Is Endogenous GLP-1 the Only Important Enhancer of Glucose-Induced Insulin Secretion in Type 2 Diabetes?

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It has been known for over a century that the small intestinal mucosa contains a substance(s) which decreases glucosuria in diabetic patients (1), with the term "incretin" (i.e., the assumption that intestinally derived substances are involved in regulation of postprandial insulin secretion) being first coined by La Barre (2) in 1932. Proof of the incretin concept came with the observation that orally administered glucose gave rise to a much larger insulin response than when the same amount of glucose was given intravenously (3,4). Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the major incretin hormones in humans (5,6). Together, they account for up to 70% of postprandial insulin secretion in healthy subjects (7). In individuals with type 2 diabetes, however, the incretin effect is severely impaired (8). It is now widely accepted that this is largely the result of reductions in the insulinotropic activity of both incretin hormones (9,10), although in some patients an impaired secretion of GLP-1 may also contribute (11). A classic method for establishing the role of a given peptide is to infuse it in such a way as to mimic normal physiological plasma concentrations. By giving GLP-1 and GIP by variable infusion rate to copy their normal postprandial plasma profiles, Vilsbøll et al. (12) demonstrated that both incretin hormones contribute almost equally to the incretin effect in healthy subjects. However, there is now some debate over whether all of the effects of GLP-1 are mediated solely via the endocrine route. It has been suggested that the insulinotropic actions may be, at least in part, mediated locally via interaction with afferent neurons close to the site of release (13). This in turn raises the question of whether peripherally infused GLP-1 can mimic fully the effects of the endogenous peptide, making it difficult to quantify the relative contributions of each incretin. Moreover, given that the incretin-based therapies use different approaches (selective GLP-1 receptor activation using pharmacological levels of the GLP-1 receptor agonists vs. enhancement of the normal pattern of release of both endogenous incretins using dipeptidyl peptidase-4 inhibitors), further exploration of these issues may improve our understanding of the mechanism of action of the two drug classes on β-cell function.

In an attempt to evaluate the contribution of endogenous GLP-1 to meal-induced insulin secretion, Salehi et al. (14) used the GLP-1 receptor antagonist exendin 9–39 and reported that postprandial insulin responses were similarly suppressed in both healthy and diabetic subjects. In this issue of *Diabetes*, Woerle et al. (15) further extend these observations, using exendin 9–39 to examine the importance of endogenous GLP-1 for first- and second-phase insulin secretion in patients with type 2 diabetes and in healthy subjects. They report that duodenal nutrient perfusion augmented insulin secretion compared with duodenal saline infusion under isoglycemic conditions, with the incretin effect being greater in healthy subjects compared with those with type 2 diabetes. Exendin 9–39 significantly reduced insulin secretion in response to duodenal nutrient infusion in both groups, although not to the same levels as seen with the saline perfusion. Accordingly, the absolute incretin effect was also reduced. Interestingly, the relative importance of GLP-1 for first-phase insulin secretion appeared to be more important in the diabetic individuals compared with healthy subjects.

One of the major strengths of the current study is the use of a hyperglycemic clamp and duodenal nutrient perfusion in order to eliminate differences in blood glucose and gastric emptying, which may complicate comparisons between the healthy subjects and those with type 2 diabetes. The present data confirm the long-standing observation that the absolute incretin effect is reduced in type 2 diabetes, although the relative responsiveness of the β-cells was unchanged (second-phase insulin secretion) or even increased (first-phase) compared with the nondiabetic subjects. Moreover, both GLP-1 and GIP plasma levels increased comparably in both groups. The data would, therefore, seem to support the hypothesis that the principal defect at the level of the β-cell involves a disturbance in glucose-mediated stimulation of insulin rather than any reduction in the amount or effect of GLP-1 per se (16). Of further interest is the observation that GLP-1 receptor antagonism did not fully block the meal-specific component enhancing insulin secretion even in the diabetic subjects, raising the question of whether endogenous (as opposed to exogenous) GIP retains more insulinotropic activity than previously thought or whether an additional pathway is present whereby orally ingested nutrients can augment insulin secretion. However, one can also speculate that the contribution of GLP-1 to overall insulin secretion in the current study may have been underestimated. Although the infusion rate of exendin 9–39 was chosen based on previous studies showing that it effectively blocked the effects of exogenously administered GLP-1 (17), it cannot be excluded that putative local effects (e.g., on afferent neurons in the intestinal wall, portal vein, liver etc., where endogenous GLP-1 concentrations will be higher than in the peripheral circulation [18,19]), may not have been fully antagonized with exendin 9–39 under the present experimental conditions. Additionally, on the control day (duodenal saline infusion),

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exendin 9–39 was not given. It is known that there is a tonic basal secretion of GLP-1, even in the fasting state, whereby even low incretin concentrations may have influenced β-cell responses on the control day (14); the calculation of the contribution of GLP-1 to overall insulin secretion may therefore have been higher had a more appropriate control (duodenal saline + exendin 9–39) been used.

In summary, Woerle et al. (15) have provided data supporting the idea that although the absolute incretin effect is reduced in type 2 diabetes, this is unlikely to be due to either reduced incretin secretion or a selective failure of the β-cell to respond to incretins. Rather, the data suggest that endogenous GLP-1 is important for enhancement of both first- and second-phase insulin secretion and that this effect is still retained in diabetic individuals, indicating perhaps that impaired incretin action may arise secondarily to a more generalized β-cell defect. Moreover, the finding that meal-stimulated insulin secretion was still augmented in type 2 diabetes even in the presence of exendin 9–39 suggests that additional non–GLP-1–mediated mechanisms contributing to enhanced meal stimulation of insulin secretion are also operative in type 2 diabetes. It would be most interesting to extend these observations by examining the contribution, if any, of endogenous GIP secretion and action in type 2 diabetes, although the probable lack of a suitable GIP antagonist may be a limiting factor. However, longer-term studies are required to further quantify the relative importance of these potential non–GLP-1 pathways and ascertain whether this has any relevance for the efficacy of the incretin-based therapies.

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