

Inhibition of sucrose intake by continuous celiac, superior mesenteric, and intravenous CCK-8 infusions

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Cox, James E., Steven M. McCown, Jonathan M. Bridges, and William J. Tyler. Inhibition of sucrose intake by continuous celiac, superior mesenteric, and intravenous CCK-8 infusions. *Am. J. Physiol.* 270 (*Regulatory Integrative Comp. Physiol.* 39): R319–R325, 1996.—Two experiments compared the potency of continuous infusions of cholecystokinin octapeptide (CCK-8) for reducing sucrose intake when administered into abdominal arteries or the jugular vein. Adult, male Sprague-Dawley rats received 22-min infusions of saline or several doses of CCK-8. Sucrose was available for 20 min, beginning 2 min after onset of infusions. In the first experiment, intraceliac CCK-8 in doses of 50, 125, and 312 ng produced significant reductions in intake, but no dose affected intake when administered into the jugular vein. In *experiment 2*, only the highest dose, 312 ng, suppressed intake when infused into the superior mesenteric artery, and jugular infusions were again ineffective. Behavioral observations indicated that intra-arterial CCK-8 had no effect on feeding within the first several minutes of test meals but accelerated the subsequent decline in incidence of feeding. These results suggest that receptors involved in cholecystokinin satiety are widely distributed within the gastrointestinal tract.

cholecystokinin octapeptide; gastrointestinal tract; rat; satiety

SEVERAL LINES OF EVIDENCE suggest that cholecystokinin reduces food intake by acting within the abdomen, possibly on cholecystokinin A receptors in the stomach and/or duodenum (23, 33, 36, 38). Consistent with this possibility are reports that cholecystokinin octapeptide (CCK-8) is more potent in reducing intake when infused into the aorta just rostral to the celiac artery than when given intravenously (4, 7). These results have been interpreted as indicating sites of action within the celiac arterial bed. This interpretation, however, is not unambiguous, because such infusions should also result in higher than control CCK-8 concentrations in other abdominal arteries, most notably the superior mesenteric artery, which exits the aorta just distal to the celiac (12). We investigated, therefore, the potency of CCK-8 for reducing intake when infused directly into the celiac or superior mesenteric artery. Results suggest that receptors involved in cholecystokinin satiety are found in both arterial beds.

METHOD

Experiment 1

Rats with celiac or jugular catheters received continuous infusions of 20–312 ng CCK-8 during tests in which they were allowed 20 min access to 30% (0.88 M) sucrose. Feeding behavior was monitored during tests to allow analysis of effects of CCK-8 on temporal intake patterns.

Adult, male Sprague-Dawley rats (325–464 g at surgery) were individually housed in a temperature-controlled room on a 12:12-h light-dark cycle with lights on at 0730. Rats were

allowed 3 h daily access to laboratory chow (Agway Prolab 1000 pellets). Behavioral tests were performed between 1300 and 1600 after 20 h food deprivation.

Surgery and adaptation to test procedures. Before surgery, rats were adapted for ~3 wk to handling, the feeding schedule, and consumption of 30% sucrose from graduated drinking tubes. They were then randomly assigned to receive celiac or jugular catheters constructed from polyurethane tubing (Microrenathane, Braintree Scientific, MRE033, 0.014 in. ID, 0.033 in. OD). To minimize interference with arterial flow, tips of celiac catheters were tapered to approximately one-half the original diameter by pulling after immersion in hot sesame oil. On the day of surgery, rats received subcutaneous injections of the antibiotic sulfamethoxazole-trimethoprim and were anesthetized with pentobarbital sodium (42 mg/kg ip). Fourteen rats underwent surgery for implantation of catheters into the celiac artery according to the following protocol: the abdominal aorta and celiac artery were exposed just rostral to the right kidney, and the aorta was clamped just above and below the celiac. The celiac artery was punctured at its base with hypodermic needle tubing, and the catheter was threaded for ~0.5 cm so that the tip lay proximal to all arterial branches. The catheter was fixed in place, and the artery was sealed by application of cyanoacrylate glue to the catheter and artery at the point of entry. The catheter was also anchored to underlying muscles with silk sutures. Its cephalic end was threaded out of the abdominal cavity and then subcutaneously to an exit on the dorsal surface of the neck, where it was secured with silk sutures tied to underlying muscles. In another seven rats, catheters were inserted into the right external jugular vein and secured as described above. Catheters were filled with a solution of 40% glucose and 100 U/ml heparin (21) and capped with monofilament fishing line. They were subsequently flushed daily with 0.5 ml normal saline followed by 0.05 ml of the glucose-heparin solution. Beginning 1 wk after surgery, rats were adapted to test procedures (described below) for ~2 wk.

Experimental design and protocol. Because of attrition from mortality or catheter failure, data were collected from six rats with celiac artery catheters and five rats with jugular catheters. Each rat underwent seven tests. On the first, fourth, and seventh tests, the infusate was normal saline. On the remaining four tests, CCK-8 was infused in doses of 20, 50, 125, and 312 ng/rat (approximately equal to 2.2, 5.4, 13.6, and 34.0 pmol·kg⁻¹·min⁻¹, respectively) given in randomized order. These doses were all below the minimum effective doses for near-celiac (400 ng) and intravenous (800 ng) infusion in a previous study (7). It was expected, therefore, that none would be effective when infused into the jugular vein. Confirmation of the hypothesis of augmented potency resulting from celiac artery administration would entail that at least some of the doses be effective in the group with arterial catheters.

Before each test, the catheter was flushed with 0.4 ml of normal saline after which it was attached to coiled polyethylene tubing that ran from a syringe pump through an opening in the top of the test cage. Normal saline or CCK-8 (Squibb) in saline was infused for 22 min at a nominal rate of 0.0197 ml/min for a total of 0.43 ml. Beginning 2 min after onset of

the infusion, 30% sucrose was presented in a graduated drinking tube and left in place for 20 min. Behavioral observations were conducted during tests; at 15-s intervals, the rat was scored as either eating or not eating. At the end of the test, the catheter was filled with glucose-heparin.

Verification of catheter placement and patency. Upon completion of each rat's tests it first received an injection of 0.15 ml (10 mg) pentobarbital sodium through the catheter. Rapidly developing ataxia, immediate for jugular catheters and within 1 min for celiac catheters, was taken as evidence that the pentobarbital had been delivered into the vasculature (47). In addition, for approximately one-half of the animals, it was still possible to withdraw blood through the catheter. Subsequently, the rat received an overdose of pentobarbital sodium and was perfused transcardially with normal saline. Green food coloring was then infused through the catheter at 0.0197 ml/min. The course of the catheter was inspected to the point of insertion for possible leakage. During infusion into the celiac artery, dye was prominent in the vasculature of the stomach and the first 2–3.5 cm of the duodenum, as well as the head of the pancreas. It was also present, though generally less prominent, in the liver. Finally, a longitudinal incision was made along the celiac artery, and in all cases the catheter tip was proximal to the three branches of the celiac (12).

Data analysis. For analysis of 20-min sucrose intake in each group, values from the three saline tests were pooled [analysis of variance (ANOVA) revealed no significant differences in intake among the three saline tests for either group; both F values < 1 and P values > 0.50]. One-tailed comparisons between pooled saline tests and each dose of CCK-8 were performed using Dunn-Sidak tests (test statistic subsequently referred to as tD) modified as proposed by Holm (39, 48). For comparison of the effectiveness of CCK-8 in the celiac and jugular infusion groups, a mixed between- and within-subjects ANOVA was performed on difference scores computed as the differences between a rat's intake on CCK-8 tests and its mean intake on the three saline tests. One-tailed comparisons at individual doses were performed using the pairwise comparison procedure described above with error terms based upon pooling of the subjects within groups and dose \times subjects within groups sums of squares (48).

For analysis of observational data, feeding scores were derived so that each score was the proportion of observations within a particular 1-min period during which the rat was observed to be eating. Feeding scores from the three saline tests were pooled to yield overall means for each minute. In a previous study (7), we found that continuous near-celiac infusions of CCK-8 had no effect on feeding during the first several minutes but produced a marked drop in feeding scores in approximately the second quarter of the test. Differences between CCK-8 and saline tests were less prominent during the last one-half of the test, primarily because of floor effects. Consequently, analyses of feeding scores from the current study were performed separately for each quarter of the test; that is, *minutes 1-5, 6-10, 11-15, and 16-20*. For each analysis, one-tailed comparisons were performed between saline and CCK-8 tests at each dose using the procedure described previously for the data on sucrose intake. The error term for each comparison was based upon pooling of the subjects \times dose and subjects \times dose \times time sums of squares from the corresponding ANOVA (48).

Experiment 2

Procedures were identical to those in the first experiment except as noted below.

Surgery. Eight rats received implantations of polyurethane catheters into the superior mesenteric artery and six received jugular catheters. Surgical procedures were essentially identical to those in *experiment 1*. Superior mesenteric catheters were inserted at the junction with the aorta and threaded for < 1 cm so that the tip lay proximal to all arterial branches. During terminal catheter assessments, dye was always prominent throughout the distal duodenum, beginning 2.5–4 cm distal to the pylorus, as well as within the adjacent region of the pancreas. Dye was also present, with varying density, in the remainder of the small intestine and part of the colon.

Experimental design and protocol. Data were collected from seven rats with superior mesenteric catheters and six rats with jugular catheters. Rats underwent six tests, so that on the first, third, and fifth test saline was infused, and on the second, fourth, and sixth test CCK-8 was infused in doses of 50, 125, and 312 ng/rat given in randomized order.

RESULTS

Experiment 1

Effects of celiac artery CCK-8 infusions on sucrose intake are shown in Fig. 1. The lowest dose to significantly reduce intake was 50 ng, which produced an average decrease of 21% [$tD(20) = 2.30$, $P < 0.05$]. Significant reductions were also produced by 125 ng [24% decrease, $tD(20) = 2.71$, $P < 0.05$] and 312 ng

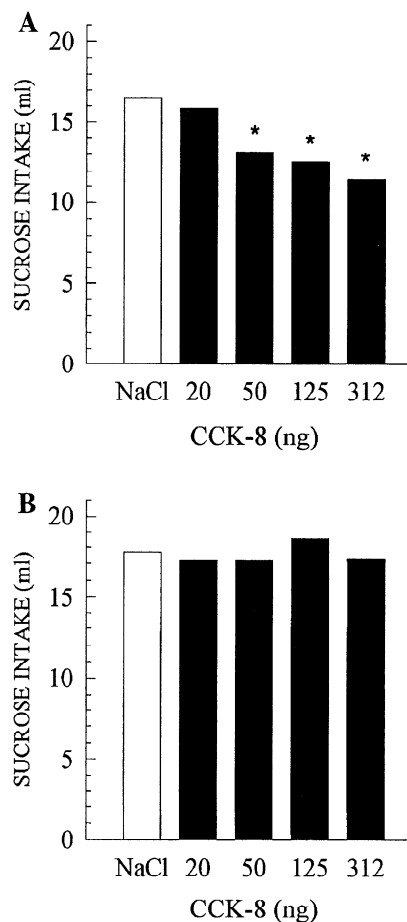


Fig. 1. Mean 20-min intake of 30% sucrose during continuous infusion of physiological saline or 20–312 ng cholecystokinin octapeptide (CCK-8) into celiac artery (A) or jugular vein (B). * $P < 0.05$ in comparison to saline by Dunn-Sidak test.

CCK-8 [30% decrease, $tD(20) = 3.46, P < 0.01$]. The 50- and 312-ng doses suppressed intake in all rats; only one rat consumed more in response to 125 ng CCK-8 than to saline. As is apparent in Fig. 1, these doses of CCK-8 did not affect intake when infused into the jugular vein (all P values > 0.05). Finally, comparison of difference scores (saline - CCK-8) revealed that the 125- and 312-ng doses of CCK-8 were significantly more effective in reducing intake when infused into the celiac artery than into the jugular vein [$tD(36) = 2.738, P < 0.05$ and $tD(36) = 2.614, P < 0.05$; respectively].

Effects of celiac CCK-8 on temporal feeding patterns, shown in Fig. 2, were similar to those we have observed previously in response to near-celiac infusions (7). That is, for all tests mean feeding scores dropped in approximately monotonic fashion across the 20-min feeding interval. For the celiac-infusion group, scores on CCK-8 and saline tests were virtually identical for the first several minutes, after which they diverged, with scores dropping more rapidly on CCK-8 tests. Moreover, the degree of the divergence appeared to increase as a function of dose. Analysis of scores from the first 5 min revealed no differences between saline and CCK-8 tests at any dose (all P values > 0.25). During the second

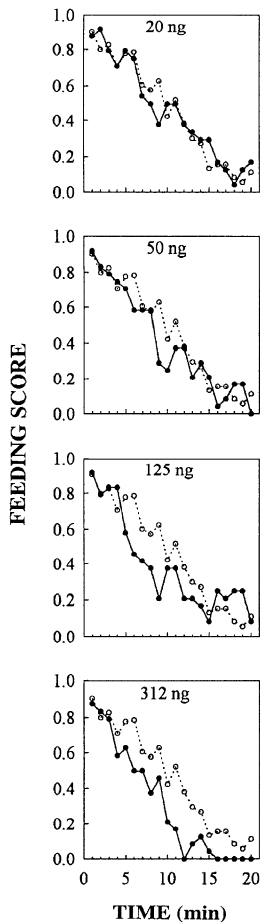


Fig. 2. Mean 1-min feeding scores during tests with continuous celiac infusion of 20–312 ng CCK-8. Scores from saline tests (○) are reproduced on each graph for comparison with CCK-8 tests (●). Feeding scores were calculated as proportion of the 4 observations within each minute at which each rat was feeding.

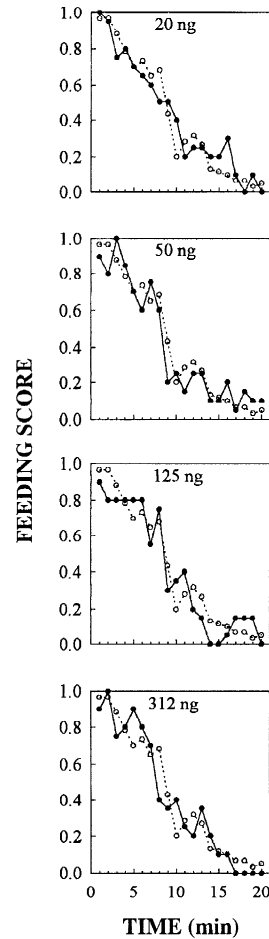


Fig. 3. Mean 1-min feeding scores during continuous jugular infusion of 20–312 ng CCK-8. Scores from saline tests (○) are reproduced on each graph for comparison with CCK-8 tests (●).

quarter of the test, doses of 125 [$tD(100) = 3.25, P < 0.01$] and 312 ng [$tD(100) = 2.68, P < 0.05$] CCK-8 significantly reduced feeding scores compared with saline tests. A strong trend in that direction was produced by the 50-ng dose, which reduced feeding during this interval in five of six rats, but the effect was not quite significant [$tD(100) = 1.99, 0.05 < P < 0.10$]. For the last two 5-min intervals, the only significant decrease was produced by 312 ng CCK-8 during the *minute 11 to minute 15* interval [$tD(100) = 3.67, P < 0.01$]. For the jugular group (Fig. 3), no dose of CCK-8 affected feeding scores within any interval (all P values > 0.10).

Experiment 2

Effects of infusions of CCK-8 into the superior mesenteric artery are shown in Fig. 4. Only the largest dose, 312 ng, significantly affected intake, reducing intake in all rats and producing a 36% decrease on average [$tD(18) = 4.87, P < 0.01$]. The 125-ng dose reduced intake in all but one of the rats, but the average decrease was not significant [$tD(18) = 1.61, P > 0.05$]. As in the previous experiment, intrajugular CCK-8 failed to reduce intake at any dose (all P values > 0.05). Analysis of difference scores revealed that the largest

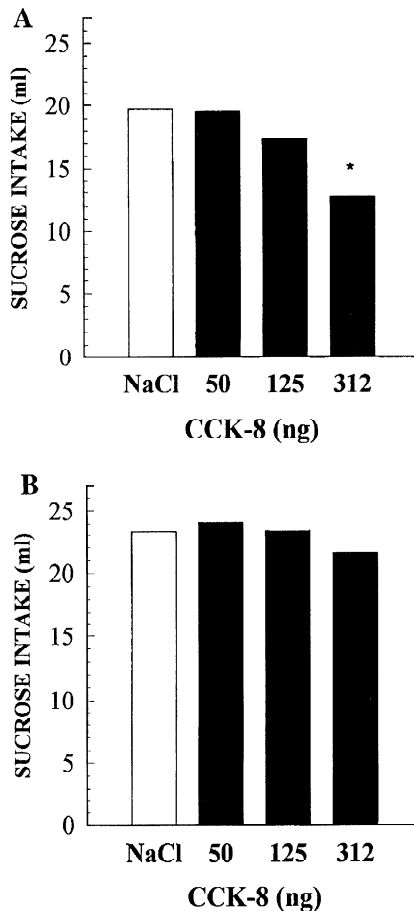


Fig. 4. Mean 20-min intake of 30% sucrose during continuous infusion of physiological saline or 50–312 ng CCK-8 into the superior mesenteric artery (A) or jugular vein (B). * $P < 0.05$ in comparison with saline by Dunn-Sidak test.

dose was significantly more effective when infused into the superior mesenteric artery compared with intravenous administration [$tD(33) = 3.00$, $P < 0.05$]. In addition, because ANOVA comparing intake on the three saline tests revealed significant differences for the superior mesenteric group ($P < 0.05$), the analyses described above were also performed based upon differences between intake on each CCK-8 test and the matched saline test (i.e., not mean intake pooling across saline tests). Results of these analyses were identical in that they revealed that only the 312-ng dose suppressed intake in the superior mesenteric group and that this dose was significantly more effective by this route than by intravenous infusion (P values < 0.05).

As shown in Fig. 5, only the 312-ng dose of CCK-8 produced changes in feeding patterns of rats receiving superior mesenteric infusions. Surprisingly, this dose produced similar changes in the jugular infusion group (Fig. 6). In both cases, the changes were like those produced by celiac infusions in *experiment 1*, that is, significant reductions across the 6- to 10- and 11- to 15-min intervals (all P values < 0.05).

DISCUSSION

The motivation for the present experiments was the ambiguity regarding interpretation of reports of aug-

mented potency of CCK-8 when administered by the near-celiac route (4, 7). In particular, this potentiation does not necessarily result from flow of the infusate through the celiac artery. That is, because of the substantial difference in the luminal diameters of the aorta and the celiac artery, it is likely that only a relatively small percentage of the near-celiac infusate enters the celiac artery. As a consequence, relatively high concentrations of cholecystokinin will be available to more distal aortal branches. Thus the nonspecificity of near-celiac administration makes interpretation problematic. We investigated, therefore, the effectiveness of infusions acting directly on the upper and middle portions of the gastrointestinal tract via the celiac and superior mesenteric arteries, respectively.

The results of *experiment 1* indicated that, when CCK-8 was infused into the celiac artery proper, potency was substantially increased over that resulting from intravenous or near-celiac administration. Doses as low as 50 ng ($\sim 5.4 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were effective in suppressing sucrose intake. None of the doses used here, up to 312 ng ($\sim 34 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), suppressed total intake when delivered into the jugular vein. Admittedly, under different test conditions, lower continuous infusion rates of intravenous CCK-8 have in some studies inhibited intake, but the minimum effective rates, $\sim 15 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (30, 45), were still substantially higher than that in the celiac group. In a previous study in our laboratory using essentially the same protocol, the minimum effective doses for near-celiac and intravenous CCK-8 were 8 and 16 times,

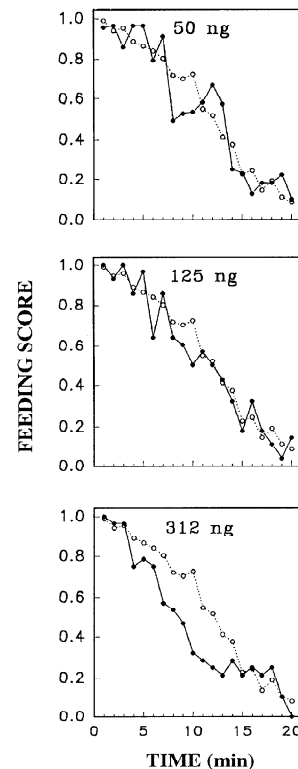


Fig. 5. Mean 1-min feeding scores throughout tests with superior mesenteric infusion of 50–312 ng CCK-8 (●). Scores from saline-infusion tests (○) are reproduced on each graph for comparison with CCK-8 tests.

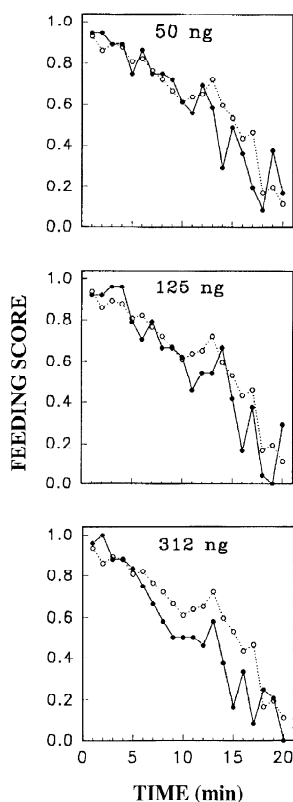


Fig. 6. Mean 1-min feeding scores from tests with jugular infusion of 50–312 ng CCK-8 (●) in *experiment 2*. Scores from saline-infusion tests (○) are reproduced on each graph for comparison.

respectively, the threshold dose for the celiac-infusion group in the present study (7).

Differences in potency of intraceliac and intrajugular CCK-8 are presumed to reflect differences in CCK-8 concentrations acting upon tissue within the celiac arterial bed. Although such concentrations were not measured, it is possible to derive estimates of these values under the different infusion conditions. During continuous intravenous infusion, systemic CCK-8 concentration should rise to plateau levels over a period of ~5–10 min on the basis of a half-life of this peptide of 1–2 min (8, 13, 22). To our knowledge, the published protocol most similar to ours involved 15-min jugular infusions of CCK-8 at $7 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in adult male rats, after which samples were taken from the carotid artery (9). Plasma levels increased by 38 pM (from a baseline of 4.4 pM). Because changes in plateau concentrations should be proportional to differences in infusion rate (22, 29), it is possible to estimate that increases in systemic concentrations, resulting from the four rates of jugular infusion used here, were ~12, 30, 75, and 185 pM. Intraceliac concentrations, resulting from infusions into that artery, should be based upon summation of 1) the immediate effect of the infusion, computed as the ratio of infusion rate to arterial flow rate, and 2) the resulting general systemic concentration. Calculation of the former was based upon a celiac artery flow rate of $20 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (16), and the latter values were assumed to be the same as for jugular infusion. Resulting estimated concentrations were ~120, 300, 750, and 1,870 pM for the four

infusions rates, from low to high. Thus celiac infusions resulted in CCK-8 concentrations within the celiac arterial bed one order of magnitude higher than those resulting from intravenous infusions. Furthermore, although these values are only rough approximations, it is interesting that all of the celiac infusions effective in reducing intake resulted in estimated intraceliac concentrations higher than that for the highest jugular infusion rate, but the (ineffective) 20-ng dose did not.

Thus the results of the first experiment strongly support the hypothesis that cholecystokinin reduces intake by acting on tissue perfused by branches of the celiac artery. Several lines of evidence, coming, for example, from electrophysiological studies (2, 27, 36, 38), selective transections of vagal branches (44), and behavioral studies employing gastric (24, 37) or duodenal infusions (5, 6, 33, 49) have suggested the stomach and duodenum as possible target organs. Because both the stomach and proximal duodenum lie within the celiac bed, our results are consistent with either or both of these areas as sites of action. Other organs perfused by the celiac artery are the liver and the pancreas. The liver is an unlikely site of action, as indicated by the relative ineffectiveness of hepatic-portal CCK-8 infusions (43, 45). Although a role for the pancreas is consistent with the observed effects of celiac (as well as superior mesenteric) infusions and its density of cholecystokinin A receptors (41), there is little additional evidence available for evaluating this possibility.

The results of *experiment 2* indicated that superior mesenteric infusion also resulted in enhanced potency compared with intravenous administration. Based upon calculations similar to those above and assuming an arterial flow rate of $40 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (16), the minimum effective dose (312 ng) resulted in a CCK-8 concentration of ~1,000 pM within the superior mesenteric artery. Because this artery supplies the distal duodenum, this experiment, like the previous one, yielded results consistent with a duodenal site of action for CCK-8. However, effectiveness of superior mesenteric infusions could also reflect action on more distal regions of the gastrointestinal tract, because this artery also perfuses the remainder of the small intestine and part of the colon. In agreement with this possibility, Houpt (14) found evidence that CCK-8 can reduce intake by acting on the ileum in pigs.

In conjunction with several lines of evidence from previous studies our results suggest, therefore, that cholecystokinin reduces intake by acting on cholecystokinin A receptors on vagal afferent terminals (25, 28, 43) with a wide distribution within the gastrointestinal tract. Additional evidence in support of this idea includes 1) reports indicating that the combined gastrointestinal innervation of the vagal branches implicated in cholecystokinin's inhibition of intake, the gastric and hepatic branches (18, 19, 44), extends from the stomach to the cecum (1, 26), and 2) recordings from putative gastric, duodenal, and ileal receptors responsive to CCK-8, as well as to intraluminal stimuli (2, 32, 36, 38). The mode of action of endogenous cholecystokinin is likely to be paracrine or neurocrine (28, 31, 33, 43), consistent with our estimates of threshold CCK-8 con-

centrations within the arterial beds being much higher than meal-stimulated plasma levels (20). Moreover, neuronal cholecystokinin has been shown to possess an extensive distribution throughout the gastrointestinal tract (10, 35), in line with the proposal of distributed sites of action.

It is possible that the difference in minimum effective doses in *experiments 1* and *2*, 50 and 312 ng, respectively, indicates that the celiac arterial bed contains a greater concentration of satiety-relevant cholecystokinin receptors than does the superior mesenteric bed. Admittedly, however, our data are only suggestive regarding this issue. For example, because the flow rate of the superior mesenteric artery is greater than that in the celiac artery in rats (16), equal infusion rates will result in lower concentrations in the former. In addition, our comparison is based upon separate groups of rats obtained at different times, which may have differed with regard to sensitivity to CCK-8. Thus a more conclusive comparison would require infusion rates adjusted to produce equal CCK-8 concentrations in these two arteries and in rats randomly sorted into the two infusion conditions.

We analyzed data from behavioral observations to address the possibility that the observed suppression of intake reflected nonspecific disruption of feeding rather than satiety. Because of the high CCK-8 concentrations perfusing gastrointestinal sites in rats with arterial catheters, intake may have been reduced because of aversion arising from abnormal gastrointestinal motor activity (34, 40, 46). However, our analysis of temporal intake patterns suggests that such aversive effects did not occur. Suppression of intake by arterial CCK-8 infusions was accompanied by effects on temporal feeding patterns similar to what we and others have observed using different routes of administration (6, 7, 11, 15, 17). Although intra-arterial CCK-8 should have been near peak concentration by the start of the feeding test, as discussed previously, even the highest dose had no effect on incidence of feeding early in the meal. Decline in feeding scores relative to saline tests first occurred after several minutes. Such a pattern, that is lack of an effect at the start of the meal with inhibition developing later, has been interpreted as indicating satiety rather than aversion (3, 42), bolstering the argument that a physiological action of this peptide is induction of satiety via action on receptors within the gastrointestinal tract.

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