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CHEMICAL STIMULATORY MECHANISM IN GASTRIC SECRETION

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SUMMARY

1. The serum gastrin level, gastric mucosal blood flow and acid secretion from the canine Heidenhain pouch have been measured in response to the introduction of bovine serum albumin, pepsin-digested albumin, an amino acid mixture, liver extract and mannitol used as control.

2. Distention of the Heidenhain pouch with mannitol or albumin at pH 5·0 produced a similar pressure-related increase of acid secretion reaching a peak of only 10% of the maximal response to histamine. Pepsin-digested albumin was capable of producing larger acid outputs than undigested albumin. The highest acid output, attaining about 80% of the maximal response to histamine, was obtained with liver extract both before and after exhaustive dialysis to remove all the amino acids and short peptide fragments. An amino acid mixture containing all essential amino acids was also found to stimulate acid secretion but to a lesser degree than liver extract.

3. It is concluded that it is not the intact protein but the products of its digestion, the polypeptides and free amino acids, which are potent chemical stimulants of acid secretion from the oxyntic gland area. Since the serum gastrin level was not changed during acid secretion induced by peptic digests bathing the oxyntic gland area, the mechanism of chemical stimulation appears to be gastrin-independent.

4. The response to chemical stimulation by peptic digests can be greatly potentiated by combining this with distention of the oxyntic gland area. Topical application of xylocaine or atropine causes a marked decrease of Heidenhain pouch response to peptic digests, suggesting a possible neural reflex component in the mechanism of chemical stimulation of the oxyntic gland area.

5. When the pH of the liver extract in the Heidenhain pouch was gradually decreased in sequential order from 5·0 to 1·0, this resulted in a pH-related decrease in acid secretion and in the mucosal blood flow falling

to the basal level at pH 1·0. Exogenous secretin given in graded doses from 0·5 to 8·0 u./kg.hr caused a small but dose-related inhibition of acid response to liver extract accompanied by a decrease of mucosal blood flow but without any significant change in the serum gastrin level.

6. The results indicate that the chemical stimulation of the oxyntic gland area by peptic digests is capable of inducing acid secretion by a local, gastrin-independent, partially neural reflex mechanism, sensitive to pH, pressure and secretin.

INTRODUCTION

It is generally accepted that food in the stomach induces acid secretion by gastrin release and nervous reflexes which interact in the stimulation of the oxyntic glands (Grossman, 1967). Recently, evidence has been presented that dietary protein components coming directly into contact with the oxyntic gland area may stimulate near maximal acid secretion by a local, gastrin-independent and pH sensitive mechanism (Debas & Grossman, 1974).

The present study was undertaken to elucidate the mechanism of chemical stimulation of the oxyntic glands, and particularly to determine the role of cholinergic innervation and the relation to pressure, pH and secretin.

METHODS

Three mongrel dogs, weighing between 20 and 28 kg, were prepared with a Heidenhain-type denervated fundic pouch (Heidenhain pouch), a gastric fistula and pancreatic fistula constructed according to the modified method of Herrera, Kemp, Tsukamoto, Woodward & Dragstedt (1968).

Secretory studies were started about 2 months after surgery. The dogs were deprived of food but not water for at least 18 hr before each test. The stomach was rinsed by irrigation through the gastric fistula and the collection of basal secretion from gastric fistula, Heidenhain pouch and pancreatic fistula was started. Test experiments were not begun until two consecutive 15 min basal collections from the Heidenhain pouch and pancreatic pouch were 1·5 ml. per 15 min or less. If basal secretion remained higher the study was cancelled for the day.

In test experiments, gastric juice from the gastric fistula was collected continuously and separated into 15 min samples for acid and pepsin determinations (Konturek, Radecki, Konturek & Demitrescu, 1974). The secretion from the Heidenhain pouch was measured by the modification of the method of intragastric titration (Fordtran & Walsh, 1973). In one series of experiments acid secretion from the main stomach was determined by intragastric titration while Heidenhain pouch secretion was collected and separated into 15 min samples for acid and pepsin determinations. The intragastric titration was performed by attaching to the cannula of the Heidenhain pouch or gastric fistula a plastic chamber of 20 ml. volume, occluded by a rubber stopper through which passed: the glass and calomel electrodes, a tube connected to a barostat containing a test meal, a tube for infusing $NaHCO_3$ from an autoburet and two mixing tubes; one with the tip in the chamber and the other with the tip in the gastric lumen. The electrodes were connected to a

pH meter (Radiometer, PHM 26), which in turn was connected to pH-stat assembly (Titrator TTT-11, autoburet ABU13, recorder SBR2c, all Radiometer). The recorder gave a cumulative amount of titrant (0·5 M-$NaHCO_3$) against time. The rate of acid secretion was calculated in terms of milliequivalents of bicarbonate infused in each 15 min period.

The barostat device was used to keep a constant pressure in the gastric lumen. The principle of barostat derives from the fact that it has a volume much larger than the gastric lumen so that any change in the volume of the stomach due to contraction or relaxation has little effect on the distending pressure. The point at which the cannula of Heidenhain pouch or gastric fistula disappeared in the abdomen was taken as the zero reference point for pressure measurement. Distending pressure was expressed as the difference in height between this point and the fluid level in the barostat. The adequacy of the barostat in maintaining the pressure was checked by measuring the actual pressure in the gastric lumen using the sensing device connected via perfused tube to transducer and a Sanborn recorder.

Gastric content subjected to intragastric titration was continuously mixed, using peristaltic pump connected with the mixing tubes and set at the delivery rate of about 600 ml./15 min.

During each test pancreatic juice was collected continuously and separated into 15 min samples for volume, bicarbonate and protein determinations according to the method described previously (Konturek *et al.* 1974).

The test meals used for intragastric titration included: 10 % bovine serum albumin, a pepsin-digested albumin solution, 10 % amino acid mixture, 10 % liver extract before and after dialysis and 10 % mannitol solution used as a control. Pepsin-digested albumin solution was prepared by incubation of 10 % bovine serum albumin with pepsin at pH 2·0 at 37 °C for 1 hr and then bringing the solution to pH 5·0 with concentrated NaOH. Amino acid mixture contained amino acids obtained by complete hydrolysis of 10 % bovine serum albumin. Liver extract was used either as original 10 % solution or after subjecting to exhaustive dialysis (48 hr) to remove all free amino acids and short peptide fragments. Mannitol was added to all test meals as required to achieve an osmolarity of about 550 m-osmole/l. Osmolarity was measured by freezing point depression with the Fiske osmometer.

Several series of tests with intragastric titration were performed. In the tests with distention each test meal was brought to pH 5·0 and introduced into the Heidenhain pouch via a polyethylene tube inserted into its lumen, care being taken to expel all the air from the pouch. The level of barostat was adjusted to the zero position and intragastric titration was continued for six successive 15 min periods to reach a plateau of acid output. The barostat was then successively raised to 10, 20, 30, 40, 50 and 60 cm, intragastric titration being made for 45 min at each level. The response was taken as the sum of acid outputs in the last two 15 min periods at each pressure level.

In the tests designed to study the role of vagal innervation, the 10 % liver extract of pH 5·0 was introduced into Heidenhain pouch and adjusted to increasing distention pressures during (1) I.V. infusion of atropine (100 μg/kg. hr, (2) irrigation of Heidenhain pouch with 50 ml. 0·1 % atropine solution, (3) irrigation of Heidenhain pouch with 50 ml. 2 % xylocaine solution, (4) I.V. infusion of urecholine (10 μg/kg. hr and (5) perfusion of the Heidenhain pouch secretion with 50 ml. 0·5 % acetylcholine solution. All substances used for the perfusion of the Heidenhain pouch secretion were first instilled into the pouch for 30 min preceding the introduction of liver extract meal and then added to the meal. Urecholine was given in a dose which was found to be without any effect on Heidenhain pouch secretion when administered alone.

In the tests with pH profile of inhibition of gastric secretion induced by a meal, the

test meal was adjusted to a selected pH varying from 5·0 to 1·0 by adding 4 M-HCl and then was introduced at a constant pressure of 0 or 30 cm H_2O into the Heidenhain pouch, where, by the intragastric, it was held at this same preselected pH for 45 min. The meal was then removed from the Heidenhain pouch and replaced by another meal at another pH. The order of change of pH was sequential from 5·0 to 1·0. In separate studies it was shown that, if a fresh meal was reintroduced at the same pH and distention pressure every 45 min for 4 hr, acid secretion from the Heidenhain pouch determined by intragastric titration was relatively well sustained throughout the experiment.

For comparison, the pH profile of inhibition of gastric response to exogenous stimuli was also studied. Pentagastrin (8 μg/kg.hr), histamine (160 μg/kg.hr) or urecholine (100 μg/kg.hr) was given I.V. in a constant dose to produce near maximal gastric secretion. Gastric juice from the main stomach was collected by gravity drainage, whereas Heidenhain pouch response was measured by intragastric titration method using 10% mannitol to fill the pouch. Constant distention pressure was maintained in the Heidenhain pouch at the zero position throughout the experiment. The pH of the pouch content was decreased gradually every 45 min in sequential order from 5·0 to 1·0. In control tests in which both distention pressure (0 cm H_2O) and pH of the contents of the Heidenhain pouch (pH 5·0) were maintained at the same levels throughout the 4 hr test, it was found that acid response to histamine or urecholine was well sustained throughout the test. In control tests with pentagastrin acid output had a tendency to steady decline and at the end of experiments decreased to about 75% of initial peak level.

In the tests with secretin 10% liver extract meal adjusted to pH 5·0 was introduced into the Heidenhain pouch or into the main stomach and kept at this same pH by intragastric titration during the test. Exogenous secretin was infused I.V. in graded doses doubling every 45 min from 0·5 to 8 u./kg.hr.

In some tests with pH profile and secretin aminopyrine clearance was used to measure mucosal blood flow according to the procedure described by Jacobson, Linford & Grossman (1966). By determining the relation of aminopyrine clearance (an estimate of mucosal blood flow) to the rate of secretion from the Heidenhain pouch, a ratio (R) was obtained which provided information concerning the dynamics of secretion (Jacobson, Swan & Grossman, 1967).

In tests with liver extract meal, gastrin concentration in serum was measured by radioimmunoassay. The routine detection limit of the assay, as employed in the present study, was 5 pg equivalent synthetic human gastrin per ml. serum (Yalow & Berson, 1970).

Mean values for gastric and pancreatic outputs, for clearances and R values and serum gastrin values were calculated. The differences of the mean for the last 30 min periods at a given pH, pressure or secretin dose were compared according to the paired t test (Siegel, 1956).

RESULTS

Acid output in response to distention and chemical stimulation

Distention of the Heidenhain pouch with 10% mannitol at pH 5·0 caused a pressure-related increase in acid secretion from the pouch reaching the peak at the pressure of 40 cm H_2O (Fig. 1). The highest acid response to distention was only 10% of the maximal response to histamine. Acid response to distention with 10% bovine serum albumin at pH 5·0 was not different from that induced by mannitol. However,

pepsin digested albumin solution containing mainly the large peptide fragments was capable of producing about twofold larger acid response than undigested albumin or mannitol when used to distend the Heidenhain pouch.

The highest acid output was achieved when the Heidenhain pouch was distended with 10% liver extract solution adjusted to pH 5·0 (Fig. 2). The peak acid secretion with liver extract meal in the Heidenhain pouch occurred at the distention pressure of 50 cm H_2O and it was about 80% of the maximal response to histamine and about 200% of the maximal response to pentagastrin. Similar acid response from the Heidenhain pouch was achieved when 10% liver extract adjusted to pH 5·0 was introduced into the main stomach and kept in there at the pressure of 10 cm H_2O.

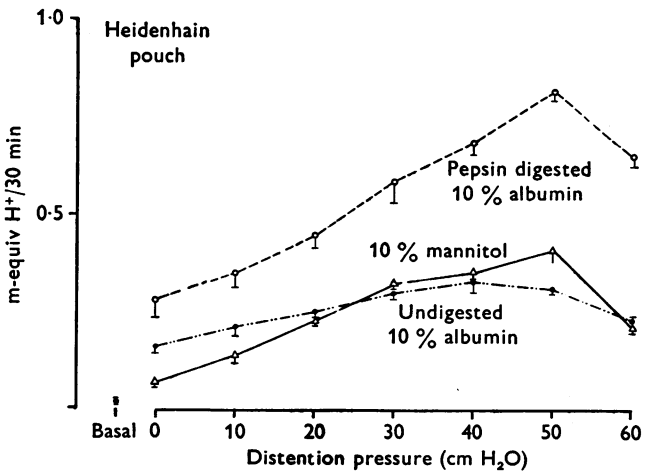

Fig. 1. Acid secretion from the Heidenhain pouch in response to distention with 10% mannitol (control), undigested 10% bovine serum albumin and pepsin digested bovine serum albumin at varying pressure and at constant pH (5·0). In this and subsequent Figures each line is a mean of four to six tests on three dogs. Vertical bars indicate the S.E. of the mean.

During the secretory stimulation of the Heidenhain pouch with liver extract solution at increasing pressure, there was a pressure-related increase in aminopyrine clearance from the pouch reaching the peak at the pressure of 30 cm H_2O. With further rise of the pressure in the Heidenhain pouch, the aminopyrine clearance showed a tendency to decline. The *R* values remained at the same level until the distention pressure exceeded 40 cm H_2O when it also showed a tendency to decline (Fig. 3).

In all tests with distention of the Heidenhain pouch by mannitol, protein, amino acids or liver extract solution the secretions from the

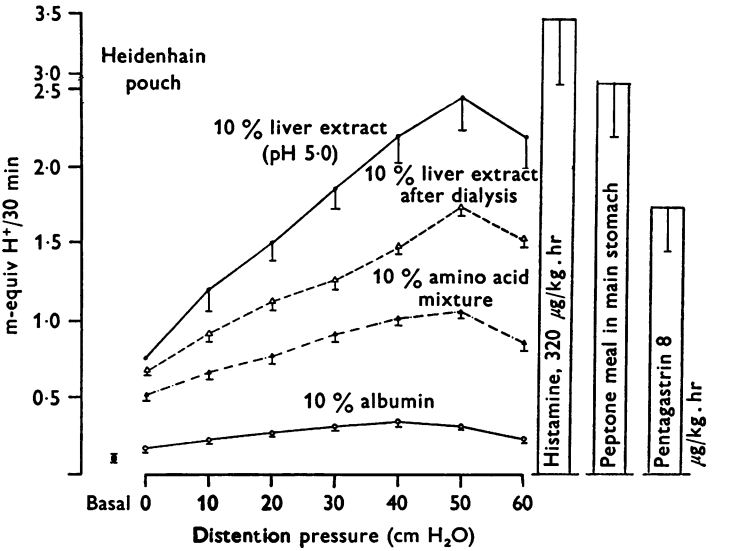

Fig. 2. Acid secretion from the Heidenhain pouch in response to distention with 10 % bovine serum albumin, 10 % amino acid mixture or 10 % liver extract before and after dialysis. The columns represent mean peak 30 min outputs in two observations on each of three dogs in tests with histamine, pentagastrin or peptone meal kept in the main stomach at distention pressure of 10 cm H_2O and at pH 5·0.

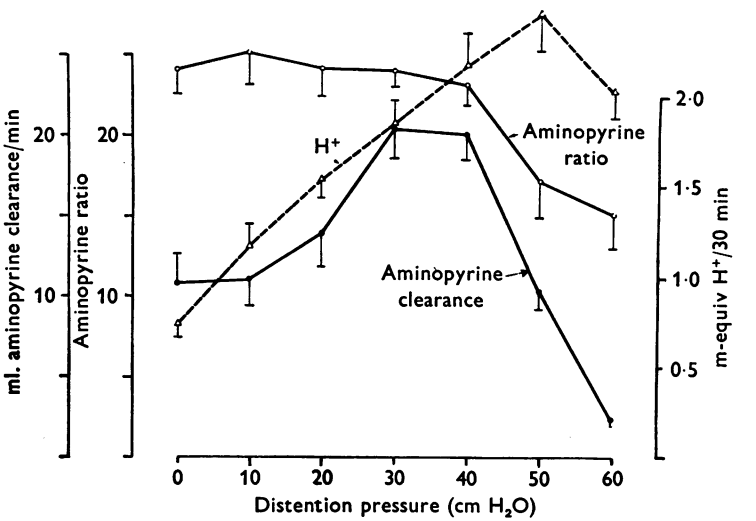

Fig. 3. Acid outputs, aminopyrine clearance and *R* (ratio) values from the Heidenhain pouch in tests with distention of the pouch with liver extract at varying pressure and at constant pH (5·0).

gastric fistula, pancreatic fistula and serum gastrin level did not change from the basal level. These results are omitted for clarity of presentation.

Effect of atropine, xylocaine, acetylcholine and urecholine given intravenously or applied topically on acid response to liver extract meal

Atropine infused I.V. in a dose of 100 μg/kg.hr caused a strong reduction of the Heidenhain pouch response to liver extract meal at all distention pressures. The highest acid output in tests with atropine background was only 30% of that induced by liver extract alone. When the Heidenhain

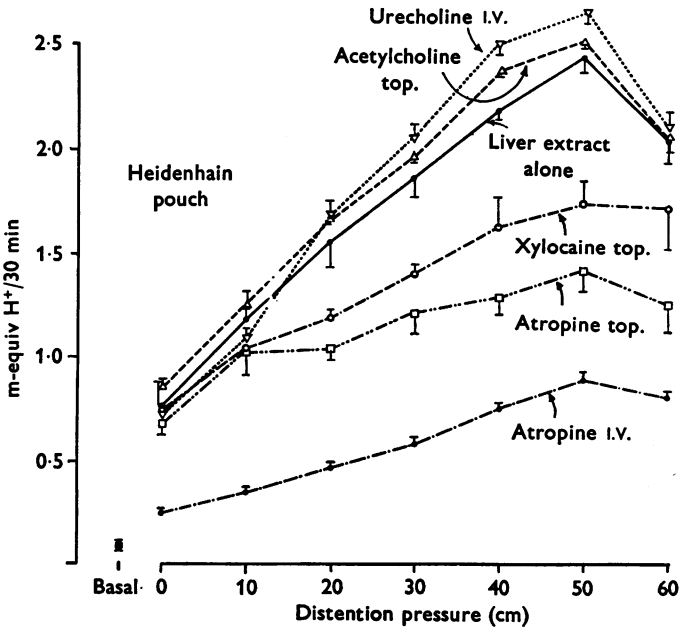

Fig. 4. Effect of urecholine, acetylcholine, xylocaine or atropine given intravenously (I.V.) or topically (top.) to the Heidenhain pouch mucosa on acid response to liver extract at varying distention pressure at constant pH 5·0.

pouch was irrigated with 50 ml. 0·1% atropine or 2% xylocaine solution, acid response from the Heidenhain pouch was significantly depressed at all pressure levels. Irrigation of the pouch with 50 ml. 0·5% acetylcholine did not affect significantly the Heidenhain pouch response to liver extract solution. Urecholine given I.V. in a dose of 10 μg/kg.hr caused a small but significant rise of the Heidenhain pouch secretion to liver extract at all levels of distention pressure (Fig. 4).

Effect of varied pH and secretin on acid response to liver extract meal

In the studies with varied intragastric pH, the pouch response to liver extract meal was not significantly different at pH 5·0 and 4·0. Below pH 4·0 there was a tendency of acid output to decrease and, at the pH 1·0, the Heidenhain pouch failed to respond to liver extract meal.

In control experiments in which peptone meal was kept in the Heidenhain pouch at the same pH 5·0 and at the same distention pressure (0 or 30 cm H_2O) acid outputs were relatively well sustained throughout the 4 hr experiment (Fig. 5).

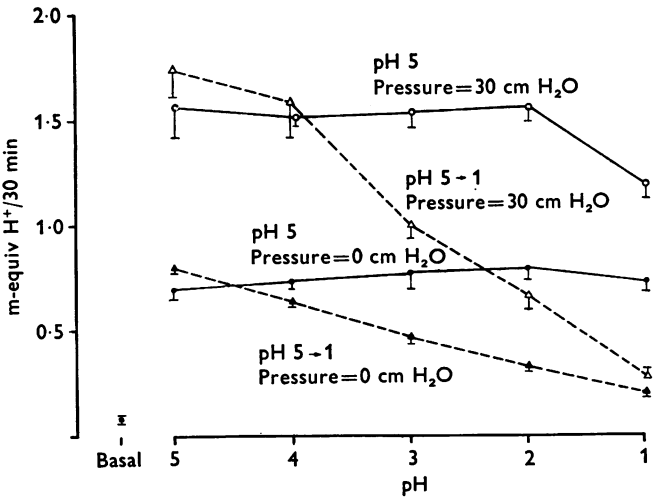

Fig. 5. Acid secretion from the Heidenhain pouch in response to distention of the pouch with liver extract at constant pressure of 0 or 30 cm H_2O but at varying pH (from 5·0 to 1·0).

Aminopyrine clearance in tests with stimulation of the Heidenhain pouch secretion by liver meal at decreasing pH showed a gradual reduction with decreasing pH. There was a partial reduction of aminopyrine clearance at pH 3·0 and almost complete reduction at pH 1·0. The *R* values were not significantly altered during gradual decrease of pH of the Heidenhain pouch content (Fig. 6). The secretions from the gastric and pancreatic fistula as well as serum gastrin level remained unchanged during gradual decrease of pH of Heidenhain pouch content and the data are not presented.

In tests with histamine, pentagastrin or urecholine stimulation, the rate of acid response from the Heidenhain pouch determined by intragastric titration at pH 5·0 was similar to that obtained with liver extract

meal kept in the pouch at the same pH. The gradual decrease of pH content of the Heidenhain pouch resulted in the progressive decline of acid secretion both in tests with histamine, pentagastrin and urecholine stimulation (Fig. 7).

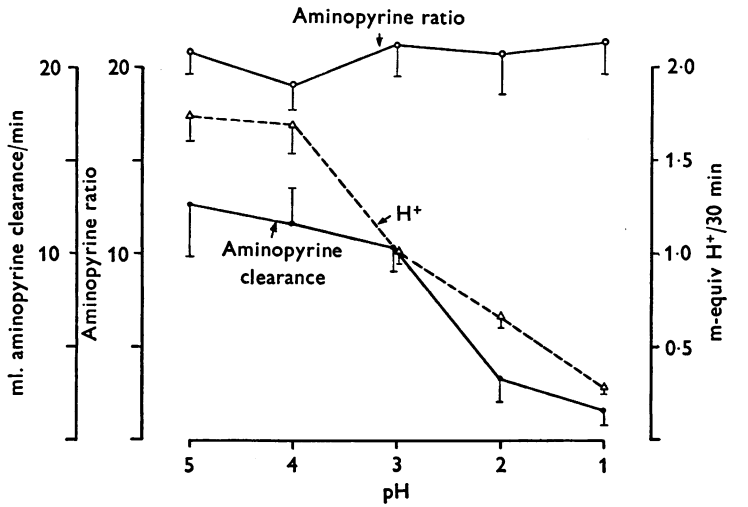

Fig. 6. Acid outputs, aminopyrine clearance and *R* (ratio) values from the Heidenhain pouch in tests with distention of the pouch with liver extract at varying pH from 5·0 to 1·0 but at constant pressure (30 cm H_2O).

Secretin administered I.V. caused a dose-related inhibition of the Heidenhain pouch response to a peptone meal. At the dose of 8 u./kg.hr, which produced the highest pancreatic volume and bicarbonate outputs from the pancreatic fistula, the Heidenhain pouch response to liver meal was inhibited by about 50% (Fig. 8). The inhibition of acid output by graded doses of secretin was accompanied by a parallel reduction of aminopyrine clearance whereas the *R* value remained unchanged during the experiment (Fig. 9). Serum gastrin level in tests with secretin was not different from that occurring with liver extract in the Heidenhain pouch without secretin administration. The response of the gastric fistula in these tests was negligible and the data are not presented.

DISCUSSION

Gastric stimulation following introduction of food into the stomach results from several integrated mechanisms. Grossman (1968) enumerated the theoretically possible mechanisms and demonstrated the following components of the gastric phase. (1) Distention of the oxyntic gland area stimulates the parietal cells to secrete acid through both local and long

(vago-vagal) fundic reflexes; (2) distention or chemical stimulation of the antrum causes gastrin release through local and perhaps long pyloric reflexes; and (3) distention of the antrum stimulates the parietal cells to secrete acid through a gastrin-independent mechanism involving a pyloro-oxyntic reflex (Debas, Konturek, Walsh & Grossman, 1974).

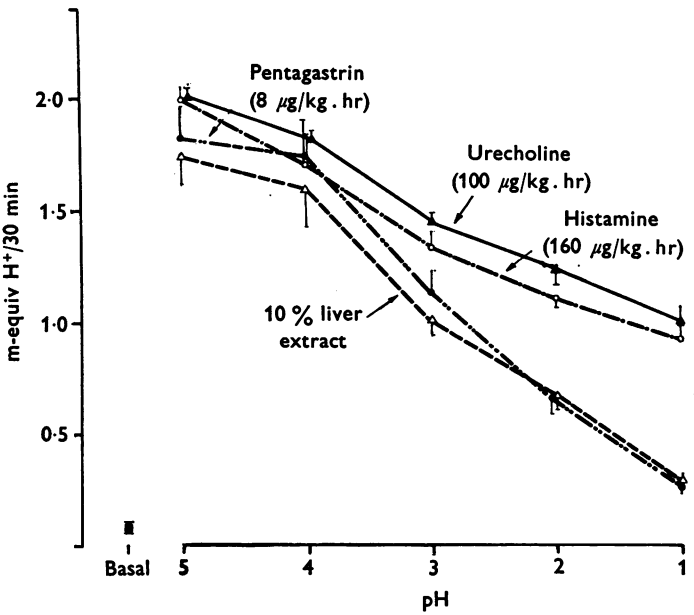

Fig. 7. Acid outputs from the Heidenhain pouch in response to pentagastrin, urecholine, histamine given I.V. or liver extract meal in tests with varying pH (from 5·0 to 1·0) of the Heidenhain pouch content.

Recently, two other gastric phase components have been described: distention of the oxyntic gland area causes the release of gastrin through an oxynto-pyloric reflex (Debas, Walsh & Grossman, 1974), and chemical stimulation of the oxyntic gland area stimulates the parietal cells to secrete acid by an unknown mechanism (Debas & Grossman, 1974).

Our study confirmed the latter observation and attempted to explain the chemical nature of the secretory stimulus and the possible mechanism of chemical stimulation of the oxyntic gland area. It was found that the whole protein molecule is not a chemical stimulus. When combined with distention, intact bovine serum albumin solution produced acid secretion not different from the rates of secretion achieved solely with distention evoked by the introduction of mannitol into the Heidenhain pouch. The ability to stimulate the oxyntic glands was shared only by peptic digests, polypeptides and free amino acids.

The physiological significance of the chemical stimulation of the oxyntic gland area is quite obvious. Peptic digestion very rapidly converts non-stimulating whole protein into peptides which are potent oxyntic gland stimuli. The finding that this mechanism acting alone can produce high rates of acid secretion suggests that it may have an important role. When combined with distention, chemical stimulation produced the highest acid output, amounting to about 80 % of the maximal response to

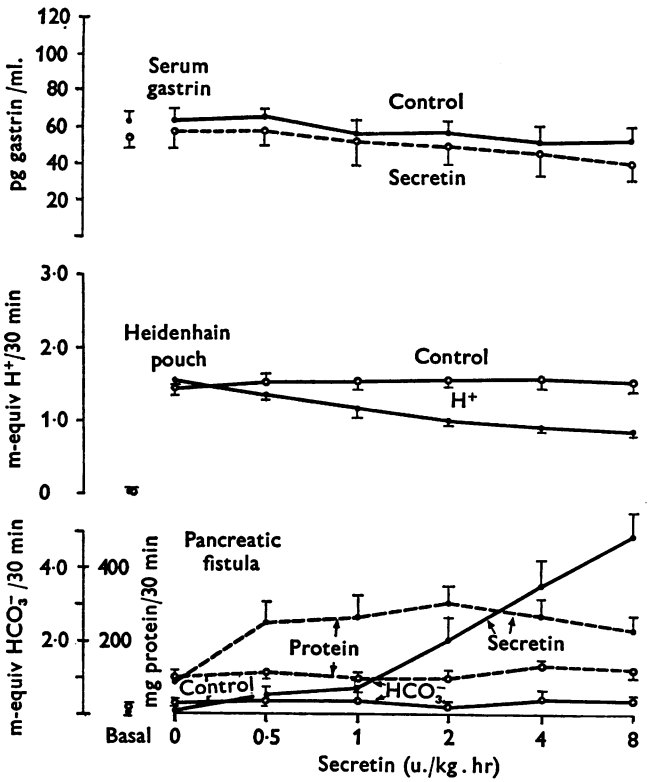

Fig. 8. Effect of graded doses of secretin on serum gastrin concentration and acid secretion from the Heidenhain pouch induced by distention with liver extract at constant pH (5·0) and pressure (30 cm H_2O). Pancreatic secretion of bicarbonate and protein is also presented.

histamine and 200 % of the maximal response to pentagastrin. This potent chemical stimulation, however, occurred at a distention pressure (50 cm H_2O) which is unlikely to operate in the stomach under normal conditions. At the lower, more physiological distention (10 cm H_2O), a chemical stimulus bathing the oxyntic gland area in the form of a liver extract meal caused acid secretion which was about 30 % of the maximal

response to histamine and only slightly lower than the maximal response to pentagastrin.

These studies indicate that, when distention is applied, the chemical stimulus cooperates with the mechanical stimulus and results in a greatly augmented acid response. The response to gastric distention plus chemical stimulation was pressure-related and exceeded the maximal response to chemical stimulation alone by about 300% and to distention alone by about 700%. Since the response to a combination of mechanical and

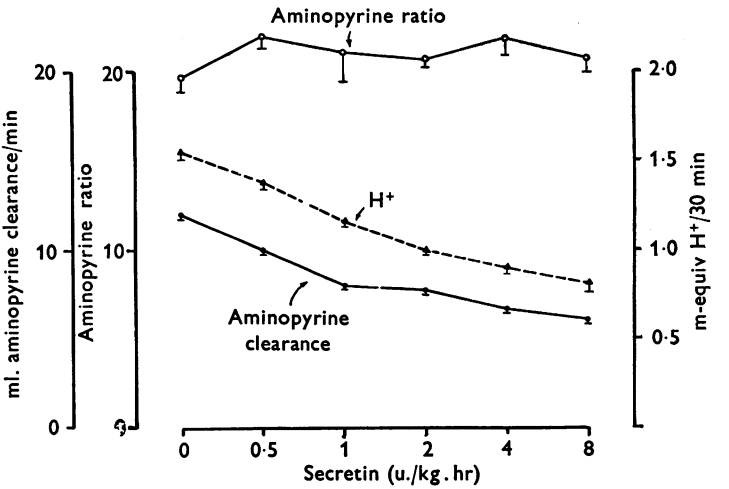

Fig. 9. Acid output, aminopyrine clearance and *R* (ratio) values from the Heidenhain pouch in tests with distention by liver extract meal and secretin administered.

chemical stimuli was well above the response to either stimulus alone, potentiation was apparently achieved. So far a variety of combinations of gastric stimuli have been shown to potentiate gastric acid secretion in the dog (Gillespie & Grossman, 1964; Johnson & Grossman, 1969) but to our knowledge no study has demonstrated the potentiation between mechanical and chemical stimulation at the level of the oxyntic gland area. This interaction is probably of great importance under the normal conditions that occur in the stomach during digestion of a meal. Postprandially, the extent of distention of the oxyntic gland area may be quite limited, so mechanical stimulation should be correspondingly small. However, this small distention with moderate chemical stimulation by peptic digests can produce high acid secretion rates similar to those seen in response to a meal.

The mechanism involved in chemical stimulation of the oxyntic gland

area has not been fully explained, but the fact that serum gastrin levels and acid secretion from the gastric fistula were unchanged in all tests with chemical stimulation of the oxyntic gland area indicates that gastrin is not involved in the mechanism of chemical stimulation. Since local anaesthetics and atropine applied topically to the oxyntic gland area or given intravenously failed to inactivate the oxyntic glands completely, and acetylcholine applied topically or urecholine given intravenously produced little or no change in the response of the oxyntic glands to chemical stimulation, it may be concluded that a meal acts on the oxyntic glands at least in part by a non-cholinergic mechanism. It is not excluded that local effects of chemical ingredients of food are mediated by direct action on oxyntic cells to stimulate acid secretion.

It is now generally accepted that in the intact stomach the effectiveness of mechanical, chemical or vagal stimulation is greatly decreased when the gastric content is acidified. This acid-induced inhibition of gastric secretion, long ago recognized by Pavlov (1910), presumably occurs because acid making contact with the pyloric glandular mucosa slows down and eventually stops further gastrin release (Schofield, 1966). Our study provides evidence that an acidified meal bathing the oxyntic gland area, without any contact with the gastric antrum, results in a pH-dependent inhibition of acid secretion induced by mechanical and chemical stimuli. The results of chemical stimulation with a liver extract meal at varying pHs showed that the peak acid response to the chemical stimulus alone (distention pressure 0 cm H_2O) or to the combination of chemical and mechanical stimuli (distention pressure 30 cm H_2O) occurred at pH 4·0 or 5·0. The rise of pH above this value failed to increase the acid response above that seen at pH 4·0 or 5·0. When the pH of the test meal was decreased in sequential order from 4·0 to 1·0, the gradual inhibition of acid secretion was observed. There was a partial inhibition at pH 2·0 and 3·0 and complete inhibition at pH 1·0. The most striking finding of the present study was that similar pH-dependent inhibition was noted when gastric acid secretion was induced by exogenous stimuli such as histamine, pentagastrin or urecholine. These studies suggest that acid acts directly on the parietal cells by decreasing their capacity to secrete acid in response to a variety of secretory stimuli of both endogenous and exogenous origin.

Thus, besides the established inhibitory mechanisms of acid secretion arising from the antrum and duodenum already recognized for more than half a century (Pavlov, 1910), another feedback inhibition of fundic origin has been demonstrated. It is important to mention that this fundic feedback inhibition does not result from interference with the blood supply of the gastric mucosa. Using the aminopyrine clearance technique we have shown that chemical stimulation and distention of the oxyntic

gland area causes a pressure-related increase of the gastric mucosal blood flow. The decrease of gastric content pH during constant distention pressure is followed by a pH-related reduction in the mucosal blood flow. Since the *R* value was well sustained throughout the study with varying pHs it may be concluded that the reduction in the mucosal blood flow with a decreasing gastric content pH was probably secondary to the inhibition of secretory activity.

Secretin is recognized as one of the enterogastrones released by acid in the intestine, which have a possible physiological role in the feed-back inhibition of gastric secretion. In the intact stomach exogenous secretin causes a dose-related inhibition of gastric response to meal, probably due to the suppression of the release of gastrin as well as to interference with its action on the parietal cells (Konturek, Biernat & Grzelec, 1973; Thompson, Reeder, Bunchman, Becker & Brandt, 1972). In the conditions of our present study, secretin caused a small but dose-related inhibition of acid secretion during chemical stimulation of the oxyntic gland area. The threshold for the inhibition appeared at the dose of 1 u./kg.hr, but a dose of 8 u./kg.hr producing maximal pancreatic bicarbonate output caused about 40% inhibition of acid secretion. The importance of secretin-dependent feedback inhibition of gastric secretion under physiological circumstances has not been established because the release of this hormone in response to a meal may be relatively small. The observed inhibition by secretin should rather be considered as a pharmacological than a physiological effect of this hormone.

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