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Ion Channels of the Islets in Type 2 Diabetes

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Abstract

Ca^{2+} is an essential signal for pancreatic β-cell function. Ca^{2+} plays critical roles in numerous β-cell pathways such as insulin secretion, transcription, metabolism, endoplasmic reticulum function and the stress response. Therefore, β-cell Ca^{2+} handling is tightly controlled. At the plasma membrane Ca^{2+} entry primarily occurs through voltage-dependent Ca^{2+} channels (VDCCs). VDCC activity is dependent on orchestrated fluctuations in the plasma membrane potential or voltage, which are mediated via the activity of many ion channels. During the pathogenesis of type-2 diabetes (T2D) the β-cell is exposed to stressful conditions, which result in alterations of Ca^{2+} handling. Some of the changes in β-cell Ca^{2+} handling that occur under stress result from perturbations in ion channel activity, expression or localization. Defective Ca^{2+} signaling in the diabetic β-cell alters function, limits insulin secretion and exacerbates hyperglycemia. In this review, we focus on the β-cell ion channels that control Ca^{2+} handling and how they impact β-cell dysfunction in T2D.

Graphical Abstract

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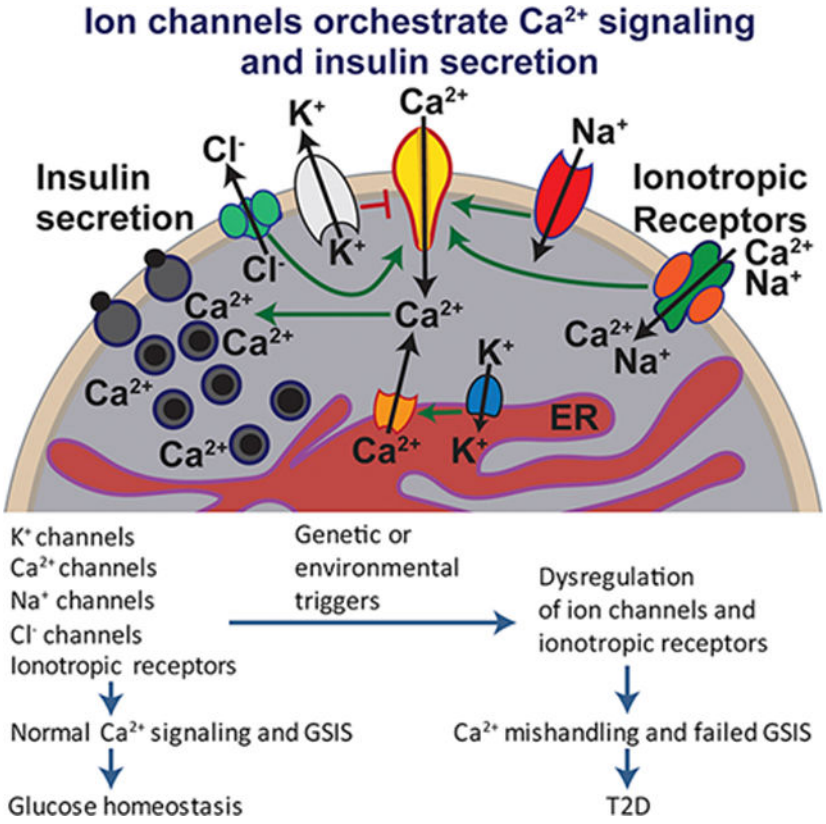

Keywords

calcium; insulin; glucagon; glucose; β-cells; secretion; metabolism

Introduction

The islets of Langerhans are micro organs embedded in the pancreas and contain endocrine cells which secrete hormones to regulate blood glucose. In rodents the most abundant cell type in the islet is the β-cell which secretes insulin to lower blood glucose and is located in the core of the islet. This is followed by the α-cell which is found in the mantle of the islet and secretes glucagon to elevate blood glucose levels. Other minor cell types, including δ-cells, ε-cells, and PP cells secrete somatostatin, ghrelin, and pancreatic polypeptide respectively. These hormones are released into the circulation to coordinate glucose storage and utilization in target tissues but also act in an autocrine or paracrine manner within the islets for feedback regulation to achieve glucose homeostasis in changing metabolic environment. Here, it is worth noting that compared to rodent islets, human islets have lower β- to α-cell ratios and β-cells form clusters that are interspersed with non-β cells rather than residing in the core; these distinct architectures likely impact signaling between cell types in the different species.

The secretory activity of each endocrine cell type is controlled mostly by ion channels. These ion channels control K^+, Na^+, Cl^-, and Ca^{2+} fluxes to generate electrical and Ca^{2+}

signals needed for secretion. The ionic mechanisms underlying secretion regulation is best understood in β-cells, as they are the sole source of insulin and indispensable for glucose regulation. β-cells are equipped with a large repertoire of channels that can be regulated at the level of transcription, translation, post-translational modifications and intracellular trafficking to respond to extracellular and intracellular signals and fine tune their secretory activities. Over sixty different ion channels are known to be expressed. Their roles in insulin secretion in physiological and pathological conditions are of primary interest in the islet biology field.

Type 2 diabetes mellitus is a complex chronic disease often associated with obesity. Initiation and progression of the disease likely involve many genetic and environmental factors. It is clear that both insulin resistance and failure of β-cells to secrete sufficient amount of insulin to curtail hyperglycemia are the two main drivers of T2D. In T2D, plasma glucose and insulin secretion become decoupled. Studies of extreme phenotypes such as monogenic forms of diabetes, genome-wide association studies, and profiling gene expression changes have implicated many ion channels and their regulatory proteins in the cause or acceleration of the disease. Understanding the ionic mechanisms that underlie this pathology is critically important for identifying therapeutic targets for the prevention and treatment of T2D.

This review will discuss ion channels that have been shown or proposed to contribute to β-cell dysfunction and T2D based on genetic and functional evidence from animal and human studies. In particular, we highlight ion channels that control Ca^{2+} entry necessary for secretion and how metabolic changes associated with insulin resistance alter ion channel regulation and Ca^{2+} handling to cause defective secretion. The primary focus will be on β-cells but other islet cell types and their involvement in T2D resulting from ion channel defects are also considered.

Ion channels in secretagogue-stimulated electrical excitability

β-cell plasma membrane electrical excitability is required for physiological glucose-stimulated Ca^{2+} entry and insulin secretion from β-cells. Electrical excitability results from changes in β-cell membrane potential (V_m) that is tightly controlled by the orchestrated opening and closing of many ion channels during glucose-stimulation (Figure 1). At rest the β-cell membrane sits near - 70 mV due to the activities of K_{ATP} channels and a slight sodium leak through other small conductance channels. During glucose-induced increases in the ATP/ADP ratio K_{ATP} channel closure leads to depolarization due to cessation of K^+ efflux but continued Na^+ leak[1]. Glucose metabolism also results in β-cell swelling that activates the volume regulatory Cl^- current through SWELL1, leading to Cl^- efflux and further V_m depolarization[2]. In human β-cells depolarization activates voltage-dependent Ca^{2+} channels (VDCCs) and voltage-gated Na^+ channels (VGSCs) resulting in the upstroke of the action potential (AP); the AP is the primary electrical signal of the β-cell. The AP upstroke depolarizes the V_m and allows even more Ca^{2+} entry via VDCC activation activating big conductance K^+ (BK) channels, which repolarizes the AP. During glucose-stimulation the V_m sits at a depolarized plateau potential where APs can rapidly fire leading to sustained Ca^{2+} entry and insulin secretion. A drop in blood glucose levels results in a

reduction in the β-cell ATP/ADP ratio leading to activation of K_{ATP} channels, which causes V_m hyperpolarization and terminates electrical excitability.

β-cell excitotoxicity

Insulin resistance results in increased β-cell electrical excitability and insulin secretion during the pathogenesis of diabetes. Too much electrical excitability and excessive Ca^{2+} entry causes disruptions in β-cell Ca^{2+} handling resulting in a stressed condition which is referred to here as β-cell excitotoxicity. During β-cell excitotoxicity the resulting changes in Ca^{2+} homeostasis leads to changes in ion channel activity as well as significant changes in many signaling cascades (e.g. mitochondrial dysfunction). These stressful conditions result in elevated cytokine secretion (such as from immune cells) that further impact β-cell ion channel activity and Ca^{2+} handling, which negatively impacts insulin secretion. Moreover, the elevations in cytoplasmic Ca^{2+} during excitotoxicity result in transcriptional changes that also impact ion channel activity and thus Ca^{2+} handling. Single cell transcriptome analysis has found that the transcription of mouse β-cell ion channels changes dramatically in response to short term insulin resistance associated with a high fat diet [3]. For example, VDCCs such as *Cacna1d* that encodes $Ca_v1.3$ are significantly reduced [3]. Whereas K^+ channel transcripts such as *KCNK16* and *Kcnb1* that encode TALK-1 and $K_v2.1$ respectively are increased[3]. β-cell transcriptome studies have also been performed on humans with or without T2D and ion channels transcript abundance are also different between these groups[4, 5]. As the human transcriptomes are from patients with long standing diabetes, the changes in β-cell ion channel transcript abundance are different from short term insulin resistance changes in rodents. For example the Transient Receptor Potential Cation Channel Subfamily M Member 3 (TRPM3) is significantly downregulated in human β-cells from T2D patients[4]. The stressful conditions of elevated β-cell electrical excitability in T2D lead to many changes that eventually impact the failure of β-cells to meet the increased demand for insulin[6]. Importantly, β-cell excitotoxicity is not only due to changes in ion channel function but also due to changes in β-cell nutrient utilization and ER stress that occur during the pathogenesis of T2D.

β-cell ion channels that control and disrupt calcium entry in T2D

K_{ATP} Channels—K_{ATP} channels are weakly inwardly rectifying K^+ channels present in the β-cell plasma membrane. Activities of K_{ATP} channels are controlled by intracellular ATP and ADP, the ratio of which fluctuates according to blood glucose levels. This enables the channel to serve as a metabolic sensor and couples serum glucose to insulin secretion. Channel response to changing ATP/ADP ratios is coordinated by the two constituent protein subunits: an inward rectifier Kir6.2 and an ABC transporter protein sulfonylurea receptor 1 (SUR1). Recent high resolution cryo-EM structures show that the channel is a hetero-octamer with four Kir6.2 subunits in the center forming the K^+ conducting pore and four SUR1 subunits in the periphery[7–9]. Each SUR1 protein interacts with a Kir6.2 via its N-terminal transmembrane domain (TMD0) which is connected to SUR1's ABC transporter core structure consisting of two transmembrane domains and two nucleotide binding domains by a long intracellular loop (L0) (Figure 2).

Both Kir6.2 and SUR1 interact with intracellular adenine nucleotides to regulate channel activity[10, 11]. ATP, and to a much lesser extent ADP, binds to a non-canonical nucleotide binding pocket formed by the N- and C-terminal cytoplasmic domains of two adjacent Kir6.2 subunits and closes the channel [12, 13]. The inhibitory effect of ATP occurs in isolated membrane patches even in the absence of Mg^{2+} thus does not involve ATP hydrolysis[10]. ATP and ADP also interact with the two nucleotide binding domains (NBDs) of SUR1 to stimulate channel activity in an Mg^{2+}-dependent manner[14]. In the intracellular milieu where most ATP and ADP are in complex with Mg^{2+}, binding of MgATP at NBD1 and MgADP at NBD2 causes dimerization of the two NBDs[9]. This conformational change is transduced to the Kir6.2 pore and antagonizes the ATP inhibition at Kir6.2, resulting in a net gain of channel activity. Thus, channel activities resulting from the tug-of-war between ATP inhibition at Kir6.2 and MgADP stimulation at SUR1 reflect the changes in ATP/ADP ratios in β-cells as the blood glucose concentration swings. It is worth noting that although NBD2 is capable of binding and hydrolyzing MgATP[15, 16], there is evidence that MgATP hydrolysis to MgADP at this site is not required for NBD dimerization and channel stimulation[17, 18]. Thus the mere increased occupancy of MgADP at NBD2 when MgADP concentrations increase following a fall of blood glucose likely underlies the MgADP stimulation effect.

The importance of K_{ATP} channels in insulin secretion and glucose regulation is evident from genetic variations in the channel genes (*KCNJ11* for Kir6.2 and *ABCC8* for SUR1) associated with a spectrum of insulin secretion disorders[19]. Loss-of-function K_{ATP} mutations were linked to congenital hyperinsulinism soon after the channel was cloned in 1995[20]. Although it was predicted that gain-of-function mutations would cause the opposite clinical phenotype, i.e. diabetes, direct demonstration did not come until almost ten years later[21]. A pioneer study showing that overexpressing an ATP-insensitive variant of Kir6.2 in mice resulted in a neonatal diabetes phenotype[22] paved the way for subsequent studies that identified many mutations in the Kir6.2 and SUR1 genes in human neonatal diabetes patients. Neonatal diabetes associated mutations in Kir6.2 typically reduce channel inhibition by ATP whereas those in SUR1 tend to increase channel stimulation by MgADP but some have also been shown to reduce ATP inhibition by allosteric mechanisms[23, 24]. In addition to neonatal diabetes, some mutations can also cause neurological defects including developmental delay and epilepsy, referred to as DEND syndrome[23]. This is most likely due to overactivity of these mutant channels in neurons[25] known to express K_{ATP} channels rather than secondary effect of hyperglycemia although detailed mechanisms are still not well understood. Aside from causing congenital diabetes, genetic variants in K_{ATP} channels have also been associated with MODY (maturity onset diabetes of the young) and one polymorphism in KCNJ11 (rs5219; resulting in E23K; Table 1) is associated with increased risk of T2D in multiple GWAS studies[26, 27]. The effects of the K allele on channel activity and insulin secretion assessed by glucose tolerance tests have been investigated in a number of studies[26, 28–30]. Although some reported a small effect, others failed to detect significant difference compared to the E allele. There is now increased appreciation that tiny effect sizes of many common risk alleles likely contribute to complex diseases such as T2D[31]. Despite strong genetic evidence, proof of genotype-phenotype association may be challenging.

Worth noting, two dominant inactivating ABCC8 mutations, E1507K and R370S, have been associated with hyperinsulinism early in life but glucose intolerance or diabetes in adult carriers[32–34]. The glucose intolerance may be attributed to glucose-blindness (i.e. impaired insulin secretion responses to acute or ramp glucose stimulations), a phenotype well documented in mice lacking K_{ATP} channels[35, 36]. The impaired insulin secretion response to glucose may be a result of chronic elevations of cytosolic Ca^{2+}. Curiously, later large scale studies of dominant congenital hyperinsulinsm-causing mutations did not find significantly increased risk for diabetes later in life[37]. An interesting possibility is that the different findings are due to differences in how the patients were treated for their hyperinsulinemia and hypoglycemia, for example with diazoxide (a K_{ATP} channel opener) versus glucose feeding, which would affect Ca^{2+} levels, hence β-cell function.

K_{ATP} channels have been a major therapeutic target for T2D for more than half a century[38]. Sulfonylureas such as glibenclamide (glyburide) and glinides such as repaglinide (prandin) inhibit K_{ATP} channel activity to stimulate insulin secretion[39] and remain a first-line T2D treatment, especially in low-income settings[40]. Although long-term use of sulfonylureas frequently results in accelerated β-cell failure likely caused by chronic hyperexcitability and ER stress[41–43], studies in mice suggest this failure is readily reversible without permanent damage to β-cells[44]. Whether periodic stops in sulfonylurea therapy can prolong drug effect in human patients remains to be seen[45]. Since the discovery that gain-of-function K_{ATP} mutations underlie neonatal diabetes, glibenclamide has also become a mainstay for treating K_{ATP}-neonatal diabetes and DEND syndrome[46]. In addition to sulfonylureas and glinides, carbamazepine, an anticonvulsant best known for its effect to block Na_v channels[47], was recently shown to also inhibit K_{ATP} channel activity[48]. Carbamazepine competes for glibenclamide binding to K_{ATP} channels with an estimated K_d of ~25 nM[49] and abolishes channel response to MgADP[50]. Structural studies using cryoEM have revealed that glibenclamide and carbamazepine as well as repaglinide share a common binding pocket in the SUR1 protein, consistent with these drugs acting via a similar mechanism to inhibit K_{ATP} channels[13, 51–53]. Given the similarity between carbamazepine and sulfonylureas in their effects on K_{ATP} channels, it would be predicted that carbamazepine would also stimulate insulin secretion. However, since carbamazepine also inhibits Na_v channels and may have other actions such as maintaining functional β-cell mass[54], its effect on insulin secretion will require further investigation.

Two-Pore-Domain Potassium (K2P) Channels—K2P channels are small conductance K^+ channels that are active at all membrane potentials and thus termed “leak” K^+ channels. Human β-cells show high expression of many K2P channels including: TASK-1, TALK-1, TALK-2, and TWIK-1. The K2P channels expressed in islets show outward rectification with small K^+ currents at hyperpolarized potentials that increase during depolarization. During glucose-induced inhibition of K_{ATP} channels most K2P channels stabilize the plateau potential from where APs fire[35, 55, 56]. Therefore, K2P channels help to regulate the V_m and Ca^{2+} entry during GSIS (Figure 3)[57]. Although the roles of K2P channels in islet biology are still being elucidated, K2P channel polymorphisms and mutations have been identified that negatively impact β-cell function. For example, a GOF polymorphism in *KCNK16* that encodes TALK-1(rs1535500 resulting in A277E) is associated with an

increased risk of developing T2D[58, 59]. This is likely due to enhanced β-cell V_m polarization, which is predicted to reduce β-cell Ca^{2+} entry and insulin secretion. Furthermore, rs1535500 also results in increased expression of the downstream gene *KCNK17* in human islets, which encodes TALK-2[60]. This suggests that higher levels of TALK-2 together with greater function of TALK-1 lead to a hyperpolarizing impact on β-cell V_m, which would limit VDCC activity and reduce insulin secretion. Interestingly a gain-of-function mutation in TALK-2 that results in severe cardiac conduction disorder does not cause overt diabetes[61]; however, patients with this mutation would be predicted to show decreased GSIS. Because *KCNK16* (that encoded TALK-1) is the most abundant and most β-cell restricted K^+ channel transcript, mutations that cause extensive TALK-1 channel gain-of-function would be predicted to cause neonatal diabetes or maturity onset diabetes of the young (MODY).

Interestingly, TALK-1 and TASK-1 channels also form function complexes on the endoplasmic reticulum (ER) membrane (Figure 3). Maintenance of ER Ca^{2+} (Ca^{2+}_{ER}) homeostasis requires that Ca^{2+} movement across the ER membrane is balanced with a simultaneous K^+ flux in the opposite direction [62–64]. Similar to other ER K^+ channels such as the trimeric intracellular cation channels, TRIC-A or TRIC-B [65, 66], TALK-1 and TASK-1 control Ca^{2+} movement across the ER membrane by balancing Ca^{2+}_{ER} release with K^+ flux in the opposite direction, [62–64]. Without this K^+ countercurrent, Ca^{2+} release from the ER rapidly generates a negative charge on the inside of the ER membrane, inhibiting further Ca^{2+}_{ER} release [67–69]. TALK-1 control of Ca^{2+}_{ER} release also impacts the β-cell V_m response to glucose[70]. Glucose-induced Ca^{2+} entry results in Ca^{2+}_{ER} release leading to activation of Ca^{2+}-activated K^+ ($K_{Ca}{}^{2+}$) channels that repolarize the V_m during the silent phases between oscillations of membrane depolarization (these $K_{Ca}{}^{2+}$ currents are collectively termed K_{slow})[70]. Therefore, TALK-1 channel control of Ca^{2+}_{ER} release slows β-cell Ca^{2+} oscillation frequency and thus is predicted to tune pulsatile insulin secretion. This suggests that polymorphisms or mutations that impact TALK-1 function would be predicted to impact Ca^{2+}_{ER} handling as well as V_m. Indeed the T2D associated GOF polymorphism (rs1535500, TALK-1-A277E) in *KCNK16* results in less Ca^{2+}_{ER}[70]. TALK-1-A277E-induced reduction in Ca^{2+}_{ER} storage also causes an increased ER stress response. Importantly, Ca^{2+}_{ER} homeostasis becomes perturbed during the pathogenesis of T2D as well as T1D, which leads to β-cell dysfunction[71–74]. Furthermore, certain mutations cause monogenic neonatal diabetes by increasing ER stress (e.g. INS-1, and WFS-1)[75, 76]. Therefore, enhanced TALK channel activity at the ER membrane with rs1535500 would be predicted to contribute to ER stress during the pathogenesis of T2D. Other K2P channels may also help control the ER stress response by tuning β-cell Ca^{2+}_{ER} handling.

Although K2P channels are K^+ selective ion channels, one of the β-cell K2P channels, TWIK-1, is not only permeable to K^+ but undergoes pore collapse under acidic conditions becoming permeable also to Na^+ [1]. In β-cells, TWIK-1 channels rapidly cycle between endosomes and the plasma membrane. When TWIK-1 channels reach the plasma membrane from acidic endosomes they are still in a conformation permeable to Na^+. Interestingly, because conformational recovery from the pore collapse upon subsequent exposure to physiological extracellular pH (>7) as the channels arrive the plasma membrane is a slow

process[1], the TWIK-1 channels are recycled back to the endosomes before they ever lose Na^+ permeability and become permeable exclusively to K^+ at the plasma membrane [1]. Under low glucose during conditions when K_{ATP} channels are active the TWIK-1 Na^+ permeability does not significantly influence the β-cell V_m. However, when K_{ATP} is inhibited during high glucose conditions the TWIK-1 Na^+ permeability helps to depolarize the β-cell V_m. Thus, mouse β-cells deficient for TWIK-1 sit at a more hyperpolarized V_m under stimulatory glucose conditions and are predicted to have less VDCC activity and reduced insulin secretion[1]. This suggests that TWIK-1 could also provide an important Na^+ leak current in human β-cells.

Calcium-activated K^+ channels (K_{Ca}^{2+})—Calcium-activated K^+ (K_{Ca}^{2+}) channels play an important role in the repolarizing phase of the β-cell action potential. The K_{Ca}^{2+} channel with the highest expression in human β-cells is the BK channel, which is activated by both depolarization as well as Ca^{2+} binding. The BK channels are the largest and most rapidly activating K^+ current that initiates during the AP upstroke and therefore these channels play an important role repolarizing the β-cell AP. Inhibition of BK channels results in increased human β-cell AP amplitude as well as increased depolarization-induced insulin secretion (during K_{ATP} inhibition)[77]. BK channels are also expressed in neurons and LOF mutations in these channels cause epilepsy with cerebellar atrophy due to increased neuronal electrical excitability[78], which may also be the case in β-cells of patients with BK channel LOF; this would be predicted to improve GSIS. Interestingly, GOF mutations in BK also cause epilepsy due to faster AP firing frequency[79], which has been suggested to be due to faster AP repolarization and increased ability to fire subsequent APs[79]. While the role of BK channel GOF mutations on glucose tolerance has not been determined, if BK GOF mutations cause greater AP firing frequency in β-cells as they do in neurons, then this would be predicted to lead to an improvement of glucose tolerance due to greater electrical excitability and Ca^{2+} entry following glucose stimulation.

Other K_{Ca}^{2+} channels are also expressed in human β-cells including the small-conductance Ca^{2+}-activated potassium channel, SK3, and the intermediate conductance Ca^{2+}-activated K^+ channel, IK[80, 81]. These channels limit the frequency of β-cell APs similar to their action in neurons[82–85]. SK3 and IK activation occurs as a consequence of Ca^{2+} influx during the AP and remains open after termination of the AP leading to after-hyperpolarization (AHP)[86, 87]. AHP limits the firing of another AP and thus reduced AP firing frequency[87]. *KCNN3* and *KCNN4* the genes that code for SK3 and IK1 are expressed at fairly low levels in human β-cells[80]. Thus, human islet insulin secretion is only modestly increased by IK inhibition and does not change with SK3 inhibition[88]. Therefore, these channels may not contribute substantially to dysfunction of Ca^{2+} handling in T2D. Gain-of-function mutations in IK channels cause hereditary xerocytosis (HX)[89]. Although certain types of HX are associated with diabetes and overactivity of IK would be predicted to limit insulin secretion[88], HX-associated diabetes is primarily due to pancreatic hemochromatosis and iron deposition[90]. It has also been found that islet SK3 expression is increased in rats following intrauterine growth restriction; a condition which increases the risk of T2D development in adulthood[91]. Therefore, conditions that

upregulate β-cell SK3 levels could potentially negatively impact β-cell function by reducing β-cell electrical excitability.

K_v channels—Many voltage-gated K^+ (K_v) channels are expressed in human islets[4, 80]. Although K_v currents can readily be recorded from human β-cells, their role in regulating electrical excitability and insulin secretion is controversial[77, 92]. $K_v2.1$ and $K_v2.2$ currents are responsible for 65–80% of human β-cell K_v activity and can be inhibited with toxins[77, 92]. Interestingly, stromatoxin inhibition of both $K_v2.2$ and $K_v2.1$ has been shown to have little impact on human β-cell electrical activity and GSIS[55]. However, another $K_v2.1$ and $K_v2.2$ toxin inhibitor (guangxitoxin-1E) causes substantial increases of human islet GSIS[92]. Furthermore, a small molecule (RY796) inhibitor of both $K_v2.1$ and $K_v2.2$ also enhances human islet GSIS[92]. While the exact roles of $K_v2.1$ and $K_v2.2$ channel activity on human β-cell GSIS remain to be determined, the *KCNB2* gene that encodes $K_v2.2$ shows much higher expression (nearly 10 fold greater) levels in β-cells when compared to *KCNB1* that encodes $K_v2.1$[4, 80]. This suggests that Kv2.2 channels may be more important in controlling human β-cell electrical activity; selective $K_v2.2$ knockdown in human β-cells will help uncover how this channel impacts electrical activity. Interestingly, the expression of human islet $K_v2.1$ is reduced in T2D[93]. However, as the *KCNB1* is expressed at a low level compared to other K^+ channel transcripts (e.g. encoding BK, Kir6.2 or TALK-1)[4, 80], the K^+ conductance of $K_v2.1$ would be expected to only modestly impact human β-cell electrical activity[77]. Mutations in *KCNB1* have been identified, which result in infantile epilepsy[94–97]. These mutations cause dominant negative inhibition of $K_v2.1$ or loss of K^+ selectivity of the $K_v2.1$ channel complex[94–97]; both of which result in increased neuronal excitability that leads to generalized or focal seizures[94–97]. Importantly, a mutation in $K_v2.1$ that results in a constitutively activated[95], nonselective cation channel that is not voltage activated would be predicted to result in a large enhancement of insulin through increased Ca^{2+} influx. While this has yet to be assessed in serum from these patients, the outstanding resource for patients with *KCNB1* mutations (KCNB1.org) could allow a clear assessment of the function or lack of function of $K_v2.1$ currents during human insulin secretion.

Other K_v channels are also expressed in the human β-cell, which presumably contribute to AP repolarization and could impact β-cell function in T2D patients. For example, the gene that encodes the $K_v1.7$ channel is in a region on chromosome 19 (19q13.3) that has SNPs linked to an increased susceptibility for developing T2D[98]. Furthermore, blocking Kv1.7 in rodent islets increases AP firing frequency and insulin secretion[99]. Other K_v channels that are expressed in and regulate human β-cell function are the human ether-á-go-go-(HERG) and related gene encoding $K_v11.1$ and $K_v11.2$ respectively[4, 80], which are also important cardiac or neuron repolarizing K^+ channels[100, 101]. Importantly, loss-of-function $K_v11.1$ mutations that cause long-QT syndrome result in increased insulin secretion and hypoglycemia[102]. This suggests that $K_v11.1$ inhibits GSIS presumably through polarizing influences on the human β-cell V_m[102]. Interestingly, however, loss-of-function mutations in *KCNH6* the gene encoding $K_v11.2$ causes maturity onset diabetes of the young[103]. The diabetic phenotype occurs in adults and individuals with these mutations also show hyperinsulinemia as children[103, 104]. Similarly, mice with a $K_v11.2$ LOF

mutation show hyperinsulinemia after birth followed by hypoinsulinemia as adults[103]. Thus, K_v11.2 LOF induces enhanced Ca^{2+} entry into β-cells that results in increased insulin secretion as well as ER stress over time leading to β-cell failure and diabetes[103]. As K_v11.x GOF mutations would be predicted to limit VDCC activity and reduce insulin secretion, these mutations would be predicted to also result in a diabetic phenotype.

K_v proteins have also been shown to have roles independent of K^+ flux. For example, K_v2.1 and K_v2.2 channels interact with vesicle-associated membrane protein-associated proteins isoforms A and B (VAPA and VAPB) to enable close association of the ER and plasma membrane[105, 106], which presumably could control Ca^{2+} handling and/or influence actin dynamics of the human β-cell. Furthermore, K_v2.1 has also been shown to interact with SNARE machinery (e.g. Syntaxin-1A and SNAP-25)[107, 108], recruit insulin granules to the plasma membrane, and enhance GSIS[109]. SNARE machinery such as Syntaxin-1A has also been shown to bind many other ion channels such as VDCCs and the K_{ATP} channel complex to modulate their function or surface expression, which may also impact insulin secretion[110, 111]. Although *KCNB1* the gene encoding K_v2.1 is expressed at much lower levels than the other β-cell ion channels that bind syntaxin-1A, reduced T2D islet *KCNB1* has been suggested to negatively impact human β-cell insulin secretion through reduced K_v2.1 syntaxin-1A interactions[93]. This suggests patients with a truncation of the C-terminus of K_v2.1 (such as chr20:47991009delG,p.S363fs*13; which does not contain a sytaxin-1A binding site) may show significantly impaired GSIS and a predisposition for developing diabetes[112](KCNB1.org).

G protein-gated inwardly rectifying K^+ (GIRK) channels—GIRK channels are activated by Gi/o-coupled receptors when they release Gβγ[113, 114]. Two primary types of Gi-coupled receptors found in human β-cells are the somatostatin receptors (SSTRs) and the α2 adrenoreceptors (α2-ADRs)[115–118]. Therefore, somatostatin and epinephrine activate β-cell GIRK channels[119], which cause β-cell V_m hyperpolarization and reduced VDCC activity[113, 120]. The importance of GIRK control of β-cell Ca^{2+} handling is exemplified by the increase in Ca^{2+} entry and insulin secretion that occurs during Gi receptor signaling inhibition with pertussis toxin (PTX; also termed islet-activating protein)[121, 122]. Although GIRK has not been directly linked to T2D, a polymorphism in the α2A-ADR encoding gene *ADRA2A* (rs553668), is associated with an increased risk of developing T2D[123]. Human islets from carriers of the rs553668 polymorphism exhibit reduced insulin secretion and greater levels of α2A-ADR[123], which causes enhanced GIRK activation and thus hyperpolarizes the β-cell reducing VDCC activity. Mutations and polymorphisms in the genes that encode GIRK channels have also been identified, which may impact glucose homeostasis. For example, single nucleotide polymorphisms in *KCNJ9* the gene encoding GIRK3 show significant correlation with increased risk of developing diabetes in a PIMA Indian population[124]. Furthermore, a gain-of-function mutation in *KCNJ5* that encodes the GIRK4 channel causes Familial Sinus Node Disease[125] but has not yet been shown to disrupt glucose homeostasis in these patients. As GIRK4 is expressed in human β-cells[80, 120], over activity of this channel would be predicted to inhibit insulin secretion.

GIRK channels are also regulated by signals other than Gβγ such as phosphatidylinositides, cholesterol and intracellular Na^+ [126–128]. Thus their activity changes under conditions associated with T2D may also lead to perturbations in β-cell function. For example phosphatidylinositol 4,5-bisphosphate (PIP_2) is required for GIRK channel opening[129–131]. As insulin resistance that occurs during the pathogenesis of T2D leads to inhibition of insulin-induced activation of the PI3K/AKT pathway[132], this may reduce GIRK activity. Furthermore certain GIRK channels activity is enhanced during conditions of high intracellular Na^+ [126, 133, 134]. Because intracellular Na^+ concentration increases during excessive electrical excitation that occurs during the excitotoxic conditions associated with T2D, Na^+-mediated activation of GIRK may eventually lead to β-cell polarization and limit VDCC activity[6]. On the other hand, GIRK activation under excitotoxic circumstances may also help protect β-cells from apoptosis by reducing the excessive Ca^{2+} entry[135]. Finally, cholesterol activates GIRK conductance and thus changes in cholesterol typically observed in patients with T2D could result in overactive β-cell GIRK, which would also reduce VDCC activity and insulin secretion[136].

Ca^{2+} channels—Voltage-dependent Ca^{2+} channels are the primary entry point for β-cell Ca^{2+} during GSIS. As Ca^{2+} entry is essential for β-cell GSIS, blocking VDCCs impairs insulin secretion[137]. The VDCCs that have been implicated in GSIS include: the L-type channels $Ca_V1.2$ and $Ca_V1.3$; the P/Q-type channel $Ca_V2.1$; and the T-type channel $Ca_V3.2$[138]. Indeed, gain-of-function mutations in VDCCs have been shown to result in hyperinsulinemia and hypoglycemia. For example a GOF mutation in the $Ca_V1.2$ channel associated with Timothy syndrome results in intermittent hypoglycemia, which may be due to enhanced insulin secretion[139]. Furthermore, a gain-of-function mutation in the $Ca_V1.3$ channel also results in hyperinsulinemia and hypoglycemia[140]. As enhanced VDCC activation causes increased insulin secretion, reduced VDCC activity would be predicted to reduce insulin secretion and result in diabetic phenotypes. Indeed, VDCC transcript abundance has been shown to be reduced in T2D. Expression of the *CACNA1D* gene that encodes $Ca_V1.3$ is reduced in T2D islets, which correlates with reduced insulin secretion[141]. This is due to polymorphisms in the promoter of *CACNA1D* that result in reduced expression of the *CACNA1D* gene[141]. The *CACNA1D* gene shows open chromatin structure in human islets and changes in transcription factor binding to this promotor are proposed to reduce $Ca_V1.3$ levels[141, 142]. As reduced $Ca_V1.3$ levels are associated with T2D, it would be predicted that a loss-of-function mutation in $Ca_V1.3$ would also disrupt insulin secretion and result in a diabetic phenotype[143]. Although $Ca_V1.3$ LOF mutations cause deafness, how $Ca_V1.3$ LOF mutations impact glucose homeostasis has not been assessed[143].

Aside from genetic contributions, during the pathogenesis of diabetes signals that regulate VDCC activity change and likely impact β-cell Ca^{2+} influx and insulin secretion. For example, PIP_2 β-cell increases VDCC activity[144]. As detailed above, PIP_2 signaling becomes disrupted under the insulin resistant conditions of T2D due to reduced insulin-induced activation of the β-cell PI3K/AKT pathway[132]. Therefore, reductions in β-cell PIP_2 levels would be predicted to impair VDCC activity in T2D. Furthermore, inflammatory cytokines are known to increase in T2D and cytokines impact VDCC activity. Short term

exposure of β-cells to cytokines has been shown to increase low-voltage activated VDCC currents[145], which would be expected to actually enhance insulin secretion. However, elevated basal β-cell Ca^{2+} levels on a background of insulin hypersecretion may also have negative impacts such as enhancing β-cell ER-stress and mitochondrial dysfunction causing deterioration of β-cell health[146]. Indeed, VDCC inhibition with verapamil has been found to protect β-cells from the stressful conditions of T2D. While this is due in-part to verapamil-mediated repression of thioredoxin-interacting protein expression that results in reduced oxidative stress[135], other agents such as diazoxide that also limit VDCC activity by hyperpolarizing the β-cell V_m protect β-cells from failure under T2D conditions[147, 148]. It is known that during the early stage of T2D development, β-cells compensate for insulin resistance by secreting more insulin through elevated total Ca^{2+} influx. Thus, the relationship between VDCC activity and β-cell function in T2D may depend on the stage of the disease[6].

While changes in VDCC activity can result in T2D [6, 141], there are also changes in location of VDCCs to the insulin granule that are negatively impacted during the pathogenesis of T2D[149]. During insulin secretion VDCCs cluster near granule release sites[149]. β-cell L-type VDCC clusters of 15 to 20 channel complexes form near insulin granules during secretion[149]. VDCC clustering allows for greater depolarization-induced Ca^{2+} entry near docked insulin granules, which helps to promote insulin granule fusion with the plasma membrane[149]. In T2D β-cells Ca^{2+} influx near granules is disrupted and total depolarization-induced Ca^{2+} entry is reduced[149]. Ca^{2+} entry at the plasma membrane micro domains near insulin granules in response to membrane depolarization is also significantly reduced in T2D β-cells[149]. Furthermore, insulin granule release does not preferentially occur near Ca^{2+} entry sites in T2D[149]. Therefore, both Ca^{2+} handling and granule location to hot spots for Ca^{2+} entry following secretagogue stimulation are perturbed in T2D β-cells.

Na^+ Channels—Voltage-gated Na^+ channels play an important role in controlling action potential firing in human β-cells. Thus, inhibition of VGSCs results in reduced human β-cell AP amplitude, diminished Ca^{2+} entry, and reduced insulin secretion [77]. β-cell ablation of rodent VGSC encoding α-subunits (e.g. Scn3a) or β-subunits (e.g. Scn1b) also leads to reduced GSIS[150, 151]. While mutations or polymorphisms in VGSC encoding genes have not been shown to increase diabetes risk, a gain-of-function mutation in $Na_v1.7$ (I739V) has been identified that causes painful neuropathy[152]. Two thirds of the patients identified with this GOF $Na_v1.7$ (I739V) mutation also developed diabetes[152], which suggests that increased VGSC may result in a diabetic phenotype but further studies are required to support this. As blocking VGSCs causes reduces insulin secretion[77], it seems counterintuitive that more activity of VGSCs could cause β-cell dysfunction. However, blockade of VGSCs with carbamazepine has been shown to protect β-cells from inflammation associated β-cell destruction[153]. VGSC inhibition may reduce β-cell excitotoxicity in response to the increased electrical excitability of β-cells required to meet increasing insulin demand in T2D; indeed this has been shown in T2D after reducing β-cell electrical excitability with the K_{ATP} activator diazoxide[147]. However, there are many off target influences of carbamazepine such as VDCCs[154], which may also play a role in the

β-cell protective influences of carbamazepine. Interestingly, there is heterogeneous expression of Scn3a in human islet β-cells, which potentially implicates that the different amounts of β-cell VGSCs could provide variability in β-cell electrical excitability and GSIS[155]. Heterogeneity of human β-cell Scn3a expression may also impact sensitivity to excitotoxicity that occurs during the pathogenesis of T2D.

Swell-Activated Cl^- Channels (SWELL)—During glucose stimulation β-cells swell leading to activation of volume-regulated anion current (VRAC), which is also termed the swell-activated Cl^- current (I_{Cl}-,SWELL)[156–158]. VRAC/SWELL activation allows for the regulatory volume decrease (RVD) that occurs following exposure of β-cells to hypoosmotic conditions[156]. Although VRAC/SWELL would be predicted to produce RVD following glucose-induced swelling, β-cells maintain an increased volume during the duration of glucose stimulation[156]. Thus, VRAC/SWELL currents activated during glucose-induced swelling remain active until euglycemia has been reached[156]. The leucine-rich repeat–containing (LRRC8) proteins form the channels termed SWELL1, which are responsible for the VRAC/SWELL currents in β-cells[159]. When SWELL1 is activated during glucose-induced β-cell swelling Cl^- efflux through these channels enhance depolarization leading to greater Ca^{2+} influx through VDCCs[156–158]. Although SWELL1 serves as a critical ion channel that controls glucose-stimulated β-cell depolarization, this channel complex has also been shown to transport neurotransmitters such as glutamate and γ-aminobutyric acid (GABA)[160, 161]. Because ionotropic glutamate and GABA receptors play an important role in regulating β-cell electrical excitability (detailed below), SWELL1 may contribute to controlling the activities of these receptors by influencing ligand release from β-cells. SWELL1 activity may change under diabetic conditions; for example, the GLUT1, GLUT-2 and glucokinase are reduced in T2D islets[162] and the resulting reduction in glucose transport and utilization in T2D β-cells could lead to reduced swelling as well as activation of SWELL1. Therefore, reduced SWELL1 in T2D could reduce glucose-stimulated depolarization, VDCC activation and insulin secretion.

Ionotropic Receptors

Neuronal innervation as well as paracrine mediated neurotransmitter release modulates islet cell function in part through ionotropic receptors, which becomes disrupted during the pathogenesis of diabetes. The main ionotropic receptors expressed in the islet are: GABA receptors, glycine receptors, purinergic receptors and glutamate receptors(Figure 4) [163–167], as we discuss below.

GABA receptors—GABA receptors (GABARs) are also expressed on human β-cells. GABARs are chloride channels that when activated depolarize the β-cell and have been shown to stimulate VDCC activity leading to insulin secretion[163]. Depolarization by GABARs is due to Cl^- efflux from the β-cell (Figure 4); a high intracellular concentration of Cl^- in β-cells allows for Cl^- efflux at the V_m from where electrical excitability occurs[168]. However, there is also evidence that activation of GABARs can inhibit insulin secretion; this results either due to voltage-dependent inactivation of VGSCs and VDCCs or potentially via Cl^- influx through GABARs instead of efflux[169]. β-cells that are depolarized above the reversal potential of Cl^- (~−40mV) would be expected to show Cl^- influx through GABARs

and this could be the case under conditions of excessive depolarization, which may occur under certain conditions such as T2D patients treated with sulfonylureas. Islets from T2D donors also show reduced expression of ionotropic GABA(A)Rs, which would be predicted to reduce GABA signaling[170]. GABA is produced and secreted from β-cells. GABA levels are reduced in T2D islets[169]. The enzyme GAD65 that produces GABA from glutamate shows reduced activity under the stressful conditions associated with T2D, which can be due to changes in transcription of GAD65 as well as perturbations in palmitoylation that change the intracellular localization of GAD65[171, 172]. Reduced GAD65 activity leads to reduced β-cell GABA in human islets from patients with T2D[169]. To compensate for the reduced GABA levels the islet GABARs show increased open probability and current in T2D β-cells when compared to nondiabetic (ND) β-cells[169]. This is not due to expression differences in the genes that encode GABARs as these receptors show equivalent expression in non-diabetic and T2D islets[169].

GABA has also been reported to have protective impacts on β-cell function, stimulate β-cell replication, as well as promoting α-cell neogenesis and conversion into β-cells[173–177]. GABA stimulated β-cell depolarization causes Ca^{2+} entry, which can activate PI3K and Akt signaling pathways that promote growth and survival[178]. While this may be one mechanism that promotes β-cell replication in response to GABA, it has also been shown that GABA promotes α-cell neogenesis and transdifferentiation to increase β-cell mass[174]. GABA induced β-cell formation through α-cells would be predicted to incorporate GABA-induced changes in V_m potentially through hyperpolarization induced inhibition of glucagon secretion, which could lead to α-cell hyperplasia that occurs during conditions of reduced liver glucagon signaling[179]. The positive impacts of GABA on β-cell number and function indicate that increasing GABA or GABA activity in islets during the pathogenesis of T2D would limit β-cell dysfunction and maintain β-cell mass[173–176]. For example, positive allosteric modulators that enhance GABA activity on GABARs result in enhanced human β-cell replication and GABAR activators (e.g. muscimol) stimulate human β-cell calcium entry and insulin secretion[180]. However, it is worth keeping in mind that recent studies call into question whether activation of GABARs enhance β-cell mass or function[181, 182]. Thus, more studies are needed to fully elucidate the functional role of GABAR in β-cells.

Glycine receptors—Human β-cells express ionotropic glycine receptors (GlyRs) including GlyRα1 and GlyRα3[164]. Glycine is also found in insulin secretory granules and can be released during GSIS[183]. GlyR activation by glycine results in β-cell Cl^- efflux leading to V_m depolarization and increased electrical excitability (Figure 4)[164]. Glycine-induced elevations of human β-cell Ca^{2+} enhance insulin-secretion and thus glycine provides autocrine feedback to enable greater GSIS. Furthermore, supplementation with glycine improves human glucose tolerance[184–188]. Patients with T2D show decreased expression of the GlyRα1 transcript as well as protein abundance[5, 164]. Reduced GlyRα1 in T2D β-cells would be predicted to reduce glycine-induced depolarization and the resulting amplification of insulin secretion. Indeed glycine induced Cl^- currents are reduced by ~50% in β-cells from T2D donors when compared to nondiabetic β-cells[164]. Moreover, T2D patients treated with conditions that increase plasma glycine levels show improved glucose

handling and a delay in diabetes onset[155; 156; 157; 158; 159]. Interestingly, insulin also stimulates GlyR activity[164, 189] and therefore the insulin resistance associated with T2D is predicted to reduce GlyR activation during glucose-stimulation. Taken together, these data suggest that glycine control of β-cell Ca^{2+} entry through activation of GlyRs is perturbed in T2D and contributes to reductions in β-cell Ca^{2+} handling and insulin secretion.

Purinergic receptors—The P2X purinoceptors (P2XRs) are activated by purinergic ligands such as ATP and are primarily permeable to Ca^{2+} (Figure 4). There are many P2X receptors expressed in human β-cells including P2X2 P2X3 P2X4 P2X6 and P2X7[165]. All P2X receptors would contribute to ATP-induced Ca^{2+} entry and enhancement of insulin secretion (Figure 4)[166]. As ATP is released from insulin granules during GSIS[190], P2XR activation augments glucose-stimulated Ca^{2+} entry and thus GSIS[166]. While the exact role for each P2X receptor of the human β-cell has yet to be conclusively established, changes in P2X receptor protein levels have been observed in T2D islets[165]. Specifically, P2X7 levels are reduced in β-cells of patients with T2D[165]. Interestingly, *P2XR7* expression and P2X7 protein levels are also controlled by glucose and saturated fatty acid levels[165]. When glucose and palmitic acid are elevated human islets show increased P2X7 levels in the short term[165]. This suggests that increased P2X7 levels can help β-cells adapt to the toxic conditions that eventually cause T2D. As P2X7 levels eventually drop in T2D, reduced P2X7 during prolonged stress may lead to reductions in GSIS due to reduced Ca^{2+} entry.

Polymorphisms near or in the *P2XR7* gene are also associated with changes in glucose homeostasis[191]. A GWAS study in a Chinese population identified many polymorphisms near *P2XR7* that is associated with an increased risk of developing T2D[192]. Certain polymorphisms in or near *P2XR7* were also found associated with changes in insulin sensitivity and variations in glucose homeostasis[191]. Moreover, a missense polymorphism (rs1718119) that results in A348T within P2RX7 was identified that is associated with increased insulin sensitivity and greater insulin secretion. Importantly, the P2RX7 A348T results in a gain-of-function that increases channel activity in response to ATP and is thus predicted to enhance β-cell Ca^{2+} entry and insulin secretion[191, 193]. On the other hand, rodents with a P2RX7 variant (P451L) that results in a loss-of channel function show impaired glucose tolerance and insulin resistance compared to controls (with a proline at position 451), which suggests a potential impairment in islet function[191]. Therefore, P2RX7 plays an important role in enhancing β-cell insulin secretion and reduced P2RX7 function leads to islet dysfunction and insulin resistance, which increases the risk of T2D.

Glutamate receptors—Many ionotropic glutamate receptors are expressed in the islet (reviewed in[194]). They are known to be responsible for controlling α-cell Ca^{2+} handling and glucagon secretion as well as δ-cell somatostatin secretion[195, 196]. In the β-cell the primary ionotropic glutamate receptor that controls membrane potential are N-methyl-d-aspartate receptors (NMDAR), which are composed of GluN subunits including the GluN1 obligatory subunit. Interestingly, NMDAR activation limits glucose-stimulated Ca^{2+} influx in human and mouse β-cells, which has been proposed to be due to activation of K^+ conductance that leads to inhibition of VDCC activity[167]. Recently, NMDARs have been

reported to regulate the trafficking of K_{ATP} channels and $K_v2.1$ channels in INS-1 and dispersed human β-cells[197]. Stimulation of NMDARs either directly by agonists or by leptin acting on β-cell leptin receptors increases the abundance of K_{ATP} and $K_v2.1$ channels at the cell surface and results in membrane hyperpolarization, which would explain how activation of NMDARs inhibits GSIS.

Patients with T2D show elevations in glutamate levels[198, 199]. This change has to do with differences in consumption but also changes in liver production of glutamate[169; 170]. Thus, elevations in glutamate in obese individuals during the pathogenesis of T2D may lead to over activation of NMDARs. Moreover, hyperglycemic conditions have been shown to lead to increased β-cell glutamate release, which could also contribute to impaired β-cell function in T2D. Importantly, inhibition of NMDARs with dextromethorphan leads to both enhanced insulin secretion as well as protecting β-cells from failure in response to the stressful conditions associated with T2D[167]. Interestingly the enhanced insulin secretion effect by NMDAR inhibitors is dependent on the presence of K_{ATP} channels as mouse islets from Kir6.2 knockout animals failed to show such response, suggesting NMDAR inhibition stimulates insulin secretion by blocking NMDAR-dependent K_{ATP} channel trafficking to the β-cell membrane. Although NMDAR inhibition allows greater glucose-stimulated Ca^{2+} entry into β-cells stimulating GSIS, elevated NMDAR activation also promotes Ca^{2+} permeability through these ionotropic receptors. Thus, continual NMDAR Ca^{2+} permeability in T2D may perturb Ca^{2+} handling, which is predicted to reduce both insulin secretion as well as negatively impact β-cell health. This is supported by experiments on rodent β-cells that show reduced cell viability and decreased GSIS with chronic NMDAR activation. Treating diabetic rodents with an NMDAR antagonist (memantine) improved β-cell function and glucose homeostasis[198]. Together, these studies show that human β-cell NMDAR activity plays an important role in Ca^{2+} handling and suggest NMDARs as a therapeutic target for T2D.

Conclusions and Future Perspectives

Recent advances in human genetics, transcriptome and proteome analyses of normal and T2D islet cells reaching single cell resolution, and mechanistic analysis of ion channel regulations in cell lines, isolated islets and animal models have markedly improved our understanding of the role of ion channels in islet biology and how ion channel dysregulation contributes to dysfunction of the islets, in particular the ability of β-cells to secrete sufficient insulin in T2D. Despite the progress, many questions remain and translating the knowledge gained into clinical practice for the prevention and treatment T2D is still challenging.

From the genetic study perspective, while GWAS data offer potential T2D risk candidates they often need to be followed up by careful mechanistic studies to demonstrate causality. In this regard, studying human extreme phenotypes such as monogenic diabetes including neonatal diabetes and maturity onset diabetes of the young (MODY) have proven fruitful in identifying ion channels that are critical for insulin secretion. However, even when there is evidence for causality, genetic variations of a specific ion channel gene alone are unlikely to serve as a strong predictor of disease propensity since genetic background, epigenetic and environmental factors could impact how genetic variations manifest. As an example, genetic

association studies in different ethnic populations often uncover different genetic risk factors. Most genetic studies thus far have focused on linkage with increased risk of T2D. It may be informative to also analyze genetic traits pertaining to ion channels of the islets that are protective against T2D. This approach has been successfully employed to identify genetic variants of proteins important for cardiovascular function, specifically in controlling cholesterol levels.

Mechanistic studies probing the functional role of ion channels have often been conducted in cell lines and transgenic mouse models. Results from these studies may or may not translate to humans as there is clear evidence that β-cell ion channel compositions are not identical in rodents and humans. Further, findings from mouse models can be clouded by the genetic background and strategies of genetic manipulations used. There is also the added caution of metabolic differences between rodents and humans. Efforts to study human islets are also met with potential variations from donors of different gender, age, ethnicity, and in the case of T2D, stage of the disease and other metabolic indicators such as obesity.

A central theme highlighted in this review is the importance of Ca^{2+} homeostasis in β-cell function and health. Intracellular Ca^{2+} is handled by not only ion channels present in the plasma membrane but also intracellular membranes including the ER, the mitochondria, and lysosomes. The coordinated actions of ion channels involved in Ca^{2+} handling and their regulation by signaling molecules afford β-cells the ability to adapt to increased insulin demands such as during pregnancy or mild insulin resistance. However, while enhanced Ca^{2+} signals are expected to augment insulin secretion and improve glucose tolerance, prolonged and unchecked Ca^{2+} signals can harm β-cells, resulting in β-cell excitotoxicity that reduces insulin secretion and causes β-cell demise. Therefore, strategies which enhance insulin secretion without causing permanent cell damage are needed. Better understanding of Ca^{2+} handling with increased temporal and spatial resolutions under physiological and pathological conditions will be important for such efforts.

Finally, pharmacological agents targeting β-cell ion channels are an essential part of the therapeutic development efforts for T2D. Currently available drugs or toxins have largely been discovered by serendipity or screening compound libraries. Rational drug design based on ion channel mechanisms has been limited by the difficulty in obtaining high resolution structures of these membrane proteins. Recent advances in single-particle cryo-electron microscopy techniques have made it possible to obtain high resolution structures of many ion channels at an astonishing pace. This presents an exciting opportunity for designing new and improved drugs that target β-cell ion channels for the treatment of T2D and other insulin secretion diseases.

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- Ca^{2+} is an essential signal for pancreatic β-cell function including insulin secretion, transcription, metabolism, and the stress response.
- β-cell Ca^{2+} signals are governed by orchestrated activities of ion channels.
- In type 2 diabetes, disruption of ion channel function and regulation leads to β-cell excitotoxicity and Ca^{2+} mishandling to impair glucose-induced insulin secretion response.
- Understanding the ionic mechanisms that regulate insulin secretion will help identify therapeutic modalities for diabetes that target the excitation-secretion pathway.

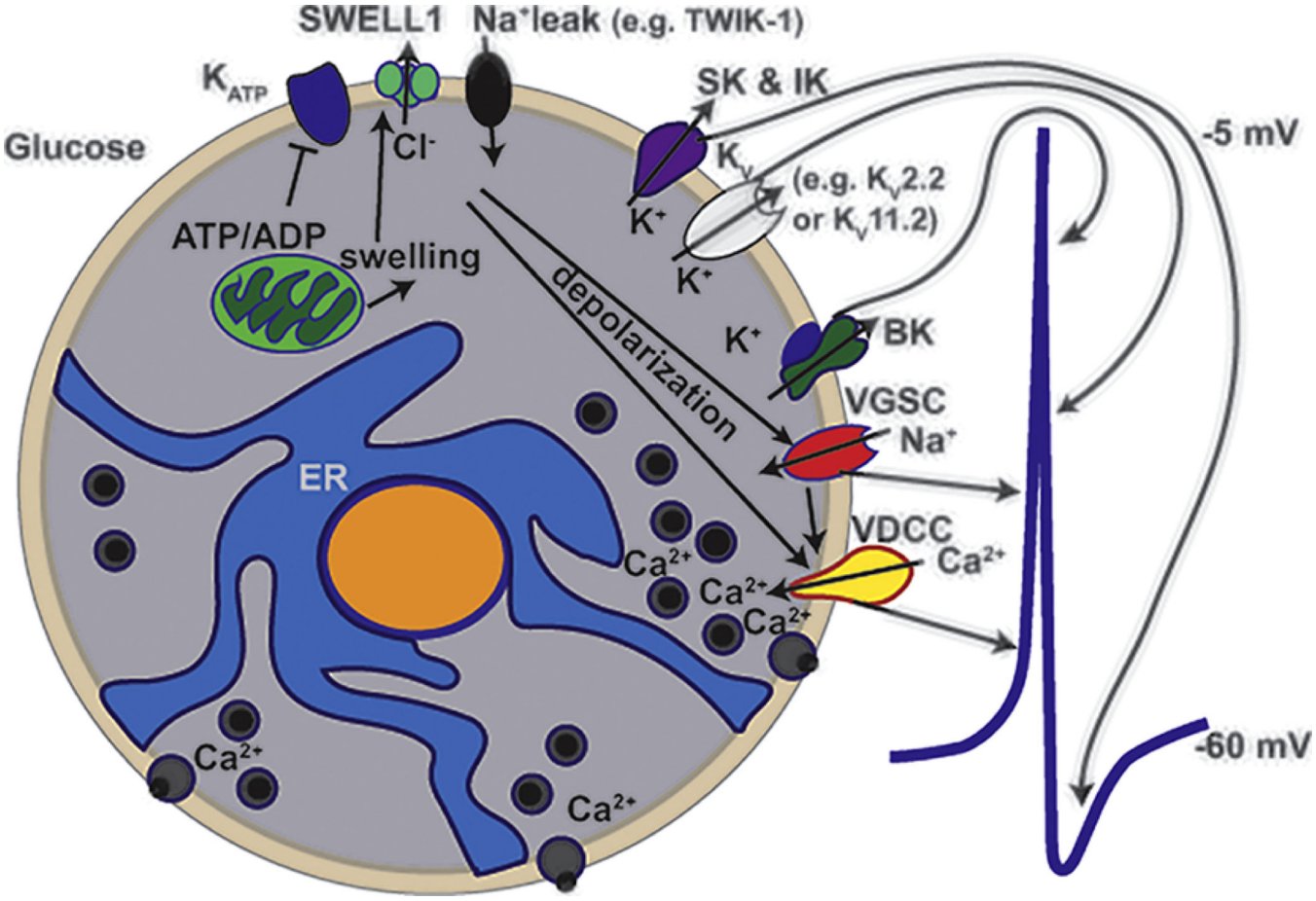

Figure 1:

Ion channels that contribute to the human β-cell action potential. Glucose is taken up and metabolized in β-cells resulting in both an increase in the ATP/ADP ratio as well as cell swelling. The increase in the ATP/ADP ratio leads to K_{ATP} closure whereas swelling activates SWELL-1 Cl^- efflux. Reduced K_{ATP} activity together with the depolarizing influences of SWELL1 mediated Cl^- efflux and Na^+ influx through Na^+ leak channels results in V_m depolarization. V_m depolarization activates voltage-dependent Ca^{2+} channels (VDCCs) and voltage-gated Na^+ channels (VGSCs) that are responsible for the upstroke of the action potential (AP); a representative human β-cell AP is shown on the right side of the β-cell. The rapid V_m depolarization as well as Ca^{2+} entry that occurs during the AP upstroke activates K^+ channels including BK, K_V, SK and IK. BK channels are voltage and calcium activated, which provide the largest conductance and fastest activating K^+ current that is responsible for the initiation of AP repolarization. K_V channels are activated by V_m depolarization and also contribute to AP repolarization. Finally, the Ca^{2+} activated K^+ channels including SK and IK are smaller conductance K^+ currents that stay active for longer following AP repolarization leading to afterhyperpolarization and a reduction in AP frequency.

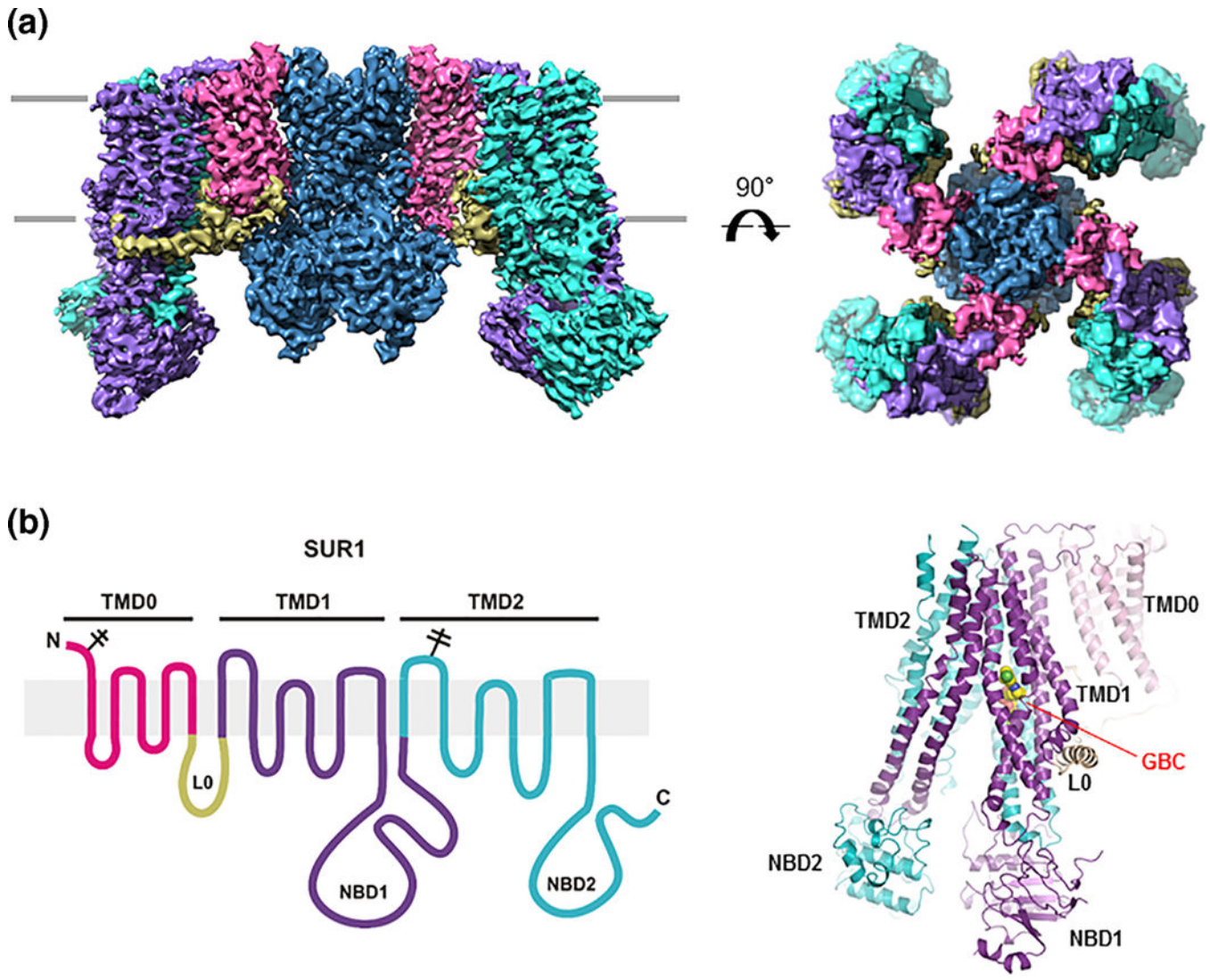

Figure 2:

(A) CryoEM structure of the K_{ATP} channel viewed from the side (*left*) and the top (*right*). (B) *Left*: SUR1 topology showing the different domains. *Right*: Structure of SUR1 built from cryoEM density map showing the glibenclamide (GBC) binding site above NBD1 in the transmembrane bundle formed by transmembrane helices from both TMD1 and TMD2.

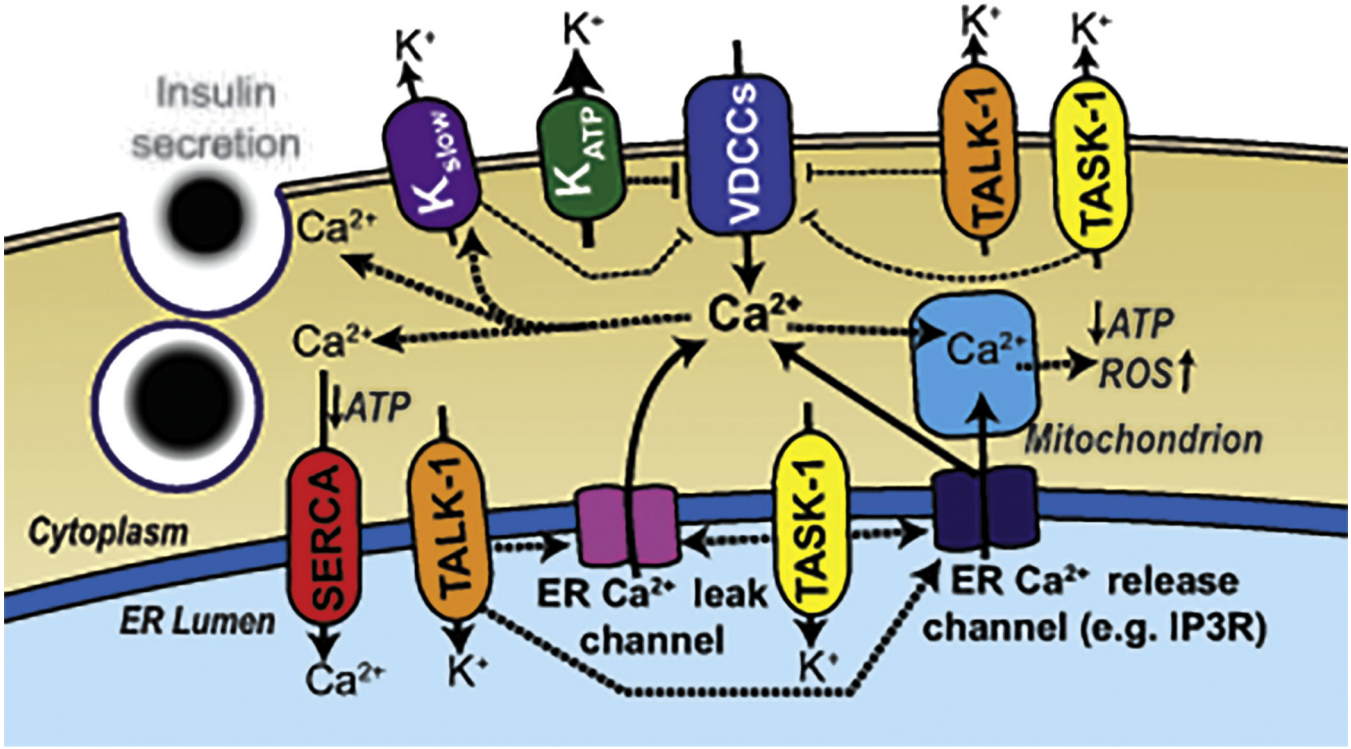

Figure 3:

Ion channels that control where the β-cell V_m sits. At rest the activity of K_{ATP} channels holds the β-cell V_m below the activation threshold for VDCCs. When blood glucose concentrations are elevated closure of K_{ATP} leads to V_m depolarization. During glucose-induced K_{ATP} closure the constitutive activity of small conductance K2P potassium channels such as TALK-1 and TASK-1 balance the depolarizing conductance from SWELL-1 and Na^+ leak channels at a depolarized plateau potential from where VDCCs and VGSCs can efficiently activate, allowing AP firing. Ca^{2+} entry which occurs during VDCC activation leads to Ca^{2+} release from the endoplasmic reticulum (ER), which results in activation of Ca^{2+} activated K^+ currents (K_{slow}) that hyperpolarize the V_m leading to VDCC closure. K_{slow} currents eventually inactivate in response to the resulting low Ca^{2+} levels caused by hyperpolarization-induced closure of VDCCs, which results in another wave of depolarization and Ca^{2+} influx. These β-cell oscillations in V_m and Ca^{2+} are responsible for pulsatile insulin secretion. K2P channels such as TALK-1 also form functional complexes on the ER membrane. ER TALK-1 channels provide a countercurrent for Ca^{2+} ions leaving the ER and potentiate ER Ca^{2+} release. This is important for increasing K_{slow} activation and therefore loss of TALK-1 channels impairs Ca^{2+} ER release limiting the K_{slow} current and increasing Ca^{2+} oscillation frequency. Other K2P channels expressed in the human β-cell (e.g. TWIK-1 and TALK-2) also presumably play roles in regulating V_m or ER Ca^{2+} handling.

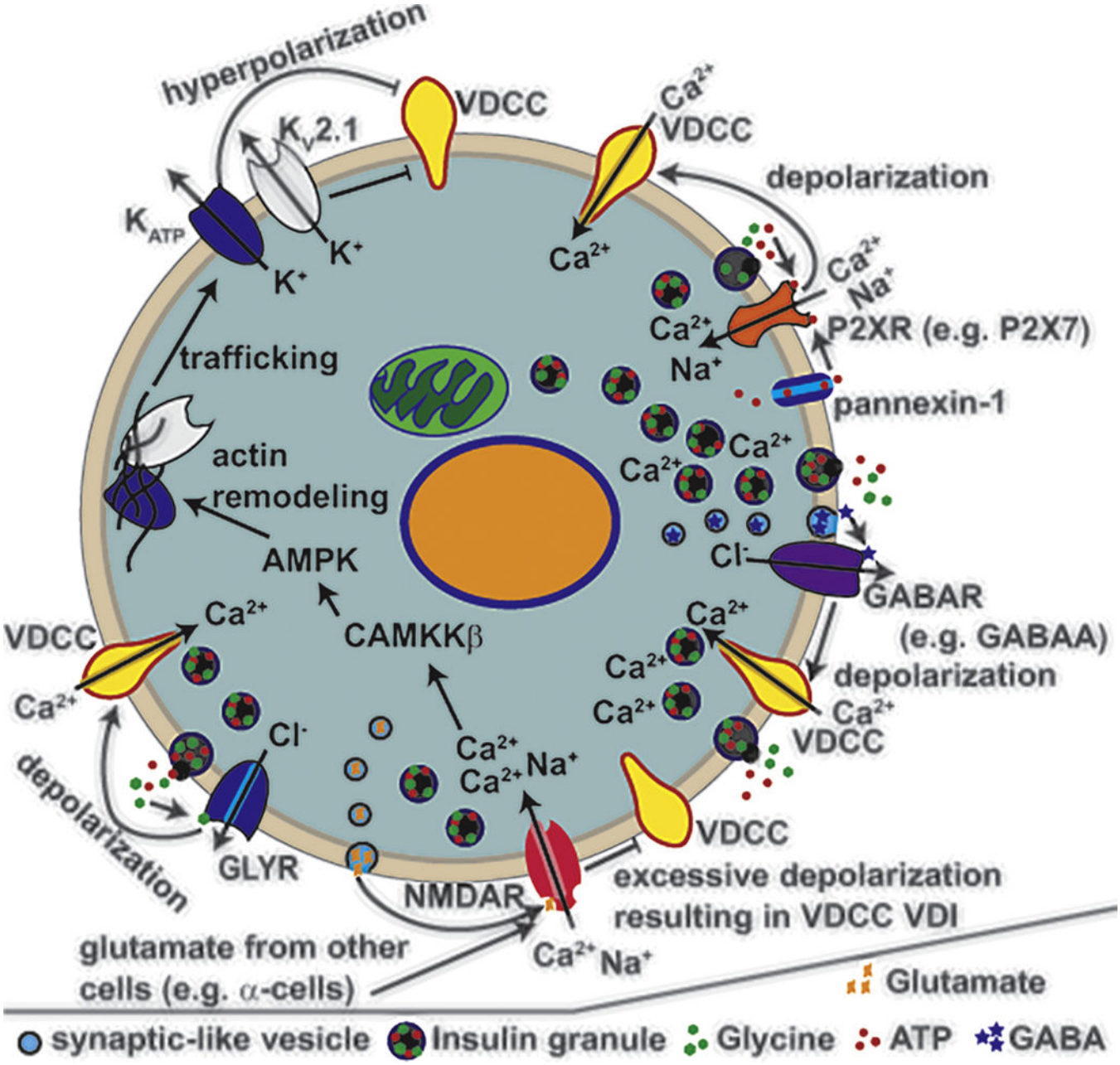

Figure 4:

Ionotropic receptors that control β-cell insulin secretion. Ionotropic receptors expressed in human β-cells are activated by ligands and selective to specific ions. Upon activation the ionotropic receptors modulate VDCC activity by controlling the V_m. Ionotropic receptors that are permeable to Cl^- such as the glycine receptors (GLYRs) and GABA receptors (GABAARs) lead to V_m depolarization upon activation due to Cl^- efflux, which results in enhanced VDCC activation and insulin secretion. Ionotropic receptors that are permeable to Ca^{2+} and Na^+ such as the NMDARs and P2XRs lead to both Ca^{2+} entry and V_m depolarization upon activation. While P2XRs enhance Ca^{2+} entry and GSIS, NMDARs cause the opposite. Two possible mechanisms for NMDAR inhibition of GSIS are through

excessive depolarization causing voltage-dependent inactivation of VDCCs or through enhanced trafficking of K^+ channels (including K_{ATP} and $K_V2.1$) to the plasma membrane leading to V_m hyperpolarization. Ionotropic receptor ligands are released from the β-cell (autocrine) or are released from other nearby cells (paracrine) to control β-cell function.

Table 1.

Genetic Variations in Ion Channels Implicated in Diabetes [1]

Gene Name	Common Name	Proposed function in β-cells	Polymorphisms or mutations	Functional effects on the channel	Impact on blood glucose	References
KCNJ11	Kir6.2 (K_{ATP} pore subunit)	setting resting V_m	p.E23K	Gain of function	Increased risk of T2D	[26, 27]
ABCC8	SUR1 (K_{ATP} regulatory subunit)	setting resting V_m	p.R370S	Loss of function	Associated with hyperinsulinemia early in life but glucose intolerance or diabetes in adult carriers	[34]
ABCC8	SUR1 (K_{ATP} regulatory subunit)	setting resting V_m	p.E1507K	Loss of function	Associated with hyperinsulinemia early in life but glucose intolerance or diabetes in adult carriers	[32, 33]
KCNK16	TALK-1	V_m; ER K^+ flux	p.A277E	Gain of function	Increased risk of T2D	[58, 59, 70]
KCNH6	hERG2 (Kv11.2)	AP repolarization?	P235L	Loss of function	Hyperinsulinemia hypoglycemia early in life and hyperinsulinemia and diabetes in adults	[103]
KCNJ9	Kir3.3 or GIRK3	GPCR activation induced V_m hyperpolarization	p.V366A	Not determined	Increased risk of T2D in PIMA Indians	[124]
SCN9A	Nav1.7	AP	p.I739V	Gain of function	Two thirds of these patients developed diabetes	[152]

[1] Note numerous gain of function mutations causing neonatal diabetes have been identified in *KCNJ11* and *ABCC8*; they are not listed in this table.