Increased sensitivity of gastrin release to adrenaline in duodenal ulcer¹

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SUMMARY Serum gastrin concentrations were measured in patients with duodenal ulcer and controls before, during, and after one-hour intravenous infusion of various doses of adrenaline (0.12 µg to 6 µg/min). Gastrin concentrations in the basal state were significantly increased in duodenal ulcer patients compared to controls. The maximal rise in serum gastrin concentrations was obtained at a dose of 4 µg/min adrenaline in both groups of subjects, and the increase was significantly higher in duodenal ulcer patients than in controls. Adrenaline increased predominantly the gastrin III component (gastrin-17 like) in both duodenal ulcer patients and controls. The threshold level of adrenaline-induced gastrin release was significantly lower in duodenal ulcer patients: intravenous infusion of adrenaline in a dose of 0.12 µg and 0.25 µg/min increased serum gastrin concentrations 23 and 43%, respectively, but had no effect in controls. Rises in plasma adrenaline concentrations were similar in both groups of subjects in response to the various doses of adrenaline employed. Only the smallest dose of adrenaline (0.12 µg/min) resulted in clearly physiological variations in plasma adrenaline concentrations. The results indicate that endogenous adrenaline may stimulate the secretion of gastrin during physiological conditions in patients with duodenal ulcer.

Adrenaline stimulates the secretion of gastrin in man and is at least partially responsible for the rise in serum gastrin concentrations during hypoglycaemia (Hayes *et al.*, 1972; Stadil and Rehfeld, 1973; Kronborg *et al.*, 1974; Brandsborg *et al.*, 1975; Kaess *et al.*, 1975).

Previous studies have demonstrated a relationship between plasma adrenaline and serum gastrin concentrations during hypoglycaemia as well as between intravenous infusion of adrenaline and rise in serum gastrin (Stadil and Rehfeld, 1973; Brandsborg *et al.*, 1975; Christensen and Stadil, 1976). However, the threshold level for plasma adrenaline-stimulated gastrin release has not been elucidated and may be reduced in patients with duodenal ulcer. We have previously observed that a fixed dose of isoprenaline resulted in much greater serum gastrin concentrations in patients with duodenal ulcer than

in control subjects (Brandsborg *et al.*, 1976).

The present study concerns the interrelationship between intravenous infusion of adrenaline, plasma adrenaline concentration, and serum gastrin in patients with duodenal ulcer and controls.

Methods

SUBJECTS AND PROCEDURE

Twenty-one normal male subjects (mean age 34 years, range 25-47 years) and 19 male patients (mean age 38 years, range 26-51 years) with radiologically verified non-obstructing duodenal ulcer participated in 35 and 40 infusion experiments, respectively. An informed consent to the procedure was obtained from all subjects examined.

The study was performed in the morning with subjects resting in the supine position after an overnight fast. Adrenaline was infused intravenously for one hour in both groups of subjects in the following doses: 0.25 µg/min, 1 µg/min, 2 µg/min, 4 µg/min, and 6 µg/min. A dose of 0.12 µg/min for one hour was given to the duodenal ulcer patients only. Each dose of adrenaline was given to six to

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eight duodenal ulcer patients and six to eight controls. For practical reasons it was not possible to give each dose of adrenaline to each individual subject. Twenty-two subjects participated in one experiment, while eight, six, two, and each of two subjects participated in two, three, four, five, and six different infusion experiments, respectively. The subjects who participated in more than one experiment were given each dose of adrenaline on different days and in a randomised order.

Adrenaline was infused into an antecubital vein. Venous blood was collected through a catheter in the opposite arm. Blood for measurement of serum gastrin concentrations was collected in the basal state (two samples) and at 10, 20, 30, 45, and 60 minutes during the infusion and 15 and 30 minutes after the infusion was stopped.

Blood for measurement of plasma noradrenaline and adrenaline was collected before and at the end of the infusion period from two duodenal ulcer patients and two controls at each dose of adrenaline employed.

TECHNIQUES

Serum gastrin concentrations were measured by radioimmunoassay using two different antisera. The gastrin antiserum (4562) (Rehfeld *et al.*, 1972) reacted on a molar base equally well with components I, II (gastrin-34 like) and III (gastrin-17 like) (Rehfeld, 1976). Monoiodinated gastrin-17 was used as tracer (Stadil and Rehfeld, 1972). The serum gastrin component III (gastrin-17 like) was determined by an antiserum (Dockray and Taylor, 1976) (L6) specific for gastrin-17 (a generous gift from G. Dockray, Liverpool). Plasma noradrenaline and

adrenaline were determined by double-isotope derivative assay (Engelman and Portnoy, 1970; Christensen, 1973).

Wilcoxon test for two samples and for pair differences was used for the statistical analysis (Geigy J. R., 1962). Regression analysis was performed according to the method of Bailey (Bailey, 1959).

Results

The basal serum gastrin concentrations were significantly greater in duodenal ulcer patients than in controls (median 50 (range 29 to 142) and median 24 (range 12 to 51) pg/ml, respectively, $2P < 0.01$).

Figure 1 shows serum gastrin concentrations in individual patients and controls before, during and after intravenous infusion of adrenaline in a dose of $2 \mu\text{g}/\text{min}$ for one hour. Serum gastrin was increased at 10 minutes after start of the infusion and returned rapidly to basal concentrations after the infusion was stopped. Rise in serum gastrin was related to basal serum gastrin concentration in duodenal ulcer patients during adrenaline infusion (0.12, 0.25 and $1 \mu\text{g}/\text{min}$, $2P < 0.05$ to 0.001).

Figure 2 shows mean rise in serum gastrin concentration in response to the different infusion doses of adrenaline employed. Results are expressed either in absolute values or expressed as percentage of basal values.

Intravenous infusion of adrenaline increased serum gastrin concentrations in duodenal ulcer patients at all levels of stimulation ($2P < 0.05$ to 0.01). The greatest response was obtained at $4 \mu\text{g}/\text{min}$. Adrenaline in a dose of $0.25 \mu\text{g}/\text{min}$ had no effect

Fig. 1 Serum gastrin (pg/ml) in individual patients and controls before, during and after intravenous infusion of adrenaline in a dose of $2 \mu\text{g}/\text{min}$ for one hour. Left: duodenal ulcer patients. Right: controls.

Fig. 2 Mean rise in serum gastrin (pg/ml) in patients (open columns) and controls (closed columns) in response to the different doses of adrenaline employed. Left: absolute values. Right: expressed as percentage of basal values. *Mean value significantly different from zero.

on serum gastrin in normal subjects while subsequent higher doses increased serum gastrin significantly ($2P < 0.05$ to 0.02).

Rise in serum gastrin concentrations was significantly greater in duodenal ulcer patients than in controls at all doses of adrenaline employed ($2P < 0.05$ to 0.01). Expressed as a percentage of basal values rise in serum gastrin was significantly higher in patients than in controls at an infusion dose of 0.25 and 1 µg/min adrenaline. ($2P < 0.02$ to 0.01) but not at 2 , 4 , and 6 µg/min. There was some variation in the gastrin response among different subjects at the same intravenous dose of adrenaline. The shape of the dose-response curve in two subjects who participated in several different experiments approximated to a straight line over the range 0.25 to 4 µg/min (Fig. 3).

Fig. 3 The relationship between intravenous infusion dose of adrenaline (abscissa) and rise in serum gastrin (pg/ml) above basal values in two patients who participated in several different experiments.

The Table shows the concentrations of component III and total gastrin in serum in two duodenal ulcer patients and three controls in response to adrenaline in a dose of 2 or 4 µg/min. The gastrin component III increased in all subjects.

Mean basal plasma noradrenaline concentrations were significantly higher in duodenal ulcer patients than in controls (0.26 and 0.16 ng/ml, respectively, $2P < 0.01$), while plasma adrenaline concentrations were similar (0.03 and 0.04 ng/ml, respectively). At the end of the infusion plasma noradrenaline averaged 0.38 ng/ml in the patients and 0.18 ng/ml in the controls ($2P < 0.02$).

Figure 4 shows the rise in plasma adrenaline concentrations at the end of the infusion periods. Each symbol is the mean of two values obtained in two different subjects at each dose of adrenaline employed. The dose-response curves are very similar in patients and controls.

Discussion

The present study shows, in agreement with our previous findings (Brandsborg *et al.*, 1976; Brandsborg *et al.*, in press), that serum gastrin and plasma noradrenaline concentrations are increased and plasma adrenaline is the same in patients with duodenal ulcer compared to normal subjects. We have previously shown (Brandsborg *et al.*, 1976) that intravenous infusion of isoprenaline, a beta-adrenergic agonist, in a dose of 2 µg/min resulted in greater serum gastrin concentrations in patients with duodenal ulcer than in normal subjects. This finding has now been extended to adrenaline, which in all doses employed resulted in a greater rise in serum gastrin concentrations in patients with duodenal

Table G-17 and total gastrin concentrations (pg/ml) in serum obtained in three normal subjects and two patients with duodenal ulcer before, during, and after a 60 minute period infusion of adrenaline

No.		Basal		Adrenaline infusion (2-4 µg/min)						Rise in per cent of basal	Post infusion	
		- 15	0	10	20	30	45	60	75		90	
		(min)		(min)							(min)	
Normal subjects												
1	G-17	23	17	37	42	52	40	46	115		25	19
	Total	32	35	40	58	60	57	40	50		37	35
	difference*	9	18	3	16	8	17	- 6	- 42		12	16
2	G-17		33	55	73	71	84	85	124		42	45
	Total		54	75	90	98	108	97	74		68	48
	difference		21	20	17	27	24	12	- 5		26	3
3	G-17	15	20	18	26	21	23	26	28		23	17
	Total	25	27	30	35	43	40	43	46		35	37
	difference	10	7	12	9	22	17	17	67		12	20
Patients with duodenal ulcer												
1	G-17	26	25	73	123	137	95	113	315		51	13
	Total	75	70	172	225	243	264	238	212		93	73
	difference	49	45	99	102	106	169	125	155		42	60
2	G-17	65	91	157	137	121	119	108	64		40	40
	Total	182	230	305	318	315	284	265	44		148	120
	difference	117	139	148	181	194	165	157	32		108	80

*Mainly gastrin component II.

Fig. 4 The relationship between intravenous infusion dose of adrenaline (abscissa) and rise in plasma adrenaline (ng/ml) above basal values (ordinate). Each symbol is the mean of two values obtained in two different subjects at each dose of adrenaline employed. (○) controls, (●) duodenal ulcer patients.

ulcer than in controls. The most important observation is, however, that the threshold level for adrenaline-stimulated gastrin release is considerably decreased in duodenal ulcer patients. The higher serum gastrin concentrations in the patients was not due to higher plasma adrenaline concentrations during intravenous adrenaline infusions, because similar concentrations were obtained in both groups of subjects in response to the various doses of adrenaline employed.

The gastrin component III in serum was determined only in a limited number of subjects. These

data suggest that adrenaline increased predominantly the component III in both patients and controls.

In normal subjects intravenous infusion of adrenaline in a dose of 1 µg/min increased serum gastrin concentrations 17% over basal values and plasma adrenaline 0.15 ng/ml, while the lower dose of 0.25 µg/min adrenaline had no effect on serum gastrin concentrations. This indicates that plasma adrenaline is unlikely to be an important regulator of gastrin secretion in normal subjects during physiological conditions except during prolonged exercise, which may increase plasma adrenaline 10-fold (Galbo *et al.*, 1976). However, our data are entirely compatible with a number of previous observations indicating that the rise in plasma adrenaline concentrations during hypoglycaemia from 0.04 ng/ml to approximately 1.00 ng/ml is responsible for the concomitant rise in serum gastrin (Hayes *et al.*, 1972; Stadil and Rehfeld, 1973; Kronborg *et al.*, 1974; Brandsborg *et al.*, 1975; Kaess *et al.*, 1975).

The situation is different in patients with duodenal ulcer. The eight-fold lower dose of adrenaline (0.12 µg/min) raised serum gastrin concentrations 23% and plasma adrenaline 0.04 ng/ml. A change as small as this in plasma adrenaline occurs in response to standing, smoking, and mild exercise, which may double plasma adrenaline concentration (Christensen and Brandsborg, 1973; Christensen and Brandsborg, 1976; Brandsborg *et al.*, in press; Brandsborg *et al.*, submitted). Studies in our laboratory have shown that smoking and exercise of moderate intensity and duration increase serum

gastrin concentrations in duodenal ulcer patients, probably because of a rise in plasma adrenaline (Brandsborg *et al.*, submitted). Adrenaline secretion may therefore influence the secretion of gastrin during physiological conditions in patients with duodenal ulcer.

The cause of the increased sensitivity of gastrin cells to adrenaline in patients with duodenal ulcer remains unexplained. It is unlikely to be due to a specific abnormality of the beta-adrenergic receptors. There is no generalised increased responsiveness to beta-adrenergic stimulation—for example, insulin secretion and pulse rate—in duodenal ulcer patients (Brandsborg *et al.*, 1976). Furthermore, meal-stimulated gastrin secretion is also considerably increased in duodenal ulcer patients and propranolol has no effect on meal-stimulated gastrin secretion in a dose which completely inhibits isoprenaline-stimulated gastrin secretion (Brandsborg *et al.*, 1976). G-cell hyperplasia may, if it exists in duodenal ulcer patients (Creutzfeldt *et al.*, 1976), explain the higher maximal response of serum gastrin to adrenaline. However, such a mechanism is unlikely to be responsible for the decreased threshold level of gastrin release to adrenaline stimulation.

The increased adrenaline sensitivity is probably secondary to an abnormality of the gastrin producing cells, either in the secretory apparatus or due to defective inhibitory secretory processes.

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