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Review Article

The effect of increased physiological potassium level on insulin secretion from pancreatic beta cells

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Abstract: Potassium (K+), a physiological regulator that influences cell excitability and the stimulus-secretion coupling through complex mechanisms, is necessary for normal insulin release from the pancreatic β-cell. Here, we look at the several ways that potassium channels and ion gradients regulate insulin production when blood glucose levels fluctuate. Modifications of voltage-gated K+ channels (Kv), inward-rectifier K+ channels (Kir), and ATP-sensitive K+ channels (K_ATP) control changes in the membrane potential that result in Ca2+ entry and β-cell depolarization, two essential components of the insulin exocytosis pathway. When insulin granules are released, excessive glucose stimulation results in increased ATP production, which causes membrane depolarization, K_ATP channel blockage, and voltage-dependent Ca2+ channel activation. Conversely, type 2 diabetes is brought on by altered K+ channel function, which reduces α-cell secretion. The article summarizes current data from electrophysiological, genetically modified animal, and pharmacological studies to give an overview of potassium's regulatory function in β-cell activity. The significance of K+ channels as a medication target in diabetes is further highlighted by this data.

Keywords: *Potassium (K^+), Insulin secretion, Pancreatic β-cells, K_ATP channels*

1. Introduction

One of the most crucial tasks performed by the endocrine pancreas is maintaining blood glucose within a specific physiological range. This is regulated by the insulin that pancreatic β cells release in response to glucose. Insulin release is closely linked to the electrical excitability of β cells, which is primarily dependent on K^+ conductance. Voltage-gated K^+ (Kv) and ATP-sensitive K^+ (KATP), two sizable categories of K+ channels, are primarily involved. While K_v channels mainly shape action potentials and regulate the kinetics of insulin release, K_ATP channels are metabolic sensors that connect cell energy levels with membrane potential (Yang et al., 2014).

As K_ATP channels are opened and K efflux threshold, low extracellular glucose levels also keep the resting membrane potential at approximately -70 mV. Because voltage-gated Ca^{2+} channels cannot open in this hyperpolarized condition, insulin release is suppressed and Ca^{2+} influx is inhibited. Thus, when there is not enough glucose available, the β cell will be resting and insulin will not be wasted to cause hypoglycemia. The intracellular ATP/ADP ratio rises when glucose levels are high because β cells metabolize glucose. Depolarization results from ATP binding to and closing K_ATP channels at the greater ATP concentration that is reached. This depolarization induces a rapid rise in intracellular [Ca^{2+}] that opens voltage-activated Ca^{2+} channels and is the primary determinant of exocytosis of insulin-containing granules. This process is responsible for the fast, short lived (first-phase) insulin response to allow a rapid adjustment of postprandial glucose levels (Berger & Zdzieblo, 2020).

K_v channels, and most particularly K_v2.1, allow the β cell action potential to repolarize. K_v channels determine when and for how long action potentials occur, thus controlling the temporal and quantitative pattern of insulin secretion to maintain a coordinated secretory response. Dysregulation of these channels results in deficits in kinetically regulated insulin release, highlighting their importance for normal glucose homeostasis (MacDonald & Wheeler, 2003).

K_ATP channel heterogeneity in this aspect Recent work has identified an additional layer of regulation

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where only a subpopulation of K_ATP channels located on insulin granule membranes, termed "granular K_ATP" (gK_ATP) are likely to be involved in second-phase insulin secretion (Geng et al., 2003). This second phase is slower and more prolonged than the first phase and this portion of glucose-induced insulin release takes on added importance with chronic control of blood glucose. They showed that insulin release is not only controlled by the membrane excitability but also by the trafficking and exocytotic machinery of beta-cell (Akrouh et al., 2009).

Perhaps genetic mutants also serve as 1 example of how K conductance functions pathophysiological. While gain-of-function mutations result in infantile diabetes with decreased or absent glucose-stimulated insulin exocytosis, loss of K_ATP channel activity results in congenital hyperinsulinism. When taken as a whole, these results show that systemic glucose homeostasis depends on a careful balance between K^+-channel activity, β-cell excitability, and the precise regulation of insulin production (Ruta et al., 2003; Quan et al., 2011).

2. Methodology

Data from electrophysiological tests, genetic models (such as mouse K_ATP channel gain and loss of function mutants), subcellular imaging, and pharmacological investigations utilizing K^+ channel modulators (such as sulfonylureas, K_ATP inhibitors) are all included in this study. The β cell ion channel's function in insulin secretion pathways has been examined and researched (Brereton & Ashcroft, 2013). The physiological roles of K_ATP and Kv channels, granule cell bouton K^+ conductance, and disease-related channelopathies were investigated.

3. Results and Discussion

3.1 K_ATP Channels: Metabolic Sensors and Secretion Switch

The molecules that detect ATP/ADP to control the electrical activity of β cells are Kir6.2 tumor pores and SUR1 regulatory subunits. At rest, these channels hyperpolarize the cell. The metabolism of glucose produces more ATP and less ADP, which closes K_ATP, depolarizes the membrane, and causes Ca^{2+}-mediated insulin secretion (Thompson & Satin, 2021). Metabolism is intimately linked to the initial stage of insulin release through this K_ATP-mediated switch.

3.2 Role in Second-Phase Insulin Secretion via Granule K_ATP

A substantial pool of K_ATP channels (gK_ATP) is present in insulin granule membranes. By regulating granule mobilization and exocytosis in a graded, glucose-dependent manner, these channels appear to affect the second phase of secretion beyond the effects of Ca^{2+} influx (Geng et al., 2003).

3.3 Ca^{2+} Activated K^+ and Voltage Gated K^+ (K_v) Channels

Insulin secretion is inhibited by K_v channels, such as K_v2.1 and KCNB1, which help repolarize β cell action potentials by reducing Ca^{2+} entrance. Secretion patterns of insulin are altered upon manipulation of these channels, and often its block increases secretory activity (Wray, 2004). Furthermore, it has been documented that the electric oscillations and burst dynamics that result in pulsatile secretion are influenced by small-conductance Ca^{2+}-dependent K^{2+} (SK) channels (Rorsman & Ashcroft, 2018).

3.4 Genetic Models and Pathophysiology

K_ATP channel loss-of-function mutations cause congenital hyperinsulinism (CHI) and poorly regulated insulin production in response to glucose, whereas mutations that gain function cause neonatal diabetes and a lack of glucose-regulated insulin release. Animal models that replicate features of human illness demonstrate the physiological ramifications of some of these changes and further highlight the significance of K_ATP channel activity in vivo. Furthermore, Holt et al. raise the possibility that hormonal and glucose cues could regulate K_ATP trafficking both acutely (a timescale on the order of glucose) and chronically (at time-scales downstream from glucose), opening up another pathway for dynamic changes in insulin release and blood sugar levels.

3.5 Subcellular Metabolism and Ion Flux Coupling

New imaging studies have showed that β-cell mitochondria in proximity of the sub plasma membrane respond to glucose more rapidly, which might create local ATP/ADP signals that support insulin pulsatility and inhibits KATP channels (compartmentalized coupling of secretion, metabolism and K^+ conductance) (Geng et al., 2003).

4. Conclusion

In a multistage mechanism, pancreatic β cells react to potassium by secreting insulin. The metabolic blockage of K ATP channels in the membrane of the blood is necessary for the Ca^{2+}-dependent early phase. This depolarization promotes insulin granule exocytosis and opens voltage-gated Ca^{2+} channels. Granule-localized KATP channels, along with their counterparts in the plasma membrane, could influence second-phase insulin secretion by altering granule motility and efficiency of exocytosis for sustained hormone release. The firing pattern of the pancreatic beta cell is also regulated by Kv and SK channels which disrupts this characteristic profile of electrical activity, which

would otherwise result in insulin over secretion. The physiologic and pathophysiologic relevance of this channel family is demonstrated by inherited channelopathies that underscore its contribution to glucose homeostasis and dysfunction.

Recommendations

1. Targeted therapeutics: Engineered drugs that can tune individual KATP subpopulations at the surface of the β-cell or inside its granules, for a more precise insulin secretion regulation.
2. Dynamic imaging studies: More experimentation are needed to study ATP/ADP submembrane microdomains in human β-cell using high-resolution-imaging (i.e., FLIM).
3. Studies of channel regulation: Investigate the metabolic and hormonal control of KATP channel trafficking to find potential long-term modulatory pathways.
4. Human-specific research: use mouse data in human β-cells, particularly those who would be different between K_v channel subtypes (e.g. BK vs SK channel; human vs mouse cell).

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