Going With the Flow: Adaptation of β-Cell Function to Glucose Fluxes After Bariatric Surgery

Marzieh Salehi[1] and David A. D'Alessio[1,2]

Roux-en-Y gastric bypass (RYGB) surgery induces remission of type 2 diabetes (T2D) at higher rates than restrictive bariatric surgeries (1) or intensive medical treatment (2). While weight loss induced by lifestyle interventions or bariatric surgery improves glucose tolerance gradually by enhancing insulin sensitivity (3–5), some of the antidiabetic effect of RYGB is immediate and independent of the amount of weight loss (5–7). The dramatic resolution of diabetes after RYGB is consistent with processes rapidly engaged by the restructured gastrointestinal system to alter postprandial glucose regulation.

Individuals with RYGB have larger postprandial glucose excursions, with higher and earlier peaks and lower glucose nadirs, as early as 1 week after surgery (7). In parallel with this change in glycemia, meal ingestion shifts the postprandial insulin response upward and to the left (7), with more rapid insulin secretion over a shorter period. It is not clear to what extent the increased β-cell secretion is a response to greater glycemic stimulus or whether other factors are at play. There is experimental support for greater stimulation by gastrointestinal hormones, especially glucagon-like peptide 1 (8), and neural inputs to the β-cell (9) following RYGB are increased. Regardless of the underlying mechanism, a majority of patients with T2D benefit from RYGB in the short term, and the enhanced insulin response is thought to contribute significantly to this outcome. Interestingly, beneficial effects of surgery on β-cell function are more difficult to ascertain in nondiabetic subjects after RYGB, since many measures of insulin secretion are actually diminished over time as insulin sensitivity improves (10). It is now apparent that RYGB also has a significant impact on glucagon secretion. The notable feature after surgery is postprandial hyperglucagonemia, a finding reported in several cohorts including both diabetic and nondiabetic subjects (8,11–13). The significantly greater glucagon concentrations after meals present a paradox given the improved glucose tolerance with surgery and the deleterious effects of relative hyperglucagonemia on postprandial glycemia (14).

In this issue, a new study by Camastra et al. (15) provides some new insights into islet function and glycemic regulation following RYGB. In this study, cohorts of T2D and nondiabetic subjects were examined before and 1 year following surgery with a mixed-meal test that included administration of glucose tracers to measure enteral, hepatic, and systemic glucose fluxes; β-cell function was assessed using a modeling approach that this group has developed and validated. The findings in this study confirm previous reports that postprandial peaks of glucose are greater and occur earlier in people with RYGB, and that this is the result of more rapid entry of intestinally absorbed glucose into the circulation (16). Additionally, meal-stimulated glucagon increased significantly after RYGB and was associated with apparent hepatic insulin resistance, with higher rates of endogenous glucose production during the test meal. Finally, sensitivity of peripheral glucose disposal to insulin improved, a finding associated with weight loss and consistent with previous studies (10). These effects were similar in diabetic and nondiabetic subjects.

While many responses to RYGB were common to diabetic and nondiabetic subjects, effects on β-cell function differed somewhat. Similar to previous reports, rates of fasting and prandial insulin secretion were decreased in nondiabetic subjects, with a significant reduction in β-cell glucose sensitivity, a measure of the insulin:glycemic dose response. However, RYGB increased the β-cell response to the rate of change in blood glucose, model-derived index of dynamic insulin secretion separate from glucose sensitivity (17). This change suggests an adaptive response to surgery whereby the principal glycemic driver of insulin secretion shifts to accommodate the dramatically increased appearance of enteral glucose caused by RYGB. β-Cell rate sensitivity also increased to a comparable degree in the T2D subjects, approximately threefold, supporting this as a generalized response to surgery. However, β-cell sensitivity to glucose also increased in this cohort, nearly doubling 1 year after RYGB, although not returning to nondiabetic levels. One straightforward explanation for the discrepancy in glucose sensitivity between the diabetic and nondiabetic subjects is the resolution of chronic hyperglycemia in the former group, who had a drop in HbA_{1c} from 7.1 to 5.4%, and possibly resolution of glucose toxicity on β-cell function.

The findings reported here raise interesting questions about the alterations in physiology induced by RYGB and how the islet responds to these. The notion of distinct β-cell responses to changing glucose concentrations, and to the rate at which these occur, is incorporated into mathematical models like the one used by Camastra et al., but was originally advanced to explain patterns of glucose-stimulated insulin secretion in vitro (18) and in physiologic studies of humans (19). That these parameters are changed significantly by RYGB in nondiabetic subjects speaks to an ability of β-cells to adapt to differences in glucose appearance, in this case to the "dumping-like" pattern of postprandial glycemia described by the authors. If this reciprocal adaptation can be verified it would provide

From the [1]Department of Medicine, Division of Endocrinology, University of Cincinnati, Cincinnati, Ohio; and the [2]Cincinnati VA Medical Center, Cincinnati, Ohio.
Corresponding author: David A. D'Alessio, dalessd@ucmail.edu.
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a novel level of β-cell regulation, with potential applicability to other patterns of meal glucose appearance. The uncertainty here is that while the β-cell glucose and rate sensitivity changes are clear in this report, they are only suggested in other studies of bariatric surgery patients by this group (20,21), and confirmation of this hypothesis of β-cell adaptation will require directed studies.

While increased flux of glucose from the gut and transient systemic hyperglycemia might explain adaptations of β-cell function in subjects with RYGB, this is difficult to square with increased postprandial glucagon release. The usual response of the α-cell to increases in circulating glucose is decreased secretion of glucagon. Thus, in subjects with RYGB there seems to be a stimulus to the α-cell that overrides usual regulation. Autonomic control of glucagon secretion is important in hypoglycemic counterregulation, and neural regulation could explain α-cell function in RYGB. Increased intestinal glucose flux is likely to elevate glycemia in the hepatic portal vein disproportionately, a setting previously demonstrated to activate portal glucose sensors and initiate reflexes important in metabolic regulation (22). Increased portal, compared with systemic, glycemia enhances the early insulin response (23) as well as shifting glucose uptake toward the liver and away from extrahepatic sites (22) (Fig. 1). Therefore one mechanism that could provide a unified explanation for the distinct effects of RYGB on islet function is activation of neural pathways by elevated glucose levels in the portal vein. While speculative at this point, this hypothesis is tractable and merits further consideration.

Camastra et al. (15) include one more interesting observation. The calculation of prehepatic insulin and glucagon levels provides a novel parameter that can be related to hepatic glucose production. This ratio shifts rapidly in subjects with RYGB and is temporally compatible with the rise of endogenous glucose production earlier in the course of meal absorption. Thus, the pattern of islet hormone secretion induced by RYGB is reflected in hepatic glucose flux, which seems to compensate for greater rates of glucose clearance. While it is not clear how these processes are linked following RYGB, although a neural mechanism originating in the portal vein is also a possibility here (22), the new balance of glucose appearance and glucose disappearance maintains normal postabsorptive glycemia, at least in most patients.

Studies of the metabolic physiology of bariatric surgery have increased in recent years, driven in great part by the dramatic effects of procedures like RYGB to improve diabetes. Moreover, the increasing numbers of people having weight-loss surgery has provided impetus to understand their metabolism, particularly when they develop problems such as reactive hypoglycemia. However, the large changes in endocrine function and glucose fluxes seen in individuals with RYGB make this an excellent model to study glycemic regulation more broadly. The study by Camastra et al. in this issue is an excellent example of how observations in surgical patients can provide insights and stimulate hypotheses related to normal physiologic regulation.

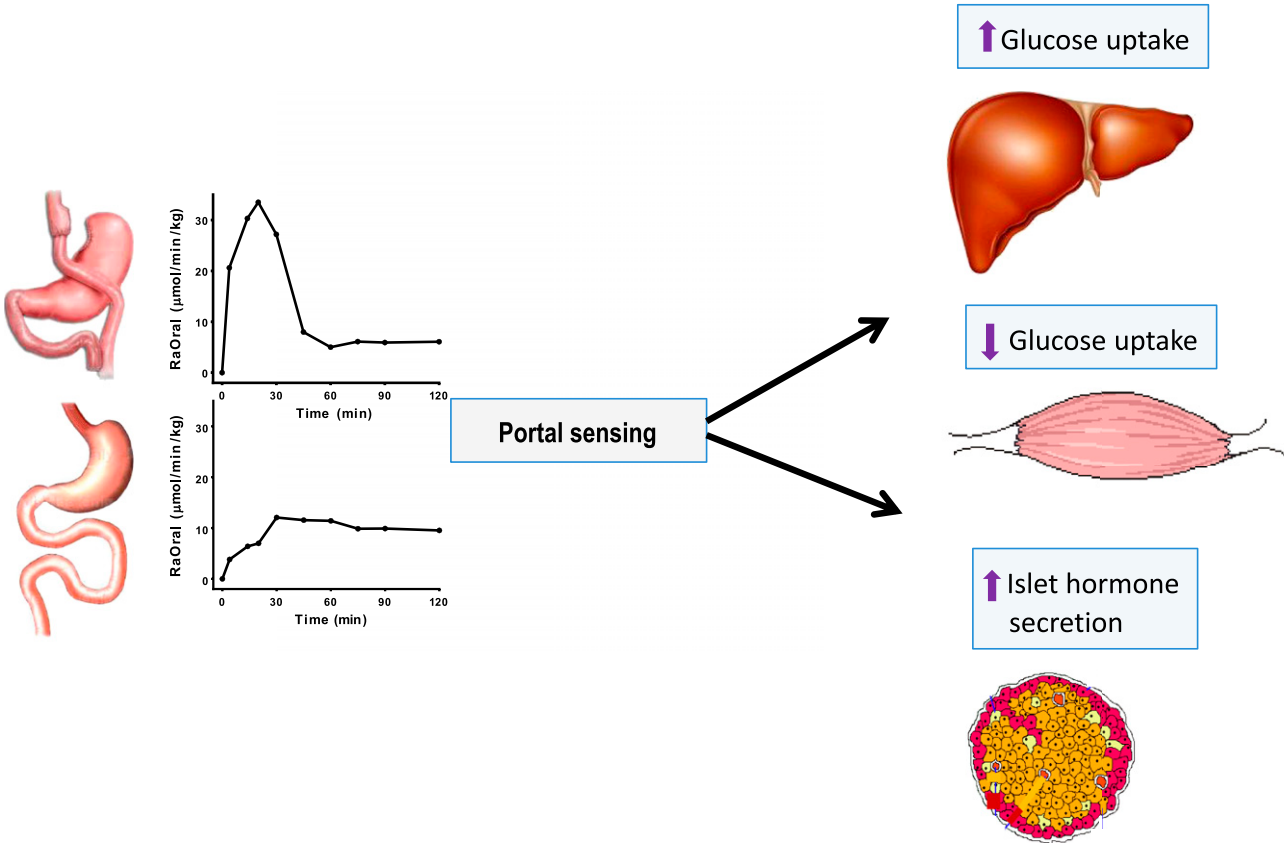

FIG. 1. Hypothetical model connecting increased appearance of meal glucose (RaOral) following RYGB and key regulatory steps for glucose metabolism. Increased rates of intestinal glucose uptake lead to higher glucose concentrations in the hepatic portal vein, initiating neural signals from portal glucose sensors that activate glucose uptake and islet hormone secretion.

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