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## Inhibitory effect of calcitonin on pure human pancreatic secretion.

Juntaro Tanaka\*      Hideo Harada†      Koji Ochi‡  
Hirofumi Miyake\*\*      Fumiko Kochi††      Ikuro Kimura‡‡

\*Okayama University,

†Oita University,

‡Okayama University,

\*\*Okayama University,

††Okayama University,

‡‡Okayama University,

# Inhibitory effect of calcitonin on pure human pancreatic secretion.\*

Juntaro Tanaka, Hideo Harada, Koji Ochi, Hirofumi Miyake, Fumiko Kochi, and Ikuro Kimura

## Abstract

The inhibitory effect of calcitonin on human pancreatic secretion was evaluated to examine whether the different results reported earlier between humans, cats and dogs can be ascribed to the different sensitivity of these species to calcitonin, as suggested by some investigators. Pancreatic juice was obtained by endoscopic cannulation of the pancreatic duct from 11 patients with relapsing pancreatitis during intravenous infusion of secretin (1 U/kg/h) plus caerulein (0.04 microgram/kg/h). After steady secretion was attained 20 min after the beginning of collection, five 2-min fractions were obtained before, and ten 2-min fractions were obtained after intravenous infusion of calcitonin (1 IU/kg/h). The pre- and post-calcitonin fractions from each patient were compared by Student's t-test. Calcitonin inhibited the secretory volume (26.8 to 65.6%) and bicarbonate secretion (21.4 to 62.0%) in 8 patients, and amylase (48.4 to 89.5%) and lipase secretion (47.4 to 90.5%) in all patients. The present studies reconfirmed that prominent inhibition of enzyme secretion occurs in humans. A new finding was that significant inhibition of the secretory volume and bicarbonate secretion occurs in humans. The inhibitory effects of calcitonin in humans did not appear to differ from those in cats and dogs, when evaluated similarly with the use of pure pancreatic juice.

**KEYWORDS:** human pancreatic secretion, calcitonin, pure pancreatic juice

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## Inhibitory Effect of Calcitonin on Pure Human Pancreatic Secretion

Juntaro Tanaka\*, Hideo Harada, Koji Ochi, Hirofumi Miyake<sup>a</sup>, Fumiko Kochi<sup>a</sup> and Ikuro Kimura<sup>a</sup>

*Institute for Environment and Diseases, Okayama University Medical School, Misasa, Tottori 682-02 and <sup>a</sup>Second Department of Medicine, Okayama University Medical School, Okayama 700, Japan*

The inhibitory effect of calcitonin on human pancreatic secretion was evaluated to examine whether the different results reported earlier between humans, cats and dogs can be ascribed to the different sensitivity of these species to calcitonin, as suggested by some investigators. Pancreatic juice was obtained by endoscopic cannulation of the pancreatic duct from 11 patients with relapsing pancreatitis during intravenous infusion of secretin (1 U/kg/h) plus caerulein (0.04 ug/kg/h). After steady secretion was attained 20 min after the beginning of collection, five 2-min fractions were obtained before, and ten 2-min fractions were obtained after intravenous infusion of calcitonin (1 IU/kg/h). The pre- and post-calcitonin fractions from each patient were compared by Student's *t*-test. Calcitonin inhibited the secretory volume (26.8 to 65.6%) and bicarbonate secretion (21.4 to 62.0%) in 8 patients, and amylase (48.4 to 89.5%) and lipase secretion (47.4 to 90.5%) in all patients. The present studies reconfirmed that prominent inhibition of enzyme secretion occurs in humans. A new finding was that significant inhibition of the secretory volume and bicarbonate secretion occurs in humans. The inhibitory effects of calcitonin in humans did not appear to differ from those in cats and dogs, when evaluated similarly with the use of pure pancreatic juice.

*Key words* : human pancreatic secretion, calcitonin, pure pancreatic juice

The inhibitory effect of intravenous administration of calcitonin on exocrine pancreatic secretion has been studied in relation to its potential application to the treatment of acute pancreatitis (1). Earlier studies, however, have shown different results between humans (2-4), cats (5) and dogs (6). The different results were attributed to the different sensitivity of the pancreas to cal-

citonin depending on the species of animal (1, 5). However, careful scrutiny of the earlier reports suggests that the different results can be attributed as well to the different methods of obtaining pancreatic juice, because similar studies on the inhibitory effect of glucagon showed discrepancies depending on the methods of obtaining pancreatic juice (7). It is of note in this context that humans have been studied only by

\*To whom correspondence should be addressed.

peroral intraduodenal intubation. We, therefore, studied the effect of calcitonin on human pancreatic secretion by endoscopic retrograde catheterization of the pancreatic duct. This new method has an advantage of providing pure pancreatic juice as in the case of animal experiments.

## Patients and Methods

Eleven patients (10 males and one female) with chronic pancreatitis and intermittent acute exacerbations were studied. The patients' ages ranged from 46 to 65 years with an average of 57 years; weight ranged from 46 to 65 kg with an average of 57 kg. All patients had symptoms, clinical findings and laboratory abnormalities suggestive of chronic pancreatitis (elevated serum amylase concentration and/or urine amylase output), and imaging findings diagnostic of chronic pancreatitis ac-

ording to the Cambridge criteria (8). Endoscopic retrograde cholangio-pancreatography showed mild changes in 8 patients and moderate to marked changes in 3 patients according to the Cambridge criteria (8). Pancreatic juice was collected during remission primarily for cytology and removal of protein plugs. Informed consent was obtained from all of the patients.

After a 12-h overnight fast, the main pancreatic duct was cannulated through the papilla of Vater to a depth of 15 to 25 mm under pharyngeal anesthesia with 4% xylocaine, using a duodenofiberscope (JF-B4 or JF-1T, Olympus Co., Ltd., Tokyo, Japan). As much gastric juice as possible was removed by endoscopic aspiration before advancing the endoscope into the duodenum. Pancreatic juice was collected in ice-cooled test tubes by manual suction at 2-min intervals during intravenous infusion of a saline solution containing secretin (Secrepan, Eisai Co., Ltd., Tokyo, Japan) and caerulein (Ceosunin, Farmitalia Carlo Erba Co., Ltd., Italy) at a speed of 1 U/kg of body weight/h

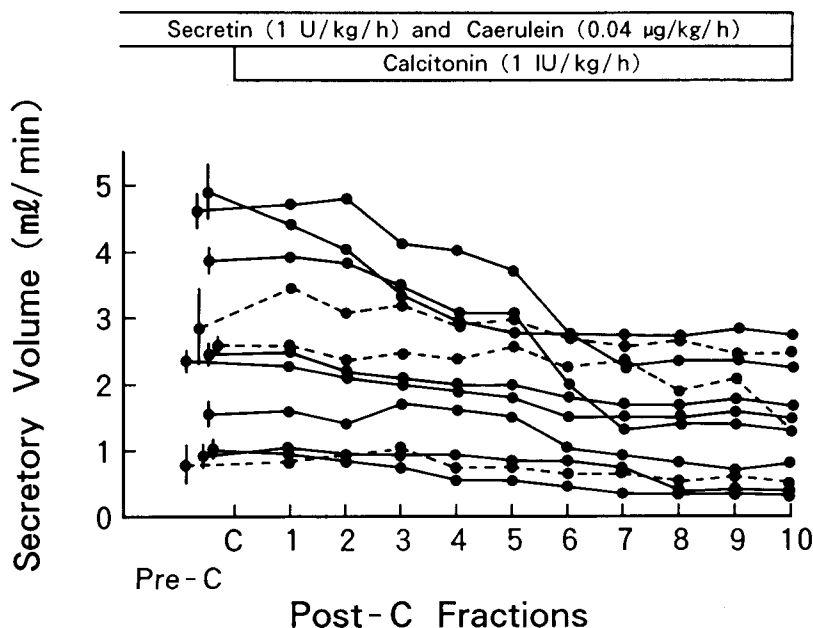


Fig. 1 Inhibitory effect of calcitonin on pancreatic secretory volume. Solid lines represent the 8 patients who showed significant inhibition ( $p < 0.05$ ); dotted lines represent the 3 patients who showed no significant inhibition. Experimental details are described under Patients and Methods. C: Start of calcitonin infusion. Pre-C: Pre-calcitonin fractions. The vertical lines indicate the mean  $\pm$  SD of the five 2-min fractions. Post-C: Post-calcitonin fractions obtained at 2-min intervals. Pre-C fractions were compared in each patient with Post-C fractions which were below the lowest Pre-C value. Statistical significance was determined by Student's *t*-test.

and 0.04  $\mu\text{g}/\text{kg}$  of body weight/h, respectively. A steady state of pancreatic secretion was established 20 min after the collection of pancreatic juice was begun. After establishment of steady secretion, five 2-min fractions were collected as pre-calcitonin fractions. Then, a saline solution containing porcine calcitonin (Calcitar, Rorer Pharmaceuticals Co., Ltd., Eastbourne, England) was infused into an arm vein at a speed of 1 IU/kg of body weight/h. Following infusion of calcitonin, ten 2-min fractions of pancreatic juice were obtained as post-calcitonin fractions. Blood samples were obtained from a leg vein at the start of collection of pancreatic juice, and 30 min and 50 min later to determine calcium, phosphorus and calcitonin.

Bicarbonate, amylase and lipase were assayed by methods described previously (9). Serum calcitonin was determined by a radioimmunoassay, using  $^{125}\text{I}$ -anticalcitonin (Calcitonin-Kit, Daiichi Radioisotope Laboratories, Tokyo, Japan) (10). The effect of calcitonin on pancreatic secretions was evaluated in each patient by comparing the values of the five pre-calcitonin fractions with the values of the post-calcitonin fractions that were lower than those of the five pre-calcitonin fractions.

Statistical analysis was carried out by Student's *t*-test; *p* values less than 0.05 were considered significant.

## Results

Fig. 1 shows that calcitonin significantly inhibited the secretory volume in 8 of the 11 patients. The inhibition reached the maximal steady level by the 8th post-calcitonin fraction in these 8 patients. The maximal inhibition rate ranged from 26.8 to 65.6%, with a median value of 46.5%.

Fig. 2 shows that calcitonin significantly inhibited bicarbonate secretion in 8 of the 11 patients. Inhibition in bicarbonate secretion always accompanied that in secretory volume. Maximal inhibition was reached by the 8th post-calcitonin fraction in the 8 patients. The maximal inhibition rate ranged from 21.4 to 62.0%, with a median value of 44.6%.

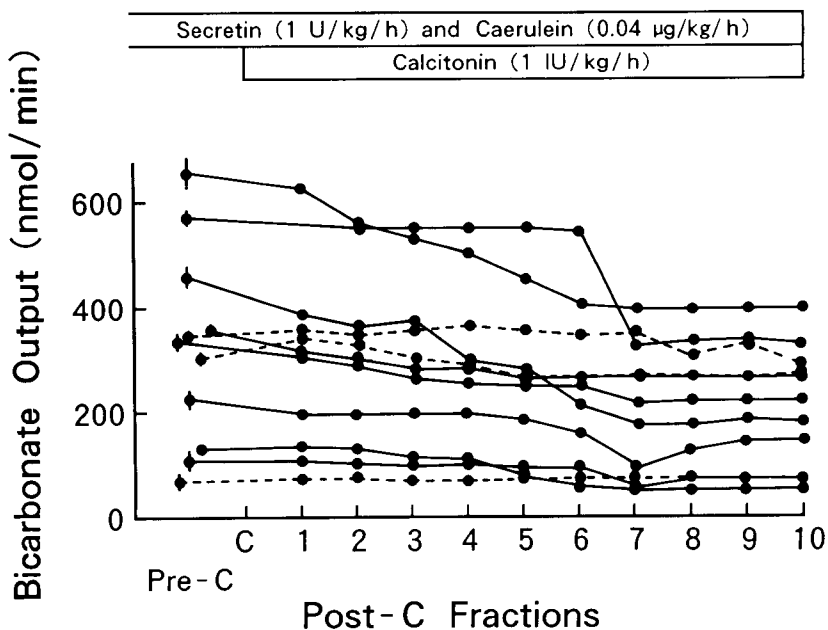


Fig. 2 Inhibitory effect of calcitonin on pancreatic bicarbonate secretion. Solid lines represent the 8 patients who showed significant inhibition ( $p < 0.05$ ); dotted lines represent the 3 patients who showed no significant inhibition. Experimental details are described under Patients and Methods. Symbols: See the legend to Fig. 1.

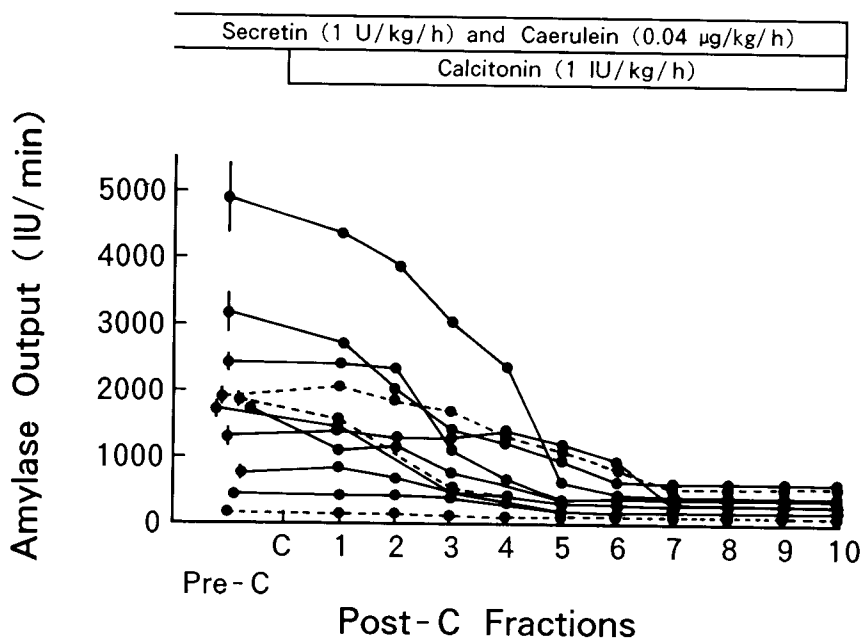


Fig. 3 Inhibitory effect of calcitonin on pancreatic amylase secretion. All 11 patients showed significant inhibition ( $p < 0.05$ ). Experimental details are described under Patients and Methods. Symbols: See the legend to Fig. 1.

Fig. 3 shows that calcitonin significantly inhibited amylase output in all 11 patients. Maximal inhibition was reached by the 7th post-calcitonin fraction, with a maximal inhibition rate ranging from 48.4 to 89.5% and a median value of 77.9%.

Calcitonin significantly inhibited lipase output in all 11 patients. The inhibition reached the maximal steady level by the 7th post-calcitonin fraction. The maximal inhibition rate ranged from 47.4 to 90.5%, with a median value of 78.7%.

Serum calcium was  $9.05 \pm 0.97$  mg/dl at the start of the collection of pancreatic juice,  $8.97 \pm 0.88$  mg/dl 30 min later, and  $8.78 \pm 0.80$  mg/dl 50 min later. Serum phosphorus was  $2.92 \pm 0.73$  mg/dl,  $2.86 \pm 0.70$  mg/dl and  $2.72 \pm 0.69$  mg/dl, respectively. Serum calcitonin was  $68.8 \pm 54.5$  pg/ml,  $76.8 \pm 50.2$  pg/ml and  $69.3 \pm 51.9$  pg/ml, respectively. No significant difference was noted.

The inhibition rate of the secretory volume, bicarbonate output and enzyme output

did not significantly correlate with the body weight of the patients, *i. e.*, the total dose of the hormones administered.

## Discussion

The present study showed that in most patients, calcitonin significantly inhibited the secretin- and caerulein-stimulated pancreatic secretory volume and bicarbonate secretion. The results agree with those of earlier studies in cats (5) and dogs (6), but disagree with those in humans (2-4). The disagreement can not be ascribed to the differences in the background stimulation of pancreatic secretion (secretin alone, CCK-PZ alone, secretin plus CCK-PZ, or secretin plus caerulein), in the dose of calcitonin (in the range of 1 to 60 IU/30 min), or in the origin of calcitonin products, because such differences do not influence the inhibitory effects of calcitonin (2, 5). In earlier stud-

ies of humans, such slight reductions in the secretory volume and bicarbonate secretion could not be detected probably because only a few fractions could be obtained by peroral intraduodenal intubation due to the patients' limited tolerance, so that the pre- and post-calcitonin values of all the tested patients had to be statistically compared as a group in spite of wide inter-individual variation. In contrast, such slight inhibition was revealed in the present study, probably because endoscopic catheterization of the pancreatic duct afforded enough fractions to statistically compare the pre- and post-calcitonin fractions in each individual patient. The present study revealed that calcitonin significantly, though slightly, inhibited the pancreatic secretory volume and bicarbonate secretion in humans.

Inhibition of enzyme secretion was prominent and consistent, but not complete as shown in the earlier studies of humans (2-4), cats (5) and dogs (6). The incomplete inhibition may explain the insufficient therapeutic effects of calcitonin in preliminary studies of human acute pancreatitis (11, 12). Calcitonin may be more effective in combination with one of the CCK-PZ receptor antagonists currently under development (13).

The wide inter-individual variation was not related to the different total dose of the hormones administered, but probably related to wide inter-individual variation in the sensitivity of the centro-acinar cells and acinar cells to the effect of calcitonin. Three patients showed no significant inhibition of the secretory volume and bicarbonate secretion, probably because their centro-acinar cells were little sensitive to calcitonin.

The present results excluded the possibility that the inhibitory effects of calcitonin were brought about through a decrease in the serum calcium concentration. Consequently other mechanisms such as changes in the intra-cellular calcium concentration

remain to be investigated, as suggested by Konturek *et al.* (5)

In summary, the present study revealed for the first time that constant intravenous infusion of calcitonin inhibited the pancreatic secretory volume and bicarbonate secretion in humans and reconfirmed earlier findings that the treatment prominently but not completely inhibited pancreatic enzyme secretion. There was wide inter-individual variation in the inhibitory effects. The results suggest that similar therapeutic effects of calcitonin may be expected in acute pancreatitis of humans, cats and dogs, but possibly with wide inter-individual variation. The therapeutic effects of calcitonin need to be re-evaluated in combination with other drugs such as CCK-PZ receptor antagonists (13).

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