Effect of Secretin and Cholecystokinin on the Response of the Gastric Fistula Rat to Pentagastrin (33835)

DANIEL B. TUMPSON AND LEONARD R. JOHNSON
(Introduced by Morton I. Grossman)
Research, Veterans Administration Center, Los Angeles, California 90073

The inhibitory effect of secretin on gastric acid secretion in the dog is well documented. Secretin has been shown to inhibit acid secretion stimulated by food and antral irrigation (1), duodenal distension (2), intestinal stimulation (3), and exogenous gastrin (4). Although pure secretin is a potent inhibitor of gastrin-stimulated secretion in the dog (5), it has little effect on gastric acid secretion in the cat (6).

That secretin can prevent electrical shock ulcers in the rat (7) suggests that it may inhibit gastric secretion in this species. In this paper we have, therefore, evaluated the inhibitory effects of secretin on pentagastrin-stimulated secretion in the rat. In addition, the effect of cholecystokinin (CCK), the other characterized duodenal hormone, on rat gastric secretion was investigated.

Methods. Fourteen male Sprague-Dawley rats weighing 325–528 g were prepared with gastric fistulas using the cannula and surgical procedure described by Lane *et al.* (8). Experiments were begun 1 week after surgery and were run on alternate days no more than 5 times in a 2-week period for any one rat.

Animals were fasted from 14 to 18 hr before each experiment. To prevent coprophagia they were restrained in a Bollman cage (9) during the period of fasting as well as during the experiment. The stomachs were then washed out with saline and allowed to drain before collecting any samples. To prevent stress from repeated skin punctures, a 22-gauge needle was inserted under the skin and allowed to remain for the duration of the experiment. Isotonic saline (1–3 ml) was injected hourly to maintain fluid and electrolyte balance.

Secretion was collected in 1-ml disposable syringes sealed at one end. A short length of PE 100 polyethylene tubing was used to lead the fluid from the cannula to the collecting tube. The volume of secretion was read to the nearest 0.01 ml every 15 min and the acid content was determined by titration with 0.2 *N* NaOH using an Autoburette and pH meter (Radiometer, Copenhagen).

After basal secretion was collected for 1 hr, pentagastrin (ICI 50, 123) or pentagastrin combined with either secretin or CCK (G.I.H. Laboratory, Karolinska Institute, Stockholm, Sweden) was injected subcutaneously. Secretion was then collected for 2 hr, at the end of which the injections were repeated giving animals which had previously received pentagastrin alone the combination of pentagastrin and one of the hormones.

In any one experiment half of the animals received pentagastrin first and the other half the combination. In the next experiment the order of injection was reversed for any one animal.

Pentagastrin was administered in doses of either 62.5 or 125 μg/kg. Secretin and CCK were both given in amounts equal to 75 units/kg.

In calculation of the results, acid output was expressed as μeq of H^+/15 min. Means and SEM were calculated for pentagastrin alone and for pentagastrin plus secretin or CCK irregardless of the order of injection during the individual experiments. Significance was determined using the t test for unpaired values (one-tailed).

Results. Secretin (75 U/kg) completely prevented the stimulation of gastric secretion seen after an injection of 62.5 μg/kg of pentagastrin. Peak acid output occurred 30 min after the injection of pentagastrin and was significantly different ($p<0.001$) than the corresponding secretion seen when secretin was injected with the pentagastrin (Fig. 1).

Acid production stimulated by a supramaximal dose of gastrin (125 μg/kg) was also prevented by 75 U/kg of secretin ($p<0.001$)

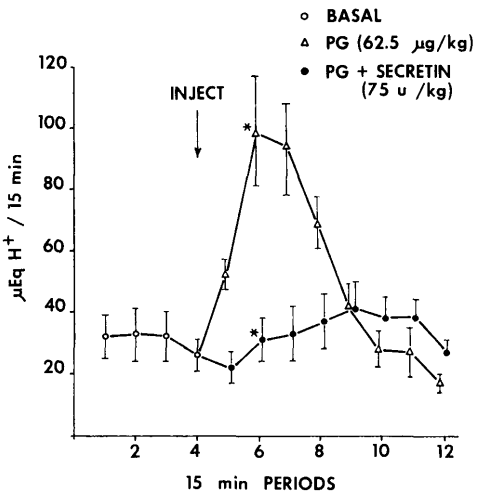

FIG. 1. Response of chronic gastric fistula rats to 62.5 μg/kg pentagastrin (PG), alone and in combination with 75 units/kg of secretin. First four points are basal secretory levels; two observations in each of 14 animals, means ± standard errors of the means; $*p<0.001$.

(Fig. 2). At this dose of gastrin inhibition persisted for a full hour after injection.

CCK in combination with pentagastrin (62.5 μg/kg) reduced the peak response to pentagastrin alone by 50% ($p<0.001$) (Fig. 3). Inhibition, however, was far from complete as it was in the case of secretin. In fact 45 min after injection the response to pentagastrin plus CCK began to increase and at 75 min was significantly higher ($p<0.05$) than the response to pentagastrin alone.

Discussion. Secretin produced a complete inhibition of gastric secretion stimulated by both maximal and supramaximal doses of pentagastrin. We have considered the possibility that the decrease in acid output was due not to secretin inhibition of gastric acid secretion, but to neutralization by secretin induced bicarbonate secretion being regurgiatated from the duodenum. If this were the case the volume of secretion would be expected to rise or stay the same with a decrease in

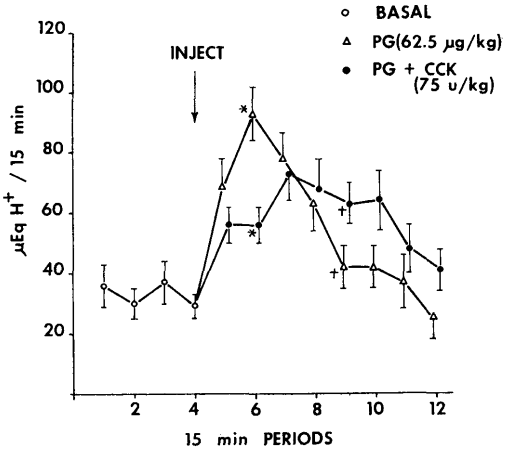

FIG. 3. Gastric acid response to 62.5 μg/kg of pentagastrin alone or in combination with 75 units/kg of CCK. Means and SEM for 2 observations in each of 14 rats; $*p<0.001$; T, $p<0.05$.

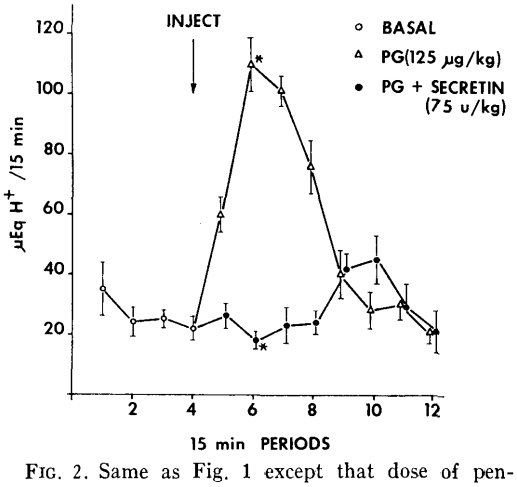

FIG. 2. Same as Fig. 1 except that dose of pentagastrin was 125 μg/kg. Two observations in each of 8 animals; $*p<0.001$.

H^+ concentration during secretin administration. In the event, the opposite occurred in that inhibition was due to a precipitous drop in volume with only a small decrease in concentration. We conclude, therefore, that secretin is a strong inhibitor of gastrin stimulated acid secretion in the rat just as it is in the dog.

Cholecystokinin did not produce as clear-cut an effect on pentagastrin-stimulated secretion. Shortly after injection a significant inhibition of gastric secretion was noted, but at 75 min after injection when the response to pentagastrin alone diminished that to CCK plus pentagastrin rose, so that at this later time a significant stimulation was recorded. An explanation for this effect can be

found, for in dogs CCK stimulates gastric secretion when given alone (10), but inhibits when given as an infusion or as a rapid intravenous injection against a background of gastrin stimulation (11). CCK would dissociate slowly. Therefore during the peak period of gastrin stimulation one CCK molecule would be occupying receptors which would otherwise be reacting with several gastrin molecules. This would lead to an inhibition of secretion.

The work by Barrett (12) was originally used as a guide line for determining doses of pentagastrin. He found that 125 μg/kg produced about 90% of the maximal acid response in anesthetized rats. This dose was supramaximal in the conscious animal, however, and we found that 62.5 μg/kg produced maximal secretion.

Summary. In rats with chronic gastric fistulas, secretin completely inhibited the gastric acid response to both maximal and supramaximal doses of pentagastrin. In the rat as in the dog, therefore, secretin is a potent inhibitor of gastrin-stimulated secretion.

The effects of CCK on pentagastrin-stimulated secretion were mixed. An early inhibitory phase was followed by a period of stimulation. This twofold effect has also been noted in the dog and depends upon the background secretory activity.

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