The Effect of Gastrin on Basal- and Glucose-Stimulated Insulin Secretion in Man

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ABSTRACT The effect of gastrin on basal- and glucose-stimulated insulin secretion was studied in 32 normal, young subjects. The concentration of gastrin and insulin in serum was measured radioimmunochemically.

Maximal physiologic limit for the concentration of gastrin in serum was of the order of 160 pmol per liter as observed during a protein-rich meal. Oral ingestion of 50 g glucose produced a small gastrin response from 28±3 to 39±5 pmol per liter (mean ±SEM, $P < 0.01$).

Intravenous injection or prolonged infusion of gastrin increased the concentration of insulin in peripheral venous blood to a maximum within 2 min followed by a decline to basal levels after a further 10 min. The minimum dose required to induce a significant insulin response (31.2 ng gastrin per kg) increased the gastrin level in serum above the physiologic range. Maximum effect was obtained with 500 ng gastrin per kg.

When 15.6 ng (7.1 pmol) gastrin per kg body weight and 25 g glucose were injected simultaneously, the glucose-induced insulin response was potentiated (from 2.32 ±0.33 to 4.33±0.98 nmol per liter per 20 min, $P < 0.02$), even though gastrin concentrations only increased to 71.2±6.6 pmol per liter. No effect, however, was noted on glucose disposal. 15.6 ng gastrin per kg given i.v. 30 min before an i.v. glucose tolerance test was without significant effect on the insulin response.

The results indicate that gastrin can stimulate a rapid and short-lived release of insulin. In physiologic concentrations gastrin potentiates the glucose-stimulated insulin secretion and is without effect on basal insulin secretion. A small release of gastrin during oral glucose ingestion may to a limited extent contribute to the nonglycemic insulin secretion. During protein ingestion, gastrin probably stimulates insulin secretion significantly.

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INTRODUCTION

Gastrointestinal hormones probably contribute significantly to the stimulation of insulin secretion during ingestion of glucose or protein (1–4). It has been suggested that more than half the insulin response to oral intake of glucose is caused by enteric hormones (5). At the present time there is a considerable debate as to which hormone or hormones mediate the insulin response.

Concerning the action of gastrin on insulin secretion, stimulation (6–11), no effect (12–16), as well as inhibition (17) have been reported. The conflicting results may in part be due to the use of pharmacological doses of crude preparations or fragments of gastrin. However, radioimmunoassay techniques for gastrin are now at hand (18–21), and hence the physiologic action of gastrin can be assessed.

In the present study the effect of endogenous and exogenous human gastrin on basal- and glucose-stimulated insulin secretion in man has been investigated and monitored by means of reliable radioimmunoassays for human gastrin and insulin.

METHODS

Experimental procedures

32 normal nonobese subjects, 24 males and 8 females, all members of the paramedical staff and aged from 24 to 42 yr participated in the study. They all had normal oral and i.v. glucose tolerance tests, and none had close relatives with diabetes mellitus. Informed consent was obtained from each subject.

The subjects were on a diet containing at least 250 g carbohydrates per day 3 days before each investigation. After an overnight fast the examination began between 8:00 and 9:00 a.m. Blood samples were collected from an i.v. canula inserted into an antecubital vein. After separation serum was stored at −20°C until assayed.

Studies on the release of endogenous gastrin and its relation to insulin secretion

Protein-rich meal. Eight subjects, five females and three males, were given an appetizing meal composed of beef-

steak, sauce, vegetables, and a glass of water (22). The subjects were told to eat as much as they liked, and the meal was finished after 20 min. Blood samples were drawn 15, 10, and 5 min before, and 2, 5, 10, 20, 30, 45, 60, 90, and 120 min after the onset of the meal.

Oral glucose loading. 20 subjects, 5 females and 15 males, were given 50 g of oral glucose in a 25% solution, flavored with lemon. Blood samples were drawn 15, 10, and 5 min before the loading, and 5, 10 ,15, 20, 30, 40, 50, 60 90, 120, 150, and 180 min after.

Intravenous glucose infusions. 1 wk after the oral load the 20 subjects were submitted to an i.v. glucose infusion designed to copy the changes in blood glucose concentrations found during the oral load. 16⅔ g glucose in concentrations from 33 to 50% were given at a constant flow rate by an infusion pump in an antecubital vein. Blood samples were drawn from the opposite arm at intervals identical with those in the oral glucose test.

Studies on the effect of exogenous gastrin on insulin secretion

Intravenous infusion of gastrin. In five subjects, one female and four males, synthetic human gastrin I (SHG I from Imperial Chemical Industries, Cheshire, England) [1] was given i.v. as a rapid injection of 62.5 ng per kg body weight followed by 30 min infusion of 12.5 ng SHG/kg per min. Blood samples were drawn 60, 45, 30, and 15 min before, and 0, 2, 5, 10, 20, 30, 45, 60, 75, and 90 min after the onset of infusion. Gastric acid was aspirated continuously by intermittent pump suction through a nasogastric tube and collected in 15-min samples. The position of the tube was checked by fluoroscopy.

Dose-response studies with gastrin given intravenously. Each of six subjects was given seven doses of gastrin (15.6, 31.2, 62.5, 125, 250, 500, 1,000 ng per kg body weight). Pyrogen-tested SHG was dissolved in 0.1 M sodium phosphate, pH 7.4, and injected rapidly in volumes from 1.0 to 5.0 ml. Venous blood samples were drawn 15, 10, and 5 min before, and 1, 2, 3, 4, 5, 7, 10, 15, and 20 min after the injection. In a few cases samples were also drawn 30 min after injection. The doses were given in randomized order.

Dose-response studies with gastrin and 25 g glucose given simultaneously intravenously. In six subjects three doses of SHG (15.6, 62.5, and 250 ng) were injected together with 25 g glucose in a 50% solution. The subjects were tested previously with an i.v. 25 g glucose tolerance test without gastrin. Blood samples were drawn 15, 10, and 5 min before, and 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 40, 50, and 60 min after the injection.

Studies on the effect of gastrin injected before glucose. In four subjects, three men and one woman, 25 g glucose was given twice with an interval of 150 min as described by Kraegen, Chisholm, Young, and Lazarus (35). 1 wk later the experiment was repeated with 15.625 ng gastrin per kg injected 30 min before the second glucose injection. Blood samples were drawn according to the following scheme: — 5, 0, 2, 5, 10, 20, 30, 45, 60, 75, 90, 105, 120,

[1] *Abbreviation used in this paper:* SHG, synthetic human gastrin I.

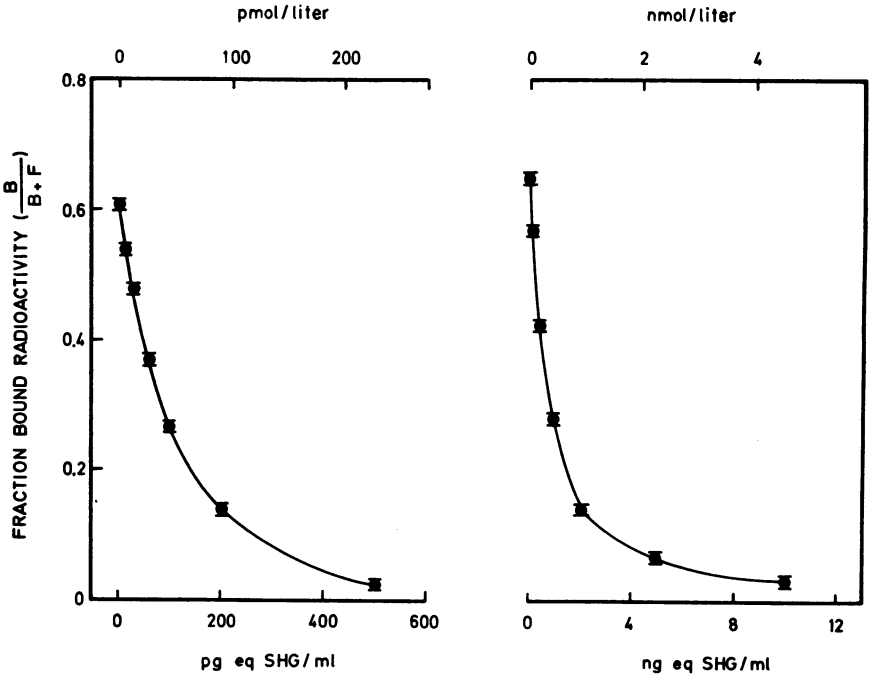

FIGURE 1 Standard calibration curves for the radioimmunoassay of gastrin. To the left a standard curve employed for determination of serum gastrin concentrations in the physiological range (0–300 pg eq SHG/ml ~ 0–140 pmol/liter, antiserum 2604). To the right a standard for determinations of serum gastrin concentrations above the physiologic range (antiserum 2609). The points on the standard curves are indicated as mean ±SD from 10 replicate determinations.

122, 125, 130, 140, 150, 152, 155, 160, 170, 180, 195, 210 min. Gastric juice was collected as before.

Laboratory methods

Serum gastrin concentrations were measured with a radioimmunoassay (21) using a purified monoiodinated gastrin preparation (23). The antisera used (2604 and 2609) were produced in rabbits against synthetic hexadecapeptide gastrin (2–17) covalently coupled by carbodiimide to bovine serum albumin (24). The binding energy, expressed by the average equilibrium constant, was 1.1×10^{12} (2604) and 4.4×10^{10} liters/mol (2609). The *detection limit* of the assays was < 20 fmol gastrin per liter (2604) and < 2 pmol per liter incubation mixture (2609). The *working range* of the assay was 2–140 (2604) and 100–5,000 pmol per liter (2609). Antiserum 2604 was used to measure physiologic concentrations of gastrin in serum, whereas antiserum 2609 was reserved for sera with high concentrations of gastrin (Fig. 1). The *specificity* of the assay was expressed by the molar ratio between the inhibition dose 50 for SHG and highly purified cholecystokinin. For antiserum 2604 the ratio was 0.006, and for antiserum 2609 it was 0.002. No other known hormone cross-reacted with the antisera. Within-assay *precision* was tested by 10 determinations of two serum samples. Mean-gastrin concentration ±1 SD was 84.4±3.9 pmol per liter and 13.4±4.8 pmol per liter respectively. Between-assay *reproducibility* was tested during 21 assays covering a period of 4 mo; for three sera the mean and standard deviations were 24.0±0.8, 8.1±1.8, and 43.4±3.0 pmol per liter. The relative *accuracy* was estimated by comparison of reference concentrations with those reported by other groups. In our laboratories the mean concentration of gastrin in serum from healthy, fasting subjects was found to be 23.6±2.1 pmol per liter or 52.0±4.6 pg eq SHG per ml (±SEM, n = 120). These concentrations are of the same order as those reported by others (18–20, 25). Superimposable dose-response curves were obtained with synthetic human gastrin in serum freed of gastrin, and with serial dilutions of sera. Measurements of gastrin concentrations in sera with added exogenous gastrin, in dilutions of sera, and in mixtures of sera with different concentrations yielded results, which deviated less than 10% from the expected values.

Serum insulin concentrations were measured by means of a wick-chromatographic radioimmunoassay (26). The *working range* of the assay was 35–1,400 pmol per liter with a *detection limit* < 10 pmol per liter. The employed antiserum measured both proinsulin and insulin. Within-assay *precision* was tested by 10 determinations of three serum samples. Mean ±1 SD was 70.7±3.4 (10.2±0.6 μU per ml), 149.8±2.8 (21.7±0.4 μU per ml), and 350.5±9.7 pmol per liter (50.8±1.4 μU per ml). Between-assay *reproducibility* was tested during 50 assays covering a period of 6 mo. For three sera the mean and 1 SD were 70.6±8.5 (10.2±1.5 μU per ml), 150.0±8.4 (21.8±1.2 μU per ml), and 350.5 ±24.1 pmol per liter (50.8±3.5 μU per ml). The mean concentration of insulin in serum in healthy fasting subjects was 58.0±4.2 pmol per liter (±SEM, n = 120) or 8.4±0.6 μU per ml in our laboratory. Measurement of insulin concentration in sera with added exogenous insulin, in dilutions of sera, and in mixtures of sera with different concentrations yielded results, which deviated less than 10% from the expected values.

Blood glucose concentrations were measured with a glucose oxidase method on Technicon Auto Analyzer (Technicon Instruments Corp., Tarrytown, N. Y.).

Gastric acid was measured by titration with 0.2 N sodium hydroxide to pH 7.0, employing an Autotitrator (Radiometer, Copenhagen, Denmark).

Calculations. The integrated insulin response and integrated gastrin stimulus were computed as the area under the serum insulin and serum gastrin curves in the time intervals indicated using fasting levels as base line. The glucose disappearance rate was calculated as $K = \ln 2/t_{\frac{1}{2}} \times 100$ from the studies with i.v. glucose administration. The significance of differences between means was tested by Student's *t* test. The concentrations of blood glucose, serum insulin, and serum gastrin are given as mean ±SEM in molar units. Concentration units used by others, e.g., mg/100 ml, μU/ml, and pg/ml, are indicated in brackets in the text.

In the tables conventional units are used.

RESULTS

Studies on endogenous gastrin

Response to a protein-rich meal (Fig. 2). Blood glucose concentrations showed an initial small decrease from 3.85±0.15 (69.3±2.7 mg per 100 ml) to 3.76±0.15 mmol per liter (67.7±2.7 mg per 100 ml). The peak concentration of 4.74±0.42 mmol per liter (85.3±7.6 mg per 100 ml), was observed after 45 min.

The increase in serum insulin concentration appeared later than the increase in gastrin concentrations. The

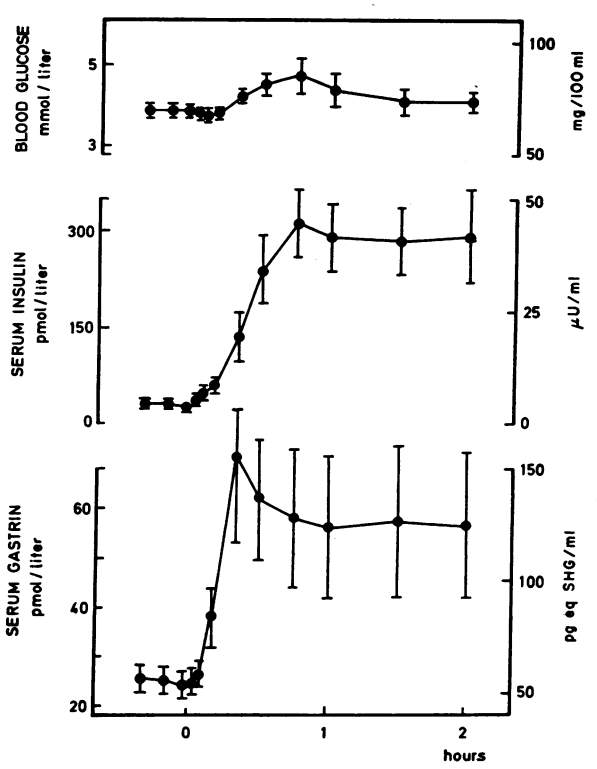

FIGURE 2 Blood glucose, serum insulin, and serum gastrin concentrations during a protein-rich meal. The concentrations are indicated as mean ±SEM (n = 8).

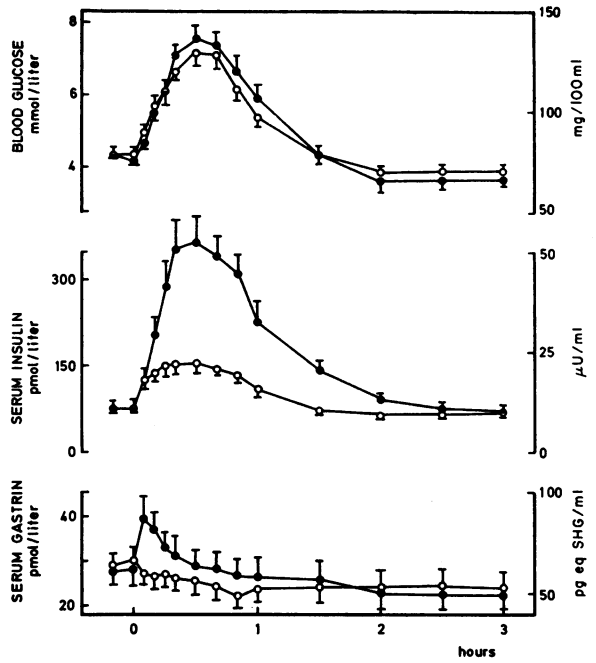

FIGURE 3 Blood glucose, serum insulin, and serum gastrin concentrations during a 50 g oral glucose load (●) and a 16.7 g i.v. glucose infusion (○). The concentrations are indicated as mean ±SEM (n = 20).

highest concentration was found after 45 min (314±51 pmol per liter) (44.9±7.3 μU per ml). The integrated insulin response was 28.2±5.9 nmol per liter (4.3±0.8 mU per ml) per the two 1st h of the meal.

Serum gastrin concentrations increased rapidly after the start of the meal. The maximum concentration (70.6 ±17.5 pmol per liter) (155.3±38.5 pg eq SHG per ml) was reached in 20 min. The integrated gastrin response during 2 h after onset of the meal was 4.1±1.6 nmol per liter (9.0±3.5 ng eq SHG per ml).

Response to oral glucose loading (*Fig. 3*). Variations in blood glucose and serum insulin concentrations are given in the figure. The basal gastrin concentration of 28.0±3.5 pmol per liter (61.6±7.7 pg eq SHG per ml) rose in 5 min to 39.0±5.6 pmol per liter (85.8±12.3 pg eq SHG per ml), and was followed by a slow decrease. The maximum concentrations differed from the fasting levels ($P < 0.01$).

Response to intravenous glucose infusion (*Fig. 3*). The glucose infusion produced variations in mean glucose concentrations in the blood almost similar to the ones observed during the oral glucose tolerance test.

The increase in insulin concentrations was less than during the oral glucose loading and the difference was highly significant.

No significant changes in serum gastrin concentrations were found. There was, however, a tendency towards a decrease from the mean fasting levels of 30.2± 2.7 pmol per liter (66.4±5.9 pg eq SHG per ml) to 24.8 ±3.5 pmol per liter (54.6±7.7 pg eq SHG per ml) after 50 min.

Studies on exogenous gastrin

Response to intravenous infusion of gastrin (*Fig. 4*). Blood glucose concentrations rose modestly. The mean concentration for the 20th, 30th, 45th, and 60th min was significantly above the mean of the four basal concentrations ($P < 0.02$).

Insulin concentrations rose promptly within 2 min to 118.0 ± 20.7 pmol per liter (16.2±3 μU per ml), but decreased to basal levels after 20 min. Serum gastrin levels rose immediately. Peak concentration was observed after 30 min.

The peak acid output was found in the 15 min collection made 45 min after the start of the infusion.

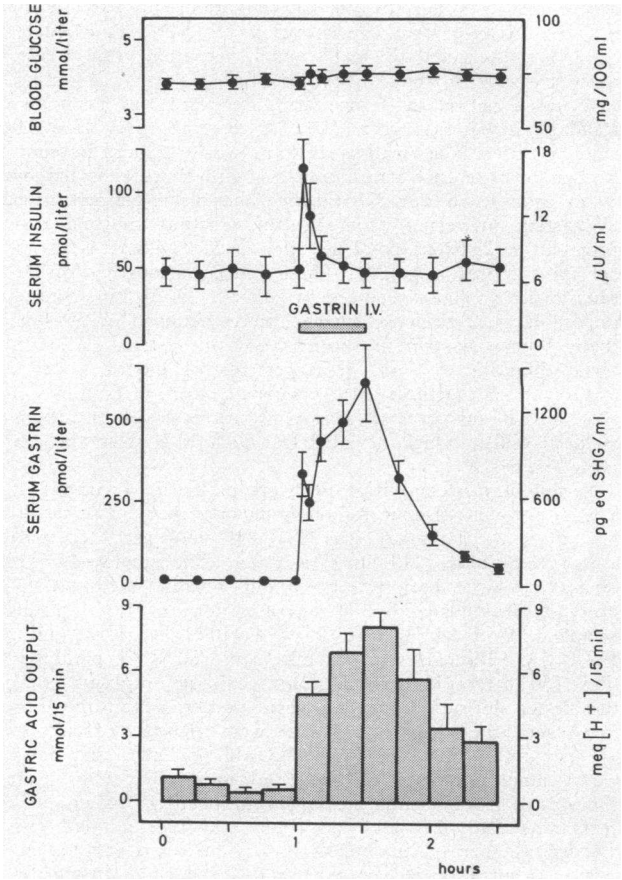

FIGURE 4 Blood glucose, serum insulin, serum gastrin concentrations, and gastric acid output during i.v. infusion of 12.5 ng SHG/kg per min. The infusion was started with a single injection of 62.5 ng gastrin/kg. The concentrations and gastric acid response are indicated as mean ±SEM (n = 5).

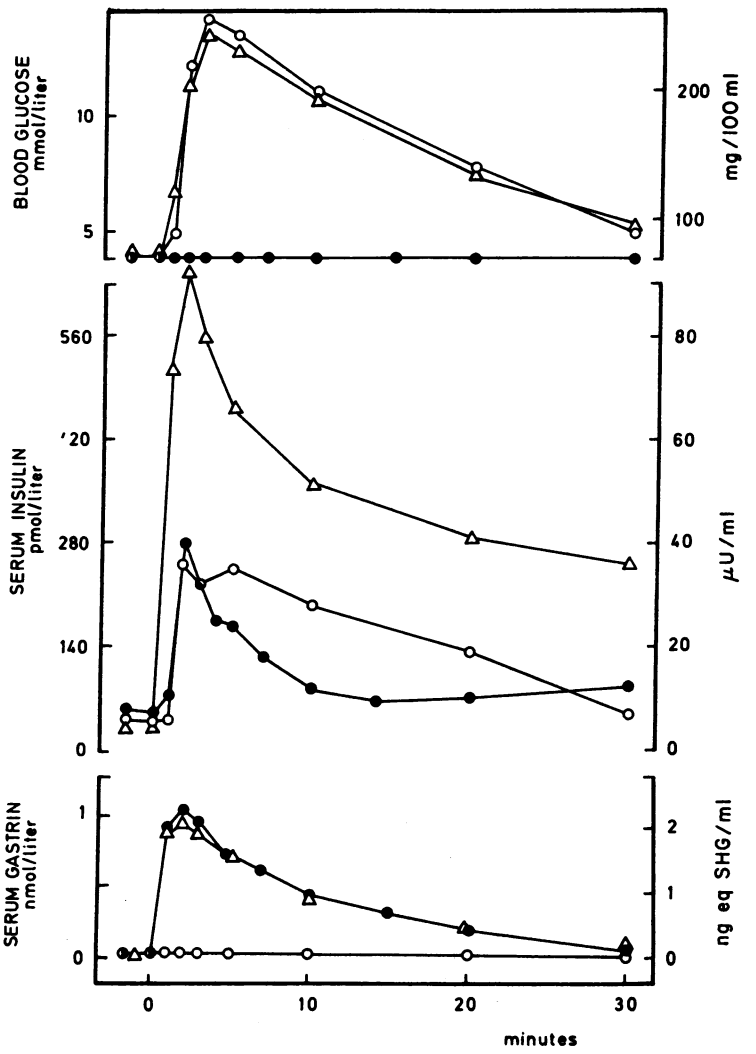

FIGURE 5 Blood glucose, serum insulin, and serum gastrin concentrations in one normal subject after i.v. injection of synthetic human gastrin I, 250 ng/kg body wt (●), after i.v. injection of 25 g glucose (○), and after a synchronous i.v. injection of both 250 ng/kg SHG and 25 g glucose (△).

Response to intravenous gastrin injections (Fig. 5 and Table I). The blood glucose concentration was elevated after gastrin injections. The rapid injection of gastrin caused an immediate insulin release with maximum concentration in peripheral venous serum after 2 min. Insulin concentrations returned to basal levels within 10 min at a time, when the concentration of gastrin was still about 20 times above fasting levels. After 20 min a slight increase in insulin concentrations was found. The immediate insulin response to gastrin lasted less than 20 min for all doses of gastrin (Table I).

The insulin response to glucose was as rapid as the one to gastrin, and in one subject it reached similar levels. The glucose-induced response was, however, considerably more sustained (Fig. 5).

The dose-response interrelationship (Fig. 6, Tables I and II). There was no detectable insulin response to the smallest gastrin dose, 15.6 ng SHG per kg. Gastrin doses of 31.25 ng per kg or more produced significant responses from the beta cells. 500 ng per kg was the gastrin dose with greatest effect on insulin release. 1,000 ng gastrin per kg produced a smaller response than 500 ng per kg. The smallest gastrin dose caused a significant rise in serum gastrin concentrations. The maximum concentration was 110.9±14.1 pmol per liter (244±31.0 pg eq SHG per ml), which is of the same order as the

TABLE I

Effect of Intravenous Injection of Increasing Doses of Synthetic Human Gastrin I on

Dose of gastrin		Time in −10	−5	0	1	2	3
ng/kg							
15.625	BG	64.8±2.6	64.0±2.5	64.5±2.8	64.8±2.6	65.5±2.5	65.5±2.5
	SI	5.0±0.7	5.7±0.5	6.0±1.4	5.3±1.3	4.3±0.9	5.0±1.2
	SG	50.3±2.7	50.8±2.6	52.0±5.0	245.8±44.8	215.0±29.0	170.3±20.4
31.25	BG	63.8±1.9	64.1±1.8	65.0±1.7	64.2±1.3	64.3±2.1	66.2±2.0
	SI	5.7±1.0	5.8±0.9	5.8±1.2	6.5±1.1	9.7±2.0	9.8±2.1
	SG	50.3±6.1	52.2±9.5	53.7±8.0	524.2±27.7	478.3±31.4	460.0±14.7
62.50	BG	66.0±2.4	66.0±2.2	67.0±2.5	66.3±2.4	67.0±2.7	66.3±2.9
	SI	5.8±1.6	5.0±1.2	5.8±1.4	7.3±2.5	10.8±2.7	10.3±2.6
	SG	52.5±3.8	53.3±3.6	53.8±3.2	931.7±40.2	765.0±64.2	613.3±33.7
125.0	BG	68.0±2.6	67.5±3.5	67.0±2.3	66.0±2.3	67.8±3.2	69.2±4.1
	SI	5.2±0.9	6.0±0.7	6.0±0.4	7.8±0.4	14.2±2.5	13.3±1.6
	SG	43.0±4.8	43.2±4.5	43.3±5.6	1550.0±241.0	1308.0±133.0	1161.0±119.0
250.0	BG	69.0±3.3	69.0±2.8	69.7±3.0	69.7±3.6	72.3±4.3	74.7±4.2
	SI	5.7±1.8	5.3±2.1	5.2±1.8	7.8±2.6	19.7±5.1	16.5±5.1
	SG	35.8±5.8	29.2±4.0	27.0±3.5	2466.7±386.8	2816.7±170.8	2533.3±138.8
500.0	BG	64.0±3.4	61.7±2.3	63.3±2.4	62.3±2.2	62.5±2.4	64.3±2.1
	SI	4.3±0.8	4.3±1.0	4.3±1.2	11.7±5.4	21.5±4.1	22.2±6.8
	SG	38.8±3.0	34.0±3.9	31.7±4.4	5050.0±283.7	5875.0±461.9	5400.0±418.0
1000	BG	68.2±3.3	68.7±3.1	69.3±3.9	69.0±2.9	71.0±2.3	71.8±2.2
	SI	3.7±0.8	3.8±0.6	3.7±0.9	6.3±1.4	16.7±4.3	14.0±2.9
	SG	28.7±5.1	30.3±4.9	24.8±4.8	10383.3±1461.6	9550.0±1330.0	8100.0±703.4

The concentrations are indicated as ±SEM, n = 6.
BG, blood glucose (mg/100 ml); SI, serum insulin (microunits per milliliter); and SG, serum gastrin (picograms per milliliter).

maximum concentration observed during a protein-rich meal (Fig. 2).

Response to simultaneous intravenous injection of gastrin and glucose (Fig. 7, Tables II and III). Addition of 15.6 ng SMG per kg to 25 g glucose increased the glucose-induced insulin response ($P < 0.05$). All doses of gastrin added to glucose increased the insulin concentrations immediately to a maximum in the 2nd or 3rd min. The potentiation was maintained throughout 1 h. Doses from 62.5 ng per kg produced, when added to glucose, an insulin response per hour of a size similar to that of a protein-rich meal (Fig. 7). The integrated insulin responses to increasing doses of gastrin with and without glucose are compared in Table II.

Effect of gastrin on glucose disappearance rate (Table IV). The glucose disappearance rate after i.v. glucose administration was not changed by the addition of increasing doses of gastrin.

Response to intravenous glucose after prior administration of gastrin (Fig. 8 and Table V). Administration of 15.6 ng SHG per kg, half an hour before i.v. injection of 25 g glucose caused an insignificant increase in insulin concentrations after the glucose administration ($P > 0.05$). The glucose disappearance rate decreased, but not significantly, after prior administration of gastrin (Table V).

DISCUSSION

The main conclusions to be drawn from the results presented above are that gastrin can stimulate a rapid and short-lived release of insulin. When gastrin concentrations are maintained within physiologic limits, gastrin potentiates only the glucose-induced insulin secretion, and is without effect on the basal insulin secretion. During oral glucose ingestion gastrin probably contributes very little to the insulin release. Gastrin may, however, stimulate the insulin secretion significantly during protein-rich meals.

Endogenous gastrin was found to be released immediately during the stimulus of an ordinary meal. The rise

the Concentrations of Blood Glucose, Serum Insulin, and Serum Gastrin

minutes					
4	5	7	10	15	20
65.8±2.6	65.0±2.9	65.0±2.7	65.3±3.0	63.3±3.4	62.3±3.6
5.2±1.2	4.8±1.1	4.7±1.0	4.5±1.0	4.3±0.7	3.8±1.0
152.8±20.3	125.8±18.9	109.0±16.3	83.3±14.1	69.7±8.5	60.3±7.3
66.2±2.2	66.2±2.4	65.0±2.1	64.0±2.0	63.8±1.9	63.7±1.8
9.2±2.1	7.2±2.1	7.2±2.5	6.2±1.5	8.0±2.3	6.5±1.2
399.2±7.1	352.0±12.4	276.2±23.3	180.7±6.8	154.5±6.6	135.8±5.1
64.7±2.0	65.0±1.5	65.3±1.2	65.3±1.1	64.3±1.1	64.3±2.3
9.2±2.5	8.5±2.4	5.5±1.3	4.7±0.8	5.3±1.1	6.4±1.2
511.7±34.9	520.0±32.0	422.0±20.1	324.0±32.6	216.2±22.2	147.8±14.4
68.0±3.7	67.3±3.6	67.3±3.6	64.5±2.1	65.8±2.3	65.2±2.2
11.8±1.9	8.7±0.8	6.5±0.7	5.3±1.1	5.5±1.0	5.5±1.1
1000.0±114.3	850.0±86.0	661.7±55.2	446.7±49.3	410.0±20.3	260.0±10.2
74.7±4.4	74.3±4.4	72.7±4.3	69.7±4.7	71.3±4.8	70.0±2.9
12.2±4.0	11.0±4.0	8.7±3.5	4.7±2.2	5.5±2.3	5.5±2.3
2058.3±123.2	1683.3±94.9	1366.7±84.6	1050.0±76.7	608.3±64.0	350.0±68.6
64.5±2.3	64.3±1.9	65.5±1.7	64.2±1.6	65.0±1.7	64.2±2.1
15.3±5.1	11.2±3.5	6.8±2.0	3.8±1.5	4.5±1.3	4.0±1.0
4766.6±321.1	4383.3±240.0	3500.0±184.4	2200.0±85.6	1366.6±58.6	1008.3±27.1
72.3±3.3	71.8±3.4	71.3±3.3	68.7±3.6	70.0±4.1	69.5±4.3
9.7±1.9	6.2±1.7	3.7±1.1	3.7±1.1	3.5±1.4	3.5±1.9
6616.6±370.1	5950.0±229.1	5316.6±246.8	4250.0±475.0	2833.3±300.0	2033.3±135.8

in serum gastrin was acute and preceded the increase in insulin concentrations. Hyperglycemia contributed little to the initial insulin response during the meal (Fig. 2). It hence appears that gastrin might be an insulin stimulator, probably in connection with other gut hormones and amino acids. A protein-rich meal is considered to be one of the strongest physiologic stimuli for gastrin secretion, and assessed from this stimulus the maximum physiologic gastrin concentrations in serum are in the order of 160 pmol per liter (350 pg eq SHG per ml). That an insulinotropic action of gut hormones may exist was originally suggested by the difference in insulin response observed after oral and i.v. glucose administration (1–3). In the present investigation the glycemic stimulus was of the same magnitude whether glucose was administered parenterally or orally. Hence the apparent difference in insulin response may be taken as a measure of the effect of the gut hormones. The size of the enteral hormonal stimulation was about two-thirds of the total insulin response to oral glucose, in accordance with the results of Perley and Kipnis (5). Since only moderate amounts of gastrin were released by ingestion of oral glucose, gastrin is probably not a major insulin secretagogue during an oral glucose loading.

The nature of the insulin response to *exogenous gastrin* was apparently independent of whether gastrin was administered as a rapid i.v. injection (Fig. 5) or as a 30 min infusion (Fig. 4). In both cases the beta cells responded with an immediate rise and a decline to basal levels within 10 min. During the infusion gastric acid was aspirated continuously which makes it unlikely that secretin or cholecystokinin secretion was activated. When insulin responses were followed during a 30 min period after gastrin injection without gastric aspiration. a moderate late increase in insulin concentration was noted (Fig. 5). This could be due to other gut hormones being released by gastric acid secreted in response to gastrin, although studies on the effect of acid installation in duodenum on insulin release are controversial so far (7, 14, 27–31). The present experiments hence suggest that

TABLE II

Integrated Insulin Response (μU/ml per 20 min) in Six Normal Subjects after Intravenous Injection of Synthetic Human Gastrin I (A) and Synchronously with 25 g Glucose (B).*

		Dose of gastrin							
		0	15.625	31.25	62.50	125.0	250.0	500.0	1000
					ng/kg				
A	Mean	—	0	5.3 (37.0)	17.3 (121.1)	28.6 (199.9)	50.3 (352.0)	79.8 (558.8)	37.7 (263.6)
	SEM	—	—	2.9 (20.6)	5.1 (35.9)	4.4 (31.0)	11.8 (82.4)	24.2 (169.5)	10.5 (73.8)
B	Mean	331.0 (2317.0)	619.2 (4333.0)	—	658.5 (4609.5)	—	713.8 (4996.6)	—	—
	SEM	43.9 (328.3)	140.6 (984.2)	—	233.5 (1681.0)	—	113.2 (791.4)	—	—

* Insulin response in pmol/liter per 20 min indicated in the brackets.

gastrin may affect the beta cells in two ways: (*a*) by a direct effect on the acutely releasable pool of insulin in accordance with the conception of a two-pool system in man (*32*), and possibly (*b*) by an indirect effect mediated through activation of other gastrointestinal hormones released by acid in duodenum and jejunum. The magnitude and steepness in the increase of gastrin concentrations seem to govern the insulin response rather than the total integrated gastrin stimulus.

The dose-response studies of the effect on basal insulin secretion showed that the gastrin doses required for a significant insulin response resulted in unphysiologic concentrations of gastrin in serum. In contrast the glucose-stimulated insulin secretion was significantly potentiated by small doses of gastrin, resulting in serum gastrin levels within physiologic limits. The effect was not additive, but obviously potentiating and direct since the increase in the glucose-mediated insulin release was observed in the 1st min (Fig. 5 and Table III). It is notable that the gastrin-potentiated insulin increase did not influence the glucose disappearance rate (Table IV). This observation supports the findings of Chisholm, Young, and Lazarus (30) and Dupré, Curtis, Unger, Waddell, and Beck (*7*), who inferred that the effect of gut hormones on glucose disposal probably does not depend solely on stimulation of insulin secretion. A simi-

TABLE III

Effect of Intravenous Injection of 25 g Glucose and Increasing Doses of Synthetic Human Gastrin I

Dose of gastrin		Time in −5	0	1	2	3
ng/kg						
0.0	BG	63.0±4.0	64.3±4.3	141.3±23.3	240.8±15.0	230.8±15.9
	SI	3.3±0.9	3.0±1.0	9.0±4.1	26.2±4.3	29.3±4.3
	SG	44.5±4.1	38.7±4.4	43.0±5.5	34.8±5.2	35.3±5.3
15.625	BG	58.7±2.8	60.3±2.2	166.7±26.7	217.7±22.5	217.7±22.6
	SI	3.7±0.9	3.5±1.1	41.5±11.6	48.0±7.6	52.8±12.5
	SG	31.5±9.6	32.8±9.9	131.7±32.9	156.7±14.5	144.4±12.0
62.50	BG	60.3±3.8	60.0±3.9	209.5±38.1	263.0±24.9	235.3±16.1
	SI	3.2±1.0	2.7±0.2	55.7±9.8	66.6±22.3	68.5±33.8
	SG	35.0±8.8	31.7±9.8	685.0±85.9	593.3±20.5	608.0±118.6
250.0	BG	60.0±2.7	58.7±2.8	143.0±22.2	204.3±22.2	210.8±12.8
	SI	4.5±0.7	4.8±0.9	34.3±10.4	58.3±14.2	55.3±8.8
	SG	31.3±6.3	29.8±4.7	2270.0±338.0	2353 ±245.9	2190.0±182.8

The concentrations are indicated as mean ±SEM, n = 6.

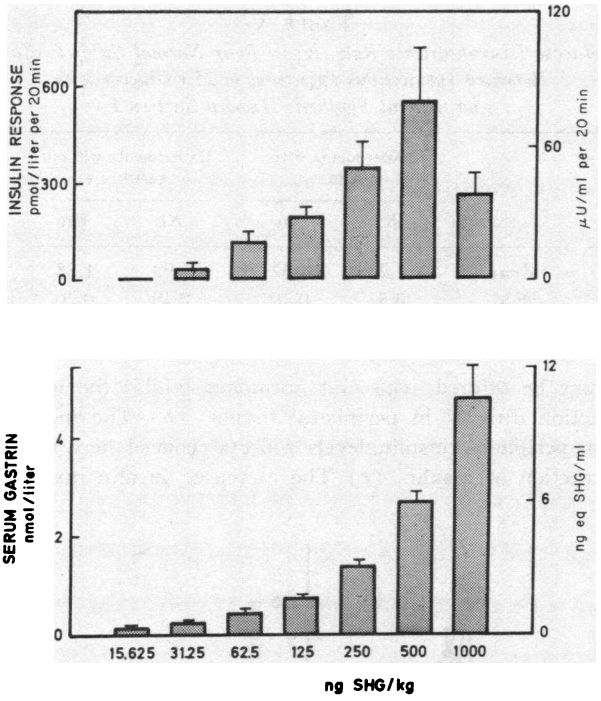

FIGURE 6 Integrated insulin response and maximal serum gastrin concentrations after i.v. injection of increasing doses of SHG. The responses and concentrations are indicated as mean ±SEM (n = 6).

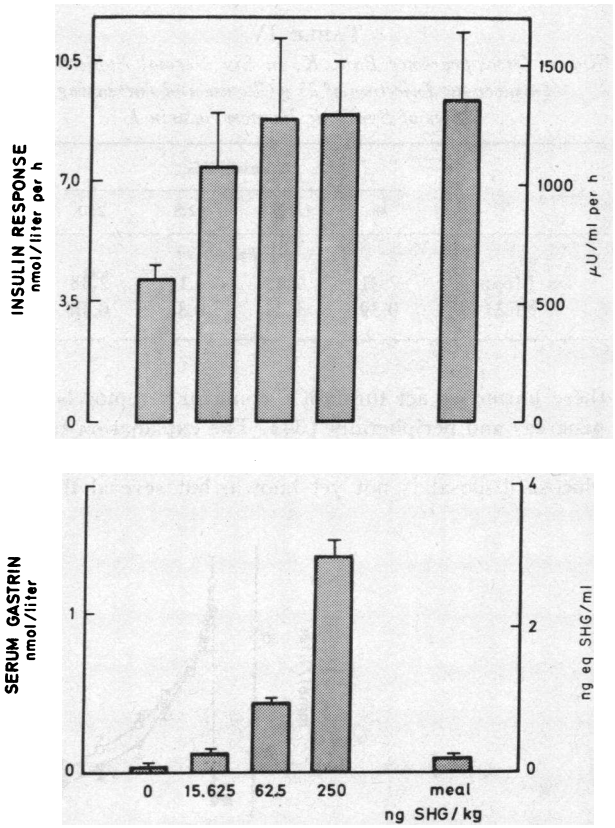

FIGURE 7 Integrated insulin response and maximal serum gastrin concentrations after i.v. injection of 25 g glucose and increasing doses of synthetic human gastrin. As reference the insulin response and gastrin concentration during a protein-rich meal are shown. The results are indicated as mean ±SEM (n = 6, for the meal n = 8).

lar result was obtained by Meade, Kneubuhler, Barboriak, and Schulte (33) as to the effect of cholecystokinin in dogs. In view of the C-terminal structural identity of gastrin and cholecystokinin, it is possible that

on the Concentrations of Blood Glucose, Serum Insulin, and Serum Gastrin

minutes						
5	10	20	30	40	50	60
213.3±12.1	180.0±13.0	136.7±9.4	109.7±11.0	91.2±12.0	75.3±9.2	68.4±8.4
24.7±3.4	17.2±2.9	14.8±1.7	11.2±1.9	9.8±2.0	8.0±2.3	4.8±2.0
38.0±4.4	35.5±4.2	36.1±4.0	35.5±5.0	37.2±4.3	35.5±4.9	36.8±4.6
213.7±23.4	178.0±4.6	145.3±8.9	109.3±7.0	87.0±10.5	71.0±9.2	59.7±7.7
45.3±11.7	32.8±8.9	21.7±5.5	19.2±4.2	12.7±3.2	10.8±2.9	10.7±2.9
121.3±12.5	80.8±17.0	57.5±19.3	47.7±13.2	42.5±11.9	37.5±11.1	34.2±9.1
220.8±16.7	183.0±10.4	141.0±7.1	119.5±10.1	94.7±9.5	76.7±7.6	66.3±4.7
47.8±21.9	28.5±7.0	22.5±5.1	22.0±4.2	19.0±3.2	15.7±2.8	11.3±2.1
502.0±106.2	276.4±69.0	145.4±32.9	80.2±10.3	54.8±15.0	48.2±13.8	44.8±14.5
203.2±6.5	170.7±3.5	130.0±5.7	105.3±8.0	82.3±10.5	73.3±9.0	66.0±6.8
48.8±7.5	39.0±6.1	31.7±5.5	22.7±4.8	17.5±3.6	11.0±2.7	9.5±3.7
1665.0±129.6	983.3±76.2	280.0±33.1	144.2±11.1	90.3±6.5	71.0±3.1	61.8±3.6

TABLE IV

Glucose Disappearance Rate, K, in Six Normal Subjects after Intravenous Injection of 25 g Glucose and Increasing Doses of Synthetic Human Gastrin I

	Dose of SHG			
	0	15.625	62.5	250
	ng/kg body wt			
Mean	2.31	2.49	2.11	2.38
SEM	0.39	0.31	0.33	0.46

TABLE V

Glucose Disappearance Rate, K, in Four Normal Subjects after Repeated Intravenous Injections of 25 g Glucose with and without Synthetic Human Gastrin I

	Experiments with gastrin i.v.		Experiments without gastrin i.v.	
	K_I	K_{II}	K_I	K_{II}
Mean	2.27	1.52	1.93	1.88
SEM	0.54	0.40	0.49	0.26

these hormones act through a common receptor both in pancreas and peripherally (34). The explanation for the apparent lack of influence of immunoreactive insulin on glucose disposal is not yet known, but several theories may be offered: (*a*) Gut hormones inhibit the insulin action directly in peripheral tissues. (*b*) The increase in peripheral insulin levels reflects reduced hepatic extraction of insulin. (*c*) The increased insulin immuno-

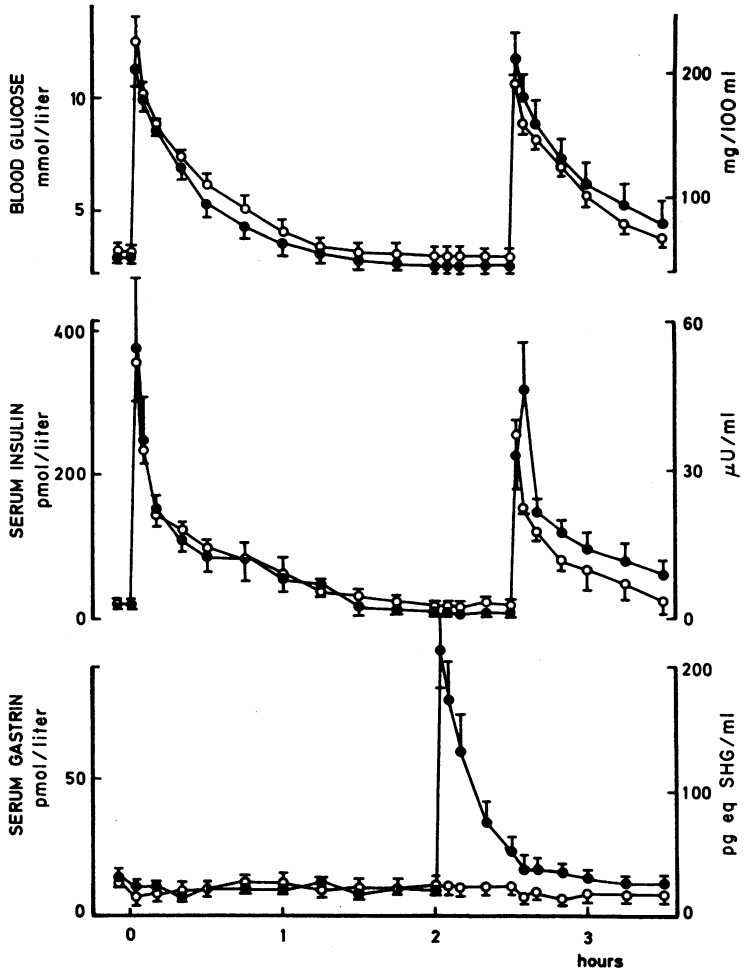

FIGURE 8 Blood glucose, serum insulin, and serum gastrin concentrations during repeated i.v. injection of 25 g glucose (○). The experiment was repeated in the same subjects with i.v. injection of 15.625 ng SHG/kg 30 min before the second glucose load (●).

reactivity represents a less active moiety of insulin, for instance proinsulin. (*d*) The glucose disappearance curve employed in the present study reflects glucose distribution unrelated to insulin action. (*e*) Gastrin stimulates glucagon secretion with ensuing glycogenolysis and gluconeogenesis.

It has been reported (35) that secretin potentiated the glucose-induced insulin secretion by a dual action. Using a similar experimental design, we could not demonstrate a dual effect of gastrin on insulin release or glucose disposal. The conclusions from the present study are drawn with two reservations. Firstly, the role of a possible local secretion of gastrin from the D-cells in the islets is still undetermined. Secondly, the different endogenous gastrin components (36, 37) may show different biological properties.

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