Inhibitory Effect of Pancreatic Secretin on Gastric Secretion

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ABSTRACT

GREENLEE, HERBERT B., ENRIQUE H. LONGHI, JOSE DELGADILLO GUERRERO, THOMAS S. NELSEN, ABDUL LATIF EL-BEDRI AND LESTER R. DRAGSTEDT. Inhibitory effect of pancreatic secretin on gastric secretion. Am. J. Physiol. 190(3): 396-402. 1957.—In dogs prepared with both a vagus denervated Heidenhain pouch and a total pancreatic fistula, the intravenous injection of pancreatic secretin (Lilly) produced a profuse secretion of pancreatic juice and a simultaneous marked inhibition of gastric secretion. In dogs prepared with an isolated antrum pouch and a Heidenhain pouch the gastric secretion induced by the instillation of food in the antrum pouch was completely inhibited by the intravenous injection of pancreatic secretin. On the other hand, the intravenous injection of pancreatic secretin had little or no effect on the secretion of gastric juice produced by insulin hypoglycemia or by the injection of histamine. It is suggested that pancreatic secretin may represent the mechanism by means of which acid food in the duodenum inhibits gastric secretion. It is probable that this inhibition is caused by prevention of gastrin release from the antrum rather than to a depressant effect on the parietal cells.

Babkin (1) credits Sokolov working in Pavlov's laboratory with being the first (1904) to demonstrate that the introduction of gastric juice into the duodenum produced a marked diminution in the secretion of gastric juice from a Pavlov pouch. Subsequently this inhibitory effect of acid in the duodenum on gastric secretion was extensively studied and in general the findings of Sokolov confirmed. Thus Day and Webster (2) found that the introduction of food acidified with gastric juice into the duodenum, surgically disconnected from the stomach, inhibited gastric secretion stimulated either by sham feeding or by the presence of foods in the intestines. Wilhelmj and his associates (3) concluded that inhibition of the gastric and intestinal phases of secretion was marked when acid was introduced into the duodenum whereas the nervous phase of secretion was little affected. Griffiths (4) reported that the experimental introduction of hydrochloric acid solutions directly into the duodenum of man greatly diminished the secretory response of the stomach to an alcohol test meal. For the most part, however, the mechanism of this acid inhibition of gastric secretion appears not to have been extensively studied. The recent finding in our laboratory that the intravenous injection of a preparation of pancreatic secretin obtained from Eli Lilly and Company produced a profuse secretion of pancreatic juice and a simultaneous marked inhibition of gastric secretion in dogs prompted the studies embodied in this report. The observation appeared interesting in view of the statement by Kosaka and Lim (5) that their preparations of enterogastrone contained no pancreatic secretin.

EXPERIMENTAL PROCEDURE

Preparations of secretin suitable for intravenous injection in human patients were secured from Eli Lilly and Company and used for the following experiments. The preparation contained 10 clinical units of pancreatic secretin per cubic centimeter, 1 clinical unit

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Fig. 1. Effect of an intravenous injection of pancreatic secretin (1.5 U/kg) on the secretion of gastric and pancreatic juice in a dog provided with a total pancreatic fistula and a Heidenhain pouch. A simultaneous stimulation of pancreatic secretion and inhibition of gastric secretion was produced.

Fig. 2. Effect of an intravenous injection of pancreatic secretin on gastric secretion in a dog with a Heidenhain pouch. This animal was also provided with an isolated pouch of the antrum which was stimulated continuously during the course of the experiment by the instillation of 3% liver solution every 15 min. Injection of pancreatic secretin produced a marked temporary depression in gastric secretion.

being equal to 1 Ivy dog unit. Unless otherwise indicated the pancreatic secretin was administered intravenously in doses of 1.5 clinical units/kg of body weight.

The first experiment was performed on a dog with both a total pancreatic fistula and a Heidenhain pouch as illustrated in figure 1. After recovery from this rather extensive surgical operation the animal was maintained in good nutrition and electrolyte balance. The daily secretion of gastric juice and pancreatic juice became relatively constant. In the experiment illustrated in the chart in figure 1, the intravenous injection of a dose of pancreatic secretin produced an immediate profuse secretion of pancreatic juice and concomitantly an almost complete cessation in the output of acid gastric juice from the Heidenhain pouch. This effect lasted from 15 to 30 minutes and at the end of 30 minutes the rate of each secretion returned to the previous level. The stimulation of pancreatic secretion was, of course, anticipated but the profound depression of gastric secretion had not, to our knowledge, been previously observed. Realizing that this finding might provide a clue to the mechanism of the inhibition of gastric secretion resulting from the introduction of acid food into the duodenum, the following experiments were performed in animals with various types of isolated stomach pouches.

Animals were prepared as illustrated in figure 2 with a Heidenhain pouch, an isolated pouch of the gastric antrum and with intestinal continuity re-established by anastomosis of the main stomach to the first part of the duodenum. The repeated introduction of 3% liver solution of pH 7 into the isolated antrum
pouch produced a continuous stimulation of gastric juice from the Heidenhain pouch. During the course of this stimulation 25 μ of pancreatic secretin (Lilly) was injected intravenously. There was an immediate depression in the output of acid from the Heidenhain pouch with a gradual return to normal after a period of 30-45 minutes.

The next step was to determine if the secretory response of the Heidenhain pouch to a test meal could be abolished by the repeated intravenous injection of pancreatic secretin. Three dogs with Heidenhain pouches were tested in this manner. First a control response of the animal to a standard test meal (200 gm of a proprietary dog food, Pard) was obtained. On the next day a similar meal was given but in addition the animal was injected with pancreatic secretin intravenously every 15 minutes. Initially all of the animals displayed a complete inhibition of gastric secretion. In two dogs there was a slight gastric secretory response beginning about one hour after the meal was consumed. In one animal illustrated in figure 3, gastric secretion was completely suppressed by the administration of pancreatic secretin.

The effect of pancreatic secretin on the nervous phase of gastric secretion was then investigated. Dogs were prepared with vagus innervated total gastric pouches by the method of Dragstedt and Ellis (6). After recovery from the surgical procedure, electrolyte balance was maintained by the daily intravenous injection of salt solution. When the daily output of gastric secretion had become relatively constant the secretory response to insulin hypoglycemia was determined. Ten units of regular insulin
FIG. 5. Graphs showing that the intravenous injection of pancreatic secretin does not inhibit the secretion of gastric juice from the Heidenhain pouch elicited by the repeated injection of histamine (0.025 mg and 0.05 mg given subcutaneously every 15 min.).

FIG. 6. Graphs showing that the intravenous injection of pancreatic secretin does not abolish the gastric secretory response of the vagus innervated Pavlov pouch to feeding or insulin hypoglycemia. Reduction in gastric juice output can probably be accounted for by the effect of pancreatic secretin on the gastric phase of secretion.

were given by intravenous injection. Gastric secretion was collected every 15 minutes, the volume measured and the free acid concentration titrated in the usual manner. The acid output was calculated by multiplying the volume expressed in liters by the acid concentration expressed in clinical units. When a standard response to insulin hypoglycemia had been determined for each animal the same test was performed but in addition 18 u of pancreatic secretin were given intravenously every 15 minutes. A representative experiment is illustrated graphically in figure 4. The intravenous injection of pancreatic secretin had little or no effect on the gastric secretory response to insulin hypoglycemia, indicating that it does not apparently depress the nervous phase of gastric secretion.

The effect of pancreatic secretin on histamine stimulated gastric secretion was also tested in Heidenhain pouch dogs. During the fasting control period these pouches secreted no gastric juice. The subcutaneous injection of histamine in doses of 0.025-0.05 mg produced a relatively constant stimulation of secretion from the Heidenhain pouch. Intravenous injections of pancreatic secretin were then made during the period of histamine stimulation. A representative experiment is graphically illustrated in figure 5. It is apparent that pancreatic secretin does not inhibit the histamine stimulated gastric secretory response of the Heidenhain pouch.

In the experiment graphically illustrated in figure 6, the secretory response of a vagus innervated Pavlov pouch to a standard test meal was determined. On the next day the same meal was given but concomitantly with the
feeding intravenous injections of pancreatic secretin were given every 15 minutes. The secretin markedly reduced but did not abolish the gastric secretory response of the Pavlov pouch to the test meal. The decrease in secretion can probably be accounted for by the inhibitory effect of pancreatic secretin on the gastric phase of secretion since the curve of the secretory response of the Pavlov pouch to insulin hypoglycemia very closely resembled the response of the pouch to the test meal and the intravenous injection of secretin.

In the experiment illustrated in figure 7, animals were prepared with both the Heidenhain pouch and a total pancreatic fistula of the type previously described from this laboratory (7). After recovery from this operation the animals were maintained in electrolyte balance by the daily intravenous administration of salt solution. After the daily output of gastric and pancreatic juice had become relatively constant, the effect of stimulation by a test meal was determined. A representative experiment is graphically illustrated in figure 7. The gastric secretory response of the Heidenhain pouch to a test meal was markedly reduced by the intravenous administration of pancreatic secretin while at the same time, the secretion of pancreatic juice was markedly increased. The output of acid from the Heidenhain pouch did not rise much above the control level until the secretin injections were stopped.

The experiment illustrated in figure 8 was performed on animals prepared initially for a different type of study of antrum physiology. A Heidenhain pouch was prepared and the antrum excluded from contact with food by a mucous membrane partition between the antrum and body of the stomach and at the

FIG. 7. Graphs showing the inhibitory effect of repeated injections of pancreatic secretin (18 \text{ u} every 15 \text{ min.}) on gastric secretion from the Heidenhain pouch and simultaneous prolonged stimulation of pancreatic secretion where stimulation was also caused by feeding.

FIG. 8. Graphs showing the profound inhibitory effect of repeated intravenous injections of pancreatic secretin on gastric secretion from the Heidenhain pouch in a dog provided also with isolated antrum pouches with vagus innervation intact. Previous work from this laboratory has demonstrated that feeding in this type of animal stimulates Heidenhain pouch secretion as a result of the liberation of gastrin from the isolated antrum pouches produced by peristaltic activity. This experiment illustrates that pancreatic secretin inhibits the gastric phase of secretion aroused by motility of the antrum in the absence of contact with food.
PANCREATIC SECRETIN AND GASTRIC SECRETION

Fig. 9. Graphs showing the inhibitory effect of an acidified meal on Heidenhain pouch secretion aroused by the instillation of liver solutions into the isolated antrum. Presumably the acidified food coming in contact with the upper jejunum or duodenum has caused the release of an inhibitory agent (possibly pancreatic secretin).

Fig. 10. Graphs showing the inhibitory effect of an acidified meal on Heidenhain pouch secretion induced by the repeated instillation of liver solution in the isolated denervated antrum pouch.

pylorus. In addition in several of the animals, the isolated antrum was again divided into two pouches by a mucous membrane partition. The vagus innervation of the antrum pouches was preserved. Intestinal continuity was restored by making an anastomosis between the main stomach and the first portion of the jejunum. In another study from this laboratory it was observed by Oberhelman, Rigler and Dragstedt (8) that an animal prepared in this way displays a vigorous secretory response from the Heidenhain pouch in response to a test meal. No food comes in contact with the antrum mucosa. During fasting the Heidenhain pouch secretes little or no gastric juice. It will respond, however, to insulin hypoglycemia. Both the secretory response of the Heidenhain pouch to insulin hypoglycemia and to the test meal have been interpreted as secondary to the peristaltic activity of the antrum pouches and the release of gastrin. If this is the correct explanation then the experiment graphically illustrated in figure 8 is in harmony with the previous experiments reported in this paper. The administration of a test meal produced a vigorous secretion from the Heidenhain pouch. When, however, pancreatic secretin was given in addition to the test meal the secretory response of the Heidenhain pouch to the test meal was almost entirely abolished. This again suggests that the inhibitory effect of pancreatic secretin on gastric secretion is manifested chiefly on the release of gastrin.

In the experiments previously described inhibition of gastric secretion attributed to the effect of pancreatic secretin has been obtained only on the intravenous injection of extracts of duodenal mucosa. In the experiment...
graphically illustrated in figure 9, the effect of an acid meal in the duodenum on Heidenhain pouch secretion was determined. The preparation was the same as that employed in figure 8, and stimulation of Heidenhain pouch secretion was secured by the installation of a neutral 3% liver solution into antrum pouch ‘A’ every 15 minutes during the entire experiment. When the secretion from the Heidenhain pouch was at a fairly constant level the animal was fed a test meal to which 14 cc of 6 N HCl had been added. The addition of acid increased the acidity of the meal to approximately pH 1. Beginning about one-half hour after the ingestion of this meal the secretion of acid from the Heidenhain pouch was markedly reduced and this depression persisted for the next hour and one-half in spite of the continued introduction of liver solution into the antrum pouch every 15 minutes. Gradually, however, the secretion from the Heidenhain pouch returned to the previous control level. This experiment shows that the presence of acid food in the jejunum and possibly also in the duodenum, causes the release of a humoral agent (pancreatic secretin) which inhibits Heidenhain pouch secretion induced by antrum stimulation.

In the experiment illustrated in figure 10, the previous experiment was repeated except that in this case a denervated isolated pouch of the antrum was employed for stimulating gastric secretion. Here again a definite inhibition in the output of acid from the Heidenhain pouch followed the ingestion of the acid meal.

DISCUSSION
The preparation of pancreatic secretin used in these studies was satisfactory for intravenous injection in human patients but is not a pure substance. It is thus entirely possible that the preparation may contain a substance, pancreatic secretin which stimulates pancreatic secretion, and a second substance which inhibits the secretion of gastric juice. Further experiments with a pure preparation of pancreatic secretin are necessary to decide this question. It seems unlikely that the inhibitory substance in the pancreatic secretin preparation employed in these studies could be entero-gastrone. According to Kosacka and Lim (5) their preparations of entero-gastrone contained no pancreatic secretin and were effective in inhibiting the secretion of gastric juice stimulated by histamine. In the experiments described in this paper pancreatic secretin had little or no inhibitory effect on histamine stimulated gastric secretion. It likewise had little or no effect on the secretion of gastric juice elicited by vagus stimulation i.e. insulin hypoglycemia or psychic stimulation by food taking in Pavlov pouch animals. It is probable that the inhibitory effect of pancreatic secretin is exerted chiefly or exclusively on the gastric phase of secretion. The fact that it does not inhibit gastric secretion stimulated by the injection of histamine suggests that the inhibitory effect is produced through prevention of the formation or release of gastrin from the antrum rather than to a depressant action on the parietal cells. In those experiments where the intestinal phase of gastric secretion was probably present, as when gastric secretion was induced in Heidenhain pouches by test meals, inhibition of the intestinal component appeared to be very little or was entirely absent. Thus there might be profound inhibition of gastric secretion for the first 2 or 3 hours but subsequently a return of gastric secretion at the time when the intestinal phase should be active. This return might occur even though the injections of pancreatic secretin were continued.

REFERENCES