Effects of peripheral CCK receptor blockade on feeding responses to duodenal nutrient infusions in rats

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CCK is a peptide that is found throughout the brain and in neurons and endocrine cells of the gastrointestinal tract. Studies demonstrating that type A CCK receptor (CCKAR) antagonists stimulate food intake in a variety of species provide compelling evidence that CCK plays an essential role in producing the satiation that occurs with ingestion of a meal (6, 13, 14, 23, 39, 48). The popular hypothesis is that CCK, secreted from enteroendocrine cells in the upper small intestine in response to duodenal delivery of nutrients, acts through paracrine stimulation of intestinal vagal sensory neurons to inhibit food intake. This hypothesis is supported by studies demonstrating the existence of CCK-secreting endocrine cells in the epithelium of the upper small intestine (7, 60), CCKARs within vagal afferent nerves (40, 66), activation of intestinal vagal afferent neurons by exogenous and endogenous CCK (17, 20, 31), and similar attenuation by CCKAR antagonists and vagal neural lesions of anorexic responses to exogenous CCK and nutrient administration (51).

Several lines of evidence suggest that this mechanism is not the only one by which CCK produces satiety. For example, we and others have demonstrated that systemic administration of the CCKAR antagonist devazepide can increase food intake in rats whether or not they are vagotomized (45) or pretreated with capsaicin to lesion visceral sensory nerves (52). CCKAR antagonists reported not to cross the blood-brain barrier [2-naphthalenesulfonyl-l-aspartyl-2-(phenethyl)-amide (25) and A-70104 (64)] have also been reported to have no effect on food intake in rats (22) or pigs (4, 24) when administered systemically under the same conditions in which devazepide stimulates food intake (22, 23). Because CCK does not readily penetrate the blood-brain barrier (41), these results suggest that endogenous CCK may also be acting as a neurotransmitter or neuromodulator within the brain to produce satiety. This conclusion is supported further by studies showing that food intake releases hypothalamic CCK (53) and that brain injections of CCK antisera (18) and CCK receptor antagonists (21, 54) stimulate food intake.

In the present study, CCKAR antagonists with different blood-brain barrier permeabilities were used to determine whether endogenous CCK produces an essential satiety action mediated by CCKARs located peripheral to the blood-brain barrier. Devazepide penetrates the blood-brain barrier [2-naphthalenesulfonyl-l-aspartyl-2-(phenethyl)-amide (25) and A-70104 (64)] have also been reported to have no effect on food intake in rats (22) or pigs (4, 24) when administered systemically under the same conditions in which devazepide stimulates food intake (22, 23). Because CCK does not readily penetrate the blood-brain barrier (41), these results suggest that endogenous CCK may also be acting as a neurotransmitter or neuromodulator within the brain to produce satiety. This conclusion is supported further by studies showing that food intake releases hypothalamic CCK (53) and that brain injections of CCK antisera (18) and CCK receptor antagonists (21, 54) stimulate food intake.

METHODS

Subjects. Male rats (Sasco Sprague-Dawley, Charles Rivers Lab, Kingston, NY; ~350 g at the start of the study) were

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housed individually in hanging wire-mesh cages in a temperature-controlled room with a 12:12-h light-dark cycle (lights off at 1600). The animals were provided rat chow (Purina no. 5001, 3.3 kcal/g) and water ad libitum. The Animal Studies Subcommittee of the Omaha Veterans Affairs Medical Center approved the experimental protocol. Animal experimentation was conducted in conformity with the “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society (1).

Surgical procedures. Gastric, duodenal, and jugular vein cannulas were implanted according to procedures described previously (49, 61). When the stainless steel gastric cannula is open, ingested liquid diet rapidly drains from the stomach. The duodenal cannula was implanted in the aboral direction with its tip located ~3 cm distal to the pyloric sphincter. The duodenal cannula was plugged with stainless steel wire and flushed with 0.5 ml of physiological saline every other day to maintain patency. The jugular vein cannula was filled with heparinized saline (20 U/ml), plugged with stainless steel wire, and flushed with 0.5 ml of heparinized saline every other day to maintain patency.

Effects of devazepide and A-70104 on CCK-8-induced inhibition of sham feeding. This series of experiments determined the effects of bolus intravenous injection of devazepide on sham feeding and on CCK-8-induced inhibition of sham feeding. The second determined the effects of continuous intravenous infusion of A-70104 on sham feeding and on CCK-8-induced inhibition of sham feeding. Devazepide was administered by bolus injection because it has a relatively long plasma half-life of ~4 h (Dr. J. Lin, Merck Sharpe & Dohme, personal communication). The half-life of A-70104 has not been determined. A-70104 was therefore administered by continuous infusion to ensure blockade of CCKARs throughout the experimental period.

After recovery from surgery, rats with gastric and jugular vein cannulas were adapted to a feeding regimen that included food deprivation for 18 h from 1600 to 1000 of the next day, access to 15% sucrose from 1000 to 1200, and access to rat chow from 1200 to 1600 of the next day. Thus rats were deprived of food no more than once every 48 h. Water was available except when sucrose was provided. The animals were then adapted to the following experiment procedures. Fifteen minutes before the beginning of a 60-min experimental period (the same time each day between 1000 and 1200 after the imposed fast), each rat was placed in a Bollman-type restraint cage, the jugular vein catheter was flushed with 0.15 M NaCl containing 20 U/ml heparin, the gastric cannula was opened, and the stomach was flushed with 5-ml volumes of 0.15 M NaCl until drainage was clear. Rats were given 15% sucrose to ingest for 30 min, the gastric cannula was then closed, and the rats were returned to their home cages and given rat chow. After adaptation to these procedures (~1 wk), rats with open gastric cannulas received a bolus intravenous injection of devazepide (1 mg/kg, Merck Sharpe & Dohme Research Laboratories) or vehicle (5% DMSO, 5% Tween 80, 90% 0.15 M NaCl) 10 min before receiving a 30-min intravenous infusion CCK-8 (10 nmol·kg·h⁻¹) and saline was used as diluent for Intralipid. The first three experiments determined the effects of devazepide (1 mg/kg) on sham feeding responses to duodenal infusions of peptone, maltose, and Intralipid. Sixteen experiments were performed. The first three experiments determined the dose-dependent effects of duodenal infusion of peptone, maltose, and Intralipid on sham feeding. Doses were as follows: peptone (0, 0.7, 1.4, 2.1, and 2.8 g/h); EZMix tryptone, Sigma), maltose (0, 0.7, 1.3, 2.6, and 5.2 g/h; Sigma), and Intralipid (0, 0.2, 0.4, 0.9, and 1.8 g/h; Baxter Healthcare). The final five experiments determined the effects of A-70104 (700 nmol·kg⁻¹·h⁻¹) and devazepide (1 mg/kg) on sham feeding responses to peptone (2.0 and 2.5 g/h). The final five experiments determined the effects of A-70104 (700 nmol·kg⁻¹·h⁻¹) and devazepide (1 mg/kg) on sham feeding responses to maltose (1.4 and 2.0 g/h). The final five experiments determined the effects of A-70104 (700 nmol·kg⁻¹·h⁻¹) and devazepide (1 mg/kg) on sham feeding responses to Intralipid (0.5, 0.7, and 1.1 g/h). Treatments were administered to groups of 12–15 rats as above for the CCK-8 experiments, with the exception that nutrient doses were infused into the duodenum at a rate of 8.9 ml/h for 30 min. Water was used as vehicle and diluent for peptone and maltose, while saline was used as diluent for Intralipid.

Statistical analyses. Values are presented as group means ± SE. Our intent was not to compare the effects of A-70104 across nutrients or doses of a specific nutrient or to compare the effects of A-70104 and devazepide. Thus data from each experiment were analyzed separately. Effects of devazepide and A-70104 on sham feeding, CCK-8-induced inhibition of sham feeding, and duodenal nutrient-induced inhibition of sham feeding were evaluated using a repeated-measures ANOVA. In each analysis, planned comparisons of treatment means were evaluated by direct contrasts of means using the computer program SYSTAT. Differences between means were considered significant when P < 0.05. A one-tailed test was used for postulated unidirectional effects.

RESULTS

Effects of devazepide and A-70104 on CCK-8-induced inhibition of sham feeding. Figure 1A shows the individual and combined effects of devazepide (1 mg/kg iv) and a maximal inhibitory dose of CCK-8 (10 nmol·kg⁻¹·h⁻¹ iv) on sham feeding. Repeated-measures ANOVA demonstrated significant main effects of devazepide and CCK-8, and a significant interaction between devazepide and CCK-8, on 30-min sucrose
Treatment means labeled with the same letter designation are not
CCK-8 or vehicle infusion. Data are presented as means
infusion of A-70104 or vehicle beginning 15 min before onset of
were given 15% sucrose to ingest for 30 min. A-70104 experiments
minutes after onset of CCK-8 infusion, rats with open gastric
receiving a 30-min intravenous infusion of CCK-8 or vehicle. Ten
and 11 rats, respectively. Food-deprived rats received a bolus intra-
intake [devazepide: F(1,9) = 15.9, P < 0.01; CCK-8:
F(1,9) = 28.7, P < 0.001; interaction of devazepide and
CCK-8: F(1,9) = 20.3, P < 0.01]. The significant interac-
tion indicates that devazepide was more effective in stimulating feeding when administered with CCK-8 than when adminis-
tered alone. Figure 1A shows that devazepide injection alone had no effect on sham feeding, CCK-8 infusion alone significantly decreased sucrose intake by 57%, and devazepide completely blocked the anorexic response to CCK-8. Coadministration of devazepide and CCK-8 resulted in a sham feeding response that was not different from that observed after A-70104 administra-
tion alone (44.1 ± 1.1 vs. 47.0 ± 2.8 ml, respectively, 
P > 0.05).

Effects of A-70104 and devazepide on sham feeding responses to duodenal infusions of peptone, maltose, and Intralipid. Figure 2A shows that duodenal infusion of peptone dose dependently reduced the volume of sucrose consumed by 49–67% [F(4,44) = 35.3, P < 0.001]. The minimal effective dose was 2.1 g/h; the maximal effective dose was 2.8 g/h, the largest dose given. Figure 3, A–D, shows the effects of A-70104 and devazepide on peptone-induced inhibition of sham feeding. Figure 3A shows that peptone (2.0 g/h) inhibited sham feeding by 41% (P < 0.001), and A-70104 (700 nmol·kg⁻¹·h⁻¹ iv) significantly attenuated this response by 42% (P < 0.05). Figure 3B shows that in a subsequent experiment the same dose of peptone (2.0 g/h) inhibited sham feeding by 31% (P < 0.001), and devazepide (1 mg/kg iv) completely blocked this response (P < 0.01). Figure 3C shows that a higher dose of peptone (2.5 g/h) inhibited sham feeding by 59% (P < 0.001), and A-70104 (700 nmol·kg⁻¹·h⁻¹ iv) did not significantly attenuate this response (P = 0.17). Figure 3D shows that in a subsequent experiment the same dose of peptone (2.5 g/h) inhibited sham feeding by 50% (P < 0.001), and devazepide (1 mg/kg iv) significantly attenuated this response by 36% (P < 0.05).

Figure 2B shows that duodenal infusion of maltose dose dependently reduced the volume of sucrose consumed by 24–79% [F(4,44) = 40.4, P < 0.001]. The minimal effective dose was 1.3 g/h; the maximal effective dose was 5.2 g/h, the largest dose given. Figure 4, A–D, shows the effects of A-70104 and devazepide on maltose-induced inhibition of sham feeding. Figure 4A shows that maltose (1.4 g/h) inhibited sham feeding by 30% (P < 0.001), and A-70104 (700 nmol·kg⁻¹·h⁻¹ iv) significantly attenuated this response by 62% (P < 0.05). Figure 4B shows that in a subsequent experiment the same dose of maltose (1.4 g/h) inhibited sham feeding by 25% (P < 0.01), and devazepide (1 mg/kg iv) completely blocked this response (P < 0.05). Figure 4C shows that a higher dose of maltose (2.0 g/h) inhibited sham feeding by 41% (P < 0.001), and A-70104 (700 nmol·kg⁻¹·h⁻¹ iv) significantly attenuated this response by 36% (P < 0.05). Figure 4D shows that in a subsequent experiment the same dose of maltose (2.0 g/h) inhibited sham feeding by 64% (P < 0.01), and devazepide (1 mg/kg iv) significantly attenuated this response by 59% (P < 0.05).
response by 37% ($P < 0.05$). Figure 5C shows that a higher dose of Intralipid (0.7 g/h) inhibited sham feeding by 38% ($P < 0.001$), and A-70104 (700 nmol·kg$^{-1}$·h$^{-1}$ iv) did not significantly attenuate this response ($P = 0.38$). Figure 5D shows that in a subsequent experiment the same dose of Intralipid (0.7 g/h) inhibited sham feeding by 50% ($P < 0.001$), and devazepide (1 mg/kg iv) significantly attenuated this response by 45% ($P < 0.05$). Figure 5E shows that an even higher dose of Intralipid (1.1 g/h) inhibited sham feeding by 66% ($P < 0.001$), and neither A-70104 (700 nmol·kg$^{-1}$·h$^{-1}$ iv) nor devazepide (1 mg/kg iv) significantly attenuated this response ($P = 0.21$ and 0.27, respectively).

**DISCUSSION**

CCKAR antagonists with different blood-brain barrier permeabilities [devazepide penetrates (43, 64); A-70104 does not (64)] were used to test the hypothesis that duodenal delivery of protein, carbohydrate, and fat produces satiety in part by CCK action at CCKARs located peripheral to the blood-brain barrier. If this hypothesis is true, intravenous administration of either antagonist should attenuate the anorexic responses to duodenal infusions of each macronutrient. The present study demonstrated that duodenal infusions of maltose, peptone, and Intralipid dose dependently inhibited sham feeding, and inhibitory responses to each macronutrient were attenuated by both A-70104 and devazepide. We previously determined that in rats, immunoneutralization of circulating CCK blocks nutrient-induced stimulation of pancreatic enzyme secretion but has no effect on food intake (50). Together, these results suggest that endogenous CCK acts by an essential paracrine and/or neurocrine mechanism at CCKARs peripheral to the blood-brain barrier to inhibit food intake.

It was not the intent of the present study to compare the effects of A-70104 across nutrients or doses of a specific nutrient or to compare the effects of A-70104 and devazepide. Only single doses of A-70104 and devazepide were tested with most nutrients. We believe that a meaningful comparison of the effects of A-70104 and devazepide would require that multiple doses of each antagonist be tested with each nutrient. Only then could A-70104 and devazepide potencies and efficacies be determined and compared in a statistically rigorous manner. This was not the intent of the present study, although we have used this approach in comparing the effects of CCK, amylin, and other amylin-related peptides on food intake and gastric emptying (46, 47).

We previously observed that devazepide’s ability to attenuate anorexic responses to duodenal nutrient infusions appears to diminish as nutrient doses are increased (61–63). We speculated that an apparent lower effectiveness of devazepide at the higher nutrient doses may be due to a greater stimulation of redundant satiety mechanisms. This is the reason that, in the present study, we first characterized the dose-response
Fig. 3. Effects of intravenous administration of A-70104 (700 nmol·kg⁻¹·h⁻¹) and devazepide (1 mg/kg) on sham feeding responses to duodenal infusions of 2.0 g/h peptone (A and B, respectively) and 2.5 g/h peptone (C and D, respectively) in 10–13 rats. Experiments were similar to those described in Figs. 1 and 2. Treatment means labeled with the same letter designation are not statistically different (P > 0.05).

Fig. 4. Effects of intravenous administration of A-70104 (700 nmol·kg⁻¹·h⁻¹) and devazepide (1 mg/kg) on sham feeding responses to duodenal infusions of 1.4 g/h maltose (A and B, respectively) and 2.0 g/h maltose (C and D, respectively) in 9–20 rats. Experiments were similar to those described in Figs. 1 and 2. Treatment means labeled with the same letter designation are not statistically different (P > 0.05).
The effects of duodenal infusion of each macronutrient on sham feeding and then tested the effects of A-70104 on sham feeding responses to low and high effective doses of each macronutrient. Devazepide, the “gold standard” CCKAR antagonist, which readily penetrates the blood-brain barrier, was used as a positive control, in that devazepide would be expected to attenuate those nutrient-induced responses that are attenuated by A-70104, which it did.

Numerous studies have demonstrated that systemic administration of CCKAR antagonists, devazepide and loxiglumide, attenuates the inhibitory effects of oral, intragastric, and duodenal delivery of various foods and macronutrients on subsequent food intake in a variety of species (6, 13, 14, 23, 34–36, 39, 48, 59, 61–63, 65). It is not clear from these studies, however, whether the antagonists blocked central and/or peripheral sites of endogenous CCK action to affect feeding, because the antagonists may have penetrated the blood-brain barrier to block central as well as peripheral CCKARs. Devazepide clearly can penetrate the blood-brain barrier (43, 64). It is less certain whether this is also true for loxiglumide, a proglumide derivative, although there is some evidence to suggest that proglumide and the proglumide derivative CR-1409 can penetrate the blood-brain barrier in dogs (27). The present study confirms and extends these earlier studies by showing that peripheral administration of A-70104, a CCKAR antagonist that does not readily penetrate the blood-brain barrier, attenuates the inhibitory effects of duodenal infusions of peptone, carbohydrate, and fat on food intake.

In contrast to our results, Ebenezer and Parrot (24) reported that systemic administration of A-70104 has
Gly-D-Trp-Nle-Asp-a-2-phenylethyl ester increases suprathreshold would be effective. In contrast, Brenner and whether a more prolonged administration of this com-

bolic injection of CCK-8. It remains to be determined

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one of several redundant satiety signals produced by a

increase food intake. However, if peripheral CCK is but

are not likely to cross the blood-brain barrier fails to

mand in the present study, A-70104 was administered to rats by continuous intravenous infusion, and under these con-

A-70104 was able to attenuate the anorexia produced by duodenal nutrient infusions in the sham feeding rats.

Studies using other CCKAR antagonists that presumably do not cross the blood-brain barrier have produced conflicting results. Baldwin and colleagues (4, 22) showed that bolus systemic injections of 2-naphthalenesulfonil-1-aspartyl-2-(phenethyl) amide (25) have no effect on ingestion of solid food in pigs (4) or rats (22) at doses that block the anorexia produced by a bolus injection of CCK-8. It remains to be determined whether a more prolonged administration of this com-

and does not penetrate the blood-brain barrier, this is the first evidence to suggest that endogenous CCK action is mediated by CCKARs peripheral to the blood-brain barrier. Cox (16) has since provided additional evidence to suggest that these CCKARs are located in proximal duodenal tissue perfused by the superior pancreaticoduodenal artery. Cox found that devazepide was more potent in stimu-

lating sucrose intake in rats when injected into the superior pancreaticoduodenal artery than when in-

jected into the jugular vein.

Baldwin et al. (5) have argued that peripheral CCK is not likely to be an important satiety factor because systemic administration of CCKAR antagonists that are not likely to cross the blood-brain barrier fails to increase food intake. However, if peripheral CCK is but one of several redundant satiety signals produced by a specific meal, then blockade of peripheral CCK action may have little if any effect on intake of that meal, and it would therefore be inappropriate under these cir-

stances to single out the CCK signal as being unimportant. There is considerable evidence to indi-

cate that food intake can trigger a cascade of satiety signals emanating from the mouth, stomach, small intestine, and liver. Previous work suggests that mask-

ing of a CCK satiety signal by other satiety signals may vary with meal size and composition. In rats, the an-

orexia produced by gastric and duodenal delivery of specific macronutrients appears to be more sensitive to reversal by devazepide and A-70104 at lower nutrient delivery rates (61–63). This is consistent with the idea that CCK plays an essential role in mediating the anorexia produced by the lower delivery rates and that larger delivery rates produce a greater stimulation of redundant CCK-independent satiety mechanisms. Thus discrepancies among the studies examining the effects of peripheral CCK receptor blockade on food intake may have been due in part to differences in redundancy of satiety signaling produced by the different experimental meals employed. Thus the possibility exists that the liquid sucrose test meals used in the studies of Brenner and Ritter (10) and Cox (16) show-

a stimulatory effect of peripheral CCKAR blockade on food intake may have produced less masking of a peripheral CCK satiety signal by other satiety signals than the mixed nutrient solid meals used in the studies showing no effect of peripheral CCKAR blockade on food intake (4, 22, 24). Certainly less redundancy in satiety signaling occurs in the sham feeding model used in the present study, because ingested food rapidly drains from a gastric cannula, which minimizes food-induced stimulation of gastric satiety mecha-

isms.

There is strong evidence that bolus intraperitoneal injections of CCK inhibit food intake by stimulating intestinal vagal sensory neurons (51). It remains to be established that endogenous CCK acts by the same pathway to inhibit food intake. The popular hypothesis is that duodenal delivery of each of the major macron-

utrients stimulates the secretion of CCK from epithelial cells in the mucosa of the upper intestine, which acts locally at CCKAR receptors on vagal sensory nerves to inhibit food intake. If this hypothesis is true, then it would be important to show that 1) vagal afferent fibers with CCKARs on their surface mem-

brane are located near intestinal CCK-secreting cells; 2) duodenal administration of each of the major macro-

nutrients increases intestinal vagal afferent nerve ac-

activity, and CCKAR blockade attenuates this response; and 3) duodenal administration of the various macro-

nutrients inhibits food intake, CCKAR blockade attenu-

ates this response, and blockade of intestinal vagal afferent transmission abolishes the CCKAR antag-

nist-induced response.

Berthoud and Patterson (7) used light microscopy to assess the anatomic relationship between intestinal CCK-secreting endocrine cells and vagal sensory neu-

rons in rat intestine. They found no close anatomic association between these cell types, although CCK-

immunoreactive cells were located ~10 to >100 μm from the axons, suggesting a possible paracrine mech-

anism of CCK action to stimulate vagal activity. Initial attempts at using immunohistochemistry to identify CCKARs on the surface of vagal afferent fibers have not been successful, although in the same studies,
CCK immunoreactivity was found on interstitial cells of Cajal, smooth muscle, and enteric neurons in rat pylorus (42) and within enteric neurons in rat intestine (58). The discovery by Sternini et al. (58) of CCKAR-like immunoreactivity in a discrete population of gastric myenteric neurons suggests the possibility that CCK may induce inhibition of gastric motility by acting at CCKARs on myenteric neurons in the stomach. CCK immunoreactivity has also been detected within intrinsic neurons of the enteric nervous system of the small intestine and stomach (26, 29, 55). These findings suggest that CCK may act in part by a neurocrine mechanism at nonvagal CCKARs within the stomach and/or small intestine to inhibit food intake.

Each of the major macronutrients has been reported to increase intestinal vagal afferent fiber activity (20, 28, 31, 37, 38, 44). Grundy and co-workers (20, 31) have also demonstrated that peripheral administration of the CCKAR antagonist devazepide abolishes the stimulatory effect of luminal oleate and casein hydrolysate on intestinal vagal afferent neurons. Numerous other studies have shown that vagal denervation, as well as CCKAR blockade or CCKAR gene mutation, attenuates the inhibitory effects of each of the major macronutrients on food intake (15, 51). The present study demonstrates that blockade of CCKARs peripheral to the blood-brain barrier also attenuates the inhibitory effects of duodenal nutrient administration on food intake. Together, these studies provide strong support for the hypothesis that endogenous CCK inhibits food intake primarily by binding to CCKARs on intestinal vagal sensory nerves. However, we and others have demonstrated that systemic administration of the CCKAR antagonist devazepide can increase food intake in rats whether or not they are vagotomized (45) or pretreated with capsaicin to lesion visceral sensory nerves (52). Thus it remains to be determined whether blockade of intestinal vagal sensory transmission abolishes the stimulatory effect of peripheral CCKAR blockade on food intake.

There is some evidence to suggest that in humans intestinal CCK may enter the bloodstream to act as a hormonal signal at distant CCKARs to inhibit food intake. Lieverse et al. (33) showed that exogenous CCK inhibits food intake in humans at a dose that reproduces postprandial plasma levels of CCK. Putative sites of action include CCKARs on vagal afferent neurons (56, 57) and myenteric neurons (58) in the stomach, interstitial cells of Cajal, enteric neurons, and smooth muscle in the pylorus (42), and enteric neurons (58) and vagal afferent neurons (20, 31) in the small intestine. Results of our previous work suggest that an endocrine mechanism of CCK action to inhibit food intake is not essential, because in rats, immunoneutralization of circulating CCK blocked nutrient-induced stimulation of pancreatic enzyme secretion but had no effect on food intake. Other work suggests that carbohydrate-induced inhibition of food intake is mediated in part by a nonendocrine mechanism of CCK action, because CCKAR blockade attenuates carbohydrate-induced inhibition of food intake (65), yet delivery of carbohydrate to the gastrointestinal tract produces little if any increase in plasma CCK (11, 19, 32).

There is some evidence to suggest that CCK may also act as a neurotransmitter or neuromodulator within the brain to inhibit food intake. This conclusion is supported by studies showing that food intake releases hypothalamic CCK (53) and that brain injections of CCK antisera (18) and CCK receptor antagonists (21, 54) stimulate food intake. Further support comes from our recent work (8, 9) showing that CCK-8 inhibits food intake in rats when injected into six hypothalamic sites (anterior hypothalamus, dorsomedial hypothalamus, lateral hypothalamus, paraventricular nucleus, supraoptic nucleus, and ventromedial hypothalamus) and two hindbrain sites (nucleus tractus solitarius and fourth ventricle) at doses that are not likely to increase plasma CCK levels sufficiently to suppress feeding by a peripheral mechanism.

In summary, the present study shows that duodenal infusions of maltose, peptone, and Intralipid dose dependently inhibit sham feeding and that inhibitory responses to each macronutrient are attenuated by systemic administration of a CCKAR antagonist, A-70104, that does not readily penetrate the blood-brain barrier. These results support the hypothesis that duodenal delivery of protein, carbohydrate, and fat produces satiety in part by an essential CCK action at CCKARs located peripheral to the blood-brain barrier. Other evidence suggests that CCK also acts as a neurotransmitter or neuromodulator within two different brain regions to produce satiety, one region that includes the nucleus tractus solitarius in the hindbrain and another more distributed region within the medial-basal hypothalamus.

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REFERENCES

CCK AND FOOD INTAKE


