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Is the Gut the "Sweet Spot" for the Treatment of Diabetes?

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Oskar Minkowski possessed a rare combination of talents: He was an internist with the intuition of a scientist and the dexterity of a surgeon. One day in 1889, he and his colleague Joseph von Mering at the University of Strasbourg performed a total pancreatectomy in a dog to investigate if pancreatic enzymes were necessary to break down fatty acids in the gut. The dog survived the operation but unexpectedly developed polyuria, thirst, hunger, and glycosuria. Minkowski joined the dots to realize the link between the pancreas and diabetes (1).

This story is just one example of how surgical manipulations of anatomy can play a major role in advancing knowledge about physiology and disease. Many lessons about the functioning of the central nervous system, the pituitary gland, and the adrenals have been learned through the help of a scalpel (2), and Minkowski's observation provided the fundamental clue that lead to the discovery of insulin by Banting and Best in 1921.

More than a century later, surgery may again provide a unique opportunity to improve our understanding of glucose homeostasis, diabetes, and β-cell growth. Readers of *Diabetes* will know that a number of gastrointestinal (GI) operations used to cause weight loss (bariatric surgery) has also been shown to cause remission of type 2 diabetes (T2D) (3,4) as well as improvement of hypertension and dyslipidemia (5) and reduction of cardiovascular disease and death associated with diabetes and obesity (6). The mechanisms by which these operations control diabetes have become the subject of intense research in recent years, fueled by the experimental evidence that GI bypass surgeries can induce very rapid antidiabetes effects, independent of weight loss (7).

The pathophysiology of T2D is complex but the disease is characterized by a combination of insulin resistance and defective insulin secretion that worsens over time (8); treatments of curative intent would need to address both defects. GI bypass procedures can improve insulin sensitivity and production (9,10), suggesting that the GI tract may be a "sweet spot" for diabetes treatment. In particular, Roux-en-Y gastric bypass (RYGB) restores first-phase insulin response (10) and results in hypersecretion of C-peptide and insulin following nutrient ingestion (11), suggesting enhancement of β-cell function (12). Increased β-cell mass has also been hypothesized following controversial reports of nesidioblastosis complicating RYGB (13). Other hints of an effect of GI surgery on β-cell growth derive from observations of increased PDX1 levels (14) and prevention of β-cell loss after experimental duodenal-jejunal bypass in rodents (15), as well as from case reports of heterotopic pancreatic mass after RYGB in humans (16).

Lindqvist et al. (17) add support to the hypothesis that RYGB can stimulate β-cell growth. In their study, morphometric analysis revealed a doubling of β-cell mass and islet number in four RYGB-treated pigs, studied 20 days after surgery and compared with pair-fed, sham-operated controls. Extraislet β-cells, a surrogate marker of islet neogenesis, also were more frequent after RYGB. There was a greater number of immune-reactive cells per area for both insulin (1.8-fold increase) and glucagon (1.5-fold) in RYGB pigs, although increments in mRNA expression did not achieve significance for either hormone. Immunereactive cells for GLP-1 receptor were also 3.8-fold higher after RYGB. The authors concluded that increased β-cell mass may explain improved glucose tolerance after RYGB.

The authors acknowledged that their study has limitations. The small sample size and the choice of the porcine model, whose regulation of energy homeostasis is less well characterized than in other animal models, limit the generalizability of the findings. The use of nondiabetic animals and their failure to lose weight after RYGB also prevent the drawing of firm conclusions about the potential to induce β-cell regeneration in human insulin-deficient diabetes and on the relative importance of β-cell growth versus changes in insulin sensitivity in the remission of diabetic glycemia after RYGB. Nevertheless, their results do support the hypothesis that modifications

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COMMENTARY

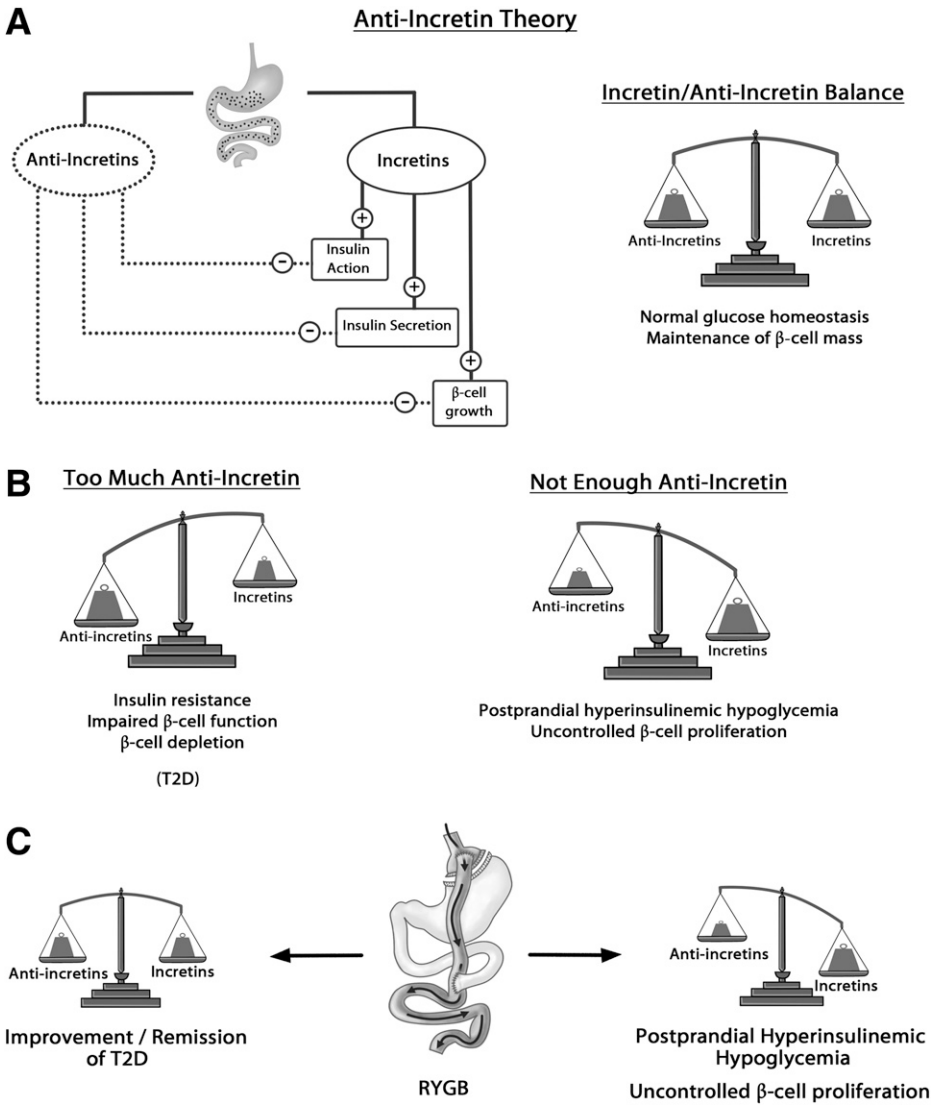

Figure 1—Anti-incretin theory and mechanisms of gastric bypass surgery. The anti-incretin theory (*A*) postulates that in addition to the well-known incretin effect (GLP-1, glucose-dependent insulinotropic polypeptide), nutrient passage in the bowel can also cause activation of negative feedback mechanisms (anti-incretins) to balance the effects of incretins and other postprandial glucose-lowering mechanisms (i.e., suppression of ghrelin, glucagon, and hepatic glucose production via activation of nutrient sensing). Incretins enhance insulin secretion, insulin action, and β-cell function and growth. In the absence of one or more control mechanisms, these effects would expose to the risk of postprandial hyperinsulinemic hypoglycemia and uncontrolled β-cell proliferation. In fact, postprandial hypoglycemia and proliferative disorders of the β-cell (i.e., nesidioblastosis and insulinomas) are rare, suggesting that the action of incretins may be physiologically balanced by anti-incretins (the name collectively indicates putative hormonal, metabolic, or neural mechanisms) to maintain normal glucose homeostasis. Predictions of the anti-incretin theory (*B*): Excess of anti-incretin signals, perhaps stimulated by macronutrient composition or chemical additives of modern diets, might cause insulin resistance, reduced insulin secretion, and β-cell depletion, leading to T2D. Conversely, reduction of anti-incretin signals below thresholds necessary to control incretin-driven responses might result in postprandial hypoglycemia and uncontrolled β-cell proliferation. Changes in the anti-incretin/incretin balance may explain benefits and complications of gastric bypass surgery (*C*). Reduction of nutrient stimuli on the gut by diet or, more radically, by operations that resect parts of the foregut or exclude segments of small bowel from nutrients transit (i.e., RYGB, duodenal-jejunal bypass, biliopancreatic diversion) could restore appropriate incretins/anti-incretins balance, explaining improvement/remission of T2D. Disruption of GI continuity, however, might reduce anti-incretin signals below minimal thresholds to compensate for incretin actions, thus explaining the postprandial hypoglycemia that can complicate RYGB. The same mechanism could also cause loss of control on β-cell proliferation, leading to increased β-cell mass even in normal subjects as seen in the study by Lindqvist et al. (17).

of GI anatomy may influence the regulation of β-cell growth and highlight the importance of further research in this area.

How RYGB exerts its effects on the islets in pigs or humans remains unclear. Enhanced incretin effect after surgery may provide a straightforward explanation. In fact, in both humans and rodents, RYGB causes a three- to fourfold increase in postprandial levels of GLP-1 (11), an incretin hormone that stimulates insulin release from the pancreas and also exerts antiapoptotic effects on the

β-cells (18). Increased expression of islet GLP-1 receptor after RYGB as reported by Lindqvist et al. could contribute to increased β-cell mass. However, GLP-1 responses to the intravenous glucose load used in the study are not given and the impact of RYGB on the β-cells and insulin in the islets was mirrored by effects on β-cell and glucagon, at odds with the known glucagon-suppressing effects of GLP-1 (19). Also, recent studies using mice models of functional GLP-1 deficiency, GLP-1 receptor knockout mice (20), and inhibition of GLP-1 receptor by exendin(9–39) in humans (21) call into question the role of GLP-1, suggesting that the mechanisms of action of RYGB are more complex.

RYGB excludes the duodenum and jejunum from the transit of nutrients, which seems to have specific antidiabetes effects (22,23). Given the close anatomic relationship between the duodenum and the pancreas, one cannot exclude that changes in regional/paracrine neuroendocrine mechanisms could also influence β-cell function and growth.

It is important to note that the increase in β-cell mass after RYGB occurred in normal animals and may therefore represent the result of a disruption of the physiologic control of β-cell proliferation that maintains normal β-cell mass. This is consistent with predictions made by the anti-incretin theory (24,25). This theory (Fig. 1) postulates that in addition to the well-known incretin effect (through GLP-1, glucose-dependent insulinotropic polypeptide), nutrient passage in the GI tract could also cause activation of negative feedback mechanisms (anti-incretins) to prevent postprandial hyperinsulinemic hypoglycemia. Given the antiapoptotic effects of incretins, the existence of anti-incretin mechanisms would also be necessary to prevent uncontrolled proliferation of β-cells (Fig. 1*A*). We note that nesidioblastosis and insulinomas are, in fact, rare. Reduction of anti-incretin signals below thresholds necessary to control incretin-driven responses would expose to the risk of hypoglycemia and uncontrolled β-cell proliferation. Inadequate anti-incretins/incretins balance due to disruption of GI continuity after RYGB might therefore explain the increase in β-cell mass seen in the study by Lindqvist et al. (17), as well as the postprandial hyperinsulinemic hypoglycemia that can complicate RYGB (26) (Fig. 1*C*).

Preliminary evidence in support of the anti-incretin theory comes from recent experiments showing that protein extracts from the duodenum and/or jejunum of diabetic rodents and humans induce insulin resistance in cell-based assays and in vivo (27).

Whatever the explanation, the findings that RYGB can influence regulation of β-cell growth in pigs contribute to the growing body of evidence that RYGB exerts complex and weight-independent effects on glucose homeostasis. The observation requires confirmation in other animal models and in humans, but it does support further research into GI mechanisms involved in islet regulation, as this may reveal new avenues for the treatment of type 2 and, possibly, type 1 diabetes.

Ten years ago, studies in diabetic rodents (7) provided initial evidence that GI bypass surgery exerts direct effects on glucose metabolism, suggesting that surgical manipulations of the GI tract may be an effective therapeutic approach for T2D as well as a powerful experimental tool to elucidate elusive physiology and pathophysiology of glucose homeostasis (7,24). Since then, several animal and human investigations have shown that RYGB and other procedures can improve T2D through a variety of GI mechanisms, including changes in gut hormones (18,19,21), bile acids metabolism (28), intestinal microbiota, nutrient sensing (29), and reprogramming of intestinal glucose metabolism (30). This demonstrates a critical and previously underappreciated role of the gut in glucose metabolism and underscores the importance of further research on the mechanisms of action of GI surgery. In fact, more than a century after Minkowski's pancreatectomy, a surgical operation may once again provide a lead for important discoveries in diabetes research.

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