EDITORIAL (SEE SOLOMON ET AL., P. 1561)

GIP: An Inconsequential Incretin or Not?

The "incretin effect" refers to the enhancement of insulin secretion in response to an oral glucose load relative to that of an isoglycemic intravenous glucose challenge (1). In humans, the incretin effect is mediated by two peptide hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from enteroendocrine cells in response to nutrients entering the gut. GLP-1 secretion from L-cells, found in highest density in the distal ileum but also throughout the small and large intestine, is stimulated by glucose, amino acids, and fat. GIP, in contrast, is produced by the K-cells in the proximal duodenum; its secretion is also stimulated by glucose, but is particularly enhanced by fat (2). Both GLP-1 and GIP are derived from prohormones (proglucagon and pro-GIP, respectively) and secreted as active hormones. The effects of both GLP-1 and GIP are mediated by specific G protein–coupled receptors present on the plasma membrane of β-cells and other target tissues. GLP-1 and GIP increase insulin secretion from β-cells in a glucose-dependent manner. In rodents, GLP-1 and GIP also enhance β-cell mass by increasing rates of proliferation and decreasing rates of apoptosis. Many physiological effects of GLP-1 and GIP do not overlap, however. GLP-1 suppresses glucagon secretion, slows gastric emptying, and has central nervous system effects to regulate appetite, whereas GIP does not. GIP, on the other hand, has direct effects on adipocytes to promote triglyceride storage (1). The incretin system, therefore, facilitates integrated physiological responses to meals of different size and composition allowing ingested nutrients to be optimally metabolized.

The incretin effect is an important determinant of glucose tolerance. In patients with type 2 diabetes, the incretin effect is markedly diminished and is less than half that observed in subjects with normal glucose tolerance (NGT) (3). This defect does not appear to be due to impairments in incretin hormone secretion, because most studies have found comparable circulating concentrations of GLP-1 and GIP in response to nutrient challenges in subjects with type 2 diabetes and nondiabetic control subjects (4). Rather, it appears that β-cell insulin secretory responses to incretin hormones are impaired in patients with type 2 diabetes. With GLP-1 this defect is modest and can be overcome with infusions that achieve higher GLP-1 levels. In contrast, even infusions that achieve supraphysiological GIP concentrations fail to elicit a significant insulin secretory response in patients with type 2 diabetes (5). Thus, GLP-1 infusions quickly normalize blood glucose levels in patients with type 2 diabetes, whereas GIP infusions do not (6). These observations created considerable enthusiasm for the development of pharmaceutical agents for the treatment of type 2 diabetes that work through the incretin axis, and particularly for those that enhance GLP-1 activity. Unfortunately, native GLP-1 is not suitable as a therapy for the treatment of type 2 diabetes because of its short half-life. In circulation, both GLP-1 and GIP are rapidly inactivated by dipeptidylpeptidase-4 (DPP-4), a ubiquitous serine protease that cleaves the two NH2-terminal amino acids from active hormones rendering them inactive. As a consequence of the action of DPP-4 as well as rapid clearance by the kidneys, the half-life of GLP-1 in circulation is 1–2 min and that of GIP around 7 min. Two approaches have been successfully employed to enhance the incretin effect. The first approach, injectable GLP-1 agonists that are resistant to DPP-4, is exemplified by exenatide and the recently approved human GLP-1 analog liraglutide. The second approach, orally available, small molecule inhibitors of DPP-4, includes the approved agents sitagliptin and saxagliptin as well as several other agents in development (7). Unlike GLP-1 agonists, DPP-4 inhibitors increase active levels of both GLP-1 and GIP. Because studies indicate GIP has minimal effects in type 2 diabetes, most of the therapeutic benefit of this class has been ascribed to the actions of GLP-1. Consequently, little attention has been paid to the physiology and pharmacological potential of GIP, even though this was the first incretin hormone identified.

In this issue of *Diabetes Care*, Solomon et al. (8) examines the contributions of GIP to changes in insulin secretion following a lifestyle intervention. A total of 29 older obese men and women with either NGT ($n = 16$) or newly-diagnosed type 2 diabetes ($n = 13$) participated in a 3-month weight loss and exercise intervention. At baseline and after the intervention, oral glucose tolerance tests were performed to measure nutrient-induced insulin secretion and GIP responses and hyperinsulinemic-euglycemic glucose clamps were performed to measure insulin action. They observed that the lifestyle intervention, which decreased body weight by around 5 kg and increased $V_{O_{2max}}$ in both groups, significantly improved glucose tolerance in the type 2 diabetes group but not in the NGT group. Insulin action increased by ~46% in the NGT group, but significantly less so (~26%) in the type 2 diabetic group. Insulin secretion decreased in the NGT group in proportion to their improvement in insulin action, but increased in the type 2 diabetes group in contrast. Similarly, incremental GIP responses to the glucose challenge increased significantly in those with type 2 diabetes, and tended to go down in those with NGT. In the group as a whole, changes in GIP were highly correlated to changes in insulin secretion corrected for the degree of insulin resistance following the intervention. A similar relation between insulin secretion and GIP was previously reported in subjects with impaired glucose tolerance by this group of investigators, although in this earlier study insulin action was not directly measured (9). These results suggest that improved β-cell–compensatory responses to insulin resistance following a lifestyle intervention are, at least in part, mediated by enhanced GIP secretion and action.

What is not clear from this study or the group's earlier work is whether the enhanced insulin secretion with the lifestyle intervention can be directly attributed to GIP, because insulin secretory responses to GIP were not directly measured. Thus, it is possible that a common mechanism altered by the lifestyle intervention could account for parallel improvements in insulin and GIP secretion, without there necessarily being a direct link between the two processes. Nevertheless, other recent data support the notion that incretin responses to GIP could

be modulated in type 2 diabetes. For example, a recent study by Højberg et al. (10) demonstrated that 4 weeks of intensive insulin treatment markedly improved insulin secretory responses to infused GIP in patients with poorly controlled type 2 diabetes. Interestingly, the same intervention did not increase GIP secretion, but did improve insulin secretory responses to a standard mixed meal in patients with type 2 diabetes, consistent with an enhancement in incretin action (11). It has been known for some time that expression of the GIP receptor on pancreatic β-cells is downregulate by hyperglycemia. Thus, the enhanced incretin response to GIP following normalization of glucose levels in the study by Højberg et al. could be due to upregulation of the GIP receptor on the β-cells of these individuals. New insights into the mechanisms by which this might occur have recently been reported by Gupta et al. (12) in preclinical models of diabetes. This group observed that the GIP receptor contains a functional peroxisome proliferator–activated receptor-γ (PPAR-γ) response element in the promoter region of the gene. Interventions that decreased or increased PPAR-γ activity (including exposure to a thiazolidinedione) resulted in corresponding changes in GIP receptor expression. Collectively, these data and the results of the present study suggest that it is possible to normalize the incretin effect in type 2 diabetes through interventions that decrease hyperglycemia, improve insulin resistance, or both. Whether treating patients with type 2 diabetes with a thiazolidinedione will enhance incretin effects mediated by GIP is not known, but is an intriguing possibility given that thiazolidinediones and DPP-4 inhibitors are now being studied in combination for the treatment of type 2 diabetes. Could an enhanced incretin effect contribute to the durable effect of thiazolidinedione drugs? We don't know, but GIP may not be the inconsequential incretin hormone in type 2 diabetes we thought it was after all.

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