Glucose Control of Glucagon Secretion: There Is More to It Than K_{ATP} Channels

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Diabetes is generally attributed to insulin deficiency, but it has become increasingly evident that glucagon excess accounts for many diabetic manifestations (1). In contrast to the consensus mechanisms by which hyperglycemia initiates insulin secretion, there are fundamentally different ideas regarding how glucagon release is stimulated by hypoglycemia. Current hypotheses fall into three categories. First, it is possible that glucose concentration is measured by extrapancreatic sensors that feed back information to glucagon-releasing α-cells via neurons (2,3). Second, since glucagon release is also regulated independently of neural coupling, glucose sensing may be accomplished within the pancreatic islets by β- and δ-cells that control the α-cells via paracrine release of inhibitory insulin (4), Zn^{2+} (5), γ-aminobutyric acid (6), or somatostatin (7). Third, there is evidence supporting intrinsic glucose sensing by α-cells. In this category, two hypotheses imply that glucose deficiency causes a depolarization with influx of Ca^{2+} that initiates glucagon secretion by providing less energy to the electrogenic Na^+/K^+ pump (8) or by activation of a depolarizing store-operated influx of Ca^{2+} when energy is insufficient to maintain Ca^{2+} in the endoplasmic reticulum (9,10). However, the most frequently cited hypothesis proposes that glucose deficit hyperpolarizes the α-cells, relieving a depolarization-induced inactivation of ion channels involved in action potential firing and glucagon release (11). AMP-activated protein kinase may also contribute to stimulation of glucagon secretion downstream of Ca^{2+} (12). Clarification of the mechanisms by which glucose regulates glucagon release should facilitate development of α-cell–centered therapies to improve glucose homeostasis in diabetes.

The ATP-sensitive K^+ (K_{ATP}) channel has been implicated in detecting glucose-induced generation of ATP in most models of glucose sensing except those with intrinsic α-cell sensing by the Na^+/K^+ pump (8), the sarco(endo) plasmatic Ca^{2+} ATPase (SERCA) (9,10) or AMP-activated protein kinase (12). Using three different genetically modified mouse strains elegantly combined with pharmacological tools, Cheng-Xue et al. (13) provide convincing evidence in this issue of *Diabetes* that glucose can regulate glucagon secretion independently of K_{ATP} channels, somatostatin, and Zn^{2+}.

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Because glucose inhibition of glucagon secretion from mouse islets is maximal at 7 mmol/L—the threshold for stimulation of insulin release (10,14)—it seems unlikely that β-cell factors should mediate inhibition in the 0–7 mmol/L glucose range. Cheng-Xue et al. confirm this idea, and also argue against a role of Zn^{2+} at 10 mmol/L glucose. This concentration consequently inhibited glucagon secretion equally from control islets and those lacking the Zn^{2+}-accumulating transporter in the secretory granules. Somatostatin is a stronger paracrine candidate because its secretion is stimulated by the low glucose concentrations that inhibit glucagon release (10). However, Cheng-Xue et al. found that glucose-inhibited glucagon secretion was not diminished in islets from somatostatin knockout mice or after blocking somatostatin signaling with pertussis toxin, findings that were consistent with previous data (10,15). Instead, these studies showed that endogenous somatostatin has a tonic inhibitory effect but does not mediate glucose inhibition.

To evaluate the role of K_{ATP} channels, Cheng-Xue et al. used depolarizing tolbutamide and hyperpolarizing diazoxide that modulate K_{ATP} channel activity, as well as knockout mice lacking K_{ATP} channels. Tolbutamide added in the presence of 1 mmol/L glucose mimicked the glucagonostatic effect of 7 mmol/L glucose in islets from one strain of mice, but there was no effect in the other. However, at 7 mmol/L glucose, tolbutamide was stimulatory in islets from both strains. Since tolbutamide caused pronounced stimulation of somatostatin secretion and stimulated glucagon secretion from somatostatin knockout and pertussis toxin–treated islets, the effect was attributed to a balance between direct stimulation of glucagon secretion from the α-cell and stimulated release of inhibitory somatostatin from the δ-cells. Consistent with previous data (10), the inhibitory effect of 7 mmol/L glucose on glucagon secretion remained when the K_{ATP} channels were blocked with tolbutamide and even after dramatic reduction of secretion by exposure to hyperpolarizing diazoxide. Moreover, Cheng-Xue et al. found that glucose inhibits glucagon secretion in islets from K_{ATP} channel knockout mice.

So why doesn't glucose reproduce the stimulatory effect of tolbutamide on glucagon secretion as it does on insulin release? Cheng-Xue et al. argue that it may be related to poor metabolism in the α-cells, but they nevertheless provide evidence that glucose metabolism is required for inhibition of glucagon secretion. Maybe a K_{ATP} channel–mediated stimulation is too weak to overcome an inhibitory action of glucose. Although the authors refrain from discussing how sensing is accomplished, they argue that a "surprising" glucose inhibition of glucagon secretion from diazoxide-hyperpolarized α-cell is consistent with lowering of the cytoplasmic Ca^{2+} concentration (9). It is notable that this lowering is caused by glucose-stimulated Ca^{2+} sequestration in the endoplasmic reticulum, a fundamental component of the store-operated hypothesis (9,10).

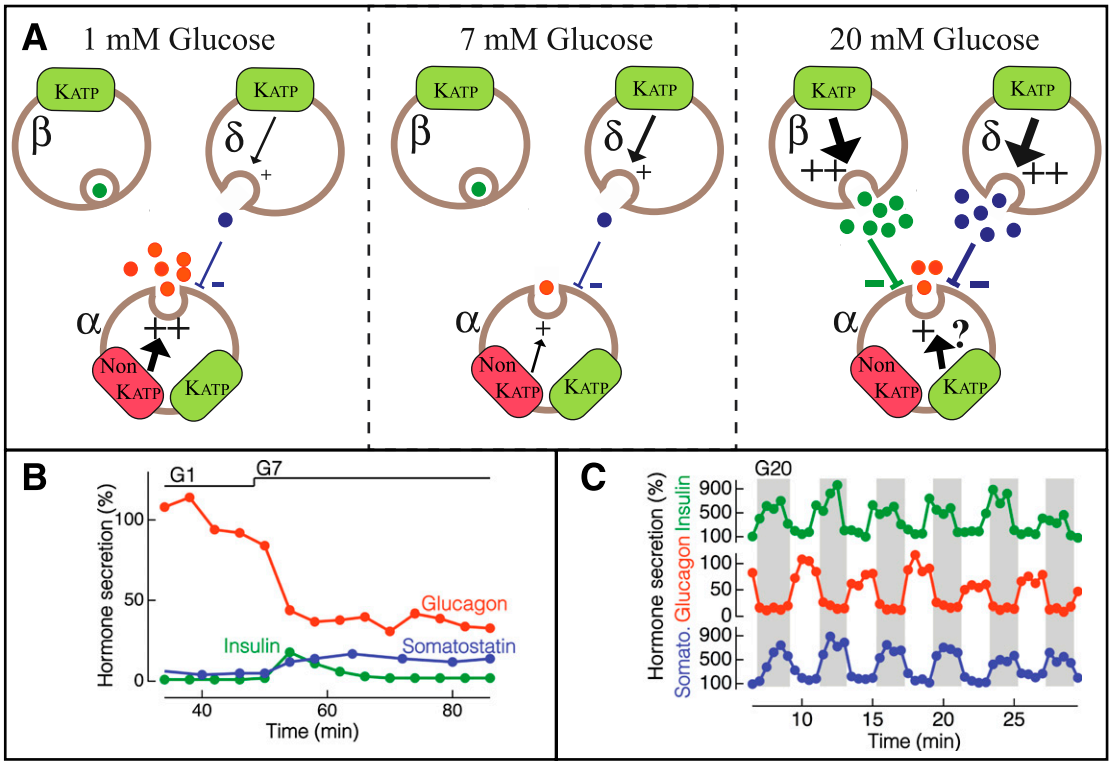

FIG. 1. ***A*** **and** ***B*****: In the 1–7 mmol/L range (G1, G7) glucose controls glucagon release via an intrinsic non-K_{ATP} channel–dependent mechanism in α-cells, and paracrine release of somatostatin from δ-cells has only a tonic inhibitory effect. The graph showing glucose inhibition of glucagon secretion is expressed in percent of stimulated secretion at 1 mmol/L glucose (from Cheng-Xue et al.). To get an impression of the relative magnitudes of the corresponding insulin and somatostatin responses, their secretions are expressed in percent of stimulated secretion in response to 0.5 mmol/L tolbutamide.** ***A*** **and** ***C*****: At 20 mmol/L glucose (G20) the K_{ATP}-independent mechanism no longer stimulates glucagon secretion and the pulsatility is generated via paracrine release of inhibitory factors from β- and δ-cells. The question mark indicates that a stimulatory effect of high glucose in the α-cell is not necessarily K_{ATP} channel-dependent. The hormone secretion data from ref. 17 have been recalculated as percentage of estimated secretion at 1 mmol/L glucose. Somato., somatostatin.**

The evidence for K_{ATP} channel-independent glucose sensing obtained by Cheng-Xue et al. is relevant for glucose counterregulation in the 0–7 mmol/L range. Much confusion about glucagon release may be explained by different experimental conditions if K_{ATP} channel-dependent release of inhibitory factors from β- and δ-cells contribute at higher glucose concentrations. In low glucose, the cytoplasmic Ca^{2+} concentration that generates hormone release remains stable in β- and δ-cells but shows pronounced oscillations in α-cells (16). Nevertheless, all three hormones are released at constant rates, and pulsatile secretion is only obtained in response to high glucose (17,18). Lack of gap junction coupling is probably why Ca^{2+} oscillations in α-cells do not coordinate to produce glucagon pulses at low glucose, whereas Ca^{2+} oscillations induced by high glucose in β-cells become synchronized by such coupling (19) to generate pulsatile insulin release. Although it is not clear how somatostatin pulses become synchronized with those of insulin, K_{ATP} channel-dependent release of inhibitory factors from β- and δ-cells likely explain why glucagon pulses are in opposing phases to the pulses of insulin and somatostatin (17,18). Since average glucagon secretion often is not further inhibited when paracrine mechanisms contribute above 7 mmol/L glucose, there is likely also a stimulatory effect of glucose (14,20). This stimulation may involve K_{ATP} channels (20) or be Ca^{2+}-independent (14) and dominate during the peaks of pulsatile glucagon release (17,18). These glucose concentration–dependent scenarios (Fig. 1) imply that separate molecular mechanisms are potential targets in future therapy to correct *1*) the impaired glucose counterregulatory response and *2*) the hyperglucagonemia that characterize diabetes.

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