Peptic activity after the administration of Pentagastrin and in gastroduodenal disease

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METHOD

The existence of more than one gastric pepsin has been reported by many authors. Herriott, Desreux, and Northrop (1940) separated two proteolytic fractions from human gastric juice by salt-fractionation methods, and similar results were described by Baker (1951) and Taylor (1959b). Using moving boundary electrophoresis, Kushner, Rapp, and Burtin (1964), Merten, Schramm, Grassmann, and Hannig (1952), and Taylor (1959a) have all identified two or more different proteolytic components in both swine and human gastric juice. Ryle and Porter (1959), Tang, Wolf, Caputto, and Trucco (1959) and Seijffers, Segal, and Miller (1963), using ion-exchange chromatography, have also isolated at least two different proteases in human gastric secretion.

The two proteases most commonly isolated both digested proteins with two *pH* maxima, one near 2.0 the other around 3.5 (Taylor, 1959a). The third pepsin found by some authors was found by Tang and by Ryle to have a single *pH* at 3.0. This, however, was only a minor component of gastric juice and was only occasionally found. There is good evidence therefore that two pepsins, and sometimes three, are present in human gastric juice. Furthermore, Taylor (1959b) has shown that these pepsins are obtainable from different parts of the stomach. Using material obtained at necropsy, he showed that one pepsin could be extracted from the fundic mucosa and the other from the pyloric mucosa. The fundic pepsin digested proteins with *pH* maxima at 2.2 and 3.5; the pyloric had more acidic peaks on the *pH*-activity curve at 1.7 and 3.1.

Peptic activity/*pH* curves drawn in the present work have shown at some time or another five peaks of peptic activity below *pH* 4.5. However, three of these peaks occurred very rarely, and attention has been focused on the two peaks that were most frequently seen, namely, *pH* 1.8 and *pH* 2.2. This paper therefore first attempts to associate stimuli with the appearance of these peaks, and then to examine the occurrence of these pepsins in different conditions of the stomach in health and disease.

Gastric juice was obtained from patients and volunteers by aspiration through a Levin tube. For every sample taken a peptic activity/*pH* curve was drawn by measuring the peptic activity at a number of different *pH* values and plotting the results. The method used to estimate pepsin was derived from that described by Hunt (1948), the main difference being the substitution of bovine haemoglobin for dried plasma as a protein substrate. The conclusions drawn depend on being able to compare one graph with another as easily as possible, so all the graphs have been drawn to the same scale, the peptic activity at *pH* 2.2, usually the point of maximum activity, being arbitrarily designated 100%.

EXPERIMENTAL

Haemoglobin was made up freshly each day and divided into 5 ml aliquots. The acidity of each was adjusted so that between them the *pH* range 1.0 to 4.0 was evenly covered. The aspirated gastric juice was centrifuged to remove mucus and debris, and 0.1 ml was added to each haemoglobin sample. Digestion was allowed to proceed for 15 minutes at 37°C, then the peptic activity in each sample was measured by Hunt's method and the graph prepared from the results.

PATIENTS AND MATERIALS

Gastric juice was aspirated in every case from normal volunteers or patients undergoing routine maximum secretion tests. All subjects had fasted overnight, and in the morning a Levin tube (14 FG or 16 FG) was passed into the stomach and its position checked by radiological screening using an image intensifier. The tip of the tube was placed in the midline and the expected position of the gastric angulus. Passing the Levin tube could in itself alter the shape of the peptic activity curve in some cases, so care was taken to eliminate this factor as far as possible. In comparing patient with patient the residual gastric juice, *ie*, the secretion already in the stomach when the tube was passed, was used; where the resting gastric secretion was compared with the stimulated juice from the same patient, the resting juice used was that obtained half an hour after the tube had been passed into the stomach, and the stimulated juice that obtained half an hour after an injection of Pentagastrin,

given in a dose of 6 μg per kilogram bodyweight subcutaneously.

The diagnosis in each case was made on radiological or surgical evidence; all patients, with the exception of those whose gastric ulcer had healed, had active symptoms at the time of the test.

The effect of Pentagastrin (6 $\mu\text{g}/\text{kg}$ bodyweight) on peptic activity was studied in 13 patients (seven with duodenal ulcer, six with *x*-ray-negative dyspepsia), and the resting and stimulated gastric juice were compared in each. The peptic activity of residual gastric juice was also studied in 52 patients and volunteers, comprising eight normal subjects and patients with dyspepsia but no radiological findings (group 1); 25 patients with duodenal ulcer (group 2); 13 patients with active gastric ulcers (group 3a), and six patients with healed or inactive gastric ulcers (group 3b).

The six patients in group 3a all had evidence of an active gastric ulcer on the lesser curvature of the stomach, with or without duodenal involvement. The patients in group 3b all had proven gastric ulcers in the past, but no evidence of activity at the time of the test.

EXPERIMENTAL RESULTS

EFFECT OF PENTAGASTRIN ON PEPTIC ACTIVITY CURVE

In 12 out of 13 cases an injection of Pentagastrin in a dose of 6 $\mu\text{g}/\text{kg}$ bodyweight resulted in an increase in peptic activity at pH 1.8 (Fig. 1). Detailed results are presented in Table I. Twelve out of 13 show a relative increase in peptic activity at pH 1.8, and it is unlikely that this result is due to chance ($P < 0.001$). Eight of the 13 patients also showed an increase in peptic activity at pH 2.7.

TABLE I

RESULTS

Patient No.	Peptic Activity at pH 1.8		Difference
	Resting	Stimulated	
1	94.5	102.5	+8.0
2	99.5	107.5	+8.0
3	98.0	106.0	+8.0
4	90.5	97.0	+6.5
5	89.0	99.0	+10.0
6	87.5	106.0	+18.5
7	86.0	86.0	0.0
8	94.5	101.0	+6.5
9	99.0	106.0	+7.0
10	99.0	103.0	+4.0
11	90.0	97.5	+7.5
12	86.0	97.0	+11.0
13	96.0	99.0	+3.0
Average	93.0	100.5	+7.5

Pentagastrin was also given to two volunteers and to a patient who had no demonstrable resting gastric secretion. The peptic activity curve of the stimulated juice showed its peak activity at pH 1.8 instead of at pH 2.2 (Fig. 2).

It appears therefore that Pentagastrin stimulates the production of a pepsin of which the peak activity

FIG. 1. Peptic activity curves for resting and Pentagastrin-stimulated gastric juice from the same patient. The graph is representative of 13 similar patients, and the pH of maximum activity in each case is marked on the x-axis

FIG. 2. Peptic activity curve of a sample of Pentagastrin-stimulated gastric juice when no resting secretion was detectable. Maximum activity is at pH 1.8.

is at pH 1.8. When there is no resting secretion, as shown in Fig. 2, this pepsin is seen alone but when there is resting secretion (Fig. 1) it appears as a peak or shoulder superimposed on the activity of the resting secretion.

PEPTIC ACTIVITY IN GASTRODUODENAL DISEASE In the normals and patients with *x*-ray negative dyspepsia (eight cases) the peptic activity curve of the residual secretion is shown in Figures 3 and 4. Activity is greatest at pH 2.2 in all cases.

In the 25 cases of duodenal ulcer a typical curve

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 3. *Peptic activity curve of a normal patient in group 1. Peak activity is at pH 2.2.*

FIG. 4. *Peptic activity curve of patients in group 1 with dyspepsia but no radiological findings. Peak activity is at pH 2.2.*

FIG. 5. *Peptic activity curve of the residual gastric juice of a patient in group 2. Peak activity is at pH 2.2.*

FIG. 6. *Peptic activity curve obtained from the residual gastric juice of a patient in group 3a. Peak activity is at pH 1.8.*

FIG. 7. *Peptic activity curve obtained from the residual gastric juice of a patient in group 3b. The peak activity is at pH 2.2.*

FIG. 6.

FIG. 7.

is illustrated in Figure 5. The activity peak is at pH 2.2 in 20 of the 25 cases; in the other five the curve is flat between pH 1.8 and pH 2.7. In 13 cases of active gastric ulcers (group 3a) the type of curve found is shown in Figure 6. In 12 of the 13 cases the peak is at pH 1.8.

In the six cases with healed and inactive gastric ulcer (group 3b) five showed a curve as illustrated in Fig. 7, with the peak at pH 2.2.

DISCUSSION

It can be seen that the curves obtained in the normal and x-ray-negative dyspepsia group are essentially similar to those in the duodenal ulcer group, the peptic activity in each case being greatest at pH 2.2. It is probable therefore that the same pepsin is dominant in both groups, although the curves differ in minor respects.

Peptic activity curves of the active gastric ulcer group, however, differ from the rest, in that the peak activity occurs at pH 1.8 instead of at pH 2.2. Also there is much less individual variation between the graphs of this group than between the graphs of the other groups. It appears therefore that in the active gastric ulcer group a second pepsin is dominant, with its peak at pH 1.8. Since a similar peptic activity curve can be obtained experimentally by administering Pentagastrin, it may be that in the active gastric ulcer patient there is an increase in the secretion of gastrin-liberated pepsin.

The peak at pH 1.8 seems to be related to the presence of an active gastric ulcer, since the activity pattern returns to normal when the ulcer heals. However, it is not possible to say whether the ulcer is causally related to the abnormal secretion or vice versa.

The two pepsins appear to be very similar to those described by Taylor (1959b). In his results pyloric pepsin had its peak activity at pH 1.7 and fundic pepsin was most active between pH 2.1 and 2.3. Both had peaks at higher pH values as well, and in the present work the graphs nearly always show a peak or at least a shoulder in the higher pH range. It is possible, therefore, that the pepsin prominent in normal subjects and in patients with simple dyspepsia or duodenal ulcer may be what

Taylor calls fundic pepsin, and that the pepsin associated with active gastric ulcers may be 'pyloric' pepsin. This study indicates the possibility that 'pyloric' pepsin may be liberated by a gastrin stimulus, although it is not possible at this stage to suggest any definite stimulus for the fundic pepsin.

SUMMARY

Two major proteolytic components of human gastric juice are known, one having its maximum activity at pH 1.8, the other being most active at pH 2.2. It has been shown that the pepsin with maximum activity at pH 2.2 is dominant in normal subjects, in patients with duodenal ulcer, and in patients with dyspepsia in whom no lesion was found. In patients with active gastric ulcer the dominant peptic activity is at pH 1.8. The administration of Pentagastrin causes a relative increase in the secretion of the pepsin with the maximum pH at 1.8. The peptic activity/pH curve of the residual gastric juice of patients with active gastric ulcers is similar to that produced by Pentagastrin.

During this work one of us (M.H.P.) was supported by a grant from Squibb & Co. Ltd., Twickenham.

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