Disparity Between Glucose-Dependent Insulinotropic Polypeptide and Insulin Responses in Obese Man

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Summary. Studies were carried out in 32 obese patients and 30 normal-weight control subjects to ascertain the response of glucose-dependent insulinotropic polypeptide (GIP) and insulin to (1) oral and intravenous glucose (10 obese and 10 control subjects), (2) oral fat and intravenous glucose (eight obese and six control subjects) and (3) mixed test meal (14 obese and 14 control subjects). Basal mean insulin was higher in the obese (99 pmol/l) than in the control group (40 pmol/l), but fasting blood glucose and GIP were not significantly different from normal. The total integrated response of insulin in obese subjects after oral glucose was 54.1 versus 33.3 nmol·l⁻¹·h⁻¹ in control subjects; glucose and GIP responses were similar in both groups. After intravenous glucose the integrated insulin

response was 8.8 in the obese versus 5.0 nmol·l⁻¹·h⁻¹ in control subjects; GIP was unaffected by intravenous glucose and glucose levels were similar. Following oral fat and intravenous glucose, insulin secretion was again abnormal in the obese, 24.5 versus 7.3 nmol·l⁻¹·h⁻¹ in controls, but GIP responses were normal. However, the control subjects became hypoglycaemic after this test: blood glucose 2.8 mmol/l at 150 min compared with 4.6 mmol/l in the obese group. The insulin response to a mixed meal was also abnormal in obesity.

Key words: Glucose-dependent insulinotropic polypeptide, insulin, obesity, glucose administration, fat administration, hypoglycaemia.

Obesity is characterised by fasting hyperinsulinaemia, and the ingestion of carbohydrate results in an exaggerated insulin response [1–4]. One explanation for this is that an increased caloric intake produces B cell hyperplasia with consequent insulin hypersecretion [5]. Recent reports [6, 7] suggest that the enteroinsular axis is overactive in obesity. Glucose-dependent insulinotropic polypeptide (GIP) has been proposed as a major mediator of the enterically induced component of insulin secretion [8]. Evidence for the involvement of GIP in the enteroinsular axis has mounted steadily in recent years, and it is natural to explore the role of this hormone in the aetiology of obesity.

The present studies were designed to investigate the release of GIP in obese patients in response to the major secretagogues of this hormone. In addition, the extent of the rôle of GIP in the exaggerated insulin re-

sponse in obesity is examined by determination of the insulin response to both intravenous and oral glucose. Since GIP is unaffected by intravenous glucose, any difference in insulin response after this stimulus must be due to factors other than GIP.

Patients and Methods

The studies were carried out on 32 obese subjects (24 women and eight men) all of whom had normal glucose tolerance, and 30 age-matched volunteers of normal weight (18 women and 12 men). Informed consent was obtained from each subject, and at the time of the investigation none was taking any medication. Both groups ate an unrestricted diet, containing at least 200 g of carbohydrate a day, for 1 week before investigation. Clinical details are shown in Table 1. Ideal body weight was derived from the Metropolitan Life Insurance Company Tables [9]. Obese and control subjects were randomly divided into sub-groups for each set of experiments. Some subjects underwent more than one investigation, but in such cases at least 1 week elapsed between experiments.

Oral Glucose Load

Each subject was given a drink containing 100 g glucose in 300 ml water. Blood samples were taken at –30, –15, 0, 15, 45, 60 and 120 min.

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Table 1. Clinical characteristics of subjects studied in obesity investigations

Test	Subjects	Mean age (years)	Range	% Ideal body weight
100 g oral glucose load	Control (<i>n</i> =10)	32	24–40	98 ± 3
20 g IV glucose infusion	Obese (<i>n</i> =10)	30	17–38	215 ± 5
Mixed test meal	Control (<i>n</i> =14)	33	23–46	106 ± 5
	Obese (<i>n</i> =14)	35	25–52	225 ± 7
Oral fat + IV glucose infusion and IV glucose infusion alone	Control (<i>n</i> =6)	30	27–34	102 ± 4
	Obese (<i>n</i> =8)	31	27–38	230 ± 6

Results expressed as mean ± SEM

Fig. 1. The response of plasma GIP (top panel) and insulin (bottom panel) in 10 obese (◆) and 10 normal weight control subjects (●) to oral glucose, and in the same obese (◇) and normal-weight (○) subjects to intravenous glucose. Values are expressed as mean ± SEM

Intravenous Glucose

A 10% solution of 20 g glucose in 0.9% saline was infused into the antecubital fossa of one arm by means of a variable-rate, constant-velocity syringe pump (Harvard Instruments, Millis, Massachusetts, USA). Arterialised capillary blood samples were taken from a warmed hand for glucose estimation using glucose oxidase strips (Dextrostix, Ames, Stoke Poges, UK) and a portable photometer (Hypocount, Hypoguard, Suffolk, UK). The glucose infusion rate was changed according to the results from the glucose oxidase strips so as to follow the oral glucose curve. Blood was drawn from the contralateral arm at the same time intervals as in the oral glucose test.

Mixed Test Meal

Each subject was given a mixed test breakfast of 2225 kJ (18 g protein, 22 g fat and 66 g CHO) (10). Blood samples were taken before (–30, –15 min), at the start (0 min) and after ingestion of the meal (15, 30, 120 and 180 min). In all cases the meal was consumed within 15 min.

Oral Fat Followed by Intravenous Glucose

Fat was given as 214 ml of unsweetened double cream consisting of 100.0 g fat, 3.1 g protein and 4.1 g carbohydrate. Two blood samples were taken before the ingestion of fat, and thereafter at 15 min intervals for 1 h. At this time, an IV glucose infusion (as described above) was given. Further blood samples were drawn at 75, 90, 105, 150 and 180 min.

Treatment of Blood Samples

Venous blood was drawn from an indwelling 19 G butterfly cannula in the antecubital fossa. The catheter was kept patent by equal volumes of 0.9% saline solution and 3.8% sodium citrate solution. For blood glucose measurement, 2.5-ml samples of whole blood were taken into fluoride oxalate tubes and kept refrigerated (+4 °C) until assay. For hormone estimation 10-ml samples of whole blood were taken into chilled heparin tubes containing aprotinin (Trasylol, Bayer, FRG). This blood was immediately centrifuged for 5–10 min at 1600 g, and the plasma was then stored at –20 °C until assay.

Plasma Hormone Measurements

Insulin was measured using commercially-obtainable ¹²⁵I-insulin (IM530 The Radiochemical Centre, Amersham, Bucks, UK) and guinea-pig anti-insulin serum (Wellcome), with a standard curve set up in plasma stripped of endogenous insulin by charcoal adsorption. The sensitivity of the assay was 6 pmol/l. GIP was estimated by radioimmunoassay [11]. The antiserum (GIP 19) was raised using carbo-diimide condensation to haemocyanin. ¹²⁵I-labelled-GIP was prepared by a modified enzymatic method using lactoperoxidase oxidation. The specific activity of this preparation was between 55 and 75 Bq/fmol. In the absence of added GIP, the antiserum used at a final dilution of 1:96000 bound approximately 50% of the 1.5 fmol of ¹²⁵I-labelled GIP added to each assay tube. Standard curve plasma was prepared by removing endogenous GIP by specific immunoadsorption. The molecular species of GIP recognised by the antiserum were analysed by gel permeation chromatography. Two major peaks were identified, the first eluting soon after cytochrome-C (*K*_{av} 0.3 ± 0.02, *n*=5) and the other co-eluting with pure porcine standard GIP (*K*_{av} 0.67 ± 0.02). The percentage of large GIP (large + small GIP being 100%) for the following conditions was: fasting plasma 73 ± 9.6 (mean ± SEM), after glucose 27 ± 5.8, after fat 49 ± 8 and after a mixed meal 40 ± 5; (*n*=5). The antibody demonstrated <1% cross reactivity with glucagon and none with other gastrointestinal hormones. The sensitivity of the assay allowed changes of 3 pmol/l GIP (±2 SD of the zero standard) to be detected between individual adjacent plasma samples.

Blood glucose was measured by the method of Gutteridge and Wright [12].

Statistical Analyses

Individual datum points are expressed as mean ± SEM (*df* = *n*–1). Integrated responses were calculated as total integrated response (TIR). TIR is the total area of the polygon under the response curve. Significance was assessed by Student's *t*-test on a paired basis for intra-group and unpaired for inter-group comparisons.

The enteroinsular component was measured as the total incremental integrated response after oral glucose divided by the total incremental integrated response after intravenous glucose.

Table 2. Mean blood glucose in obese subjects and in normal weight control subjects after 100 g oral glucose, 20 g intravenous glucose and a mixed test meal

Stimulus	Subjects	Blood glucose (mmol/l) at times (min)								
		-30	-15	0	15	30	45	60	120	180
Oral glucose	Control (<i>n</i> =10)	3.8±0.2	3.7±0.1	3.6±0.2	4.8±0.3	6.3±0.4	6.6±0.6	4.7±0.4	4.7±0.4	–
	Obese (<i>n</i> =10)	4.0±0.3	3.9±0.2	3.8±0.2	4.8±0.2	6.4±0.3	6.4±0.5	6.1±0.4	4.5±0.3	–
	<i>p</i>	NS	NS	NS	NS	NS	NS	NS	NS	
Intravenous glucose	Control (<i>n</i> =10)	3.8±0.1	3.7±0.1	3.7±0.2	4.9±1.1	5.8±0.3	5.7±0.3	5.7±0.4	3.6±0.1	–
	Obese (<i>n</i> =10)	4.2±0.2	4.1±0.2	4.1±0.2	5.0±1.2	5.7±0.5	5.7±0.5	5.4±0.3	4.0±0.1	–
	<i>p</i>	NS	NS	NS	NS	NS	NS	NS	NS	
Test meal	Control (<i>n</i> =14)	4.2±0.1	4.3±0.2	4.2±0.1	4.6±0.1	5.9±0.3	–	5.5±0.5	4.4±0.2	3.9±0.2
	Obese (<i>n</i> =14)	5.2±0.5	5.3±0.5	5.3±0.5	5.5±0.5	6.5±0.6	–	7.0±0.7	6.1±0.7	5.5±0.6
	<i>p</i>	NS	NS	NS	NS	NS		NS	<0.025	<0.002

Results expressed as mean ± SEM

Fig. 2. The response of plasma GIP (top panel) and insulin (bottom panel) to a mixed test meal in 14 obese patients (broken line) and 14 normal-weight control subjects (solid line). All values expressed as mean ± SEM

Results

Oral Versus Intravenous Glucose

The responses of GIP and insulin to each stimulus are shown in Figure 1. There was no statistically significant difference between the obese and control groups in GIP

or glucose, either basally or after either glucose stimulus (Table 2). GIP remained at basal levels throughout the intravenous glucose test. Blood glucose was similar after both oral and intravenous glucose. The obese group had basal hyperinsulinaemia and exaggerated insulin responses to both oral and intravenous glucose. The enteroinsular component was similar in the obese and control groups. The insulin response to oral glucose in both groups was six times as great as that seen after intravenous glucose.

Test Meal

The responses of GIP and insulin to the test meal are shown in Figure 2. The basal GIP was slightly higher in the obese group and this gave rise to a significantly higher GIP at 15 min. The degree of response, however, was similar in both groups. Basal insulin was augmented in the obese group and once again the response to food resulted in an exaggeration of plasma concentrations of this hormone. Fasting blood glucose was similar in both groups, but towards the end of the experiment significantly greater glucose levels were seen in obesity.

Oral Fat with Intravenous Glucose, Versus Intravenous Glucose

Mean concentrations of GIP and insulin over the course of the experiment are shown in Figure 3, and those of glucose in Table 3. GIP concentrations were similar in both groups for each test and were, if anything more augmented in the control group. A biphasic response of GIP was noted in the control group. The glucose response to intravenous glucose was similar in both groups. However, after fat and intravenous glucose the control subjects developed significant hypoglycaemia at the conclusion of the test. As with the other tests both basal and stimulated insulin concentrations were higher in the obese group. The insulin response to fat and intravenous glucose was greater in both groups

Table 3. Mean blood glucose in obese subjects and in normal weight control subjects after 100 g oral fat (as unsweetened cream) and 20 g intravenous glucose or after 20 g intravenous glucose alone

Stimulus	Subjects	Blood glucose (mmol/l) at times (min):											
		-15	0	15	30	45	60	75	90	105	120	150	180
Oral fat + IV glucose	Control (n=6)	4.1±0.2	4.1±0.1	4.1±0.1	4.0±0.1	3.8±0.1	3.6±0.1	5.0±0.1	6.8±0.6	6.4±0.6	5.8±0.3	2.8±0.1	2.9±0.2
	obese (n=8)	4.5±0.2	4.4±0.2	4.5±0.2	4.5±0.2	4.3±0.2	4.1±0.2	5.4±0.2	6.2±0.3	6.5±0.3	6.8±0.4	4.6±0.3	3.9±0.2
	p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	<0.005	<0.05
20 g IV glucose	Control (n=6)	—	—	—	—	4.3±0.2	4.3±0.1	5.7±0.8	6.9±0.8	4.6±1.0	8.4±1.1	5.6±0.4	4.0±0.2
	Obese (n=8)	—	—	—	—	4.3±0.2	4.5±0.2	5.8±0.4	6.8±0.4	7.2±0.3	7.5±0.5	5.4±0.3	4.2±0.1
	p					NS	NS	NS	NS	NS	NS	NS	NS

Results expressed as mean ± SEM

Fig. 3. The response of GIP (top panel) and insulin (bottom panel) in eight obese patients following oral fat and intravenous glucose (◆) or intravenous glucose alone (◇) and in six normal-weight control subjects to oral fat and intravenous glucose (●) or intravenous glucose alone (○). All values expressed as mean ± SEM

than after intravenous glucose alone (peak insulin in controls after fat and intravenous glucose; 323 ± 100 pmol/l, after intravenous glucose = 150 ± 32 pmol/l, $p < 0.01$; peak insulin in obesity after fat/intravenous glucose = 840 ± 214 pmol/l, after intravenous

glucose = 465 ± 52 pmol/l, $p < 0.05$) and this represented an approximate twofold difference in each case.

Inter-Experiment Comparison

The integrated responses of GIP, insulin and blood glucose for each experiment are given in Table 4. In spite of similar GIP and glucose concentrations the insulin response of the control subjects to fat and intravenous glucose was significantly lower (TIR 7.3 ± 1 nmol·l⁻¹·h⁻¹) than after oral glucose (TIR 33.6 ± 6 nmol·l⁻¹·h⁻¹, $p < 0.001$). The pattern was similar in obesity with reduced insulin secretion to fat and intravenous glucose (TIR 24.5 ± 3.3 nmol·l⁻¹·h⁻¹ compared to that seen after oral glucose (TIR 54.1 ± 6.5 nmol·l⁻¹·h⁻¹, $p < 0.01$) in spite of a better GIP response to fat.

Discussion

During all the experiments detailed above, there was no difference in the magnitude of the GIP response between subjects who were grossly obese and normal weight controls. In contrast the basal insulin and the insulin response to all stimuli was dramatically elevated in obesity. Previous reports have shown markedly increased GIP secretion in obesity after ingestion of a liquid mixed meal or triglycerides [6, 7, 13] and it has been proposed that this is brought about by a defect in the feedback mechanism of insulin on the GIP cell. This, in turn, may be related to the increased peripheral insulin resistance.

The increased GIP secretion reported in obesity following oral fat, however, cannot be attributed to this mechanism since fat-mediated GIP release does not of itself potentiate insulin secretion. It is difficult to compare directly the results reported here with those of others. Firstly, the absolute values of GIP found in the circulation in both the fasting and the stimulated are markedly lower when measured with the assay used here [11], than those obtained using assays reported earlier [13–15] although they are comparable to more re-

Table 4. Total integrated responses of GIP, insulin and blood glucose in obesity and normal weight control subjects

Stimulus	Hormone/ glucose	Subject (n)	Total integrated response (nmol·l ⁻¹ ·h ⁻¹)
100 g oral glucose	GIP	Control (10)	2.2 ± 0.2
		Obese (10)	1.6 ± 0.2
	Insulin	Control (10)	NS
		Obese (10)	33 ± 6
	Glucose ^a	Control (10)	54 ± 7
		Obese (10)	<i>p</i> < 0.05
20 g intravenous glucose	GIP	Control (10)	0.30 ± 0.02
		Obese (10)	0.35 ± 0.02
	Insulin	Control (10)	NS
		Obese (10)	1.0 ± 0.3
	Glucose ^a	Control (10)	0.8 ± 0.2
		Obese (10)	NS
Oral fat intravenous glucose	GIP	Control (10)	5.0 ± 1.0
		Obese (10)	8.8 ± 1.0
	Insulin	Control (10)	<i>p</i> < 0.001
		Obese (10)	0.30 ± 0.02
	Glucose ^a	Control (10)	0.30 ± 0.02
		Obese (10)	NS
Intravenous glucose	GIP	Control (6)	2.8 ± 0.3
		Obese (8)	2.2 ± 0.2
	Insulin	Control (6)	NS
		Obese (8)	7.3 ± 1.0
	Glucose ^a	Control (6)	24.5 ± 3.3
		Obese (8)	<i>p</i> < 0.001
Test meal	GIP	Control (6)	0.4 ± 0.01
		Obese (8)	0.3 ± 0.01
	Insulin	Control (6)	NS
		Obese (8)	1.4 ± 0.4
	Glucose ^a	Control (6)	0.9 ± 0.2
		Obese (8)	NS
Test meal	GIP	Control (6)	6.4 ± 1.0
		Obese (8)	18.2 ± 0.2
	Insulin	Control (6)	<i>p</i> < 0.002
		Obese (8)	0.3 ± 0.02
	Glucose ^a	Control (6)	0.3 ± 0.03
		Obese (8)	NS
Test meal	GIP	Control (14)	1.8 ± 0.25
		Obese (14)	2.2 ± 0.2
	Insulin	Control (14)	19.0 ± 3.0
		Obese (14)	26.3 ± 1.2
	Glucose ^a	Control (14)	<i>p</i> < 0.05
		Obese (14)	0.23 ± 0.02
Test meal	Glucose ^a	Control (14)	0.30 ± 0.02
		Obese (14)	NS

^a Glucose is expressed as mmol·l⁻¹·h⁻¹. Results expressed as mean ± SEM

cently reported results [16]. The reason for this disparity probably relates to the greater sensitivity and specificity of the antibody used here (GIP 19).

Secondly, differences exist in the type and amount of stimulus to GIP release used in the various other studies. No difference can be found in the response of GIP between obese subjects and normal weight controls after giving the two major stimulants (fat and carbohydrate) either individually, or as a mixture in the meal. The comparison between intravenous and oral glucose studies is of considerable interest. By matching the glucose curves for both situations the behaviour of

the enteroinsular axis and the role of GIP could be observed. The enteroinsular component, that is, the ratio of the insulin responses to oral and intravenous glucose, was 6:1 in both obese and normal weight subjects, although Perley and Kipnis found a ratio of 3:1 [17] and Lauritsen et al. 4:1 [18]. The absolute quantities of insulin involved, however, were substantially different, while the GIP response was identical and showed no depression, even though, according to previously reported results, any postulated insulin feedback mechanism on GIP secretion should be present at least in normal weight controls [6, 13].

The results of these studies raise certain questions as to the importance of GIP in the control of insulin secretion, since the insulin response seen after the fat and intravenous glucose was considerably smaller than after oral glucose. Because the GIP concentrations were somewhat higher and the blood glucose levels closely similar to those seen after oral glucose, a similar insulin rise would have been predicted. There are three possible explanations for this discrepancy: firstly, that GIP plays only a minor role in the release of insulin; secondly that fat releases an inhibitor to insulin release; thirdly that fat stimulates a different molecular species of GIP which has limited insulinotropic activity. Since fat alone was not given after insulin stimulation, the second possibility cannot yet be answered. Preliminary investigations by gel chromatography have shown that similar absolute quantities of the 5000-dalton form of GIP were present after both glucose and fat stimulation [11]. Clearly further work is required to provide firm conclusions regarding the humoral control of the enteroinsular response.

The biphasic response of GIP noted in the oral fat intravenous glucose experiment is in agreement with earlier studies [6, 19], but the underlying mechanism is, as yet, unexplained, and may reflect insulin feedback on GIP secretion or the late release of a different molecular species of this hormone.

An interesting, but unexpected, finding was that of reactive hypoglycaemia in the control subjects on discontinuation of the intravenous glucose infusion which followed the ingestion of fat. Previous studies have failed to show this effect when fat and intravenous glucose were administered. However, all but one of these [6, 19] gave fat on a background of hyperglycaemia while the other study [20] was of fat followed by a bolus injection of glucose; thus differences in protocol may be responsible. All the normal volunteers used for the fat/glucose experiment reported sensations of 'light-headedness', hunger and tremor and, in each case, this was associated with substantially reduced blood glucose concentrations. It is of interest that the nadir of glucose was concomitant with the secondary rise of GIP at the end of the experimental regimen. Although no detailed data exist, two previous reports [21, 22] have suggested that GIP release may be involved in the development of reactive hypoglycaemia. Thomford et al. [21]

attributed the late phase of dumping seen after vagotomy and pyloroplasty to an increased GIP release found in these patients, and Cataland [22] also reported increased GIP secretion in cases of reactive hypoglycaemia after glucose administration. In the present study no finding of increased GIP release was made in the controls who experienced hypoglycaemia. The absence of hypoglycaemia in obese subjects is interesting and may be due to the peripheral insulin resistance characteristic of obesity [23].

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