# Secretion and Dipeptidyl Peptidase-4-Mediated Metabolism of Incretin Hormones after a Mixed Meal or Glucose Ingestion in Obese Compared to Lean, Nondiabetic Men

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**Context:** Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are cleaved by dipeptidyl peptidase-4 (DPP-4); plasma activity of DPP-4 may be increased in obesity. The impact of this increase on incretin hormone secretion and metabolism is not known.

**Objective:** The aim of the study was to assess incretin hormone secretion and degradation in lean and obese nondiabetic subjects.

**Design, Settings, and Participants:** We studied the ingestion of a mixed meal (560 kcal) or oral glucose (2 g/kg) in healthy lean (n = 12; body mass index, 20–25 kg/m$^2$) or obese (n = 13; body mass index, 30–35 kg/m$^2$) males at a University Clinical Research Unit.

**Main Outcome Measures:** We measured the area under the curve of plasma intact (i) and total (t) GIP and GLP-1 after meal ingestion and oral glucose.

**Results:** Plasma DPP-4 activity was higher in the obese subjects (38.5 $\pm$ 3.0 *vs.* 26.7 $\pm$ 1.6 mmol/min $\cdot$ $\mu$l; $P = 0.002$). Although GIP secretion ($AUC_{tGIP}$) was not reduced in obese subjects after meal ingestion or oral glucose, $AUC_{iGIP}$ was lower in obese subjects (8.5 $\pm$ 0.6 *vs.* 12.7 $\pm$ 0.9 nmol/liter $\times$ 300 min; $P < 0.001$) after meal ingestion. GLP-1 secretion ($AUC_{tGLP\text{-}1}$) was reduced in obese subjects after both meal ingestion (7.3 $\pm$ 0.9 *vs.* 10.0 $\pm$ 0.6 nmol/liter $\times$ 300 min; $P = 0.022$) and oral glucose (6.6 $\pm$ 0.8 *vs.* 9.6 $\pm$ 1.1 nmol/liter $\times$ 180 min; $P = 0.035$). iGLP-1 was reduced in parallel to tGLP-1.

**Conclusions:** 1) Release and degradation of the two incretin hormones show dissociated changes in obesity: GLP-1 but not GIP secretion is lower after meal ingestion and oral glucose, whereas GIP but not GLP-1 metabolism is increased after meal ingestion. 2) Increased plasma DPP-4 activity in obesity is not associated with a generalized augmented incretin hormone metabolism. **(*J Clin Endocrinol Metab* 95: 872–878, 2010)**

The incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are released after meal and oral glucose ingestion and subsequently contribute to insulin and possibly also glucagon secretion (1–4). Both incretin hormones are rapidly degraded and removed from the circulation by the enzyme dipeptidyl peptidase 4 (DPP-4); consequently, intact GLP-1 and GIP are important for regulation of insulin release via the endocrine pathway, whereas total levels of the incretins reflect their secretion more (5). DPP-4 is a serine protease that is widely distributed in the body, including the vascular endothelium, and is also present as a

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Abbreviations: AUC, Area under the curve; DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HOMA-IR, homeostasis model of assessment for insulin resistance; i-, intact; NS, not significant; t-, total.

circulating form (6, 7). Plasma DPP-4 activity has previously been reported to be elevated in obese subjects compared with normal-weight subjects (8), but the impact of this on the clearance of the incretin hormones is unknown. High circulating levels of the enzyme could indicate that the incretins might be degraded more rapidly in obese than in lean subjects, and it could, therefore, be speculated that increased rates of metabolism of the incretin hormones in obesity may contribute to changes in postprandial incretin and islet hormone secretion. However, although incretin hormone secretion and metabolism have been examined in subjects with type 2 diabetes or insulin resistance (9–12), simultaneous measurements of DPP-4 activity and plasma concentrations of the intact incretin hormones and their metabolites after ingestion of a mixed meal or oral glucose have not been performed in obese *vs.* lean nondiabetic subjects. To obtain such information, we investigated the relationship between total and intact incretins and the islet hormones throughout a 5-h period after ingestion of a mixed meal or glucose in lean and obese healthy subjects.

## Subjects and Methods

### Subjects

Healthy lean [n = 12; body mass index (BMI; mean ± SD), 22.3 ± 0.3 kg/m$^2$; range, 20–25 kg/m$^2$] and obese (n = 13; BMI, 33.8 ± 0.6 kg/m$^2$; range, 30–35 kg/m$^2$) male volunteers, aged 20–34 yr (lean males, 22.0 ± 1.8 yr; obese males, 25.6 ± 4.0 yr), were included. They had no personal or family history of diabetes or gastrointestinal disease, and they were not taking any medication. They were recruited through advertisements in Lund, Sweden. The study was approved by the ethics committee of Lund University, Sweden, and all subjects gave written informed consent before entrance into the study.

### Study protocol

On two occasions, separated by at least 4 wk and, maximally, 8 wk, overnight fasted subjects were provided with an antecubital vein catheter and given either a mixed meal (560 kcal), consisting of 200 g cottage cheese (4% Keso; 162 kcal), 100 g canned pineapple with juice (79 kcal), 12 g "Wasa" multigrain bread (38 kcal), 60 g roast beef (244 kcal), and 200 ml skimmed milk (<0.1% fat, 57 kcal), or an oral glucose (2 g/kg) challenge. Blood samples were taken at 5 and 2 min before the meal or glucose ingestion and at predefined time intervals throughout a 300-min study period after the meal or glucose challenge. At 30 min before all tests, paracetamol (1 g; GlaxoSmithKline, Mölndal, Sweden) was administered for an indirect determination of gastric emptying; this method has shown good correlation when validated against the tracer techniques (13).

### Analyses

Blood samples, collected in chilled tubes containing EDTA (7.4 mmol/liter; final concentration) and aprotinin (500 kallikrein inhibitor units/ml blood; Novo Nordisk, Bagsvaerd, Denmark), were immediately centrifuged at 4 C, and plasma was frozen at −20 C until analysis. Insulin and glucagon were analyzed with double antibody RIA (Linco Research, St. Charles, MO). Blood samples for determination of intact and total GLP-1 were collected into chilled tubes containing EDTA and aprotinin as above, with the addition of diprotin A (0.1 mmol/liter final concentration; Bachem, Bubendorf, Switzerland). Plasma was separated and stored at −20 C until analysis. Intact GLP-1 was determined by an amino terminal-specific assay using guinea pig anti-GLP-1 and $^{125}$I-labeled GLP-1 (Linco Research). Total GLP-1 was determined using the C-terminally directed antiserum 89390 (14). Total GIP concentrations were measured using the C-terminally directed antiserum R65, and intact GIP was measured using antiserum 98171, which is specific for the intact N terminus of GIP (15). DPP-4 activity was assessed kinetically using Gly-Pro-*p*-nitroaniline (1 mmol/liter) as substrate by monitoring the release of *p*-nitroaniline at 405 nm (16). Paracetamol was analyzed by a colorimetric assay (Cambridge Life Science, Ely, Cambridgeshire, UK).

### Statistics

Means ± SE are shown throughout, except when otherwise stated. Areas under curves (AUC) were calculated by applying the trapezoid rule for glucose, insulin, glucagon, intact and total GLP-1, and GIP levels for the 300 min (unless stated otherwise) after ingestion of mixed meal or glucose. Insulin resistance was estimated as the homeostasis model of assessment for insulin resistance (HOMA-IR) index as fasting insulin (in pmol/liter) × fasting glucose (in mmol/liter)/22.5. ANOVA with Tukey's *post hoc* test was used for test of significance between the two groups.

## Results

### Baseline samples

Mean baseline values of incretins and islet hormones, glucose, plasma DPP-4 activity, and HOMA-IR in the lean and obese subjects, as determined by the mean values for the two separate days of studies in each subject, are shown in Table 1. Although all subjects had fasting glucose levels below the upper limit of normality, mean fasting glucose and also insulin levels and HOMA-IR were higher in obese subjects than in lean subjects, whereas there was no significant difference in baseline levels of intact or total GLP-1 and GIP or glucagon. Notably, plasma DPP-4 activity was significantly and markedly higher in obese subjects than in lean subjects.

### Mixed meal ingestion

#### *Glucose, insulin, glucagon, DPP-4, and paracetamol (Fig. 1 and Table 2)*

After ingestion of the mixed meal, there was a rapid increase in circulating glucose and insulin during the initial 30-min period. Thereafter, the levels returned to baseline. Glucagon levels also increased after mixed meal, but the increase continued for a longer period of time and started to decline only after 120 min. $AUC_{glucose}$ and $AUC_{insulin}$ were

**TABLE 1.** Fasting glucose, insulin, glucagon, intact and total GIP and GLP-1, HOMA-IR, DPP-4, and lipids in lean and obese subjects

| | Lean | Obese | *P* |
|---|---|---|---|
| n | 12 | 13 | |
| Fasting glucose (mmol/liter) | 4.4 ± 0.3 | 4.9 ± 0.1 | 0.003 |
| Fasting insulin (pmol/liter) | 52 ± 3 | 92 ± 8 | <0.001 |
| Fasting glucagon (pg/ml) | 69 ± 4 | 71 ± 9 | NS |
| HOMA-IR (pmol × mmol/liter$^2$) | 10.1 ± 1.0 | 19.8 ± 2.1 | <0.001 |
| DPP-4 activity (mmol/min · μl) | 26.7 ± 1.6 | 38.5 ± 3.0 | 0.002 |
| Fasting iGLP-1 (pmol/liter) | 4.0 ± 1.4 | 2.3 ± 0.6 | NS |
| Fasting tGLP-1 (pmol/liter) | 19.9 ± 1.3 | 17.0 ± 2.5 | NS |
| Fasting iGIP (pmol/liter) | 18.4 ± 1.6 | 12.9 ± 1.5 | 0.018 |
| Fasting tGIP (pmol/liter) | 16.7 ± 2.2 | 19.2 ± 4.4 | NS |
| Free fatty acids (mmol/liter) | 0.38 ± 0.03 | 0.61 ± 0.06 | 0.005 |
| Triglycerides (mmol/liter) | 0.61 ± 0.07 | 0.61 ± 0.14 | NS |

Means ± SEM of −5- and −2-min values before ingestion of mixed meal and oral glucose are shown.

higher in obese than in lean subjects, whereas $AUC_{glucagon}$ did not differ between the groups. The 2-h glucose value after meal ingestion was 3.5 ± 0.3 mmol/liter in the lean subjects and 4.7 ± 0.1 mmol/liter in the obese subjects ($P < 0.001$). Plasma DPP-4 activity did not change during the 300-min study period and therefore remained higher in obese subjects through the study period (data not shown). The 120-min $AUC_{paracetamol}$ was 8.7 ± 1.3 mmol/liter × 120 min in the lean subjects *vs.* 8.0 ± 1.0 mmol/liter × 120 min in the obese subjects [$P$ = not significant (NS)].

### *GIP and GLP-1 (Fig. 2 and Table 2)*

In both lean and obese subjects, total GIP (tGIP) and total GLP-1 (tGLP-1), which reflect secretion of the two incretins, increased promptly after ingestion of the mixed meal, to peak at 30 min; thereafter, the levels gradually returned to baseline values, which were reached after 300 min. Although $AUC_{tGIP}$ did not differ between groups, $AUC_{tGLP\text{-}1}$ was lower in the obese subjects compared with lean subjects ($P = 0.022$). Moreover, intact GIP (iGIP) and intact GLP-1 (iGLP-1), *i.e.* the insulinotropic forms of the two hormones, increased promptly after ingestion of the mixed meal, with levels peaking after 30 min. Thereafter, iGIP gradually returned to baseline levels, which were reached after 300 min. In contrast, iGLP-1 was increased above baseline only shortly after its peak at 30 min; thereafter, it rapidly returned to baseline values that were reached within 45 min. Both $AUC_{iGIP}$ ($P < 0.001$) and $AUC_{iGLP\text{-}1}$ ($P = 0.01$) were lower in obese than in lean subjects.

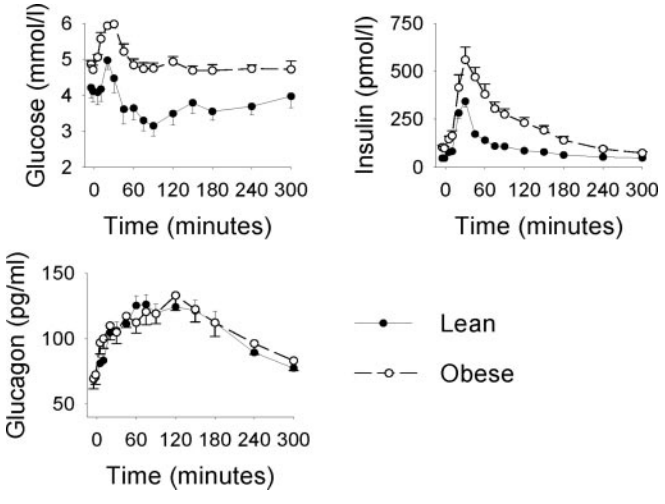


**FIG. 1.** Plasma levels of glucose, insulin, and glucagon before and during 300 min after ingestion of a mixed meal (560 kcal) in overnight fasted lean (n = 12) or obese (n = 13) healthy male volunteers. Means ± SE are shown.

## Oral glucose ingestion

### *Glucose, insulin, glucagon, DPP-4, and paracetamol (Fig. 3 and Table 2)*

Glucose and insulin levels increased after oral glucose, with marked augmentation of the responses in the obese subjects. In lean subjects, peak levels of glucose and insulin were reached after 45 min, whereas in obese subjects, glucose peaked at 60 min and insulin after 150 min. $AUC_{glucose}$ and $AUC_{insulin}$ were higher in obese than in lean subjects (both $P < 0.001$). The 2-h glucose value after oral glucose was 5.2 ± 0.2 mmol/liter in the lean subjects and 7.8 ± 0.6 mmol/liter in the obese subjects ($P < 0.001$). Glucagon levels were suppressed by the oral glucose. The reduction was augmented in obese subjects: the 90-min suppression of glucagon was 11.0 ± 3.3 pg/ml in lean subjects *vs.* 29.4 ± 6.8 pg/ml in obese subjects ($P = 0.026$). As a consequence, $AUC_{glucagon}$ was significantly lower in the obese group ($P = 0.007$). Plasma DPP-4 activity did not change during the 300-min study period and therefore remained higher in obese subjects through the study period (data not shown). The 120-min $AUC_{paracetamol}$ was 5.9 ± 0.9 mmol/liter × 120 min in the lean subjects *vs.* 5.3 ± 1.0 mmol/liter × 120 min in the obese subjects (NS).

### *GIP and GLP-1 (Fig. 4 and Table 2)*

After oral glucose, tGIP and tGLP-1 increased promptly to reach maximal levels after 30 min. Thereafter, tGIP and tGLP-1 reached a plateau at these increased levels until 150 min (tGIP) and 120 min (tGLP-1); thereafter, they gradually returned to baseline levels. The tGIP levels were not reduced in obese subjects; on the contrary, a slightly higher $AUC_{tGIP}$ was observed in obese subjects ($P = 0.041$). In contrast, by inspecting the curves, it was obvious that there was a clearly impaired tGLP-1 secretion during the initial 180 min. Therefore, the $AUC_{tGLP\text{-}1}$ for 0–180 min was also assessed. It was

**TABLE 2.** The 300-min AUC for glucose, insulin, active and total GIP, and GLP-1 after ingestion of mixed meal or oral glucose in lean (n = 12) and obese (n = 13) subjects

| | Mixed meal | | | Oral glucose | | |
|---|---|---|---|---|---|---|
| | Lean | Obese | *P* | Lean | Obese | *P* |
| $AUC_{glucose}$ ($\mu$mol/liter × 300 min) | 1.38 ± 0.08 | 1.87 ± 0.04 | <0.001 | 1.68 ± 0.06 | 2.42 ± 0.12 | <0.001 |
| $AUC_{insulin}$ (nmol/liter × 300 min) | 25.4 ± 3.1 | 68.4 ± 6.7 | <0.001 | 83.9 ± 8.8 | 309.4 ± 53.3 | <0.001 |
| $AUC_{glucagon}$ (pg/liter × 300 min) | 36.0 ± 1.8 | 37.2 ± 3.0 | NS | 23.0 ± 1.5 | 18.1 ± 2.4 | 0.007 |
| $AUC_{tGIP}$ (nmol/liter × 300 min) | 16.8 ± 1.9 | 14.8 ± 1.8 | NS | 17.9 ± 2.0 | 30.3 ± 5.1 | 0.041 |
| $AUC_{iGIP}$ (nmol/liter × 300 min) | 12.7 ± 0.9 | 8.5 ± 0,6 | <0.001 | 9.8 ± 0.6 | 11.9 ± 1.7 | NS |
| $AUC_{tGLP-1}$ (nmol/liter × 300 min) | 10.0 ± 0.6 | 7.3 ± 0.9 | 0.022 | 14.3 ± 1.5 | 12.2 ± 1.5 | NS |
| $AUC_{iGLP-1}$ (nmol/liter × 300 min) | 1.817 ± 0.46 | 0.36 ± 0.04 | 0.010 | 2.38 ± 0.47 | 1.31 ± 0.18 | 0.046 |

Values are means ± SE. *P* indicates probability level of random difference between the two groups.

then found that $AUC_{tGLP-1}$ was 9.6 ± 1.1 nmol/liter × 180 min in lean subjects and 6.6 ± 0.8 nmol/liter × 180 min in obese subjects ($P = 0.035$). In contrast, when including the entire 300 min, $AUC_{tGLP-1}$ did not differ between lean and obese subjects after oral glucose. Levels of iGIP and iGLP-1 also increased after oral glucose and remained above baseline levels until min 180. Whereas iGIP did not differ between the groups, $AUC_{iGLP-1}$ was lower in the obese subjects compared with lean subjects ($P = 0.046$).

## Discussion

We examined the temporal responses of incretin and pancreatic hormones in both lean and obese subjects for up to 5 h after ingestion of mixed meal or oral glucose to establish whether the reported increase in DPP-4 activity in obesity could influence the levels of active incretin hormones. A main result of the study is that secretion of the two incretins is regulated in a dissociative manner in obese *vs.* lean subjects. Thus, GLP-1 secretion, but not GIP secretion, was reduced in obese subjects after both mixed meal and oral glucose. Reduced GLP-1 secretion in obese subjects is in agreement with previous reports (17–19) and with findings in insulin-resistant nondiabetic subjects (11) and in subjects with impaired glucose tolerance (20). Additionally, several studies in patients with type 2 diabetes have shown reduced GLP-1 secretion (9, 10, 12), although others reported a normal GLP-1 secretion in diabetes (21, 22). This would suggest that different patient groups with type 2 diabetes exhibit different degree of changes in incretin hormone release and, therefore, that impaired GLP-1 secretion is not a general phenomenon in diabetes. One hypothesis could be that impairments in GLP-1 secretion are related not to diabetes *per se*, but rather to the degree of hyperglycemia. Indeed, patients with more poorly regulated glycemic control exhibit reduced GLP-1 secretion, as is evident from the impairment in subjects with high glycosylated hemoglobin levels (9). This would be supported by a recent study showing reduced GLP-1

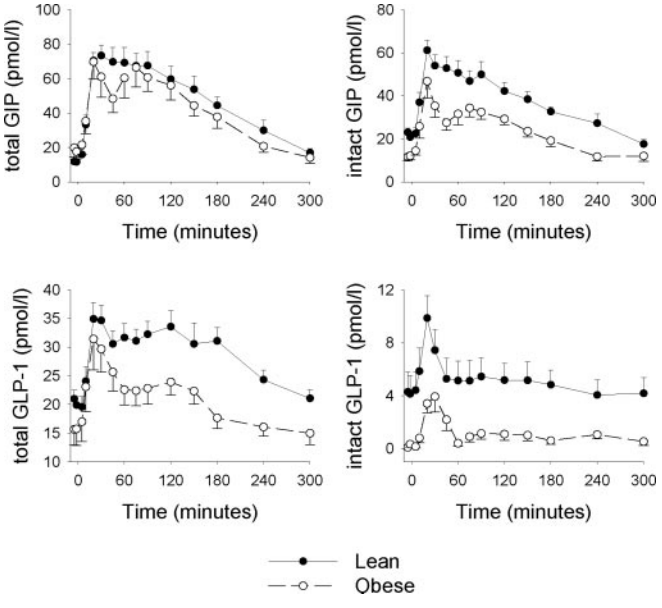


**FIG. 2.** Plasma total and intact GIP and GLP-1 before and during 300 min after ingestion of a mixed meal (560 kcal) in overnight fasted lean (n = 12) or obese (n = 13) healthy male volunteers. Means ± SE are shown.

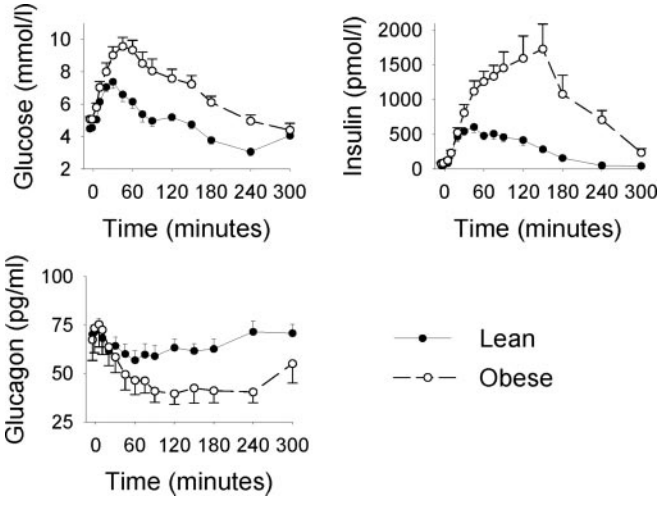


**FIG. 3.** Plasma levels of glucose, insulin, and glucagon before and during the 300 min after ingestion of glucose (2 g/kg) in overnight fasted lean (n = 12) or obese (n = 13) healthy male volunteers. Means ± SE are shown.

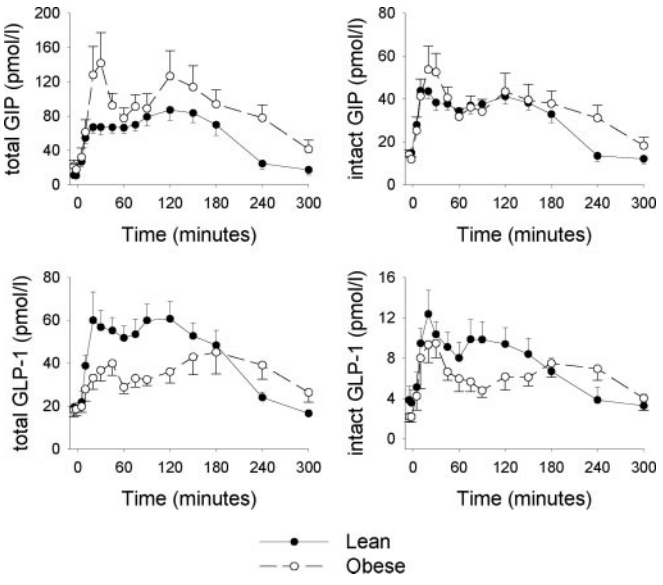


**FIG. 4.** Plasma total and intact GIP and GLP-1 before and during the 300 min after ingestion of glucose in overnight fasted lean (n = 12) or obese (n = 13) healthy male volunteers. Means ± SE are shown.

secretion in normal individuals who are rendered acutely hyperglycemic using hyperglycemic clamping (23). Another explanation would be that different patient groups in regard to different treatment and different duration of diabetes have been examined in the different studies. A potential explanation for reduced incretin hormone response in obesity would be that gastric emptying is reduced because degree of gastric emptying is of importance for the incretin hormone secretion (24). However, there is no consensus that obese subjects have a reduced rate of gastric emptying (25), and in the present study, we found that the indirect determination of gastric emptying by the paracetamol test did not disclose any differences between the groups. Therefore, it is unlikely that the reduced GLP-1 secretion after mixed meal and oral glucose in the obese subjects is due to a reduced gastric emptying.

In the present study, we found that the reduction in GLP-1 secretion was larger after the mixed meal (~25%) than after oral glucose (~15%). This would suggest that the impairment is due not only to impaired glucose effects but also to impaired action of noncarbohydrate components of the mixed meal, which also are important for the incretin hormone secretion (26). Furthermore, the impairment in GLP-1 secretion in the obese subjects was apparent during the early postprandial period, as evident from the $AUC_{tGLP-1}$ for the initial 180 min, whereas the overall response for the entire 300-min study period was not different from the lean subjects. This is in contrast to the reduction of the late postprandial GLP-1 response after meal ingestion in subjects with type 2 diabetes (9) and may suggest that insulin resistance and obesity affect different mechanisms than in type 2 diabetes.

In contrast to the reduced GLP-1 secretion in obese subjects after the mixed meal or oral glucose, there was no evidence of a secretory defect in GIP secretion in obese subjects. On the contrary, there was actually a tendency for GIP secretion to be slightly augmented after oral glucose (but not after the mixed meal) in obese subjects. This would be in line with previous reports that GIP secretion is augmented in subjects with type 2 diabetes (12). The mechanism behind this discrepancy between the two incretins remains to be established, but this would suggest that the GLP-1-producing L cells display impaired function earlier than the GIP-producing K cell during the development of obesity and type 2 diabetes.

In this study, we determined both total and intact incretin hormones, allowing conclusions on the metabolism of GIP and GLP-1 after mixed meal and oral glucose. It is known that the initial step in the degradation of the incretins is the rapid cleavage by the enzyme DPP-4, and because we confirm that the plasma DPP-4 activity is increased in the obese subjects (8), it might be anticipated that the incretins would be metabolized more extensively in obese subjects. If so, the levels of intact incretins should have been reduced to a greater extent than the levels of the total incretins. This was, however, not observed for GLP-1. Hence, although iGLP-1 was reduced in obese subjects after both the mixed meal and oral glucose, this reduction was parallel to the reduction of tGLP-1. This suggests that the reduction in iGLP-1 is secondary to the lowered GLP-1 secretion in obese subjects and therefore not due to enhanced metabolism. This in turn would suggest that increased plasma DPP-4 activity in obese subjects has only marginal, if any, impact on degradation of GLP-1. Instead, tissue DPP-4 might be of greater importance for inactivation of GLP-1, as suggested by the finding that DPP-4 is localized closely to the GLP-1 producing L cells and thereby inactivates GLP-1 already before it reaches the circulation (27). Our finding of a parallel reduction in tGLP-1 and iGLP-1 after mixed meal and oral glucose in obesity suggests that this tissue DPP-4 is not altered in obesity, and the reduction in iGLP-1 reflects the reduced secretion of GLP-1.

In contrast, our results do suggest that enhanced degradation of GIP may occur after mixed meals in obese subjects. This could indicate a relationship between the increased DPP-4 activity and GIP metabolism in obese subjects. However, if this were the case, then we should have expected to find a similar pattern after oral glucose, where plasma DPP-4 activity was also higher in the obese subjects, but this was not the case. Together, these results therefore suggest that, as for GLP-1, plasma DPP-4 activity is of less importance also for GIP metabolism. This would be supported by the knowledge that DPP-4 is

mainly a tissue enzyme, and it is not known whether local tissue DPP-4 activity is regulated in parallel with plasma DPP-4; a tentative hypothesis would be that DPP-4 activity in tissue close to the production site for GIP, *i.e.* the upper intestine, is increased by the noncarbohydrate constituent of the mixed meal, resulting in lower iGIP but not tGIP after mixed meal. Hence, a potential overall conclusion from our results is that plasma DPP-4 activity is of less relevance for incretin hormone metabolism. This is also supported from a recent study in subjects with type 2 diabetes, where a higher plasma DPP-4 activity was not associated with a decrease in the active concentrations of the incretin hormones (22). Moreover, because the concentrations of the incretin hormones are low relative to the Vmax of the enzyme, it is unlikely that small differences in plasma DPP-4 activity would have any measurable effect on the rate of GLP-1 or GIP degradation.

We also determined the islet hormone and glucose responses to mixed meal and oral glucose. The obese subjects were, as expected, insulin resistant, as evident by the high fasting insulin and increased HOMA-IR. As a consequence, the insulin response to both the meal ingestion and, in particular, the oral glucose was augmented in the obese subjects, which is a sign of the adaptation to insulin resistance of ß-cell function (28). Despite this hyperinsulinemia, however, the postload glycemia was higher in obese subjects, after both mixed meal and oral glucose. Similarly, the fasting glucose concentrations, although below the upper limit of normality in all subjects, were slightly higher in the obese than in the lean subjects. Together, this suggests that ß-cell function was impaired in the obese subjects because the degree of hyperinsulinemia was not sufficient in obese subjects to completely normalize the glycemia, whereas a normal ß-cell function results in adequate hyperinsulinemia in insulin resistance to maintain glycemia (28). Whether the obese subjects met the criteria for impaired glucose tolerance cannot be established in this study because the oral glucose load was not a standardized World Health Organization 75-g glucose load. Nevertheless, the higher postload glucose levels after oral glucose in the obese subjects indicate that they were glucose intolerant compared with the lean subjects. The hyperinsulinemia associated with insulin resistance in the obese subjects may support an idea that the reduced GLP-1 response would be executed through a negative feedback of insulin. In contrast, glucagon levels increased similarly in lean and obese subjects after the mixed meal. Furthermore, after the glucose challenge, glucagon levels were reduced, and this reduction was augmented in the obese subjects. This probably reflects that these subjects had higher glucose and higher insulin levels after oral glucose and that both glucose and insulin inhibit glucagon secretion (4).

In conclusion, this study has shown that release and degradation of the two incretin hormones show dissociated differences in obesity in that GLP-1 secretion, but not GIP secretion, is inhibited after mixed meal and oral glucose, and that GIP metabolism, but not GLP-1 metabolism, is increased after meal ingestion in obese subjects. The study also verifies that obesity is associated with increased plasma DPP-4 activity, but the results suggest that this is not associated with a generalized augmented incretin hormone metabolism.

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Disclosure Summary: R.D.C. is employed by and is a shareholder in Merck Inc. M.O.L. and K.J. are employed by and are shareholders in Novo Nordisk A/S. O.L., J.V., J.J.H., C.F.D., and B.A. have no disclosure to declare.

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