Postprandial Suppression of Glucagon Secretion: A Puzzlement

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Pancreatic glucagon is a 29–amino acid hormone processed from proglucagon by prohormone convertase 2 in the pancreatic α-cells (1). Glucagon's best-established function is to defend against decreases in glucose availability during fasting, stress, and exercise by stimulating hepatic glycogenolysis phasically and hepatic gluconeogenesis tonically (1–5).

Glucagon also increases phasically during mixed-nutrient meals (6,7). Although many individual controls of glucagon secretion have been identified (Fig. 1), their interaction under physiological conditions is poorly understood.

Glucagon secretion is disturbed in diabetes (1,3–5,8,9). In patients with type 2 diabetes (T2D), fasting plasma glucagon levels are typically increased ~25%, leading to increases in hepatic glucose production and plasma glucose. Furthermore, glucagon levels do not decrease as much following mixed-nutrient or glucose ingestion as they do in healthy individuals ("glucagon nonsuppression"). Fasting plasma glucagon is also increased in type 1 diabetes (T1D) and in the streptozotocin mouse model of T1D, prevention of glucagon action by knockdown of the glucagon receptor prevented diabetes from developing (10). These and other data support the "bihormonal hypothesis of diabetes" that a relative lack of insulin secretion coupled to a relative surfeit of glucagon secretion leads to excessive hepatic glucose production and diabetes (5,9).

The role of postprandial glucagon nonsuppression in the progression to T2D is unclear. If glucagon nonsuppression appears early in the progression, it may provide useful insights as to specific pathophysiological changes that increase diabetes risk. Furthermore, understanding its mechanism may provide novel targets for antidiabetes therapy. For these reasons, two groups recently investigated glucagon nonsuppression during oral glucose tolerance tests (OGTT) and reported their findings in *Diabetes* (11,12). Both were cross-sectional studies involving considerably larger numbers of individuals (1,437 and 4,194, respectively) than studied heretofore (13–19) and including individuals with prediabetes. Nevertheless, the outcomes of the two studies were surprisingly different.

In the first study, Færch et al. (11) found that fasting glucagon levels were increased and postprandial glucagon suppression was reduced 30 min after glucose ingestion in individuals with T2D or prediabetes compared with healthy individuals. The data were similar when stratified by insulin sensitivity; i.e., better insulin sensitivity was associated with lower fasting glucagon levels and better 30-min postglucose glucagon suppression. By 120 min, however, glucagon levels were similar in all three groups. Overall, these findings suggest that defective 30-min postprandial glucagon suppression is a relatively early aspect of diabetes risk that is related to insulin insensitivity.

In the second new study, presented in this issue of *Diabetes*, Wagner et al. (12) studied individuals with normal glucose tolerance or prediabetes. Their data appear quite different from the data from Færch et al. (11). First, Wagner et al. found that that many individuals had higher plasma glucagon levels 120 min after ingesting glucose, whereas Færch et al. found that by 120 min, essentially all participants had lower glucagon levels. Second, Wagner et al. found that individuals with 120-min nonsuppression had lower fasting glucagon levels rather than the association between higher fasting glucagon levels and 30-min glucagon nonsuppression reported by Færch et al. Third, again in contrast to the 30-min data from Færch et al., Wagner et al. found that individuals in whom glucagon was not reduced at 120 min were more insulin sensitive and had a lower risk of impaired glucose tolerance compared with individuals in whom glucagon was reduced. Wagner et al. fail to bring these apparent discrepancies between their data and those from Færch et al. into sharp focus but do provide an interesting discussion of how glucagon nonsuppression might be related mechanistically to improved glucose metabolism.

How might this controversy be resolved? Subject variables may have some influence on the data but seem unlikely to account fully for the differences. For example, patients with prediabetes in the study by Færch et al. (11)

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COMMENTARY

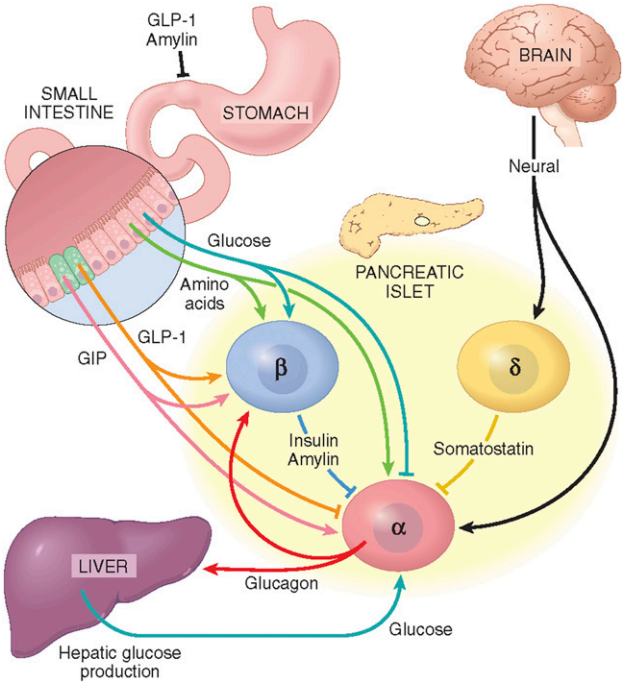

Figure 1—Some controls of glucagon secretion that may be involved in glucagon nonsuppression or tonically increased fasting glucagon levels in insulin resistance or diabetes (note that receptor mechanisms are not shown). As reviewed in detail elsewhere (1–5,26–28), nutrient, neural, endocrine, paracrine, and autocrine effects control glucagon secretion. The dynamic interactions among these controls are poorly understood. As the figure indicates, there are many possibilities for positive- and negative-feedback loops (e.g., glucagon stimulates both hepatic glucose production and insulin secretion, and both glucose and insulin inhibit glucagon secretion), for indirect effects (e.g., the incretin hormone glucagon-like peptide 1 [GLP-1] stimulates insulin and amylin secretion, both of which inhibit glucagon secretion, both by acting directly on the α-cells and by reducing gastric emptying), and for antagonistic effects (one example is that the incretin hormone GLP-1 inhibits glucagon secretion but the incretin hormone glucose-dependent insulinotropic polypeptide [GIP] stimulates it; another example is that mixed-nutrient meals increase both plasma glucose, which inhibits glucagon secretion, and plasma amino acids, which stimulates glucagon secretion, with the net result a brief stimulation of glucagon secretion). Somatostatin may contribute in situations in which insulin and glucagon secretion do not change in a simple inverse fashion, such as after mixed-nutrient meals. Finally, central and peripheral glucose-sensing neurons converge onto sympathetic and vagal efferents that drive insulin and glucagon secretion. α, pancreatic α-cell (glucagon); β, pancreatic β-cell (insulin); δ, pancreatic δ-cell (somatostatin); arrows, stimulatory inputs; T-ends, inhibitory inputs.

had significantly higher mean fasting glucose levels than their normal control subjects (6.3 vs. 5.6 mmol/L), whereas there was no such difference in the study by Wagner et al. (12). Fasting glucagon levels were also lower in all of the groups from Færch et al. (~9–11 pmol/L) than in the groups from Wagner et al. (~18–22 pmol/L), but this is likely due to differences in the assays used and would not vitiate comparisons based on relative changes. It should be noted, however, that assaying plasma glucagon remains difficult, and many commercial assays are not sufficiently sensitive to measure the low glucagon concentrations occurring in glucagon suppression tests (5,20).

A long-term longitudinal approach may best contribute to resolving the controversial relationships among postprandial glucagon suppression, fasting glucagon levels, insulin sensitivity, and T2D. Such a study should determine whether changes in postprandial glucagon suppression precede changes in insulin sensitivity or not and whether they are predictive of the development of fasting hyperglucagonemia or T2D. If altered postprandial glucagon suppression precedes the development of insulin sensitivity or predicts development of fasting hyperglucagonemia or T2D, then the phenomenon seems worthy of intense investigation. But if it does not, it seems unlikely to be of major clinical significance (at least early on in diabetes progression; other mechanisms may contribute to clinically relevant glucagon nonsuppression later in T2D or in T1D [21]).

Of course, longitudinal studies should be complemented by studies to determine *1*) whether changes in prandial insulin secretion associated with the development of insulin insensitivity and diabetes alter glucagon's potency to stimulate hepatic glucose production, as indicated by a classic study by Shah et al. (22), and *2*) what mechanisms underlie alterations in postprandial glucagon secretion (Fig. 1 summarizes some candidates).

It would also be useful for future research to include studies of glucagon dynamics after mixed-nutrient meals in addition to OGTT. As mentioned above (6,7), glucagon secretion normally increases briefly during mixed-nutrient meals, so postprandial glucagon suppression should be more marked after such meals than after glucose ingestion. In addition, measures of gastric emptying would be useful. This is because intersubject variability in gastric emptying of glucose accounts for significant amounts of the variability in plasma glucose responses in OGTT in both healthy subjects and patients with T2D (23,24). More generally, gastrointestinal motor function and endocrine changes during and after meals are intimately and bidirectionally related, so that one cannot be understood fully without the other (25).

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