

Disturbed Islet-Cell Function Related to Endogenous Gastrin Release

STUDIES ON INSULIN SECRETION AND GLUCOSE TOLERANCE IN PERNICIOUS ANEMIA

JENS F. REHFELD

From the Department of Clinical Chemistry, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark

ABSTRACT The insulin and gastrin response to oral glucose, intravenous glucose, or a protein-rich meal were measured in 44 nondiabetic patients with pernicious anemia (PA) and in 44 control subjects. 36 of the PA-patients had hypergastrinemia, while serum gastrin concentrations in the remaining eight patients were below normal. Three hypergastrinemic PA-patients were in addition studied during an oral glucose loading with synchronous intravenous infusion of gastrin-17.

During both oral and intravenous glucose tests blood glucose concentrations were similar in patients and in controls. After ingestion of protein blood glucose concentrations in PA-patients with hypergastrinemia were above those of the controls ($P < 0.05$). Parenteral infusion of gastrin-17 during oral glucose loading also increased blood glucose concentrations above the levels observed after glucose alone. In PA-patients with hypergastrinemia the insulin response was augmented in all tests. In patients with hypogastrinemia serum insulin concentrations were lower than normal in the fasting state and during stimulation with glucose intravenously ($P < 0.01$). In hypergastrinemic patients serum gastrin concentrations decreased after oral as well as intravenous glucose administration. The decrease was larger during the oral test. In hypogastrinemia oral glucose induced, as in controls, a small initial rise followed by a slow fall in serum gastrin concentrations. No variations were seen in these patients during the intravenous glucose infusion. Gel filtration of serum from hypergastrinemic patients disclosed a decrease in the concentrations of all

four main components of gastrin during the glucose loadings.

Taken together with earlier studies on the effect of exogenous gastrin the results suggest that endogenous hypergastrinemia induces hyperglycemia and potentiates insulin secretion. In contrast hypogastrinemia is associated with hypoinsulinism.

INTRODUCTION

Exogenous gastrin in form of the heptadecapeptide amide (gastrin-17)¹ and its C-terminal tetrapeptide amide can stimulate insulin release in man (1-3). But dose-response studies with exogenous gastrin-17 correlated to endogenous gastrin concentrations in serum during meals point to a limited role of gastrin in the regulation of insulin secretion in normal human subjects (4). However, since gastrin-17 in high doses releases large amounts of insulin and moreover increases blood glucose concentrations (4), endogenous hypergastrinemia might also influence insulin secretion and glucose metabolism.

Endogenous hypergastrinemia is most often found in patients with achlorhydria, among which those with pernicious anemia (PA) constitute a well-defined group. Approximately 75% of PA-patients have increased concentrations of gastrin in serum (5). A relationship between PA and impaired glucose tolerance and insulin secretion was suggested already in 1910 (6), and it is now well-known that the frequency of diabetes mellitus in PA is increased (7-9). The pathogenetic link between PA and diabetes of juvenile-onset type is possibly of

Dr. Rehfeld's present address is Institute of Medical Biochemistry, University of Aarhus, DK-8000 Aarhus C, Denmark.

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¹Abbreviations used in this paper: gastrin-17, heptadecapeptide; PA, pernicious anemia.

autoimmune nature (10–14). But diabetes mellitus of maturity-onset type in PA might be due, at least in part to hypergastrinemia.

The present study is an attempt to evaluate whether the disturbed gastrin release in PA influences insulin secretion and glucose homeostasis.

METHODS

Patients and control subjects

44 patients with treated PA and 44 healthy control subjects participated in the study. All patients and controls were within 10% of their desirable weight (15). The PA-diagnosis was established on the basis of analysis of vitamin B₁₂ concentration in serum, bone marrow examination, Schilling test without and with oral hog intrinsic factor, and an augmented histamine test. None of the patients had diseases other than PA, except five with vitiligo and two having rheumatoid arthritis. Neither diabetes mellitus nor thyroid diseases were known in the patients, nor had any been submitted to gastrointestinal surgery before the investigation.

The PA-patients were divided into three groups: *Group I* comprised 27 patients with gastrin concentrations in serum in the fasting state ranging from 120 to 1,614 pmol·l⁻¹. Their age ranged from 30 to 83 yr, with a mean of 64 yr. 21 of these patients were females. *Group II* comprised eight patients with gastrin concentrations in serum below the upper limit of the normal reference group in the fasting state, which in this department is 50 pmol·l⁻¹ (mean±2 SD). Their age ranged from 55 to 80 yr, with the mean being 68 yr. Five were females. *Group III* comprised nine patients with enhanced gastrin concentration in serum in the fasting state, range: 167–2,000 pmol·l⁻¹. Their age ranged from 32 to 79 yr and the mean was 60 yr. Eight were females.

Age (±2 years) and sex matched subjects without PA, known gastrointestinal disorders or family history of diabetes mellitus, and with gastrin concentrations in serum below 50 pmol·l⁻¹ in the fasting state served as controls. Informed consent was obtained from all patients and controls.

Both patients and controls 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 drawn from an antecubital vein. Serum was stored at –20°C until assay.

Experimental procedures

Oral glucose loading. Groups I and II and corresponding controls were given 50 g glucose as a 25% solution flavoured with lemon. Blood samples were drawn 10 and 5 min before glucose loading and 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, and 180 min after.

Intravenous glucose infusion. 1 wk after the oral test each patient in groups I and II and the corresponding control subjects was submitted to an intravenous glucose infusion test designed to imitate the changes in blood glucose concentrations measured during the oral glucose test: 16.7 g glucose in concentrations from 33 to 50% was given intravenously at a constant infusion rate. Termination of the infusion was aimed to coincide with the peak blood glucose concentration reached during the oral test in the same in-

dividual. Blood samples were drawn from the contralateral arm at the same intervals as those in the oral glucose test. The simple infusion test described here has been evaluated in detail elsewhere (16). It is based on the observation that approximately one third of the glucose given orally escapes hepatic extraction in subjects with a normal glucose tolerance (17).

Protein-rich meal. Group III of the PA-patients and the respective controls were given an appetizing meal composed of beefsteak, sauce, vegetables, and a glass of water. The meal was finished within 20 min. Blood samples were drawn 15, 10, and 5 min before, and 5, 10, 20, 30, 45, 60, and 90 min after the onset of the meal.

Intravenous gastrin infusion. In three PA-patients from group III, who previously were submitted to a 50-g oral glucose load, pure human nonsulfated gastrin-17, 2 µg/kg/h (a generous gift from Professor R. A. Gregory and Dr. H. J. Tracy, Liverpool, England) was infused intravenously 30 min before and 90 min after administration of 50 g glucose per os. Blood samples were drawn from the contralateral arm 30, 20, and 10 min before, and 5, 10, 20, 30, 40, 50, 60, 90, 105, 120, 150, and 180 min after the onset of the glucose load.

Laboratory methods

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

Serum insulin. Concentrations were measured radioimmunochemically. Reliability criteria of the actual assay have been given in detail previously (4). The antiserum employed binds monocomponent human insulin and human proinsulin with equimolar potency.

Serum gastrin. Concentrations were measured radioimmunochemically. Reagents, procedure, and reliability parameters for the assay have been described in detail previously (5, 18, 19). In the present study antiserum no. 2604-8 was employed (18). Gastrin components^a in PA-serum were studied on Sephadex G-50 superfine columns (25 × 2,000 mm) eluted with 0.25 mol·l⁻¹ ammonium bicarbonate, pH 8.2 at 4°C. The columns were calibrated with pure human gastrin-34, -17, and -14 (generous gifts from Professor R. A. Gregory and Dr. H. J. Tracy [Liverpool, England]) and with ¹²⁵I-human albumin and ²²NaCl (Amersham, England) for indication of void volume and total volume. The relative affinity of the large gastrins in PA-serum, components I and II, to antiserum 2604-8 was measured as shown in Fig. 1. It appears that the affinity of components I, II (gastrin-34-like), and III (gastrin-17-like) to antiserum 2604-8 are

^aThere are four main components of gastrin in human serum (20, 21). They have been named I–IV according to their molecular size (22). From tumour and antral tissue Gregory and Tracy have purified three pairs of gastrin with a known sequence of 34, 17, and 14 amino acids, respectively (23–25). Walsh et al. (26) have proposed that they should be named gastrin-34, gastrin-17, and gastrin-14. The tissue gastrins have roughly the same molecular size and charge as Components II, III, and IV, respectively, but there are also indications that serum components and tissue gastrins are not quite identical (27). Until the serum components are characterized better and possible identity with tissue gastrin is proven the flexible component nomenclature should be used for circulating gastrins, whereas the rigid amino acid-number nomenclature can be maintained for the well-characterized tissue gastrins.

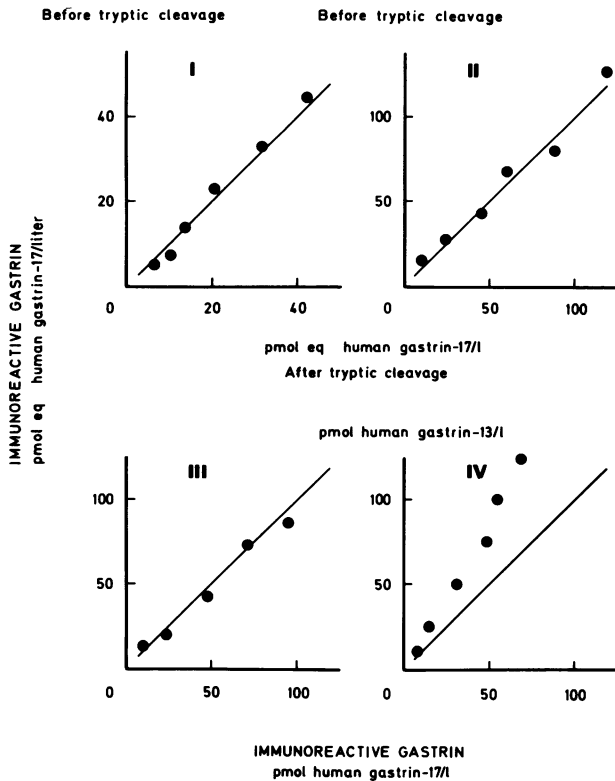


FIGURE 1 Comparison of immunoreactivity of the main components of gastrins, I-IV, in human serum against the standard gastrin of the assay (synthetic human gastrin-17 [nonsulphated]), employing antiserum 2604-8 and monoiodinated gastrin-17. Components I, II, and III from sera of hypergastrinemic patients with PA were separated by gel filtration, pooled, and concentrated by lyophilization. Components I and II (diagrams I and II, respectively) were each divided in two equal volumes, of which one was incubated with trypsin. This converts these large components to the smaller component III. After termination of tryptic cleavage by boiling the immunoreactivity of each volume was quantitated in six different dilutions. Component III (diagram III) was compared with the standard gastrin-17 in five different dilutions. Component IV was only present in PA-sera in very low amounts. Instead pure, natural gastrin-13 (nonsulphated) (diagram IV) in known concentrations was compared with standard gastrin-17.

similar on a molar basis. Separate experiments with gastrin-14 disclosed a binding of 60% to antiserum 2604-8 compared with gastrin-17 (Fig. 1). However, since the gastrin-14-like component IV constitutes only a few per cent of the total concentration of gastrin in serum, the concentration measured with antiserum 2604-8 in molar terms closely reflects the total amount of gastrin components present.

Calculations

The integrated glucose stimulation and insulin response for each experiment were computed by planimetry of the area under the blood glucose and serum insulin curves in the time intervals indicated using the lowest levels observed as base line. The significance of differences between means

was tested by Student's *t* test. The concentrations are given as mean \pm SEM.

RESULTS

Response to oral glucose loading

Group I (Fig. 2 and Table I). The blood glucose curves and the total glucose stimulation in patients were similar to that of controls. Serum insulin concentrations in the patients rose from 62 ± 10 to 560 ± 69 pmol \cdot l⁻¹ after 60 min. Controls showed an increase from 60 ± 10 to 371 ± 45 pmol \cdot l⁻¹ in the same period. The mean peak concentration in PA was above normal ($P < 0.01$). So also were the insulin responses in the 0.5-2 h interval and the total insulin response ($P < 0.05$). Mean serum gastrin concentration in PA fell rapidly ($P < 0.01$). The controls showed a small rise initially but otherwise displayed no variations in serum gastrin levels.

Group II (Fig. 3 and Table I). Blood glucose concentrations rose faster than normal to a peak after 30

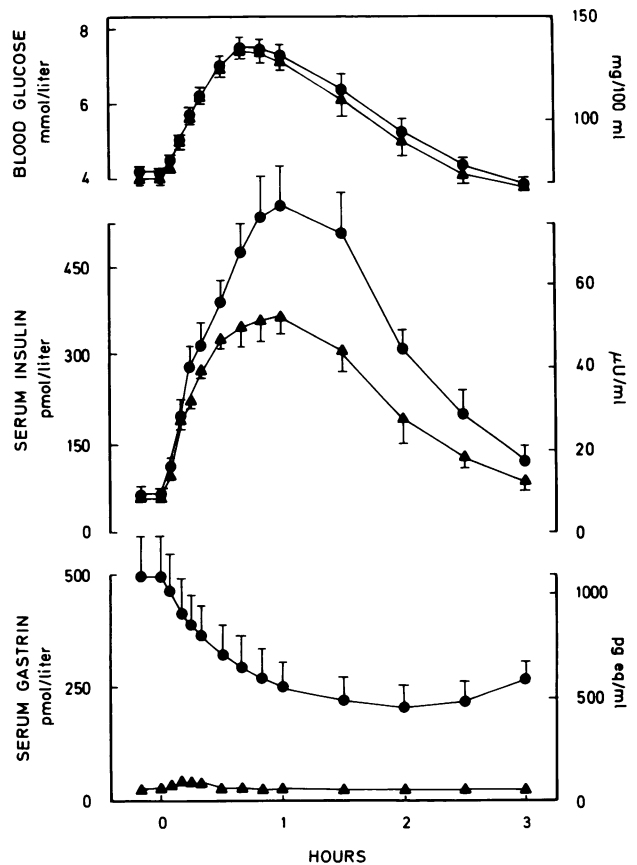


FIGURE 2 Blood glucose, serum insulin, and serum gastrin concentrations in 27 hypergastrinemic PA-patients (group I: ●—●) and in 27 matched controls (▲—▲) during a 50 g oral glucose tolerance test. Mean \pm SEM of concentrations.

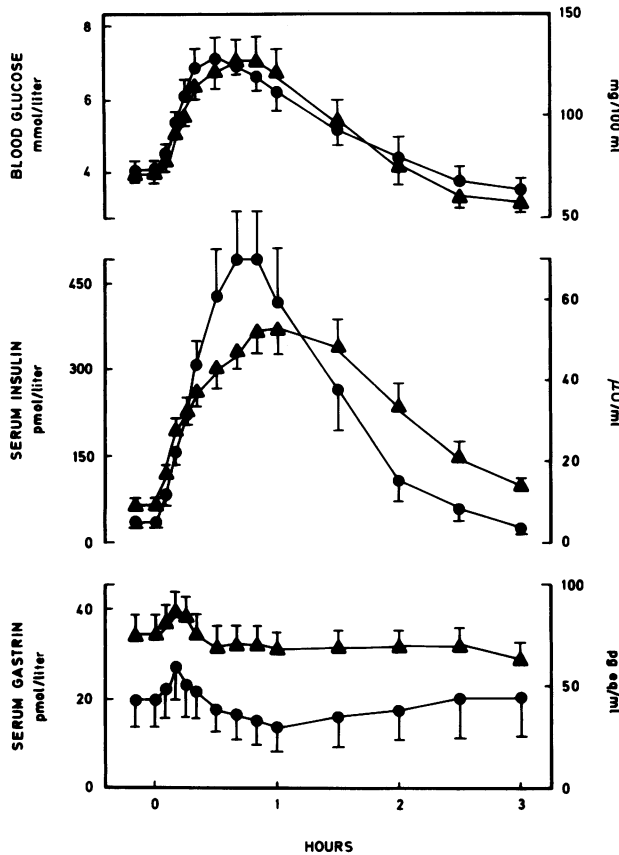


FIGURE 3 Blood glucose, serum insulin, and serum gastrin concentrations in eight hypogastrinemic PA-patients (group II: ●—●) and in eight matched controls (▲—▲) during a 50 g oral glucose tolerance test. Mean±SEM of concentrations.

min. The controls reached peak concentration after 50 min from the same basal level. Serum insulin concentration in the patients in the fasting state was $32 \pm 14 \text{ pmol} \cdot \text{l}^{-1}$, which is below that of controls, $77 \pm 7 \text{ pmol} \cdot \text{l}^{-1}$ ($P < 0.02$). The rise of insulin concentration in patients after oral glucose was higher than normal ($P < 0.05$). After 1 h the insulin concentrations fell below those of the controls ($P < 0.05$), so that the entire insulin response to oral glucose in patients was similar to that of normal subjects (Table I). The gastrin concentrations in the fasting PA-patients were lower than normal ($P < 0.05$). The gastrin concentrations varied as in controls during glucose ingestion, but at a lower level.

Response to intravenous glucose infusion

Group I (Fig. 4 and Table I). Blood glucose curves were almost similar in patients and in controls. The total glucose stimulation in PA was normal although the patients had insignificantly higher glucose concentrations throughout the test. Serum insulin concentra-

tions rose in 30 min in PA's from 65 ± 11 to $228 \pm 24 \text{ pmol} \cdot \text{l}^{-1}$. This peak concentration is above the 30-min concentration in normals of $142 \pm 16 \text{ pmol} \cdot \text{l}^{-1}$ ($P < 0.01$). The insulin response was increased in the patients, most pronounced in the first 30 min after onset of the glucose infusion ($P < 0.05$). The intravenous glucose produced a slight decrease in serum gastrin concentrations in PA-patients, whereas serum gastrin concentrations in controls remained constant.

Group II (Fig. 5 and Table I). Blood glucose curves and concentrations in patients and controls were similar. Serum insulin concentrations in the patients were decreased both in the fasting state ($P < 0.01$), and in response to intravenous glucose being 38% of the normal response ($P < 0.01$). Serum gastrin concentrations in patients were lower than normal throughout the test ($P < 0.01$) and showed no significant variations.

Response to a protein-rich meal

Group III (Fig. 6). Blood glucose concentrations in PA-patients rose from 4.85 ± 0.20 to $6.49 \pm 0.36 \text{ mmol} \cdot \text{l}^{-1}$.

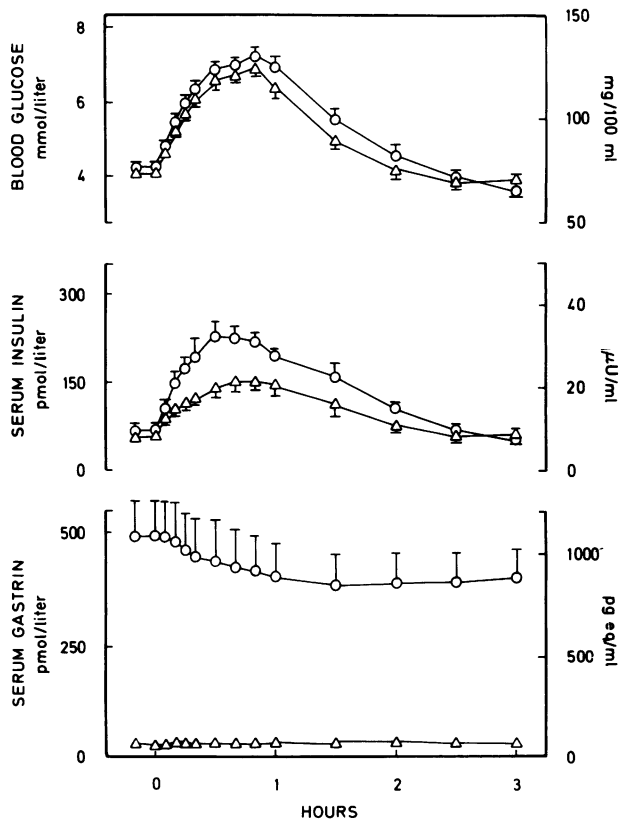


FIGURE 4 Blood glucose, serum insulin, and serum gastrin concentrations in 27 hypergastrinemic PA-patients (group I: ○—○) and in 27 matched controls (△—△) during an intravenous infusion of 16.7 g glucose. Mean±SEM of concentrations.

TABLE I

Integrated Glucose Stimulation (*G*, in mmol/liter × min) and Insulin Response (*I*, in nmol/liter × min) during Oral and Intravenous Glucose Administration in Two Groups of Patients with Pernicious Anemia and in Control Subjects (mean ± SEM)

Interval, minutes	Oral glucose tolerance test, 50 g					Intravenous glucose infusion test, 16.7 g					
	0-30	30-60	60-120	120-180	0-180	0-30	30-60	60-120	120-180	0-180	
PA-group I*	(G)	88 ± 5	139 ± 10	217 ± 26	115 ± 15	559 ± 39	97 ± 6	126 ± 6	167 ± 16	85 ± 8	475 ± 28
	(I)	0.72 ± 0.08	1.54 ± 0.17‡	2.66 ± 0.33‡	1.23 ± 0.16‡	6.12 ± 0.58‡	0.51 ± 0.07‡	0.65 ± 0.07	0.93 ± 0.15	0.40 ± 0.04	2.50 ± 0.30
Control group I	(G)	93 ± 6	145 ± 7	211 ± 29	116 ± 22	565 ± 46	97 ± 8	131 ± 6	166 ± 16	103 ± 16	497 ± 65
	(I)	0.71 ± 0.10	1.10 ± 0.12	1.82 ± 0.23	0.90 ± 0.15	4.53 ± 0.35	0.38 ± 0.05	0.51 ± 0.09	0.72 ± 0.09	0.46 ± 0.13	2.07 ± 0.26
PA-group II‡	(G)	114 ± 4‡	131 ± 9	177 ± 23	105 ± 18	527 ± 39	102 ± 9	129 ± 13	165 ± 17	108 ± 14	504 ± 40
	(I)	0.74 ± 0.08	1.44 ± 0.20‡	1.59 ± 0.30	0.36 ± 0.08‡	4.13 ± 0.55	0.18 ± 0.02‡	0.26 ± 0.04‡	0.28 ± 0.05‡	0.14 ± 0.03‡	0.86 ± 0.12‡
Control group II	(G)	90 ± 9	136 ± 12	195 ± 25	100 ± 17	521 ± 49	101 ± 10	144 ± 12	167 ± 27	109 ± 27	520 ± 65
	(I)	0.63 ± 0.05	0.98 ± 0.07	1.73 ± 0.21	0.87 ± 0.20	4.21 ± 0.45	0.40 ± 0.04	0.58 ± 0.22	0.76 ± 0.10	0.44 ± 0.08	2.19 ± 0.23

* PA patients with hypergastrinemia.
 ‡ Significant difference between PA patients.
 § PA patients without hypergastrinemia.

l⁻¹. The peak concentrations were reached after 45 min. In control subjects blood glucose concentration decreased initially from 4.90 ± 0.15 to 4.72 ± 0.18 mmol · l⁻¹, after which a rise to 5.85 ± 0.39 mmol · l⁻¹ was observed after 45 min. Blood glucose concentrations in PA-pa-

tients were above normal throughout the 90-min period after onset of the meal (*P* < 0.05). Serum insulin concentrations rose in PA-patients from 77 ± 9 to 468 ± 137 pmol · l⁻¹ within 45 min, after which the concentrations were reduced to half the peak value. In control subjects

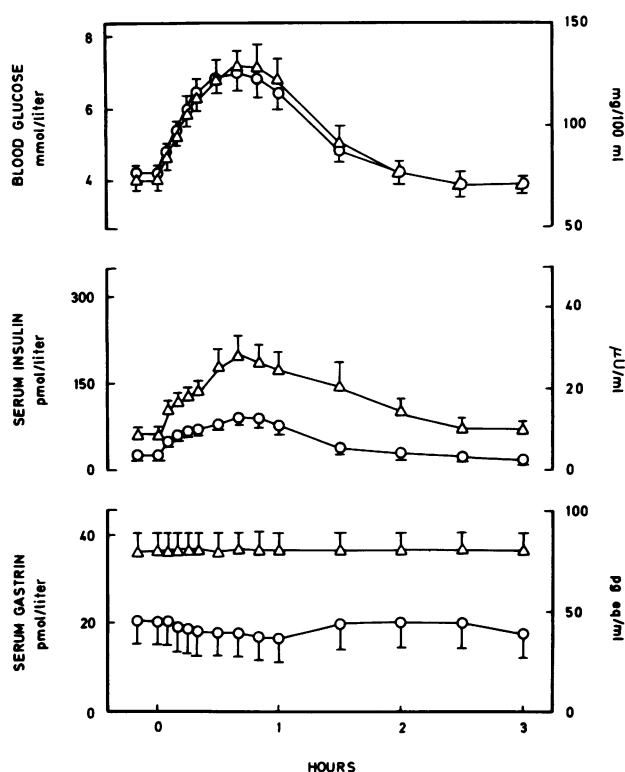


FIGURE 5 Blood glucose, serum insulin, and serum gastrin concentrations in eight hypogastrinemic PA-patients (group III: ○—○) and in eight matched controls (△—△) during an intravenous infusion of 16.7 g glucose. Mean ± SEM of concentrations.

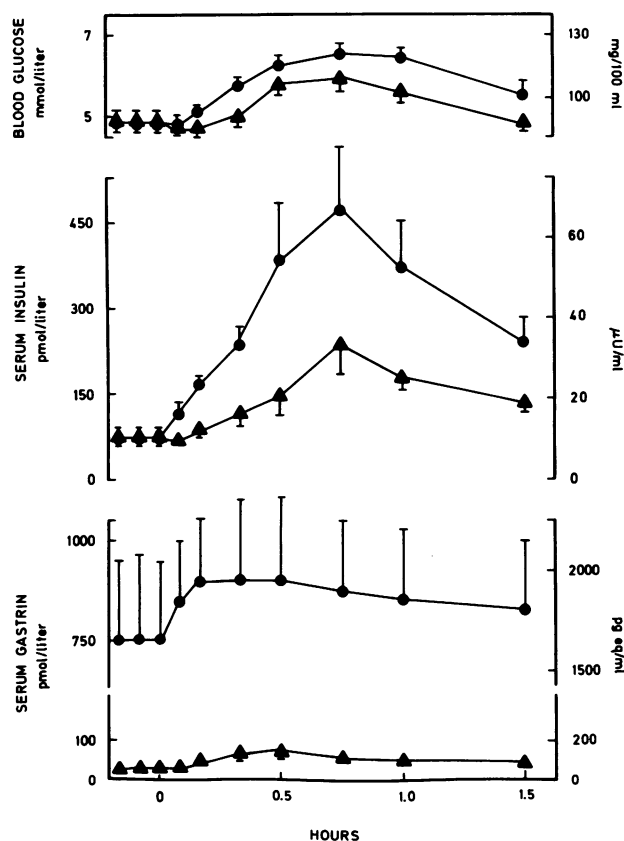


FIGURE 6 Blood glucose, serum insulin, and serum gastrin concentrations in nine hypergastrinemic PA-patients (●—●) and in nine matched control subjects (▲—▲) after a protein-rich meal. Mean ± SEM of concentrations.

the increase was from 82 ± 6 to 234 ± 40 pmol \cdot l $^{-1}$, which is below the peak concentration ($P < 0.02$). Serum gastrin concentrations in the patients rose within 10 min, and remained above basal concentrations throughout the test period. Control subjects responded rapidly to the food.

Response to oral glucose loading combined with intravenous gastrin infusions (Fig. 7)

Blood glucose concentrations were slightly enhanced after gastrin infusion, both in the basal state and during glucose ingestion in comparison to the levels found during the usual oral glucose tolerance test. Basal serum insulin concentrations rose immediately after onset of the gastrin infusion, and remained above control levels throughout the infusion period. Serum gastrin concentrations were doubled during the infusion period.

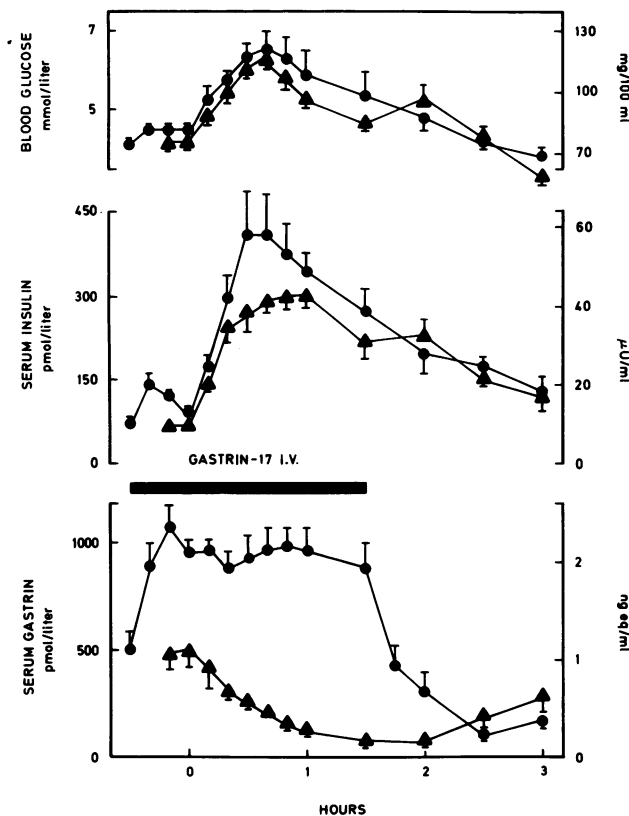


FIGURE 7 Blood glucose, serum insulin, and serum gastrin concentrations in three hypergastrinemic PA-patients during a 50-g oral glucose tolerance test (\blacktriangle — \blacktriangle) and in the same three PA-patients during a 50-g oral glucose tolerance test combined with intravenous infusion of 2 μ g pure natural gastrin-17 (nonsulfated) per kg per hour (\bullet — \bullet). The infusion of gastrin began 0.5 h before glucose ingestion and continued 1.5 h after. Mean \pm SEM of concentrations.

Effect of oral and intravenous glucose administration on gastrin component pattern in serum (Table II)

Comparison of components in the fasting state and at nadir showed unchanged patterns after intravenous glucose infusion. After oral glucose the concentration of all components was reduced.

DISCUSSION

The present study shows that both hyper- and hypogastrinemia are associated with abnormalities in insulin secretion. Moreover it shows that protein-rich food, which maintains enhanced gastrin levels in hypergastrinemia patients, increases blood glucose concentrations above normal in spite of hyperinsulinemia. Combination of these results with the dose-response study in normal subjects (4), and the results of parenteral gastrin-infusion in PA suggest that gastrin may be important in regulation of islet-cell secretion in certain diseases.

Selection of patients with hypergastrinemia. In contrast to other diseases with increased serum gastrin levels achlorhydria is, in the form found in PA, useful for studies on the effect of endogenous hypergastrinemia on islet-cell function because: 1) gastrin in PA, as in normal subjects, is produced mainly by the antrum (28). 2) All evidence available so far indicates that circulating gastrins in normal subjects and PA-patients are qualitatively similar (20, 21, 27). 3) The increased gastrin release in PA is probably caused only by lack of inhibition from gastric acid, and the gastrins in serum are metabolized at a normal rate (29). 4) Zollinger-Ellison patients are unsuited for studies like the present in that gastrinomas often are associated with subclinical neoplasias of alpha- and beta cells (30, 31). Insulin and glucagon secretion in the Zollinger-Ellison syndrome may consequently deviate a priori, and thereby invalidate studies on the insulinogenic effect of gastrin based on gastrinoma patients (32, 33). Anyway, Zollinger-Ellison patients display increased insulin response to glucose and diabetic glucose tolerance (34). 5) Gastrin secretion in duodenal ulcer patients is also abnormally increased, at least during meals (35, 36). Serum levels in these patients and those of food-stimulated normal subjects (37) are, however, placed so much to the left on the dose-response curve (4) that it is difficult to demarcate insulinogenic effects of endogenous gastrins in these conditions. 6) Patients with severe kidney damage are hypergastrinemic, but their general metabolic derangement, including abnormal levels of betacytotoxic hormones other than gastrin, makes them unfit for studies like the present.

Little is known about secretion of hormones with betacytotoxic actions in PA other than gastrin. Secretin levels are apparently normal in PA (29), but the

TABLE II
*Fractions of Gastrin Components during Oral and Intravenous Glucose Administration in Sera
of Five Patients with Pernicious Anemia (mean ± SEM)*

	Oral glucose tolerance test, 50 g				Intravenous glucose infusion test, 16.7 g			
	I	Components		IV	I	Components		IV
		II	III			II	III	
Basal state	0.17 ±0.04	0.59 ±0.02	0.16 ±0.05	0.08 ±0.03	0.14 ±0.04	0.67 ±0.06	0.15 ±0.04	0.04 ±0.02
At nadir	0.17 ±0.01	0.60 ±0.07	0.17 ±0.06	0.06 ±0.02	0.16 ±0.05	0.65 ±0.07	0.17 ±0.05	0.02 ±0.01

secretion of other insulinogenic hormones in achlorhydria awaits further studies. So far there is, however, no reason to expect abnormal release of these hormones.

Insulin secretion and glucose homeostasis in endogenous hypergastrinemia. Gastrin probably has a direct effect on the beta cell, since indirect actions through acid-induced release of duodenal hormones in achlorhydria is precluded. The suggestion that gastrin cannot act directly upon the beta cell (32), because it has failed to stimulate insulin release from isolated islets (38, 39) is dubious, and reflects rather destruction of gastrin receptors during preparation of the isolated islets. The normal basal levels of insulin in fasting PA-patients with hypergastrinemia is in accordance with the observation that gastrin-17 has poor effect on basal insulin secretion, but potentiates the glucose-stimulated insulin release significantly even in moderate doses (4).

Not only were insulin levels raised above normal in hypergastrinemic PA-patients, but blood glucose concentrations were abnormally enhanced when gastrin levels were not suppressed. Since ingestion of protein-rich food is a daily and frequent event, at least in some parts of the world, hyperglycemia in this situation is important. The present study has shown that the food-induced hyperglycemia lasted more than 1.5 h after meals in hypergastrinemic patients, and the patients hence have long periods of abnormal hyperglycemia every day. The normal blood glucose variations during the unphysiological glucose tolerance test in these patients consequently mask their daily hyperglycemia by defining them as normal in respect to glucose tolerance.

There are reasons to believe that the above mentioned hyperglycemia in hypergastrinemia is due to increased gastrin stimulation of α_2 -cells: 1) gastrin stimulates glucagon secretion (40, 41), also in doses which in normal subjects result in serum gastrin concentrations similar to those of the PA-patients in this study.⁸ Moreover in these doses gastrin raises glucose levels significantly

in spite of an immediate insulin release (4). 2) The normal glucose concentrations in PA after glucose ingestion may reflect the fact that glucose administration suppresses glucagon secretion. However, since the insulin response to glucose is increased there is still an abnormal relative hyperglycemia after glucose ingestion, which may suggest that α_2 -cells are not normally suppressed by glucose in hypergastrinemia. This corresponds to the previous observation in normal subjects that addition of even small doses of gastrin to intravenous glucose potentiates the glucose-induced insulin release dramatically without increase of glucose assimilation (4).

Insulin secretion in endogenous hypogastrinemia. Hypogastrinemia in PA is probably caused by progression of atrophic gastritis from the fundic mucosa into the antrum (42, 43). It was unexpected to find hypoinsulinism in these patients. The decrease in insulin concentrations was only significant during the intravenous glucose infusion, which may suggest that a certain basal gastrin level is necessary for a normal beta cell response to glucose. This is further supported by studies on patients with more pronounced hypogastrinemia due to resection of antrum, duodenum, and the proximal jejunum (Whipple's operation). These patients had similarly reduced insulin response to parenteral glucose administration (44). The normal magnitude of the insulin response to oral glucose in hypogastrinemic PA is in accordance with the previously held view (4, 16, 44) that gastrin in normal and low concentrations plays only a small role as enteral insulin-stimulator during glucose ingestion. In contrast gastric inhibitory polypeptide may be responsible for most of the incremental effect after oral glucose (45, 46). Hypoinsulinism in hypogastrinemia may explain why insulin secretion in PA was found normal in one study (47) and increased after oral glucose, but normal after intravenous glucose in another study (48). PA-patients in these investigations were not subdivided according to gastrin levels, since gastrin measurements were not available at that time.

⁸ Holst, J. J., C. Köhl, and J. F. Rehfeld. Manuscript in preparation.

The effect of glucose on serum gastrin components in endogenous hypergastrinemia. Endogenous gastrin circulates in four main components both in normal subjects and hypergastrinemic patients (20, 22, 49). The gastrins are stimulated by protein-rich food (29, 49, 50); but, as shown in hypergastrinemic PA-patients, the concentration of the components is effectively depressed by oral glucose. The suppression is probably to a small extent due to direct inhibition of gastrin release by glucose per se, because intravenous glucose administration lowers the gastrin concentrations slightly (Figs. 4 and 5). The mechanism behind the remaining fall in gastrin concentrations after oral glucose is unknown. A possibility is that gut hormones released by enteral glucose like entero-glucagon and GIP inhibits the secretion of gastrin.

The present study has not disclosed which of the gastrin components is most active and important in the regulation of insulin and glucagon secretion. Further dose-response studies are now needed to decide whether the various gastrins stimulate the endocrine pancreas in a molar ratio similar to their stimulation of gastric acid (26, 51).

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