Diminished satiation in rats exposed to elevated levels of endogenous or exogenous cholecystokinin

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Covasa, Mihai, Jeremy K. Marcuson, and Robert C. Ritter. Diminished satiation in rats exposed to elevated levels of endogenous or exogenous cholecystokinin. Am J Physiol Regulatory Integrative Comp Physiol 280: R331–R337, 2001.—Rats maintained on a high-fat (HF) diet exhibit reduced sensitivity to the satiation-producing effect of exogenous CCK. Because more CCK is released in response to HF meals than low-fat (LF) meals, we hypothesized that increased circulating CCK associated with ingestion of HF diets contributes to the development of decreased CCK sensitivity. To test this hypothesis, we implanted osmotic minipumps filled with either NaCl or CCK octapeptide into the peritoneal cavity. Subsequently, we examined the effect of intraperitoneal NaCl or CCK (0.5 μg/kg) injection on 30-min food intake. CCK significantly reduced 30-min food intake in rats implanted with CCK-releasing minipumps compared with those with NaCl-releasing minipumps. Because dietary protein is a potent releaser of endogenous CCK, we hypothesized that rats adapted to a high-protein (HP) diet might also exhibit reduced sensitivity to exogenous CCK. Therefore, in a second experiment, we examined CCK-induced reduction of food intake in rats maintained on LF and rats maintained on HF or HP. Ingestion of LF stimulates very little endogenous CCK secretion, whereas both HF and HP markedly increase plasma CCK concentrations. Both doses of CCK reduced food intake significantly less in HF and HP rats compared with LF rats. There were no differences in 24-h food intake, body weight, or body fat composition among LF-, HF-, and HP-fed rats. These results are consistent with the hypothesis that sustained elevation of CCK either by infusion of exogenous CCK or by dietary-induced elevation of plasma CCK contributes to the development of reduced sensitivity to exogenous CCK.

Previously, we reported that rats maintained on a high-fat (HF) diet exhibit reduced satiation in response to administration of exogenous CCK (13, 14). Ingestion of dietary fat is associated with increased postprandial plasma CCK concentrations both in rats (7, 55, 61) and humans (20). Therefore, it is plausible that chronic or repeated elevation of circulating CCK contributes to development of the decreased sensitivity to CCK that we observed in HF-adapted rats. In this study, we report the results of two separate experiments performed to test this hypothesis. In the first study, we sought to maintain high levels of endogenous CCK by continuous infusion of CCK using osmotic minipumps (Alzet), which has been shown to produce persistent elevation of plasma CCK concentrations (34, 43). In the second study, we maintained rats on a low-fat-high-protein (HP) diet. HP diets have been shown to increase plasma CCK concentrations (22, 24, 32, 57) and induce changes in pancreatic enzyme content (6, 22, 23). Reduction of the satiation effects of CCK either by chronic minipump infusion of CCK or by adaptation to an HP diet would support our hypothesis that chronic exposure to elevated CCK itself may mediate the reduction of CCK-induced satiation we observed after HF adaptation.

It is conceivable that increased fat storage often associated with feeding HF diets could contribute to reduced CCK-sensitivity in rats adapted to HF diets. Therefore, in these experiments, we also examined fat pad weights and body fat content of the whole carcass of rats maintained on low-fat (LF), HF, and HP diets.

METHODS

Experiment 1. Male Sprague-Dawley rats weighing 390–400 g at the beginning of the experiment (n = 24) were individually housed in a temperature- and light-controlled environment with a 12:12-h light-dark cycle. Before minipump implantation, rats were divided in two groups with equal body weights. The rats were maintained ad libitum rat chow and water throughout the experiment, except when they were deprived of food but not water overnight (17 h), in preparation for testing reduction of food intake in response to an acute intraperitoneal injection of CCK octapeptide (CCK-8; 0.5 μg/kg). The first acute CCK test was performed before osmotic pump implantation to ensure that there was no difference in the CCK sensitivity between the two groups at the start of the experiment. This test and all other tests with acute CCK were conducted in exactly the same manner. Briefly, the rats were deprived of food overnight for 17 h. In the morning (at 1000), each rat was weighed and then injected intraperitoneally with either sterile NaCl or CCK-8 (0.5 μg/kg). Food was returned 5 min after the injection, and intake of pelleted rodent chow (Harlan, Teklad, Madison, WI) was recorded for the ensuing 30 min. These tests were conducted every 48 h. Two tests of intake...
after CCK were bracketed by tests after 0.9% NaCl that preceded and followed CCK tests by 48 h. This protocol provided for a complete series of CCK and NaCl tests every 7 days.

The osmotic minipumps (Alza, Palo Alto, CA; Model 2004, 0.25 μl/h, 28 days) were surgically implanted in the peritoneal cavity of overnight fasted rats through a small midline incision under methoxyflurane anesthesia. Pumps with an expected infusion duration of 28 days were filled with 0.9% NaCl or CCK-8 (Peptides International, Louisville, KY) dissolved in 0.9% NaCl. CCK-filled pumps were calculated to deliver 0.035 μg CCK-8/kg body wt−1·h−1. After pumps were filled, they were prewarmed to ensure an immediate, uniform infusion rate beginning at the time of implantation. Subsequently, we examined the effects of acute intraperitoneal administration of NaCl or CCK (0.5 μg/kg) on 30 min of food intake after an overnight fast, as described above. Acute CCK injection tests bracketed by NaCl tests were conducted every other day over the 28-day postimplantation period and continued for an additional 7 days after the pumps were emptied. Although the rats appeared to be fully recovered from pump implantation, within a few hours after surgery, food deprivation for the first feeding test did not begin until 24 h after minipump implantation. Food consumption as well as body weight of the rats were recorded daily.

After the behavioral experiments were completed, the rats were euthanized by an overdose of pentobarbital sodium and the minipumps and abdominal cavity were inspected for adhesions and tissue reaction as well as positioning of the minipumps. All pumps appeared to have functioned properly, without obstruction, and remained approximately in the position they were originally implanted. There were no adhesions or tissue reactions associated with either the saline- or CCK-filled pumps.

**Experiment 2.** Adult male Sprague-Dawley rats weighing 260–300 g at the beginning of the experiment were divided into three groups (n = 9 per group) equated for body weight. They were maintained on one of three semipurified diets for 3 wk before and during the experimental period. The diets used were as follows: low fat/high carbohydrate (LF); high fat/low carbohydrate (HF); low fat/high protein (HP). All three diets were calorically equivalent (3.88 kcal/g, Table 1) and immediately returned to their home cages, in which

<table>
<thead>
<tr>
<th>Constituent (% by wt)</th>
<th>LF</th>
<th>HF</th>
<th>HP</th>
</tr>
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<tbody>
<tr>
<td>Casein</td>
<td>20</td>
<td>20</td>
<td>71</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>63.5</td>
<td>8.5</td>
<td>12.4</td>
</tr>
<tr>
<td>Fat</td>
<td>6.0</td>
<td>30.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Vitamin mix</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Mineral mix</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Alphacal</td>
<td>3.9</td>
<td>39.4</td>
<td>4.0</td>
</tr>
<tr>
<td>dl-Methionine</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Caloric content, kcal/g</td>
<td>3.88</td>
<td>3.88</td>
<td>3.88</td>
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Fat source is 80% lard, 20% vegetable oil. Vitamin (F8135) and mineral (F8575) mixes were purchased from Bio-Serv. LF, low fat; HF, high fat; HP, high protein.

weighed amounts of the appropriate maintenance diet were provided. Food intake was recorded after the ensuing 30 min. A minimum of 48 h elapsed between each trial with either NaCl or CCK. Body weights and 24-h food consumption were recorded daily during the course of the experiment.

**Fat pad measurements and carcass analysis.** After feeding experiments were completed, the rats were euthanized by an overdose of intraperitoneal pentobarbital sodium (50 mg/ml, Abbott Laboratories). Epididymal, retroperitoneal, and subcutaneous adipose tissues were carefully dissected and weighed according to previously established procedures (29). After the fat pads were weighed, they were placed in the abdominal cavity and the carcasses, minus exanguinated blood, were frozen and later analyzed for lipid content gravimetrically using the diethyl ether extraction procedure (5).

**Statistical analysis.** Results were expressed as means ± SE. Data from the minipump experiment were analyzed by two-way repeated-measures ANOVA with chronic and acute treatments as main factors. Results from the diet-adaptation experiment were analyzed by repeated-measures ANOVA with diet and treatment as main factors. Reductions of intake by acute CCK injections were expressed as mean percentage reductions relative to injection of saline for each individual in each experimental group. Significant differences (P < 0.05) among factors and their interactions were assessed with Tukey’s multiple-comparison test.

**RESULTS**

**Effects of acute administration of CCK-8 on food intake of rats receiving continuous infusion of exogenous CCK.** Intraperitoneal administration of CCK-8 (0.5 μg/kg) reduced food intake significantly compared with NaCl injection in all rats before minipump implantation. However, after pumps were implanted, acute administration of CCK decreased 30-min food intake less in rats implanted with CCK-releasing pumps compared with rats whose pumps contained saline. Figure 1 shows 30-min food intake (in grams) after NaCl or CCK injections in rats implanted with NaCl- and CCK-infusing minipumps, before, during, and after minipump implantation. There was an overall significant effect [F(1,119) = 19.9, P < 0.001] of chronic CCK treatment on grams consumed by rats challenged with an acute dose of intraperitoneal CCK compared with rats infused chronically with saline. The significant difference between groups was evident after each test following an acute administration of CCK during the infusion period (P < 0.05). After the pump contents were exhausted, both groups of rats exhibited equivalent reductions of food intake in response to an intraperitoneal challenge dose of CCK (0.5 μg/kg). Total daily food consumption of rats infused with CCK was not significantly different from saline-infused control rats at any time point during or after the 28-day infusion period (P > 0.05; Fig. 2). Overall, the average body weight of CCK-infused rats was 8.7 g lower than that of rats infused with NaCl during the 28-day period [F(1,215) = 27.1; P = 0.001]. However, there was not a significant treatment-by-day interaction, indicating no difference in weight gain between the two groups at any day during the infusion [F(17,215) = 39.6; P = 0.9; Fig. 3].
Effects of CCK-8 on food intake of rats maintained on HP, HF, and LF diets. Injections of CCK-8 at doses of 0.125 and 0.250 mg/kg reduced food intake significantly in all rats compared with saline injection, irrespective of their maintenance diet. Significant differences in food intake between CCK-infused rats and NaCl-infused rats in response to a challenge dose of 500 ng/kg of CCK are indicated with asterisks (*P < 0.05; **P < 0.01). Rats infused with CCK reduced food intake less than rats infused with NaCl in response to an intraperitoneal injection of CCK on all tests during the minipump infusion period. Responses to the acute CCK administration returned to the preinfusion levels after the pump's contents were exhausted. Values are expressed as means ± SE.

DISCUSSION

Our results indicate that chronic infusion of exogenous CCK is associated with reduced satiation in response to a challenge injection of exogenous CCK. In addition, our results indicate that diets that are known to release endogenous CCK (13, 22, 61) also diminish satiation in response to exogenous CCK. These find-
DIMINISHED SATIATION AND CHRONIC CCK

Table 2. Food intake, body weight, fat pads, and carcass lipid composition of rats fed an LF, HF, and/or HP diet for 9 wk

<table>
<thead>
<tr>
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<th>Diet</th>
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<tr>
<td></td>
<td>LF</td>
</tr>
<tr>
<td>Food intake, g/day</td>
<td>19.5 ± 0.39</td>
</tr>
<tr>
<td>Initial body wt, g</td>
<td>286 ± 4.6</td>
</tr>
<tr>
<td>Final body wt, g</td>
<td>421 ± 14.0</td>
</tr>
<tr>
<td>Epi, % wt</td>
<td>1.49 ± 0.1</td>
</tr>
<tr>
<td>RP fat, % wt</td>
<td>1.11 ± 0.13</td>
</tr>
<tr>
<td>SC fat, % wt</td>
<td>2.3 ± 0.11</td>
</tr>
<tr>
<td>Carcass lipid, % dry matter</td>
<td>36.0 ± 1.0</td>
</tr>
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</table>

Values are means ± SE. Food intake represents the 24-h average for each group of rats (LF, HF, and HP) for total of 9 wk of the study. The rats were 8 wk old at the beginning of the study. Epi, epididymal; RP, retroperitoneal; SC, subcutaneous; NS, not significantly different (P > 0.05).

ings suggest that continuous exposure to endogenous or exogenous CCK results in diminished sensitivity to satiation effects of this peptide.

The ability of prior CCK exposure to reduce responses to subsequent CCK administration is well documented for several model systems of CCK action, including enzyme secretion by pancreatic acini in vitro (1, 17, 44, 65). In addition, Goke et al. (21) reported that CCK-induced release of amylase was reduced in pancreatic acini from rats, in which plasma CCK concentrations were elevated by feeding trypsin inhibitor, before harvesting pancreatic tissue. With in vitro systems, CCK-induced desensitization occurs rapidly and is reversed within tens of minutes (1). Therefore, the rapid onset and reversibility of reduced CCK sensitivity in our study is consistent with studies of CCK-induced desensitization at the cellular level.

In contrast to numerous reports of CCK-induced desensitization of pancreatic secretory function, Crawley and Beinfeld (15) have provided the sole report that chronic peripheral infusion of CCK reduces behavioral responses to subsequent CCK injections. In their study, rats received chronic infusions of CCK or vehicle via osmotic minipumps. Rats receiving CCK via minipump exhibited less suppression of exploratory behavior in response to acute CCK injections than did rats receiving saline infusions. Crawley and Beinfeld did not report the effects of their treatments on short-term food intake, but they pointed out that the effects they observed were compatible with attenuation of the CCK-induced behavioral satiety sequence (3). Thus it appears that our study was the first to directly demonstrate reduction of the satiation effects of CCK in rats chronically exposed to exogenous CCK. Similarly, we are not aware of any reports, other than our previous work, indicating that dietary treatments that release endogenous CCK reduce sensitivity to exogenous CCK.

The nominal infusion duration for the osmotic pumps we used was 28 days. We cannot be certain of the exact time when our pumps were exhausted or, for that matter, how much of the CCK present in the minipumps retained bioactivity during the infusion period. However, the fact that rats with CCK-infusing pumps exhibited significantly less reduction of food intake in response to intraperitoneal CCK on day 26 postinfusion but were not less sensitive to intraperitoneal CCK from day 29 onward suggests that the pumps became exhausted by day 28 or sooner. Similarly, a number of studies in which CCK was delivered via osmotic minipumps, either centrally or peripherally, reported a significant suppression of food intake during the duration of the infusion (34, 41, 52), indicating that CCK retained levels of bioactivity sufficient to produce a feeding effect. In some of these studies, CCK concentrations were measured in minipumps maintained either in vivo or in vitro at 37°C. For example, Lukaszewski and Praissman (34) reported that 22 μM solutions of CCK-8 retained 100% of their immunoreactivity during the 10-day period over which they were incubated at 37°C. On the other hand, Crawley and Beinfeld (15) found that CCK-8 concentrations in residual fluid removed from their minipumps at 14 days were just 12–23% of the concentration originally loaded. In both cases, however, minipump infusions of CCK-8 produced significant behavioral or pancreatic effects. Therefore, we would argue that while the pumps were active, they released sufficient bioactive CCK-8 to maintain the rats in a state of reduced CCK sensitivity.

The mechanisms by which exogenous CCK, HF, and -HP diets reduce sensitivity to the satiation effects of CCK are not known. We have previously demonstrated that feeding HF diets attenuates inhibition of gastric emptying after CCK injection (12). Chronic exposure to an HP diet has been reported to result in significant acceleration of gastric emptying of a protein meal (57). Therefore, the reduced sensitivity to CCK in animals fed an HP or HF diet might be a direct consequence of changes in the rate on gastric emptying. It is likely that the development of accelerated gastric emptying in rats fed HP diet is mediated by CCK, because pre-treatment of rats with devazepide, a CCK-A receptor antagonist, prevented development of accelerated gastric emptying (56). Thus chronic exposure to exogenous CCK or adaptation to HP or HF diets might alter the gastric-emptying response to CCK and thereby attenuate CCK-induced reduction of food intake. On the other hand, it is also possible that reduced sensitivity to the satiation effects of CCK and the gastric-emptying effects of CCK are signs of reduced sensitivity in a shared neural control system.

Both inhibition of food intake and that of gastric emptying by CCK are mediated by CCK-induced activation of small unmyelinated vagal sensory neurons (27, 51, 59, 60, 66). Destruction of these vagal sensory neurons, which synapse in the nucleus of the solitary tract, attenuates both the gastric and feeding effects of exogenous CCK and intestinal nutrient infusions (see Ref. 50 for review). Expression of CCK-A receptors by vagal sensory neurons is well documented (25, 26, 30, 31, 40). Therefore, it seems plausible that reduced CCK...
sensitivity in rats treated chronically with exogenous CCK or fed HP or HF diets could be due to diminished vagal sensory responding to CCK. In support of this hypothesis, we have reported that increased expression of immediate early gene, c-fos, in response to exogenous CCK injection or intestinal infusion of oleic acid is attenuated in rats fed an HF diet (10, 11).

Reduction of vagal responses to CCK could be mediated either by downregulation of CCK-A receptors or by downregulation of a postreceptor transduction process. Recently, Broberger (8) reported that he was unable to detect changes in vagal CCK-A-receptor mRNA expression in rats fed HF diet. This result would suggest that HF diets and chronic CCK exposure do not reduce CCK sensitivity of vagal sensory neurons at the transcriptional level. It is also possible that reducing the number of binding sites at the neuronal membrane surface downregulates vagal sensitivity. Studies of CCK-receptor function in pancreatic acini and Chinese hamster ovary cells (48) indicate that receptor internalization and phosphorylation are important mechanisms for CCK-induced desensitization in vitro. Therefore, it seems plausible that reduced sensitivity to CCK could be mediated either by altered receptor protein translation or increased sequestration of previously translated receptors. Downregulation of transduction cascades has also been associated with CCK-induced desensitization of pancreatic amylase secretion (46). Therefore, a change in postreceptor transduction is yet another potential mechanism for reduced vagal sensory response to CCK.

The second experiment reported in this paper confirms our previous reports that ingestion of an HF diet results in reduced satiation in response to exogenous CCK. In addition, our current results demonstrated that chronic ingestion of an HP diet also reduces sensitivity to exogenous CCK. Although we did not assay plasma CCK concentrations as part of our experimental protocol, there is ample published evidence demonstrating that rats eating an HF diet exhibit elevated postprandial plasma CCK concentrations (see Ref. 50 for review). Furthermore, Green et al. (22) demonstrated that rats fed an HP diet, which was virtually identical to the one we used, displayed marked elevation of plasma CCK concentration. Therefore, we are confident that our HP and HF dietary conditions resulted in increased circulating CCK concentrations. The fact that both HF and HP diets elevate plasma CCK is consistent with our interpretation that diet-induced increase in secretion of endogenous CCK contributes to reduced sensitivity to the satiation-producing effects of the exogenous peptide.

It remains possible that factors other than elevation of circulating CCK contribute to reduced sensitivity to the satiation effects of CCK. Whereas this possibility seems remote in the case of exogenous CCK, administered by minipump, other factors might contribute to reduction of CCK sensitivity during HF- or HP-diet feeding. For example, others have reported reduced satiation in response to CCK in genetically obese rats (35, 39, 43, 62). Thus it is conceivable that obesity, due to fat ingestion, directly downregulates CCK sensitivity. In these studies, as in our previously reported experiments, we included an HF diet that was made isocaloric with our LF diet. Although rats fed this isocaloric HF diet gained no more weight than LF-fed rats, increased adiposity, without overall increase in body weight, has been reported for rats fed HF diets (42, 47, 58). These observations raise the possibility that diet-induced changes in CCK sensitivity might be related to increased adiposity. We consider this possibility very unlikely for two reasons. First, our previous work demonstrates that rats fed high-calorie, HF diets gain more weight than LF-fed rats. However, rats fed an HF diet, made isocaloric with the LF diet by dilution with cellulose, do not gain more weight than LF-fed rats, suggesting that increased body weight cannot account for the changes in CCK sensitivity that we observe. Second, fat pad measurements and carcass analyses from rats in our current study reveal no differences in fat pad weights or body compositions between rats fed HF (isocaloric with LF), LF, or HP diets. Consequently, differences in adiposity cannot account for the diet-induced changes in CCK sensitivity that we observed.

**Perspectives**

The implications of reduced CCK sensitivity for control of 24-h food intake and body weight remain unclear. Several investigators have examined 24-h food intake and/or body weight during chronic or repeated CCK administration (15, 34, 52, 64). In most instances, they have observed little change either in body weight or total food intake. However, recent reports by Matson et al. (36) and Matson and Ritter (37) indicate that CCK dramatically enhances body weight loss after intracerebral administration of the adipocyte hormone leptin. Therefore, it is possible that reduced sensitivity to CCK could diminish the behavioral and metabolic responses to leptin. Presumably, reduced response to leptin would favor the increased body fat accumulation reported for rats eating high-calorie, HF diets. In this regard, it is interesting that several groups have reported that feeding an HF diet does indeed reduce sensitivity to weight loss and the feeding inhibitory effects of leptin (19, 33, 63), and it is conceivable that diminished sensitivity to CCK contributes to reduced leptin sensitivity during HF feeding.

Several investigators have now reported that leptin enhances reduction of meal size by injections of CCK (4, 18, 38). Exposure to HF diets has been reported to lower circulating leptin concentrations in rats (2, 9). Collectively, these observations encourage speculation that diet-induced decreases in plasma leptin concentrations might diminish CCK sensitivity, as in the case with rats maintained on an HF diet. Currently, there is very little information available regarding leptin levels with rats maintained on an HF diet. Although rats fed this isocaloric HF diet gained no more weight than LF-fed rats, increased adiposity, without overall increase in body weight, has been reported for rats fed HF diets (42, 47, 58). These observations raise the possibility that diet-induced changes in CCK sensitivity might be related to increased adiposity. We consider this possibility very unlikely for two reasons. First, our previous work demonstrates that rats fed high-calorie, HF diets gain more weight than LF-fed rats. However, rats fed an HF diet, made isocaloric with the LF diet by dilution with cellulose, do not gain more weight than LF-fed rats, suggesting that increased body weight cannot account for the changes in CCK sensitivity that we observe. Second, fat pad measurements and carcass analyses from rats in our current study reveal no differences in fat pad weights or body compositions between rats fed HF (isocaloric with LF), LF, or HP diets. Consequently, differences in adiposity cannot account for the diet-induced changes in CCK sensitivity that we observed.

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tions (16, 54). Further work will be required to assess the potential role of leptin in diet-induced reduction of CCK sensitivity and the role of reduced CCK sensitivity in the development of obesity.

In conclusion, our results indicate that either chronic exposure to exogenously infused CCK or maintenance on diets that increase secretion of endogenous CCK reduces sensitivity to the satiation effects of CCK. Reduction of meal size by CCK is well documented in rats and other species, including humans (50). Furthermore, recent reports suggest that CCK may interact with other hormones to control food intake (4, 18, 49) and body weight (36). Consequently, reduced sensitivity to the satiation effects of CCK could contribute to overeating and obesity during exposure to diets that result in sustained elevations of plasma CCK.

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DIMINISHED SATIATION AND CHRONIC CCK

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