

Pepsin 1 secretion in chronic peptic ulceration

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SUMMARY In patients with peptic ulceration, both vagal stimulation by insulin hypoglycaemia and stimulation by pentagastrin cause pepsin 1 to be secreted into gastric juice. There is a secretory threshold for pepsin 1, below which only pepsins 3 and 5 are secreted. Pepsin 1 accounts for an increasing proportion of the total peptic activity/ml of gastric juice as the total activity increases. Higher concentrations of pepsin 1 in the basal gastric secretion occurred significantly more frequently in patients with duodenal ulcer than with gastric ulcer. In these patients there may be an increased 'background' secretory drive.

On agar gel electrophoresis of normal human gastric juice at pH 5.0, up to eight zones of proteolytic activity may be recognised, at least five of which represent unique pepsins.¹ Using the nomenclature suggested by these authors,² the pepsins are numbered 1, 2, 3a, 3, and 5 in order of electrophoretic mobility to the anode with reference to a porcine pepsin marker. Pepsin 3 is always the most abundant of the pepsins present, usually followed by pepsin 5. The proportional contribution made by pepsin 1 to the total peptic activity is variable.

Taylor³ found that in response to histamine, patients with chronic peptic ulceration secreted pepsin 1 significantly more often and in greater quantity than did control subjects. Vagally stimulated gastric secretions were not studied. In the cat, prolonged electrical stimulation of the vagi results in the secretion of increasing amounts of the most electronegative pepsin, 'cat pepsin 1'.⁴ This observation prompted further study of pepsin 1 secretion by patients with chronic peptic ulceration, both in response to vagal stimulation by insulin hypoglycaemia and to pentagastrin.

Methods

PATIENTS

Thirty-three patients were studied who were under the care of Dr J H Baron (Hammersmith Hospital, London) or Dr R B McConnell (Broadgreen Hospital, Liverpool). All had peptic ulceration

confirmed radiologically and/or by gastroscopy, and underwent gastric acid output tests during their pre-treatment assessment.

Gastric juice was obtained via nasogastric tube. The resting (overnight) secretion was aspirated, and the basal secretions collected in 15 minute aliquots using continuous pump suction for 60 minutes (Hammersmith) or 45 minutes (Broadgreen). Twenty-five patients (12 with duodenal ulcer, 13 with gastric ulcer) then received pentagastrin by intramuscular or subcutaneous injection (6 µg/kg body weight) and the stimulated gastric secretion was collected for 60 minutes or 90 minutes. The remaining eight patients (six with duodenal ulcer; two with gastric ulcer) were given instead 0.15 units soluble insulin intravenously, and the stimulated secretion was collected for 90 minutes (seven patients) or 120 minutes (one patient). In each case, the blood glucose fell below 2.2 mmol/l. One other patient was studied four months after successful complete vagotomy for duodenal ulcer. After basal collections, gastric juice was collected for 90 minutes after intravenous insulin, 0.15 units/kg body weight, and for a further 60 minutes after subcutaneous pentagastrin (6 µg/kg).

Gastric juice was transported to the laboratory in ice/water and kept at 0-4° until it was assayed, within 48 hours of collection.

TECHNIQUES

Determination of proteolytic activity

The total peptic activity of the gastric juice samples was determined at pH 2.0, using the method of Anson and Mirsky⁵ as modified by Hanley *et al.*⁶ and further by Etherington and Taylor.¹ Solutions of crystalline porcine pepsin (Sigma Chemical Co

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Ltd, St. Louis, USA) of increasing concentration were analysed similarly. By reference to the proteolytic activity curve obtained, the activities of human gastric juice samples could therefore be expressed in terms of μg porcine pepsin equivalent.

Agar gel electrophoresis and semi-quantification of pepsin 1

As fully quantitative methods are not yet available for the determination of the individual pepsins in the presence of each other, the enzyme concentrations are measured semi-quantitatively from agar gel electrophoretograms as described by Walker and Taylor⁷ and Waft, Roberts and Taylor.⁸ Each pepsin was assigned a grade of 0, for no activity, to + + + + for maximal activity. By comparison with electrophoretograms of known amounts of porcine pepsin, grade + + + + is approximately equivalent to 750 μg of porcine pepsin per ml of undiluted gastric juice and grades + + +, + +, +, and 'trace' to 250, 60, 22.5, and 10.5 $\mu\text{g}/\text{ml}$ respectively. Grading was by two observers, one of whom knew nothing of the details of the individual patients or of their gastric secretions. In instances of uncertainty the intermediate grades +(+) and ++(+) were sometimes used.

Results

BASAL AND STIMULATED PEPSIN 1 SECRETION Basal conditions

Under basal conditions (Table 1) the gastric secretions of eight of the 33 patients, three with gastric ulcer, five with duodenal ulcer, were of neutral pH and no peptic activity was detected. In two patients with gastric ulcer, electrophoresis was not carried out, so that quantification of pepsin 1 was not possible. Three patients whose secretions were acid secreted pepsin 1 in only trace amounts. Although the mean total pepsin concentration of the gastric juice of patients with duodenal ulcer was not significantly higher than that of patients with gastric ulcer ($P > 0.3$), significantly more patients with duodenal

ulcer (eight of 13 whose basal secretion was acid) secreted pepsin 1 in amounts graded ++ than did comparable patients with gastric ulcer (1 of 10) ($0.02 < P < 0.05$). No patient secreted a high concentration of pepsin 1 (+++ or more).

Vagal stimulation by insulin hypoglycaemia

In response to this stimulation all eight patients studied secreted pepsin 1 in greater than trace amounts. Four patients, who all had duodenal ulceration, secreted a high concentration (+++ or more). When all patients with peptic ulceration are considered together, significantly more patients secreted ++ or more after insulin than basally ($P < 0.01$), but when only patients with duodenal ulcer are considered (whether including all 18 basal observations or only those of the six insulin stimulated patients) the difference is no longer significant ($P > 0.05$). The mean concentration of total pepsin secreted by patients with duodenal ulcer was significantly higher after insulin than in the basal state ($P < 0.001$). A similar comparison is not meaningful for patients with gastric ulcer (only two had insulin tests).

Electrophoretograms of one patient with duodenal ulcer are shown in Fig. 1. The total peptic activity of the first 15 minute sample after insulin was 730 $\mu\text{g}/\text{ml}$ (porcine pepsin equivalent) to which pepsin 1 made a negligible contribution. With the onset of hypoglycaemia, the total peptic activity increased to 4050 $\mu\text{g}/\text{ml}$ in sample 2, and a striking increase in pepsin 1 secretion occurred.

Pentagastrin administration

After pentagastrin administration the secretory response with respect to pepsin 1 and total pepsin concentrations was similar among patients with gastric ulcer to that among patients with duodenal ulcer. Twenty-four of the 25 patients secreted more than trace amounts of pepsin 1. The incidence of patients with duodenal ulcer secreting ++ or more pepsin 1 was not significantly different from that under basal conditions ($P > 0.20$) or after insulin

Table 1 Pepsin 1 secretion by patients with peptic ulcer

Stimulant	Patients (no.)	Pepsin 1 (nos. with)				Total pepsin concentration* ($\mu\text{g}/\text{ml}$) Mean (range)
		'Trace'	+	++	+++	
Basal	Duodenal ulcer (18)	1	4	8	0	596 (0-1210)
	Gastric ulcer† (13)	2	7	1	0	469 (0-1100)
Insulin	DU (6)	0	0	2	4	2290 (1705-4200)
	GU (2)	0	1	1	0	1500 (1480; 1505)
Pentagastrin	DU (12)	1	2	6	3	1160 (595-2040)
	GU (13)	0	4	6	3	980 (640-1350)

*For insulin and pentagastrin stimulation, total pepsin concentration was the highest observed in any 15 minute period in each patient. Total pepsin concentration under basal conditions was the mean of all the 15 minute basal gastric juice collections from each patient. The pepsin 1 grades are the highest observed for each patient for each stimulant.

†Two patients with gastric ulcer whose basal pepsin 1 secretion was not determined have been excluded.

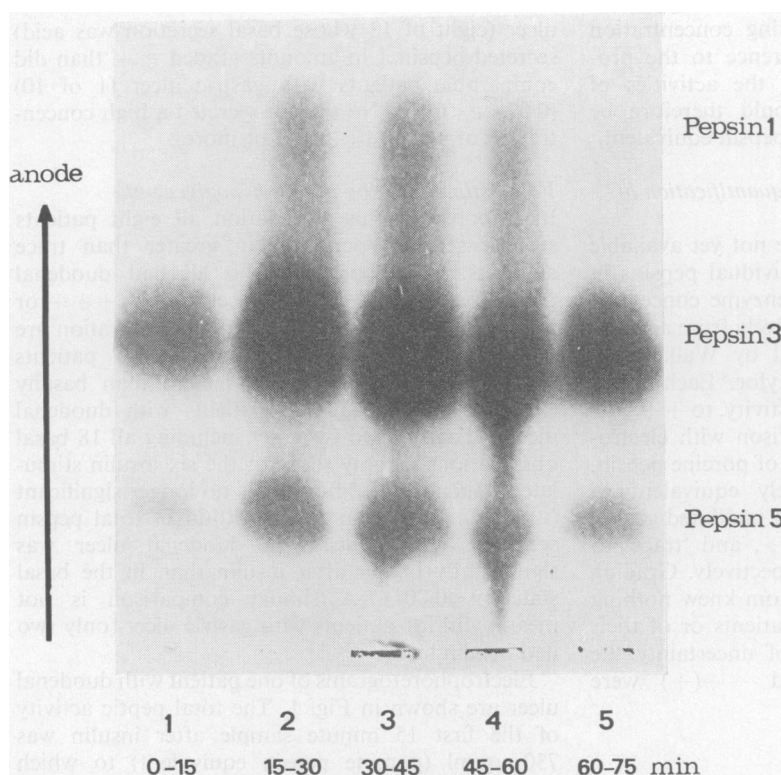


Fig. 1 Pepsin electrophoretograms of the gastric juice secreted by a patient with chronic duodenal ulcer after intravenous insulin. Gastric juice samples 1, 2, 3, 4, and 5, were collected 0-15, 15-30, 30-45, 45-60, and 60-75 minutes respectively after insulin, and had total peptic activities of 730, 4200, 4075, 3125, and 1480 $\mu\text{g/ml}$ porcine pepsin equivalent, respectively. All samples were diluted 1 in 15 for electrophoresis.

hypoglycaemia ($P > 0.50$). Of the 10 patients whose basal secretions were acid, six secreted ++ of pepsin 1 basally and eight of them secreted ++ or more in response to pentagastrin. On the other hand, significantly more patients with gastric ulcer secreted ++ or more pepsin 1 in response to pentagastrin than basally ($P < 0.001$). Of the nine patients whose basal secretions were acid, one secreted ++ basally and six secreted ++ after pentagastrin. Three patients with gastric ulcer and three with duodenal ulcer secreted high concentrations of pepsin 1 (+++ or more).

Pepsin 1 secretion after complete vagotomy

One patient was studied opportunistically who had undergone vagotomy and gastroenterostomy four months before a combined insulin/pentagastrin test. He was asymptomatic, and vagal section was complete according to the criteria of Bank *et al.*⁹ Pepsin 1 was secreted basally, in consecutive 15 minute periods, in amounts graded ++, + and +; after insulin in amounts graded 0, 0, +, ++, and 0; and after pentagastrin in amounts graded ++, ++, +, and +.

Table 2 Total pepsin concentrations (mean \pm 1SEM) of gastric juice 15 minute samples, graded according to pepsin 1 content

Pepsin 1 concn. ($\mu\text{g/ml}$)	Duodenal ulcer			Gastric ulcer		
	Total pepsin concentration ($\mu\text{g/ml}$; mean \pm 1 SEM)			Total pepsin concentration ($\mu\text{g/ml}$; mean \pm 1 SEM)		
	Basal	Post-pentagastrin	Post-insulin	Basal	Post-pentagastrin	Post-insulin
0	105 (one sample only)		310 \pm 152 (5 samples)	310 \pm 117 (4 samples)		
Trace (10-5)	460 \pm 71	615 \pm 29		617 \pm 91	580 \pm 9	350 (260; 440) (2 samples)
+ (22-5)	795 \pm 51	930 \pm 50	1098 \pm 145	680 \pm 51	663 \pm 23	764 \pm 89
+ (+) (36-8)			1370 \pm 222			1215 (930; 1500) (2 samples)
++ (60-0)	1035 \pm 36	950 \pm 66	1550 \pm 113		920 \pm 32	1480 (1 sample)
++ (+) (122-6)			1850 \pm 103			
+++ (250-5)		1515 \pm 246	3060 \pm 550		1080 \pm 80	

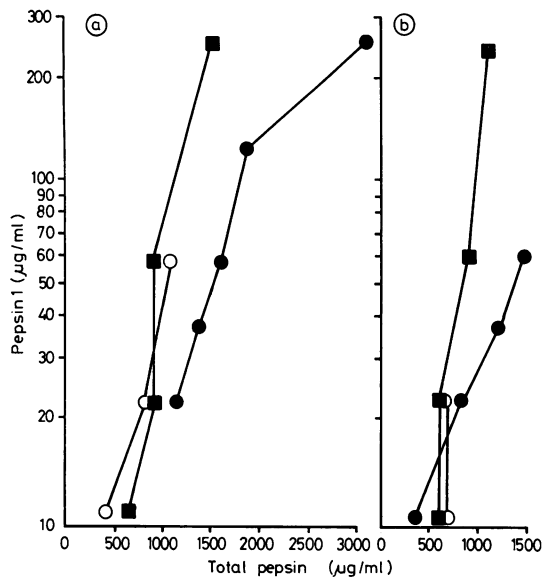


Fig. 2 The relationship between pepsin 1 grade and mean total peptic activity/ml of the basal, pentagastrin-, and insulin-stimulated gastric secretion of patients with (a) duodenal and (b) gastric ulcer. ○—○ basal; ■—■ after pentagastrin; ●—● after insulin.

Total peptic activities of samples containing pepsin 1 in undetectable or in trace amounts

Five basal samples of gastric juice of acid pH in which pepsin 1 was undetectable—that is, less than 10.5 µg/ml of pepsin 1 was present—had a mean total peptic activity of 269 µg/ml, and five similar samples collected after insulin, before the secretory response to hypoglycaemia started, had a mean total peptic activity of 310 µg/ml (Table 2). The mean values are lower than those observed for all samples containing trace amounts of pepsin 1 (512 µg/ml under basal conditions, 603 µg/ml after

pentagastrin, 350 µg/ml after insulin hypoglycaemia), although the ranges overlap.

Relationship of pepsin 1 secretion to total peptic activity of gastric juice

The results for all the 15 minute gastric juice samples collected basally or after stimulation were grouped according to the pepsin 1 grade, and the mean peptic activity (±1 SEM) was calculated for each group (Table 2). The mean values are plotted semilogarithmically against the pepsin 1 grades, expressed as porcine pepsin equivalent (Figs. 2a and b); pepsin 1 concentration was also calculated as a percentage of the total pepsin concentration (Table 3). From these (approximate) representations of the relationship between pepsin 1 and total pepsin concentration, it is apparent that the proportionate contribution made by pepsin 1 to the total activity increases progressively as the total activity increases. Thus, in response to pentagastrin, samples from patients with duodenal ulcer which contain a 'trace' of pepsin 1 have a mean total peptic activity of 615 µg/ml, approximately 1.7% being contributed by pepsin 1. Samples with +++ of pepsin 1 on the other hand have a mean total activity which is 2.5 times higher, yet the contribution made by pepsin 1 is around 16.5%. It is also apparent (Fig. 2a) that, for patients with duodenal ulcer at least, the pepsin secretory response after insulin differs from that after pentagastrin: higher total pepsin concentrations are secreted in response to insulin, yet pepsin 1 makes a smaller proportional contribution to the increase (Table 3). Of the 12 15 minute samples collected after insulin from two patients with gastric ulcer, three samples, collected before the secretory response began, were of neutral pH and had no peptic activity. Figures for the remaining nine samples are shown in Tables 2 and 3. Although the numbers are small, the pattern is similar to that of patients with duodenal ulcer.

Table 3 Pepsin 1 as percentage of total pepsin concentration

Pepsin 1 concn.	Pepsin 1 as percentage of total pepsin concentration (mean and range)					
	Duodenal ulcer			Gastric ulcer		
	Basal	Post-pentag.*	Post-insulin	Basal	Post-pentag.	Post-insulin
Trace	2.3 (1.4-4.8)	1.7 (1.4-2.0)		1.7 (1.3-3.0)	1.8 (1.8-1.9)	3.2 (2.4; 4.0)
+	3.0 (2.1-6.6)	2.4 (1.8-6.6)	2.1 (1.5-3.1)	3.3 (2.0-11.8)	3.4 (2.4-5.2)	2.9 (2.3-3.9)
+(+)			2.7 (2.0-3.8)			3.3 (2.5; 4.0)
++	5.8 (5.2-8.1)	6.3 (3.5-18.2)	3.9 (2.9-6.1)		6.5 (4.5-10.3)	4.1 (1 sample)
++(+)			6.6 (6.3-8.6)			
+++		16.5 (12.2-19.5)	8.2 (5.7-14.6)		23.2 (20.5-26.9)	

*Post-pentagastrin.

Discussion

These observations on patients with chronic peptic ulceration reveal a number of interesting features of pepsin 1 secretion. First, it was found that at low levels of gastric stimulation—for example, in the basal state—pepsin 1 may be undetectable in gastric juice which contains both of the other two major pepsins, pepsins 3 and 5. As pepsin 1 was detected in the gastric juice of all the subjects after gastric stimulation, all had the capacity to produce this pepsin. It may be postulated, therefore, that the threshold level of stimulation for pepsin 1 secretion is higher than that for secretions of pepsins 3 and 5. As little as 10.5 µg/ml of pepsin 1 is detectable by electrophoresis, and this represented approximately 2.0% of the mean total pepsin concentration of samples containing a 'trace' of pepsin 1 (Table 3). It is unlikely, therefore, that the apparent threshold is an artefact arising from insensitivity of the method. Wright¹⁰ has previously suggested that, in the cat, certain pepsins are secreted only when stimulation exceeds a threshold level.

The vagus is known to stimulate pepsin secretion in man¹¹ and acetylcholine was shown to stimulate pepsinogen secretion in a dose-dependent fashion by rabbit gastric mucosa in organ culture.¹² In response to vagal stimulation by insulin hypoglycaemia, all the patients in the present study secreted pepsin 1, together with increased amounts of pepsins 3 and 5. The increase in pepsin 1 concentration did not parallel the increase in total pepsin concentration, however, but had an approximately logarithmic relation to it—thus pepsin 1 accounted for proportionately more of the total peptic activity when this was high than for lower total activities. Wright *et al.*⁴ observed that prolonged electrical stimulation of the vagi in the cat resulted in the secretion of increasing amounts of the most electronegative pepsin, 'cat pepsin 1'. Thus it appears that vagal stimulation not only increases the total quantity of pepsin secreted by the gastric mucosa, but also influences the composition of the pepsin mixture released. Pentagastrin was also found to stimulate pepsin 1 secretion in patients with peptic ulceration. In the case of patients with duodenal ulcer, there was a difference in the responses to insulin and to pentagastrin: the total concentration of pepsins secreted was smaller after pentagastrin, yet the contribution made by pepsin 1 to the increase was proportionally higher. Again, this situation may be analogous to that in the cat, in which, although the total pepsin response to pentagastrin is small, 'pepsin 1' is a major contributor.¹⁰ In patients with gastric ulcer, the numbers studied are too few to enable a comparison between pentagastrin and

insulin stimulation to be made.

In the present investigation pepsin 1 was found when present, to account for 1.3% to 26.9% of the total peptic activity (upon globin) of the gastric juice samples (Table 3). Using a different method of assay, which does not involve agar gel electrophoresis, but which utilises the different activities of pepsins 1, 3, and 5 upon ovalbumin, Walker¹³ found the proportion of pepsin 1 to vary from 4.5% to 21.7% of the total peptic activity. The two differing methods thus give values in the same range.

Gastric juice samples collected under basal conditions from some patients with duodenal ulcer contained a moderately high concentration (++) of pepsin 1. Under the conditions of a gastric function test, truly basal conditions are not always achieved. If an increased secretion of pepsin 1 is indicative of stimulation of the gastric mucosa, then in some patients with duodenal ulcer—and in significantly more than patients with gastric ulcer—there was either an increased level of stimulation basally or the gastric chief cells were more sensitive to a normal level of basal stimulation. There is evidence that in some patients with duodenal ulcer there may be increased 'vagal drive' on the gastric mucosa.¹⁴ Stimulation by endogenous gastrin seems a less likely possibility, as fasting serum gastrin levels in duodenal ulcer lie in the lower part of the normal range when measured by radio-immunoassay.¹⁵

The question now arises as to whether pepsin 1 plays a greater aetiological role in peptic ulceration than do the other pepsins of gastric juice. Although patients with duodenal ulcer as a group have a higher total pepsin secretion than normal subjects, most investigators have found that the ranges for normal and duodenal ulcer subjects overlap. Patients with gastric ulceration usually secrete normal amounts of pepsin. Thus peptic ulceration in many individuals cannot be attributed to an increased total secretion of pepsins. Work in animals has shown that, although solutions of porcine pepsin in hydrochloric acid are considerably more ulcerogenic to jejunal mucosa than hydrochloric acid alone, the severity of ulceration does not depend closely on the concentration of pepsin applied.^{16,17} A qualitative change in the pepsins secreted might on the other hand increase the 'peptic aggression' of gastric juice.^{18,19} In some of its proteolytic actions, pepsin 1 resembles closely the predominant pepsin of gastric juice, pepsin 3^{20,21} however, pepsin 1 digests the glycoprotein ovalbumin more readily than pepsin 3 does²² and is more active towards collagen.²³ It is not inconceivable that pepsin 1 may augment the 'peptic aggression' of the other pepsins towards the gastric or duodenal mucosa to a significant degree in some

circumstances. Taylor,³ using a rather less sensitive electrophoretic technique, found that 68% of patients with duodenal ulcer and 78% with gastric ulcer secreted pepsin I in response to histamine—significantly higher incidences than among patients without ulceration (47%).

Pepsin I has been observed in increased concentration in groups of individuals having an increased risk of acute or chronic ulceration: in children after cardiac surgery, and in some patients requiring intensive care after trauma,²⁴ and in non-secretors of blood group substances.⁸ Cigarette smokers with chronic peptic ulceration secrete more pepsin I as a group than non-smokers with ulcers.⁷ Finally, a decrease in pepsin I secretion was observed in patients with chronic peptic ulcer who responded well to treatment with carbenoxolone but not in those who failed to respond.²⁵ In some of these situations the changes in pepsin I secretion probably reflect changes in the intensity of gastric mucosal stimulation, and in this context the enzyme may be looked upon as a sensitive 'marker' of such stimulation. Pepsin I may, however, make a considerable contribution to a stimulated juice; thus from Tables 2 and 3, in gastric ulcer the difference of total pepsin concentration between the highest basal level (680 $\mu\text{g/ml}$) and the highest stimulated level (1080 $\mu\text{g/ml}$) is 400 $\mu\text{g/ml}$, of which about 227 $\mu\text{g/ml}$ is pepsin I. The possible special role of pepsin I in ulcerogenesis should therefore repay continuing study.

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