Comment on: Knop et al. (2007) Reduced Incretin Effect in Type 2 Diabetes: Cause or Consequence of the Diabetic State? *Diabetes* 56:1951–1959

Simeon Pierre Choukem[1] and Jean-François Gautier[1,2]

In the excellent article by Knop et al. (1), the authors use an interesting design to show that the decreased incretin effect observed in patients with type 2 diabetes is a consequence of the diabetic state rather than a causal factor. However, analyses concerning glucagon-like peptide-1 (GLP-1) concentrations seem a bit disturbing. Looking at Fig. 3 in their article, it is obvious that a 50-g glucose ingestion induces a peak of intact GLP-1 concentrations in patients with type 2 diabetes that seems similar to or even better than what is observed in the healthy control group. Surprisingly, they do not find any significant difference in integrated response of that hormone between the oral glucose tolerance test and the isoglycemic intravenous infusion test in the type 2 diabetic group. We think that this discrepancy may be related to the way they estimate the GLP-1 secretory response. Indeed, because they use the incremental (from the baseline level) area under the curve (AUC), each subsequent measure that falls below the baseline level generates negative values that are subtracted from positive values stemming from the initial peak. We suggest that in such situations, the AUC "with respect to ground," i.e., from zero, might be more suitable. This might have yielded a significant difference in intact GLP-1 level between the two tests, as in healthy control subjects. Furthermore, since the computation of the incremental AUC is based on the difference between the first and the subsequent measures (nine measures in their study), there is an accumulation (nine times) of the error of that first measurement, which is not the case when the AUC from zero is used (2). Another method is to use the incremental AUC but stop at the point where the hormone concentration returns to baseline level (at around the 90th min, as seen in Fig. 3 of their article) because what occurs after that time leads to negative values and might therefore not be physiologically relevant in terms of hormone secretion. In conclusion, the study by Knop et al. confirms that type 2 diabetes is characterized by an impaired incretin effect and that this abnormality is secondary to the diabetic state. However, contrary to what has been previously reported (3,4), they do not evidence a defect in GLP-1 secretion.

From the [1]Department of Diabetes and Endocrinology, Saint Louis University Hospital, Paris, France; and [2]INSERM UMRS 872, Centre de Recherche des Cordeliers, Paris, France.

Address correspondence and reprint requests to Jean-François Gautier, Department of Diabetes and Endocrinology, Saint Louis University Hospital , 1 Avenue Claude Vellefaux, 75475 Paris Cedex 10, France. E-mail: jean-francois.gautier@sls.aphp.fr.

Received for publication 15 October 2007 and accepted 16 October 2007.
DOI: 10.2337/db07-1470

REFERENCES

1. Knop FK, Vilsboll T, Hojberg PV, Larsen S, Madsbad S, Volund A, Holst JJ, Krarup T: Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes* 56:1951–1959, 2007
2. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH: Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 28:916–931, 2003
3. Vilsboll T, Krarup T, Deacon CF, Madsbad S, Holst JJ: Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes* 50:609–613, 2001
4. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, Holst JJ: Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab* 86:3717–3723, 2001