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Review

Alpha cell dysfunction in type 1 diabetes

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ABSTRACT

Type 1 diabetes is characterized by selective loss of beta cells and insulin secretion, which significantly impact glucose homeostasis. However, this progressive disease is also associated with dysfunction of the alpha cell component of the islet, which can exacerbate hyperglycemia due to paradoxical hyperglucagonemia or lead to severe hypoglycemia as a result of failed counterregulation. In this review, the physiology of alpha cell secretion and the potential mechanisms underlying alpha cell dysfunction in type 1 diabetes will be explored. Because type 1 diabetes is a progressive disease, a synthesized timeline of aberrant alpha cell function will be presented as an attempt to delineate the natural history of type 1 diabetes with respect to the alpha cell.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by selective destruction of the pancreatic beta cells [2,50]. Beta cell loss can occur over extended periods of time (months to years), but due to the remarkable compensatory capacity of the beta cells, overt diabetes symptoms such as hyperglycemia and resulting polydipsia and polyuria might not be present until ~80% of beta cells have been lost [2,50]. The Islets of Langerhans are comprised of multiple cell types that are intimately linked through an incompletely understood intercellular communication network, such that isolation of one islet cell type renders those cells incapable of a normal secretory response to their normal stimuli. Thus it is not surprising that the loss of beta cells during the progression of T1D leads to a progressive dysfunction of other islet cell types, particularly the alpha cells. Hyper- or hyposecretion of glucagon from the alpha cells can lead to significant and severe disruptions in glucose homeostasis, thus exacerbating hyperglycemia or preventing a normal counterregulatory response to hypoglycemia. The purpose of this review is to highlight the potential mechanisms underlying alpha cell dysfunction in T1D and to provide a synthesized timeline of the progression of the dysregulation of glucagon release in patients with T1D.

2. Regulation of glucagon secretion (Fig. 1)

Although the regulation of insulin release from the beta cells by glucose has been well characterized and described, low glucose-stimulated glucagon secretion from the alpha cell is not fully understood. Investigation of the mechanisms driving glucagon inhibition by glucose or stimulation by low glucose levels has been hampered by multiple species-specific differences in islet architecture and cell signaling. For example, although most studies of alpha cell function utilize mouse or rat models, rodent islets are characterized by the localization of beta cells predominantly in the center of the islet, surrounded by alpha, delta, and other cell types, which comprise the outer layer of the islets [40,53]. This is in sharp contrast to human islets, in which alpha, beta, and delta cells are randomly distributed throughout the islet [8,53]. Furthermore, while rodent islets are composed predominantly of beta cells (60–80% of total cell numbers, compared to 15–20% alpha cell content), the composition of the human islet is more heterogeneous, with fewer beta cells (50–60%) and higher numbers of alpha cells (30–45%) [5,6,8]. These differences could have important implications for the role of paracrine signaling and intercellular communication on alpha cell regulation and glucagon secretion. In addition, important species-specific variations in protein expression could drive differences in the regulation of glucagon secretion between mice, rats, and humans. While mouse alpha cells produce L-, N-, T-, and R-type calcium channels, rats alpha cells express L- and N-type calcium channels [14,16,29]. However, the expression of N-type calcium channels in mouse alpha cells is relatively low, and studies evaluating their activity using ω-connotoxin are hampered by the finding that ω-connotoxin exerts a non-specific effect in alpha cells [43]. Human alpha cells produce L-, T-, and P/Q-type calcium channels [41]. These differences could significantly impact how electrical coupling of glucose concentration to glucagon secretion is controlled between rodent models and humans. Thus, although human islets and purified alpha cells can be difficult to obtain, it is essential to confirm the findings of rodent alpha cell studies using human cells in order to fully understand human alpha cell physiology. However, comparative studies have highlighted fundamental similarities in the regulation of glucagon secretion with respect to both

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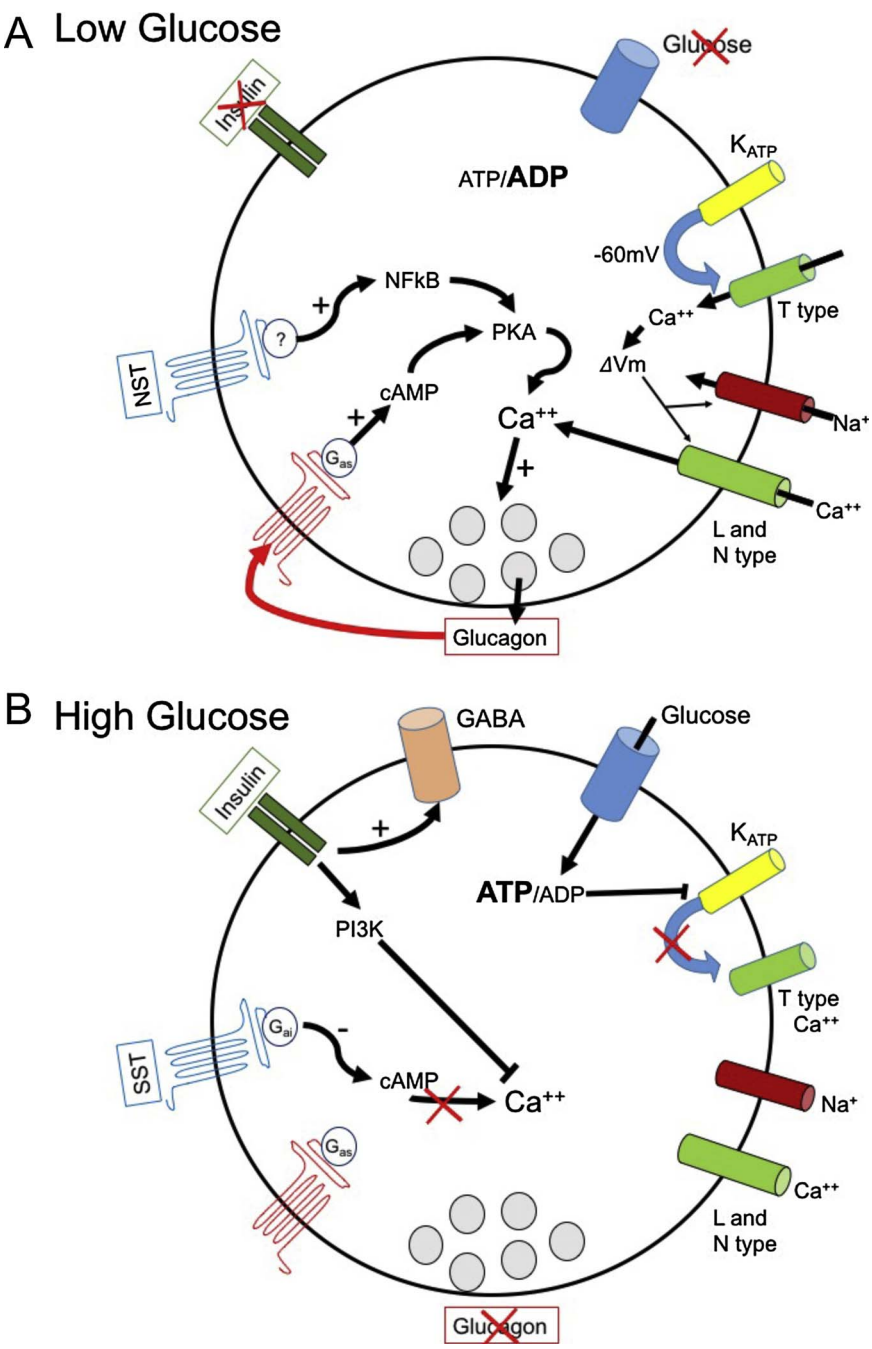

Fig. 1. Regulation of glucagon secretion. A) In low glucose, a decrease in the ATP/ADP ratio causes ATP-sensitive postassium channels (K_{ATP}) to generate a membrane potential of ~60 mV, leading to opening of low voltage (T type) calcium channels. This causes a downstream opening of sodium and high voltage (L and N type) calcium channels, intracellular accumulation of calcium, which drives fusion of glucagon-containing vesicles with the membrane and release of glucagon from the alpha cell. In addition, glucagon secretion is stimulated by neuronostatin (NST) from the delta cell and by glucagon itself. The inhibitory effect of insulin is negligible due to reduced release of insulin from the beta under low glucose conditions. B) In high glucose conditions, the ATP/ADP ratio increases, leading to closure of K_{ATP} channels and membrane depolarization to an extent that downstream ion channels involved in action potentials are deactivated. In addition, insulin exerts potent inhibitory actions through PI3 K and the translocation of GABA receptors to the membrane. Somatostatin (SST) from the delta cells inhibits cAMP production, thus reducing downstream calcium flux.

electrical activity and endocrine and paracrine signaling.

2.1. Electrical regulation of glucagon release

Like beta cells, alpha cells produce multiple ion channels that are capable of generating action potentials depending on extracellular glucose concentrations [16]. Many of these channels are similar or the same as proteins expressed by the beta cells, particularly the ATP-sensitive potassium channels, which couple extracellular glucose concentrations to calcium-stimulated hormone secretion in both beta and alpha cells. Several models of stimulus-secretion electrical coupling in alpha cells have been proposed and reviewed extensively elsewhere [40,44]. Briefly, the "regenerative model," [14,29,40] posits that at low glucose levels, the intracellular ATP/ADP ratio is low, causing the ATP-sensitive potassium channels to generate a membrane potential of approximately −60 mV. This results in the opening of low voltage-activated calcium channels (i.e. T-type), leading to membrane depolarization to the extent that sodium and high voltage-activated calcium channels (i.e. N-type) channels are activated, and subsequently the formation of regenerative action potentials and calcium-induced glucagon secretion (Fig. 1A). However, Rorsman and colleagues have shown that exposure to a suppressive concentration of glucose (6 mM) altered the electrical activity of alpha cells such that action potentials occurred at a higher frequency and lower amplitude [64]. This led to a reduction of P/Q-type calcium channel activity, which subsequently inhibited glucagon secretion [64]. Thus, stimulus-secretion electrical coupling may not be due to electrical silencing, but rather the result of electrical tuning. A second model suggests that exposure to high glucose inhibits secretion of glucagon via an ATP-sensitive potassium channel-independent mechanism [26,60]. In this model, a depolarizing calcium store-operated current would be suppressed. Regardless, the direct stimulus-secretion coupling of extracellular glucose concentration to