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GLP-1: The Oracle for Gastric Bypass?

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Despite enormous efforts to find effective pharmacological targets, bariatric surgery is still the most effective treatment for morbid obesity. Beyond weight loss, this procedure often results in remarkable improvements in type 2 diabetes (T2D). However, several clinical trials have shown that between 22 and 28% of patients with T2D did not experience improvements in their diabetes after surgery (1). Personalized medicine seeks to identify the best possible therapeutic outcome with minimal adverse events. However, it requires an understanding of the molecular underpinnings of disease as well as signaling pathways triggered by both pharmacological and surgical treatments that predict an individual's likelihood of responding favorably to treatment.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is released into the bloodstream postprandially from the ileum and colon. Among its multiple biological actions (2), GLP-1 stimulates insulin secretion in a glucose-dependent manner (3,4) and decreases appetite (5). GLP-1–based T2D therapies are now commonly used in combination with other drugs with the added weight-loss effect broadening its therapeutic application in human obesity (6,7). Since bariatric surgery causes weight loss and T2D remission with enhanced postprandial GLP-1 secretion, the role of GLP-1 as a mediator of surgery-associated benefits has been investigated (8,9). However, to date, this hypothesis remains inconclusive because mice lacking GLP-1 receptors (GLP-1Rs) responded similarly to controls after vertical sleeve gastrectomy (10).

In this issue, Habegger et al. (11) demonstrated that response to pharmacological administration of GLP-1R agonists predicts the efficacy of Roux-en-Y gastric bypass (RYGB) on glucose tolerance in diet-induced obese rats. The authors studied almost 200 diet-induced obese rats and treated them with the GLP-1R agonist exendin-4 for 4 days, after which a glucose tolerance test was performed. As expected, considerable variability in weight loss and glucose tolerance was observed. Therefore, the investigators selected the 25 most responsive and the 25 least responsive rats and subjected these animals to RYGB. At 130 days postsurgery, both responders and nonresponders exhibited significant weight loss and concomitant fat mass reduction, indicating that the exendin-4 test is not indicative of these two parameters. However, glucose and insulin tolerance tests performed at 130 days after surgery indicated that nonresponders had impaired glucose tolerance and higher fasting glucose compared with responders, whereas no differences in insulin sensitivity were observed (Fig. 1).

A key question is why GLP-1 might be a useful biomarker/predictor of glucose responsiveness after RYGB if it is not related to postsurgical glycemic improvement. It might be possible that the response to pharmacological GLP-1 challenges is more important than the endogenous GLP-1/GLP-1R system in terms of glucose homeostasis (Fig. 1). Most previous studies assessing a potential relationship between RYGB and GLP-1 rely on basal or postprandial measurements of circulating GLP-1 levels or on data obtained from mice lacking GLP-1 from birth, but not on the GLP-1R sensitivity to exogenous stimuli as highlighted in Habegger et al. Given the pleiotropic actions of GLP-1, further studies will be necessary to assess if the variability in GLP-1R sensitivity is similar in different metabolically sensitive tissues. Since both responders and nonresponders showed similar weight loss and food intake, the improvement in glucose tolerance after RYGB observed in responders might relate

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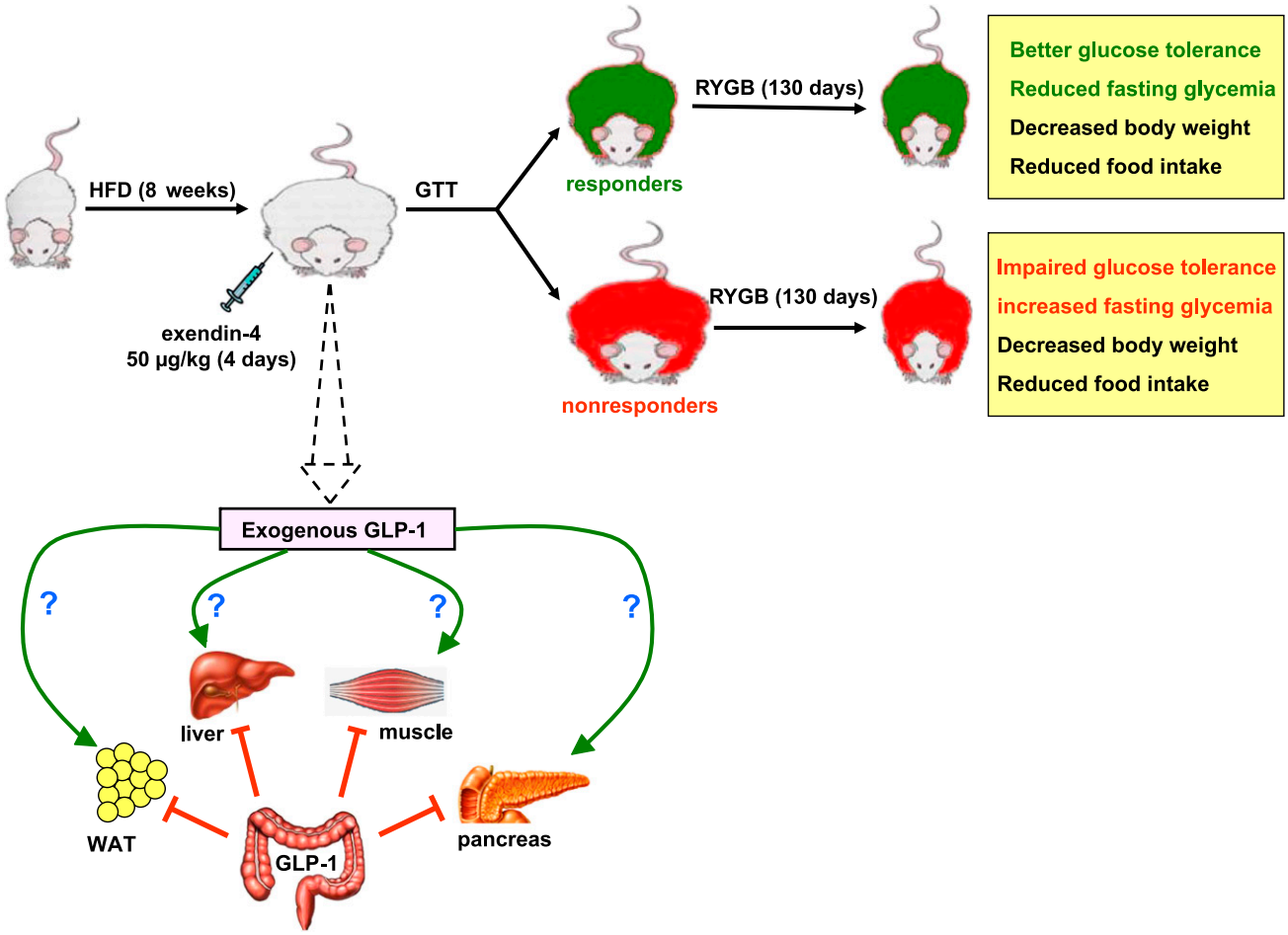

Figure 1—Responsiveness to exogenous GLP-1 predicts RYGB efficacy on glucose metabolism. Diet-induced obese rats, achieved by high-fat diet (HFD) feeding for 8 weeks, were treated with the GLP-1R agonist exendin-4 and subsequently split into two different groups: responders vs. nonresponders, according to the effect of exendin-4 on weight loss and the glucose tolerance test (GTT). After RYGB, both groups showed a decreased body weight, but responders showed an enhanced glucose tolerance compared to nonresponders. The tissues and molecular pathways explaining the prediction of glucose tolerance improvement in responders remain elusive. The key might be the response to the pharmacological administration of GLP-1R agonists rather than the endogenous GLP-1 levels, and it is plausible that not all the GLP-1–targeting tissues respond equally to the stimulation. WAT, white adipose tissue.

specifically to the pancreatic response rather than to the response of adipose tissue, liver, or muscle, which are closely associated with weight change. Analysis of β-cells (functionality, proliferation, and/or apoptosis) before and after RYGB in responders and nonresponders would clarify this issue. Obviously, signals other than GLP-1 may also predict response to surgery. Some potential candidates include ghrelin, cholecystokinin, peptide YY, amylin, oxyntomodulin, or currently unidentified peptides (12,13). The assessment of independent or synergistic responses to these candidates in individuals before surgery rather than measurements of their circulating levels may yield additional valuable information.

Hints of variable GLP-1 responsiveness in humans to both pharmacological and surgical treatments have been reported (14–18), thereby highlighting the potential translational value of GLP-1R agonist testing. Could GLP-1R responsiveness represent a valid strategy for assessing patient eligibility for RYGB? If obese patients have similar profiles as rodents, with nonresponders losing weight and appetite after RYGB, the surgical intervention would be justified in these patients despite the lack of T2D remission because weight loss implies an improvement in many other obesity comorbidities. With this line of thinking, GLP-1R testing may not be essential for determining patient eligibility for bariatric surgery. However, it would be interesting to investigate the validity of this test in nonmorbidly obese diabetic individuals undergoing metabolic surgery, which aims to cure T2D independently of weight change. In this sense, what would be the advantage of GLP-1R responsiveness over the glucagon test? Glucagon is a potent stimulus for islet β-cells, with an intravenous bolus injection widely used to assess endogenous insulin secretion and to predict amelioration of T2D (19). Because the glucagon test is easy, quick, and reliable for evaluation of the pancreatic reserve of diabetic

patients, whether GLP-1R responsiveness adds value above glucagon testing could be investigated as a means to enhance personalized information.

Finally, would GLP-1R responsiveness alone be enough to predict the long-term efficacy of RYGB in curing T2D, a condition based on complex, interrelated pathophysiological mechanisms? Would it be applicable to other bariatric surgery procedures like vertical sleeve gastrectomy, biliopancreatic diversion, or adjustable gastric banding? Since each type of surgery is performed on different anatomical parts of the gastrointestinal tract, each with different physiological properties, it is likely that the GLP-1R responsiveness may vary between them.

In summary, findings by Habegger et al. (11) represent an important contribution to identifying a predictive biomarker of surgery-associated benefits. Confirmation of these findings in humans is eagerly awaited. It is well recognized that functional approaches beyond BMI are urgently needed in obesity management (20). This approach should encourage testing of other gastrointestinal-related factors that may predict weight loss and ultimately translate into improved understanding of underlying mechanisms as well as improved patient eligibility and decision-making algorithms.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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