Reduced Sensitivity to Cholecystokinin in Male Rats Fed a High-Fat Diet Is Reversible

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Abstract

Adult rats chronically fed a high-fat (HF) diet maintain reduced sensitivity to cholecystokinin (CCK). We hypothesized that, similar to adult rats, pups fed a HF diet would also exhibit reduced sensitivity to CCK. To test this, male pups fed low-fat (LF) and HF isoenergetic (16.2 kJ/g) diets were administered CCK intraperitoneally (0.125–1 g/kg) 1 wk following dietary adaptation. After receiving 0.5 g/kg CCK, pups fed the HF diet suppressed food intake less (8.9 ± 5.0%) than pups fed the LF diet (28.9 ± 4.7%; P < 0.05) relative to intakes after saline administration. We then assessed the development and extinction of changes in CCK sensitivity by switching the diets between the groups. The HF-fed group, when switched to the LF diet, regained sensitivity by wk 4 and suppressed food intake following administration of 0.25 g/kg CCK (33.1 ± 5.7%; P < 0.05). The LF-fed group, when switched to the HF diet, lost sensitivity by wk 2 and did not suppress food intake after administrations of CCK compared with saline. Finally, we examined if HF-fed rats have an increased sensitivity to corn oil during brief access tests using a multibottle gustometer. At oil concentrations of 25, 75, and 100%, rats fed the HF diet sampled more oil than LF-fed rats (P < 0.05). These findings demonstrate that male rat pups fed a HF diet exhibit reduced sensitivity to CCK, the development of this reduced sensitivity is quicker than its extinction, and rats consuming a HF diet have increased oral sensitivity to oils. J. Nutr. 140: 1698–1703, 2010.

Introduction

Prolonged ingestion of a high-fat (HF) diet often is associated with passive overconsumption and obesity (1). Increased orostimulation by fats (2) as well as deficits in satiation signals are thought to contribute to the extreme eating of a HF diet. Specifically, chronic ingestion of a HF diet leads to reduction in sensitivity to the feeding suppressing effects of intestinal lipids and the potent biological satiety peptide, cholecystokinin (CCK), compared with consumption of a low-fat (LF) diet (3–8). Additionally, rats fed HF diets exhibit diminished sensitivity to the satiating properties of a palatable high-energy, HF food, thus consuming more food compared with rats fed an isoenergetic LF diet (8). Together, these findings suggest that chronic consumption of HF diets reduces the ability of dietary fat to inhibit further food intake.

Similar to adult rats, rat pups significantly reduce food intake after administration of CCK (9–12). Overfeeding and feeding of HF diets during the neonatal and postnatal period is associated with alterations in behavioral, neuronal, and metabolic pathways that perpetuate overconsumption and obesity [see (13) for review]. Studies examining peripheral satiation deficits during early postnatal development due to specific dietary conditions have been sparse. Of interest is whether, in rat pups, HF feeding results in altered sensitivity to satiation signals such as CCK, similar to the findings documented in adult rats (3–5,7,8,14). Therefore, our first aim in this study was to examine the sensitivity to CCK in male rat pups fed a HF diet.

Chronic consumption of diets rich in fats results in adaptive changes involving digestive, absorptive, and transport mechanisms (15–19). Several of these changes are associated with altered responses to satiation signals such as CCK (19,20). These responses to gastrointestinal satiation signals are not fixed and vary with dietary conditions and changes in endocrine milieu. In vitro data show that the effects of chronic exposure to either HF diet or CCK are malleable and reversible. For example, rapid loss as well as reacquisition of sensitivity to CCK has been demonstrated in pancreatic CCK-responsive cell lines (21,22). Whether these changes translate in altered behavioral responses to CCK has not been examined. Thus, our second aim in this study was to determine the relative time course of the HF diet-induced changes in CCK sensitivity, the persistence, and the reversibility of this phenomenon.

The orosensory properties of fats are sufficient to stimulate and maintain ingestion in both acceptance and preference tests (23–25). However, postigestive nutritional factors such as dietary experience can influence hedonic valence of fats and modulate intake [(26–30) and for review see (31)]. Although
increased preference for fats in rats fed a HF diet has been documented (2,28,32,33), whether this can be attributed solely to oral stimulation is still unclear. In intact rats, maintenance on a HF diet correlates with increased consumption of oils (2,33) or test foods with high portion of energy derived from fat compared with LF-fed controls (8,24). Furthermore, post-ingestive effects in combination with sensory properties of oils are required for increased consumption in HF-fed rats (32). Therefore, to examine whether maintenance on a HF diet results in changes in preference for oil, based primarily on its orosensory properties, we limited postingestive influence by using brief access tests and measured licks of increasing concentrations of corn oil using a multibottle gustometer.

Methods

Rats
Male rat pups used in the first and second experiments were born from female Sprague-Dawley rats (purchased from Charles River Laboratories) mated in our animal facility. Adult male Sprague-Dawley rats (Harlan Laboratories) were used in Expt. 3. All rats were housed individually in hanging wire-bottom cages and adapted to a 12-h-light-dark cycle (lights on at 0600 h) in a temperature-controlled vivarium. Water was freely available throughout all experiments, except during gustometer training, and body weight was recorded daily. All experiments were approved by the Institutional Animal Care and Use Committee at The Pennsylvania State University.

Diets
Male rat pups (n = 16) weaned to nonpurified rat diet (Purina, 5001) starting at postnatal d 21 (P21) were divided into 2 groups (n = 8/group) with similar mean body weights (LF: 66 ± 1.6 g; HF: 69 ± 2.1 g). They were then switched to isonenergetic (16.2kJ/g) powdered diets that were either low (LF, 6% fat wt:wt) or high (HF, 30.4% fat wt:wt) in fat at P25. Diets were prepared in our laboratory from commercially available sources (Bio-Serv, ICN Biomedicals, and Sigma Chemical). The composition of the diets have been described previously (8). Once rats were offered maintenance LF or HF diets, they did not again receive the nonpurified diet. The diets were presented in spill-resistant glass jars that were secured to the inside front of the cage by a stainless steel clip. Rats consumed fresh food everyday ad libitum except when removed for weighing or as noted otherwise. Food intake was recorded daily for each rat throughout all experiments. Corn oil (Mazola; ACH Food Companies) used in Expt. 3 was prepared in increasing concentrations (5, 12.5, 25, 75, and 100%) of oil were presented at least 4 times to each rat and were available for 10-s access tests used is described elsewhere (35, 36). Briefly, 24 h before water training, water bottles were removed from the home cages of all rats. During 5-d training, each rat was placed in the gustometer and provided access to water from the drinking spout for a 20-min period. In subsequent daily test sessions, all concentrations (0.5, 12.5, 25, 75, and 100%) of oil were presented at least 4 times to each rat and were available for 10-s access periods in a randomized order. A trial was initiated when a rat licked the drinking spout within 10 s. The minimum inter-trial interval (i.e. between solutions) was 5 s, the amount of time required for the shutter operation and the rig to change positions. Only data from the second sessions with each concentration were used for analysis to minimize the effect of novelty and experience factors in the first sessions.

Expt. 1: CCK sensitivity in rat pups. Our objective in this study was to determine whether rat pups fed a HF diet exhibit reduced sensitivity to CCK compared with rat pups fed a LF diet. Beginning on d 7 of diet adaptation (P32), rats were tested for their sensitivity to the anorectic effects of increasing doses (0.125, 0.25, 0.5, and 1.0 g/kg) of CCK octapeptide (American Peptide). Following 4 h of food deprivation (0800–1200 h), rats received an intraperitoneal (IP) CCK injection followed by presentation of their respective maintenance diet. After 30 min, the remaining food, including spillage, was collected and weighed. Tests took place every day from Saturday through Wednesday, and 24-h food intake was recorded daily. Each CCK injection was bracketed by a saline vehicle injection and each dose of CCK was tested at least once.

Expt. 2: Development and extinction of CCK sensitivity. In this study, we examined the relative time course for the development and extinction of reduced sensitivity to CCK-induced satiation in rats fed the HF diet. Rats used in the previous experiment (n = 8/group) adapted to LF and HF diets with mean body weights of 387 ± 19 and 389 ± 15.6 g, respectively, were fed their respective diets for an additional 3 wk (wk 8–10). During this time (wk 9–10, phase I), the rats were tested for CCK sensitivity (0.25 and 0.5 g/kg) following the same protocol as described above. Two tests were conducted for each dose of CCK and saline vehicle injection was administered before and after each CCK injection.

At the end of wk 10, maintenance diets were switched so that HF-fed rats received the LF diet and LF-fed rats received the HF diet. Testing began on the second day following diet switch (phase II). IP injections of 0.25 g/kg CCK were bracketed by injections of saline (control) and testing was conducted across 4 consecutive weeks (wk 11–14). This single dose of CCK was selected, because it suppressed food intake significantly in LF- but not HF-fed rats during phase I.

Following testing, rats continued to receive their respective diets for 5 wk (wk 15–19) during which time no manipulations occurred. To further examine the development and extinction of reduced sensitivity to CCK, at the end of wk 19, rats were returned to their original maintenance diets and testing began on the following day (phase III). IP injections of 0.25 g/kg CCK were bracketed by injections of saline and testing was conducted over 4 wk (wk 20–23) using the same protocol as described above. The time course of experimental manipulations is depicted in Figure 1. Testing followed the daily schedule described for Expt. 1. Similar to our previous experiment, rats were deprived of food for 4 h (0800–1200 h) and injected with either CCK or saline. A total of 12 CCK tests were performed, each bracketed by saline injection. After the injection, the maintenance diet was presented and 30-min food intake was recorded.

Diets were prepared in our laboratory from commercially available sources (Bio-Serv, ICN Biomedicals, and Sigma Chemical). The composition of the diets have been described previously (8). Once rats were offered maintenance LF or HF diets, they did not again receive the nonpurified diet. The diets were presented in spill-resistant glass jars that were secured to the inside front of the cage by a stainless steel clip. Rats consumed fresh food everyday ad libitum except when removed for weighing or as noted otherwise. Food intake was recorded daily for each rat throughout all experiments. Corn oil (Mazola; ACH Food Companies) used in Expt. 3 was prepared in increasing concentrations (5, 12.5, 25, 75, and 100%) of oil were presented at least 4 times to each rat and were available for 10-s access periods in a randomized order. A trial was initiated when a rat licked the drinking spout within 10 s. The minimum inter-trial interval (i.e. between solutions) was 5 s, the amount of time required for the shutter operation and the rig to change positions. Only data from the second sessions with each concentration were used for analysis to minimize the effect of novelty and experience factors in the first sessions.

Statistical analysis
All statistics were computed using SAS (version 9.0). Body weight and 24-h food intake were analyzed with 2 way (diet × time) repeated-measures ANOVA (rmANOVA). For Expt. 1, 30-min raw food intake following CCK or saline was analyzed by 2-way (diet × treatment) rmANOVA. Because food intake after saline increased in the rat pups during testing period, intake data after each CCK dose was analyzed against the mean intakes after saline on the days prior to and after CCK

Figure 1

![Figure 1][1]

**FIGURE 1** Protocol for Expt. 2. Phase I: Rats fed either LF or HF diets since P25 were tested for CCK sensitivity during wk 9 and 10. Phase II: Rats were switched (indicated by arrow) to the opposite maintenance diet. CCK tests occurred during wk 11–14. Phase III: Rats were returned to their original diets from phase I. Sensitivity to CCK was tested 3 times each wk in phases II and III, with control (saline) tests occurring between each CCK test.

Cholecystokinin sensitivity and fat adaptation
Results

Food intake and body weight

Expt. 1: Rat pups. Baseline body weights (LF: 66 ± 1.6 g; HF: 69 ± 2.1 g) and body weight gain (LF: 320.1 ± 18.5 g; HF: 320.0 ± 15.7 g) in the 2 groups were similar throughout the first 8 wk of feeding the diets. Food intake significantly increased throughout the first 8 wk, with LF- (19.8 ± 0.6) and HF-fed rats (21.2 ± 1.0 g/kg dose) consuming the same amount of food.

Expt. 2: Extinction phases. Daily food intakes during phase II (LF: 19.9 ± 0.2 g; HF: 18.3 ± 0.2 g) and phase III (LF: 18.8 ± 0.2 g; HF: 17.4 ± 0.5 g) of the experiment were similar in the 2 groups.

CCK sensitivity in rat pups fed LF or HF diets (Expt. 1)

Compared with saline, in rat pups adapted to either LF or HF diets (LF: 1.1 ± 0.08 g/kg; HF: 1.4 ± 0.11 g/kg), food intake was not significantly different following the 0.125-g/kg dose of CCK (LF: 1.3 ± 1.33 g/kg; HF: 1.7 ± 0.15 g/kg) or 0.25 g/kg (LF: 1.2 ± 0.11 g/kg; HF: 1.2 ± 0.14 g/kg). After injection of 0.5 g/kg CCK, however, LF-fed rats ate less compared with intake after saline (P < 0.001), whereas HF-fed rats did not (Table 1). Following administration of 1.0 g/kg CCK, rats fed either LF or HF diets suppressed food intake compared with saline injections (P < 0.001 for both groups); however, the groups did not differ.

When data were expressed as the percentage suppression from saline baseline, there was a difference between groups after the 0.5-g/kg dose of CCK, with LF-fed rats suppressing food intake 28.9% and their HF-fed counterparts suppressing it only 9% (P < 0.05) (Fig. 2). The percent suppression from baseline after the 1.0-g/kg CCK dose did not differ between the groups.

TABLE 1

<table>
<thead>
<tr>
<th>CCK Dose</th>
<th>LF</th>
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<tr>
<td>μg/kg</td>
<td></td>
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<tr>
<td>0</td>
<td>1.4 ± 0.1 a</td>
<td>1.7 ± 0.1 a</td>
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<tr>
<td>0.1</td>
<td>1.0 ± 0.1 b</td>
<td>1.5 ± 0.1 b</td>
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<tr>
<td>1</td>
<td>0.8 ± 0.1 b</td>
<td>1.1 ± 0.1 b</td>
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1 Values are means ± SEM, n = 8. Means in a column without a common letter differ, P < 0.05.

Development and extinction of CCK sensitivity (Expt. 2)

Phase I. When testing for sensitivity to CCK, LF-fed rats suppressed food intake after both doses of CCK (0.25 g/kg: 1.06 ± 0.11 g/kg; 0.5 g/kg: 1.03 ± 0.10 g/kg) compared with saline (1.62 ± 0.07 g/kg; P < 0.0001 for both doses). In HF-fed rats, however, the 0.25 g/kg of CCK did not decrease food intake (saline: 2.06 ± 0.12 g/kg; CCK: 1.88 ± 0.18 g/kg), whereas the 0.5-g/kg CCK dose suppressed food intake compared with saline (1.66 ± 0.12 g/kg; P < 0.05). When expressed as percentage suppression of intake, LF-fed rats (33.4 ± 5.54%) suppressed food intake more than HF-fed rats (5.1 ± 5.98%; P < 0.001) after injection of 0.25 g/kg but not 0.5 g/kg CCK.

Phase II. During phase II, there was an interaction between diet and time on food intake following CCK administration (P < 0.001). When HF-fed rats were switched to the LF diet, they regained sensitivity to CCK by wk 3 of the diet switch, resulting in 29.2% suppression of intake compared with saline (P < 0.0001) (Table 2). On the other hand, originally LF-fed rats switched to the HF diet had reduced sensitivity to CCK as early as wk 1 following the diet switch compared with saline. Between groups, the suppression of food intake was greater in LF-fed rats compared with HF-fed rats beginning at wk 3 after the diet switch, with the difference between groups remaining significant until the end of the testing period (P < 0.05).

Phase III. In phase III, there was an interaction between diet and time following CCK injection (P < 0.001). During wk 1 after administration of CCK, food intake after switching to LF was 2.7 ± 0.1 g/kg (P < 0.05), whereas switching to HF resulted in suppression of food intake (1.3 ± 0.1 kg/kg; P < 0.05).

FIGURE 2 Thirty-minute percent suppression of food intake in LF- and HF-fed rat pups after administration of 0.5 and 1 μg/kg CCK (Expt. 1). Values are means ± SEM, n = 8. *Different from LF-fed rats, P < 0.05.
returning to their original maintenance diet, HF-fed rats still retained their sensitivity to CCK, suppressing food intake compared with saline injection \( (P < 0.001) \). However, the suppressive effects of CCK were significantly diminished beginning at wk 2 after returning to the HF diet (Table 2). In contrast, rats returned to their original LF diet exhibited diminished sensitivity to CCK-induced satiation during wk 1 and 2, after which they reduced food intake in response to CCK injection during wk 3 and wk 4 \( (P < 0.001 \text{ for both}) \). Between groups, HF-fed rats exhibited greater sensitivity to CCK-induced satiation than LF-fed rats through wk 1 \( (P < 0.05 \text{ for each CCK test}) \). Beginning with wk 2, HF-fed rats suppressed food intake less than LF-fed rats and this trend remained significant throughout phase III \( (P < 0.05 \text{ for each wk}) \).

**Changes in CCK sensitivity between phases**

When data across phases were analyzed as percent suppression of intake, there was an interaction of diet \( \times \) time \( (P < 0.001) \) and time \( \times \) phase \( (P < 0.05) \), but no interaction between diet \( \times \) time \( \times \) phase. Compared with phase I, rats switched from a LF to HF diet during phase II suppressed intake less beginning 2 wk post-diet switch \( (P < 0.001) \). On the other hand, rats switched from the HF to LF diet during phase II suppressed intake more compared with intake during phase I \( (P < 0.05) \) (Fig. 3). When returned to their original diets in phase III, LF-fed rats regained sensitivity to CCK and suppressed food intake more than intake during phase II \( (P < 0.05) \). HF-fed rats, however, lost sensitivity to CCK and suppressed intake less during phase III than intake in phase II \( (P < 0.01) \).

**Expt. 3: Oral sensitivity to corn oil.** There was an interaction of diet and concentration \( (P < 0.001) \) as well as a difference in the total number of licks between HF- and LF-fed rats for both water and all oil concentrations tested \( (P < 0.001 \text{ for each}) \) except 5% \( (P = 0.47) \). When difference scores were calculated, there was an interaction of diet \( \times \) concentration \( (P < 0.001) \), but no significant difference in lick numbers between groups at 5 and 12.5% corn oil solutions. At higher oil concentrations \( (25, 75, 100\%) \), however, HF- and LF-fed rats differed in the number of licks \( (P < 0.01 \text{ for each oil concentration}) \) (Fig. 4).

**Discussion**

In this study, we showed that adaptation to a HF diet reduces sensitivity to CCK-induced satiation in rat pups similar to adult rats. Furthermore, diminished sensitivity to CCK in HF-fed rats occurs relatively quickly whereas the reversal is prolonged. Specifically, maintenance on a HF diet results in loss of sensitivity to the feeding suppressing effects of CCK only 2 wk following adaptation. On the other hand, the reacquisition of sensitivity to CCK-induced satiation after rats were switched from HF to LF diet took ~4 wk to restore. Finally, we found that relative to a LF diet, the maintenance of a HF diet results in increased oral sensitivity and avidity to oils when post ingestive feedback is nearly absent.

We and others have shown that adult rats fed a HF diet exhibit reduced sensitivity to both lipid- and CCK-induced satiation compared with LF-fed rats \( (4–6) \). Using a similar paradigm, this study extends previous findings and demonstrates, for the first time, to our knowledge, that rat pups also develop reduced sensitivity to CCK when chronically eating a HF-diet. Numerous studies have shown that CCK or nutrients that stimulate CCK secretion are effective in reducing food intake in rat pups \( (9–12,37) \). The CCK-1 receptor (CCK-1R) mediates these behavioral effects, because antagonism of the receptor attenuates nutrient- and CCK-induced satiation \( (12,37) \). The mechanisms by which dietary fat alters the potency of CCK to inhibit food intake are not entirely clear and have been discussed previously \( (3–5) \). Fat is a potent CCK secretagogue and consumption of diets high in fat increases CCK levels in rodents and humans \( (3,38) \). Continuous high circulating levels of CCK via osmotic minipump delivery \( (3) \) or dietary fats \( (38,39) \) results in reduced CCK tolerance and sensitivity \( (3) \) and desensitization or downregulation of CCK-1R \( (40,41) \). For example, mice fed a HF diet have reduced CCK-1R expression in the nodose ganglia \( (42) \). However, in rats, Broberger et al. \( (42) \) found no difference in CCK-1R expression in the nodose ganglia following maintenance on a similar HF diet. It remains to be seen whether changes in the membrane-bound receptor number

![FIGURE 3](image-url) Thirty-minute percent suppression of food intake in rats fed LF and HF diets for 18 wk after receiving 0.25 \( \mu \)g/kg CCK (Expt 2). Values are means \( \pm \) SEM, \( n = 8 \). *Different from rats fed the other diet, \( P < 0.05 \). †Different from previous phase within the same dietary group, \( P < 0.05 \).

![FIGURE 4](image-url) Total licks/10 s \( (A) \) and lick score difference (total licks – water licks) \( (B) \) in rats fed LF and HF diets. Values are means \( \pm \) SEM, \( n = 3 \). Different from corresponding LF-fed rats, **\( P < 0.01 \), ***\( P < 0.001 \).
in the nodose ganglia or other tissues occurs during chronic HF diet consumption. In in vitro models, prior CCK exposure results in desensitization of pancreatic enzyme secretion (21,43) and downregulation of the receptor gene expression in pancreatic acinar cells. Therefore, changes in receptor internalization, phosphorylation, sequestration, or postreceptor transduction cascade are all possible mechanisms associated with reduced sensitivity to CCK.

Restoration of sensitivity to exogenous administration of CCK after diet switch demonstrates that dietary fat-induced behavioral changes are not permanent. We have shown that the inhibitory effects of CCK can be fully restored once a LF diet, similar in nutrient and energy composition to a standard rat diet, is resumed. However, the relative time required for reacquisition of CCK sensitivity (~4 wk) is longer than the time needed to develop reduced sensitivity to CCK when fed a HF diet (~2 wk).

Similar to our behavioral findings, in vitro data suggests that sensitivity to CCK-responsive tissues can be restored. Specifically, Collins et al. (22) found that desensitization of pancreatic sensitivity to CCK-responsive tissues can be restored. Similar to our results, Collins et al. (22) found that desensitization of pancreatic sensitivity to CCK-responsive tissues can be restored. However, the relative time required for reacquisition of CCK sensitivity (~4 wk) is longer than the time needed to develop reduced sensitivity to CCK when fed a HF diet (~2 wk).

The degree of sensitivity to the suppressing effects of CCK appears to be slightly different between pups and adult rats. Here, regardless of diet, rat pups did not suppress food intake in response to low doses (0.125 and 0.25 g/kg) of CCK. This is in agreement with findings reported by Robinson et al. (11) showing that the threshold for sensitivity to CCK-induced satiation increases with age. The increased dose needed to induce satiation may be explained by the early exposure to CCK, reducing later effectiveness of the peptide in inhibiting food intake. As such, pups injected with CCK during the postnatal period exhibit marked reductions in CCK sensitivity when adults (37). Thus, elevated endogenous CCK levels in the pups may result in higher threshold dose needed to reduce food intake. Although the HF diet contains more fiber than the LF diet and fiber has been shown to elevate postprandial CCK in humans (47,48), there are no data demonstrating a correlation between plasma CCK and fiber intake in rodents. Furthermore, fiber supplementation results in similar CCK expression in duodenal tissue in rats (49). Therefore, the effects observed in our study are most likely due to dietary fat content differences, not fiber.

This study also shows that rats adapted to a HF diet exhibit an increased appetite for oils. Several studies have previously demonstrated that HF feeding increases acceptance and preference of various fatty stimuli, most likely through postigestive feedback (2,28,32,33,50). In particular, Reed et al. (32) showed that in the relative absence of postigestive feedback, rats fed a HF diet consumed significantly more 100% corn oil than LF-fed rats in 1-bottle acceptance tests. Following 4 exposures to the oil, the differences between diet groups were diminished. Whether this was due to postigestive consequences associated with learned oral satiation (51) is largely unknown, because only 60-min intakes were reported. Using brief-access testing (10 s), thus limiting postigestive effects, we tested orosensory acceptance of oil in LF- and HF-adapted rats. We found that HF-adapted rats had increased sensitivity and avidity to corn oil compared with LF-fed rats. Specifically, HF-fed rats sampled increased amounts of 25, 75, and 100% corn oil as measured by licks of solution during the test session. These data suggest that HF feeding not only increases the sensitivity for detection of oil but also increases avidity for higher concentrations of oil, because intake increased as a function of concentration in HF- but not LF-fed rats. Several mechanisms may be responsible for increased sensitivity and avidity to oils in HF-fed rats. For example, epithelial expression of fatty acid transporters (52,53) or metabolism of fats (2,32,33,50,54) are known to contribute to fat preference and may be altered in HF-fed rats. Additionally, favorable characteristics of the diet, such as greasiness (55), may promote intake of fats. CCK and its mRNA also are present in taste cells and alter their electrical excitability (56). Thus, differences in oral oil detection by HF rats may be associated with changes in CCK signaling within the taste bud. Furthermore, perturbations in dopamine signaling have been shown to contribute to increased preference and acceptance of palatable foods, including oils (57, 58). Therefore, it is plausible that the alteration in preference function and reward sensitivity at least in part is due to a maladaptive feedback mechanism that develops in response to sustained overconsumption of HF diets.

In summary, the results of our study show that HF diet induces decreased sensitivity to CCK in both pups as well as adult rats. Furthermore, we demonstrated that HF-induced behavioral changes in CCK sensitivity can be entirely reversed by a LF diet. Finally, by limiting postigestive feedback, we have shown that rats adapted to HF diets maintain increased sensitivity and avidity to oil compared with LF-adapted rats. Together, these findings denote the ability of a HF diet to modulate both oral and postoral inputs controlling ingestion resulting in short-term overconsumption.

Acknowledgments
All authors designed and conducted the research; T.D.S., analyzed data; T.D.S. and M.C. wrote the manuscript; and M.C. had primary responsibility for final content. All authors read and approved the final manuscript.

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