

Gastrin cell function in familial multiple endocrine neoplasia type I

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SUMMARY Recent studies have suggested that patients with multiple endocrine neoplasia type I (MEN I) may have abnormal serum gastrin secretion in the absence of gastrin producing tumours. G-(gastrin) cell function by three provocation tests in 20 patients with hyperparathyroidism from six MEN I-families were studied: each patient was an obligate carrier of the MEN I-gene. The serum gastrin response to secretin was used to identify the presence of gastrinoma, that to a test meal of G-cell hyperfunction of the antral and/or duodenal mucosa, and that to bombesin to differentiate antral from duodenal G-cell hyperfunction. Seven patients had basal hypergastrinaemia and hyperchlorhydria. These patients had increased serum gastrin responses to secretin ($p < 0.01$) and to bombesin ($p < 0.02$), but normal postprandial responses. In the 13 normogastrinaemic patients the responses to the three stimuli were normal. In families with MEN-I gastrinoma is the only endocrine disorder accounting for abnormal gastrin secretion. G-cell function is normal in obligate carriers of the MEN I-gene.

Multiple endocrine neoplasia type I (MEN-I) is an autosomal dominant inherited disorder characterised principally by tumours of the parathyroid glands, the pituitary, and the pancreatic islets.¹⁻⁴ Less common are tumours of the adrenal cortex and various types of carcinoids. An individual carrying the MEN-I gene may have one or any combination of these tumours. In such patients hypergastrinaemia is usually caused by gastrin producing tumours leading to marked gastric hypersecretion and severe ulcer, the Zollinger-Ellison syndrome.²⁻⁶ Other abnormalities of gastrin secretion have recently been described, however, in patients with the MEN I-syndrome without gastrin producing tumours. Such patients showed an enlarged serum gastrin response to a standard test meal suggesting hyperplasia or hyperfunction of antroduodenal G-(gastrin) cells.⁷ In this respect it is interesting to note that Friesen *et al* have described hyperplasia of G-cells in the antral mucosa of members of MEN I-families in association with the development of clinical endocrinopathies.^{8,9} This

finding may indicate that hypergastrinaemia of antral origin could be a distinct phenotypic manifestation of the MEN I-gene. Furthermore, antral G-cell hyperplasia and raised serum gastrin concentrations have been described in hyperparathyroidism,¹⁰⁻¹³ while antral G-cell hyperplasia has also been reported in patients with acromegaly,¹⁰ disorders that can be components of the MEN I syndrome.

The present study was undertaken to characterise G-cell function in patients who were obligate carriers of the MEN I-gene, as determined by their being members of families with well characterised MEN-I and also having evidence of hyperparathyroidism.

Methods

PATIENTS

The subjects consisted of 20 patients with hyperparathyroidism originating from six families with MEN I. Family members who had undergone prior gastric surgery were excluded from this study. The patients and families were ascertained in a population genetic study of 10 Zollinger-Ellison patients (for the complete pedigrees, see ref 6). In that study a total of 109 family members, including all living first

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Received for publication 9 May 1988.

Table Serum gastrin responses to secretin, bombesin and feeding in 20 hyperparathyroid patients from MEN I-families

		Sex	Age (yr)	Serum calcium (mmol/l)	Basal gastrin (pg/ml)	Δ Gastrin after secretin (pg/ml)	Δ Gastrin after bombesin (pg/ml)	Δ Gastrin after feeding (pg/ml)	Basal acid output (mmol/hr)
Patients	1	M	45	2.69	243–530	288	550	99	19.2
	2	M	45	2.80	595–1180	705	160	55	71.0
	3	F	33	2.30*	340–1050	1100	120	220	43.5
	4	F	32	2.66	380–550	830	240	52	90.8
	5	F	55	3.17*	142–260	298	70	62	15.0
	6	F	52	2.82*	250–300	360	145	145	25.4
	7	F	48	2.95	340–435	300	77	180	15.1
	8	F	68	2.77	35–63	12	52	75	–
	9	M	59	2.78	73–82	11	–	387	–
	10	F	30	2.90	28–51	14	61	77	–
	11	M	30	2.98	42–56	14	62	24	–
	12	F	34	2.68	23–53	0	76	71	–
	13	M	31	2.81	38–51	10	62	97	–
	14	M	24	2.75	24–41	28	96	155	–
	15	M	20	2.68	24–34	6	69	26	–
	16	F	48	2.58*	66	42	–	–	–
	17	M	38	2.74	39–79	41	129	45	1.0
	18	M	29	3.00	32–45	7	29	46	–
	19	F	57	2.84*	44–50	101	135	126	0
	20	M	22	2.86	26–47	0	62	60	–
normal controls	21–40	11M–9F	20–64	2.20–2.55	23–84	0–43	42–209	32–158	–

*previous parathyroid surgery.

degree relatives over 15 years of age, were screened for endocrine abnormalities. All six patients with evidence of MEN I were found to have relatives with endocrinopathies, while no endocrine abnormalities were found among family members of four patients with isolated Zollinger-Ellison syndrome.⁶ There were 10 men and 10 women, ranging in age between 20 and 68 (Table). Five had been operated on for hyperparathyroidism, and three had recurrent hypercalcaemia. Two had coexisting pituitary tumours documented by sellar radiography and increased serum prolactin (cases 1 and 17), and one had been operated on for insulinoma (case 3). A diagnosis of ulcer disease had been established in two patients (cases 3 and 4), epigastric pain without documented ulcers occurred in an additional six (cases 1, 5, 6, 7, 17, 19) and chronic diarrhoea in five (cases 1, 2, 3, 4, 6). Gastric acid secretion was measured in all nine subjects with gastrointestinal complaints (Table). Gastrin cell function was evaluated in the 20 hyperparathyroid members of MEN I families and a control group of 20 healthy subjects by the following studies: (1) repeated measurements of basal serum gastrin concentrations, (2) secretin stimulated serum gastrin as a means of identifying gastrinomas,^{14–16} (3) meal stimulation serum gastrin as an index of the G-cell function of the antroduodenal mucosa,^{17,18} and (4) bombesin stimulated serum gastrin as an index of the antral G-cell function.^{19–21}

Serum gastrin was measured by radioimmunoassay

as described previously.^{16,17,20} Secretin, 1 CU/kg body weight (Karolinska Institute, Stockholm, Sweden), was administered as a slow bolus injection to determine its effect on serum gastrin concentrations.^{15,16} Blood samples were drawn at –5, 0, 5, 10, and 15 minutes. For the meal stimulation test of serum gastrin, patients ingested a standard test meal consisting of one slice of bread, 50 g cheese, one boiled egg, and 200 ml milk (30 g protein, 25 g carbohydrate, and 20 g fat). Blood was drawn –5, 0, 15, 30, 45, 60, 90, and 120 minutes. Bombesin-14 (Boehringer Mannheim Biochemicals, Indianapolis, Indiana, USA), 100 ng/kg body weight, was infused over 20 minutes. Blood was drawn at –5, 0, 5, 10, 15, 20, and 30 minutes. Serum calcium was measured by atomic absorption spectrophotometry. Statistical analyses were performed by Wilcoxon's rank-sum test. The study was done in accordance with the declarations of Helsinki and Tokyo, and informed consent was obtained from all patients.

Results

Seven of the 20 patients, five women, had basal hypergastrinaemia on all three occasions (cases 1–7 in the Table). There were no significant differences between the hypergastrinaemic and normogastrinaemic patients in age (44 (9) v 38 (15) years, mean (SD)) or serum calcium (2.77 (0.27) v 2.80 (0.12) mmol/l). One hypergastrinaemic patient (case

3) was normocalcaemic at the time of study due to prior parathyroid surgery. The serum gastrin response to secretin was significantly greater ($p < 0.01$) in the patients with basal hypergastrinaemia than in those who were normogastrinaemic (Figs 1, 2). The increment above basal was greater than 200 pg/ml in all seven hypergastrinaemic patients and there was no overlap with the subjects who had normal basal serum gastrin concentrations. The serum gastrin response to secretin in the 13 normogastrinaemic patients was no different from that in the normal control subjects. Among these normogastrinaemic patients, two did not have any increase in serum gastrin after secretin, 10 had a modest increase in gastrin, and one (case 19) had a relatively large increase of 101 pg/ml, corresponding to 230% of basal value. Gastric acid secretion, however, was normal in this patient (BAO 0 mmol/h, MAO 24.0 mmol/h) and CT-scan of the

abdomen did not reveal tumours. Serum gastrin concentrations rose in response to the test meal in all 19 subjects studied (Figs 1, 2). There was no significant difference between the hyper and normogastrinaemic patients in the absolute postprandial rise in gastrin and the normal control group (Fig. 1). When expressed as percentage change over basal, the patients with basal hypergastrinaemia had a significantly ($p < 0.01$) lower increase (Fig. 2), but there was considerable overlap between the groups. Case 9 is of particular interest because of the markedly exaggerated serum gastrin response to feeding (Table). Bombesin infusion induced an increase in serum gastrin in all patients studied. The mean increase was significantly greater ($p < 0.02$) in the hypergastrinaemic patients (Fig. 1), but when the results were expressed as percentage of basal, the hypergastrinaemic patients had a significantly lower ($p < 0.01$) percentage increment in serum gastrin after bombesin (Fig. 2).

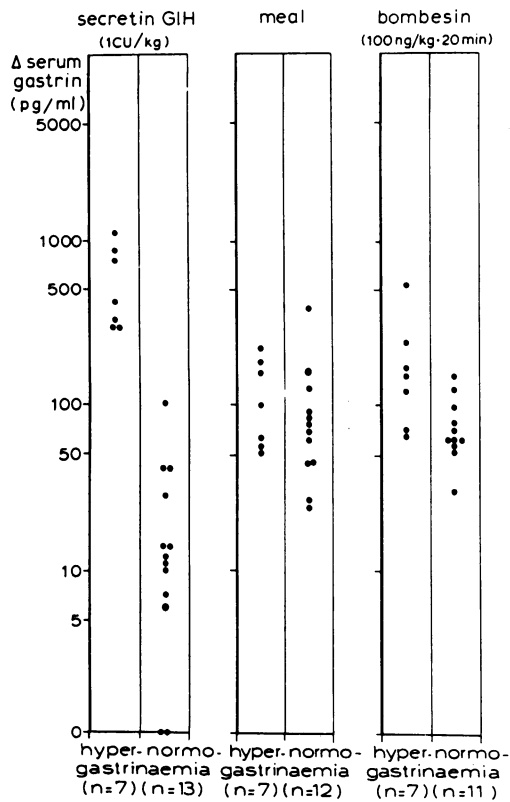


Fig. 1 Serum gastrin responses to secretin, meal and bombesin in hypergastrinaemic and normogastrinaemic patients with hyperparathyroidism from families with multiple endocrine neoplasia type I. The results are depicted on a logarithmic scale.

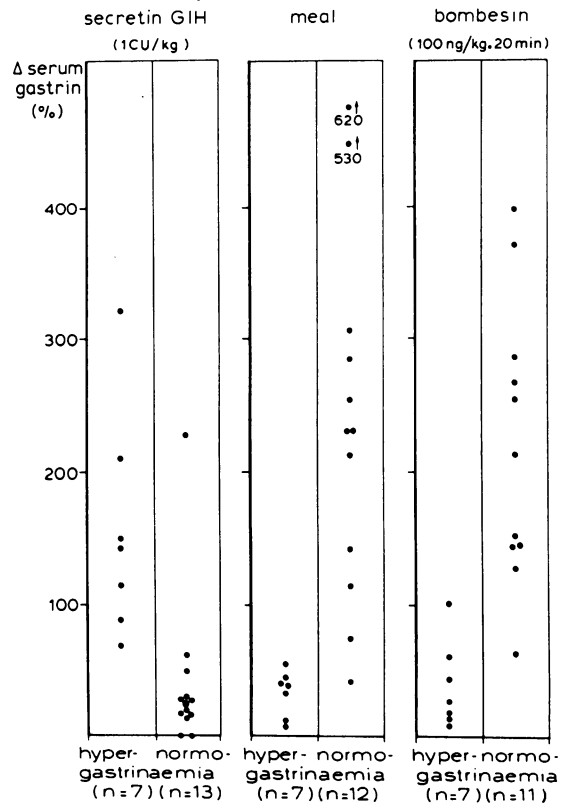


Fig. 2 Serum gastrin responses to secretin, meal or bombesin, expressed as percentage increases over basal value, in hypergastrinaemic and normogastrinaemic patients with hyperparathyroidism from families with multiple endocrine neoplasia type I.

Discussion

This is the first report in which G-cell function was evaluated in MEN I-patients by comparing serum gastrin responses to three different stimuli – that is, secretin, food and bombesin. Measurement of serum gastrin is of great importance in patients from MEN I-families, because hyperparathyroidism, present in about 90% of MEN I-patients, has been reported to be associated with peptic ulcer disease.^{11 22 23}

The results of this study indicate that in obligate carriers of the MEN I-gene the measurement of basal serum gastrin concentrations is an excellent discriminant between the patients with and without gastrin producing tumours. In seven of the individuals serum gastrin was raised on all three occasions, whereas in the other 13 patients serum gastrin was repeatedly normal. It can be argued that the presence of gastrinomas has not been histologically proven in all seven hypergastrinaemic patients, and that a pancreatic tumour has not definitely been ruled out in the other 13 patients. There was no clinical indication, however, for undertaking laparotomy in these patients. First, because the hypergastrinaemic patients were effectively treated with histamine H₂-receptor antagonists (cimetidine or ranitidine) or omeprazole, obviating the need for total gastrectomy,^{24 25} and, second, because it is generally accepted that, because of multiplicity of tumours, attempts to curatively resect the gastrin producing tumours in MEN I-patients are unsuccessful.^{26 27} Furthermore, all hypergastrinaemic patients had markedly increased basal gastric acid secretion, whereas such hypersecretion of gastric acid was excluded in the two normogastrinaemic patients with gastric complaints. The results of this study, showing normal basal serum gastrin concentrations in hyperparathyroid patients without gastrin producing tumours, contrast with two recent reports indicating basal hypergastrinaemia in 22 and 25% of such patients.^{12 13} This discrepancy is not because of the characteristics of the gastrin assay used in this study, as it has been shown that the gastrin antiserum used has equal binding to all known sulphated and non-sulphated carboxy-terminal forms of gastrin.¹⁶ Furthermore, the discrepancy is not due to the fact that in our study only patients with MEN I-hyperparathyroidism were investigated, as we have previously reported normal serum gastrin concentrations in patients with non-MEN I-hyperparathyroidism and in those with non-hyperparathyroid hypercalcaemia.²⁸

The serum gastrin increment after secretin was above 200 pg/ml in all hypergastrinaemic MEN I-patients, but the response was modest in all but one of the normogastrinaemic patients. In the latter

patient, however (case 19) with an increment of 101 pg/ml there was not gastric hypersecretion or CT-evidence of pancreatic tumours, and serum gastrin concentrations remained normal during a follow up of more than three years. Therefore, this study confirms previous reports indicating that an exaggerated serum gastrin response to secretin is highly specific for gastrin producing tumours in MEN I-patients with combined basal hypergastrinaemia and hyperchlorhydria.^{15 16} In this respect, it is noteworthy that in patients with gastrinoma the serum gastrin response to secretin is influenced by the serum calcium concentration.^{29 30} In fact, acute hypercalcaemia enhances, while acute hypocalcaemia reduces the serum gastrin secretion after secretin provocation in patients with Zollinger-Ellison syndrome.²⁹ On the other hand hypercalcaemia induced by infusion of calcium, did not induce false positive secretin provocation tests in peptic ulcer patients without gastrinoma.²⁹ Furthermore, normalisation of serum calcium by parathyroidectomy in MEN I-patients with combined hyperparathyroidism and Zollinger-Ellison syndrome diminished secretin induced serum gastrin secretion.³⁰ Another interesting finding of the present study is that the absolute amount of gastrin released from the antroduodenal mucosa after a meal is normal in MEN I-patients independent of the presence of hyper- or normogastrinaemia. This is remarkable because a reduced gastrin secretion would have been anticipated in the presence of gastric hypersecretion in the patients with gastrinomas. This finding may indicate an impaired feedback mechanism between gastric acid and antral gastrin secretion in such patients. Skogseid *et al*⁷ have studied the serum gastrin response to feeding in a single MEN I-patient with basal hypergastrinaemia, but the large variation in postprandial serum gastrin concentrations precluded a definite conclusion. The present finding of normal postprandial gastrin secretion in the normogastrinemic MEN I-patients is in contrast with the aforementioned study of Skogseid *et al*,⁷ showing an enlarged serum gastrin response to feeding in such patients. Analysis of the data, however, shows that in the latter study exaggerated postprandial serum gastrin secretion occurred in only five of the 12 patients studied and that the mean basal serum gastrin concentration in the 'normogastrinaemic' MEN I-patients was significantly higher than in the control group. In this respect it may be interesting to note that the single normogastrinaemic patient with an enlarged postprandial serum gastrin response in the present study (case 9) had a relatively high basal serum gastrin concentration when compared with the other normogastrinaemic patients. In this patient achlorhydria was excluded as the cause of the increased post-

prandial gastrin secretion by the finding of a slightly raised serum pepsinogen I level of 126 ng/ml. Skogseid *et al*⁷ suggested that the exaggerated serum gastrin response to the meal in normogastrinaemic MEN I-patients was caused by islet-cell hyperplasia of the pancreas. Because the serum gastrin response to feeding is accepted to be a reliable measure of the G-cell function of the antroduodenal mucosa, however, antral G-cell hyperfunction is a more likely explanation.^{17,18} Antral G-cell hyperplasia has been described by Friesen in a family with the MEN I-syndrome, but this author did not report whether the antral G-cell hyperplasia in antral biopsies was accompanied by an exaggerated postprandial serum gastrin secretion.^{8,9} This hyperplasia appears to be restricted to certain families and surprisingly appears to occur in both affected and otherwise unaffected members.^{8,9} It should, however, be realised that the diagnosis of antral G-cell hyperplasia, established by G-cell counting of these cells in antral mucosal biopsies, may not accurately reflect overall G-cell function because of the variable size of the antrum and patchy distribution of G-cells.¹⁷ Antral G-cell hyperplasia has also been described in hyperparathyroidism,¹⁰ but Skogseid *et al*⁷ found a normal postprandial serum gastrin secretion in four hyperparathyroidism who had no evidence of the MEN I-syndrome. The present study, however, clearly indicates that antral G-cell hyperfunction is not a frequent manifestation of the MEN I-syndrome and thus that neither the MEN I-syndrome *per se* nor the hypercalcaemia of hyperparathyroidism affects the G-cell function. This finding was supported by the absence of an increased serum gastrin response to infusion of bombesin in the normogastrinaemic MEN I-patients. Because bombesin is reported to release gastrin selectively from the antral and not from the duodenal mucosa,¹⁹ it is suggested to be a more specific stimulus of gastrin secretion by the antral G-cells than a meal. In fact, it has been shown that the serum gastrin response to bombesin can be used to accurately identify hyperfunction and hypofunction of antral G-cells.²¹ The present study, however, indicates that an enlarged serum gastrin response to bombesin is not specific for antral G-cell hyperfunction but also occurs in patients with gastrin producing tumours. It has recently been shown that the gastrin secretion induced by bombesin in patients with gastrinoma is probably because of a direct stimulation of gastrin secretion from the tumour, as bombesin increases gastrin release from gastrinoma cells in longterm culture.³¹

In conclusion, the main findings of the present study were as follows: (i) gastrinoma was the only endocrine disorder in MEN I accounting for abnormal gastrin secretion, (ii) repeated measure-

ments of basal serum gastrin could readily identify patients with gastrinoma in MEN I-families, provided that achlorhydria had been excluded, (iii) antral G-cell hyperfunction was not a frequent manifestation of the MEN I-syndrome, and (iv) bombesin was not a specific stimulus of antral gastrin secretion but also released gastrin from tumours in hypergastrinaemic MEN I-patients.

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