High-fat diet preference and overeating mediated by postigestive factors in rats

FRANÇOIS LUCAS, KAREN ACKROFF, AND ANTHONY SCLAFANI
Department of Psychology, Brooklyn College and the Graduate School,
The City University of New York, Brooklyn, New York 11210

Lucas, François, Karen Ackroff, and Anthony Sclafani. High-fat diet preference and overeating mediated by postigestive factors in rats. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1511–R1522, 1998.—The role of postigestive factors in the preference for and overconsumption of high-fat (HF) foods, relative to high-carbohydrate (HC) foods, was investigated using a self-regulated intragastric feeding procedure. On one-bottle training days, rats drank one flavored saccharin solution [conditioned stimulus (CS) + HF] paired with intragastric infusions of an HF liquid diet, a second flavored solution (CS + HC) paired with an HC liquid diet, and a third flavored solution (CS + H2O) paired with intragastric water. The diets had the same energy and protein content; the CS solutions and infusions along with chow were available ad libitum. The rats drank more CS and self-infused more diet on HF than HC training days. In two-bottle choice tests, the rats preferred the CS + HF to the CS + HC and both CS + HF and CS + HC to the CS −. The rats consumed more CS + HF than CS + HC by taking more bouts per day; bout sizes did not reliably differ. In a subsequent experiment, rats preferred the CS + HF even though diet intakes in training were matched. In a final experiment, the CS + HC and CS + HF intakes were equated in training by diluting the HC diet. Now the rats did not reliably prefer the CS + HF to the CS + HC, yet caloric intakes were much higher on CS + HF than CS + HC training days. Thus, relative to an isocaloric HC diet, the postigestive effects of HF diets stimulate overeating and condition a stronger flavor preference. Reduced satiety rather than increased reinforcement may be the direct promoter of overeating. However, postigestive reinforcement may enhance the selection of HF foods when a choice of HF and HC foods is available.

The preference for, and hyperphagia- and obesity-promoting effects of, high-fat (HF) diets relative to high-carbohydrate (HC) diets are the subject of considerable interest. Several features of HF foods are thought to contribute to the overeating response: their palatable flavor, high energy density, and reduced satiating action, although this remains an unresolved issue (18, 19, 24). In addition, HF diets may produce obesity even in the absence of hyperphagia because of increased feed efficiency; dietary fat requires less energy to be converted into body fat than does dietary carbohydrate or protein (24).

In a recent “behavioral dissection” of HF hyperphagia, Warwick and Weingarten (26) fed rats HF and HC liquid diets that were equal in caloric density and protein content. Over a 16-day period the rats consumed more energy and gained more weight on the HF diet than on the HC diet. A second experiment assessed the palatability response to the flavors of the HF and HC diets using two-bottle, sham-feeding tests to minimize postigestive influences. The rats preferred the HF to the HC diet, indicating that the palatable flavor of the HF may have contributed to the hyperphagic response. The feeding effects of the two diets were then compared in the absence of flavor differences by using a self-regulated intragastric infusion procedure. Rats were infused intragastrically with HF or HC diet as their sole source of nutrition whenever they drank a saccharin solution available ad libitum 23 h/day. The rats in the HF group drank more saccharin and thus infused themselves with more diet and gained more weight than the rats in the HC group. These results demonstrate that when flavor differences are eliminated and caloric density is equated, the postigestive effects of the HF diet were sufficient to induce overeating relative to the HC diet. The authors (26) hypothesized that this occurred because the HF diet is less satiating than the HC diet, i.e., produced less suppression of ongoing eating (reduced satiation) and less suppression of eating during the postmeal interval (reduced satiety).

The postigestive actions of nutrients on food intake are usually considered to be inhibitory (satiation and satiety), but recent work demonstrates that nutrients can have positive postigestive effects that can increase food preferences and acceptance. This is demonstrated by reports that pairing the intake of a novel flavored solution with intragastric nutrient infusions increases the relative intake of that flavor in two-bottle preference tests and the absolute intake of the flavor in one-bottle preference tests (20). Furthermore, separate physiological systems appear to mediate the postigestive positive and negative feedback so that the reinforcing and satiating actions of nutrients are not necessarily correlated (20). In theory, at least, the hyperphagia induced by the postigestive actions of HF diets may result from increased positive feedback as well as, or instead of, decreased negative feedback. Also, the preference for HF over HC foods in choice tests may occur, at least in part, because of differences in the positive postigestive actions of the foods. Evidence to support these possibilities is lacking, and what data are available suggest that dietary fat has weaker, not stronger, postigestive stimulatory effects than dietary carbohydrates (13, 17). However, these data are based on...
studies of pure nutrients, and the positive postingestive effects of mixed diets high in fat or carbohydrate have not been investigated.

The aims of the present study, therefore, were to replicate the finding that intragastric self-infusions of an HF liquid diet promote hyperphagia relative to an HC liquid diet and to compare the effectiveness of the two diets to condition flavor preferences. This was accomplished by training rats to drink different flavored saccharin solutions paired with intragastric infusions of isocaloric HF and HC diets. The HF diet contained 60% fat (in kcal) and 34% carbohydrate, and the HC diet contained 15% fat and 79% carbohydrate; the diets were equivalent in protein content. Amounts consumed during one-bottle training and preferences in two-bottle choice tests were evaluated. In addition, drinking patterns were recorded to determine the effects of the different diet infusions on bout size and frequency. Variations of daily intake may result from changes in one or both of these bout parameters, which may reflect different components of ingestive behavior related to postingestive satiation, satiety, and reinforcement.

**GENERAL METHODS**

Subjects. Adult female Sprague-Dawley rats (260–350 g at the beginning of the experiments) obtained from Charles River Laboratories (Wilmington, MA) or bred in our laboratory from this stock were used. The animals were individually housed in wire-mesh cages in a room maintained at 21°C under a 12:12-h light-dark cycle (lights on at 0800).

Surgery. The rats were surgically implanted with stainless steel gastric cannulas as described by Elizalde and Sclafani (7). The animals were allowed to recover from surgery for at least 1 wk before the start of training. When not in use, the cannulas were kept closed with stainless steel screws.

Apparatus. Intragastric infusions were accomplished using an "electronic esophagus" apparatus described in detail elsewhere (7). In brief, the rats were housed in standard stainless steel cages modified so that powdered chow was available from a food cup accessible through a hole in the back wall of the cage. Drinking fluids were available through stainless steel sipper tubes available through two 19-mm holes in the front of the cage. Trays below the sipper tubes collected spillage. A slot in the cage floor permitted a stainless steel spring containing two catheters to connect the rat's gastric cannula to outputs of a dual-channel infusion swivel located below the cage. Plastic tubing connected the swivel's inputs to two peristaltic infusion pumps. The infusion pumps were operated automatically by drinkometer circuits and a microcomputer whenever the rat licked one of the two sipper tubes; the computer stored the number of licks per minute for offline drinking pattern analysis. The rate of infusion was 1.5 ml/min, and ±1 ml of fluid was infused intragastrically for each 1 ml of fluid orally consumed. With this infusion system, the rats were relatively unrestrained and free to eat and drink normally 22 h/day. The equipment was serviced during the remaining 2 h/day.

Test solutions and diets. The oral test solutions (conditioned stimuli (CSs)) consisted of 0.2% sodium saccharin (Sigma, St. Louis, MO) solutions flavored with 0.05% cherry, grape, or orange unsweetened Kool-Aid (General Foods, White Plains, NY). These flavors are equally preferred by naive rats (unpublished observations). The rats were infused with tap water or an HF or HC liquid diet. The liquid diets used for the intragastric infusions were based on the evaporated milk diets described by Warwick and Weingarten (26). The HF and HC versions were prepared by adding extra carbohydrate (sucrose in expt 1 or maltodextrin in expts 2–4) and fat emulsion (corn oil) to the milk (see Table 1). The HF and HC diets were equal in caloric density (2.1 kcal/ml) except in expt 4, in which the HC diet was diluted with water to 1.4 kcal/ml. The diet caloric densities and macronutrient compositions differ slightly from those reported by Warwick and Weingarten (26), presumably because of small differences in caloric values used for the individual diet ingredients. The following values were used here: sucrose = 3.85 kcal/g, maltodextrin = 3.8 kcal/g, corn oil = 9.0 kcal/g, and evaporated milk = 1.19 kcal/g. Note that the net caloric density of the liquid diets in the stomach was reduced by one-half as they were mixed with the orally consumed CS solutions. In addition to the liquid diet infusions, powdered Purina chow (no. 5001) was available ad libitum; the chow was low in fat (12.1% by calories) and high in carbohydrate (59.4%) and had a caloric density of 3.3 kcal/g. Chow intakes were recorded by weighing the nearest 0.1 g. Intakes of CS solutions and intragastric diets were recorded in grams (±0.1 g) and converted to volumes and energy, respectively.

Conditioning procedure. The rats were trained to associate flavors (the CSs) with intragastric infusions during one-bottle training sessions (22 h/day). The flavors paired with HF, HC, and water infusions are referred to as CS+HF, CS+HC, and CS−, respectively. The specific flavor (orange, cherry, grape) paired with each infusion was counterbalanced across subjects. Flavor preferences were assessed in two-bottle choice tests (22 h/day) with all possible pairs of CS flavors, still paired with their associated intragastric infusions. Chow was available ad libitum throughout training and testing. Water was available during one-bottle CS training days, but intakes were negligible (<4 ml/day) and are not reported.

Note that if after one-bottle training the rats failed to display a preference between the CS+HF and CS+HC in the two-bottle tests, this could mean that the rats had not learned the flavor-diet association or that they found the two diets equally reinforcing. To distinguish between these two possibilities, the CS− with water infusion training was included. Preferences for the CS+HF and CS+HC over the CS− would demonstrate that the rats had learned the CS-diet associations.

<table>
<thead>
<tr>
<th>Table 1. Composition of HF and HC diets</th>
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<tr>
<td>Evaporated milk, g</td>
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<td>Sucrose* or maltodextrin*, g</td>
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<td>Sodium stearoyl lactylate, g</td>
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*HF, high fat; HC, high carbohydrate; HC, diluted HC. For HF diet, a corn oil–water emulsion is first prepared using sodium stearoyl lactylate as an emulsifier; see Ref. 13. *Pathmark Supermarket Brand; Maltrin M580, Grain Processing, Muscatine, IA; Mazola Corn Oil, Best Foods, Englewood Cliffs, NJ; Emplyx, American Products, Kansas City, MO.
Data analysis. Intakes during training and preference testing were averaged over sessions within the same condition (i.e., 2- to 6-day means) before being submitted to repeated-measures analysis of variance. Individual comparisons were evaluated by simple main effects or t-tests when appropriate. Intakes of the CS during two-bottle tests were also expressed as a percentage of total intake. Drinking patterns (bout frequency and size) were analyzed using the licks per minute and 22-h intake data. A bout was defined as a period of drinking containing a minimum of 10 licks and interlick intervals no larger than 10 min. Bout frequency was expressed as number of bouts per 22-h session. Mean bout size was calculated by dividing total 22-h intake by bout frequency.

EXPERIMENT 1

Experiment 1 compared the effects of HF and HC diets developed by Warwick and Weingarten (26) on food intake and flavor preference conditioning. In their study, separate groups of rats were infused intragastrically with HF or HC diet whenever they drank a plain saccharin solution. In the present experiment, all rats were infused with HF and HC diets when they drank different flavored saccharin solutions; a third flavor was paired with intragastric water infusions. Chow was also available so that the rats were not food deprived on water-infusion days.

Originally the rats were tested with the different flavored solutions in short-term (30 min/day) sessions, but intakes were rather low, presumably because the rats were not food deprived and were tested at midday. The rats were then trained during long-term (22 h/day) sessions, and only these data are reported below.

Methods. Ten rats fitted with an intragastric cannula were adapted to the infusion apparatus, where they were maintained on ad libitum powdered chow and water. As noted above, they were initially trained with the CS solutions for 30 min/day but were then switched to 22 h/day sessions. Before the start of long-term training, the rats were given ad libitum access to only chow and water for 3 days. On training day 1, one-half the rats were given the CS + HF paired with intragastric infusion of the HF diet; followed on day 2 by the CS− paired with intragastric water and on day 3 by the CS + HC paired with intragastric infusion of the HC diet. The remaining rats were trained with the CS + HC on day 1 and CS + HF on day 3. This 3-day pattern was repeated twice for a total of nine training sessions. Two-bottle preference tests were then conducted, with one-half the rats being offered the CS + HF vs. CS− for 2 days, followed by the CS + HC vs. CS− for 2 days; the remaining rats were given the CS + HF and CS + HC in the reverse order. All rats were then given the choice between the CS + HF and the CS + HC for 6 days. During the first 4 days of this choice, the CS + HF and CS + HC were paired with their corresponding liquid diets (reinforced test); during the next 2 days, the CS + HF and CS + HC were paired with intragastric water (extinction test).

Results. Table 2 summarizes daily CS intakes, intragastric diet intakes, and drinking patterns during one-bottle training days. The rats differed in their total daily intakes of the three CS solutions [F(2,18) = 30.34, P < 0.001]: CS− intake (paired with intragastric water) exceeded (P < 0.05) CS + HF intake (paired with intragastric HF diet), which, in turn, exceeded (P < 0.05) CS + HC intake (paired with intragastric HC diet). These differences in total intakes were due primarily to differences in bout frequency [F(2,18) = 44.48, P < 0.001]. The highest bout frequencies were obtained with the CS−, followed (P < 0.05) by the CS + HF, followed (P < 0.05) by the CS + HC. Mean bout sizes did not vary reliably, although CS + HF bouts tended to be larger than CS + HC bouts. Because they drank more CS + HF than CS + HC, the rats also infused themselves with more HF diet than HC diet (t(9) = 7.65, P < 0.001).

Table 2 also includes chow intake data from the pretraining baseline period and during one-bottle training. Chow intake varied as a function of training condition [F(3,27) = 100.7, P < 0.001]. Chow intakes did not differ on CS + HF and CS + HC training days but were suppressed (P values < 0.05) compared with CS− days; in addition, CS− Chow intakes were reduced relative to the baseline period. Total energy intake (chow and diet intake) was also influenced by training condition [F(3,27) = 127.1, P < 0.001]. The rats consumed more (P < 0.05) energy on CS + HF days than CS + HC days, and more (P < 0.05) with both diet types than during baseline or CS− days.

In the two-bottle tests (Fig. 1), the rats consumed substantially more of both the CS + HC and CS + HF than of the CS− [F(1,9) = 155.0, P < 0.001]; the percent intakes of the CS + HC and CS + HF were 84 and 91%, respectively. CS + HF intake was greater than that of the CS + HC, while CS− intakes were comparable (and very low) [diet × CS interaction: F(1,9) = 16.37, P < 0.01]. When given the choice between the CS + HF and CS + HC paired with their respective diet infusions, the rats consumed more CS + HF than CS + HC [t(9) = 4.22, P < 0.01]; their percent CS + HF intake was 72%. The difference in CS intakes was due to a difference in daily bout frequency [CS + HF: 9.4, CS + HC: 4.2; (t(9) = 3.51, P < 0.01), not in bout size (CS + HF: 3.6 ml, CS + HC: 2.9 ml; NS). The rats continued to drink more CS + HF than
CS+HC in the extinction test when CS+HF and CS+HC were paired with intragastric water infusions (44.3 vs. 26.7 ml/22 h); the preference was somewhat weaker (63%), but this decrease was not significant. Analysis of both types of tests revealed that overall the rats consumed more CS+HF than CS+HC [F(1,9) = 11.7, P < 0.01] and more total fluid in the extinction test than the reinforced test [F(1,9) = 20.6, P < 0.01].

Discussion. During the one-bottle training period, the rats consumed more CS+HF than CS+HC and thus infused themselves with more HF diet than HC diet. Although they reduced their chow intake when the liquid diet infusions were available, this did not compensate fully for the energy provided by the diets. Consequently, total caloric intakes were increased above chow baseline when the rats had the CS+HF and CS+HC with diet infusions available, and the degree of hyperphagia was greater with the CS+HF and HF diet than with the CS+HC and HC diet. Chow intake was suppressed on CS− days, relative to baseline, and this presumably represents a compensatory response to the elevated caloric intakes on preceding CS+HF and CS+HC days. Rats trained with CS+HF and CS+HC flavors paired with dilute nutrient infusions do not suppress their chow intake on CS− days, which indicates that the CS− flavor and water infusions do not have direct inhibitory effects on chow intake (2).

The present finding that rats self-infused 36% more diet when offered the HF diet than when offered the HC diet is similar to the 30% difference reported by Warwick and Weingarten (26). This similarity is remarkable because, although the two studies used the same diets and self-infusion procedures, they differed in several important respects. That is, Warwick and Weingarten used male rats and a between-group design with the liquid diets as the sole source of nutrition, whereas the present experiment used female rats and a within-group design with chow available in addition to liquid diet.

The overconsumption of the HF diet relative to the HC diet was due primarily to increased bout frequency; the rats took about two more bouts on CS+HF days than on CS+HC days. Bout size also tended to be larger with the HF diet than with the HC diet, but this difference was not reliable. Warwick and Weingarten (26) also observed that bout size tended to be larger with the HF than with the HC diet; they measured only the first eating bout of the day and thus bout frequency data were not available. Taken together, these data indicate that, relative to the HC diet, the HF diet produced less satiety (between-bout feeding suppression) and tended to produce less satiation (within-bout feeding suppression). An additional measure of satiety available in the present study was provided by the chow intake data. Chow intakes were the same on CS+HF and CS+HC days, although the rats consumed 23 kcal/day more of the HF than the HC diet. Thus, on a calorie basis, the HF diet suppressed chow intake less than the HC diet.

The rats not only consumed more CS+HF than CS+HC on one-bottle days, they also preferred the CS+HF to the CS+HC during the two-bottle tests. This preference (72%) was not as strong as the preferences the rats showed for the CS+HF and CS+HC over the CS− (91 and 84%, respectively) but is notable given that the CS+HF and CS+HC were paired with iso-caloric diets. The rats took more than twice as many CS+HF bouts than CS+HC bouts during the CS+ choice tests; CS+HF bout size tended to be larger as well, but this difference was not reliable. The bout data indicate that the preference for the CS+HF over the CS+HC was a true preference. That is, the preference was not secondary to a reduced satiating effect of the HF diet such that the rats took larger CS+HF bouts than CS+HC resulting in a greater daily intake of the CS+HF. Further evidence that the rats had acquired a preference for the CS+HF flavor itself is provided by the extinction test, in which both CS+HF and CS+HC solutions were paired with intragastric water. The next three experiments investigated possible reasons why the HF-paired flavor was preferred to the HC-paired flavor.

**EXPERIMENT 2**

Following Warwick and Weingarten (26), the carbohydrate used to prepare the HC and HF diets in exp 1 was sucrose. However, we have found that the postigestive effects of fructose-containing carbohydrates (fructose, sucrose) are less reinforcing than those of glucose-based carbohydrates (glucose, maltose, maltodextrins) (1, 21). Thus the stronger preference conditioned by the HF diet relative to the HC diet in exp 1 may have occurred because the diets was prepared with a “suboptimal” carbohydrate, not because HF diets are, in general, more reinforcing than HC diets. Experiment 2 tested this possibility by comparing the preferences conditioned by HF and HC diets prepared with maltodextrin rather than sucrose.
Due exclusively to differences in bout frequencies, the highest bout frequency was seen with the CS−, followed (P < 0.05) by the CS+HF, followed (P < 0.05) by the CS+HC. CS bout sizes did not reliably differ. The rats infused themselves with more liquid diet on CS+HF days than on CS+HC days [t(11) = 7.10, P < 0.001]. Chow intakes did not reliably differ on CS+HF and CS+HC training days but were suppressed (P < 0.05) compared with CS− and baseline days; chow intake on CS− days was also less (P < 0.05) than baseline intake [F(3,27) = 120.8, P < 0.001]. Total energy intake also varied as a function of training condition [F(3,27) = 162.7, P < 0.001]; intake on CS+HF days exceeded (P < 0.05) that on CS+HC days, which, in turn, was greater (P < 0.05) than the intakes on baseline and CS− days.

In the CS+HF and CS+HC vs. CS− tests (Fig. 2), the rats consumed substantially more of both the CS+HF and CS+HC than of the CS− [F(1,11) = 160.21, P < 0.001]; their CS+HF and CS+HC preferences were 91 and 84%, respectively. In addition, they consumed more CS+HF than CS+HC, whereas CS− intakes were comparable (and very low) [diet × CS interaction: F(1,11) = 22.07, P < 0.001]. When given the choice between CS+HF and CS+HC, the rats drank more CS+HF than CS+HC [t(11) = 2.41, P < 0.05]; their CS+HF preference was 64%. The difference in CS intakes was due to a difference in bout frequency [CS+HF: 7.6, CS+HC: 3.9; t(11) = 2.76, P < 0.05], not in bout size (CS+HF: 3.6 ml, CS+HC: 3.2 ml; NS).

Discussion. The results of this experiment are very similar to those of expt 1. Most importantly, the CS+HF was significantly preferred to the CS−, and this was due to the rats taking almost twice as many CS+HF bouts than CS− bouts in the two-bottle tests. The CS+HF preference was somewhat weaker than that observed in expt 1 (64 vs. 72%), which is consistent with other findings showing that maltodextrin, the carbohydrate used in this experiment, has a more potent reinforcing effect than sucrose, the carbohydrate used in expt 1. A pilot study also revealed that rats trained with the two different HC diets developed a preference for the CS flavor paired with the maltodextrin-based diet over the CS flavor paired with the sucrose-based diet (unpublished findings).

As in expt 1, the rats infused themselves with more HF diet than HC diet on one-bottle training days, in this case 50% more, taking more CS+HF bouts than CS− bouts; bout sizes did not differ. In addition, total energy intake (chow + liquid diet) was 27% greater on HF days than on HC days, although both diets produced hyperphagia relative to the chow baseline and CS− days.

Although the postigestive effects of the sucrose- and maltodextrin-based HC diets were similar in being less preferred than those of the HF diet, the orosensory effects of the two HC diets have been found to differ. In short-term (30 min/day) taste tests with naive rats, the sucrose-HC diet was reliably preferred (76%) to the corresponding HF diet, whereas the HF diet was reliably preferred (75%) to the maltodextrin-HC diet (Lucas and Scafani, unpublished observations). The sucrose-HC diet preference conflicts with the HF diet preference reported by Warwick and Weingarten (26) using the same diets. Because they used male rats and we used females, sex differences, as well as procedural differences, may account for the discrepant results. Nevertheless, although the female rats initially preferred the sucrose-HC diet, after being given ad libitum one-bottle access to the two diets on alternating days, they reversed their preference and consumed significantly more HF diet than HC diet in a 23 h/day two-bottle test (Lucas and Scafani, unpublished observations). This indicates that the postigestive reinforc-
ing effects of the HF diet can overcome the greater initial palatability of the sucrose-HC diet.

**EXPERIMENT 3**

Experiments 1 and 2 revealed that, although the magnitude of the preference may differ as a function of the carbohydrate used, the HF diet conditioned a stronger preference relative to both HC diets. Conceivably, the rats may have developed the CS+HF preference not because the HF diet is inherently more reinforcing than the HC diets but because they consumed more CS+HF than CS+HC and were infused with more HF than HC diet because the HF diet was less satiating than the HC diet. Experiment 3 determined whether the amount of exposure to the CS+HF and CS+HC solutions and/or amount of intragastric diet infused is responsible for the CS+HF preference. This was accomplished by limiting the amount of CS consumed and diet infused during one-bottle training. The maltodextrin-based HF and HC diets of exp 2 were used.

**Methods.** A new group of rats (n = 11) was adapted to the infusion cages. The cages were modified in that the drinking bottles were mounted on retractable bottle holders controlled by the computer. The rats were first given ad libitum access to chow and water for 2 days. Next, they were given an unflavored 0.2% saccharin solution to drink paired with intragastric water infusions during 10 30-min access periods per day. At specified times, the retractable bottle holder brought the drinking spout within reach of the rat, and 30 min later it was retracted out of reach. The first access period was in the light phase (1810–1840), and the remaining nine periods occurred during the night phase, starting at 2010 and then every 80 min. This approximated the rats’ natural nocturnal drinking pattern. During the first four saccharin “pretraining” days, saccharin intake during the 30-min access periods was unlimited. For the next 3 days, the rats could only drink a maximum of 3 ml per access period; the amount of water infused intragastrically approximately matched the amount of saccharin consumed. Intake was limited individually for each rat by the computer retracting that rat’s drinking bottle after a fixed number of licks (equivalent to 3 ml of intake) had been emitted. The maximum number of access periods (10/day) and maximum amount of total intake (30 ml/day) were selected on the basis of observation that most rats in exp 2 would take at least this many bouts and consumed at least 30 ml/day of the CS+HF and CS+HC solutions. Chow was available ad libitum, but water was not provided to increase the likelihood that rats would drink during the limited-access periods.

After saccharin pretraining, formal one-bottle training with the CS solutions began. The CS+HF, CS+HC, and CS− solutions, paired with their appropriate infusions, were presented for a total of 12 days (4 days/CS) according to the schedule described in exp 1. Access to the CSs was limited to 10 30-min periods/day and a maximum of 3 ml/period. As described in Results below, the rats consumed slightly more CS+HF than CS+HC during training. To equate their infusions of the HF and HC diets, the oral-to-infusion intake ratios were adjusted slightly as training proceeded.

The rats were next given two-bottle tests as in exp 1: CS+HF and CS+HC vs. CS− (2 days each with CS+HF and CS+HC) and CS+HF vs. CS+HC (6 days). However, access to the CSs was restricted to 10 30-min periods/day and a limit of 3 ml per CS and period. The animals were then given an additional CS+HF vs. CS+HC test (2 days) with unrestricted access to the two CSs and their paired diet infusions.

**Results.** The one-bottle training data are summarized in Table 4. Despite the limited-access schedule, the rats differed slightly in their CS intakes [F (2,22) = 4.88, P < 0.05]: CS− and CS+HF intakes were similar and modestly greater (P < 0.05) than that of the CS+HC. This small intake difference resulted because the rats took 1.3 fewer bouts per day of the CS+HC than of the CS+HF and CS− [F (2,20) = 11.92, P < 0.001 (with all CSs the rats did not take every bout that was available)]. Bout sizes did not vary, and the rats usually reached the limit imposed by the access schedule. The amounts of HF and HC diets infused per day did not differ because of the adjustment in the intake-to-infusion ratios. Chow intakes varied as a function of training condition [F (3,30) = 66.6, P < 0.001]. Relative to the water infusions, the diet infusions reduced chow intakes, although the HF diet reduced chow consumption less (P < 0.05) than did the HC diet. Total caloric intakes varied as a function of training condition [F (3,30) = 73.2, P < 0.001]; caloric intake was greater (P < 0.05) on CS+HF days than CS+HC days, and greater on CS+HF and CS+HC days than CS− days. In addition, caloric intakes on CS+HF and CS+HC days exceeded (P < 0.01) the baseline level, whereas intake on CS− days was less (P < 0.05) than baseline.

As illustrated in Fig. 3, the rats consumed more CS+HF and CS+HC than CS− in the CS+HF and CS+HC vs. CS− two-bottle tests [F (1,10) = 16.48, P < 0.01]. In the limited-access choice test with CS+HF and CS+HC, they consumed more CS+HF than CS+HC. When access to the CS+HF and CS+HC was unrestricted, the rats tended to show an even stronger CS+HF preference; their percent CS+HF intakes were

**Table 4.** Experiment 3: CS and energy intakes and CS bout patterns during 22-h, one-bottle training sessions

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<th>CS−</th>
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<td>CS bout size, ml</td>
<td>2.9 ± 0.1a</td>
<td>3.0 ± 0.2a</td>
<td>2.9 ± 0.1a</td>
<td></td>
</tr>
<tr>
<td>Intragastric diet, kcal/22 h</td>
<td>42.5 ± 2.6a</td>
<td>43.3 ± 1.4a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chow intake, kcal/22 h</td>
<td>66.0 ± 3.6b</td>
<td>58.3 ± 2.7b</td>
<td>42.1 ± 2.7b</td>
<td>47.9 ± 2.8b</td>
</tr>
<tr>
<td>Total energy, kcal/22 h</td>
<td>66.0 ± 3.6b</td>
<td>58.3 ± 2.7b</td>
<td>84.6 ± 3.4c</td>
<td>91.2 ± 3.6d</td>
</tr>
</tbody>
</table>

Data are 2-day means ± SE for baseline and 4-day means ± SE for each CS training condition. Within a row, means sharing a common superscript are not reliably different at the 0.05 level.
7.2, CS

HC: 2.9; 1

CS

HF and CS

bout pattern analysis revealed that the difference in

HC in the unrestricted test

more total CS

1

HC that was

different than in

HC (to only 3 ml/day) and eliminated the

greatly reduced the intake differences of the CS

HF

HC: 3.8 ml; NS).

water, HC diet, and HF diet, respectively. Rats also had ad libitum

counterbalancing). In a final test (right), rats had a choice

HC vs. CS

HF with unlimited access (Ad Lib). Intakes of CS–,

HC, and CS+HF were paired with intragastric infusions

water, HC diet, and HF diet, respectively. Rats also had ad libitum

NH.

Discussion. The limited-access training procedure

greatly reduced the intake differences of the CS+HF

and CS+HC (to only 3 ml/day) and eliminated the

difference in HF and HC diet infusions. In addition, the

bout sizes were similar, and bout frequencies were less

different than in expt 2. Yet the rats developed a

preference for the CS+HF over the CS+HC that was

nearly identical to that seen in expt 2 (63 vs. 64%). This

indicates that the CS+HF preferences obtained in

expts 1 and 2 were not due to the rats overconsuming

the CS+HF and HF diet relative to the CS+HC and HC

diet during one-bottle training. Rather, the data sug-

gest that the HF diet is more reinforcing per amount

infused than the HC diet. This issue is addressed

further in expt 4.

The preferences for the CS+HF and CS+HC relative
to the CS– were not as strong as those obtained in expts

1 and 2 (69–72% vs. 84–91%). This may have occurred

because the rats received less total reinforcement
during training and/or because the restricted access during

the two-bottle testing limited the rats’ CS+HF and

CS+HC bout frequency and size.

Although the rats were infused with nearly identical
amounts of HF and HC diet (in volume and energy)
during one-bottle training, they suppressed their chow
intake less on HF days than HC days. This confirms the

results of expts 1 and 2 indicating that the HF diet
produces less satiety than the HC diet. Because of the
differential suppression in chow intakes, total energy
intakes were slightly higher on CS+HF days than

CS+HC days, which, it could be argued, may have been

responsible for the learned preference for the CS+HF

over the CS+HC. However, as expt 4 shows, even large

differences in total caloric intake do not necessarily

result in a CS+HF preference.

EXPERIMENT 4

Experiment 4 investigated the possibility that the

conditioned preference for the CS+HF resulted from

the different satiety potencies of the HF and HC diets. Al-

though it might seem that the food that produces less

satiety should also be less reinforcing, recent data

discuss the satiety actions of the HF diet. Because of the

HC days, which, it could be argued, may have been

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rats infused themselves with similar volumes of the HF and Hc diets (46 and 47 ml/day, respectively). Because the HF diet was calorically denser than the Hc diet, more energy was infused on CS+HF than CS+Hc days \([t(10) = 10.51, P < 0.001]\). Chow intakes did not reliably differ on CS+HF and CS+Hc days and were reduced (P values < 0.001) on CS+HF and CS+Hc days relative to CS− and baseline days \([F(3,30) = 150.1, P < 0.001]\). Total energy intake was greatest on CS+HF days, followed by CS+Hc days, then baseline days, and finally CS− days, all differences P < 0.05 \([F(3,30) = 263.1, P < 0.001]\).

In the CS+HF and CS+Hc vs. CS− choice tests (Fig. 4), the rats consumed significantly more CS+HF and CS+Hc than CS−; their absolute and percent intakes (88 and 91%) of the CS+HF and CS+Hc were similar. When given the choice between the CS+HF and CS+Hc, the rats consumed slightly but not reliably more CS+HF than CS+Hc (Fig. 4); their percent CS+HF intake was 58%. The CS+HF and CS+Hc bout frequencies (7.4 and 5.5 bouts/day) and sizes (4.0 vs. 3.8 ml/bout) during the two-bottle test also did not reliably differ. The volumes infused of HF and Hc diets (27.6 vs. 22.2 ml/day) closely matched the intakes of the CS+HF and CS+Hc solutions and did not reliably differ. The rats self-infused more calories as HF than Hc during the two-bottle test (50.6 vs. 27.2 kcal/day), but this difference was not statistically significant.

Discussion. The CS+HF was not reliably preferred to the CS+Hc, which contrasts with the significant CS+HF preferences obtained in the preceding experiments. Admittedly, the nonreliable 58% CS+HF preference obtained here was not that much less than the significant 63–71% CS+HF preferences obtained with the maltodextrin-based diets in expts 2 and 3. Nevertheless, the fact that calorically diluting the HC diet enhanced the preference for its paired flavor relative to the CS+HF flavor is noteworthy. Diluting the HC diet also increased CS+Hc total intake and bout frequency to the levels of the CS+HF; mean bout size was similar between the two diets. Thus on a volume basis the CS+Hc and CS+HF and their associated infusions had similar satiating and reinforcing effects even though the HF infusions provided 50% more energy than did the Hc infusions. Taken together, these findings support the idea that the HF diet has a stronger reinforcing effect than the full-strength HC diet, not because it stimulates greater energy intake but because it produces less satiety.

**GENERAL DISCUSSION**

The present study compares the hyperphagia-promoting and flavor-conditioning effects of HF and HC liquid diets and also provides data related to the satiating actions of the diets. These findings will be discussed in turn.

HF and HC diet-induced hyperphagia. HF diets have often been found to produce excessive energy intake compared with HC diets (24). Typically, the HF and HC diets have differed in flavor, caloric density, and nutrient composition so that the cause(s) of the overeating are not certain. Following the lead of Warwick and Weingarten (26), the present study eliminated the inherent flavor and caloric density differences between HF and HC diets by having the rats self-infuse isocaloric liquid diets into the stomach. Although our design and focus were different (e.g., use of CS flavors, within-group design, availability of chow), we confirmed Warwick and Weingarten’s (26) finding that rats self-infused more HF diet than HC diet. In exp 1, given sucrose-based diets, the rats self-infused 36% more HF than HC, which is similar to the 30% difference reported by Warwick and Weingarten using the same diets. An even greater difference (50%) in HF and HC infusions was obtained in exp 2 using maltodextrin-based diets. In terms of total caloric intake (liquid diet and chow), the rats consumed 22–26% more energy on HF days than HC days in expts 1 and 2.

The present data along with those of Warwick and Weingarten (26) demonstrate that increased caloric density is not required to obtain HF-induced overeating. In fact, the degree of overconsumption obtained in exp 4, in which the caloric density of the HF diet was greater than that of the HC diet, was comparable to that obtained with isocaloric diets in exp 2. Nevertheless, some prior studies report that fat-induced overeating is reduced or blocked when the caloric density of the HF diet is reduced (24). These studies involved solid rather than liquid diets, and fiber rather than water was used to manipulate caloric density. Thus, with some diet formulations, energy density and diluant composition may be a critical factor in HF diet-induced overeating.

The diet-infusion data of the present and prior studies (26) also demonstrate that fat-related flavors are not required to obtain fat-induced overconsumption. In these experiments the same sweet taste (with or without added CS flavors) was associated with both the HF and HC diet infusions. However, as discussed further below, this does not mean that orosensory
factors do not have a significant role in food intake and choice.

Higher intakes of HF than HC diets may result from increased bout size, increased bout frequency, or both. The present data revealed that with isocaloric diets, the rats consumed more HF than HC diet primarily by taking more frequent bouts. HF bouts also tended to be larger than HC bouts in expts 1 and 2, but this difference was not significant. However, in expt 4, in which the HF diet was more energy dense than the HC diet, bout frequencies were equivalent and the rats overconsumed the HF diet by taking larger (in energy but not volume) bouts. Thus, although caloric density did not affect the degree of overeating produced by the HF diet relative to the HC diet, it did affect its behavioral expression: increased bout frequency with isocaloric diets (expt 2) and increased bout size (in kcal) with “anisocaloric” diets (expt 4).

In addition to promoting more liquid diet intake, the HF diet suppressed chow intake less than did the HC diet. This is most clearly documented in expt 3, in which the rats were infused with comparable amounts of the two diets but consumed more chow on HF days than HC days. In expts 1, 2, and 4, the rats did not differ in their chow intakes on HF and HC days, although they infused themselves with 35–50% more energy on HF days than HC days. Chow intake patterns were not recorded, and thus it is not known how the HF and HC diet infusions altered chow meal size and frequency.

Although the rats consumed more total energy on HF days than HC days, both diets stimulated overconsumption relative to the chow baseline. Total energy intake was elevated by 31–40% on HC days and 65–75% on HF days, both diets stimulated overconsumption. Total energy intake may largely account for the overconsumption of the rats when the two diets were presented as mixed diets.

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Although the rats consumed more total energy on HF days than HC days, both diets stimulated overconsumption relative to the chow baseline. Total energy intake was elevated by 31–40% on HC days and 65–75% on HF days over baseline intake in expts 1, 2, and 4. The HC and chow diets were similar in that they were both high in carbohydrate and low in fat, but they differed in several other respects (protein content, micronutrient composition, water content). The difference in hydramine may largely account for the overconsumption produced by the HC liquid diet in view of prior studies showing that adding water to HC mixed diets promotes hyperphagia (15).

HF- and HC-conditioned flavor preferences. Consistent with many earlier studies using different types of nutrient infusions, the rats in expts 1–4 acquired preferences for the flavors paired with the diet infusions (HF and HC diets) over the flavor paired with water. The new finding here is that in three of the experiments the rats also developed a preference for the flavor paired with the HF diet infusions over the flavor paired with the HC diet infusions. The magnitude of the preference was consistent across experiments (63–72%) and, although moderate, it is significant given that the diets had the same caloric density and differed only in their fat-to-carbohydrate ratio.

Furthermore, prior experiments using pure macronutrient infusions indicate that fat is less reinforcing than carbohydrate. In long-term studies, carbohydrate (maltodextrin solution) infusions conditioned stronger flavor preferences and increased flavor acceptance more than did isocaloric fat (corn oil emulsion) infusions (13, 17). Taken together, these data suggest that the relative reinforcing effects of fat and carbohydrate depend on whether the nutrients are presented in pure form or as components of mixed diets.

Several possible reasons why the HF diet conditioned a stronger preference than the HC diet were explored. It was first determined that although the strength of the preference may be influenced by the carbohydrate used, the HF diet was more reinforcing than HC diets prepared with sucrose or maltodextrin. This issue was addressed because other findings indicate that the postigestive reinforcing effects of sucrose are weaker than those of glucose-based carbohydrates (1). It was next determined whether the greater hyperphagic response to the HF diet, relative to the HC diet, was responsible for the HF diet’s stronger reinforcing effect. The results indicate that the preference for the CS + HF over the CS + HC was not due to the rats being infused with more HF diet than HC diet. In expt 2, caloric intakes were greater with the HF diet than the HC diet, whereas in expt 3 they were similar, yet CS + HF preferences of similar magnitudes were obtained. In expt 4, caloric intakes were much larger with the HF diet relative to the diluted HC diet, but the CS + HF was not reliably preferred to the CS + HC. Thus caloric payoff was not a determinant of the greater effectiveness of the HF diet to condition a preference relative to the HC diet.

A third issue examined was the relationship between the postigestive reinforcing and satiety effects of the HF and HC diets. In expt 4, caloricically diluting the HC diet decreased its satiety effect to the level of the HF diet; at the same time, it made the reinforcing effects of the two diets more equivalent. This finding suggests that the reduced satiating potency of the HF diet compared with the full-strength HC diets was responsible for the CS + HF preference obtained in expts 1–3. Prior work with pure carbohydrate infusions indicate that very dilute infusions are minimally reinforcing and that increasing nutrient concentration increases reinforcement (2). However, above a certain point (e.g., between 0.6 and 1.2 kcal/ml for maltodextrin), the reinforcing action of the infusion levels off and may even decrease (12). These and other data (27) indicate that concentrated and highly satiating nutrient sources have a negative component that reduces their postigestive reinforcing actions. The same may be true for different nutrient mixes (e.g., HF and HC diets) that are equal in caloric density but differ in their satiating potency. According to this interpretation, the enhanced reinforcing potency of the HF diet occurred because of its reduced satiety action. In fact, as discussed above, prior work with pure macronutrient infusions indicates that fat is less reinforcing than carbohydrates. These studies used infusions less calorically dense (≤0.64 kcal/ml) and thus less satiating than the milk diet infusions (2.1 kcal/ml) of the present experiment. It is possible, then, that if the milk diets are infused at isocaloric but more dilute concentrations, the HC diet might be more reinforcing than the HF diet. This remains to be tested.
An alternative interpretation for the preference for the CS+HF over the CS+HC is that satiety feedback does not directly affect postingestive reinforcement but influences flavor preference via a separate conditioning process. In particular, Warwick and Weingarten (27) proposed that two-bottle choice behavior is the outcome of the opposing effects of positive reinforcement and anticipated (learned) satiation. (They, in fact, used the term satiety, but were referring to the learned control of meal size that, according to present usage, refers to satiation.) In fact, the HC and HF diets had similar satiation effects, i.e., CS+HC and CS+HF bout sizes were similar, but differed in their satiety effects, i.e., bout frequencies were higher with the CS+HF than with the CS+HC. Conceivably, the rats learned to anticipate the reduced satiety effect of the HF diet by increasing their bout frequency, which led to the CS+HF preference in the two-bottle tests. Whether satiety feedback affected preference directly or via postingestive reinforcement cannot be determined given the present data, although conditioned increases in bout frequency have not, to our knowledge, been directly demonstrated.

Hyperphagic, reinforcing, and satiating effects of HF and HC diets. The finding that HF infusions conditioned a stronger preference than did isocaloric HC diet infusions raises the possibility that HF hyperphagia occurs, at least in part, because HF diets have stronger positive postingestive actions than do HC diets. That the postingestive reinforcing effects of nutrients can actually stimulate consumption is demonstrated by reports that rats increase their daily intake of flavored solutions paired with intragastric carbohydrate infusions rather than water (16). Note though that dilute fat infusions are less effective than isocaloric carbohydrate infusions in stimulating flavor acceptance (17), which is consistent with their reduced ability to condition a flavor preference. More concentrated infusions do not increase total intake, but they may have a stimulatory effect that is obscured by the satiating actions of the nutrient infusions (16). In theory, the nutrient’s reinforcing action may counteract its satiating action such that the net inhibitory effect on intake is reduced. The present results, however, indicate that the reinforcing effect of the HF diet was not highly correlated with the degree of hyperphagia seen with the diets. This is illustrated in Fig. 5, which plots HF diet overconsumption in one-bottle training as a function of CS+HF preference in two-bottle tests, relative to the HC diet and CS+HC, respectively. The overall correlation using the data from expts 1, 2, and 4 was only 0.057. The r² values obtained in the individual experiments were 0.090, 0.031, and 0.279, none of which were significant. (Data from expt 3 were not included because the diet infusions were restricted.) This analysis suggests that the hyperphagic response to the HF diet was not primarily a result of the diet’s postingestive reinforcing action.

Rather, as proposed by prior investigators (26), it may be the reduced satiety effect of the HF diet that caused the rats to overconsume the diet relative to the HC diet. The idea that fat produces less satiety than carbohydrate is supported by studies showing that oral or intragastric preloads of fat suppress intake less than isocaloric carbohydrate preloads (5, 8, 25). The present findings that the HF diet was taken in more frequent bouts and that it reduced chow intake less, relative to the HC diet, are consistent with the concept of reduced satiety. Other findings indicate that intragastric fat infusions suppress ongoing eating less than isocaloric carbohydrate infusions (Lucas and Sclafani, unpublished observations). In the present experiments, however, bout sizes did not reliably differ when the HF and HC diets were infused at isocaloric concentrations, which suggests that the diets were similar in their ability to promote satiation. The physiological processes responsible for the differential potency of the HF and HC diets to inhibit feeding remain to be identified.

The present findings and the studies cited above are at odds with a recent report by Burton-Freeman et al. (6) that HF infusions produce more satiety than HC infusions. In their study, rats given isocaloric intraduodenal infusions at the start of a 6 h/day feeding period showed longer intermeal intervals (IMI) when infused with high-fat loads than when infused with high-carbohydrate loads. This contrasts with the reduced IMI (i.e., increased meal frequency) observed in the present study with the HF diet relative to the isocaloric HC diet. The Burton-Freeman et al. (6) study differed from the present one in several ways, but perhaps the most important difference was the route of administration: intraduodenal rather than intragastric infusions. Although direct comparisons are not available, data from different studies indicate that, relative to carbohydrate, fat is very effective in suppressing eating when infused intraduodenally (6, 9) but less so when it is
infused intragastrically or orally consumed (5, 8, 25). It may be that infusing fat and carbohydrate intraduodenally at the same rate overestimates the satiating effect of fat because gastric emptying of fat is slower than that of carbohydrate (23). This issue requires clarification for a full understanding of the effects of HF and HC diets on feeding behavior.

Influence of flavor on food intake and preference. In the present study and prior work (26), flavor differences inherent to HF and HC diets were eliminated by having the rats self-infuse the diets when they drank either identical saccharin solutions or flavored saccharin solutions that did not differ in their initial palatability. In both cases, the rats overconsumed the solution paired with the HF diet infusions, which would seem to indicate that flavor stimuli are not important in diet-induced overeating. However, other findings document the importance of flavor in food intake and choice. Warwick and Weingarten (26) observed that rats did not learn to self-infuse liquid diet if plain water rather than saccharin was used as the oral cue. This is consistent with earlier reports that rats do not readily self-infuse liquid diets when required to bar press in the absence of oral cues (10). Thus, flavor cues are essential to maintain ingestion and allow for the expression of diet-induced overeating.

Evidence that flavor palatability can promote diet-induced overeating is provided by a self-infusion study in which flavor cues rather than nutrient infusions were varied (22). The rats were given ad libitum access to chow and either a preferred Polycose + saccharin (P+S) solution or an unpreferred sucrose octaacetate (SOA) solution paired with an intragastric Polycose infusion. Animals given the P+S solution consumed twice as much solution and therefore self-infused twice as much Polycose as did the rats given the SOA solution to drink. Note that the SOA solution did not suppress fluid intake relative to a water control group; it simply did not stimulate intake like the P+S solution. The total caloric intake and weight gain of the rats offered the P+S solution was also greater than those of the rats given the SOA solution. It is possible, then, that the overconsumption of the HF diet relative to HC diet observed in the present study would be reduced if the HF infusion was paired with an unpreferred flavor while the HC infusion was paired with a preferred flavor.

A final point is that flavor cues provide critical information used in nutrient selection. In some cases, the flavor-nutrient association is innate (e.g., sodium appetite), but probably most cases involve learned associations between the flavor and postingestive consequences of the nutrient. The present findings along with other recent data demonstrate that rats can distinguish not only between nutrient and nonnutrient intragastric infusions but also between isocaloric nutrient infusions that differ in their nutrient composition (14, 21).

In conclusion, in confirmation of other recent findings (26), the present results demonstrate that the post-esthetic action of an HF food promotes overeating relative to an HC food even when caloric density and initial flavor palatability are equated. The findings further demonstrate for the first time that postigestive consequences can condition a preference for a flavor associated with an HF, moderate-carbohydrate diet over a flavor associated with an isocaloric low-fat, HC diet. The conditioned preference was obtained with an ad libitum feeding regimen and in the presence of an alternate low-fat and high-quality food (chow). Thus, in addition to possible unlearned preferences for fat-related flavors, differential postigestive reinforcement may explain why HF foods are often preferred to HC foods. Yet the available data suggest that fat is not inherently more reinforcing than carbohydrates, but rather this outcome may be secondary to the reduced satiety effects of dietary fat. Because liquid diets and only one type of fat (corn oil) were used in this study, the generality of the results to other types of diets remains to be established.

Perspectives

It is widely accepted that high dietary fat intake contributes to human obesity and other diseases. The palatability, reduced satiating effect, and energy density of fat-rich foods are thought to contribute to high fat intakes (3), although inconsistent results have been reported concerning the relative satiating effects of fat and carbohydrate in humans (18). Postigestive effects of fat and carbohydrate can condition flavor preferences in humans as they do in rats (4, 11). The present findings suggest that postigestive feedback may condition human preferences for HF foods over HC foods. Investigation of the relationship between postigestive reinforcement and satiety in humans may provide further insights into the development of food preferences.

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Address for reprint requests: A. Sclafani, Dept. of Psychology, Brooklyn College of CUNY, 2900 Bedford Ave, Brooklyn, NY 11210-2889.

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