function (LOF) mutations in K_{ATP} lead to membrane depolarization, constitutive calcium entry, and excessive insulin secretion (Figures 1 and 2, Tables 1 and 2) [30]. These mutations reduce K_{ATP} channel activity by: 1) Introduction of a premature stop codon, resulting in a nonfunctional channel [12, 42]; 2) Reducing the ability of MgADP to activate of the K_{ATP} channel complex (these mutations cluster near the second of the two NBDs of SUR1 (NBD2), Figure 1, Table 1) [33]; and 3) Reduced trafficking of the K_{ATP} channel complex to the plasma membrane [41]. Importantly, the hypoglycemia associated with most dominantly transmitted cases of HI can be treated with the K_{ATP} channel openers diazoxide and chlorothiazide (Box1) [43]. Non-responders typically require partial pancreatectomy surgery to improve their blood glucose levels [30, 43].

Type-2 diabetes

Polymorphisms in the K_{ATP} channel subunit genes *ABCC8* and *KCNJ11* have also been associated with increased risk of developing type-2 diabetes [44, 45]. Two polymorphisms that show strong linkage disequilibrium and therefore segregate together include a polymorphism in *KCNJ11* (exon 18, codon 23, T/C) resulting in E23K (glutamate 23 to lysine substitution) and a polymorphism of *ABCC8* (exon 33, codon 1369, T/G) resulting in S1369A (serine 1369 to alanine substitution) [45]. Large association studies suggest that linkage of these polymorphisms with type-2 diabetes occurs in the homozygous state [46, 47]. The E23K and S1369A variants lead to a modest gain in K_{ATP} channel function, in vitro, however, the exact mechanism of increased K_{ATP} channel activity is controversial [22, 48, 49]. Development of type-2 diabetes is, therefore, presumably influenced by age related factors that exacerbate the slight GOF in K_{ATP} channel activity induced by these variants [50].

The E23K and S1369A variants of K_{ATP} channel subunits have been associated with a reduction in GSIS, which may increase the risk of developing type-2 diabetes [49, 51, 52]. Impaired GSIS might result from the slight increase in β -cell K_{ATP} channel activity, which

would reduce glucose stimulated β -cell calcium influx and insulin secretion [22, 48, 49]. However, reduced GSIS caused by the E23K and S1369A variants does not lead to significant hyperglycemia early in life; thus, decreased insulin secretion is compensated for, possibly through increased insulin sensitivity [49]. Aging related changes in metabolism may exacerbate the slight increase in K_{ATP} channel activity observed with these two variants and cause a further diminution of GSIS [50]. Obesity or insulin resistance could also exacerbate the reduction in GSIS observed in carriers of the E23K and S1369A variants [49, 51]. Therefore, one may speculate that a small decrease in GSIS may predispose carriers of E23K and S1369A variants to type-2 diabetes when combined with other factors that reduce either insulin secretion or insulin sensitivity [49, 51]. However, carriers of these variants do not always show reduced GSIS; thus, other K_{ATP} associated mechanisms may influence the progression of type-2 diabetes [53, 54].

The E23K and S1369A variants of K_{ATP} channel subunits have also been associated with aberrant glucose-induced inhibition of glucagon secretion [54]. This may result from a direct role of K_{ATP} channel activity regulating human glucagon secretion from α -cells [5, 6, 55]. The putative mechanism responsible for the K_{ATP} regulation of glucagon secretion has to do with VDCC activity [5, 55]. Calcium entry through VDCCs is essential for human α -cell glucagon secretion and is elevated under low glucose conditions as well as by K_{ATP} activation [6, 56]. Membrane depolarization activates α -cell VDCCs, however, these channels become inactivated if depolarization persists [6, 7]. Human α -cell depolarization induced with K_{ATP} inhibition results in significant inactivation of the VDCCs, which reduces α -cell calcium influx and glucagon secretion [5, 6], whereas activation of K_{ATP} channels under low glucose conditions results in membrane polarization to a level that sustains significant VDCC activity, calcium entry and glucagon secretion [5, 6]. Thus, the K_{ATP} channel GOF variants E23K and S1369A may reduce α -cell depolarization induced inactivation of VDCCs under high glucose conditions, which would increase calcium influx and glucagon secretion [6, 54, 55]. The resulting increase in hepatic glucose output combined with reduced GSIS in carriers of these variants could increase the risk of developing hyperglycemia and type-2 diabetes. However, only a small number of studies have implicated K_{ATP} in regulating human α -cell glucagon secretion [5, 6, 54, 55]. Future studies will improve the understanding of the role K_{ATP} channels play in regulating glucagon secretion.

K_{ATP} channel activity might also regulate α -cell glucagon secretion indirectly, through control of paracrine signals released by β -cells. Paracrine signals such as insulin, γ -aminobutyric acid [GABA], or Zn^{2+} ions, are released from β -cells in a glucose-dependent manner and modulate α -cell glucagon release [4, 57]. The exact paracrine signals that influence human islet glucagon secretion are controversial; however, aberrant GSIS caused by type-1 and type-2 diabetes leads to dysregulated α -cell glucagon secretion [6, 57]. Thus, alterations in GSIS and β -cell paracrine signaling that occur with K_{ATP} channel variants, such as E23K and S1369A, may also influence glucagon secretion [55, 57]. However, the exact role that human K_{ATP} mutations and polymorphisms play in modulating human glucagon secretion via islet cell paracrine signaling is still being determined [57].

Non- K_{ATP} ion channels associated with diabetic conditions

Type-2 diabetes and KCNJ15 polymorphisms

Single nucleotide polymorphisms (SNPs) in the *KCNJ15* gene encoding the inward rectifier potassium channel Kir4.2 (Table 2) are associated with type-2 diabetes [14]. The SNPs are located in exon 4 of the *KCNJ15* and are specifically associated with the development of lean type-2 diabetes in the Japanese population [14]. Kir4.2 expression has been identified in human pancreatic β -cells and Kir4.2 potassium channel activity, similar to that of K_{ATP} , is

predicted to polarize the β -cell membrane and thus antagonize the ability of the β -cell to depolarize in response to glucose [14, 58]. One of the *KCNJ15* SNPs associated with type-2 diabetes, rs3746876 (T), increases Kir4.2 mRNA stability in human peripheral blood cells [14]; an observation that has led to the speculation that increased Kir4.2 channel transcript stability and density in β -cells may limit insulin secretion during the progression of diabetes [14]. However, this preliminary work requires confirmation in human β -cells to determine the potential role of Kir4.2 during GSIS. Future studies will also determine if Kir4.2 channel activity in other glucose sensitive tissues influences glucose homeostasis or if *KCNJ15* polymorphisms regulate nearby genes that modulate the progression of type-2 diabetes.

Type-2 diabetes and *KCNQ1* polymorphisms

Polymorphisms in *KCNQ1*, which encodes a voltage-gated delayed rectifier potassium channel, Kv7.1, are associated with type-2 diabetes (Table 2). The most significant association with type-2 diabetes occurs with carriers of the *KCNQ1* SNP rs2237892 (C) in intron 15 [15]. Mutations in the *KCNQ1* gene (also known as KvLQT1) cause perturbations in cardiac tissue action potential repolarization during contraction, causing a syndrome termed long QT (the interval between the Q wave and T wave of an electrocardiogram recording), an observation that underscores the important role Kv7.1 channels play in regulating membrane repolarization of cardiac cells [59]. However, mutations in Kv7.1 that result in long QT syndrome do not predispose these subjects to diabetes [15, 16, 60]. How polymorphisms in *KCNQ1* associate with type-2 diabetes is currently being determined and three independent potential mechanisms have recently emerged [61–64].

One mechanism implicates a role of *KCNQ1* polymorphisms in decreasing islet insulin secretion. Human islets isolated from nondiabetic donors with and without the *KCNQ1* SNP, rs2237892 (C) were analyzed for insulin secretion [61]. Islets from carriers of the diabetic-associated *KCNQ1* SNP, rs2237892 (C), obtained from the Nordic network for clinical islets, showed significantly reduced GSIS compared with controls, despite equivalent levels of *KCNQ1* mRNA [61]. Although these data suggest a role for human islet Kv7.1 channels in regulating islet insulin secretion, human β -cells have little to no endogenous Kv7.1 current [8]. Therefore, the rs2237892 (C) SNP may influence insulin secretion through signaling from a glucose sensitive cell other than the β -cell.

The *KCNQ1* SNP, rs2237892 (C) has been implicated in modulating GSIS indirectly from pancreatic islets through perturbations in glucagon like peptide-1 (GLP-1) levels [62]. A study of a German cohort has suggested that oral GSIS, which is dependent on intestinal incretin secretion, is significantly impaired in subjects carrying the rs151290 (C) SNP [62]. L-cells of the intestine secrete the incretin GLP-1 in response to oral glucose stimulation, thus, L-cells may be regulated by Kv7.1 channel activity. Although Kv7.1 expression in human L-cells has not been determined, mouse L-cells express significant amounts of Kv7.1 [65]. Subjects with the type-2 diabetes associated *KCNQ1* SNP rs151290 (C) also have significantly reduced GLP-1 levels in response to oral glucose, compared with controls [62]. Therefore, Kv7.1 channel activity may regulate L-cell GLP-1 secretion and thus influence GSIS from the β -cell. Although changes in Kv7.1 channel activity or expression could predispose carriers of the *KCNQ1* SNP rs151290 (C) to diabetes, there is currently no evidence that this polymorphism regulates Kv7.1 channel activity. Another possibility is that the *KCNQ1* SNP rs151290 (C) does not influence Kv7.1 but instead influences DNA signaling from the *KCNQ1* locus, which could regulate secondary gene expression and influence glucose homeostasis.

A DNA signaling perturbation of an imprinting domain located in intron 10 of *KCNQ1* has been implicated in linking *KCNQ1* polymorphisms to type-2 diabetes [63, 64]. The *KCNQ1* gene is itself imprinted and harbors an imprinting control element that influences

neighboring gene expression [66, 67]. Thus, polymorphisms near the *KCNQ1* imprinting control element may lead to aberrant expression of the genes that it influences in a parent-of-origin specific manner. Evidence for this has been established by looking at the heritability of type-2 diabetes association with *KCNQ1* SNPs [63]. Interestingly, significant association of *KCNQ1* SNPs rs2237892 (C) or rs231362 (C) with type-2 diabetes occurs only when maternally transmitted [63]. Therefore, perturbed imprinting in the *KCNQ1* gene locus may result in diabetes through influences on secondary gene expression that regulate glucose homeostasis [66, 67]. For example, the *KCNQ1* gene locus has been shown to influence expression of insulin-like growth factor 2 (IGF2), thus, dysregulation of IGF2 expression by *KCNQ1* polymorphisms may lead to aberrant islet cell development and function [66–68]. Future studies will determine differences in the expression of genes that are impacted by polymorphisms in the *KCNQ1* imprinting control region and how they affect progression of type-2 diabetes.

Type-2 diabetes and *CACNA1E* polymorphisms

Polymorphisms of the human *CACNA1E* gene, which encodes the VDCC $\text{Ca}_v2.3$, are associated with the development of type-2 diabetes (Table 2) [17, 18]. Two association studies, one done on a Swedish and Botnia prospective cohort, and one done with a Pima Indian cohort identified strong association of SNPs within the *CACNA1E* gene, with type-2 diabetes [17, 18]. Carriers of the SNP rs679931 (TT) in *CACNA1E* show reductions in both intravenous and oral glucose tolerance as well as a diminished 2nd phase GSIS [17]. Although these data suggest a possible involvement of $\text{Ca}_v2.3$ in human GSIS during the progression of type-2 diabetes, other data show 1) no detectable expression of $\text{Ca}_v2.3$ mRNA in human islets [8] and 2) that human β -cells VDCC currents are not inhibited by a potent and specific peptide inhibitor of $\text{Ca}_v2.3$ [8]. Therefore, the role for $\text{Ca}_v2.3$ in regulating human islet insulin secretion is unclear. One may speculate that human $\text{Ca}_v2.3$ channel activity plays a more prominent role influencing β -cell insulin secretion when insulin demand is increased and blood glucose levels are elevated during the progression of type-2 diabetes. Future studies will determine if the *CACNA1E* SNP rs679931 (TT) modulates the expression or function of human $\text{Ca}_v2.3$, which glucose sensitive cells $\text{Ca}_v2.3$ influences and how this modulates human glucose homeostasis.

Cystic fibrosis-related diabetes

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which cause cystic fibrosis (CF), can perturb islet cell function and result in diabetes. The first description of CF in 1938 described pancreatic fibrosis and its relation to celiac disease [69]. Almost all CF patients show exocrine tissue damage in the pancreas due to impairments in pancreatic duct epithelium salt and water transport. Although exocrine pancreas damage may influence the development of cystic fibrosis related diabetes (CFRD), some CF patients develop diabetes in the first decade of life indicating that CFRD may be a condition coincident with exocrine disease [70]. CFRD results in part from a reduction in pancreatic β -cell number and function leading to decreased GSIS [71]. CFTR is an important anion channel that regulates epithelial cell function, however, a role for CFTR in human islet hormone secretion as well as its expression in human β -cells is not known and should be determined. Three possible mechanisms for CFRD-induced reduction of insulin secretion have emerged: 1) Mutant CFTR induces severe pancreas pathology resulting in β -cell stress and reduced β -cell number and function [19]; 2) Mutant CFTR expression in the β -cell induces ER stress, accounting for reduced β -cell function [19, 72]; and 3) CFTR expression in the human anterior hypothalamus regulates glucose sensitive neuron excitability [73], which may perturb insulin secretion. The exact mechanism of how mutations in CFTR reduce human islet function remains to be determined. Future studies using specific channel

inhibitors will begin to address how CFTR regulates hormone secretion from human islet cells [74].

Conclusions

The orchestrated activity of functionally diverse ion channels regulates islet cell calcium entry, which is influenced by blood glucose levels and coupled to islet hormone secretion. The importance of ion channels in maintaining glucose homeostasis has become clear with the identification of heritable mutations and polymorphisms in ion channel encoding genes that alter glucose regulated islet hormone secretion. Currently mutations or polymorphisms in or near the genes of five ion channels have been associated with human conditions that show aberrant islet hormone secretion. More are certain to follow. However, there is a virtual continuum of metabolic conditions with overlapping symptoms resulting from defects in islet hormone secretion, making it difficult to pinpoint metabolic conditions caused by individual gene mutations. Ongoing studies utilizing new technologies such as exome and whole-genome sequencing, coupled with conventional methods in electrophysiology and imaging, should yield exciting new insights into the functions of ion channels in the regulation of islet hormone secretion. This work will lead to novel therapeutic strategies for fighting diabetes.

K_{ATP} pharmacology utilized to treat diabetes

Sulfonylureas were found to inhibit β -cell K_{ATP} currents 43 years after a treatment study for typhoid fever identified that these sulfonamide derivatives caused hypoglycemia [75, 76]. Sulfonylureas have been successfully utilized to treat diabetes since the mid-1950s [77]. The sulfonamide derivatives diazoxide and chlorothiazide were found to cause hyperglycemia, which was subsequently shown to be caused by activation of the β -cell K_{ATP} channel complex [78, 79], and have been utilized to treat hypoglycemia since the mid-1960s [80]. Sulfonamide derivatives bind to the SUR subunits of the K_{ATP} channel complex resulting in either K_{ATP} channel inhibition or activation depending on their structure [25] and remain the only K_{ATP} modulators used clinically to regulate insulin secretion.

Although sulfonylureas induce β -cell insulin secretion primarily via K_{ATP} channel inhibition, they may also act through K_{ATP} independent mechanism(s) to modulate GSIS [81–83]. For example, SUR1 deficient mouse β -cells show enhanced GSIS in the presence of tolbutamide, thus, implicating a non-K_{ATP} induced mechanism of sulfonylurea action [83]. One mechanism that has been implicated in SUR1-independent regulation of mouse GSIS by sulfonylureas is their activation of the exchange protein directly activated by cAMP (Epac2) [81–83]. However, recent reports fail to replicate activation of rodent Epac2 by sulfonylureas [84, 85]. Therefore, addressing if sulfonylureas regulate human β -cell GSIS independently of SUR1 should be determined. Interestingly, SUR1 also regulates mouse insulin granule priming, which enhances GSIS independently from its interactions with Kir6.2 [83, 86]. Thus, it is important to assess if any human SUR1 mutations, which result in dysglycemia, modulate human insulin granule priming independently of K_{ATP}. The mechanisms responsible for the K_{ATP}-independent modulation of GSIS by sulfonylureas and SUR1 subunits are important pathways with potential therapeutic implications for diabetes. However, closure of K_{ATP} channels by sulfonylureas is the primary mechanism for increasing GSIS in diabetic patients [20, 21].

Sulfonamide derivatives restore euglycemia in a majority of patients with K_{ATP} channel mutations; however, some of the conditions caused by these mutations are not rescued with sulfonamide derivative treatment [26, 40, 87]. Sulfonamide derivative resistant

K_{ATP} channel mutations are associated with dysglycemia. Furthermore, sulfonylurea treatment does not completely rescue the mental deficits caused by certain GOF K_{ATP} mutations [26, 87]. Therefore, potent and selective Kir6.2 activators or inhibitors might provide a therapeutic option for treating sulfonamide derivative resistant dysglycemia and sulfonylurea resistant mental deficits caused by K_{ATP} mutations [88].

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Glossary

Action Potential	a brief depolarization of the membrane potential.
Cystic fibrosis transmembrane conductance regulator (CFTR)	an ATP dependent plasma membrane transporter of chloride and thiocyanate.
Developmental delay, epilepsy, and neonatal diabetes (DEND)	a syndrome caused by significant overactivity of K _{ATP} channels.
Hyperinsulinemia (HI)	a condition characterized by excessive insulin secretion, which is commonly associated with mutations that decrease K _{ATP} channel activity.
K_{ATP} Gain of Function (GOF)	Mutation in a K _{ATP} subunit gene that results in increased activity of the K _{ATP} channel complex.
K_{ATP} Loss of Function (LOF)	mutation in a K _{ATP} subunit gene that results in decreased activity of the K _{ATP} channel complex.
Nucleotide Binding Domain (NBD)	protein motifs that bind nucleotides such as ATP, MgATP, or MgADP.
Permanent Neonatal Diabetes Mellitus (PNDM)	a monogenic form of diabetes that typically develops within the first six months of life.
Transient Neonatal Diabetes Mellitus (TNDM)	a type of diabetes that develops shortly after birth preceding normal glycemia in infancy; some TNDM patients (~50%) become hyperglycemic again later in life.
Voltage Dependent Calcium Channel (VDCC)	calcium channels that are activated by membrane depolarization.

Figure 1.

Kir6.2 and SUR1 subunit mutations that result in either K_{ATP} channel gain of function or loss of function. a) Selected mutations in SUR1 that result in a K_{ATP} channel with GOF in red or LOF in green (please see table 1); TMD=transmembrane domain, L0 = intracellular linker domain, NBD1= first nucleotide binding domain, NBD2= second nucleotide binding domain. b) Diagram of a functional K_{ATP} channel complex octamer, in islet cells. The complex contains four Kir6.2 subunits and four SUR1 subunits; c) Selected mutations in Kir6.2 that result in K_{ATP} channels with either GOF in red or LOF in green (please see table 1).

Figure 2.

Molecular architecture of a prototypical mammalian Kir6.2 potassium channel. a) Ribbon diagram of Kir6.2 tetramer modeled on the chicken Kir2.2 crystal structure (Kir6.2 alpha-subunits in red, yellow, blue, and light blue; potassium ions in green) b) Top view of the tetramer, c) Bottom view of the tetramer, and d) Ribbon diagram of two Kir6.2 subunits modeled on the Kir2.2 crystal, showing approximate location of selected Kir6.2 mutations which result in LOF (green) or GOF (red) of the K_{ATP} channel complex. The crystal structure graphics of chicken Kir2.2 (PDB code 3JYC) were generated using the UCSF Chimera package from the Computer Graphics Laboratory, University of California, San Francisco (supported by NIH P41 RR-01081) [89, 90].

Table 1

Selected gain and loss of function (GOF and LOF) mutations of K_{ATP} channel subunits illustrated in figure 1

SUR 1		Kir6.2	
GOF	LOF	GOF	LOF
1. P45L; 2. N72S 3. V86A/G; 4. A90V	1.H125Q	1. F35L, F35V, G35S	1. R34H
5. F132L/V, L135P	2. V187D	2. H46Y, N48D	2. G40D
6. P207S, E208K, D209E, Q211K D212L/N, L213R	3. D310N	3. R50P, R50Q, Q52R, G53R	3. F55L
7.L225P, T229I; 8.Y263D, A269D/N	4. R370G	4. V59M, V59G, F60Y	4. K67N
9. R306H; 10.V324M	5. F591L	5. L164P	5. W91R
11. Y356C; 12. E382K	6. T1139M	6. I167L	6. A101D
13. C435R; L438F; 14. L451P; 15. R521Q	7. R1353H	7. K170T	7. S116P
16. L582V, R826W	8. K1374R	8. I182V	
17. H1024Y; 18. T1043Q	9. G1382S	9. R201H	8. G134A, R136L
19. N1123D, R1153G	10. S1386P	10. R201C	9. L147P
20. R1183W/Q, A1185E	11. F1388 deletion	11. E227K, E227L, E229K	10. A187V
21. M1290V; 22. R1314H	12. R1394H	12. V252A	11. P254L, H259R
23. E1327K; 24. R1380C/H/L	13. G1478V	13. E292G, T293N, I296L	12. P266L
25. G1401R; 26. I1425V	14. G1479R	14. E322K	13. E282K
27. V1523A/L, V1524M, R1531A	15. E1507; 16. R1539Q	15. G334D	14. R301H

* The numbers correspond to the location of the mutations illustrated in figure 1 (normal amino acid residue, position, mutant amino acid residue).

Table 2

Association of ion channel genes with aberrant islet hormone secretion

Gene (protein)	Islet expression	Human disease association	Change in human islet function	Reference
<i>KCNJ11</i> (Kir6.2)	Beta, Alpha (human)	Gain of function = neonatal diabetes or type-2 diabetes	Reduced GSIS	[10–13]
		Loss of function = hyperinsulinemia	Glucose independent insulin secretion	[12, 41]
<i>ABCC8</i> (SUR1)	Beta, Alpha (human)	Gain of function = neonatal diabetes or type-2 diabetes	Reduced GSIS	[12, 13, 44]
		Loss of function= hyperinsulinemia	Glucose independent insulin secretion	[12, 33]
<i>KCNJ15</i> (Kir4.2)	Beta (human)	Type-2 diabetes	Undetermined	[14]
<i>KCNQ1</i> (Kv7.1)	Islet (human)	Type-2 diabetes	Reduced GSIS	[15, 16, 60–62]
<i>CACNA1E</i> (CaV2.3)	Not found in human islets	Type-2 diabetes	Reduced second phase GSIS	[17, 18]
<i>ABCC7</i> (CFTR)	Undetermined	Cystic Fibrosis Related Diabetes	Reduced GSIS	[19]