On the role of glucose-dependent insulintropic polypeptide in postprandial metabolism in humans

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Am J Physiol Endocrinol Metab 298: E614–E621, 2010. First published December 8, 2009; doi:10.1152/ajpendo.00639.2009.—We investigated the role of glucose-dependent insulintropic polypeptide (GIP) in the regulation of gastric emptying (GE), appetite, energy intake (EI), energy expenditure (EE), plasma levels of triglycerides (TAG), and free fatty acids (FFA) in humans. First, 20 healthy males received intravenous infusions of Intralipid, glucose, or Intralipid plus glucose, with and without GIP (1.5 pmol·kg−1·min−1) for 300 min and after a fixed meal (protocol 1). GE was measured using paracetamol, appetite sensations using visual analog scales, EE using indirect calorimetry, and EI during a subsequent ad libitum meal (at 300 min). Next, 10 healthy males received intravenous infusions of Intralipid, glucose, or Intralipid plus glucose, with and without GIP (1.5 pmol·kg−1·min−1) for 300 min (protocol 2). In protocol 1, GIP did not have any effect on GE, EI, EE, removal of TAG, or FFA and did not influence the subjective feeling of hunger, satiety, fullness or prospective food consumption compared with saline. In protocol 2, no difference was seen in the plasma TAG on Intralipid + GIP/saline and Intralipid + glucose + GIP/saline days. FFA concentrations were lower on Intralipid + glucose + GIP/saline days (P < 0.05) compared with Intralipid + GIP/saline days and on Intralipid + GIP day (P < 0.004) compared with Intralipid + saline day. Insulin increased on all GIP days compared with saline days (P < 0.05). In conclusion, while confirming its insulinitropic effects, these data suggest that GIP does not affect GE, appetite, energy intake, EE, or the clearance rate of the applied TAG formulation in humans. However, both insulin and GIP lower post-Intralipid FFA concentration, GIP probably via stimulation of insulin secretion, increasing FFA reesterification.

gastric emptying; energy intake; energy expenditure; appetite; insulin

Obesity is a consequence of an imbalance between food intake and energy expenditure, and several lines of evidence suggest a role for glucose-dependent insulintropic polypeptide (GIP) in the development of obesity. GIP is a hormone secreted from endocrine K cells located in the proximal part of the small intestine in connection with food intake (18, 31, 38), and it stimulates insulin secretion in a glucose-dependent manner (2, 11, 36). Early observations of elevated plasma GIP concentrations in type 2 diabetic patients (8, 12, 14, 43) and obese diabetic ob/ob mice (21) drew attention to a possible role of GIP in fat metabolism. This is supported by studies (3) demonstrating that high-fat feeding induced K-cell hyperplasia and enhanced GIP gene expression. Furthermore, it has been shown that GIP is released by lipids and that 24-h GIP profiles parallel the plasma concentration of triglycerides (TAG; Ref. 15), leading to speculation that GIP might play a part in the postprandial regulation of TAG. In dogs, infusion of GIP significantly lowered the rise in plasma TAG after infusion of chylomicrons (45), while in rats exogenous and endogenous GIP lowered the plasma TAG response to a fat load (13). In adipose tissue, GIP has been shown to stimulate glucose transport and increase fatty acid synthesis (24), enhance lipoprotein lipase (LPL) activity (30), and stimulate fatty acid incorporation (5). GIP may exert its effect on adipose tissue by both insulin-dependent and -independent mechanisms. Thus, in rats, GIP alone induced a limited increase in fatty acid incorporation into adipose tissue that was significantly enhanced in the presence of insulin (4). Miyawaki et al. (33) demonstrated that GIP stimulates glucose uptake in an insulin-dependent manner in 3T3-L1 adipocyte cell lines, whereas GIP by itself had no effect, and Starich et al. (41) found that GIP potentiated insulin-mediated glucose uptake in rat adipocytes and increased insulin receptor affinity.

Considerable support for the hypothesis that GIP plays a key role in the development of obesity has recently been demonstrated using GIP receptor-deficient (GIP−/−) mice (33). These animals, unlike wild-type controls, were resistant to the development of obesity when given a high-fat diet.

In humans, however, there is no clear evidence for an effect of GIP on lipid metabolism. In light of the current proposals to use GIP antagonists in the treatment and prevention of human obesity (20), it appears important to characterize the effects of GIP on plasma lipid concentrations in humans in more detail. Therefore, in the present study, the effects of GIP on the plasma concentrations of TAG and free fatty acids (FFA) were evaluated in healthy human subjects. Furthermore, the role of GIP in the regulation of short-term energy balance was evaluated. The study was divided into two parts. In protocol 1, we studied

Table 1. Subject characteristics for protocol 1

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<th>Means ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>26.2 ± 3.2</td>
<td>23–36</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.4 ± 8.5</td>
<td>65.6–99</td>
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<tr>
<td>Height, m</td>
<td>1.84 ± 0.87</td>
<td>1.76–1.91</td>
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<tr>
<td>BMI, kg/m²</td>
<td>23.2 ± 1.7</td>
<td>20.9–27.4</td>
</tr>
<tr>
<td>Fat mass, %</td>
<td>17.1 ± 3.9*</td>
<td>7.9–25.6*</td>
</tr>
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BMI, body mass index. *Fat mass was measured using bioelectrical impedance.
the effect of intravenous infusions of GIP on gastric emptying, postprandial concentrations of TAG and FFA (after ingestion of a fat-rich meal), postprandial appetite sensations, energy expenditure, and subsequent ad libitum food intake. In this experiment, the fixed meal elicited a robust plasma GIP response. To avoid the influence of endogenous GIP, protocol 2 consisted of intravenous infusions of GIP with and without infusions of Intralipid and/or glucose to mimic postprandial lipid and glycemic levels.

MATERIALS AND METHODS

Subjects

For the first protocol, we studied 20 healthy young males with a mean age of 26.2 ± 3.2 yr (means ± SD), body mass index (BMI) of 23.2 ± 1.7 kg/m², and fat mass of 17.1 ± 3.9% (Table 1). For the second protocol, we studied 10 healthy young males with a mean age of 25.1 yr ± 2.5 and BMI of 22.8 ± 1.4 kg/m² (Table 2). The study was performed in men to avoid the effect of menstrual cycle on appetite, food intake, and gastric emptying (6).

They were all without family history of diabetes or gastrointestinal disease and had a normal oral glucose tolerance test. All subjects signed a consent declaration after having received written and oral information about the study. The ethics committee in Copenhagen Municipality approved the protocol, and the study was performed in accordance with the Helsinki Declaration II.

Experimental Protocol

The evening before each test day, and no later than 1900, the subjects ingested a weight maintaining standardized meal [37 energy percent (E%) fat, 13 E% from protein, 50 E% carbohydrates, and 2.0 g/MJ fiber] estimated to meet their individual energy requirements, adjusted to the nearest 0.5 MJ. The subjects were instructed to abstain from drinking alcohol or doing strenuous physical activities for 2 days before the test days to ensure equally filled glycogen stores.

Protocol 1. The subjects were tested on two different occasions in a randomized, placebo-controlled, double-blinded crossover study. On the test day, the subjects arrived at the department at 0745 after having fasted for at least 12 h. The subjects then rested in the supine position with the head slightly elevated, and venflon catheters were inserted in the cubital vein of both arms, one for blood sampling and one for infusion. The forearm with the sampling catheter was heated to 60°C to arterialize the blood. After another 20-min rest, the resting metabolic rate was measured for 30 min. At 0945 (t = 0), a continuous intravenous infusion of GIP (0.8 pmol·kg⁻¹·min⁻¹) or saline was started and continued for the rest of the experiment. The breakfast was performed in men to avoid the effect of menstrual cycle on appetite, food intake, and gastric emptying (6).

Table 2. Subject characteristics for protocol 2

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<th>Means ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>25.1 ± 2.5</td>
<td>23–29</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 ± 5.5</td>
<td>70–83</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.84 ± 0.1</td>
<td>1.75–1.97</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8 ± 1.4</td>
<td>20.7–24.9</td>
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Fig. 1. A: plasma glucose-dependent insulintropic polypeptide (GIP) concentrations. B: plasma glucagon-like peptide (GLP)-1 concentrations. C: plasma GLP-2 concentrations. D: plasma glucose concentrations. E: plasma insulin concentrations during GIP (○) and saline (●) infusions. Data are means ± SE.
meal, with 1.5 g paracetamol for measurements of the rate of gastric emptying, was served at 0945 and consumed within 15 min, with the exact time being the same on the 2 test days for each individual subject. Postprandial resting metabolic rate was measured for 5 h with a 10-min break every hour. Blood samples were taken 15, 30, 45, 60, 90, 120, 180, 240, and 300 min after the start of the breakfast. After 300 min of infusion, at 1445, the lunch was served and the subjects were instructed to eat ad libitum comfortably satisfied. The time spent on eating was recorded, and the amount of food eaten was measured by weighing. Appetite ratings were made on 100-mm visual analog scales with text expressing the most positive and most negative rating anchored at each end (22). Visual analog scales was used to assess hunger, satiety, fullness, prospective food consumption, desires for special foods, thirst, comfort, and palatability of the test meal (taste, smell, visual appeal, aftertaste, and overall palatability). Appetite sensations were recorded immediately before and throughout a 5 h period after breakfast and right after lunch. Palatability ratings were assessed immediately after the consumption of each test meal. The ad libitum water intake at lunch was registered on the first test day and repeated on the second test day. Water consumption was allowed when necessary, but the volume was noted and a similar amount was given on the second test day.

Protocol 2. The subjects were tested on six different occasions in a placebo-controlled, crossover design. On the test day, the subjects arrived at the department 8 h after having fasted for at least 12 h. Two cannulas were inserted into the cubital veins, one for infusion of GIP, Intralipid 20%, and/or glucose and one for blood sampling. The experiments were carried out in a randomized order and consisted of an Intralipid infusion combined with or without GIP or of a glucose infusion combined with or without GIP.

At time 0, Intralipid was infused in a dose of 0.15 g/kg over 30 min followed by a continuous infusion of 0.225 g·kg⁻¹·h⁻¹ for half an hour. Glucose (25 g) was infused over 30 min to mimic the meal-induced glucose excursions. Continuous infusion of GIP (1.5 pmol·kg⁻¹·min⁻¹) or saline was maintained for a period of 300 min. This dose was chosen to mimic high physiological postprandial concentrations.

Venous blood was sampled 15, 10, and 0 min before and 15, 30, 45, 60, 90, 120, 150, 180, 240, and 300 min after the start of the infusions.

**Infusions**

**GIP.** Synthetic human GIP-(1-42) (PolyPeptide Laboratories, Wolfenbüttel, Germany) was dissolved in sterilized water containing 2% human serum albumin (CSL Behring, Marburg, Germany; viral safety achieved by the procedures specified in The European Pharmacopoeia) and subjected to sterile filtration. Appropriate amounts of peptide for each experimental subject were dispensed into glass ampoules and stored frozen (−20°C) until analysis. Vial content was tested for sterility and bacterial endotoxins (Ph. Eur. 2.6.14, Method C., Turbidimetric Kinetic Method). The peptide was demonstrated to be >97% pure and identical to the natural human peptide by HPLC, mass, and sequence analysis.

**Intralipid.** Intralipid 20% (Fresenius Kabi) was used as a TAG source; this emulsion is to some extent chylomicron-like, because its lipid droplets have a size and metabolic fate similar to those of chylomicrons. However, the emulsion does not contain cholesterol or apoB.

**Test Meals**

The test meals were a breakfast of fixed energy and macronutrient content, consisting of yogurt, bread, butter, cheese, jam, kiwi-fruit, orange juice, and water, and an ad libitum lunch, pasta salad consisting of pasta, ham, carrots, peas, sour cream, mayonnaise, olive oil, and basil. Total available energy content of the fixed meal (protocol 1) was calculated to be 20% of each subject’s individual energy requirements, adjusted to the nearest 0.5 MJ. The distribution of energy was 50 E%, carbohydrates, 37 E% fat, and 13 E% protein in both meals.

**Resting Energy Expenditure and Substrate Oxidation**

Resting energy expenditure was measured by indirect calorimetry using an open-air-circuit, computerized, ventilated hood system (19, 37). Energy expenditure and oxidation of carbohydrate, fat, and protein were calculated as previously described from the gas exchange (37). The respiratory quotient is the relationship between oxidation of carbohydrate and fat (37).

**Blood Analysis**

Blood was drawn without stasis into iced chilled syringes (Vacutett; Greiner Labortecnic, Kremsmünster, Australia). Syringes for GIP and TAG contained EDTA and syringes for insulin and C-peptide contained heparin. Blood for glucose and lactate was collected in EDTA tubes prepared with fluoride. Blood for FFA was collected into plain glass bottles. All samples were centrifuged within 15 min for 10 min at 2,800 g at 4°C and stored at −20°C (GIP and paracetamol) or −80°C (TAG, FFA, C-peptide, and insulin) until analysis.

**Protocol 1.** Plasma FFA was quantified by an enzymatic colorimetric method (Wako Chemical). Plasma TAG concentration was determined by enzymatic methods (44). Plasma glucose concentrations was analyzed by standard enzymatic methods (10). Plasma insulin, total GIP, total glucagon-like peptide (GLP)-1, and intact GLP-2 concentrations were measured by radioimmunoassay as previously described (1, 9, 23, 25). Paracetamol was analyzed by fluo-

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**Fig. 2.** A: plasma triglycerides (TAG) concentrations. B: plasma free fatty acids (FFA) during GIP (○) and saline ( ●) infusions. Data are means ± SE.
rescence polarization immunoassay technology (Diagnostic Division, Abbott Park, IL).

Protocol 2. Plasma TAG, FFA, and GIP were measured as mentioned above. Blood samples for PG analysis were measured immediately in duplicate by the glucose oxidase method on a Beckman glucose analyzer (Ramco). Plasma insulin and C-peptide concentrations were measured by auto-DELPHIA automatic fluoroimmunoassay (Wallac, Turku, Finland).

Statistical Analyses and Calculations

All results are presented as means ± SE unless otherwise stated. Area under the curves were calculated using the trapezoidal rule and are presented as total AUC if nothing else is indicated. Fasting and peak values, energy intake, gastric emptying, and energy expenditure were compared using a paired t-test. Differences in appetite rating and plasma TAG, FFA, and insulin responses were compared using mixed linear models with repeated measures. Time, treatment and the interaction time × treatment were included in the model as fixed factors, and subjects were included as a random effect. Differences resulting in P values of <0.05 were considered statistically significant. The Statistical Analysis Software, version 9.1, was used for the statistical calculations. The TAG data were log transformed, and the rate constants were determined by linear regression.

RESULTS

Protocol 1

The postprandial plasma GIP concentrations were significantly higher during the infusion of GIP compared with saline (P < 0.0001; Fig. 1A). During the infusion plasma GIP concentrations increased for the first 90 min from 1.2 ± 0.8 pM in the basal state to a peak concentration of 259 ± 14 pM (P < 0.0001). From 90 to 300 min, the plasma GIP concentration decreased slightly to 173 ± 7 pM at 300 min. During the saline infusion, the plasma GIP concentrations increased from 1.2 ± 0.8 to a peak of 105 ± 11.7 pM 90 min after the start of the infusion (P < 0.0001) and decreased thereafter, returning to fasting concentration at 300 min.

The levels of GLP-1 and GLP-2 increased significantly from 17.2 ± 2.6 and 9.7 ± 1.2 pM, respectively, in the basal state to a peak concentration at 29 ± 3.2 and 25.5 ± 2 pM, respectively (P < 0.001), at 30 min and decreased slowly thereafter reaching fasting levels at 300 min (Fig. 1, B and C).

No significant differences in plasma GLP-1 and GLP-2 concentrations were seen during saline and GIP infusions.

After meal ingestion, plasma glucose concentrations increased significantly during both GIP and saline (P < 0.0001; Fig. 1D). This was accompanied by a rise in insulin secretion during the first 30 min from 22.5 ± 1.3 to 235 ± 18 and 246 ± 93 pM, respectively, followed by a rapid decreased to fasting levels (P < 0.0001; Fig. 1E). Plasma glucose and insulin concentrations were similar during GIP and saline infusions (P = NS).

On both GIP and saline days, plasma TAG concentrations increased significantly from 0.97 ± 0.1 and 1.02 ± 0.1 mM, respectively, in the basal state to peak concentrations of 1.37 ± 0.7 and 1.57 ± 0.2 mM, respectively, at 180 min (P = 0.001;...
Figure 2A). Plasma FFA concentrations decreased rapidly and significantly during the first 60 min from 0.31 ± 0.03 mM at time 0 to 0.11 ± 0.02 mM and increased slowly from 120 to 300 min reaching 0.48 ± 0.04 mM at 300 min. Plasma TAG and FFA concentrations did not differ during GIP and saline infusions (P = NS; Fig. 2, A and B).

Energy intake (Fig. 3), gastric emptying, energy expenditure, respiratory quotient (Fig. 4), and appetite (not shown) were measured in the first protocol. The GIP infusion had no effect on any of these parameters.

**Protocol 2**

Plasma GIP concentrations were similar on Intralipid + GIP, Intralipid + glucose + GIP, and glucose + GIP days, increasing from 11.3 ± 0.8 pM in the fasting state to a mean plateau level at ~350 pM from 105 to 300 min (P < 0.0001; Fig. 5A). Plasma GIP concentrations were similar in the basal state (10.3 ± 0.3 pM) and during the infusions (9.9 ± 0.6 pM) on Intralipid + saline, Intralipid + glucose + saline, and glucose + saline days.

Plasma glucose mean concentrations reached their peak at 30 min after the 25-g doses of glucose (P < 0.0001; Fig. 5B). At 120 min, mean plasma glucose concentrations had returned towards baseline.

On Intralipid glucose + GIP/saline days and glucose + GIP/saline days, there was a significant increase in insulin concentrations during the first 30 min from 26.8 ± 1.4 pM in the basal state to peak concentrations of 384 ± 56 and 356 ± 55 pM (GIP days) and 144 ± 13 and 168 ± 32 pM (saline days; Fig. 5C). The AUC was significantly greater during the first 60 min on Intralipid + glucose + GIP day compared with Intralipid + glucose + saline day (13,203 ± 1,743 vs. 6,263 ± 607 pM min; P = 0.001) but no difference was seen during 60–300 min. On Intralipid + GIP day, insulin AUC increased significantly during the first 60 min on glucose + GIP day compared with glucose + saline day (11,383 ± 1,792 vs. 6,561 ± 942 pM × min; P = 0.009) and no difference occurred during 60–300 min. On Intralipid + GIP day, insulin AUC increased significantly during the first 60 min compared with Intralipid + saline day (2,133 ± 188 vs. 1,538 ± 156 pM 24 min; P 26 0.001; Fig. 5D) but was similar during the rest of the experiment.

On Intralipid + GIP/saline and Intralipid glucose + GIP/saline days, maximal TAG concentrations were reached after 1 h of infusion of Intralipid, increasing from 0.9 ± 0.1 to 3.3 mM (P < 0.0001; Fig. 6A). No differences were seen in the plasma TAG clearance between the 4 Intralipid days (P = NS). On glucose + GIP/saline days, there was a small but significant decrease in plasma TAG during the first 150 min from 0.9 ± 0.1 to 0.6 ± 0.1 mM (P < 0.004).

The elimination of TAG was purely monoexponential with approximately same elimination rate constant on all 4 Intralipid days (P = NS, data not shown).

![Fig. 5. Plasma GIP (A) concentrations, plasma glucose concentrations (B), and plasma insulin concentrations (C and D) during Intralipid (IL) + GIP (○), IL + NaCl (●), IL + glucose (Glu) + GIP (○), IL + Glu + NaCl (●), Glu + GIP (○), and Glu + NaCl (●). Data are means ± SE.](http://ajpendo.physiology.org/)

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**Fig. 5.** Plasma GIP (A) concentrations, plasma glucose concentrations (B), and plasma insulin concentrations (C and D) during Intralipid (IL) + GIP (○), IL + NaCl (●), IL + glucose (Glu) + GIP (○), IL + Glu + NaCl (●), Glu + GIP (○), and Glu + NaCl (●). Data are means ± SE.
The increase in plasma TAG resulted in a concomitant plasma FFA increase on Intralipid + GIP/saline and Intralipid + glucose + GIP/saline days during the first 60 min (Fig. 6B). There was a difference in peak concentrations on these days. On Intralipid + saline day, the peak concentration was highest at 60 min and amounted to $1.17 \pm 0.03$ mM, significantly different from Intralipid + GIP day with a peak concentration at $0.8 \pm 0.1$ mM ($P = 0.03$). Corresponding results were $0.51 \pm 0.04$ and $0.54 \pm 0.03$ mM, respectively, on Intralipid + glucose + GIP/saline days, significantly lower than on Intralipid + GIP/saline days ($P = 0.009$).

The plasma FFA concentration was significantly reduced at 60–300 min on Intralipid + GIP day compared with Intralipid + saline day ($P = 0.007$). No difference was seen in plasma FFA concentration between Intralipid + glucose + GIP and Intralipid + glucose + saline days, but on both days the FFA concentration was significantly reduced at 60–300 min compared with Intralipid + GIP/saline days ($P < 0.05$).

DISCUSSION

The main finding of the present study is that GIP alone or in combination with insulin does not seem to have any effect on the clearance of Intralipid TAG in man. As shown in Fig. 6 and in agreement with a previous study (35), the kinetics of removal of TAG from the circulation was strictly first order with the same rate constants on the 4 experimental days with the infusion of Intralipid. Our inability to demonstrate any effect of GIP therefore is hardly due to saturation of the LPL activity due to the high plasma TAG concentration applied, because saturation would result in deviation from first order kinetics. Our finding that addition of glucose to the infusions was without effects on the TAG removal is also in accord with previous findings (27). It is not possible from the present results to identify in which tissue the TAG removal takes place. Adipose tissue, skeletal muscle, and liver are the most likely sites. It has previously been shown that both adipose tissue and skeletal muscle contribute to the removal of TAG after an intravenous fat load, however, to a smaller extent than after an oral fat load (17). While there is evidence showing that the liver takes up the lipid particles from lipid emulsions without prior lipolysis, these particles are lipolyzed via LPL in adipose tissue and skeletal muscle (26). The fatty acids generated due to this may either be taken up in the tissue or may escape to the circulation. The increase in circulating fatty acid concentrations found in the present experiments is probably due to the latter process. The difference between the fatty acid concentrations found under the different experimental conditions must result from differences in tissue uptake and release of fatty acids. During GIP and Intralipid infusions, insulin secretion increased significantly during the first 60 min compared with the control experiment, confirming the ability of GIP to stimulate insulin secretion at fasting glucose levels (42). We found that GIP in combination with insulin secretion decreased the plasma FFA levels. One explanation for this is that insulin inhibits adipose tissue HSL activity and thereby adipose tissue fatty acid release. In addition, insulin may enhance adipose tissue fatty acid reesterification under these conditions (17). It is difficult to distinguish between direct GIP effects on fatty acid metabolism and an indirect effect based on the insulinotropic effect of GIP. Several in vitro studies (4, 33, 40) have shown that GIP exerts its effect on adipose tissue by both insulin-independent and -dependent mechanisms. Recent data obtained in mice with a GIP receptor knockout showed that a high-fat diet did not lead to obesity in these animals (33). This could suggest that GIP acts as an “insulin-sensitizer” in adipose tissue. However, adding GIP to glucose and Intralipid did not change FFA levels compared with the control experiment (Intralipid + glucose + saline). Most likely, the insulin levels reached in response to glucose infusion had a maximal effect on the FFA release and uptake and therefore no further changes were seen when GIP was added. The first part of the present study showed no effect of GIP alone on the plasma concentrations of FFA compared with saline, in spite of the fact that insulin was increased. Surprisingly, adding exogenous GIP to endogenously secreted GIP did not affect the insulin secretion (in the first part of the study). One explanation could be that the GIP levels reached in response to the meal were already maximally effective so that a further increase in GIP concentrations did not result in additional effects on insulin secretion and clearance of plasma lipids. However, although the insulinotropic effects of GIP were confirmed in the second part of the study, the elevated GIP levels still did not influence TAG clearance. In contrast to our study, Wasada et al. (45) found that the TAG levels following intravenous infusion of chylomicrons in dogs were significantly lowered by exogenous GIP (45). While some studies (7, 46) have indicated that Intralipid and chylomicrons exhibit similar decay kinetics after intrave-
nous administration in humans, other studies indicate that LPL more effectively hydrolyzes chylomicrons than Intralipid lipid droplets both in adipose tissue and in skeletal muscle. Therefore, it cannot be excluded that the lack of GIP effect found in the present experiments may be due to the artificial lipid formulation applied. A similar observation was made by Jorde et al. (29) who studied the effect of porcine GIP on clearance of plasma TAG after a 2-min intravenous Intralipid infusion for a period of only 25 min and in only six subjects. Also, in this study GIP failed to modify the levels of plasma TAG levels.

The infusion rate of GIP chosen in both parts of the present study raised GIP plasma levels into the high physiological range. Therefore, inappropriately low dosing of GIP does not explain the absence of the effects of GIP. Moreover, because of the surprising lack of effects in the first protocol, even on insulin secretion, the insulinotropic activity of the infused GIP was tested using isolated perfused pancreas as previously described (28), demonstrating equipotence with fresh ampoules of synthetic GIP. In the first part of the study, GIP was released endogenously in response to the meal. As mentioned above, the lack of an additional effect of infused GIP could be due to endogenous GIP already reaching maximally effective concentrations. However, toward the end of the infusion the secretion of endogenous GIP appeared to have ceased, at least in the control study, leaving only exogenous GIP in the circulation. Also in this period, there was no effect on plasma TAG of GIP compared with saline. The missing effect on the plasma TAG concentrations may also be explained by a rather slow gastric emptying giving rise to a prolonged absorption of the meal. A prolonged absorption may blunt the simultaneous decrease in plasma TAG concentration due to lipid storage. In the present study, the gastric emptying rate estimated from the paracetamol concentrations was about two times longer than that found in comparable subjects given a meal with less lipid content (16).

The present data demonstrate no effect of GIP on gastric emptying, appetite, energy intake, or energy expenditure. The lack of effect of GIP on gastric emptying is in agreement with previous studies (32, 39). One previous study (8a) has shown that infusion of GIP lowered resting energy expenditure and increased subjective feelings of hunger in normal weight healthy subjects, an observation that we have not been able to confirm. However, in that study, as in ours, no effect of GIP was seen on energy intake. There was also no effect of GIP on the secretion of GLP-2 as well as GLP-1 as previously reported (34).

In conclusion, these data suggest that GIP does not affect gastric emptying, appetite, food intake, energy expenditure, or clearance rate of the applied TAG formulation in humans. However, both insulin and GIP lowered post-Intralipid FFA concentration, GIP probably via stimulation of insulin secretion, which inhibits adipose tissue fatty acid release and increases FFA reesterification. To further explore the role of GIP in the regulation of energy balance and lipid metabolism in healthy subjects, experiments elucidating the local metabolic effects of GIP in adipose tissue are needed.

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GRANTS

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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GIP AND LIPID METABOLISM