

## Effect of Cholecystokinin Receptor Antagonist on Pancreatic Responses to Exogenous Gastrin and Cholecystokinin and to Meal Stimuli

S. J. KONTUREK, J. TASLER, M. CIESZKOWSKI, K. SZEWCZYK, and M. HLADIJ

Institute of Physiology, Academy of Medicine, Krakow, Poland

**Exocrine pancreatic response to food is believed to result from the interaction of neural and hormonal factors, but their contribution in the net postprandial secretion is unknown. Recent description of a highly specific and potent cholecystokinin (CCK)-receptor antagonist permitted the evaluation of the physiologic role of CCK in postprandial pancreatic secretion. In dogs with chronic pancreatic fistula, CCK antagonism caused little alteration in sham feeding- or urecholine-induced pancreatic protein secretion, but reduced by ~60% the pancreatic protein response to a gastrointestinal meal and virtually abolished the pancreatic responses to duodenal perfusion with amino acids or oleate and to exogenous CCK, but not to secretin or neurotensin. The pancreatic protein responses, particularly to lower doses of gastrin, were also reduced by CCK-receptor antagonist, but no changes in the responses to secretin or neurotensin were detected. Cholecystokinin antagonism also significantly reduced the pancreatic polypeptide responses to CCK, gastrin, and the gastrointestinal meal, possibly due to removal of the CCK-mediated release of pancreatic polypeptide. We conclude that CCK plays a crucial role in the mediation of the gastrointestinal phase, but not the cephalic phase, of pancreatic secretion.**

**E**xocrine pancreatic secretion in response to ingested food results from the overlapping phases of cephalic, gastric, and intestinal stimulation (1,2). Although it is generally accepted that the pancreatic secretion is controlled by interacting neural and hormonal mechanisms, the controversy continues over the relative contribution of these mechanisms in the interdigestive and postprandial secretion (1).

The old suggestion that the reflex vagal-cholinergic mechanisms play a considerable role in the cephalic and gastrointestinal phases (2-4) of pancreatic secre-

tion has been undermined by recent evidence that antral gastrin (5,6) and intestinal cholecystokinin (CCK) (7,8) may also be important physiologic mediators in postprandial pancreatic secretion. The assessment of the hormonal contribution has been possible because of the recent description of highly specific and potent CCK-receptor antagonists (9-12), which allow pancreatic responses to be measured in the absence of the effect of CCK.

This study was undertaken to clarify the role of CCK and gastrin in the cephalic and gastrointestinal phases of pancreatic secretion, as well as in the pancreatic responses to exogenous gut hormones. This was accomplished by using one of the most potent antagonists (CR-1409) of CCK action and binding to the pancreas (9-12) in conscious dogs with chronic gastric and pancreatic fistulas.

### Materials and Methods

Studies *in vivo* were carried out on 6 mongrel dogs, weighing 18-20 kg and prepared surgically with esophageal, gastric, and pancreatic fistulas as described previously (8,13). The studies reported here started ~5 mo after surgery. Food was withheld for at least 18 h before each test. Throughout all tests, except those with feeding, the gastric fistula was left open to allow for draining of gastric juice to the outside to prevent gastric acid from entering the duodenum and releasing endogenous hormones.

Secretions from the gastric fistula and pancreatic fistula were collected continuously and divided into 15-min aliquots. The volume was recorded to the nearest 0.1 ml. Acid concentration in the gastric juice and bicarbonate and protein concentrations in the pancreatic juice were

*Abbreviations used in this paper:* CCK, cholecystokinin; CCK-8, cholecystokinin-octapeptide;  $D_{50}$ , dose producing half-maximal stimulation; PP, pancreatic polypeptide.

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measured in each sample and presented as 15- or 30-min outputs.

Several tests were performed in each animal. In tests with basal secretion, the CCK-receptor antagonist DL-4-(3,4-dichloro-benzoyl-amino)-5(di-n-pentyl-amino)-5-oxo-pentanoic acid (gift of Dr. L. Rovati from Rotta Research Lab., Milano, Italy) was infused intravenously in graded doses (0.03–2.0  $\mu\text{mol/kg} \cdot \text{h}$ ), each dose being given for 60 min and then doubled during separate tests. This compound is named CR-1409 (10), but it is also known from other reports as compound 53 (9), proglumide analogue 10 (11), or compound B (12).

In tests with meal-induced secretion, two types of experiments were performed: sham feeding and ordinary feeding. For the sham feeding procedure, the esophagus was totally obstructed distal to the esophageal fistula so that the possibility of entry of food particles into the stomach was completely excluded (13). Each dog was offered 500 g of cooked homogenized ground beef for 15 min; the ingested meal fell from the esophagus back into the feeding pan and was repeatedly reconsumed. Gastric and pancreatic collections were made for 60 min before, during, and 90 min after the sham feeding. CR-1409 (1.0  $\mu\text{mol/kg} \cdot \text{h}$ ) was given for 30 min before, during, and after sham feeding. In tests with the gastrointestinal phase, 500 g of cooked beef liver homogenized with 100 ml of water was introduced from the plastic bag directly into the stomach through the esophageal fistula, without animals being allowed to see or smell the meal. The gastric fistula was kept closed and pancreatic secretion was measured during the next 3 h. CR-1409 (0.5 or 1.0  $\mu\text{mol/kg} \cdot \text{h}$ ) was infused intravenously 30 min before and throughout the postprandial period.

In tests with duodenal acidification, a solution of 100 mM HCl was instilled into the duodenum through the intestinal limb of the pancreatic cannulas at a constant rate (8 mmol/h) to evoke near-maximal pancreatic bicarbonate secretion. In tests with duodenal perfusion with oleate, oleic acid (Sigma Chemical Co., St. Louis, Mo.) was prepared as the sodium soap by adding the desired amount of fatty acid to an aqueous solution of NaOH and stirring vigorously for as long as 60 min to obtain proper dispersion (8). The final pH was 9.4 and the final concentration of oleate used was 100 mM. L-Isomers of tryptophan and phenylalanine (Calbiochem, San Diego, Calif.) were used in solutions containing 100 mM of each, adjusted to pH 6.0. All solutions were prepared on the day of the experiment and were made isotonic ( $300 \pm 10$  mosmol/kg) by the addition of NaCl as needed. Solutions were infused at a constant rate of 80 ml/h. CR-1409 (1.0  $\mu\text{mol/kg} \cdot \text{h}$ ) was infused in the middle hour of duodenal instillation of HCl, oleate, or amino acid mixture. In control tests, the duodenal HCl, oleate, or amino acid mixture was administered alone for the duration of the experiment.

In tests with exogenous hormonal stimulation, synthetic CCK-octapeptide (CCK-8) (Squibb Institute for Medical Research, Princeton, N.J.) was infused intravenously either in graded doses (25–800 pmol/kg  $\cdot$  h) doubled every 30-min period or in a constant dose (100 pmol/kg  $\cdot$  h) given for a 5-h period. CR-1409 was administered either in a constant dose (0.5, 1.0, or 2.0  $\mu\text{mol/kg} \cdot \text{h}$ ) given through-

out the period of infusion of graded doses of CCK or in gradually increasing doses (0.03–2.0  $\mu\text{mol/kg} \cdot \text{h}$ ) administered during a constant administration of CCK-8. Gastrin heptadecapeptide (a gift of Professor R. A. Gregory, Liverpool, U.K.) was administered intravenously either in graded doses (31–2000 pmol/kg  $\cdot$  h) doubled every 30-min period or in a constant dose (250 pmol/kg  $\cdot$  h) given for 5.5 h. CR-1409 was added to an intravenous infusion of gastrin either in a constant dose (1.0, 2.0, or 4.0  $\mu\text{mol/kg} \cdot \text{h}$ ) or in gradually increasing doses (0.03–4.0  $\mu\text{mol/kg} \cdot \text{h}$ ), changed every 30 min. In tests with graded doses of CCK and gastrin without and with CR-1409, actual maximal pancreatic protein and gastric acid responses were determined in each dog and then combined from 6 dogs to calculate the mean maximum and the mean dose of CCK or gastrin producing half-maximal stimulation ( $D_{50}$ ). In tests with secretin (82 pmol/kg  $\cdot$  h) and neurotensin (50 pmol/kg  $\cdot$  h), each of these hormones was infused intravenously in a constant dose throughout the experiment to achieve a secretory rate similar to that obtained with duodenal perfusion of HCl or oleate, respectively. When the pancreatic secretion reached a well-sustained plateau, CR-1409 was added to the infusion in a constant dose (1.0  $\mu\text{mol/kg} \cdot \text{h}$ ). Secretin and neurotensin were purchased from Peninsula Laboratories, Belmont, Calif.

In all tests involving administration of CCK, gastrin, secretin, or neurotensin, a solution of 0.5% albumin (Sigma) was used to dissolve these peptides to prevent their degradation and adsorption into the plastic tubes during intravenous infusion.

In tests with sham feeding and ordinary feeding, and in tests with infusion of exogenous gastrin, blood samples were taken from the peripheral vein at 15–30-min intervals for radioimmunoassay of plasma gastrin and pancreatic polypeptide (PP). Blood samples were collected in chilled tubes with 10 U of heparin and 400 KIU of aprotinin (Trasyolol, Bayer Farma, Copenhagen, Denmark) per milliliter and centrifuged, and the plasma was frozen within 15 min of sampling. The plasma gastrin level was determined using gastrin antiserum 4562 (a gift of Prof. J. F. Rehfeld, Aarhus, Denmark) and plasma PP was assayed using PP antiserum (a gift of Dr. R. E. Chance, Eli-Lilly, Indianapolis, Ind.) as presented previously (13).

Results are expressed as mean  $\pm$  SEM. In tests comparing various nutrients and hormones with and without CR-1409, the increments in pancreatic secretory outputs and plasma hormone concentrations were calculated and averaged to provide the incremental secretory outputs and incremental plasma hormone levels for the experimental period. The significance of the differences between means was evaluated using Student's *t*-test for paired values. Differences were considered significant if  $p < 0.05$ .

## Results

### *Effects of CR-1409 on Basal Pancreatic Secretion*

In fasted dogs, basal gastric acid secretion from the gastric fistula was negligible, whereas the pancreatic secretion showed some fluctuations in

individual dogs. Protein outputs varied from ~20 to 240 mg/15 min, averaging  $80 \pm 15$  mg/15 min during the 2-h basal collection period (Table 1).  $\text{HCO}_3^-$  output also fluctuated from  $30 \pm 5$  to  $76 \pm 12$   $\mu\text{mol}/15$  min, averaging  $32 \pm 8$   $\mu\text{mol}/15$  min. Intravenous infusion of CR-1409 in doses of 0.25–2.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$  tended to reduce mean basal protein secretion, but this was significant only at the highest dose of CCK antagonist. No changes in basal gastrin or PP levels were observed after intravenous infusion of CR-1409 (Table 1).

#### Effects of CR-1409 on Pancreatic Responses to Exogenous Hormones

Infusion of CCK-8 resulted in a dose-related increase in pancreatic secretion that was reflected mainly in the protein outputs (Figure 1), whereas the volume flow and  $\text{HCO}_3^-$  outputs showed only a small increase (data not shown).

The maximal observed protein outputs in tests with CCK-8 occurred at a dose of 400 pmol/kg · h and averaged  $2350 \pm 250$  mg/30 min. The dose of CCK-8 required for half-maximal protein output averaged  $86 \pm 12$  pmol/kg · h. When CR-1409 was added at 0.5 and 1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$  to the CCK infusion, the respective maximal protein responses to CCK-8 averaged  $780 \pm 168$  and  $460 \pm 96$  mg/30 min. The respective  $D_{50}$  values in these tests were  $67 \pm 18$  and  $134 \pm 28$  pmol/kg · h. At the highest dose of CR-1409 (2.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) the pancreatic protein responses to all doses of CCK-8 were almost completely suppressed. Thus, in the presence of CR-1409 the maximal pancreatic protein responses to CCK were significantly reduced in a dose-dependent fashion, whereas the  $D_{50}$  was not changed significantly.

Plasma gastrin levels were unchanged by the intravenous infusion of CCK-8 with or without the addition of CR-1409. Plasma PP levels showed a

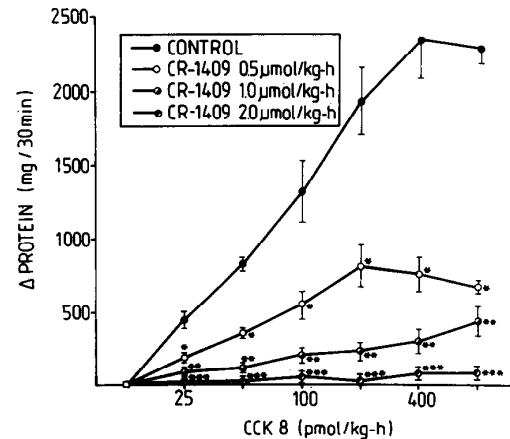


Figure 1. Increments in pancreatic outputs in response to graded doses of CCK-8 (25–800 pmol/kg · h). Mean  $\pm$  SEM of six tests on 6 dogs. Single asterisks indicate significant decrease below the control value obtained with CCK-8 alone. Double asterisks indicate significant decrease below the values obtained with CCK-8 plus CR-1409 at a dose of 0.5  $\mu\text{mol}/\text{kg} \cdot \text{h}$ . Triple asterisks indicate significant decrease below the values obtained with CR-1409 at a dose of 1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ .

dose-dependent rise with increasing doses of CCK-8. Treatment with CR-1409 did not affect basal PP levels, but reduced significantly the PP responses to all doses of CCK-8, including that producing the maximal PP response. At the higher dose of CR-1409 (2.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ), CCK-8 failed to produce any significant alterations in plasma levels of PP (Table 2).

In tests with a constant-dose (100 pmol/kg · h) infusion of CCK-8 producing ~50% maximal stimulation of pancreatic protein output, the addition of CR-1409 in gradually increasing doses (0.03–2.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) resulted in a significant decrease in protein secretion at a dose of 0.03  $\mu\text{mol}/\text{kg} \cdot \text{h}$  and almost complete suppression of the protein response to CCK at doses of 1.0 and 2.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$  (Figure 2).

In tests with gastrin heptadecapeptide, graded doses of hormone infused intravenously resulted in a dose-dependent increase in both gastric acid and pancreatic protein outputs, reaching the maximal observed outputs at a dose of 500 pmol/kg · h. These observed acid and protein maximums averaged  $7940 \pm 1090$   $\mu\text{mol}/30$  min and  $1410 \pm 230$  mg/30 min, respectively. Addition of CR-1409 to the intravenous infusion reduced both gastric acid and pancreatic protein responses to gastrin in a dose-dependent fashion. Gastric acid responses to lower doses of gastrin (31–125 pmol/kg · h) were significantly reduced by CR-1409 at a dose of 1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$  and completely suppressed at doses of 2.0 and 4.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ . With higher doses of gastrin, such as 500 and 2000 pmol/kg · h, the acid output was not

Table 1. Pancreatic  $\text{HCO}_3^-$  and Protein Outputs and Plasma Gastrin and Pancreatic Polypeptide Concentrations in Fasted Dogs Without and With Intravenous Administration of CR-1409 in Gradually Increasing Doses

	$\text{HCO}_3^-$ ( $\mu\text{mol}/15$ min)	Protein (mg/15 min)	Gastrin (pM)	PP (pM)
Basal	$32 \pm 6$	$80 \pm 15$	$21 \pm 4$	$14 \pm 2$
CR-1409				
0.25 $\mu\text{mol}/\text{kg} \cdot \text{h}$	$34 \pm 6$	$94 \pm 18$	$29 \pm 5$	$16 \pm 2$
0.5 $\mu\text{mol}/\text{kg} \cdot \text{h}$	$42 \pm 9$	$70 \pm 12$	$30 \pm 4$	$15 \pm 2$
1.0 $\mu\text{mol}/\text{kg} \cdot \text{h}$	$35 \pm 7$	$62 \pm 14$	$26 \pm 3$	$17 \pm 4$
2.0 $\mu\text{mol}/\text{kg} \cdot \text{h}$	$26 \pm 7$	$42 \pm 10^a$	$24 \pm 6$	$11 \pm 2$

PP, pancreatic polypeptide. Values shown are mean  $\pm$  SEM of six tests in 6 dogs. <sup>a</sup> Significant ( $p < 0.05$ ) decrease below the basal value.

Table 2. Plasma Gastrin and Pancreatic Polypeptide Levels in Tests With Increasing Doses of Cholecystokinin-Octapeptide Without and With Addition of CR-1409 Throughout the Experiment

	Gastrin (pM)	PP (pM)
Basal	22 ± 4	12 ± 3
CCK-8		
25 pmol/kg · h	26 ± 2	18 ± 4
50 pmol/kg · h	28 ± 6	24 ± 2 <sup>a</sup>
100 pmol/kg · h	25 ± 5	32 ± 4 <sup>a</sup>
200 pmol/kg · h	30 ± 3	56 ± 8 <sup>a</sup>
400 pmol/kg · h	31 ± 4	79 ± 14 <sup>a</sup>
800 pmol/kg · h	32 ± 6	92 ± 17 <sup>a</sup>
CR-1409 (1.0 μmol/kg · h) + CCK-8		
25 pmol/kg · h	26 ± 5	11 ± 2
50 pmol/kg · h	30 ± 4	10 ± 1 <sup>b</sup>
100 pmol/kg · h	32 ± 5	12 ± 2 <sup>b</sup>
200 pmol/kg · h	34 ± 7	27 ± 4 <sup>b</sup>
400 pmol/kg · h	30 ± 2	33 ± 9 <sup>b</sup>
800 pmol/kg · h	31 ± 5	39 ± 12 <sup>b</sup>
CR-1409 (2.0 μmol/kg · h) + CCK-8		
25 pmol/kg · h	23 ± 3	12 ± 5
50 pmol/kg · h	24 ± 5	14 ± 4
100 pmol/kg · h	26 ± 5	12 ± 3 <sup>b</sup>
200 pmol/kg · h	28 ± 4	16 ± 5 <sup>b</sup>
400 pmol/kg · h	27 ± 7	12 ± 6 <sup>c</sup>
800 pmol/kg · h	30 ± 9	14 ± 4 <sup>c</sup>

CCK-8, cholecystokinin-octapeptide; PP, pancreatic polypeptide. Values shown are mean ± SEM of six tests in 6 dogs. <sup>a</sup> Significant (p < 0.05) increase above basal value. <sup>b</sup> Significant (p < 0.05) decrease below the value obtained with the respective dose of CCK-8 alone. <sup>c</sup> Significant (p < 0.05) decrease below the value obtained with the respective dose of CCK-8 + CR-1409 at 1.0 μmol/kg · h.

affected by the lower dose of CR-1409 (1.0 μmol/kg · h), but it was reduced significantly by higher doses of CR-1409 (2.0 and 4.0 μmol/kg · h), the maximal acid response being diminished by ~50% by these doses of CR-1409. The D<sub>50</sub> for gastrin

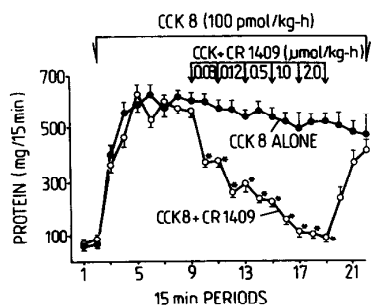


Figure 2. Effects of graded doses (0.03–2.0 μmol/kg · h) of CR-1409 on pancreatic protein responses to a constant dose of CCK-8 (100 pmol/kg · h). Mean ± SEM of six tests on 6 dogs. Asterisks indicate significant decrease below the values obtained with CCK-8 alone.

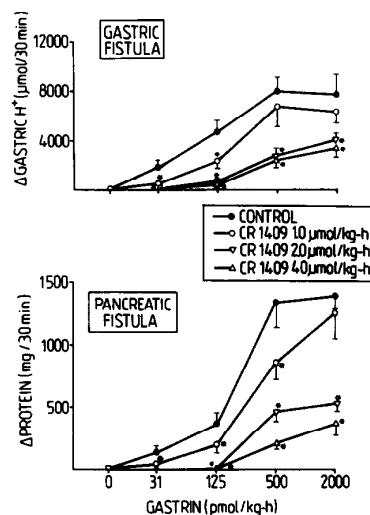


Figure 3. Increments in gastric H<sup>+</sup> and pancreatic protein outputs in response to graded doses of gastrin (31–2000 pmol/kg · h) without and with CR-1409 (1.0, 2.0, and 4.0 μmol/kg · h). Mean ± SEM of six tests on 6 dogs. Asterisks indicate significant decrease below the control values obtained with CCK-8 alone.

alone averaged 92 ± 12 pmol/kg · h, and the addition of CR-1409 at doses of 1.0, 2.0, and 4.0 μmol/kg · h increased the D<sub>50</sub> value to 132 ± 18, 294 ± 35, and 246 ± 42 pmol/kg · h, respectively (Figure 3).

Pancreatic protein responses to low doses (31–125 pmol/kg · h) of gastrin were reduced by low doses of CR-1409 and abolished by high doses of CR-1409. The maximal protein response to gastrin, which was not affected by CR-1409 at a dose of 1.0 μmol/kg · h, was reduced by 67% and 74% by CR-1409 at doses of 2.0 and 4.0 μmol/kg · h, respectively. The D<sub>50</sub> for gastrin alone averaged 172 ± 26 pmol/kg · h and the addition of CR-1409 at doses of 1.0, 2.0, and 4.0 μmol/kg · h increased the D<sub>50</sub> to respective values of 380 ± 32, 254 ± 27, and 480 ± 57 pmol/kg · h.

Gastrin infused intravenously in a constant dose of 250 pmol/kg · h produced a pancreatic protein response similar to that occurring during the administration of CCK at a dose of 100 pmol/kg · h in these animals. CR-1409 added to the intravenous infusion in graded doses resulted in a dose-dependent decrease in both gastric acid and pancreatic protein secretion. At the highest dose of CR-1409 (4.0 μmol/kg · h) the gastric acid and pancreatic protein responses to gastrin were reduced by ~60% (Figure 4). After withdrawal of the infusion of CR-1409, there was an immediate increase in gastric and pancreatic secretion toward the control level. Plasma gastrin and PP levels in tests with intravenous infusion of gastrin heptadecapeptide are shown in Table 3. Gastrin concentrations showed a gradual increase

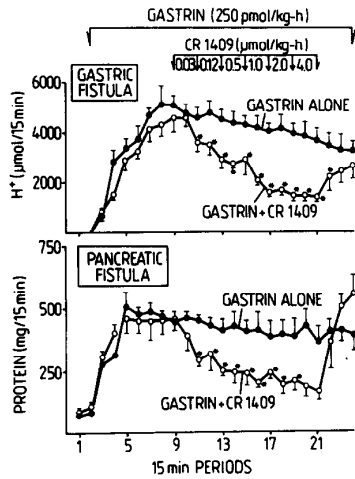


Figure 4. Effects of graded doses (0.03–4.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) of CR-1409 on gastric acid and pancreatic protein responses to a constant dose of gastrin (250  $\text{pmol}/\text{kg} \cdot \text{h}$ ). Mean  $\pm$  SEM of six tests on 6 dogs. Asterisks indicate significant decrease below the control values obtained with gastrin alone.

Table 3. Plasma Gastrin and Pancreatic Polypeptide Concentrations During Intravenous Infusion of Graded Doses of Gastrin in Tests Without and With the Addition of CR-1409

	Gastrin (pM)	PP (pM)
Basal	26 $\pm$ 3	9 $\pm$ 2
Gastrin		
31 $\text{pmol}/\text{kg} \cdot \text{h}$	45 $\pm$ 5 <sup>a</sup>	12 $\pm$ 2
125 $\text{pmol}/\text{kg} \cdot \text{h}$	91 $\pm$ 11 <sup>a</sup>	18 $\pm$ 2 <sup>a</sup>
500 $\text{pmol}/\text{kg} \cdot \text{h}$	231 $\pm$ 33 <sup>a</sup>	23 $\pm$ 5 <sup>a</sup>
2000 $\text{pmol}/\text{kg} \cdot \text{h}$	685 $\pm$ 74 <sup>a</sup>	27 $\pm$ 4 <sup>a</sup>
CR-1409 (1.0 $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) + gastrin		
31 $\text{pmol}/\text{kg} \cdot \text{h}$	39 $\pm$ 4 <sup>a</sup>	10 $\pm$ 1
125 $\text{pmol}/\text{kg} \cdot \text{h}$	112 $\pm$ 24 <sup>a</sup>	11 $\pm$ 2
500 $\text{pmol}/\text{kg} \cdot \text{h}$	552 $\pm$ 48 <sup>a</sup>	14 $\pm$ 2 <sup>b</sup>
2000 $\text{pmol}/\text{kg} \cdot \text{h}$	852 $\pm$ 140 <sup>a</sup>	20 $\pm$ 4 <sup>b</sup>
CR-1409 (2.0 $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) + gastrin		
31 $\text{pmol}/\text{kg} \cdot \text{h}$	38 $\pm$ 4	12 $\pm$ 3
125 $\text{pmol}/\text{kg} \cdot \text{h}$	110 $\pm$ 21	10 $\pm$ 2
500 $\text{pmol}/\text{kg} \cdot \text{h}$	358 $\pm$ 87	14 $\pm$ 2 <sup>b</sup>
2000 $\text{pmol}/\text{kg} \cdot \text{h}$	992 $\pm$ 127	18 $\pm$ 9 <sup>b</sup>
CR-1409 (4.0 $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) + gastrin		
31 $\text{pmol}/\text{kg} \cdot \text{h}$	31 $\pm$ 12	9 $\pm$ 3
125 $\text{pmol}/\text{kg} \cdot \text{h}$	121 $\pm$ 26	18 $\pm$ 5
500 $\text{pmol}/\text{kg} \cdot \text{h}$	424 $\pm$ 118	21 $\pm$ 3
2000 $\text{pmol}/\text{kg} \cdot \text{h}$	792 $\pm$ 180	20 $\pm$ 2 <sup>b</sup>

PP, pancreatic polypeptide. Values shown are mean  $\pm$  SEM of six tests in 6 dogs. <sup>a</sup> Significant ( $p < 0.05$ ) increase above basal value. <sup>b</sup> Significant ( $p < 0.05$ ) decrease below the values obtained with respective dose of gastrin alone.

Table 4. Increments in Pancreatic  $\text{HCO}_3^-$  and Protein Outputs in Response to Secretin and Neurotensin in Tests Without and With the Addition of CR-1409

	$\text{HCO}_3^-$ ( $\mu\text{mol}/30 \text{ min}$ )	Protein (mg/30 min)
Secretin <sup>a</sup>	3668 $\pm$ 720	210 $\pm$ 34
Secretin <sup>a</sup> + CR-1409 <sup>b</sup>	3248 $\pm$ 460	287 $\pm$ 52
Neurotensin <sup>c</sup>	828 $\pm$ 104	772 $\pm$ 82
Neurotensin <sup>c</sup> + CR-1409 <sup>b</sup>	750 $\pm$ 92	848 $\pm$ 66

Values shown are mean  $\pm$  SEM of six tests in 6 dogs. <sup>a</sup> 82  $\text{pmol}/\text{kg} \cdot \text{h}$ . <sup>b</sup> 1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ . <sup>c</sup> 50  $\text{pmol}/\text{kg} \cdot \text{h}$ .

during the infusion of graded doses of gastrin, and these increments were not significantly different in tests without and with CR-1409. Plasma PP levels, which showed a small but significant increase during infusion of higher doses of gastrin, were significantly reduced by the addition of CR-1409.

Secretin (82  $\text{pmol}/\text{kg} \cdot \text{h}$ ) and neurotensin (50  $\text{pmol}/\text{kg} \cdot \text{h}$ ) infusion produced a potent stimulation of pancreatic  $\text{HCO}_3^-$  secretion. The increment in protein output was negligible in tests with secretin and somewhat higher in tests with neurotensin. CR-1409 given intravenously did not affect  $\text{HCO}_3^-$  or protein responses to secretin or neurotensin (Table 4).

Urecholine infused intravenously in graded doses resulted in a dose-dependent increase in pancreatic protein secretion, reaching a peak that amounted to ~42% of the maximum attained with CCK-8. There was also a small increase in gastric acid secretion, but it was not dose-dependent, and these results have not been included. CR-1409 added to the intravenous infusion (1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) did not affect significantly the gastric acid or pancreatic protein secretion (Figure 5).

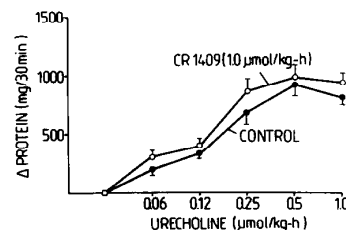


Figure 5. Increments in pancreatic protein outputs in response to graded doses of urecholine (0.06–1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ) without and with CR-1409 (1.0  $\mu\text{mol}/\text{kg} \cdot \text{h}$ ). Mean  $\pm$  SEM of six tests on 6 dogs.

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