Effect of Secretin on Gastric Acid Secretion Stimulated by Gastrin II, Caerulein and Desulfated Caerulein* (34030)

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In dogs secretin inhibits gastric acid secretion stimulated by porcine gastrin, a 17 amino acid peptide (1), and by pentagastrin a pentapeptide related to the C-terminal tetrapeptide amide of gastrin (2). The present study demonstrated that secretin is also an effective inhibitor of acid secretion provoked by caerulein and desulfated caerulein, decapeptides whose structures closely resemble those of gastrin and cholecystokinin (Fig. 1).

Methods. Four dogs weighing 14–21 kg were prepared with a Gregory cannula (3) in a Heidenhain pouch and a Thomas cannula (4) in the main stomach. Experiments were started at least 2 weeks following surgery and were conducted at intervals of 48–72 hr. Three of the dogs were used in the studies of gastrin II and caerulein; one of these was replaced in the desulfated caerulein experiments.

Following an 18-hr fast, 15-min collections of gastric juice were obtained from the gastric fistula (GF) and the Heidenhain pouch (HP). Volumes were measured and a 0.2-ml sample was titrated with 0.2 *M* NaOH to pH 7 on an automatic titrator (Radiometer, Copenhagen, Denmark).

An intravenous infusion of 154 m*M* NaCl was delivered at a rate of 60 ml/hr via peristaltic pump (Harvard Apparatus Co., Doer, Mass.) throughout each study. Test substances were added to the NaCl infusion.

Four basal 15-min colections were obtained while the animals received an infusion of 154 m*M* NaCl. A gastric stimulant was then added to the infusion and gastric juice was collected for a further thirteen 15-min periods. The stimulants were: (a) porcine gastrin II (a gift from Professor R. A. Gregory and Dr. Hilda J. Tracy, Liverpool, England), 1.0 μg/kg-hr (5 observations in 3 dogs). (b) caerulein, 0.15 μg/kg-hr (5 observations in 3 dogs). (c) Desulfated caerulein, 0.60 μg/kg-hr (6 observations in 3 dogs). Both caeruleins were a gift from Professor V. Erspamer, Rome, Italy. The same number of tests were conducted using the same stimulants in the same dogs, with the addition of pure natural secretin (GIH Laboratory, Karolinska Institute, Stockholm, Sweden, Batch no. 16861), 1 unit/kg-hr, to the intravenous infusion during the tenth through thirteenth 15-min collection periods.

C-TERMINAL HEPTAPEPTIDE AMIDES

GASTRIN II	^{HSO_3}-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2
CCK	^{HSO_3}-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2
CAERULEIN	^{HSO_3}-Tyr-Thr-Gly-Trp-Met-Asp-Phe-NH_2

Fig. 1. The carboxy-terminal heptapeptide amides of gastrin II (17 amino acids), cholecystokinin (33 amino acids) and caerulein (10 amino acids).

Results. Secretin profoundly inhibited acid secretion from the HP during infusion of gastrin II (Fig. 2) caerulein (Fig. 3) and desulfated caerulein (Fig. 4). Acid output fell to 20–36% of control levels during the final 2 periods of secretin infusion ($p<0.05$) although there was only a slight decrease in acid concentration (Table I). In the GF stimulated by gastrin II and caerulein, secretin produced a decrease in acid output and acid concentration similar to that observed in the HP. Duodenal reflux into the stomach during

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TABLE I. Effect of Secretin on Heidenhain Pouch Acid Concentration and Output.[a]

Stimulant	Acid concentration (meq/liter)		Decrease (%)	
	Control experiments	Secretin experiments	Acid concentration	Acid output
Gastrin II	145 ± 5	117 ± 11	19	66
Caerulein	147 ± 5	129 ± 7	12	80
Desulfated caerulein	112 ± 11	99 ± 12	12	64

[a] The values shown are the mean ± SE of the mean for the last 2 periods of secretin infusion (periods 12 and 13).

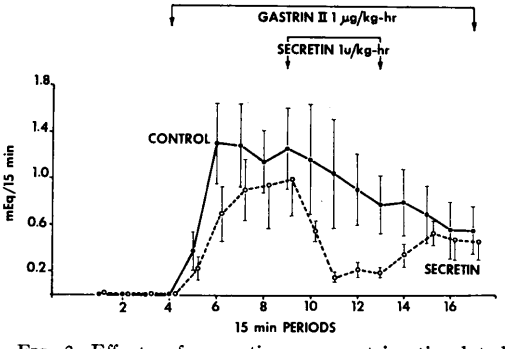

FIG. 2. Effect of secretin on gastrin-stimulated acid output from the Heidenhain pouch; each point represents the mean of 5 observations on 3 dogs.

the desulfated caerulein studies produced high volumes with low titratable acidity. Because of the possible contribution of duodenal reflux to all studies on the GF, none of these data are presented.

Even though the data from the GF studies are not reliable, it is important that tests of this kind be conducted in animals with open gastric fistulas so acid from the main stomach cannot enter the duodenum and release unknown amounts of endogenous secretin (5).

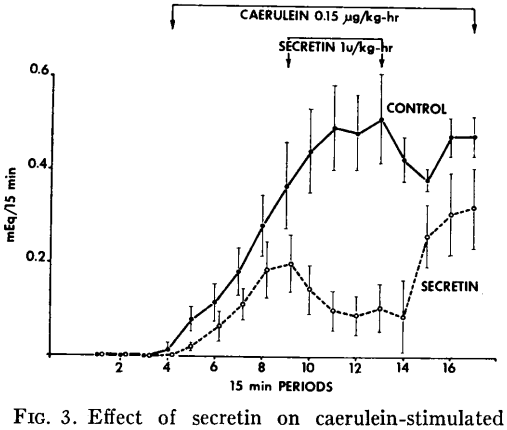

FIG. 3. Effect of secretin on caerulein-stimulated acid output from the Heidenhain pouch; each point represents the mean of 5 observations on 3 dogs.

Discussion. Caerulein is a decapeptide obtained from the skin of the frog *Hyla caerulea* (6). Its cholecystokinetic activity and stimulatory effects on gastric, pancreatic, and biliary secretion resemble those of cholecystokinin (7, 8), but it is more potent on a molar basis (9). Both caerulein and cholecystokinin also inhibit gastrin-stimulated gastric secretion (10).

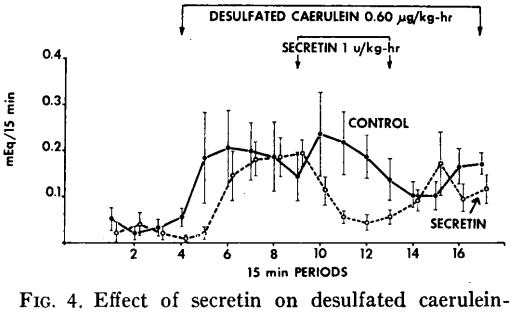

FIG. 4. Effect of secretin on desulfated caerulein-stimulated acid output from the Heidenhain pouch; each point represents the mean of 6 observations on 3 dogs.

The C-terminal heptapeptide amides of cholecystokinin and caerulein are identical with the C-terminal hexapeptide amide of gastrin II except that they have an additional amino acid interposed between glycine and the sulfated tyrosine (Fig. 1). In cholecystokinin this amino acid is methionine and in caerulein it is threonine. Desulfation of the caerulein moelcule reduces its cholecystokinetic and acid stimulating potency (9); desulfation of porcine gastrin II produces no recognized alteration of its biological properties (11).

Gastrin-stimulated gastric acid secretion in the dog is inhibited by crude secretion (1), highly purified porcine secretin (12), synthetic secretin (12) and endogenous secretin released by duodenal acidification (5). Johnson and Grossman recently demonstraged that the pattern of this inhibition fit the dynamics of a pharmacologic noncompetitive inhibitor.[1] Secretin also inhibits acid secretion from denervated canine pouches stimulated by the synthetic pentapeptide "pentagastrin" which contains the C-terminal tetrapeptide amide sequence of gastrin (2).

This study demonstrated that the inhibitory spectrum of secretin extends to sulfated and desulfated caerulein, molecules intermediate in length between gastrin and pentagastrin and possessing the C-terminal heptapeptide sequence analogous to cholecystokinin (Fig. 1). Although sulfation of the tyrosine residue has a marked effect on the potency of the caerulein decapeptide, secretin appears to be an effective inhibitor of both the sulfated and desulfated forms.

Summary. Gastric acid secretion in dogs with Heidenhain pouches (with gastric fistulas open to divert acid from the main stomach to the exterior) was stimulated with porcine gastrin II and with natural and desulfated caerulein, decapeptides whose C-terminal structure closely resembles that of gastrin and cholecystokinin. Pure natural secretin, 1 unit/kg-hr, inhibited 64–80% of the acid output from the Heidenhain pouches induced by these stimulants.

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