Secretin: the enterogastrone released by acid in the duodenum

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METHODS

Four dogs, weighing between 13 and 19 kg, were prepared with a Gregory cannula (5) in a Heidenhain pouch and a Thomas cannula in the main stomach (13). In addition, a duodenal fistula was made by placing another Gregory cannula in the duodenum about 10 cm distal to the pylorus (Fig. 1). Three weeks were allowed for recovery from surgery before experiments were begun.

During an experiment the secretion from the Heidenhain pouch was collected every 15 min for 4.25 hr. The volume of the samples was read to the nearest 0.1 ml and acid content was determined by titration with 0.2 N sodium hydroxide to pH 7.0 on an autoburette titrator and pH meter (Radiometer, Copenhagen, Denmark). Throughout an experiment the gastric fistula remained open and constant infusions into the duodenal cannula (160 ml/hr) and into an intravenous catheter (60 ml/hr) were maintained by Harvard peristaltic pumps. The duodenal infusate was 154 mm NaCl or 160 mm HCl; the intravenous infusate was 154 mm NaCl with or without added secretory stimulants and secretin.

Basal secretion was collected from the pouch for four 15-min periods. Gastrin (0.4 or 0.8 g/kg per hr) or histamine dihydrochloride (0.04 mg/kg per hr) was then added to the saline in the intravenous infusion. The gastrin used was prepared by the method of Gregory and Tracy (7) carried only through the isopropanol stage; the dose is expressed in grams of the equivalent wet weight of mucosa. Seventy-five minutes later, when the rate of secretion was about 1 mEq/15 min, either 160 mm HCl was substituted for NaCl in the duodenal infusate or 4 U/kg per hr pure secretin (GIH Laboratory, Karolinska Institute, Stockholm, Sweden, batch 16771) was added to the intravenous infusion. Acid or secretin was removed from the infusions after 1 hr. The animals then continued for an additional hour to receive saline through the duodenal cannula and stimulant intravenously. During control experiments saline was infused continuously into the duodenum.
Each point in the graphs is the mean acid output for a 15-min period, taken from two observations on each of four dogs; the vertical lines are standard errors of the means.

RESULTS

Gastrin-stimulated secretion. The intraduodenal infusion of 160 mM HCl (40 ml/15 min) produced an 85% inhibition of pouch secretion stimulated by 0.4 g gastrin/kg per hr (Fig. 2). Against the same stimulation a physiological dose (see discussion) of secretin (4 U/kg per hr) caused complete inhibition of secretion. The time courses of the two inhibitions were almost identical, except that against this submaximal dose of gastrin, secretin inhibition lasted longer after the infusion was over than did acid inhibition.

When secretion was stimulated with a dose of gastrin known to be near maximal (0.8 g/kg per hr), the same infusate of acid produced a 75% inhibition, while the same dose of secretin inhibited secretion 90% (Fig. 3). Again the inhibition caused by secretin was greater than that caused by acid.

Histamine-stimulated secretion. The above experiments were repeated using a dose of 0.04 mg histamine dihydrochloride/kg per hr to stimulate secretion (Fig. 4). The responses to this dose of histamine and to the higher dose of gastrin were about equal. Neither the duodenal infusion of acid nor the intravenous infusion of secretin produced any inhibition of gastric secretion. In this respect, too, the responses to acid and secretin were identical.

DISCUSSION

Enterogastrone1 is defined as a hormone that is released from the upper duodenum when acid, fat or its

1 Although the word enterogastrone was coined by Kosaka and Lim (10) to designate the intestinal inhibitor of gastric secretion and motility released by fat, more recent usage (e.g., Gregory (6)) has extended the definition to include gastric inhibitors released from the intestine by acid and hypertonic solutions as well as by fat. We use the term enterogastrone in this latter broader sense.
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digestion products, or hypertonic solution come in contact with the duodenal mucosa, and which inhibits gastric secretion and motility. The hormone was discovered by Ivy and Farrell in 1925 (9) when they observed that feeding fat inhibited the motility of a transplanted fundic pouch. Evidence soon followed that the inhibition of gastric secretion by fat was also hormonal in nature. Feng et al. (2) showed that if fat were added to a meat meal, the expected secretion from a transplanted fundic pouch failed to materialize. They offered proof that the inhibitory agent was not an absorbed digestion product of fat and presumed it to be a hormone liberated from the duodenal mucosa.

Inhibition of gastric secretion by acid in the duodenum is well documented (11,15). The evidence also shows that this inhibition is, at least in part, hormonal in nature (1,15).

The conclusion that a hormone existed in the duodenum which inhibited gastric secretion prompted a search for it in duodenal extracts. Kosaka and Lim found that an extract of duodenum made after exposure to olive oil inhibited secretion and named the active principle enterogastrone (10). Subsequent attempts to extract enterogastrone were made by many investigators, who found it relatively easy to obtain substances which would inhibit the acid response to a meal. This work has been reviewed recently by Gregory (6).

The most recent chapter in the enterogastrone story concerns the effects of other duodenal hormones on gastric secretion. Greenlee et al. (4) found that a crude commercial extract of secretin inhibited pouch secretion stimulated by gastrin. Gillespie and Grossman (3) showed that a duodenal preparation having cholecystokinin-pancreozymin activity also inhibited gastric secretion.

In an earlier study from this laboratory (14) synthetic secretin was shown to inhibit gastrin-stimulated secretion, leaving no doubt that secretin per se is an inhibitor. In the experiments reported here a pure form of secretin was administered by continuous intravenous infusion, which more closely mimics physiological release than does a single injection. In studies conducted on four other dogs with pancreatic fistulas the dose of secretin used here (4 U/kg per hr) was found to produce approximately 90% of the maximal pancreatic response and is therefore regarded as a “physiological” dose since it is submaximal. The effects of this dose of secretin on gastric secretion from Heidenhain pouches stimulated by gastrin and histamine were compared to the effects produced by irrigating the duodenums with exogenous acid. The duodenums were infused with 40 μl of 160 mm hydrochloric acid/15 min. This is approximately the highest concentration and volume rate of acid produced by the maximally stimulated stomach, and it is no doubt higher than the concentration found in the duodenum during a meal. Secretin reproduced in every way the effects of the endogenous hormone. The inhibition seen with the exogenous secretin was actually more complete than that seen with acid, for against stimulation with 0.4 g gastrin/kg per hr exogenous secretin produced complete inhibition in every animal for at least one 15-min period. The observation of Wormsley and Grossman (15) that exogenous secretin produced no further inhibition of gastric secretion from a Heidenhain pouch after the gastric fistula had been closed is further evidence favoring the view that the exogenous and endogenous hormone are identical. We obtained greater inhibition with both exogenous and endogenous secretin than did Wormsley and Grossman. Perhaps this may be explained by our use of a constant infusion of secretin rather than a single shot and exogenous rather than endogenous acid.

Grossman (8) has recently suggested two criteria to be used to help decide whether the action of a hormone is physiological. First, the effect must be produced by a dose given by constant intravenous infusion that is submaximal for the primary response to the hormone. Second, it must be possible to reproduce the effect in kind and magnitude by endogenous hormone. The inhibitory effect of secretin on gastric acid secretion clearly meets these criteria. With near-maximal stimulation by exogenous gastrin we obtained nearly complete inhibition of gastric secretion using a physiological dose of secretin. In addition these experiments show that secretin can account for all the inhibition of gastric acid secretion produced by acid in the duodenum. Therefore, we conclude that secretin is probably the only enterogastrone released by acid in the duodenum. Whether there is a separate enterogastrone released by the presence of other substances in the duodenum remains an open question.

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REFERENCES