Pharmacology Biochemistry & Behavior, Vol. 31, pp. 297–303. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Cholecystokinin Suppresses Food Intake in Cats: Structure-Activity Characterization[1]

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Received 11 January 1988

BADO, A., M. RODRIGUEZ, M. J. M. LEWIN, J. MARTINEZ AND M. DUBRASQUET. *Cholecystokinin suppresses food intake in cats: Structure-activity characterization.* PHARMACOL BIOCHEM BEHAV 31(2) 297–303, 1988.—Our experimental models in this study were cats fitted with gastric fistulae. Intravenous infusion of sulfated CCK 8 and nonsulfated Boc CCK 7 inhibited both sham-feeding and feeding in fasted cats. The threshold dose (1.2 pmol/kg·hr) required for inhibition of sham-feeding was identical to that required to inhibit feeding in the same animals. However, the gastric secretory studies indicated that this dose was 90 times lower than the threshold dose stimulating gastric acid secretion (109 pmol/kg·hr). In nonfasted animals, sulfated CCK 8 and nonsulfated Boc CCK 7 (219 and 875 pmol/kg·hr) are both capable of decreasing the food intake at different intervals following the infusion with no significant effect on daily food intake. Our findings clearly show that there is no difference in the sensitivity of CCK's ability to inhibit sham-feeding and feeding, suggesting that CCK's suppressive effect on food intake does not solely involve gastric distension mechanisms. In contrast to gastric acid secretion, the sulfate group is not a "restrictive" factor for peripherally-induced CCK satiety.

Cats Cholecystokinin Feeding behavior Sham-feeding and feeding Structure-activity relationship

DURING eating CCK is released from the intestine and from hypothalamic neurons (2, 15, 21). Since 1973, it has been shown that peripheral administration of CCK can decrease food intake in rats (1, 9–11), lean and obese mice (26), and rabbits and monkeys (7, 8, 14). In humans, a decrease of ingested food after IV injection of CCK has been reported and either an increase or decrease in eating after slow infusion of the peptide. The suppressive effect of food intake by CCK in studies on humans occurred without side effects (12, 16, 25).

The mechanisms by which CCK exerts this satiety effect are not yet well established. A central action on brain satiety centers has been suggested as has a peripheral method of action (24). It has been postulated that the CCK satiety effect was related to the inhibition of gastric emptying leading to distension of the stomach which then acts through a vagally mediated central reflex to inhibit food intake (18,23). However, other authors have shown that duodenal infusion of a liquid diet or peripheral administration of CCK can suppress food intake in sham-fed rats and monkeys in the absence of gastric distension. The doses required to inhibit sham-feeding (without gastric distension) were higher than those inhibiting feeding (with gastric distension) (1, 7, 8, 17, 19).

CCK's suppressive effects on food intake mimic the satiety effect of ingested food (23). In spite of such observations, it remained to be proved that the satiety action of the peptide is a physiological function of the endogenous hormone.

With respect to the physiological nature of CCK satiety effect, a comparison of the doses required to reduce food intake with those doses required to produce other physiological CCK effects appears useful (20). The present study was designed to determine in the cat:

1) The suppressive effect of IV administered CCK on food intake during sham-feeding and feeding experiments in order to ascertain the role of gastric distension.

2) The effects of CCK on food intake at different intervals and daily food intake in nonfasted animals.

3) The relationship between the doses of CCK required

[1]Part of this work was presented at the International Symposium on Gastrin and Cholecystokinin, Chemistry, Physiology and Pharmacology, 7–11 Septembre 1987, Cap d'Agde, France.

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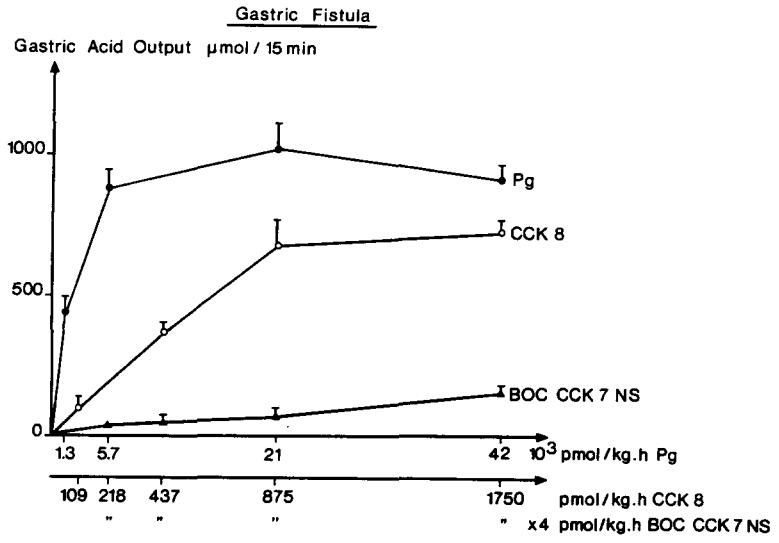

FIG. 1. Dose response curves (six cats) of gastric acid secretion stimulated by pentagastrin (n=24), sulfated CCK 8 (109, 437, 875 and 1750 pmol/kg·hr; n=24), and nonsulfated Boc CCK 7 (n=18). The doses of Boc CCK 7NS are four times higher than those of the sulfated CCK 8.

to inhibit food intake and those stimulating gastric acid secretion.

4) The importance of the SO3 group of the molecule in the suppressive effect of food consumption.

METHOD

Animals

Six cats of either sex operated upon 6 months earlier and weighing 2.4 to 4.5 kg were used in these experiments. Under pentobarbital anesthesia three of them were provided with a vagally denervated fundic pouch (Heindenhain Pouch, HP) drained by a plastic cannula, and a gastric fistula (GF) to drain the vagally innervated main stomach. The remaining three cats were provided with a GF only installed in the most dependent portion of the stomach.

Gastric Secretory Studies

The secretory studies were performed twice a week on the conscious animal resting in a sling frame.

After an overnight fast, the canulas were opened, and a catheter was inserted into the saphenous vein and 0.9% saline was then infused at a rate of 15 ml/hr. The gastric secretion was collected for 15 min periods, beginning 30 min before the administration of the peptides to ensure the absence of notable basal secretion. The acid concentration of each sample was determined by titration at pH 7 with NaOH 0.1 N and the volume determined by weighing the samples in tared flasks and assuming a density of 1.

At time zero, a solution of sulfated CCK 8 or nonsulfated Boc CCK 7 dissolved in saline containing 0.1 p 100 bovine serum albumin was administered in place of the saline infusion. Each dose of peptide (doses ranging from 1.2 to 7000 pmol/kg·hr) was perfused for one hour.

Nonsulfated Boc CCK 7 was synthetised by Doctor J. Martinez using the method described elsewhere (3). Sulfated CCK 8 was purchased from Sigma Chemical, St. Louis, MO.

The stimulated acid secretion for each hour was taken to be the mean of the two highest consecutive acid outputs. Results were expressed as acid output per 15-min period and represented the mean±SEM.

Feeding Studies

Sham-feeding and feeding in fasted cats. Cats were deprived of food 18 hours before the experiment, but had free access to water. Each experiment was performed at 11.30 a.m., and no more than once a week, on conscious animals resting in sling frames. Thirty minutes prior to testing, the plug occluding the gastric cannula was removed and gastric contents were flushed out with water through the gastric cannula. In feeding experiments the gastric cannula was then closed. In sham-feeding experiments, a drainage tube inserted on the cannula enabled the milk and gastric contents to be drained out.

Animals were allowed free access to commercial milk (UHT sterilized full cream milk) for 12 min with either open GF (sham-feeding, SF) or a closed GF (feeding). Peptides or 0.9% NaCl were infused for 27 min beginning 15 min before the test and also during the test. The milk intake was determined by the difference between the total volume available to the animal and that which remained after the experiment. In sham-feeding experiments, the recovery of ingested milk drained through the cannula was usually complete. The test was discarded if the volume collected from the GF did not equal or exceed the volume of ingested milk. Results were expressed as a percentage of the control milk intake.

In feeding and sham-feeding experiments the secretions were 38% and 27% of Pg maximum stimulated secretion respectively, thus showing that milk did stimulate acid secretion in these cats.

Whole day feeding behavior in nonfasted cats. Cats weighing from 2.4 to 4 kg provided with a gastric cannula were housed in individual cages and were submitted no more than once a week to a study of the free food intake during

TABLE 1

REPRODUCIBILITY OF SHAM-FEEDING AND FEEDING IN CATS

Experiment No.	Milk Intake (ml) Sham-Feeding (fistula opened)	Feeding (fistula closed)
1st	455 ± 35	299 ± 30
2nd	480 ± 20	250 ± 45
3rd	405 ± 70	270 ± 15
4th	425 ± 50	249 ± 30

Milk intake during sham-feeding (fistula opened) and during feeding (fistula closed). NaCl 0.9% was infused intravenously 15 min before cats had access to milk and 12 min during milk ingestion. Experiments were repeated at intervals of at least 5 days. Values shown are the mean ± SEM (n=4 for each experiment).

both day and night. They received their daily ration of food at 11.30 a.m.; the food containers were withdrawn the following morning at 9 a.m. The experimental design was as follows: cats were taken from the animal room in their sling frames to the laboratory where they were infused for 90 min (9.45 a.m. to 11.15 a.m.) with either saline, sulfated CCK 8 or nonsulfated Boc CCK 7 (1.2, 219 and 875 pmol/kg·hr). The doses of peptide used represented subthreshold, threshold and submaximal dosages of CCK 8 required to stimulate acid secretion in the same cats. The gastric fistula was opened to avoid both the accumulation of acid secretion in the stomach and also its passage into the intestine. In so doing we avoided activation of acid-stimulated gastric and postgastric mechanisms. At the end of infusion, the gastric fistula was closed and the cats returned to their cages in the animal room. At 11.30 a.m., a meal of liver was offered to the cats. At 12 a.m., 2 a.m., and 4 p.m., (i.e., 30, 150 and 270 min) the container of food was removed weighed and replaced. The following morning, at 9 a.m., the container of food was removed and weighed again. The amount of food at each of these times was calculated and the daily food intake (11.30 a.m. to 9 a.m.) was determined.

Results were expressed as mean±SEM. All of the observations on each cat were averaged and the resulting number was used for the statistical calculations. Student's t-test was used to compare control and treated animals. Differences were considered significant when $p<0.05$ or $p<0.01$.

RESULTS

Gastric Secretory Studies

Gastric acid responses to CCK (Fig. 1). Sulfated CCK 8 stimulated acid output in a dose-related manner for the doses ranging from 109 to 1750 pmol/kg·hr. The 1750 pmol/kg induced a comparable response to that of 42.10^3 pmol/kg·hr of pentagastrin in the same animals (720±46 μmoles/15 min vs. 849±99 μmoles/15 min). Because of a constant biliary reflux, it was impossible to determine the acid responses to higher doses of sulfated CCK 8.

Boc CCK 7NS was a weak stimulant of gastric acid secretion. The threshold dose stimulating acid output was 7000 pmol/kg·hr (46±18 μmoles/15 min).

Feeding Studies

Sham-feeding and feeding. In every experiment, the cats ate as soon as the milk was offered to them. In control experiments with open gastric fistula (SF) or closed GF (F) and IV saline infusion, the cats ate in the same manner during the first 5 min. However total milk intake during the 12 min period of the test was greater in sham-feeding than in feeding (441±44 ml vs. 267±30 ml). When saline infusion experiments were repeated at intervals of a least 5 days, intake during sham-feeding and feeding did not change significantly (Table 1).

Intravenous infusion of 1.2, 219 and 875 pmol/kg·hr of sulfated CCK 8 resulted in a significant reduction of milk intake during normal feeding and sham-feeding. A dose of 1.2 pmol/kg·hr of sulfated CCK 8 reduced intake during sham-feeding by 40±12% ($p<0.01$) and during normal feeding by 14±5% ($p<0.01$). The dose of sulfated CCK 8 (875 pmol/kg·hr) which produced maximal gastric acid secretion, significantly decreased sham-feeding intake by 57±5% ($p<0.01$), whereas the reduction was only 30±6% ($p<0.01$) in feeding experiments (Fig. 2).

Administration of Boc CCK 7NS decreased milk intake during feeding and sham-feeding. Eight hundred and seventy-five pmol/kg·hr of Boc CCK 7NS reduced sham-feeding by 21±9% and the feeding intake by 38±10% ($p<0.01$) (Fig. 3).

Feeding behavior in nonfasted cats.

Control experiments. The cats had free access to food from 11.30 a.m. to 9.00 a.m. The first meal was taken within 30 min (11.30 a.m. to 12.00 p.m.) and the cats ate 33% of their daily food intake during this time. Between 12.00 p.m. to 2 p.m. and 2 p.m. to 4 p.m., the cats consumed an equal amount of food equivalent to 17–18% of the daily food intake. Between 4 p.m. to 9 a.m. the amount eaten was 32% of the daily food intake. The experiments and the results repeated 3 times over three months were reproducible; the stability of the system under test allowed us to test the effects of the peptides on food intake.

CCK infusion. Infusion of 219 and 875 pmol/kg-hr sulfated CCK 8 decreased the first period intake by 51% and 41% respectively (Fig. 4a). The second period was decreased with 1.2 and 219 pmol/kg·hr by 44% and 56% respectively. The third period was not affected by infusion of sulfated CCK 8. Only 875 pmol/kg·hr of sulfated CCK 8 was able to significantly increase the amount eaten from 4 p.m. to 9 a.m.

Infusion of 219 and 875 pmol/kg·hr of Boc CCK 7NS decreased the food intake of the first period by 34% and 40% respectively. For the second period, we observed a trend towards a decrease in food intake and an increase in food intake for the third period (Fig. 4b).

The cumulative food intake was significantly decreased after infusion of sulfated CCK 8 at doses of 1.2, 219 and 875 pmol/kg·hr (Table 2). For 219 and 875 pmol/kg·hr of sulfated CCK 8, the suppressive effect started during the first 30 min and reached a maximum suppression of 51% and 41% respectively. This significant reduction effect persisted for 270 min at these 2 doses (24% and 39% respectively). A significant reduction was observed with 219 and 875 pmol/kg·hr of Boc CCK 7NS (Table 2). This reduction effect lasted 270 min for the high dose of Boc CCK 7NS used (875 pmol/kg·hr).

None of the doses of the two CCK peptide derivatives used (sulfated CCK 8 and nonsulfated Boc CCK 7) significantly modified daily food intake (Fig. 5).

DISCUSSION

The experiments on cats described herein provide a feeding model for studying the short- and long-term effects on

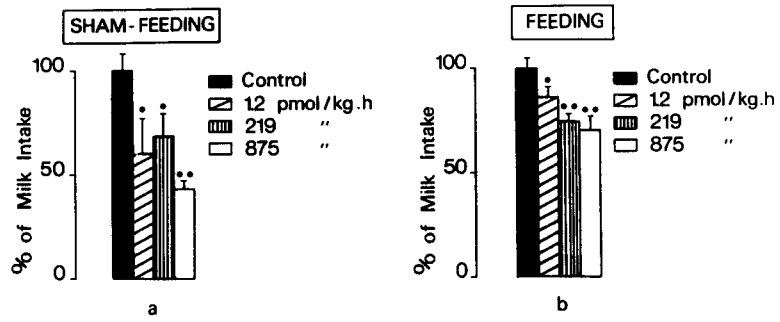

FIG. 2. Effects of intravenous sulfated CCK 8 on milk intake from 0 to 12 min in 4 cats during sham-feeding [fistula opened (a)] and feeding [fistula closed (b)]. Results (means±SEM) are expressed as % milk intake for each cat. Columns represent means±SEM. Control experiments n=36 and n=20 for each dose of sulfated CCK 8. Statistical differences vs. control. $*p<0.05$, $**p<0.01$, by Student's t-test.

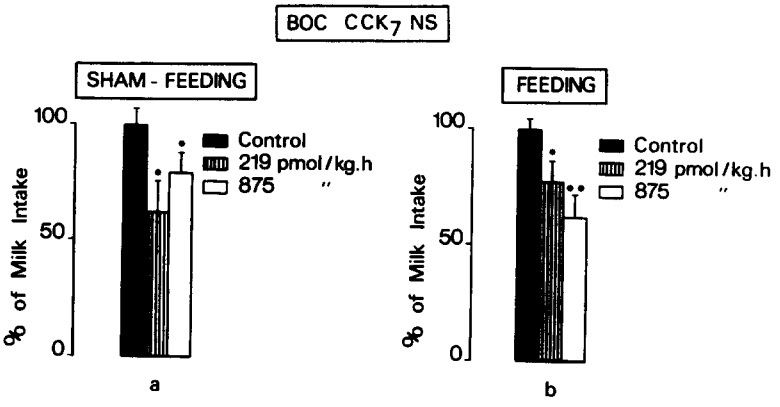

FIG. 3. Effects of intravenous nonsulfated Boc CCK 7 on milk intake from 0 to 12 min in 4 cats during sham-feeding [opened gastric fistula (a)] and feeding [closed gastric fistula (b)]. Results are expressed as % milk intake for each cat. Columns represent means±SEM. Control experiments n=36 and n=16 for each dose of Boc CCK 7NS. Statistical differences vs. control. $*p<0.05$, $**p<0.01$, by Student's t-test.

satiety in nonfasted animals. Nonfasted cats had a feeding behavior pattern characterized by a division of their food intake over the day. Indeed, 32% of the daily intake was eaten within 30 min (11.30 a.m.–12.00 a.m.), at this moment cats showed satiety behavior (sleeping and grooming). Two hours later the total intake reached 50% of daily intake and 4 hours later 65% of daily intake has been consumed. Finally 33% of the daily intake was consumed between 4 p.m. to 9 a.m. The method was not able to distinguish the sequential amount of food eaten during the night, however the amounts eaten during this period were constant and reproducible. Thus the effects of peptides could be investigated over one day. The presence of a gastric fistula did not modify this eating pattern in cats after surgery as compared with before surgery, but permitted the measurement of additional physiological events (measurements of gastric secretion, gastric emptying . . .). Most of the studies on the CCK satiety effect have been performed on food-deprived animals. This fasting condition has been proved to increase the probability of eating. Thus, the nonfasting conditions seemed to be close to physiological conditions at least in our laboratory and as such could be useful in generating additional information regarding the method of action of CCK in the regulation of food intake.

Our results demonstrated four properties attributable to CCK with respect to food intake in cats. First, the minimal effective dose of CCK for inhibition of liquid food intake was 90 times lower than the threshold dose stimulating acid secretion. Second, the inhibition of sham-feeding (absence of gastric distension) and normal feeding required the same doses of IV CCK, however the inhibition of SF was greater than the inhibition of normal feeding. Third, in nonfasted animals, CCK IV infusion, in doses ranging subthreshold to submaximal dose stimulating acid secretion, reduces food intake without a significant modification of daily food intake. Fourth, the two CCK peptide derivatives (sulfated CCK 8 and the nonsulfated Boc CCK 7) are both able to reduce food intake.

This study shows that intravenous CCK has a satiety effect in cats in both fasted and nonfasted animals. These results are in agreement with earlier reports demonstrating a suppressive effect of CCK on food consumption in other species (8–11, 14). Our findings indicate that IV CCK does not affect daily food intake. CCK suppressed feeding by

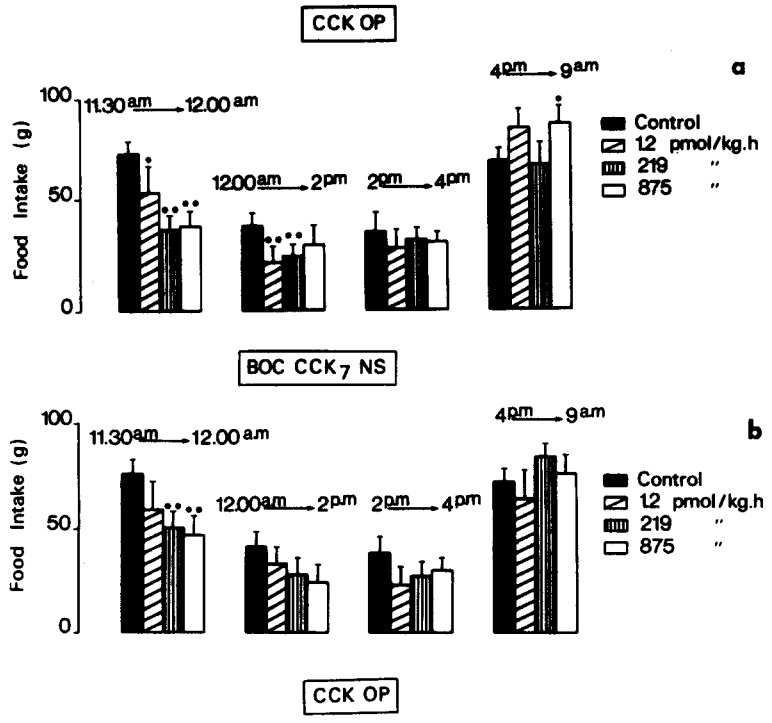

FIG. 4. Effect of intravenous CCK [sulfated CCK 8 (a) and nonsulfated CCK 7 (b)] on food intake at different intervals in 4 nonfasted cats. CCK or NaCl 0.9% were infused 90 min on a separate day before they had free access to food. Results are expressed as means±SEM of food intake during each period. Column represent: saline experiments n=60 and n=16 for 1.2 and 219 pmol/kg·hr of CCK and n=24 for 875 pmol/kg·hr. Statistical differences vs. control. $*p<0.05$, $**p<0.01$ by Student's t-test.

TABLE 2

SUPPRESSIVE EFFECT OF CCK ON CUMULATIVE FOOD INTAKE

	Cumulative Food Intake						
		Sulfated CCK 8 pmol/kg·hr			Nonsulfated Boc CCK 7 pmol/kg·hr		
Times	Control 0.9% NaCl	1.2	219	875	1.2	219	875
0– 30 min	76 ± 7	65 ± 11	37 ± 7**	45 ± 6**	60 ± 12	50 ± 7**	46 ± 7**
0–150 min	95 ± 13	60 ± 7**	59 ± 8**	55 ± 12**	91 ± 13	79 ± 9	69 ± 8**
0–270 min	127 ± 9	127 ± 17	97 ± 12**	78 ± 10**	114 ± 11	113 ± 9	87 ± 6**

Effects of IV CCK on food intake (cumulative value) in 4 nonfasted cats. Peptides were infused 90 min before cats had access to food (liver). Food intake was expressed as mean ± SEM. Control experiments with saline infusion, n=60; 1.2 and 219 pmol/kg·hr of CCK n=16 and for 875 pmol/kg·hr of CCK, n=28. Statistical differences $*p<0.05$, $\dagger p<0.01$ was achieved by Student's t-test.

modifying the amount of food eaten in the different periods of food intake. We observed that IV CCK decreased food intake in sham and normally-fed animals and clearly shows that the threshold dose required to inhibit feeding is the same as that which inhibits sham-feeding. These findings are in agreement with one set of experiments in rats (20). By contrast, several reports have demonstrated that sham-feeding in rats is less sensitive to inhibition by exogenous CCK than feeding in rats since doses required to inhibit sham-feeding were much larger than those required to inhibit normal feeding (7, 11, 17, 18). However, most of these studies did not attempt a direct comparison of the effects of IV CCK on the same animals. Our data are not in accordance with the findings of Moran and McHugh (18) and question their hypothesis that "the satiety effect of CCK is a consequence of decreased gastric emptying" leading to the supposedly major role of gastric distension in decreasing food intake. Our study clearly demonstrates that the suppressive effect of food intake did not necessary required gastric distension. In addition, the threshold dose of sulfated CCK-8 for inhibition

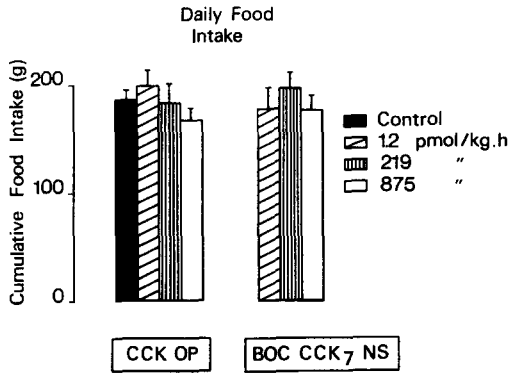

FIG. 5. Effect of intravenous CCKOP (sulfated CCK 8) and Boc 7NS on the daily food intake in 4 nonfasted cats. CCK or NaCl 0.9% (control) were infused 90 min on a separate day before the animals had access to food. Results are expressed as means±SEM. Control n=60 and n=16 for 1.2 and 219 pmol/kg·hr and n=24 for 875 pmol/kg·hr. Using Student's *t*-test, no statistical significant differences between control and treated animals were found.

of sham-feeding and feeding (1.2 pmol/kg·hr) did not modify gastric emptying of a protein meal given intragastrically (control: n=40, 49±2% vs. CCK 8 1.2 pmol/kg 48.7±6%, n=16). If gastric distension mechanisms are of greater importance than "pregastric acting factors" in the CCK-reducing food intake, one would expect a greater inhibition of food intake in those cats in the gastric distension series as compared with cats in the "pregastric acting factors" series. Our results actually showed the contrary: i.e., a greater inhibition of food intake occurred in "pregastric acting factors" series than in the gastric distension series. In cats, the CCK satiety effect seems not solely due to the gastric emptying hypothesis reducing food intake.

The secretory studies performed in the present study indicates that sulfated CCK 8 is a potent stimulant of gastric acid secretion. This finding confirms earlier studies on acid secretion (6). On the basis of these secretory studies, subthreshold, threshold and submaximal doses of sulfated CCK 8 stimulating acid secretion used in feeding studies, clearly demonstrated that the minimal effective dose of CCK for inhibition of food intake was 90 times lower than the threshold dose stimulating acid secretion. Studies performed in rats have shown that the lowest dose to decrease food intake was larger than the dose producing maximal pancreatic enzyme secretion (20). These results raise an important question; are the CCK receptors implicated in these biological systems identical to those implicated in the peripheral CCK effect on food intake? The characteristics of the site(s) acting in the periphery to alter food intake may be assessed by the use of CCK compounds of different structures. Evidence has been obtained that the sulfate group on tyrosine in position 7 is essential for biological activity and particularly in the stimulation of gastric secretion (13,27). Our present report indicates that the sulfated CCK 8 and the nonsulfated Boc CCK 7 share the same capacity to decrease food intake in cats. Thus, the structural requirement for peripheral CCK satiety is independent of the sulfate group, in contrast to the requirement for gastric acid secretion. However, studies performed in rats have shown that central administration of sulfated CCK 8 decreases food intake, whereas the nonsulfated CCK 8 does not (22). It has also been reported that centrally-administered sulfated CCK 8 and sulfated CCK 7 were equally active in their effects on the exploratory behavior in mice (4,5). These above data indicate that the sulfate group is important for agonistic efficacy in central nervous system. A role for the sulfate group has also been reported in acid secretion (6) and amylase release from pancreatic acini (3,27) induced by peripheral CCK octapeptide. Our findings in cats lead us to consider that the peripheral receptors implicated in CCK satiety are different from other receptors since the presence of the sulfate group is not necessary for the reduction of food consumption. However, the fact that the suppressive effect was maintained longer with the sulfated compound compared with the nonsulfated compound suggests that the agonist efficacy may be affected.

In summary, this study performed in cats confirms that exogenous CCK reduces food intake in fasted and nonfasted animals. The suppressive effect of food intake by CCK does not appear to be mediated solely by a mechanism that involves gastric distension because CCK had similar effects in both the presence and absence of gastric distension. Furthermore, a possible interaction with other neural and/or humoral factors in the production of satiety effects remains to be determined. In contrast to gastric acid secretion, the sulfate group is not a "restricting" factor for peripherally CCK satiety effect.

ACKNOWLEDGEMENTS

The authors thank M. C. Degrandi for secretarial assistance, J. P. Laigneau and L. Moizo for the illustrations, and would like to acknowledge Mrs. C. Eastcourt for the linguistic revision of the manuscript.

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