The α-Cell Conundrum: ATP-Sensitive K^+ Channels and Glucose Sensing

David A. Jacobson, Barton L. Wicksteed, and Louis H. Philipson

The α-cell of the pancreatic islet modulates glucose homeostasis by secreting glucagon that acts primarily by driving hepatic glucose production. Glucose sensing of the α-cell becomes defective in both type 1 and type 2 diabetes, resulting in hyperglucagonemia that likely contributes to hyperglycemia (1). Thus, it is important to elucidate the signals that trigger glucagon secretion and the transduction of these signals within the α-cell. Glucagon secretion has been linked to several triggers: the α-cell detecting a fall in circulating glucose levels directly, a paracrine response to signal(s) from the islet β-cell (e.g., insulin, γ-aminobutyric acid [GABA], or Zn^{2+} ions) or the islet δ-cell (somatostatin), or a response to neural signals (2–8). In all likelihood, an interaction of several signals regulates glucagon secretion in vivo.

There is good reason to believe that glucagon release, like insulin release, is influenced by physiological α-cell electrical activity and Ca^{2+} influx and fundamentally resembles the excitation-secretion coupling seen in many secretory cell types (9). Stimulus-induced α-cell electrical activity results from depolarization-induced opening of voltage-gated Ca^{2+} and K^+ channels (2,9–11). The depolarization first activates the low voltage–activated T-type Ca^{2+} channels, which have been implicated in action potential initiation (10). Activation of K^+ channels then shapes the α-cell action potential upstroke. The resulting depolarization activates high voltage–activated Ca^{2+} channels including the N-type and L-type Ca^{2+} channels, which coordinate Ca^{2+}-induced glucagon release (11). Action potential repolarization then follows with the activation of voltage-gated potassium (N) channels (12).

Hypoglycemic conditions can promote glucagon secretion by stimulating α-cell electrical activity and Ca^{2+} entry. In islet β-cells, elevations in glucose increase the ATP-to-ADP ratio, resulting in the closure of ATP-sensitive K^+ (K_{ATP}) channels and causing action potential firing. α-Cell electrical activity is also sensitive to modulators of the K_{ATP} channel; thus, glucose responsiveness has been linked to the activity of K_{ATP}, which sets the resting membrane potential of pancreatic β-cells. In contrast to β-cells, K_{ATP} channel closure in α-cells has been linked to the termination of action potential firing (10). K_{ATP} channels can affect human glucagon secretion as evidenced in carriers of the E23K variant of K_{ATP}, which is linked to an increased incidence in adult-onset diabetes and perturbations in glucose regulation of glucagon secretion (13). Similarly, a mouse model with a defective K_{ATP} channel subunit sulfonurea receptor 1 (SUR1) also shows perturbations in glucagon secretion (14). Thus, one might suspect that K_{ATP} channels are involved in the α-cell response to hypoglycemia. In addition, islet paracrine factors such as insulin, somatostatin, Zn^{2+}, and GABA have the ability to cause islet α-cells to fire action potentials (2–8), in some cases by regulating ion channels such as K_{ATP} (15).

In this issue of *Diabetes*, Quoix et al. (16) investigated the relationship of K_{ATP} channels and paracrine factors with glucose sensing. Electrical activity and Ca^{2+} flux were examined in dispersed islets isolated from mice expressing a fluorescent protein specifically in islet α-cells. A subset of these α-cells responded to low glucose (0.5 mmol/l), adrenaline, and K_{ATP} channel inhibition with Ca^{2+} elevations in a manner similar to the responses in control α-cells. On the other hand, when K_{ATP} channels were opened with diazoxide or inhibitors of metabolism, Ca^{2+} fluctuations induced by low glucose or K_{ATP} channel inhibition returned to basal levels. Interestingly, this predicts that K_{ATP} channels may be mainly closed under low glucose conditions in α-cells due to metabolism. The authors confirm that K_{ATP} channel currents are mostly closed in low glucose (0.5 mmol/l) and can be activated by diazoxide or metabolic poisons. To address whether this may be due to increased metabolism in α-cells under low glucose conditions, the authors determined changes in the metabolic product NAD(P)H. Levels of NAD(P)H in β-cells were found to respond to glucose, as expected; however, α-cell NAD(P)H levels did not vary substantially, thereby corroborating previous α-cell studies in which equivalent ATP-to-ADP ratios and NAD(P)H or FAD fluorescence under low- and high-glucose conditions were observed (16,17). Thus, this work leads to several important conclusions concerning α-cell glucose-sensing mechanisms. First, glucose sensing in α-cells is independent of glucose metabolism, whereas the responses to glucose are independent of K_{ATP} channels, as illustrated in Fig. 1. However, these data do confirm that K_{ATP} activity can regulate α-cell Ca^{2+} entry.

So, if islet α-cells do not signal via the glucose-ATP-K_{ATP} channel system to control glucagon secretion in response to glucose levels, how do they detect and respond to hypoglycemia? Paracrine factors released from β-cells have been linked to K_{ATP} channel modulation in α-cells and, thus, may regulate the total glucose-dependent glucagon secretion independently of ATP (15). α-Cells may require interaction with an intact islet or islet paracrine factors for normal glucose sensing. Quoix et al. (16) found that on single α-cells the islet paracrine factors Zn^{2+}, insulin, or GABA have modest effects on α-cell Ca^{2+} levels under low glucose conditions (2–6). However, the α-cell

From the Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, The University of Chicago, Chicago, Illinois.
Corresponding author: Louis H. Philipson, l-philipson@uchicago.edu.
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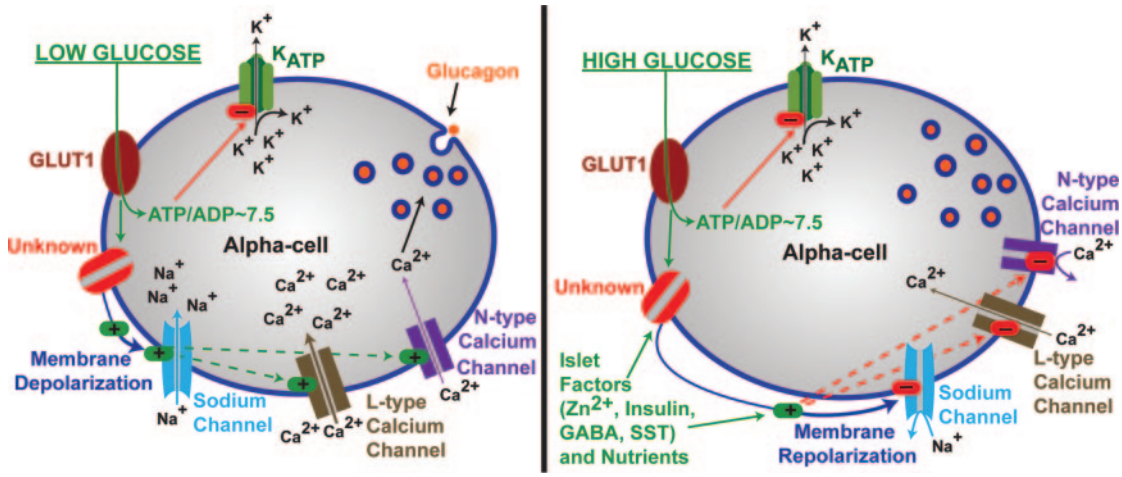

FIG. 1. K_{ATP}-independent glucose regulation of α-cell glucagon secretion. Hypoglycemic stimulation of glucagon secretion occurs through membrane depolarization, which is independent of K_{ATP} activity (*left panel*). The stimulation of α-cells with glucose leads to reduction of glucagon secretion in part by reducing calcium influx presumably through membrane repolarization through an unresolved pathway, which is illustrated as "Unknown" and labeled in red. The unknown is sensitive to glucose levels, whereas it is insensitive to glucose metabolites; it may be an ion channel or receptor and may also be an intracellular signaling mechanism. SST, somatostatin.

Ca^{2+} levels are reduced by only 28% when switching from low to high glucose, thus implicating another unknown modulator that may work with glucose to further reduce α-cell electrical signaling and Ca^{2+} influx. All three paracrine factors are secreted under elevated glucose conditions, and it could be that these factors may further reduce the Ca^{2+} level while glucose conditions are elevated (2–6). The authors find that glucose can reduce glucagon secretion by 70% while incubated with insulin, indicating that glucose is significantly more important to glucagon secretion than insulin. There are contradictory reports on the role of paracrine factors in the regulation of glucagon secretion, and it could be that β-cell paracrine regulation of α-cell Ca^{2+} fluctuation is minimal (2–6,18–19). However, it may also be that the α-cell population is heterogeneous and that some of the α-cells in this report that do not respond to low glucose with Ca^{2+} fluctuations are the cells that can respond to paracrine factors in intact islets. The regulation of paracrine factors may also require intact β-cell–to–α-cell contacts to exert influence on α-cell Ca^{2+} dynamics. These might include gap junctions.

Finally, it should not be forgotten that autonomic influences play an important role in α-cell electrical activity and may modulate glucose sensing through innervation and circulating neurotransmitter levels (8). It is likely that such neurotransmitters play major roles in regulating glucagon secretion in ways both dependent and independent of the K_{ATP} channel.

In summary, the work of Quoix et al. provides evidence that the K_{ATP} channel is not the primary α-cell target responsible for hypoglycemia-induced glucagon secretion (16). Interestingly, the work also shows that, at least in isolated cells, Zn^{2+}, insulin, or GABA minimally regulates α-cell glucose-induced Ca^{2+} flux. These are intriguing observations that should stimulate future studies designed to understand the glucose-sensing mechanisms of the α-cell.

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