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THE EFFECTS OF ANTRAL ACIDIFICATION ON THE GASTRIC SECRETION STIMULATED BY ENDOGENOUS AND EXOGENOUS GASTRIN

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SUMMARY

1. In conscious dogs with Heidenhain fundic pouches and denervated antral pouches control dose–response curves to gastrin pentapeptide or methacholine were constructed, both when the antral pouch was empty and when it was stimulated with ACh (0·5 g/100 ml.) in citrate buffer adjusted to pH 5·5 or 1·5.

2. When the antral pouches were irrigated with ACh (0·5 g/100 ml.) at pH 1·5 the acid outputs from the Heidenhain pouch in response to graded doses of gastrin pentapeptide or methacholine were significantly less at each dose level than those obtained with ACh at pH 5·5.

3. The acid outputs from the Heidenhain pouch in response to either pentapeptide or methacholine with or without antral irrigation with ACh at pH 1·5 were approximately equal. Therefore the difference between the dose–response curves obtained by stimulation with ACh at pH 5·5 and those obtained by stimulation with ACh at pH 1·5 represents gastrin release rather than release of an inhibitory hormone.

4. The pepsin outputs from the Heidenhain pouch during antral irrigation with ACh at pH 1·5 were significantly less than those obtained with ACh at pH 5·5 at each dose of methacholine.

5. The maximal pepsin output was significantly greater in response to methacholine than to gastrin pentapeptide.

6. Gastrin pentapeptide was not a significant stimulant of pepsin secretion from the Heidenhain pouch.

7. The intestinal phase of parietal secretion was not inhibited by bathing the separated antrum with acid.

INTRODUCTION

Since Sokolov (1904) discovered the inhibitory effect on gastric secretion of acidifying the contents of the stomach it has been established that antral acidification inhibits parietal cell secretion. There has been controversy since then concerning the mechanism. Is it due to failure of formation or release of gastrin from the antrum, or to depression of the parietal cell by an inhibitory hormone or chalone liberated from the gastric antrum? The following experiments were designed to determine the existence or importance of an antral inhibitory hormone.

METHODS

Eight adult mongrel dogs weighing from 14 to 20 kg were prepared with Heidenhain fundic pouches and denervated antral pouches. Experiments were started only after complete recovery. The animals were fasted for 17 hr before each test. They were tested only if the basal acid secretion from the Heidenhain pouch was 0·1 m-equiv or less per 10 minute sample. The experiments were conducted in pairs as follows: in the first the antral pouch was irrigated through a self-retaining catheter at a rate of 115 ml./hr (Fig. 1). The solutions used were acetylcholine chloride (ACh) 0·5 g/100 ml., in citrate buffer adjusted with HCl to either pH 5·5 or 1·5. Each pair of experiments was always completed in each dog on the same day. The sequence of pairs and of doses within each pair was randomized. After a continuous intravenous infusion of saline (0·9 g/100 ml.) at 1 ml./min for 30 min either metacholine or gastrin pentapeptide was added to the saline infusion to give the desired dosage. Doses of methacholine or gastrin were changed every 30 min, or when secretion had become stable.

The other pair of experiments was conducted as the first pair except that a control dose–response curve with gastrin pentapeptide or methacholine was obtained without either antral irrigation or an antral catheter. This was for comparison with dose–response curves obtained with antral irrigation at pH 1·5, in the usual way on the same day. The last two collections at each dose were used for calculation in all experiments. Group means and their standard errors are shown in the figures, but the statistical differences cited throughout the text are all based on the paired t test. In five double pouch dogs the effect of antral acidification on the secretory response of the Heidenhain pouch to feeding was studied. In this preparation only the intestinal phase of gastric secretion remained intact. Meat was fed at 20 min intervals; on attainment of a plateau the antrum was irrigated with HCl citrate buffer at pH 1·5 as before for 60–90 min.

The Heidenhain pouch was filled with 25 ml. of (0·9 g/100 ml.) saline which was collected and the pouch washed through with a further 25 ml. of saline at the end of each 10 min collection period. The perfusate and the washout were combined and a 10 ml. aliquot of each sample was used for acid determination. Acid output was determined by titration with 0·1 N-NaOH to pH 7·0 using an automatic titrator (Radiometer, Copenhagen). Measurement of peptic activity was by a modification of the method of Anson (1938). The output of pepsin was expressed in mg tyrosine/10 min. The gastrin pentapeptide used (I.C.I. 50,123) was a gift from Ayerst Research Laboratory.

The pH of juice from the antral pouches during methacholine or gastrin stimulation remained above 7·0 in each animal.

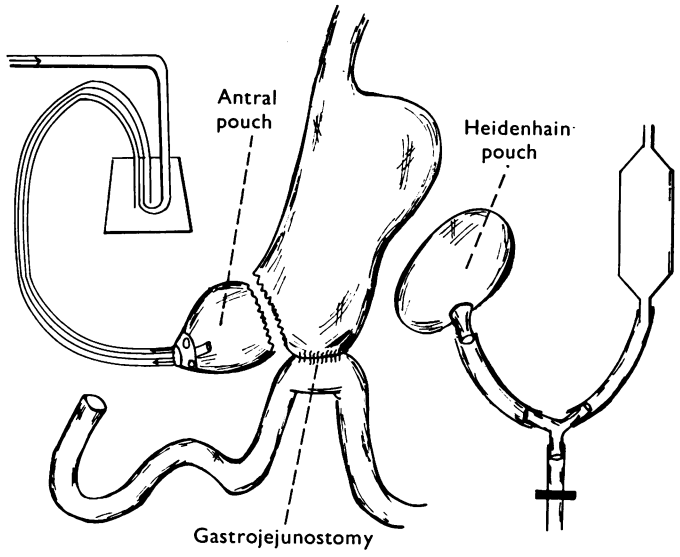

Fig. 1. The operation, the irrigation apparatus and the method of collecting samples. The irrigation fluid was driven through the inner and returned via the outer tube to a reservoir at the level of the dog's back.

RESULTS

Gastrin pentapeptide. The dose–response relationships between gastrin pentapeptide and gastric secretion during antral irrigation with ACh (0·5 g/100 ml.) at pH 5·5 and pH 1·5 are compared in Fig. 2. When the antral pouches were irrigated with ACh at pH 1·5 the acid outputs from the Heidenhain pouch in response to graded doses of pentapeptide ranging from 0·25 to 4·0 μg/min were significantly less ($P < 0·01$) at each dose level than those obtained with ACh at pH 5·5. The mean percentage difference between the two dose–response curves was 60·4% ($\pm$6·7 S.E.M.). In three dogs there was an evident plateauing of the pH 5·5 dose–response curves at 2·0 μg/min of the pentapeptide. But in the other five dogs acid output increased all the way. The pepsin outputs from the Heidenhain pouch during antral irrigation with ACh at pH 1·5 were less at each dose of pentapeptide than those obtained with ACh at pH 5·5, but these differences were not significant ($P > 0·05$). The mean percentage differences between the two curves was 50·6% ($\pm$3·4 S.E.M.). In neither case did pepsin output increase with dose. The slopes were not significantly different from zero.

Metacholine. Dose–response relationships to methacholine during antral irrigation with ACh (0·5 g/100 ml.) at pH 5·5 and pH 1·5 are compared in Figs. 3 and 4. In five dogs when the antral pouch was irrigated with ACh

at pH 5·5 a graded response of acid secretion was evoked from the Heidenhain pouch. In three dogs, however, a small inhibition occurred at the largest dose of methacholine at pH 5·5. In five dogs a graded response was seen all the way. The acid outputs from the Heidenhain pouch in

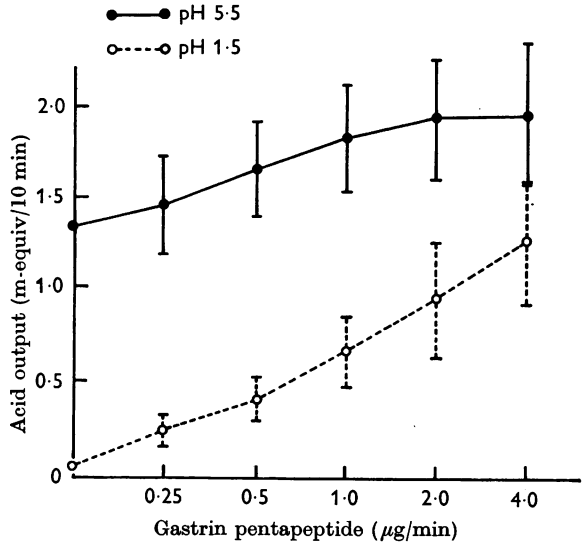

Fig. 2. Dose–response curves for continuous intravenous gastrin pentapeptide and acid secretion with antral acetylcholine at pH 5·5 and 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean.

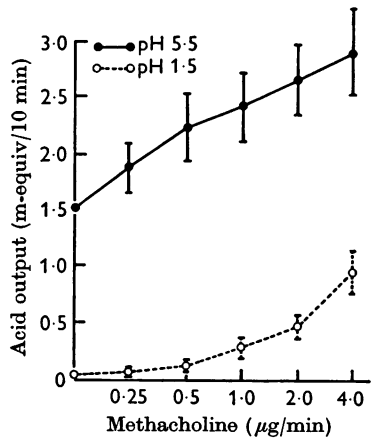

Fig. 3. Dose–response curves for continuous intravenous methacholine and acid secretion with antral acetylcholine at pH 5·5 and 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean.

response to graded doses of methacholine during antral irrigation with ACh at pH 1·5 were significantly less at each methacholine dose level than those obtained with ACh at pH 5·5 ($P < 0·001$). The mean percentage difference between the two dose–response curves was 87·4% (± 5·6 S.E.M.).

The pepsin output from the Heidenhain pouch in response to graded doses of methacholine during antral irrigation increased as the dose increased in all eight dogs. The pepsin outputs during antral irrigation at

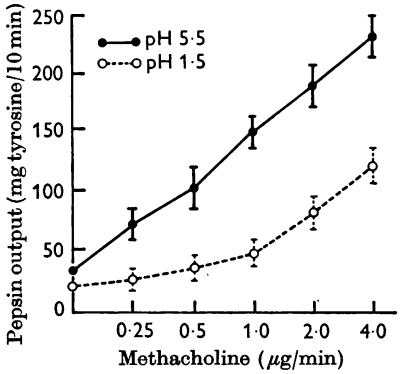

Fig. 4. Dose–response curves for continuous intravenous methacholine and pepsin secretion with antral acetylcholine at pH 5·5 and 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean.

pH 1·5 were significantly less at each dose of methacholine than those obtained with ACh (0·5 g/100 ml.) at pH 5·5 ($P < 0·05$). The mean percentage difference was 54·8% (± 4·5 S.E.M.). The maximal pepsin output (pH 5·5) was significantly greater in response to methacholine than to gastrin pentapeptide ($P < 0·001$).

Comparison of acid and pepsin output in response to gastrin pentaptide alone and pentapeptide plus antral irrigation with ACh at pH 1·5. Dose–response relationships to pentapeptide alone and pentapeptide plus antral irrigation with ACh (0·5 g/100 ml.) at pH 1·5 are compared in Figs. 5 and 6. The acid outputs from the Heidenhain pouch were approximately equal in response to pentapeptide alone and pentapeptide plus antral irrigation at pH 1·5 except at the lowest dose of pentapeptide ($P < 0·05$ at 0·25 μg/min). The pepsin output from the Heidenhain pouch in response to pentapeptide alone showed a transient increase at the dose of 0·25 μg/min and then the output fell below the previous resting levels in all eight dogs. Neither this inhibition nor the transient stimulation was statistically significant ($P > 0·1$). The pepsin outputs in response to pentapeptide plus antral irrigation with ACh (0·5 g/100 ml.) at pH 1·5 were greater than those to pentapeptide alone at each dose of pentapeptide, but the difference

was not significant except at a dose of 0·5 and 4·0 μg/min of pentapeptide ($P < 0{\cdot}05$ at 0·5 and 4·0 μg/min). Again no dose–response relationship was seen between the pentapeptide and pepsin secretion since the slopes of the two curves were not significantly greater than zero.

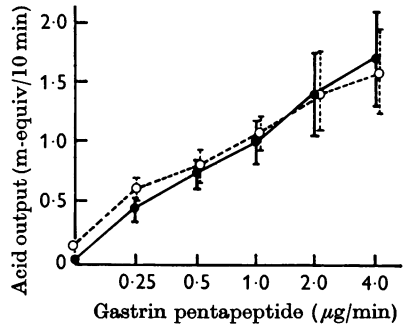

Fig. 5. Dose–response curves for continuous intravenous gastrin pentapeptide and acid secretion with an empty antrum and one containing acetylcholine at pH 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean. ●—● Gastrin alone. ○----○ Gastrin +perfusion of antral pouch with ACh (0·5 g/100 ml.) citric acid buffer (pH 1·5).

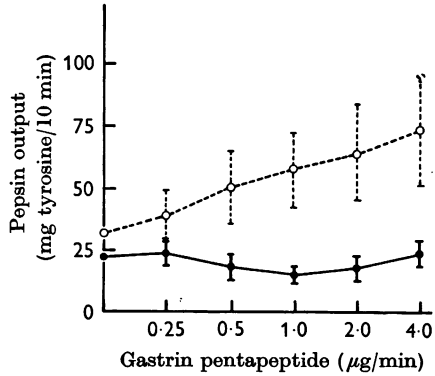

Fig. 6. Dose–response curves for continuous intravenous gastrin pentapeptide and pepsin secretion with an empty antrum and during irrigation with acetylcholine at pH 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean. ●—● Gastrin alone. ○----○ Gastrin+perfusion of antral pouch with ACh (0·5 g/100 ml.) citric acid buffer (pH 1·5).

Comparison of acid and pepsin output in response to methacholine alone and methacholine plus antral irrigation with ACh at pH 1·5. Dose–response relationships to methacholine alone and methacholine plus antral irrigation with ACh (0·5 g/100 ml.) at pH 1·5 are compared in Figs. 7 and 8.

The acid outputs from the Heidenhain pouch were approximately equal in response to methacholine alone and methacholine plus antral

irrigation at pH 1·5 at each dose level ($P > 0{\cdot}05$). The pepsin outputs from the Heidenhain pouch in response to small doses of methacholine were approximately equal. ($P > 0{\cdot}1$ at 1·0 μg/min methacholine and below.) Above a dose 1·0 μg/min of methacholine they were less with antral irrigation than without it.

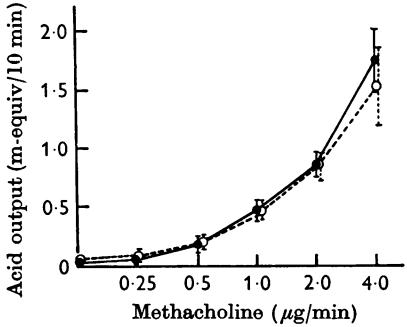

Fig. 7. Dose–response curves for continuous intravenous methacholine and acid secretion with the antrum empty and during antral irrigation with acetylcholine at pH 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean. ●——● Methacholine alone. ○----○ Methacholine + perfusion of antral pouch with ACh (0·5 g/100 ml.) citric acid buffer (pH 1·5).

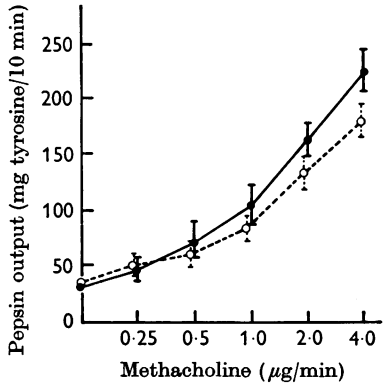

Fig. 8. Dose–response curves for continuous intravenous methacholine and pepsin section with the antrum empty and during antral irrigation with acetylcholine at pH 1·5. Each point is the mean of eight experiments in eight dogs, the vertical bars represent the standard error of the mean. ●—● Methacholine alone. ○----○ Methacholine + perfusion of antral pouch with ACh (0·5 g/100 ml.) citric acid buffer (pH 1·5).

The intestinal phase of parietal secretion. With repeated meat feeding a constant secretion of acid was reached usually after 1–1½ hr. The mean acid output per 10 minutes for five experiments in five dogs from the intestinal phase (1·7 m-equiv ± 0·57 S.E.M.) was not significantly different

from that obtained during antral acidification (1·6 m-equiv ± 0·51 S.E.M.) ($P > 0·5$).

DISCUSSION

The difference between the dose–response curves obtained by stimulation with ACh (0·5 g/100 ml.) citrate buffer at pH 5·5 and those obtained by stimulation with ACh (0·5 g/100 ml.) citrate buffer at pH 1·5 represents gastrin release from the antrum because the dose–response curves for acid output, obtained by stimulation with ACh citrate buffer at pH 1·5, were statistically the same as those obtained with gastrin pentapeptide alone or methacholine alone when antral pouches were empty. These data are against the hypothesis that an acid antrum inhibits gastric acid secretion by way of an inhibitory hormone with a depressant effect on parietal secretion. If an inhibitory hormone is released when the antrum is acidified to an antral pH of 1·5, dose–response curves identical to those obtained with an empty antrum should not be expected. If endogenous gastrin release is prevented when the antral mucosa is pH 1·5 and an inhibitory hormone is released a parallel curve to the right of that for methacholine and gastrin alone should be expected. If endogenous gastrin release is not prevented and an inhibitory hormone is released a curve to the right of and parallel to that obtained when the antral pH is 5·5 should be expected. Our curves indicate that when the pH of the antral stimulant is 1·5 the exogenous stimuli (methacholine or gastrin pentapeptide) alone are acting on the parietal cell.

Statistical analysis of our data shows that whether the actual data or reciprocals are used the slopes of the lines relating gastrin pentapeptide or methacholine dose to acid output with an empty antrum are not significantly different from those obtained with ACh (0·5 g/100 ml.) at either pH 1·5 or pH 5·5 in the antrum (Table 1). In fact, we cannot conclude statistically that these lines are not parallel to each other.

Our data shed no light on the possibility that there may be a hormone which inhibits gastrin release rather than acid secretion by the parietal cell. Gillespsie & Grossman (1962) have maintained that acidification of the antrum does not antagonize the action of exogenous gastrin. Our results are in agreement with them.

Exogenous gastrin pentapeptide unlike the complete gastrin polypeptide (Gregory & Tracy, 1964) does not seem to be a significant stimulant of pepsin secretion from the Heidenhain pouch. This is in agreement with Cooke's (1967) data, but not with his conclusion. Endogenous gastrin on the other hand clearly stimulates pepsin secretion since the antral stimulant invariably results in higher pepsin secretion at pH 5·5 than 1·5.

The feeding experiments indicate that the intestinal phase of parietal

secretion is not inhibited by antral acidification in agreement with Woodward, Lyon, Landor & Dragstedt (1954). This is additional evidence against the existence of an antral inhibitory hormone.

TABLE 1. Statistical evaluation of the slopes of the lines. Regression equations calculated from raw experimental data

	Equation of regression line	Significance of a difference between regression coefficients
Gastrin: Antral pH 5·5	$y_1 = 0{\cdot}11x + 1{\cdot}67$	$t = 1{\cdot}538$, $P > 0{\cdot}1$ (y_1 and y_3)
Antral pH 1·5	$y_2 = 0{\cdot}27x + 0{\cdot}33$	$t = 0{\cdot}362$, $P > 0{\cdot}1$ (y_2 and y_3)
Empty antrum	$y_3 = 0{\cdot}31x + 0{\cdot}63$	
Methacholine: Antral pH 5·5	$y_4 = 0{\cdot}23x + 2{\cdot}11$	$t = 1{\cdot}890$, $P > 0{\cdot}05$ (y_4 and y_6)
Antral pH 1·5	$y_5 = 0{\cdot}38x + 0{\cdot}05$	$t = 0{\cdot}885$, $P > 0{\cdot}1$ (y_5 and y_6)
Empty antrum	$y_6 = 0{\cdot}44x - 0{\cdot}02$	

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