

INVESTIGATIONS ON GLUCOSE-STIMULATED INSULIN SECRETION AND ITS POSSIBLE ROLE IN PATHOLOGY OF VIRAL-INFECTION-TRIGGERED TYPE 1 DIABETES.

Firdos 2016BLZ8374

Abstract

Type 1 Diabetes (T1D) disrupts the intricate equilibrium of glucose levels by specifically targeting and eliminating pancreatic β -cells responsible for insulin secretion, resulting in compromised control of glucose. This condition, commonly known as insulin-dependent diabetes, is characterized by low insulin levels. The intricate coordination of signaling pathways, transcription factors, and molecular mechanisms is crucial for the functioning of pancreatic β -cells, which respond to glucose stimulation by secreting insulin. The MIN6 cell line, derived from Mouse Insulinoma 6, proves to be a valuable model for uncovering the mechanistic complexities associated with the functions of pancreatic β -cells. Although a correlation is evident between elevated glucose consumption and heightened insulin secretion, it has been noted that intracellular ATP levels remain relatively constant once a specific extracellular glucose concentration is reached. This prompts inquiries regarding the cause-and-effect connection between glucose consumption (GC) and increased insulin secretion (eIS). Furthermore, our examination indicates that both total cellular protein levels and proteins in the culture "supernatant" remain consistent regardless of changes in extracellular glucose concentrations. This suggests that enhanced insulin secretion (eIS) might be associated with a trade-off involving the intracellular synthesis of other proteins, the secretion of secretory proteins, or both, potentially influenced by glucose consumption (GC) in cells. To acquire a more profound understanding, we conducted a transcriptome study on MIN6 cells exposed to hypoglycemic (HoG = 2.8 mM EG) and hyperglycemic (HyG = 25 mM EG) conditions. Our findings indicate that in hyperglycemic extracellular conditions, insulin secretion increases by approximately two-fold compared to hypoglycemic conditions. Interestingly, transcripts of secreted proteins and their isoforms decrease in hyperglycemic conditions, suggesting that enhanced insulin secretion in high glucose conditions is linked to a decrease in the transcription of other secreted proteins, alongside increased glucose consumption. Further exploration excavate into the direct involvement of intracellular glucose in insulin secretion, revealing significant differences between the amount of glucose transported into pancreatic β -cells and

the amount phosphorylated inside these cells. The differential expression of genes associated with energy processes, particularly Gapdh, Atp6v0a4, and Cox20, provides valuable insights. Notably, upregulated genes in high glucose conditions, such as Atp6v0a4, Cacnb4, and Kif11, are linked to cellular secretion, adding complexity to the correlation. Our investigation extends to exploring the potential link between viral infections and their role in triggering T1D. Genetic and environmental factors, including viral infections like enteroviruses, contribute significantly to T1D onset patterns. Mechanisms such as virus persistence, bystander activation, and molecular mimicry are implicated, but the precise pathogenesis remains elusive. Glucose-Stimulated Insulin Secretion (GSIS) underscores the importance of understanding intricate mechanisms like Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)-potentiated GSIS in glycemic control and diabetes management. We have identified viral peptides in Chikungunya Virus (CHIKV) and Dengue virus (DV) proteomes that mimic PACAP. Our study suggests a potential impact on insulin secretion through PACAP-potentiated GSIS in pancreatic β -cells. The CHIKV peptide CV1, bearing high similarity to P38, may disrupt PACAP-potentiated insulin secretion, potentially contributing to diabetes-like conditions. Our research shows a molecular mechanism linking viral infection and T1D, indicating a temporal relationship and shedding light on the condition's nature. Interestingly, viral peptides can induce insensitivity to glucose and disturb PACAP-potentiated GSIS, expanding the scope of molecular mimic exploration. This research contributes to our understanding of a conserved cellular mechanism affecting insulin production, with implications for various cell types and critical relevance in T1D research.