

Interaction of Fat-stimulated Gastric Inhibitory Polypeptide on Pancreatic Alpha and Beta Cell Function

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Research Article

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Under hypoglycemic clamp conditions there was no increase in C-peptide nor glucagon after Lipomul ingestion, despite an increase of GIP of 51.7 ± 8.7 ng/ml per 120 min. Under euglycemic clamp conditions, small and inconsistent increases in C-peptide and glucagon were observed after fat ingestion and a concomitant increase of GIP of 35.2 ± 9.4 ng/ml per 120 min. Under hyperglycemic clamp conditions after fat ingestion and a GIP increase of 24.0 ± 5.7 ng/ml per 120 min, C-peptide increased from 6.4 ± 5 ng/ml to 11.0 ± 1.1 ng/ml ($P < 0.01$) but glucagon did not change. These findings confirm that in healthy man GIP exerts its insulinotropic properties only under hyperglycemic conditions and indicate that GIP is not glucagonotropic.

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Interaction of Fat-stimulated Gastric Inhibitory Polypeptide on Pancreatic Alpha and Beta Cell Function

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ABSTRACT Gastric inhibitory polypeptide (GIP) is considered to be the principal mediator of the enteroinsular axis. A glucose-insulin clamp technique was used to study the effects of differing blood glucose levels on the insulinotropic and glucagonotropic actions of fat-stimulated GIP in seven healthy subjects, as well as the effect of physiologic hyperinsulinemia on GIP secretion. Blood glucose levels were clamped for 4 h at 43 ± 2 mg/dl (hypoglycemic clamp), 88 ± 1 mg/dl (euglycemic clamp), and 141 ± 2 mg/dl (hyperglycemic clamp) in the presence of a constant insulin infusion (100 mU/kg per h).

Under hypoglycemic clamp conditions there was no increase in C-peptide nor glucagon after Lipomul ingestion, despite an increase of GIP of 51.7 ± 8.7 ng/ml per 120 min. Under euglycemic clamp conditions, small and inconsistent increases in C-peptide and glucagon were observed after fat ingestion and a concomitant increase of GIP of 35.2 ± 9.4 ng/ml per 120 min. Under hyperglycemic clamp conditions after fat ingestion and a GIP increase of 24.0 ± 5.7 ng/ml per 120 min, C-peptide increased from 6.4 ± 5 ng/ml to 11.0 ± 1.1 ng/ml ($P < 0.01$) but glucagon did not change. These findings confirm that in healthy man GIP exerts its insulinotropic properties only under hyperglycemic conditions and indicate that GIP is not glucagonotropic.

Under euglycemic clamp conditions (plasma glucose, 89 ± 1 mg/dl) and physiologic hyperinsulinemia (serum immunoreactive insulin, 137 ± 3 μ U/ml) GIP responses to fat ingestion (39.7 ± 9.8 ng/ml per 120 min) were not different from the GIP responses to fat ingestion in the absence of hyperinsulinemia (39.7 ± 11.1 ng/ml per 120 min). Therefore, insulin under normogly-

cemic conditions does not exert an inhibitory effect on fat-stimulated GIP secretion. The higher GIP response to oral fat in the hypoglycemic clamp, and the lower GIP response in the hyperglycemic clamp compared to the response in the euglycemic clamp suggests an effect of glycemia itself on GIP secretion in the presence of hyperinsulinemia.

INTRODUCTION

Gastric inhibitory polypeptide (GIP)¹ is considered to be the gastrointestinal factor primarily responsible for the greater plasma insulin response to oral compared to parenteral nutrient administration (1-3). Although ingestion of carbohydrate, fat (4), and some amino acids (5) results in increased levels of GIP, increased levels of insulin are observed only after oral carbohydrate (4) and amino acid (5) and not after oral fat (4). These observations suggest that the insulin secretory responsiveness of the beta cell to GIP is influenced by substrate or hormonal factors. There is *in vitro* evidence that the insulinogenic effect of GIP is glucose dependent (2, 6). Studies in humans, however, have shown conflicting results. There is evidence, using a glucose clamp technique, that the insulinotropic action of oral glucose-stimulated GIP (7) occurs only during hyperglycemia, but also evidence that amino acid-stimulated GIP is insulinotropic in the absence of hyperglycemia (5, 8). The involvement of a glucose-dependent mechanism for the insulinotropic action of fat-stimulated GIP has been reported from nonsteady-state conditions (8-10), but has not been investigated using a glucose clamp.

Whether insulin released after nutrient ingestion also regulates the secretion of GIP as part of a negative feedback system is presently controversial. The reduced GIP responses to oral fat observed after an intra-

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¹ Abbreviation used in this paper: GIP, gastric inhibitory polypeptide.

venous bolus of insulin or during a concomitant infusion of glucose supported an inhibitory action of insulin on the secretion of GIP (4, 8–11). However, Andersen et al. (7), using a glucose-insulin clamp technique at euglycemia and hyperglycemia, found no feedback inhibition of insulin on glucose-stimulated GIP secretion.

The current studies were undertaken to examine whether the level of glycemia modulates the insulinotropic effect of fat-stimulated GIP, to determine whether insulin inhibits the secretion of fat-stimulated GIP, and to determine whether the level of glycemia itself may influence the GIP response to oral fat. GIP, C-peptide, and glucagon responses to fat ingestion were measured in healthy subjects while glycemia was maintained by a glucose-insulin clamp technique in the hypoglycemic, euglycemic, and hyperglycemic ranges during a concomitant infusion of insulin at a rate sufficient to achieve physiologic hyperinsulinemia.

METHODS

Informed consent was obtained from seven normal nonobese subjects (three males, four females) ages 36 ± 5 yr (mean \pm SEM). All were within 10% of their ideal body weight and none had a family history of diabetes mellitus.

Each subject was studied in the overnight fasted state at each glycemic clamp level, and six of the seven subjects were studied during saline infusion in the absence of glucose-insulin clamp with and without the ingestion of Lipomul. Each study was separated by 1–2 wk.

For each glucose clamp study 18-gauge indwelling catheters were inserted into contralateral antecubital veins, one for the continuous infusion of crystalline insulin (pork U100, Eli Lilly & Co., Indianapolis, Ind.), at the rate of 100 mU/kg per h by means of a Harvard pump (Harvard Apparatus, Millis, Mass.) and one for the intermittent (every 20 min) withdrawal of blood for the determination of hormones. Distal to the insulin infusion site in a separate forearm vein, a double-lumen catheter was inserted for continuous withdrawal of blood at a rate of 2 ml/h for glucose analysis by the Biostator.

The glucose clamp was achieved using the Biostator GCIIIS (Life Science Instruments, Elkhart, Ind.), which permits continuous analysis and minute-by-minute recording of plasma glucose levels (glucose-oxidase) as well as the infusion of glucose according to predetermined computer-contained algorithms (12). Glucose (50 g/dl) was infused through the insulin infusion access site at rates determined by the Biostator (mode 7:1). In each subject the glucose clamp was maintained at 45 mg/dl (hypoglycemic clamp), 140 mg/dl (hyperglycemic clamp), and at the basal overnight fasting plasma glucose level (euglycemic clamp). The glucose infusion rate at the desired plasma glucose level, determined in preliminary studies, was 0.97 ± 0.06 mg/kg per min, 6.0 ± 1.1 mg/kg per min, and 7.4 ± 1.1 mg/kg per min and the inverse of the static gain for glucose infusion was 18, 45, and 45 for the hypoglycemic, euglycemic, and hyperglycemic clamps, respectively. Because the maximal infusion rate of glucose that can be infused by the Biostator is 1 g/min, additional glucose for the euglycemic and hyperglycemic clamps was given by a variable-speed infusion Harvard pump.

Each glucose clamp study was conducted for a total of 240 min. The first 120 min were devoted to obtaining stable plasma glucose and insulin concentrations. Emulsified cornoil

(Lipomul, Upjohn Co., Kalamazoo, Mich.), 67 g, was administered orally at 120 min. At 20-min intervals during the clamps, glucose levels obtained by the Biostator were checked against the reference method, YSI 23A glucose analyzer, Yellow Springs Instrument Co., Yellow Springs, Ohio. The Biostator glucose values for the hyperglycemic and euglycemic clamps were found to be consistently within $\pm 10\%$ of the YSI readings. The median percent difference between the two methods was 3.5%. For the hypoglycemic clamp the YSI glucose readings were consistently greater than the Biostator values with a median difference of 15%.

For the two studies without the insulin-glucose clamp, with and without the Lipomul ingestion, blood samples were obtained for 20-min intervals for glucose, insulin, and GIP determinations for 140 min.

Serum samples were frozen for insulin assay. Blood samples for GIP and C-peptide were collected on ice in tubes containing EDTA and Trasylol (500 kallikrein inhibitor units/ml; Sigma Chemical Co., St. Louis, Mo.) centrifuged at 4°C after which the plasma was frozen until assay. Blood for glucagon was processed similarly except for the use of benzamidine (0.1 M) instead of Trasylol.

Hormone assays. Plasma GIP was measured by the method of Kuzio et al. (13). Purified GIP, obtained from Dr. J. C. Brown (University of British Columbia, Vancouver, British Columbia, Canada) was used as standard and tracer. Antiserum R4817 was used at a final dilution of 1:100,000. This antiserum detects the two molecular forms of immunoreactive GIP (5,000 and 7,500 mol wt) present in postprandial blood. The limit of detection, intraassay and interassay coefficient of variation for the plasma internal reference standards were 50 pg/ml, 7 and 13%, respectively. No cross-reactivity was detected with glucagon (crystalline porcine glucagon, Eli Lilly & Co.), human pancreatic polypeptide (Eli Lilly & Co.), highly purified cholecystokinin, secretin, vasoactive intestinal peptide (all gifts from Dr. V. Mutt, Stockholm, Sweden), motilin (Dr. J. C. Brown), and gastrin (Imperial Chemical Industries LTD, London, England) in concentrations up to 10 ng/ml.

Insulin and glucagon were measured by the methods of Herbert et al. (14) and Faloona et al. (15), respectively.

Plasma C-peptide was measured using the reagents and procedure obtained from Calbiochem-Behring Corp., American Hoechst Corp. (San Diego, Calif.). The characteristics of the rabbit antiserum against synthetic human C-peptide have been described (16). ^{125}I synthetic tyrosyl C-peptide was used as tracer, and synthetic human C-peptide as standard.

Analytic methods. Data in the text and figures are given as mean \pm SEM. The integrated plasma GIP response after ingestion of Lipomul was calculated from the area circumscribed by the curve (using the mean of the 100 and 120 min for basal) in each person and expressed as ng/ml per 120 min. The coefficient of variation of the glucose clamps was calculated with the Biostator glucose values at 5-min intervals during the 60–240-min period of each clamp.

Statistical evaluation was performed by means of the two-tailed paired *t* tests. The rank sum test was used to compare the plasma GIP responses after Lipomul ingestion under the various clamp conditions, since these responses were not normally distributed (17).

RESULTS

Hypoglycemic clamp. Fig. 1 shows the glucose, GIP, C-peptide, insulin, and glucagon levels before and after Lipomul ingestion during the hypoglycemic clamp. Glucose levels decreased progressively and

HORMONE RESPONSES DURING HYPOGLYCEMIC CLAMP BEFORE AND AFTER LIPOMUL (67g) INGESTION

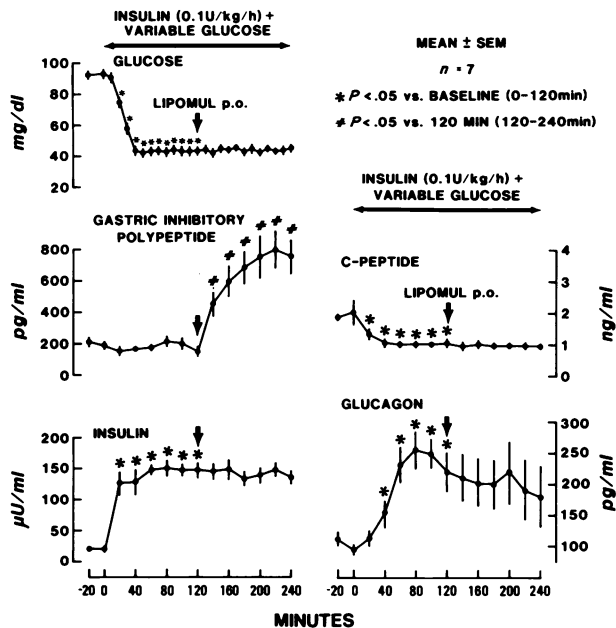


FIGURE 1 Glucose and hormone levels before and after fat ingestion during the hypoglycemic glucose-insulin clamp.

reached a stable plateau after 40 min (43 ± 2 mg/dl) with a coefficient of variation of $6.8 \pm 8\%$. During the 0–120-min period, GIP levels decreased from basal values of 186 ± 24 to 145 ± 30 pg/ml. After Lipomul ingestion, the GIP levels increased to a maximum of 784 ± 130 pg/ml at 220 min ($P < 0.01$ vs. basal). The integrated GIP response over 120 min was 51.7 ± 8.1 ng/ml. C-peptide levels decreased from basal levels at 2.2 ± 0.3 to 1.1 ± 0.1 ng/ml at 120 min ($P < 0.01$). After Lipomul ingestion the C-peptide levels remained unchanged. Insulin levels were at a stable plateau of 144 ± 3 μ U/ml for the 20–120-min period and did not change after fat ingestion. Glucagon levels increased from basal levels of 111 ± 11 pg/ml and peaked at 80 min at 254 ± 29 pg/ml

($P < 0.01$). After Lipomul ingestion there was no further increase but a slight decrease in glucagon levels from 221 ± 56 pg/ml at 120 min to 181 ± 56 pg/ml at 240 min.

The ingestion of Lipomul did not alter the glucose requirement for maintenance of the hypoglycemic clamp (Table I).

Euglycemic clamp. The glucose and hormone levels before and after Lipomul ingestion during the euglycemic clamp are shown in Fig. 2. Glucose levels averaged 88 ± 1 mg/dl throughout the clamp with a coefficient of variation of $5.1 \pm 0.4\%$. During the 0–120-min period, GIP decreased from 248 ± 40 to 127 ± 30 pg/ml. After fat ingestion, GIP increased to a maximum of 631 ± 98 pg/ml at 240 min ($P < 0.01$ vs. basal). The integrated GIP response over 120 min (35.2 ± 9.4 ng/ml) was less than ($P < 0.05$) that observed in the hypoglycemia clamp (Fig. 3). C-peptide levels decreased from basal concentrations of 1.9 ± 0.2 to 1.3 ± 0.2 ng/ml at 120 min ($P < 0.02$). After fat ingestion, small and inconsistent increases in C-peptide not exceeding basal levels were observed. Insulin levels were at a stable plateau of 141 ± 2 μ U/ml for the 20–120-min period and remained unchanged after fat ingestion. Glucagon levels, which had decreased during the first 120 min from basal levels of 116 ± 8 to 77 ± 7 pg/ml ($P < 0.05$) showed very small and inconsistent increases of < 20 pg/ml while not exceeding basal levels after fat ingestion.

After Lipomul ingestion the amount of intravenous glucose required to maintain the euglycemic clamp was greater compared to that required during the 60–120-min period ($P < 0.05$) (Table I). However, it was not different when compared to the 90–120-min period (8.2 ± 0.5 mg/kg per min).

Hyperglycemic clamp. The glucose and hormone levels before and after Lipomul ingestion during the hyperglycemic clamp are shown in Fig. 4. Glucose levels in the 60–240-min period averaged 142 ± 2 mg/dl with a coefficient of variation of $4.4 \pm 0.5\%$. During the 0–120-min period GIP decreased from basal levels of 131 ± 25 to 78 ± 12 pg/ml. After fat ingestion GIP

TABLE I
Glucose Infusion Rates during Glucose-Insulin Clamps*

Time, min	0 to 60	60 to 120	120 to 180	180 to 240
	$\text{mg kg}^{-1} \text{min}^{-1}$			
Hypoglycemic clamp	0.9 ± 0.3	2.2 ± 0.5	2.3 ± 0.5	2.1 ± 0.5
Euglycemic clamp	4.7 ± 0.3	7.6 ± 0.3	8.6 ± 0.3	8.7 ± 0.3
Hyperglycemic clamp	11.5 ± 0.7	12.6 ± 0.5	13.2 ± 0.3	15.2 ± 0.7

Lipomul was ingested at 120 min.

* Average amounts of glucose administered over 1-h periods are shown, since the amount infused at any minute for each individual is variable according to the computerized equations of the Biostat.

HORMONE RESPONSES DURING EUGLYCEMIC CLAMP BEFORE AND AFTER LIPOMUL (67g) INGESTION

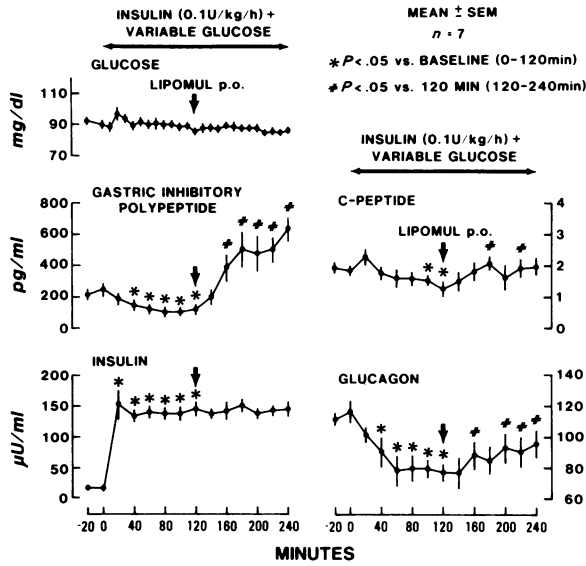


FIGURE 2 Glucose and hormone levels before and after fat ingestion during the euglycemic glucose-insulin clamp.

levels increased to a maximum of 377 ± 58 pg/ml at 240 min ($P < 0.01$). The integrated GIP response over 120 min was 24 ± 5.7 ng/ml. Both the peak and integrated GIP responses in the hyperglycemic clamp were less than those observed in euglycemic clamp ($P < 0.05$) and hypoglycemic clamp ($P < 0.01$) (Fig. 3).

C-peptide levels increased from basal levels of 2.0 ± 0.2

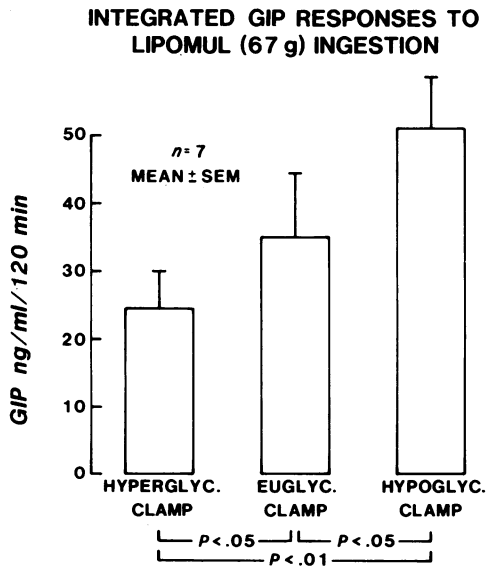


FIGURE 3 Integrated GIP responses to fat ingestion during the hypoglycemic, euglycemic, and hyperglycemic glucose-insulin clamps.

HORMONE RESPONSES DURING HYPERGLYCEMIC CLAMP BEFORE AND AFTER LIPOMUL (67g) INGESTION

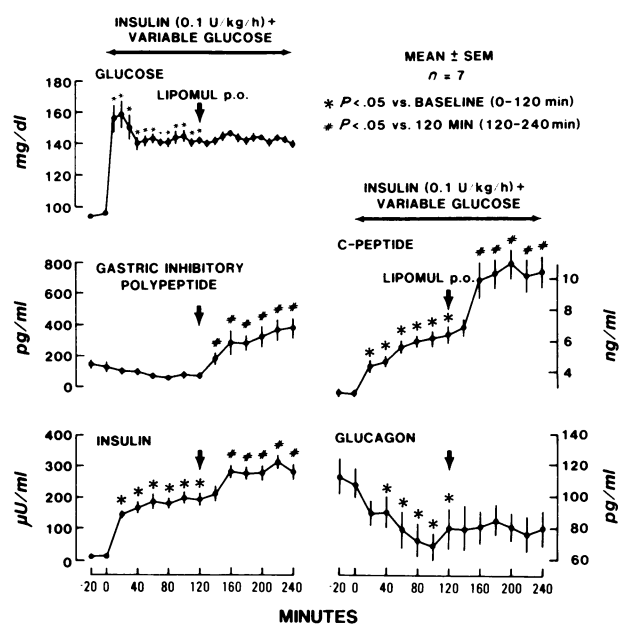


FIGURE 4 Glucose and hormone levels before and after fat ingestion during the hyperglycemic glucose-insulin clamp.

to 6.4 ± 0.5 ng/ml at 120 min. After Lipomul ingestion there was an increase to a maximum of 11 ± 1.1 ng/ml at 200 min ($P < 0.01$). The slope of the C-peptide increase between 60 and 120 min and between 120 and 180 min was 0.013 ± 0.004 and 0.075 ± 0.025 , respectively ($P < 0.02$). Insulin levels showed a similar pattern, increasing from 193 ± 19 μ U/ml at 120 min to a maximum of 312 ± 21 μ U/ml ($P < 0.01$) after Lipomul ingestion at 220 min.

Glucagon decreased from basal levels of 107 ± 10 to 80 ± 14 pg/ml ($P < 0.05$) at 120 min and did not change after Lipomul ingestion.

Greater amounts of intravenous glucose were required to maintain the hyperglycemic glucose clamp after Lipomul ingestion ($P < 0.02$) than before (Table I).

Saline infusions with and without Lipomul ingestion. The glucose and hormone concentrations during saline infusions with and without Lipomul ingestion in the absence of insulin-glucose clamps are contrasted to the euglycemic clamp in Fig. 5. During the 0–120 min period of saline infusion without Lipomul there was no change in glucose or insulin, but there was a decrease in GIP from 253 ± 50 to 194 ± 43 pg/ml. For the 0–120-min period of the euglycemic clamp in the same six subjects GIP decreased by a similar amount from 244 ± 46 to 140 ± 32 pg/ml. During the saline infusion with Lipomul ingestion, glucose and insulin did not change after Lipomul, whereas GIP levels increased from basal levels of 181 ± 32 pg/ml to a maximum of 809 ± 165

EFFECT OF INSULIN ON GASTRIC INHIBITORY POLYPEPTIDE RESPONSES TO FAT INGESTION

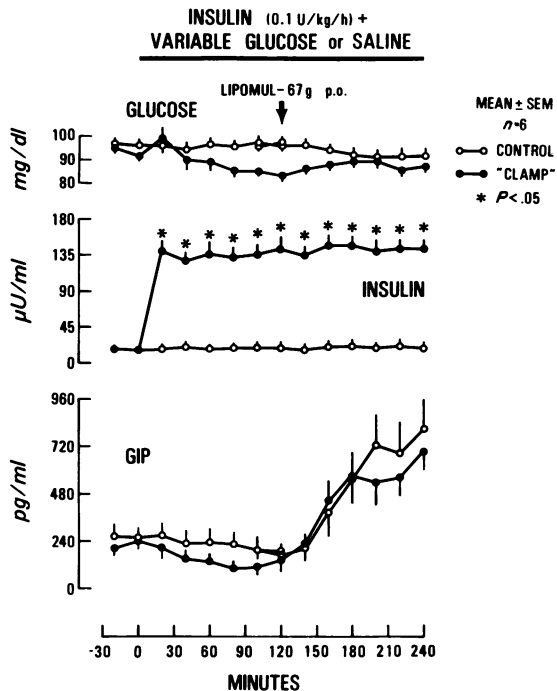


FIGURE 5 Glucose and hormone levels in two saline infusion studies, one without Lipomul (–20–120 min) and one with Lipomul (100–240 min) are plotted with overlapping data at the 100 and 120 points for ease of comparison with the euglycemic clamp in the same subjects.

pg/ml at 240 min ($P < 0.01$). The integrated GIP response for the 120-min period after Lipomul ingestion, 39.7 ± 9.8 ng/ml, in the euglycemic glucose-insulin clamp study ($n = 6$) was not different from that (39.7 ± 11.1 ng/ml) during the same 120-min period after Lipomul during the saline infusion.

DISCUSSION

The hormonal interactions for glucose homeostasis are different for each major nutrient. Ingestion of carbohydrate results in an increase in plasma glucose accompanied by an increase in plasma GIP and insulin and a decrease in plasma glucagon (4). Amino acid ingestion results in increases in plasma GIP, insulin (5), and glucagon (18) with no change in plasma glucose. Oral fat results in no changes in plasma glucose, insulin, and glucagon (4, 19) despite increases in plasma GIP (4). Primary among the factors that may determine the insulin secretory responsiveness of the beta cell to GIP is the ambient plasma glucose concentration. Despite the report that the infusion of porcine GIP into animals (which resulted in supraphysiologic concentrations of GIP) was insulinotropic at basal blood glucose levels (20), the infusion of porcine GIP (which results in

physiologic levels of GIP) into man is insulinotropic only during hyperglycemia (1, 21). Glucose dependency of the insulinotropic action of glucose-stimulated GIP has been demonstrated in a recent report (7) on the basis of changes in serum immunoreactive insulin (rather than C-peptide) after oral glucose during insulin-glucose clamps at euglycemia and supraphysiologic hyperglycemia. The studies reported here, using fat instead of glucose as the GIP secretagogue, demonstrate that GIP is insulinotropic during moderate hyperglycemia and not at euglycemia or moderate hypoglycemia. Whether GIP has a glucagonotropic action has not been settled. In vitro data from the perfused pancreas indicate that this effect occurs only at glucose concentrations in the perfusate below 5.5 mM (22). In man a glucagonotropic effect of GIP has been suggested in adult-onset diabetics (9) and for some patients with cirrhosis (23). Fat ingestion is not associated with a change in circulating glucagon. Since it is not known whether a glucagonotropic effect of GIP might be evident during hypoglycemia, i.e., whether there may be a reverse glucose dependency of the glucagonotropic action of GIP, glucagon was measured in the studies reported here. However, it was observed that fat-stimulated GIP was not glucagonotropic at any of the glucose clamp levels. The inconsistent increases in glucagon after oral fat during the euglycemic glucose-insulin clamp were very small and did not exceed basal levels. Despite the increase in glucagon in response to the lowered glucose levels in the hypoglycemic clamp, no further increase in glucagon occurred after oral fat ingestion. This contrasts to the brisk increase in the already elevated C-peptide levels that occurred after Lipomul ingestion in the hyperglycemic clamp. The decreases of C-peptide and glucagon concentrations observed during the 0–120-min period of the euglycemic clamp are consistent with the previously reported direct suppression effect of insulin on C-peptide and glucagon (24).

Andersen et al. (7) have demonstrated, using a euglycemic glucose-clamp technique, that concentrations of insulin of approximately $300 \mu\text{U/ml}$ did not inhibit plasma GIP responses after glucose ingestion. Indirect evidence has been generated favoring an inhibition by insulin on the fat-induced release of GIP. It has been reported that a bolus injection of insulin in pharmacologic doses given coincident with fat ingestion blunted the subsequent increase in plasma GIP (4). Continuous infusions of glucose given to stimulate endogenous release of insulin were found to blunt the plasma GIP response after ingestion of either fat or galactose (8–10, 25). In all of the above studies, however, neither insulin nor glucose concentrations were maintained at steady-state levels. The current studies demonstrated no difference in fat-stimulated GIP response in the presence or absence of physiologic hyperinsulinemia

at euglycemia. Although the GIP levels 120 min after Lipomul were not returning to base-line, they were close to a plateau configuration in the last 60 min. The observed levels likely represent maximal responses as they are similar to those reported by others after fat ingestion (8, 9, 11). In addition, further sampling beyond 120 min was unlikely to have shown a difference in GIP between control and euglycemic clamp studies because differences observed in GIP by others between control and glucose infusion studies occurred before 120 min after fat or galactose ingestion. The slight decreases in basal GIP during the 120-min pre-Lipomul period in the presence and absence of hyperinsulinemia may represent the effect of fasting on GIP.

The observation of a reduced GIP response after fat ingestion during hyperglycemia compared to the response after the same stimulus in the presence of euglycemia is consistent with previous reports (8–10, 25), but is open to an interpretation different from an inhibition of GIP by insulin alone. The increased GIP response to oral fat during hypoglycemia compared to euglycemia coupled with the reduced GIP response in hyperglycemia (Fig. 3) in the presence of similar serum insulin levels ($144 \pm 3 \mu\text{U/ml}$ for hypoglycemia, $141 \pm 2 \mu\text{U/ml}$ for euglycemia, and $183 \pm 5 \mu\text{U/ml}$ for hyperglycemia) suggests that the glucose level itself in the presence of hyperinsulinemia affects the GIP response to oral fat. Whether this effect is on one or both molecular species remains to be determined.

In summary, fat-stimulated GIP has insulinotropic activity that is glucose dependent, is not glucagonotropic, is not inhibited by physiologic hyperinsulinemia at euglycemia, but is influenced by the ambient glucose level in the presence of hyperinsulinemia.

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