β-Cells: So Sensitive

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The overweight and obesity epidemic, increasing rates of low physical activity (1), and poor-quality diets (2), especially those that are high in ultraprocessed foods (3), have driven a parallel increase in type 2 diabetes (T2D). Obesity-induced insulin resistance significantly increases the demand on pancreatic β-cells to produce greater amounts of insulin to maintain normal blood glucose levels (BGL). The ability of β-cells to meet this heightened demand is influenced by a combination of genetic factors and environmental conditions, which collectively determine the resilience and adaptability of β-cells under metabolic stress (4,5).

Diabetes develops when β-cells fail to produce sufficient insulin to maintain BGL. This is often a result of impairments in critical processes such as β-cell development, proliferation, survival, and/or insulin production and secretion, underscoring the multifactorial nature of the disease (6,7).

In individuals with normal glucose tolerance, β-cell mass remains stable with age, even beyond 90 years of age (8). Individuals with overweight or obesity (BMI $\geq$27 kg/m^2) who maintain normal glucose tolerance exhibit ∼50% greater β-cell mass than their age-matched lean counterparts (8). In contrast, people who develop T2D fail to achieve this compensatory increase in β-cell mass compared with their weight-matched counterparts (9).

β-Cell compensation has been extensively studied in many animal models (10–14), elucidating essential processes such as proliferation, functional enhancement, dedifferentiation, and even failure. These studies underscore the complexity of β-cell adaptation. In animals that maintain normal glucose tolerance, β-cell function improves through a combination of increased β-cell mass and enhanced insulin secretion in response to insulin resistance, maintaining euglycemia. Assessing drivers of increased β-cell mass in humans is very challenging. Currently, β-cell mass can only be assessed at autopsy. In people with normal blood glucose, β-cell function increases with increasing body weight and insulin resistance (15). The compensatory response is impaired in relatives of people with abnormal glucose tolerance (16). Early-phase insulin secretion is impaired in people with impaired glucose tolerance or impaired fasting glucose, and late-phase insulin secretion is further compromised in those with impaired glucose tolerance (15). It was unclear whether small increases in glucose, within the normal range, can trigger significant changes in β-cell function.

In this issue of *Diabetes*, Bruce et al. (17) offer valuable insight into the nuanced interplay between small glycemic fluctuations and metabolic regulation. Through meticulously conducted human studies, they demonstrate that small increments in BGL of ∼0.3 mmol/L (5.5 mg/dL) induced by glucose infusion can produce an ∼20% rise in insulin and C-peptide and a 20–30% increase in insulin secretion rate (ISR) in apparently healthy, normal-weight individuals (Fig. 1) compared with a saline infusion. These small increases in insulin resulted in an ∼35% reduction in circulating glucagon and an ∼25% decrease in free fatty acids (FFAs). Together, these changes, observed through glucose infusion, were associated with a 40% reduction in endogenous glucose production (EGP) compared with the EGP at baseline glucose.

These findings clearly demonstrate that even minor increases in glucose availability signal increased insulin demand to β-cells. The study also highlights the critical role of the pancreatic-liver axis in maintaining glucose homeostasis under minimal physiological stress. EGP rapidly decreased within 10 min of glucose infusion. Notably, the reduction in EGP approximated the amount of glucose infused; 1 mg/kg/min.

However, despite the excellent β-cell sensitivity, even in these normal volunteers, by 1 h, blood glucose was not maintained exactly at baseline, although they remained very clearly in the normal fasting range despite infusion of ∼6.5 g glucose. We speculate that perhaps a small increase in blood glucose is a physiological way to reduce

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See accompanying article, p. 898.

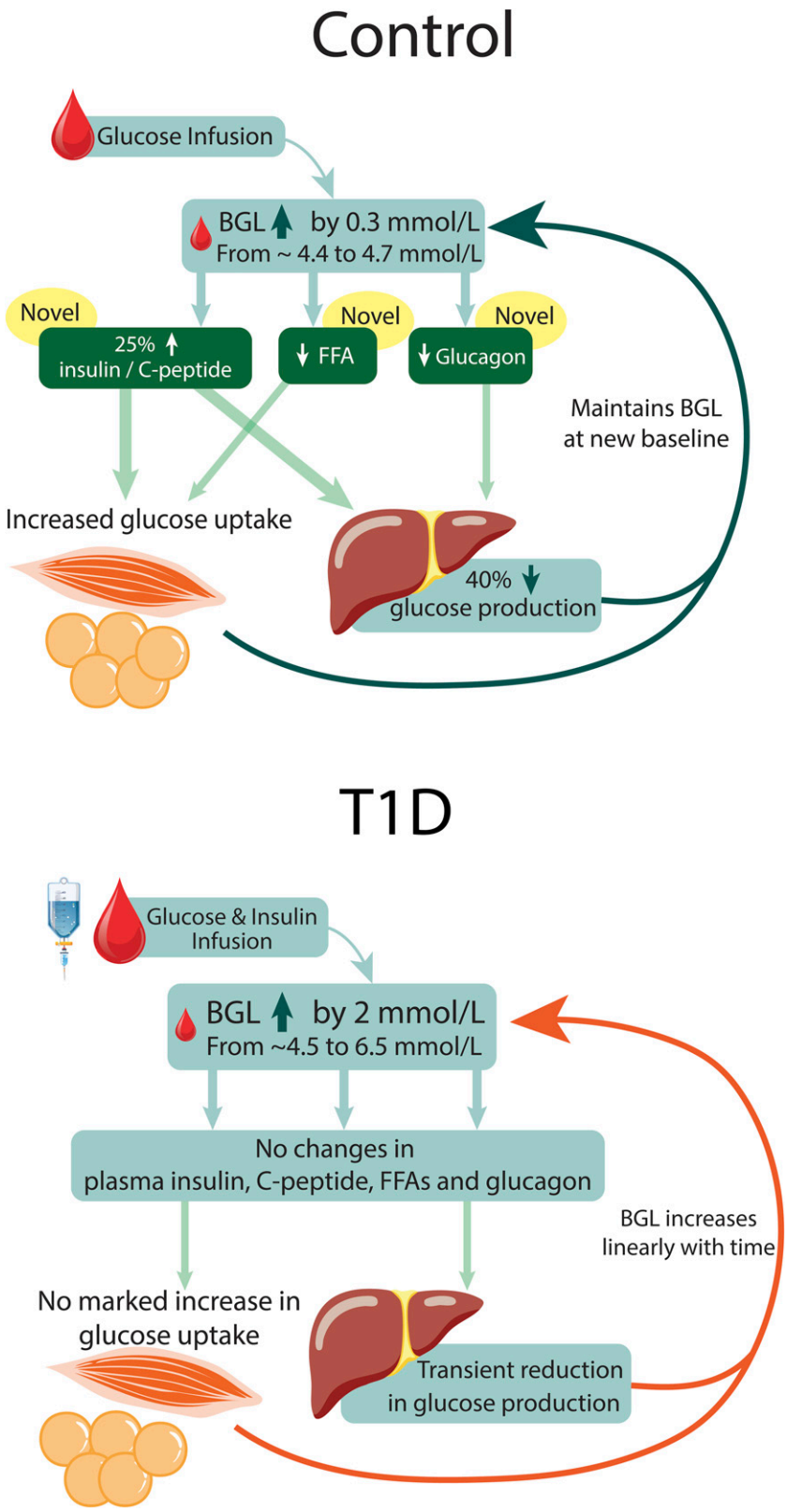

Figure 1—Pancreatic β-cell responses to small increments in glucose.

likelihood of later hypoglycemia, as insulin action is much longer-lasting than its secretion. A future study examining whether these very small changes are maintained or become dysregulated in individuals with overweight or obesity with normal glucose tolerance would be of interest.

A clear strength of this study lies in its use of participants with longstanding type 1 diabetes (T1D) and comparisons with people with normal glucose tolerance. In participants with T1D, glucose infusion with pump-delivered usual basal subcutaneous insulin resulted in a similar, but very transient, reduction in EGP, leading to a steady, nearly linear increase in BGL over 90 min (~2 mmol/L). Glucagon and FFA levels remained constant (Fig. 1, bottom). This is in stark contrast to healthy participants, in whom the small increase in glucose and subsequent insulin secretion rapidly suppresses EGP and FFA levels. Subcutaneous insulin infusion does not provide concentrated insulin delivery to the portal vein, which normal β-cells do, and is thus less effective at suppressing EGP.

It is not possible to study human β-cell proliferation in vivo in people. However, Levitt et al. (18) studied humanized mice that had streptozotocin-induced diabetes cured by human islet transplant. In these mice, 4 days of glucose infusion raised BGL from 3.6–4.4 mmol/L to 5.3–8.1 mmol/L, resulting in a >2-fold increase in human β-cell proliferation. There was a correlation with achieved glucose; higher blood glucose values were associated with greater β-cell proliferation. It is plausible, based on this new study by Bruce et al. (17), that smaller increases in glucose may also trigger β-cell proliferation.

The study does have limitations. Participants with T1D were not tightly age or BMI matched to the control group. For obvious ethical reasons, it is not feasible to study people who have T1D without insulin cover to prevent diabetic ketoacidosis, so the patients were all receiving low-dose systemic insulin treatment. Parenteral insulin delivery fails to replicate the normally high and pulsatile insulin concentrations seen in the portal circulation (19), which likely affected the ability to reduce hepatic glucose production in people with T1D. This has clinical implications, and indeed, there are studies suggesting benefits of pulsatile insulin delivery in people (20,21). Further, the observed suppression of glucagon during glucose infusion is likely the result of the interplay between insulin and other glucoregulatory hormones. While insulin plays a major role, it is unclear whether FFA and glucagon suppression was mediated solely by insulin. Other hormones may also contribute to this regulatory feedback to maintain glucose and lipid homeostasis (22).

Overall, these studies indicate that human β-cells both detect and respond to very small changes in BGL and that compensation for those changes is robust in healthy individuals. The findings suggest that even "normal" glycemic fluctuations within the fasting range can play an adaptive role in insulin secretion. Future research should investigate whether these mechanisms persist in insulin-resistant states or are altered under chronic hyperglycemia. Further exploration of the interactions between subtle glycemic changes and glucagon and incretin secretion could provide deeper insights into the pancreatic responses to minimal glucose stimuli.

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