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REVIEW

Electrophysiology of pancreatic beta cells: a comprehensive review of ion channel function, electrical activity, and secretory mechanisms

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ABSTRACT
Pancreatic β-cells play a crucial role in maintaining glucose homeostasis through the regulation of insulin secretion. The electrophysiological properties of these cells, including ion channel function, electrical activity, and secretory mechanisms, are essential for their proper physiological function. In this comprehensive review, we provide an in-depth analysis of the electrophysiology of pancreatic β-cells. We discuss the various ion channels involved in the generation and modulation of electrical signals, such as voltage-gated ion channels, ATP-sensitive and delayed rectifier potassium ion channels, calcium ion channels, chloride channels and transient receptor potential channels. Additionally, we examine the intricate interplay between intracellular calcium dynamics and insulin release. Furthermore, we explore the physiological and pathological factors that influence the electrophysiology of β-cells. A comprehensive understanding of the electrophysiological mechanisms governing pancreatic beta cell function is crucial for elucidating the pathogenesis of diabetes mellitus and developing novel therapeutic strategies.

Keywords: Pancreatic beta cell, insulin; electrophysiology, K_{ATP} channels, BK channels, TRPM channels

ÖZET
Pankreas Beta Hücrelerinin Elektrofizyolojisi: İyon Kanal Fonksiyonları, Elektriksel Aktivite ve Sekresyon Mekanizmalarının Kapsamlı Bir Derlemesi
Pankreatik β-hücreler, insülin salınımının düzenlenmesi yoluyla glukoz homeostazının korunmasında hayati bir rol oynar. Bu hücrelerin iyon kanalı fonksiyonu, elektriksel aktivite ve sekresyon mekanizmaları gibi elektrofizyolojik özellikleri, fizyolojik görevlerini sağlıklı bir şekilde yerine getirebilmeleri açısından kritik öneme sahiptir. Bu kapsamlı derlemede, pankreatik β-hücrelerin elektrofizyolojisi ayrıntılı olarak ele alınmaktadır. Elektriksel sinyallerin oluşumu ve modülasyonunda rol oynayan voltaj kapılı iyon kanalları, ATP'ye duyarlı ve gecikmeli rektifiye potasyum kanalları, kalsiyum iyon kanalları, klor kanalları ve geçici reseptör potansiyel (TRP) kanalları gibi çeşitli iyon kanalları tartışılmıştır. Ayrıca, hücre içi kalsiyum dinamiği ile insülin salınımı arasındaki karmaşık etkileşim incelenmiştir. Bunun yanı sıra, β-hücre elektrofizyolojisini etkileyen fizyolojik ve patolojik faktörler de gözden geçirilmiştir. Pankreatik beta hücre fonksiyonlarını yöneten elektrofizyolojik mekanizmaların kapsamlı bir şekilde anlaşılması, diyabetes mellitus patogenezinin aydınlatılması ve yeni tedavi stratejilerinin geliştirilmesi açısından büyük önem taşımaktadır.

Anahtar kelimeler: Pankreatik beta hücreleri, insülin, elektrofizyoloji, K_{ATP} kanalları, BK kanalları, TRPM kanalları

INTRODUCTION

Insulin is a hormone that plays a major role in regulating glucose levels because it is the only known hormone in the human body that lowers blood sugar levels. Insulin is secreted by β-cells, which are located in the islets of Langerhans and make up the largest population in the islets, at 60-90%. Patch-clamp studies revealed that there are a wide variety of ion channels in pancreatic β-cells [2]. The major role of these ion channels is to regulate the electrical activities of the cells. With the discovery of ATP-sensitive potassium ion (K_{ATP}) channels, which are considered to be the cornerstone of this subject, the understanding of

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the mechanism of insulin release has greatly improved [3]. These K_{ATP} channels in β-cells show spontaneous activity at low glucose levels, creating a negative charge inside the cell by allowing the efflux of positively charged K ions from the cell, thus creating a negative membrane potential in the unstimulated beta cell. On the other hand, glucose inhibits K_{ATP} channels in a concentration-dependent manner by increasing the ATP/ADP ratio, thus depolarizing the cell. This depolarization causes voltage-sensitive Ca^{2+} channels to open (mostly the L, T and P/Q types) and maintains plateau-like depolarization [4]. In addition, increased intracellular Ca^{2+} concentrations also trigger insulin release. The triggering of insulin release by glucose stimulation is summarized in Figure1.

Although the factors stimulating insulin release act by increasing beta cell electrical activity, it is still not clear exactly which channels are involved or the roles of these channels during insulin release. In this review, we focused on the electrical activity properties of β-cells and the structural and electrophysiological properties of the ion channels that generate these activities.

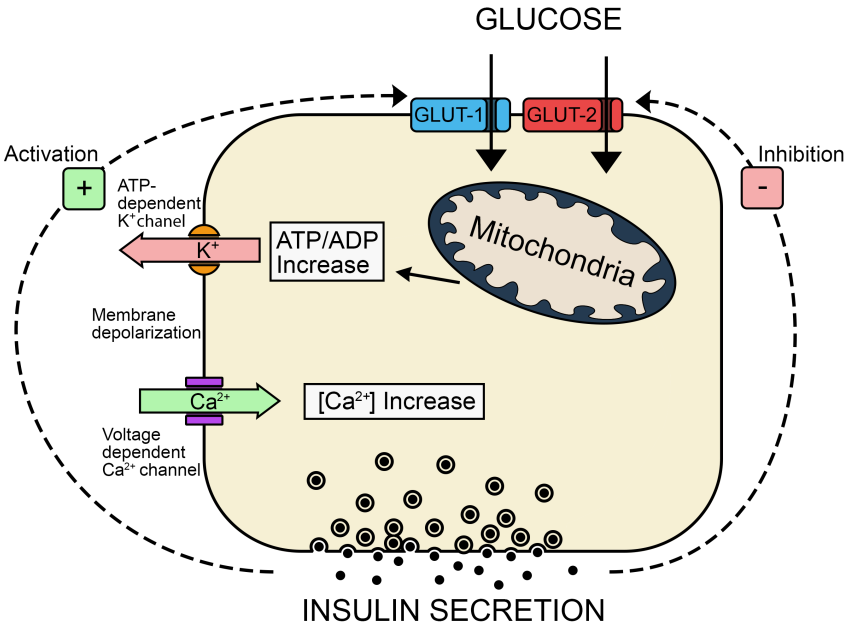

Figure 1. Insulin release by glucose stimulation

1.Basic properties of electrical potentials of β-cells

The properties of the electrical potentials of β-cells were observed via patch-clamp studies and were first described by Dean and Matthews in 1968 [5]. When glucose falls below 3 mmol/l in the cell, an electrically quiescent resting membrane potential of -70 mV is recorded in β-cells by activating K_{ATP} channels [6]. With an increase in glucose levels, a slow depolarization begins to be observed. When the intracellular glucose concentration reaches 5 mmol/l, K_{ATP} channels exhibit 10% activity, and in this case, action potential formation still does not occur. However, when the intracellular glucose concentration rises above 7 mmol/l, all the K_{ATP} channels in the cell are suppressed, and the cell reaches the threshold value (average of -50 mV) necessary to generate an action potential. The electrical activity observed in β-cells is characterized by oscillations that occur in the form of explosions. The most important feature of these oscillations is that they consist of plateau phases lasting approximately 10 seconds in which overlapping action potentials are observed, and there are periods of electrically slow depolarizations between the two plateau phases [7]. Each electrical burst first starts with a fast action potential, during which the membrane potential increases to -20 mV and then decreases to -40 mV, which is expressed as the plateau potential. The frequency of these 20 mV oscillations observed above the plateau decreases as the plateau progresses, and eventually, the plateau ends as a result of the repolarization that occurs when the membrane potential remains below the threshold value. A slow depolarization wave then begins and continues until the resting membrane potential exceeds the threshold. When the threshold value is exceeded, a new burst starts, and a new cycle is entered. As the glucose levels in the cell increase, the amplitudes and frequencies of the burst action potentials observed above the plateau increase, and the duration of the intervals observed between the plateaus become shorter. When the intracellular glucose concentration rises above 16 mmol/l, the inter-

vals between the plateau completely disappear, and the burst potential become uninterrupted [2].

In fact, there is a strong correlation between the levels of insulin secreted into the blood and the plateau time observed in β-cells [8]. Since voltage-gated Ca^{2+} channels play a role in the depolarization phase of the action potential observed in β-cells, blockade of Ca^{2+} channels leads to electrical electrical impulses, and suppressing the activity or reducing the amount of extracellular Ca^{2+} greatly reduces insulin secretion [10]. Although approximately 65% of the calcium current in β-cells is generated by L-type Ca^{2+} channels [9], blockade of L-type Ca^{2+} channels with nifedipine only temporarily inhibits the action potential generation via an unknown mechanism [10]. In contrast to this small change in the action potential, a large inhibition of insulin release is observed, indicating that the rapid exocytosis of insulin is calcium dependent [9]. R-type Ca^{2+} channels, are also found at a rate of 18% and are thought to be responsible for second-phase insulin secretion [11]. In R-type Ca^{2+} channel knockout rats, no change is observbed in rapid (action potential-dependent) phase insulin secretion; however, second-phase secretion was impaired, and R-type Ca^{2+} channels were found to be responsible for filling the emptied insulin vesicles [12]. P/Q- and N-type Ca^{2+} channels are responsible for 8-10% of the total calcium flow and are thought to be responsible for exocytosis as a result of depolarization [9].

The repolarization phase occurs with outward K^+ channels. The first K channels detected in β-cells are channels that provide K transients outward depending on Ca influx, and these channels were later found to be Ca-activated K ion channels (Big-conductance calcium-activated potassium ion channels: BKs) that provide high conductance [13]. Considering the working principle of these channels (which will be discussed in detail later), Ca^{2+} influx into β-cells is responsible not only for slow and rapid depolarization but also for K^+ output, which indirectly induces repolarization. In addition to BK channels, there are delayed rectifier K^+ channels with a conductivity of 8-9 picosiemens/meter (pS/m) in β-cells [14]. These channels provide K^+ output independent of Ca^{2+} concentration but are voltage dependent during repolarization, and MacDonald et al. showed that they are Kv2.1-type ion channels [15].

2.Ion channels involved in the electrical activity of β-cells

As mentioned above, the channels involved in the formation of oscillatory electrical activity in β-cells are very diverse. The main ones are K_{ATP} channels regulated by the intracellular ATP/ADP ratio; voltage-dependent L, P/Q, R and N-type Ca^{2+} channels; voltage-dependent Ca^{2+} inward current and intracellular Ca^{2+} inward current channels; BK channels triggered by the emptying of Ca^{2+} stores; and delayed rectifier K channels. In this section, the general features of these channels and other minor channels are described.

2.1 ATP-sensitive K^+ channels (K_{ATP} Channels)

K_{ATP} channels in β-cells make the greatest contribution to the negative resting membrane potential in β-cells [3,16]. They provide an ionic gradient with $[K^+]_o$ on average of 5 mM and $[K^+]_i$ on average of 150 mM (net 140-145 mM) while operating, and the resting beta cell membrane reaches an electrical value of -70 mV, which is very close to the K^+ equilibrium value [16]. One of the important features of these channels is that they contain Na^+ and Mg^{2+} binding sites on their inner surfaces. These cations prevent K^+ outflow from the channels at certain concentrations (34 mmol, Na^+; 46 mmol, Mg^{2+}). While the single channel permeability of the channels is highest at 140 mM external K^+ concentrations, they show saturation as $[K^+]_o$ increases and reach 50% saturation at a 220 mM external K^+ [17]. K_{ATP} channels opens in explosive bursts with variable closed intervals between them; opening voltages range from -60 and -90 mV, and each burst lasts 0.5 and 2 ms [18]. The dominant effect of ATP is to decrease the number of channels opened in each burst, to make the bursts shorter, and to increase the duration of the intervals [19]. Notably, in addition to inhibiting K_{ATP} channels, ATP also provides channel reusability by binding with Mg^{2+} [20].

2.1.1. Mechanism by which ATP inhibits K_{ATP} channels

ATP inhibits K_{ATP} channels depending on intracellular concentrion, and this inhibition occurs independently of membrane potential changes [20]. Even at different membrane potentials, 50% inhibition was observed when intracellular ATP reached 50 mM, and a full inhibitory effect was observed when it reached the millimole level; therefore, it was suggested that ATP has a specific binding site on K^+ channels [3,20,21].

In general, K_{ATP} channels exhibit an octamer structure and consist of 4 alpha (Kir6.2) and 4 beta (sulfonylurea receptor [SUR]) subunits [18,21]. Alpha-subunits are common in K_{ATP} in all tissues and participate in pore formation [22]. Beta subunits are a member of the ABCC family and have an ATP-binding cassette transporter where ATP binds to create inhibition and has regulatory functions. Three different forms of these beta subunits have been identified: SUR1, SUR2A and SUR2B. Unlike alpha-subunits, these forms differ according to the tissues in which the channels are located [23] (Figure 2a).

The binding of ATP to beta subunits closes Kir6.2 and causes depolarization in the cell. In other words, the alpha-subunit creates actual depolarization. Thus, Kir6.2 mutation, which causes a loss-of-function (LOF), persistent hyperinsulinemic hypoglycemia occurs in infants due to uncontrolled beta cell depolarization and insulin secretion [4,23-27].

LOF mutations in the Kir6.2 and SUR1 subunits are the primary cause of hyperinsulinemia and are responsible for approximately 70% of all hyperinsulinemia cases (Figure 2b) [26,27]. These mutations interfere with electrical signals in β-cells by either reducing the sensitivity of K_{ATP} or the number of active K_{ATP} channels, leading to impaired insulin release. K_{ATP} LOF

mutations can be categorized into two types: mutations that decrease channel expression on the cell surface by disrupting channel biosynthesis, structure, or assembly and mutations that reduce channel activity without affecting the number of channels [21]. Both conditions lead to decreased K_{ATP} activity, causing continuous membrane depolarization, persistent high $[Ca^{2+}]_i$ current, and uncontrolled insulin secretion, independent of blood sugar levels (Figure 2c).

Not all of the complexes formed by beta subunits reach the cell membrane, and some of them are linked to the smooth endoplasmic reticulum and are regulated by Ca^{2+} signaling [28]. Although this bond is more common in the SUR2A subtype, which is located on smooth muscle and cardiac muscle and regulates contraction, it has also been observed in the SUR1 subtype located in β-cells [3,29]. Although ATP inhibits the channels by binding to alpha-subunits, beta subunits modulate the permeability of the channels by modulating ATP sensitivity [2,8]. In particular, the subtype SUR1, located in β-cells, shows greater sensitivity to sulfonylurea drugs, the Mg–ADP complex and metabolic stress [2,3,6,16].

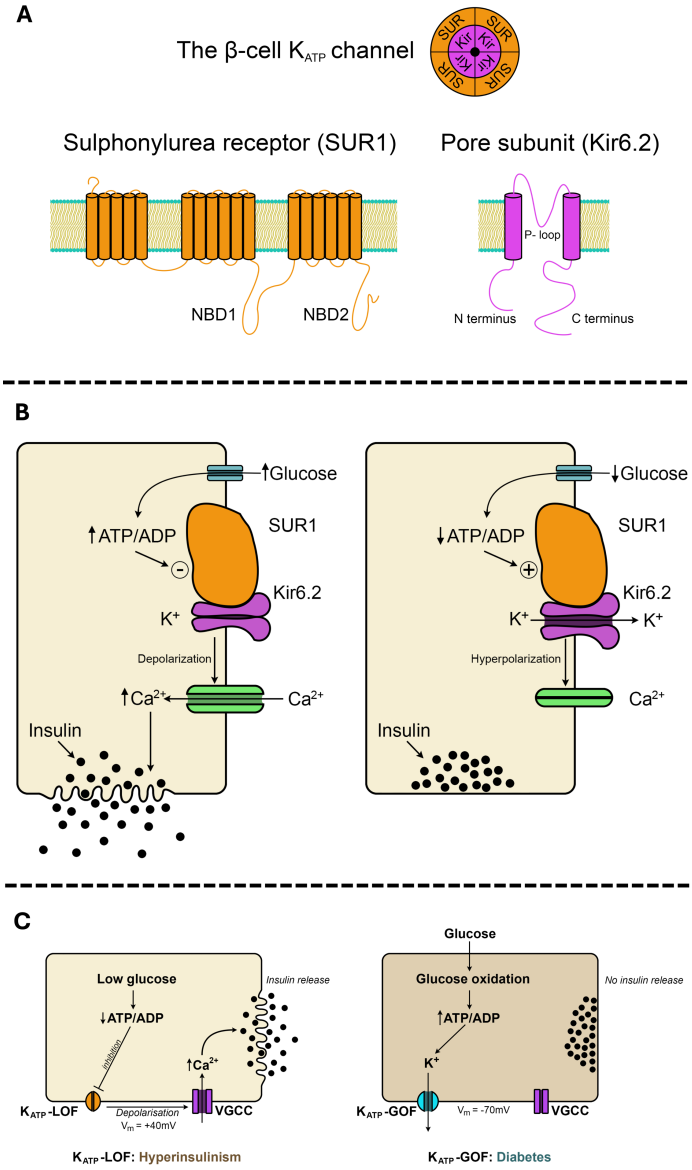

Figure 2. a. The structure of K_{ATP} channels in β-cells. While Kir6.2 s, which act as alpha-subunits in K_{ATP} channels, are responsible for forming pores, the beta subunits are composed of sulfonylurea receptor (SUR) types. K_{ATP} in β-cells contains SUR1 and the nucleotide binding domain (NBD) structures of SUR1 (adapted from [24]). **b.** Activation and inactivation of Kir 6.2 depending on ATP/ADP ratios sensed by the SUR1 subunit. (adapted from [25]). **c.** Loss-of-function (LOF) and gain-of-function (GOF) mutations in K_{ATP} channels and the resulting hyperinsulinism and diabetes, respectively (adapted from: [26]).

Although the exact mechanism by which ATP inhibits K_{ATP} channels is still unclear, phosphorylation-mediated modulation has been shown to play a role in this mechanism. Among the studies on this subject, it was shown for the first time in 1989 that phosphorylation of K_{ATP} channels prevents K^+ outflow [30]. In later studies, K_{ATP} channels were found to be activated by phosphorylation by protein kinase A (PKA) in vascular smooth muscle in response to stimulation of the D1 receptor of dopamine, which was first observed in renal artery vascular smooth muscle [31]. It has been shown that the D1 receptor activates K_{ATP} channels by stimulating PKA and it exerts a vasodilator effect due to hyperpolarization [32]. However, Hatakeyama et al. suggested that PKC-dependent phosphorylation causes vasoconstriction by inhibiting K_{ATP} in vascular smooth muscle cells [33]. This difference in the effects of PKA and PKC suggested that these two enzymes phosphorylate the protein at different sites. Lin et al. noted that the effects of protein kinases are still observed in SUR1 subunit; therefore, the alpha-subunit (Kir6.2) is phosphorylated for modulation purposes [34]. Indeed, two-phosphorylation sites have been identified on Kir6.2 (Serine 372, Threonine 224), and it has been shown that the main site to be phosphorylated during channel activation is T224 [2,3]. This suggests that K_{ATP} channels may be inhibited by the phosphorylation of ATP via S372 via PKC.

ATP is the key molecule in K_{ATP} channel activation, ATP cannot adequately induce channel inhibition in the presence of intracellular ADP and GDP [21, 35]. Since there is a decrease in the amount of ADP during glucose metabolism, many studies have showed that the effect of the change in the ATP/ADP ratio on the channels is stronger than the effect of ATP alone [16,35,36]. K_{ATP} activity was not inhibited even when $[ATP]_i$ was increased to millimolar concentrations, provided that an ATP/ADP ratio similar to that of intact β-cells was maintained [36]. However, how ADP inhibits ATP-induced inhibition is still unclear. Some studies have suggested that ADP acts as a weak agonist of K_{ATP} and competes with ATP, preventing its binding and thereby weakening its effect [16]. However, the need for Mg^{2+} while performing this task and the inability to inhibit ATP even at high levels in the absence of Mg^{2+} suggest areas where ATP and ADP binding may differ [2,3].

2.1.2. Activation and repolarization of K_{ATP} channels

Various studies have suggested that Mg^{2+}-ATP complex reactivates the channel, while decreasing ATP/ADP ratios in Mg^{2+}-deficient conditions is not effective in preventing the inhibition of the channel [26,27]. In parallel, diazoxide-derived drugs, which increase the efficiency of K_{ATP} channels, hyperpolarize β-cells and suppress insulin secretion, do not have the expected effect in patients with insulinoma. The effect of diazoxide treatment is parallel to the intracellular Mg^{2+}-ATP concentration [25,27]. It has been shown that the Mg^{2+}-ADP complex, rather than the Mg^{2+}-ATP complex, has a more potent effect on the activation of the channel, which may explain the disappearance of the inhibition of the channel in the presence of Mg^{2+} as a result of the decrease in the ATP/ADP ratio [27,36,37] (Figure 3).

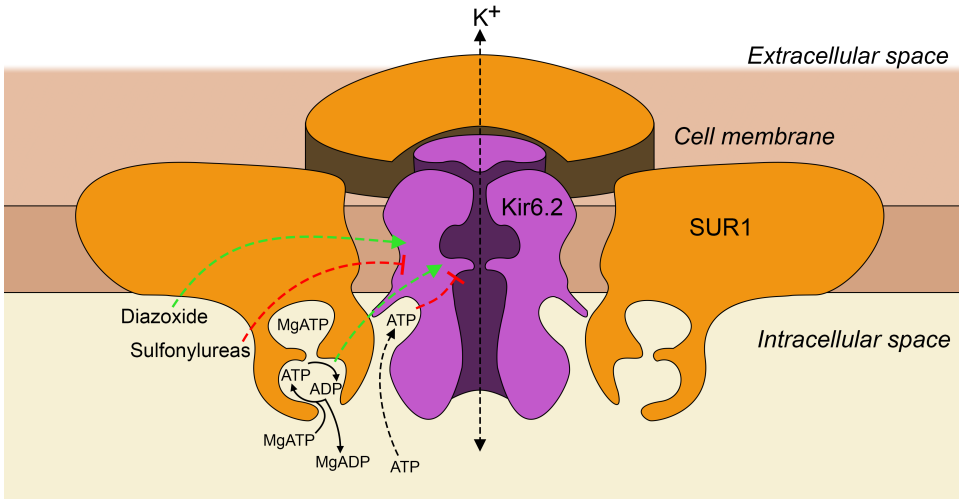

Figure 3. Signals responsible for the reactivation of Kir6.2 s. An increased intracellular concentration of the Mg–ATP complex reopens Kir 6.2 via SUR1s, providing $[K^+]_o$ current and ending the depolarization that results in insulin release. Diazoxide also acts like Mg–ATP (Adapted from: [26]).

Many LOF mutations primarily impact the SUR1 subunit, with mutations associated with the Kir6.2 subunit being much less prevalent [38]. Most mutations in SUR1 are localized in the NBDs, resulting in the loss of the activating and repolarizing effect of the Mg^{2+}-ADP complex on the K_{ATP} channel [39]. However, in certain types of NBD mutations, there may be a partial response to Mg^{2+}-ADP, preserving some residual channel activation. Compared with those with a complete loss of function, hyperinsulinemia phenotypes linked to these NBD mutations generally exhibit milder symptoms [27].

Many phosphatase enzymes work in an intracellular Ca^{2+}-dependent manner or use Mg^{2+} as a cofactor. However, since most of the studies on K_{ATP} buffer intracellular Ca^{2+}, it can be said that calcium does not have much of a role at this point; Mg^{2+} may be involved in the dephosphorylation of K_{ATP}. Activation of K_{ATP} in β-cells by phosphatases is increased, but this effect cannot be observed by buffering intracellular Mg^{2+} [40].

2.1.3. Potential role of K_{ATP} channels in diabetes pathogenesis

As previously mentioned, LOF mutations in the K_{ATP} channel have been associated with congenital hyperinsulinism. Conversely, a gain-of-function (GOF) mutation in the K_{ATP} channel led to glucose intolerance in a mouse model [41]. Subsequently, it became evident that various mutations in the K_{ATP} channel could also contribute to the development of diabetes in humans by reducing insulin secretion [42,43]. Additional studies further supported the idea that different mutation types could result in a GOF in the K_{ATP} channel. In a study involving patients with type 2 diabetes mellitus (T2DM), genetic variance at the 23rd residue (E23K) of Kir6.2 found to be common [44] (Figure 2c).

The first instance of neonatal diabetes associated with a GOF mutation in the K_{ATP} channel [45]. Neonatal diabetes is characterized by the onset of symptoms within six months after birth [21]. Nearly half of neonatal diabetes cases are attributed to mutations in the Kir6.2 and SUR1 (ABCC8) genes [19,46]. Specifically, Kir6.2 mutations were found in 31% of the patients, while ABCC8 mutations were identified in 13% [3].

Mutations in both Kir6.2 and SUR1 increase the channel currents by doing one of the following: Prolongation of activation time by reducing the ability of ATP to inhibit the channel by binding to the Kir6.2 subunit or, in rarer cases, by increasing the sensitivity of the SUR1 subunit to Mg^{2+}–ADP [16, 22, 23, 47]. The first mechanism has been reported as a common cause of neonatal diabetes and it causes hyperactivation of the channel regardless of the presence or absence of Mg^{2+}. In this case, the resting membrane potential of β-cells decreases from the normal value of -70 mV to a more negative value, on average -120 mV, causing hyperpolarization of β-cells [16,47].

Despite SUR1 mutations, the absence of neonatal diabetes or delayed onset of T2DM indicates that additional genetic or environmental modifiers influence β-cell dysfunction [38, 48]. Moreover, electrophysiological investigations concerning E23K, a frequently encountered variant of the Kir 6.2 channel, have demonstrated that the presence of this variant augments the likelihood of K_{ATP} channel activation while diminishing ATP sensitivity. Consequently, this configuration increases susceptibility to T2DM [20, 49].

2.2 Delayed rectifier K^+ channels

Delayed rectifier K^+ channels (K_{DR}) were first detected in β-cells in rat insulinoma serial cells (RINm5f) in 1986 [50] and were detected in human β-cells in 1990 [51]. The potassium current in K_{DR} channels is observed as a slow outflow that starts during depolarization and continues throughout repolarization. Its activation begins at -30 mV under physiological conditions, and it increases sigmoidally during depolarization [52]. When voltage-dependent states are examined in vitro, they show half-maximal activation at -20 mV and an activation time of 2 ms at 0 mV [53]. Afterward, it slows down after a slope factor of 2-8 mV and provides a -50 mV return in the membrane potential with an activation time of 30 ms. At high extracellular K^+ concentrations, the activation potentials decrease to -50 mV, but the activation times decrease 2-3 times [53]. This situation causes the prolongation of the plateau observed in the membrane and shortens the intervals, thus triggering insulin secretion. This provides insight into how hyperkalemia increases insulin release.

On the other hand, in vivo voltage values in humans and rats differ from those in vitro. Opening of K_{DR} channels is regulated by divalent cations, and the opening potential of the channels shifts to approximately 10 mV positive at an increase of 10 mM Ca^{2+} [52]. Therefore, physiologically, in the presence of 5 mM extracellular ionized calcium, the channels show half-maximal activity at a value of -2 mV [54]. In chronic hypercalcemia states, this may affect the electrical potential of the cells by causing an increase in intracellular K^+ in β-cells and may disrupt the balance of insulin secretion by making it difficult to transition from the plateau phase to intervals. Similarly, chronic hypercalcemia may pose a risk for T2DM by impairing insulin secretion [53].

2.2.1. Inactivation of delayed rectifier K^+ channels

K_{DR} channels are slowly inactivated during depolarization, and half-maximal inactivation voltages are +20 mV in β-cells [52, 55, 56]. Several pharmacological agents modulate β-cell KDR channels. Quinine, for instance, blocks channel currents by binding to multiple regions at 4 μM, resulting in ~80% shortening of open times and ~25% prolongation of closure times [57]. Although forskolin stimulates adenyl cyclase and enhances insulin secretion via cAMP, it also promotes

secretion by blocking KDR channel currents [58]. In contrast, sulfonylureas show no effect on KDR channels [56].

2.2.2. Subtypes of delayed rectifier K^+ channels and their role in insulin secretion

In human β-cells, there is a diverse range of delayed rectifier K channels, although the functions of most of these channels remain ambiguous. Two specific subtypes, Kv2.1 and Kv2.2, are known to significantly impact insulin secretion (Figure 4). Research in mice has indicated that Kv2.1 serves as the primary channel responsible for the delayed outward current in β-cells. When this channel opens, it leads to a return to the resting membrane potential of β-cells (averaging -60 mV), and its inhibition has been shown to enhance glucose-induced insulin release [55,56,59]. Kv2.2 reduces K efflux by suppressing the effects of Kv2.1 and triggering both Kv2.1 and Kv2.2 together in rat insulinoma cells limits K efflux [59, 60].

The Kv1.5 and Kv1.6 subtypes are also present in human β-cells, although their role in repolarization is not fully understood [59]. Research has revealed that Kv1.5 modulates apoptotic signals, and persistent activation of Kv1.5 channels can increase apoptosis by inducing endoplasmic reticulum stress [61]. Additionally, studies have shown that the degradation of Kv1.5 is inhibited by the insulinotropic incretins glucagon-like peptide-1 and gastric inhibitory peptide [62].

Recent research indicates that Kv7.1, a protein highly expressed in cardiomyocytes, is also present in β-cells and is involved in regulating insulin secretion [61]. A study on the MIN6 mouse beta cell line revealed that inhibiting Kv7.1 led to a decrease in potassium ion efflux, while its overexpression reduced insulin release triggered by both glucose and the K_{ATP} blocker tolbutamide [63]. Although the impact of Kv7.1 on humans is not yet fully understood, a patient with type 1 long QT syndrome (LQT1), which involves a Kv7.1 LOF mutation, exhibited excessive insulin secretion and subsequent hypoglycemia during an oral glucose tolerance test [64]. Furthermore, a patient with a GOF mutation in Kv7.1 showed reduced insulin levels following an oral glucose load [65] (Figure 4). Based on this evidence, it can be inferred that Kv7.1 repolarizes β-cells by facilitating potassium efflux and inhibiting insulin release. However, further research is required to elucidate its role in the development of diabetes.

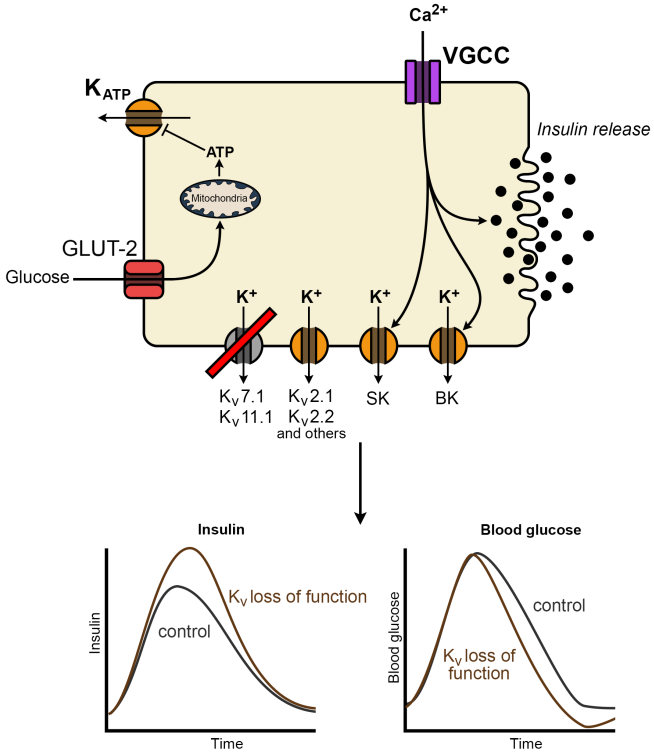

Figure 4. Delayed rectifier K^+ ion (Kv2.1, Kv2.2, Kv7.1, Kv11.1) and Ca^{2+}-activated K^+ ion (BK and SK) channels. LOF mutations in Kv7.1 or Kv11.1 channels cause hyperinsulinemia and subsequent hypoglycemia after glucose administration (Adapted from: [57]). **VGCC,** Voltage gated calcium ion channel; **BK,** Big potassium ion channel; **SK,** Small potassium ion channel

Like Kv7.1, Kv11.1 has been detected in both cardiomyocytes and β-cells [2]. Similar to the Kv7.1 mutation, excessive insulin secretion causing hypoglycemia was observed in people with type 2 long QT syndrome (LQT2), which occurs with a LOF mutation in Kv11.1 [66]. Similarly, increased glucose-induced insulin release was observed in rats given dofetilide, a Kv11.1 blocker, and in the Kv11.1 knockout MIN6 mouse beta cell line [59,66] (Figure 4). In other studies, selective blockade of Kv11.1 prolonged the action potential plateau phase, increased the number of spikes in human β-cells, and increased the intracellular calcium current [64, 65]. However, this enhancing effect of Kv11.1 blockade on insulin release lasts only 5 minutes, after which the effect decreases; that is, Kv11.1 blockade has a temporary effect [2,65]. Therefore, further studies are needed on physiological insulin release and its role in the pathogenesis of diabetes.

2.3 Ca^{2+}-activated K^+ channels

BK channels in β-cells were first identified by patch-clamp studies in 1984 [67]. The properties of BK channels in β-cells have been demonstrated by various studies, some of which are as follows: a decrease in Ca^{2+} concentrations in the extracellular environment has been shown to cause a decrease in the amplitude of $[K^+]_o$ current [2, 13, 68]. In single-cell recordings taken simultaneously, it has also been observed that the amplitude of $[K^+]_o$ currents in β-cells decreases when Ca^{2+} entry into the cell is reduced by the use of Ca^{2+} antagonists, and a high $[K^+]_o$ current was recorded while $[Ca^{2+}]_i$ currents were simultaneously recorded [9, 68]. In in vitro studies, when Ca^{2+} is not buffered, BK channels are responsible for 60% of the total K^+ outflow current in β-cells, while the percentage decreases to 20% when the physiological Ca^{2+} level is buffered [2,13]. In parallel with the increase in intracellular Ca^{2+} concentration, the increase in BK channel activity and the increase in K^+ outflow bring the membrane closer to a more negative membrane potential (Figure 4). Due to these properties, BK channels may be responsible for the transition to the plateau phase from the explosive rise of the action potential in β-cells, which is accompanied by Ca^{2+} elevation.

BK channels are not only dependent on the Ca^{2+} level but also operate in a voltage-dependent manner. Although the minimum Ca^{2+} concentration required for the activation of the channels is approximately 4 mmol/l, these values are valid when the membrane potential is close to +20 mV. At lower membrane potentials, higher concentrations of calcium are required for the activation of the channels. At threshold (-50 to -20 mV), the Ca^{2+} requirement of β-cells is 10–22 mM, whereas at the resting membrane potential (~ -60 mV) it rises to about 30 mM [2,13,69]. BK channels do not contribute to resting K^+ permeability, as human β-cells can never have such a high intracellular Ca^{2+} concentration under physiological conditions at rest. In humans, beta cell BK channels begin to activate at an average of 0 mV during depolarization [2].

The activation of BK channels is also dependent on the intracellular pH. While BK channel activation is maximal at a pH_i of 7.6, channel activation stops at a pH_i of 6.8 [67,70]. Although it triggers the outflow of intracellular buffers during a decrease in pH_e and increases Ca^{2+} entry into the cell and an increase in intracellular Ca^{2+} compensates for the decrease in BK activity [9, 68], this situation is ineffective in chronic acidosis and decreases the $[K]_o$ current. Thus, the electrical potential becomes positive and may disrupt the regulation of insulin secretion. Recent studies, most notably in 2021, indicate that chronic acidosis contributes to insulin resistance, partly via BK channel inhibition [71].

2.3.1. Modulation of Ca-activated K^+ channels

BK channels in β-cells have complex kinetics with two open and three closed states. Two of these three off states are observed during burst depolarization, and one is observed during intervals [2,4,70]. The opening and closing times of the channels are regulated by the abovementioned mechanisms and intracellular Ca^{2+} levels [70,72]. The functions of BK channels are also regulated by intracellular glucose concentrations. An increase in intracellular glucose metabolism inhibits BK channels and contributes to the increase in the membrane potential of the cell and to insulin release [2,72].

Small-conductance calcium-activated K^+ (SK) channels have also been demonstrated in β-cells, but unlike BK channels, their mechanism of contributing to insulin regulation has not yet been fully elucidated [73,74] (Figure 4).

2.3.2. Relationships between Ca-activated K^+ channels and glucose intolerance: Could these channels be new therapeutic targets?

Some of the previous studies suggested that no change in membrane potential oscillations was observed with the inhibition of BK channels [69]. Action potentials and insulin release can still occur in β-cells of SUR1 and Kir6.2 knockout mice and that bursts in these action potentials occur with Ca^{2+} entry. In addition, during Ca^{2+} bursts, K permeability and [K]o current increase in the cells, and in parallel, repolarization occurs in β-cells [70, 75]. BK channels are required for rapid membrane repolarization; after blockade of BK channels with iberiotoxin, the peak voltage of the action potentials of β-cells triggered by 6 mmol/l glucose ranges from −13±5 mV to 4±7 mV eventually increasing the amplitude of the beta cell action potential [9].

Düfer et al. examined the contributions of BK channels to beta cell electrical potential and reported that neither the resting membrane potential at 0.5 mmol/l glucose nor the plateau potential at 15 mmol/l glucose was significantly altered in β-cells of BK knockout mice compared to wild type. Compared with those in wild-type cells, the resting membrane potential in BK knockout cells changed from −70±1 mV to 69±1 mV, and the plateau potential changed from −48±1 mV to −47±1 mV. However, they reported that the pattern of

Ca^{2+} spike potentials varied in BK knockout cells. In Bk knockout cells, the spike time of action potentials at the half maximum amplitude increased from 12±1 ms to 18±1 ms, and the typical after-hyperpolarization period was shorter than that in the wild type. They observed the same findings with the addition of iberiotoxin to wild-type cells, suggesting that BK channels play an important role in repolarization. As a result, they reported that there was a decrease in insulin secretion and impaired glucose tolerance in BK knockout mice [68].

Also SK4 channels examined in glucose-stimulated insulin release in mice. In SK4 knockout mice, an improvement in glucose tolerance, an increase in Ca^{2+} action potential frequency and broadening of action potentials, and an increase in the glucose sensitivity of insulin secretion were observed. In addition, they observed similar findings when wild-type mice were given the SK4 channel blocker TRAM-34 [74]. Overall, Ca-activated K-channels can be considered a new target for the development of insulinotropic drugs.

2.4 Cl^- Channels

Unlike cations and cation channels, which play a role in the functions of β-cells, much less detailed information is available about anion channels. Sehlin J showed that there was a chloride current in β-cells and Lindström et al. showed that chlorine currents play a role in regulating the volume of β-cells, the role of chloride ions in the electrophysiology of β-cells and insulin secretion began to gain attention [75, 76]. The presence of a glucose-sensitive anion flux in β-cells suggests that this flux has a major role in insulin release, and furthermore, the blockade of these anion fluxes with 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid (DIDS), a chloride channel blocker, inhibits glucose-induced β-cells and has been shown to strongly modulate their electrical activities [77].

Since β-cells have an intracellular chloride concentration as high as 35 mM, there is a Cl^- reversal potential of 35 mV in the cells, and at more negative potentials, the opening of Cl^- channels causes Cl^- to flow out of the cell [80]. As a result, the opening of Cl^- channels leads to the depolarization of β-cells and increased insulin secretion via the activation of voltage-activated Ca^{2+} channels [2].

Thus, islet activation in β-cells may be partially responsible for the depolarizing effects of various islet stimulants, such as cAMP or glucose itself [77,79]. These effects may synergize with the better-known effects of glucose metabolism to depolarize β-cells and stimulate insulin release by closing K_{ATP} channels in the membrane [79].

Three types of major chloride channels that contribute to insulin release by changing the electrical potential of β-cells have recently been identified [2, 79] (Figure 5a).

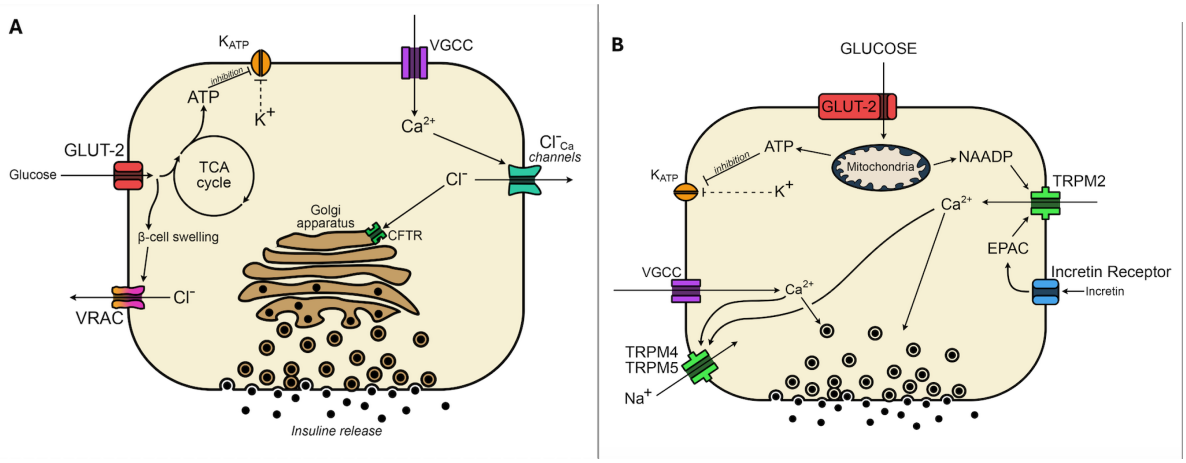

Figure 5. a. Major Cl^- channels in β-cell. Glucose uptake and metabolism results in beta cell swelling and opening of VRAC. In addition, influx of Ca^{2+} through VGCC activates calcium-activated Cl^- channels and insulin exocytosis from Golgi apparatus via CFTR (Adapted from: [79]). **b.** Major TRP channels regulating the electrical activities of β-cells. The increase in NAADP resulting from glucose metabolism in the cell and the increase in EPAC resulting from stimulation by incretins trigger calcium entry into the cell through TRPM2 channels. Additionally, calcium enters the cell through voltage-dependent calcium channels, and TRPM2 stimulates sodium entry through TRPM4/TRPM5 channels. **VGCC,** Voltage gated calcium ion channel; **VRAC,** Volume-regulated anion channels; **CFTR,** Cystic Fibrosis Transmembrane Conductance Regulator **TRPM:** transient receptor potential melastatin; NAADP: nicotinic acid adenine nucleotide phosphate; EPAC: exchange proteins directly activated by cAMP

2.4.1. Volume-regulated anion channels (VRAC)

VRACs are outwardly rectifying Cl^- channels that are opened by swelling of the beta cell in a hypotonic environment or by an increase in intracellular cAMP [79,80]. The observation of a temporary increase in insulin secretion when rat β-cells are placed in hypotonic solutions and the observation of depolarization in the cells with an increase in beta cell volume suggests the existence of these channels [81] or that they may be under metabolic control due to beta cell swelling associated with increased glucose metabolism [81].

With the identification of the molecular structure of VRAC proteins, also known as leucine-rich repeat-containing family 8 (Lrrc8a-e) proteins, it became possible to test the VRAC hypothesis in detail with animals lacking Lrrc8a [82]. Glucose entry causes swelling of β cells and depolarizes the cell by triggering Cl^- currents through VRAC channels [83]. Best et al. suggested that not only glucose entry but also metabolic products released as a result of glucose metabolism, especially lactate, may be responsible for this swelling [84] (Figure 4). Consistent with this finding, it has been reported that the loss of LRRC8a reduces Cl^- currents in response to cell swelling and reduces insulin secretion in response to glucose. However, it was not possible to completely stop insulin secretion with the disappearance of VRAC currents [84]. It is therefore possible that VRAC is not the only Cl^- channel required by β-cells to reach the depolarization threshold for voltage-gated Ca^{2+} channel-dependent Ca^{2+} entry and insulin secretion [81,84].

2.4.2. Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

The fact that diabetes occurs in more than 30% of cystic fibrosis (CF) patients with CFTR protein mutations has raised the question of whether CFTR-related Cl^- channels play an important role in the electrical potential of β-cells and insulin release [85]. As in many other nonepithelial cells, the presence of CFTR in β-cells is reported to be low, and its expression is heterogeneous, making it difficult to study CFTR in these cells [86, 87].

However, the addition of the CFTR inhibitors CFTRinh-172 (10 μM) and glyH-101 (10 μM) to mouse β-cells (RINm5F) induced membrane hyperpolarization independently of any stimulus. As a result, they reported that CFTR contributes to the formation of the resting membrane potential by providing Cl^- efflux under basal conditions. In the same study, they observed that 10 mM glucose-induced action potential spikes decreased from 23.4±3.0 mV to 15.6±1.7 mV with the addition of CFTRinh-172 (10 μM). Overall, they found that CFTR contributes to glucose-induced burst potentials in addition to the resting membrane potential [85].

Similarly, Edlund et al. detected weak CFTR conductance in both human and mouse β-cells and reported that CFTR plays a role in insulin exocytosis. They reported that there was an increase in insulin release as a result of the induction of CFTR with cAMP (forskolin or glucagon-like peptide 1 (GLP-1)) under 16.7 mM glucose, and this increase was prevented by the addition of GlyH-101 and/or CFTRinh-172 [88].

However, on the contrary, the conductance of a glucose-activated CFTR is 5 times higher than the conductance of a beta cell under basal conditions, and even 10 times higher than the voltage-dependent peak Ca^{2+} current; therefore, at such a large CFTR current, Cl^- is also suggested to be clamped to the equilibrium potential of -35 mV. In this case, CFTR cannot contribute to a glucose-induced current [2].

On the other hand, one issue that should not be overlooked is that CFTR is not only a chloride channel in the cell membrane but also a protein responsible for the posttranslational modification of secretory proteins in the Golgi complex and the preparation of vesicles for docking. In a study conducted by Edlund et al. in 2019, they observed both a decrease in the number of docked insulin granules and insufficient cleavage of proinsulin in mice with F508del, a common mutation of CFTR [89] (Figure 4).

Taken together, these findings indicate that CFTR contributes to insulin release in various situations, and further studies are needed to elucidate the underlying mechanisms involved.

2.4.3. Calcium-activated Chloride Channels

Recent studies suggest that there are Cl^- channels in β-cells that are triggered by an increase in Ca^{2+}. In their study on guinea pig β-cells, for the first time, Kozak and Logothetis described a chloride current triggered by an increase in Ca^{2+} with a reverse potential of –22 mV [90]. These channels are defined as Anoctamin (Ano) 1 and/or Ano2 channels and were suggested to have a role in glucose-induced insulin release by β-cells [88] (Figure 4).

Later, Crutzen et al. showed that there is a 2 μM outwardly rectifying Cl^- current (8.37 pS) in the presence of 1 μM intracellular Ca^{2+}. In addition, they reported the mRNA expression of Ano1 at the protein level in rat β-cells, and with the administration of Ano1 antibody and T-A16AInh-AO1 (T-AO1), an Ano1-specific inhibitor, these Cl^- currents disappeared, membrane repolarization occurred, and the glucose-induced action potential firing was reduced [91]. Additionally, it has been suggested that Ano1 gene expression is responsive to glucose, while siRNA-mediated silencing of Ano1 inhibits insulin secretion by human islets [92].

2.5 TRP Channels

Transient receptor potential (TRP) channels are a large family of channels consisting of nonselective cation channels (NSCCs), and recent studies suggest that they may play a role in regulating the electrical activities of β-cell by providing an inward cation current [93]. The major TRP channels expressed in mouse and human β-cells were identified as TRP canonical (TRPC) 1, TRP melastanin (TRPM) 2, TRPM3, and TRPM7, which function as nonspecific cation channels, especially Ca^{2+} and Na^+, and TRPM4

and TRPM5, which do not have Ca permeability [94]. Among these channels, TRPM2, TRPM4 and TRPM5 have significant effects on the electrical potential of β-cells, as explained in detail below.

2.5.1. TRPM2 channels

Studies on TRPM2 have reported that TRPM2 is activated by nicotinic acid dinucleotide phosphate (NAADP), which increases in response to glucose entry in β-cells and consequently increases the inward cation current into β-cells [95]. In addition TRPM2s, which function as NSCCs, are further opened by K_{ATP} closure and that this opening is essentially required to effectively evoke depolarization. At the same time, TRPM2 is triggered in a cAMP-dependent manner by exendin (ex)-4, GLP-1, and its analog liraglutide, but this increase in cAMP acts not by increasing PKA but by exchange proteins directly activated by cAMP (EPACs) (Figure 5b). In the same study, they also showed that there was a decrease in glucose-induced insulin release with the inhibition of TRPM2, which supports this finding. In light of this information, they suggested that TRPM2s could be targets to increase glucose- and incretin-induced insulin release in T2DM patients [96].

2.5.2. TRPM4 and TRPM5 channels

Studies showing that there is no change in the electrical activity of mouse β-cells upon glucose stimulation despite the inhibition of TRPM4 and TRPM5 suggest that TRPM4 and TRPM5 do not have a direct role in electrical activity [97]. TRPM5 channels are monovalent cation channels that are opened by increasing Ca^{2+} in β-cells and that they assist in the electrical oscillations that occur, with the overall effect of increasing Ca^{2+} ions during glucose-induced insulin release. In support of this, they suggested that in mouse β-cells lacking TRPM5 expression, rapid oscillations secondary to the increase in glucose and Ca^{2+} disappear, resulting in decreased insulin secretion and impaired glucose tolerance [98] (Figure 5b).

GLP-1 activates protein kinase C in both human and mouse β-cells, causing membrane depolarization and an increase in action potential firing. GLP-1 continued to exert this depolarizing effect in the presence of PKA inhibitors, the K_{ATP} channel blocker tolbutamide, and the L-type Ca^{2+} channel inhibitor isradipine, but depolarization stopped with decreasing extracellular Na^{2+} concentrations. In addition, the electrical activity of GLP-1 was silenced in TRPM4 and TRPM5 knockout β-cells, and as a result, they suggested that the effect of GLP-1 on β-cells occurs through TRPM4 and TRPM5, which act as Na^{+} channels [97].

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