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A Role for Sweet Taste: Calorie Predictive Relations in Energy Regulation by Rats

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Animals may use sweet taste to predict the caloric contents of food. Eating sweet noncaloric substances may degrade this predictive relationship, leading to positive energy balance through increased food intake and/or diminished energy expenditure. These experiments were designed to test the hypothesis that experiences that reduce the validity of sweet taste as a predictor of the caloric or nutritive consequences of eating may contribute to deficits in the regulation of energy by reducing the ability of sweet-tasting foods that contain calories to evoke physiological responses that underlie tight regulation. Adult male Sprague–Dawley rats were given differential experience with a sweet taste that either predicted increased caloric content (glucose) or did not predict increased calories (saccharin). We found that reducing the correlation between sweet taste and the caloric content of foods using artificial sweeteners in rats resulted in increased caloric intake, increased body weight, and increased adiposity, as well as diminished caloric compensation and blunted thermic responses to sweet-tasting diets. These results suggest that consumption of products containing artificial sweeteners may lead to increased body weight and obesity by interfering with fundamental homeostatic, physiological processes.

Keywords: learning, energy balance, cephalic-phase responses, thermic effect of food

One of the most well-established concepts in psychology is that animals can detect and learn about relationships among the events they experience and that sensitivity to these relationships can be indexed by changes in behavioral and physiological responses (e.g., Dworkin & Dworkin, 1995; Pavlov, 1927; Siegel, 2005). The purpose of the present research is to explore some of the implications of a Pavlovian analysis for understanding the control of food intake and body weight. During the past 30 years, the incidence of people who are overweight or obese has increased dramatically both in the U.S. and throughout the rest of the world (Flegal, 2005; Rigby, Kumanyika, & James, 2004). Although much research has focused on identifying disturbances in the neural and hormonal mechanisms involved with maintaining energy balance, the rate of body-weight gain during this period suggests that the current obesity epidemic has environmental origins (Hill & Peters, 1998; Lowe, 2003; Nicklas, Baranowski, Cullen, & Berenson, 2001).

One change in the food environment that is correlated with current obesity trends is the wide scale introduction of noncaloric, high-intensity sweeteners (The Freedonia Group, 2001; Schiweck, 1999; Zuckerindustrie, 1999). In nature, sweetness might be described as a salient orosensory stimulus that is a highly valid predictor of the postingestive caloric consequences of eating, as humans and other animals repeatedly encounter, beginning very early in life (e.g., at first contact with breast milk), naturally sweet foods that are more calorically dense than less sweet foods. With the growing use of noncaloric sweeteners in the current food environment, millions of people are being exposed to sweet tastes that are not associated with caloric or nutritive consequences. On the basis of Pavlovian conditioning principles, we suggested that a consequence of this type of exposure might be impaired energy regulation (Davidson & Swithers, 2004; Swithers & Davidson, 2005b).

It is well established that orosensory cues (e.g., the taste, flavor, texture of food) can be quickly and strongly associated with the postingestive consequences of eating. For example, the phenomenon of conditioned taste aversion demonstrates that animals will rapidly learn to avoid consuming a taste that is paired with gastric malaise (Welzl, D'Adamo, & Lipp, 2001). More recent studies indicate that animals also readily associate orosensory cues with the postingestive caloric or nutritive consequences of eating (e.g., Sclafani, 1997, 2001).

Sweet tasting substances have also been identified as strong elicitors of a number of preabsorptive (e.g., hormonal, thermogenic, metabolic) "cephalic-phase" reflexes related to ingestion (Berthoud, Trimble, Siegel, Bereiter, & Jeanrenaud, 1980; Bruce, Storlien, Furler, & Chisholm, 1987; Teff, Devine, & Engelman, 1995; Tordoff, 1988). Functionally, cephalic-phase reflexes are thought to anticipate and prepare for the arrival of nutrients in the gastrointestinal tract, thereby increasing the efficiency of nutrient utilization and minimizing the degree to which those nutrients perturb homeostasis by producing positive energy balance (Mattes, 1997; Powley & Berthoud, 1985; Teff, 2000). By some accounts (e.g., Woods & Ramsay, 2000), even small changes in the evocation of these cephalic-phase responses could produce changes in

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the efficiency of energy utilization, leading to significant long-term increases in food intake and body weight (Cooling & Blundell, 2000).

If the efficiency of energy regulation depends, at least in part, on the elicitation of cephalic-phase responses, and if the elicitation of cephalic-phase responses depends, in part, on the ability of sweet tastes to signal calories, then experiences that weaken this signaling or predictive relationship might also disturb the control of food intake and body weight. The present research evaluated this basic hypothesis. We manipulated the strength of this relationship by exposing rats to sweet tastes that were either highly valid predictors of, or did not predict, an increase in the caloric content of plain yogurt. In our studies, rats were given both plain unsweetened and sweetened yogurt. When the yogurt was sweetened with glucose, the sweet taste was a valid predictor of increased calories, whereas when the yogurt was sweetened with nonnutritive saccharin, the sweet taste was not predictive of increased calories. The total volume of yogurt consumed was equated across groups by offering identical quantities and by excluding rats that failed to consume at least 70% of the yogurt diets offered. As a result, although the predictive group received more calories from the yogurt supplements than did the nonpredictive group (because of the caloric sweetener), the hypothesis was that the nonpredictive group would demonstrate increased food intake and body weight gain and decreased caloric compensation relative to that seen in the predictive group. Experiment 1 examined the effects of varying the strength of the predictive relationship between sweet taste and the caloric consequences of eating on food intake, body weight, and body adiposity. Experiment 2 assessed the effects of this manipulation on the ability of rats to compensate for calories consumed on one occasion by reducing intake at a subsequent meal. Experiment 3 assessed whether or not the increment in core body temperature produced by food intake (i.e., the thermic effect of food; de Jonge & Bray, 1997, 2002) can be modified by prior exposure to a nonpredictive relationship between sweet tastes and calories.

Experiment 1

Method

Subjects were adult male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing 375–425 g at the start of testing. Rats were housed individually in hanging wire cages with pellet laboratory chow (Lab Diets 5001) and water available ad libitum except during testing as described below. The colony room was maintained on a 14:10-hr light–dark cycle with lights on at 7:00 a.m. Dietary supplements were provided at approximately 11:00 a.m. each day. Temperature in the colony room was maintained at 21–23 °C.

Dietary manipulation. During testing, rats received 30 g of low-fat, plain yogurt (Dannon, Allentown, PA) daily for 6 days per week in addition to ad-lib lab chow and water. On the 7th day, only lab chow and water were provided. Yogurt diets and lab chow were provided in small enamel camping cups attached to the inside of the cage. Diets were available for approximately 23 hr per day, and yogurt and chow intake were recorded daily by weighing the cups, with chow intake adjusted for spillage; Rats were weighed daily and were randomly assigned to one of three yogurt diet conditions: Rats in the sweet predictive group received plain, unsweetened yogurt (~0.6 kcal/g) for 3 of the 6 days each week that yogurt was provided and received yogurt sweetened with 20% glucose (wt/wt; ~ 1.2 kcal/g) for the other 3 days that week. Thus, for rats in the sweet predictive group, the sweetened diet was associated with more calories than was the unsweetened diet. Rats in the sweet nonpredictive group received plain, unsweetened yogurt for 3 of the 6 days each week that yogurt was provided and received yogurt sweetened with 0.3% saccharin for the other 3 days that week. Thus, for rats in the sweet nonpredictive group, the sweetened diet was not associated with more calories than was the unsweetened diet. Across each week of testing, the sweet predictive group received a total of approximately 162 kcal per week from the yogurt supplements, whereas the sweet nonpredictive group received a total of approximately 104 kcal per week from the yogurt supplements. Therefore, a third group, the sweet predictive control group, was included to control for the total number of calories from the yogurt supplement per week (approximately 104 kcal per week). This group received only yogurt sweetened with 20% glucose (wt/wt; ~ 1.2 kcal/g) on the 3 days per week that rats in the sweet nonpredictive group received sweetened yogurt (i.e., this group did not receive any unsweetened yogurt). The order of presentation of the sweetened and unsweetened diet was randomized each week.

After excluding rats that did not consume at least 70% of the yogurt, there were eight rats in the sweet predictive group, 9 rats in the sweet nonpredictive group, and 10 rats in the sweet predictive control group. Rats received the yogurt diet supplements for 5 weeks. At the end of 5 weeks, rats were lightly anesthetized with ketamine and xylazine (10 mg/kg–70 mg/kg ip), and body composition was determined using dual-energy x-ray absorptiometry (DEXA; pDEXA Sabre, Norland, Cranberry, NJ), which has been used and validated in multiple species as a reliable estimate of fat and lean mass (e.g., 8, 11, 12, 70)

Statistical analysis. The principal outcome measure in this study was cumulative body weight gain, which was analyzed at the end of each of the 5 weeks of training with a two-way, repeated measures analysis of covariance (ANCOVA) using group as a between-subjects factor, exposure week as a within-subjects factor, and initial body weight as the covariate, followed by one-way ANCOVAs on each week. In addition, consumption of the sweetened and unsweetened yogurts were analyzed using separate three-way (Group × Yogurt Type [sweetened vs. unsweetened] × Week) repeated measures analyses, with unsweetened yogurt consumption assessed for only the sweet predictive and sweet nonpredictive groups (as sweet predictive control rats did not receive unsweetened yogurt). Total caloric intake at the end of each of the 5 weeks of training was analyzed with separate two-way, repeated measures analyses of variance (ANOVAs) using group as a between-subjects factor and exposure week as a within-subjects factor. In addition, total cumulative caloric intake across all 5 weeks of training was analyzed with a one-way ANOVA. Adiposity, expressed as percent fat derived from DEXA analysis, was analyzed with a one-way (group) ANOVA. Post hoc tests were done using Newman-Keuls tests where indicated, and $p < .05$ was taken as significant for all analyses.

Results

Body weights across predictive (404 ± 5 g), predictive control (394 ± 3g) and nonpredictive (398 ± 4 g) groups did not differ at the start of the experiment, $F(2, 24) = 1.62$, $p = .22$. An ANCOVA indicated that during the 5 weeks of training, body weight gain was significantly predicted by the covariate (starting body weight)—main effect of body weight, $F(1, 23) = 9.19$, $p < .05$. In addition, the diet group and the week of exposure significantly affected cumulative body weight gain (see Figure 1)— main effect of group, $F(2, 23) = 4.44$, $p < .05$; main effect of week, $F(4, 92) = 3.92$, $p < .05$; Week × Starting Body Weight interaction, $F(4, 92) = 6.55$, $p < .05$; Week × Group interaction, $F(8, 92) = 2.34$, $p < .05$. Post hoc analyses using one-way ANCOVAs revealed that during the first week, there were no significant effects of group on body weight gain. However, during Weeks 2, 3, and 5, rats in the sweet nonpredictive group had gained significantly more weight than did rats in either the sweet predictive or sweet predictive control groups.

Analysis of mean food intake per week during the 5 week training period revealed that yogurt consumption varied by week, but not by group (see Figure 2)—main effect of week, $F(4, 96) = 9.45$, $p < .05$. An effect of week, but not of group, was significant when total caloric intake per week (yogurt plus chow) was evaluated across the 5 weeks of consumption, with intake during the 1st week significantly lower than intake during the remaining 4 weeks (see Figure 3)—main effect of week, $F(4, 96) = 9.58$, $p < .05$. Differences due to group also failed to achieve significance when cumulative caloric intake was calculated across the entire 5 week training period (predictive = 3,837 ± 109 kcal, predictive control = 3,809 ± 75 kcal, nonpredictive = 3,986 ± 67 kcal), $F(2, 24) = 1.33$, $p = .28$.

Because of technical difficulties, DEXA analysis was not completed on 3 rats (1 sweet predictive control rat and 2 sweet nonpredictive rats). Analysis of the remaining rats indicated that body fat composition was significantly affected by group (see Figure 4)—main effect of group, $F(2, 21) = 7.27$, $p < .05$, with sweet nonpredictive rats having significantly greater adiposity than that seen in sweet predictive and sweet predictive control rats.

Experiment 2

Caloric compensation involves the ability to adjust for excess calories consumed on one occasion by reducing intake at other times (Booth, 1972; Foltin, Fischman, Moran, Rolls, & Kelly, 1990; Mattes, 1996; Mazlan, Horgan, & Stubbs, 2006; Rowland, Nasrallah, & Robertson, 2005). Weakened caloric compensation could therefore result in positive energy balance and increased tendencies toward being overweight and toward obesity. Experiment 2 examined whether or not the strength of the predictive relationship between sweet taste and calories could influence the strength of caloric compensation. One group of rats was trained under conditions in which sweet taste was a highly valid predictor of increased calories, and another group was trained under conditions in which sweet taste did not predict more calories. After completion of this training, both groups consumed a small amount of a novel high-calorie sweet tasting premeal. The ability to compensate for the calories contained in this premeal by reducing their caloric intake of lab chow at a subsequent test meal was compared for the two groups.

Method

The subjects were adult male Sprague–Dawley rats (Harlan) weighing 300–350 g at the start of testing. Rats were housed individually in hanging wire cages with pellet laboratory chow (Lab Diets 5001) and water available ad libitum except during testing as described below. The colony room was maintained on a 14:10-hr light–dark cycle, with lights on at 7:00 a.m. Dietary

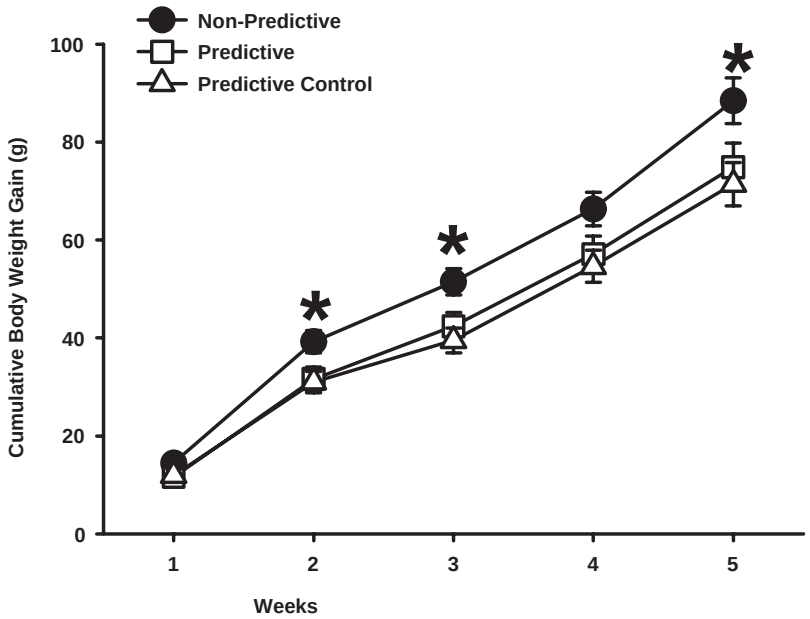

Figure 1. Cumulative body weight gain across 5 weeks exposure to sweet predictive, sweet nonpredictive, or sweet predictive control diets. Error bars represent standard error. $^{*}p < .05$.

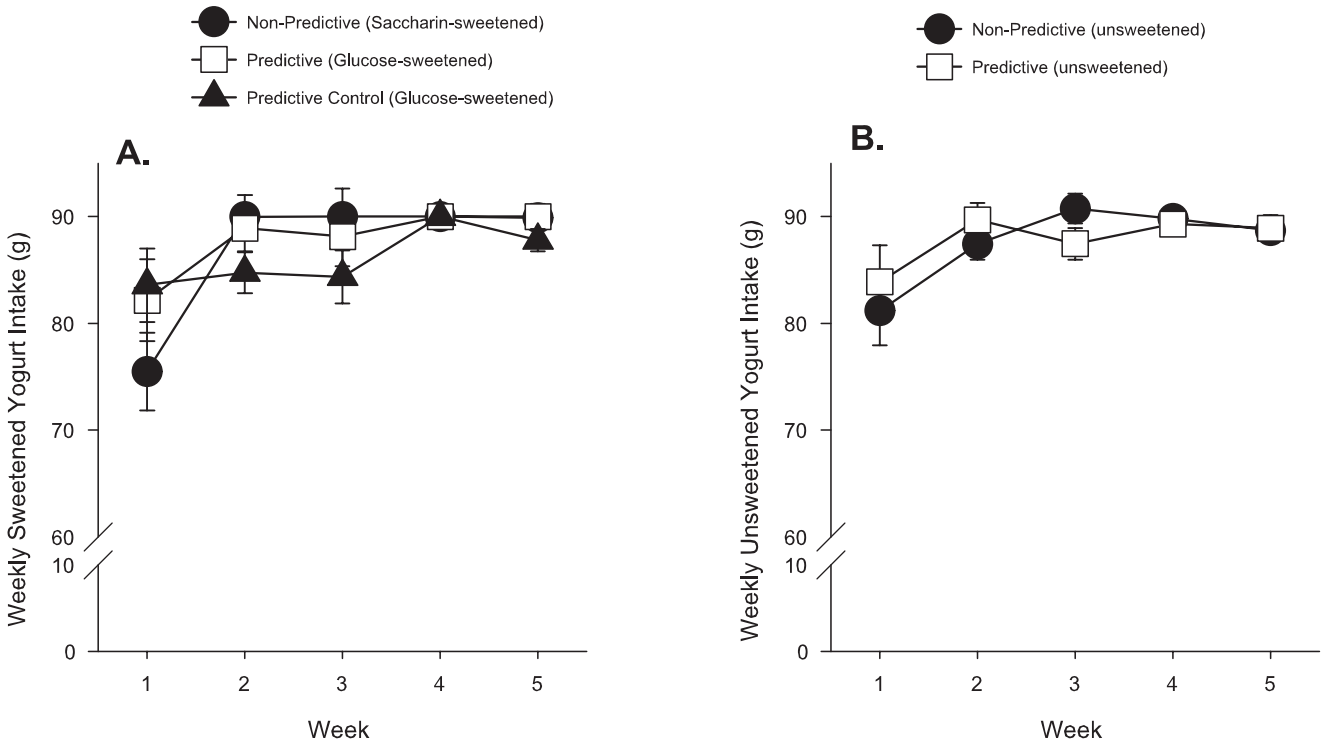

Figure 2. Sweetened (A) and unsweetened (B) yogurt intake across 5 weeks of exposure. Yogurt intake was significantly lower during the 1st week than for all other weeks. Error bars represent standard error.

supplements were provided at approximately 11:00 a.m. each day. Temperature in the colony room was maintained at 21–23 °C. During testing, premeals were provided at 11:00 a.m.

Training. During training, rats received 30 g of a low-fat, plain yogurt (Dannon) daily for 14 days in addition to ad-lib lab chow and water. An exposure of 14 days was chosen because significant effects on body weight were observed after 2 weeks exposure in Experiment 1. Diets were available for approximately 23 hr per day, and yogurt and chow intake were recorded daily by weighing the cups, with chow intake adjusted for spillage. Rats were weighed daily and were randomly assigned to one of two yogurt diet conditions as described for Experiment 1. Rats in the sweet predictive group ($n = 13$) received plain, unsweetened yogurt (~0.6 kcal/g) for 7 of the 14 days and yogurt sweetened with 20% glucose (wt/wt; ~1.2 kcal/g) for 7 of the 14 days. Rats in the sweet nonpredictive group ($n = 12$) received plain, unsweetened yogurt for 7 days and yogurt sweetened with 0.3% saccharin for 7 days. The order of presentation of the sweetened and unsweetened diet was semirandomized such that no rat received the same yogurt (sweetened or unsweetened) more than 3 days in a row. At the end of training, total consumption of the sweetened and unsweetened diets for each group of rats was determined, and rats that failed to consume at least 70% of the yogurt diets were excluded from analysis, resulting in final sample sizes of 11 rats in the predictive group and 9 rats in the nonpredictive group.

Testing. Following the 14 days of daily yogurt consumption, rats were given 1 day of chow and water alone—the chow was then removed overnight. Half of the rats in each group were then offered a premeal of 5 g of a novel sweet diet, Chocolate Ensure Plus, thickened with 2% guar to approximate the viscosity of yogurt (1.4 kcal/g). The premeal was provided for 30 min; the remaining rats were given no premeal. Chow was then returned to all rats, and chow intake was measured after 1, 2, 4, and 24 hr. Rats then received 3 days of chow and water alone; the chow was then removed overnight, and the rats were tested with the premeal conditions reversed. The order of testing was counterbalanced.

Statistical analysis. Intake of yogurt diets and total caloric intake during the 14-day training period were analyzed with separate one-way ANOVAs. Body weight gain during the 14-day training period as analyzed with a one-way ANCOVA with initial body weight as the covariate. Premeal intake was analyzed with a one-way ANOVA. Chow intake following premeal was initially assessed using a four-way (Testing Order × Premeal × Training Diet × Time) ANOVA. There were no significant main effects or interactions of testing order (premeal vs. no premeal)—therefore, the data were collapsed across testing order and analyzed with a three-way ANOVA (Premeal × Training Diet × Time). Post hoc tests were done using Newman-Keuls tests where indicated, and a $p < .05$ was taken as significant for all analyses.

Results

Even after excluding rats that did not consume at least 70% of the yogurt diet offered, there were significant differences in the quantity of unsweetened and sweetened diets consumed by rats in the sweet predictive and sweet nonpredictive groups during training—main effect of yogurt type, $F(1, 18) = 13.03$, $p < .05$; Yogurt Type × Group interaction, $F(1, 18) = 5.79$, $p < .05$. Post hoc analyses revealed that rats in the sweet predictive group consumed

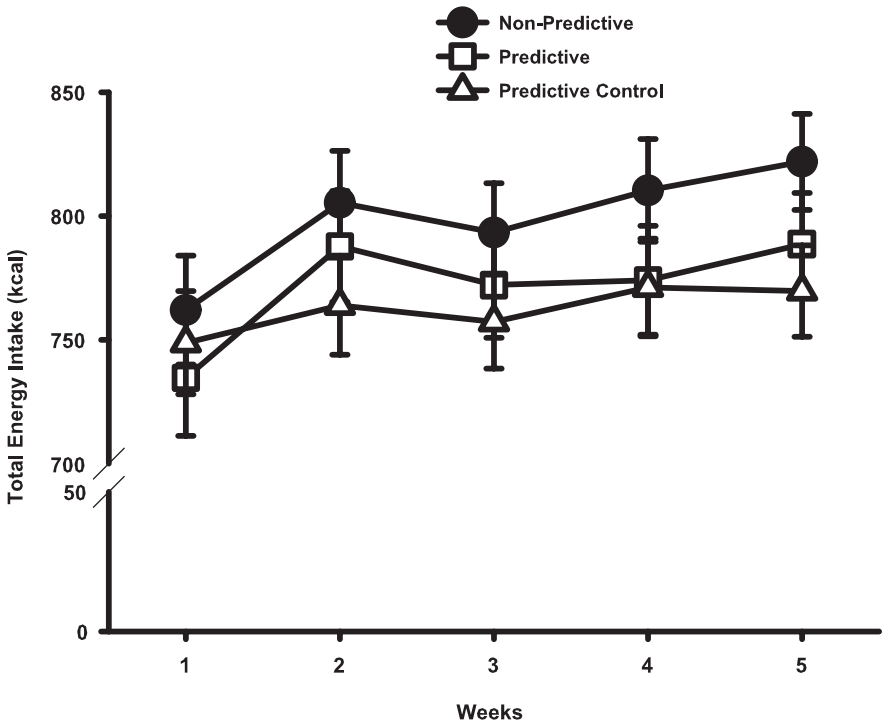

Figure 3. Total energy intake (chow plus yogurt diets) across 5 weeks of yogurt diet consumption. Energy intake was significantly lower during Week 1 than for all other weeks. Error bars represent standard error.

significantly more sweetened yogurt than unsweetened yogurt (208 ± 4 g vs. 177 ± 7 g; *M* ± *SEM*); there were no significant differences in yogurt intake between the predictive and nonpredictive groups (187 ± 4 g sweetened and 181 ± 8 g unsweetened yogurt in the nonpredictive group). Total caloric intake at the end of training (chow plus yogurt) was significantly affected by group (see Figure 5), main effect of group, $F(1, 18) = 5.99$, $p < .05$, with sweet nonpredictive rats consuming significantly more calories over the course of training than did sweet predictive rats. Body weights at the start of training did not differ across the groups

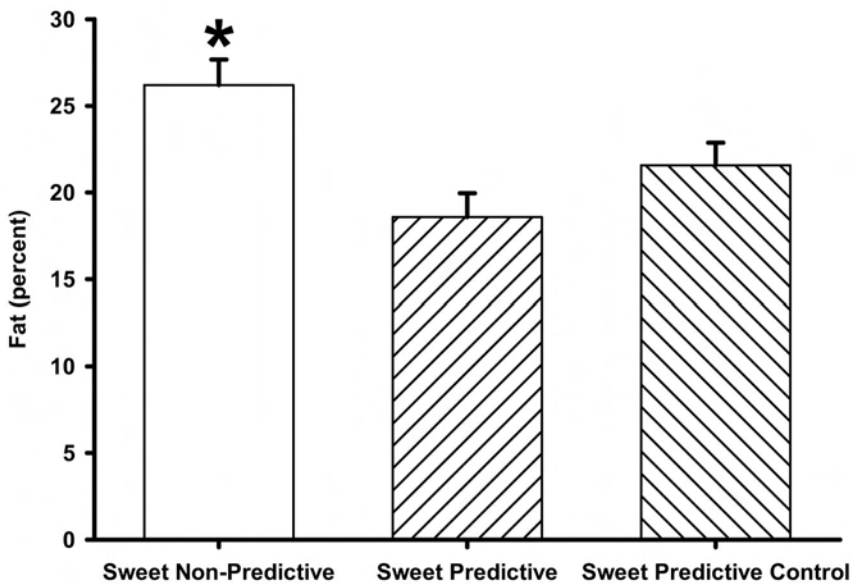

Figure 4. Adiposity as determined by dual-energy x-ray absorptiometry analysis. Error bars represent standard error. $^{*}p < .05$.

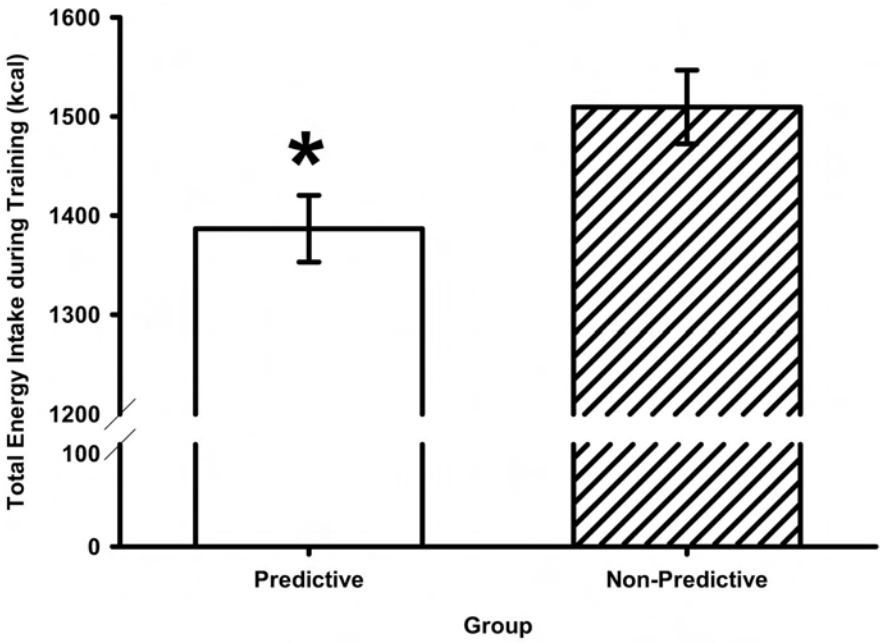

Figure 5. Total energy intake during 14 days of consumption of sweet predictive or sweet nonpredictive yogurt diets in Experiment 2. Error bars represent standard error. $^{*}p < .05$.

(330 ± 5 g vs. 325 ± 5 g, predictive vs. nonpredictive, respectively), $F(1, 18) < 1$. During training, sweet nonpredictive rats gained significantly more weight than did sweet predictive rats (see Figure 6)—main effect of group, $F(1, 17) = 7.31$, $p < .05$; no effect of initial body weight, ($F < 1$).

During testing, there were no significant differences in the quantity of premeal consumed (7.0 ± 0.2 kcal for the predictive group and 6.6 + 0.2 kcal for the nonpredictive group), $F(1, 18) = 2.7$, $p = .12$. However, chow intake following the premeal was significantly affected by training history, premeal, and time of

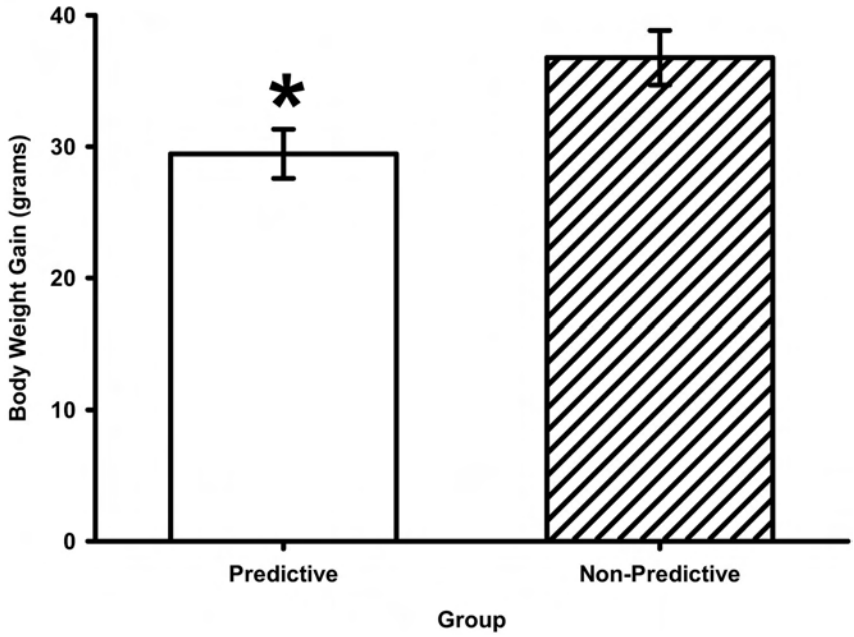

Figure 6. Body weight gain during 14 days of consumption of sweet predictive or sweet nonpredictive yogurt diets in Experiment 2. Error bars represent standard error. $^{*}p < .05$.

test—main effect of group, $F(1, 18) = 12.51$, $p < .05$; main effect of time, $F(3, 54) = 1{,}833$, $p < .05$; Premeal × Group interaction, $F(1, 18) = 6.18$, $p < .05$. Post hoc analyses revealed that rats in the sweet predictive group consumed significantly less chow on the day they consumed the premeal than they did on the day they did not consume the premeal (see Figure 7a). In contrast, there were no significant differences in chow intake in rats in the sweet nonpredictive group on the test day when the premeal was consumed or on the test day when no premeal was consumed (see Figure 7b). In other words, sweet predictive rats showed caloric compensation for novel sweet-tasting calories by decreasing subsequent chow intake, whereas sweet nonpredictive rats did not. These results confirm and extend preliminary findings we reported with rats that were exposed to calorically and noncalorically sweetened fluids (Davidson & Swithers, 2004)

Experiment 3

Ingestion of food evokes a reflexive thermogenic response (Jequier, 1983; Tappy, 1996), and this form of heat production appears to be mediated in both humans and animals by preabsorptive (e.g., orosensory) food cues. For example, in humans and in sham-feeding dogs, when food is tasted but not swallowed, the thermic response can exceed that produced by a normal meal (Diamond, Brondel, & LeBlanc, 1985; LeBlanc & Cabanac, 1989). In contrast, for both humans and dogs, when nutrients bypass the oropharyngeal cavity (e.g., via gavage or feeding tube), cephalic-phase thermogenic responses are either not observed or are much weaker than those produced by normal feeding (Diamond et al., 1985; LeBlanc, Cabanac, & Samson, 1984). If sweet tastes evoke thermic responses based, in part, on the degree to which they predict the arrival of calories in the gut, one might expect that tasting a sweet, high-calorie food would evoke a greater increase in core body temperature for rats that have been exposed to a highly reliable predictive relationship between sweet tastes and calories than it would in rats that that have not been exposed to this relationship. Experiment 3 tested this prediction.

Method

Subjects were 16 adult male Sprague–Dawley rats (Harlan) weighing 375–425 g at the time of surgery; these rats had previously been used in an unrelated study that did not involve provision of diets other than standard rat chow. Rats were housed individually in polycarbonate cages lined with aspen bedding to allow for continuous monitoring of core body temperature and gross motor activity. Laboratory chow (Lab Diets 5001) and water were available ad libitum except during testing as described below. The colony room was maintained on a 14:10-hr light–dark cycle, with lights on at 7:00 a.m. Dietary supplements were provided at approximately 12:40 p.m. each day. Temperature in the colony room was maintained at 21–23 °C.

Surgery. For remote monitoring of core body temperature and activity, intraperitoneal implantation of transmitters for a battery-free radiotelemetry system (HR E-Mitters; PDT-4000 HR; Mini Mitter, Sun River, OR) was performed after the rats were anaesthetized with xylazine/ketamine (10 mg/kg/90 mg/kg ip) following procedures similar to those described elsewhere (Harkin, O'Donnell, & Kelly, 2002). After the rat was flaccid and unresponsive to foot-pad pinch, the ventral surface of the abdomen was shaved. The shaved area was swabbed with Betadine, and the rat was placed on a warm, sterile

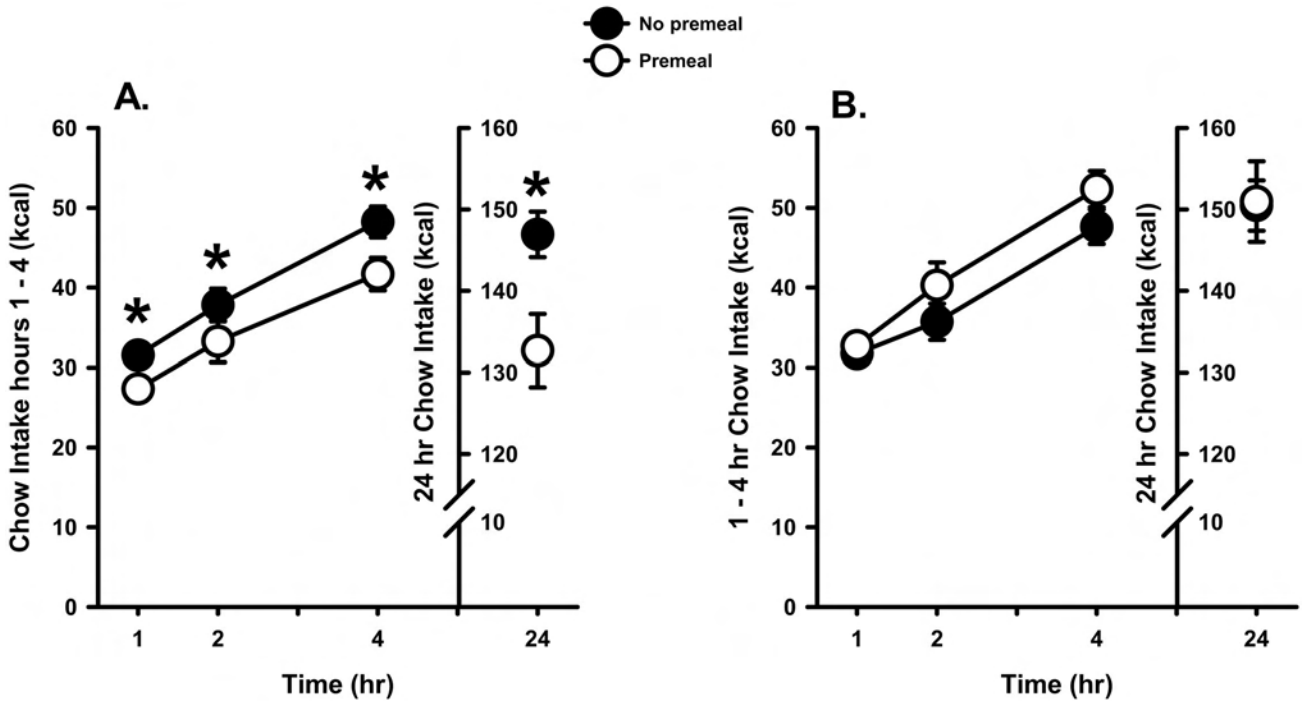

Figure 7. Chow intake following a novel sweet premeal or no premeal in sweet predictive (A) or sweet nonpredictive (B) groups. Error bars represent standard error. $^{*}p < .05$.

surgical surface. The abdomen was opened by making a 2-cm incision below the diaphragm along the white line of fascia where the abdominal muscles join on the midline. The E-mitter was inserted into the abdominal cavity and was positioned dorsal to the digestive organs and in front of the caudal arteries and tethered to the muscle wall with a single stay suture. The abdominal cavity was then massaged gently to allow the internal organs to settle in place before nondissolvable suture was used to close the muscle layer of the abdominal incision. The skin layer of the abdominal opening was then closed using dissolvable suture in combination with stainless steel wound clips. Rats were allowed to recover for 2 weeks prior to the start of yogurt exposure.

Training and testing. At the start of training exposures, rats were matched on baseline core body temperature and assigned to sweet predictive or sweet nonpredictive groups as in Experiment 2. Training was identical to Experiment 2. After training, all the rats were tested following overnight food deprivation with a premeal of 5-g thickened Chocolate Ensure Plus. During training, one rat in the sweet nonpredictive group failed to consume at least 70% of the diet, and we removed its data from analysis. In addition, a transmitter in one of the sweet nonpredictive rats failed during training. Final sample sizes were 8 rats in the sweet predictive group and 6 rats in the sweet nonpredictive group. During training and testing, a receiver placed under each cage monitored transmitter output of the implanted emitters. Both temperature and activity data were collected at 1-min intervals using the VitalView data-acquisition system (Mini Mitter; see Harkin et al., 2002). Temperature and activity readings were averaged over 5-min time intervals 30 min prior to and during presentations of taste stimuli (premeal) and during short-term (0-4 hr) food-intake testing. To minimize disturbances to the rats during collection of body temperature and activity data, we did not measure food intake.

Statistical analysis. Temperature and activity data from the 2 min prior to presentation of the yogurt diets during training or prior to the premeal during testing were averaged to determine baseline body temperatures and activity. Departures from baseline were analyzed every 5 min for 60 min following presentation of the yogurt diets during training and every 5 min for 30 min following presentation of the premeal during testing. Effects of consumption of sweetened and plain yogurt on core body temperature during training were examined using three-way, ANOVAs (Yogurt Type [sweetened vs. unsweetened] × Group × Time (5-min period after presentation of the premeal). Effects of predictive and nonpredictive training history on core body temperature and activity during testing were examined with a separate two-way, repeated measures ANOVA, with training group treated as a between-subjects variable and with time after premeal presentation treated as a within-subjects variable. Post hoc analyses were done using Newman-Keuls tests where indicated, and $p < .05$ was taken as significant for all tests.

Results

During training, departures from core body temperature during the first 60 min following presentation of the diet were affected by time after presentation of yogurt, the type of yogurt presented, and the training group (see Figure 8)—main effect of time, $F(11, 132) = 82.5$, $p < .05$; Time × Group interaction, $F(11, 132) = 2.39$, $p < .05$; Yogurt Type (sweet vs. plain) × Time interaction,

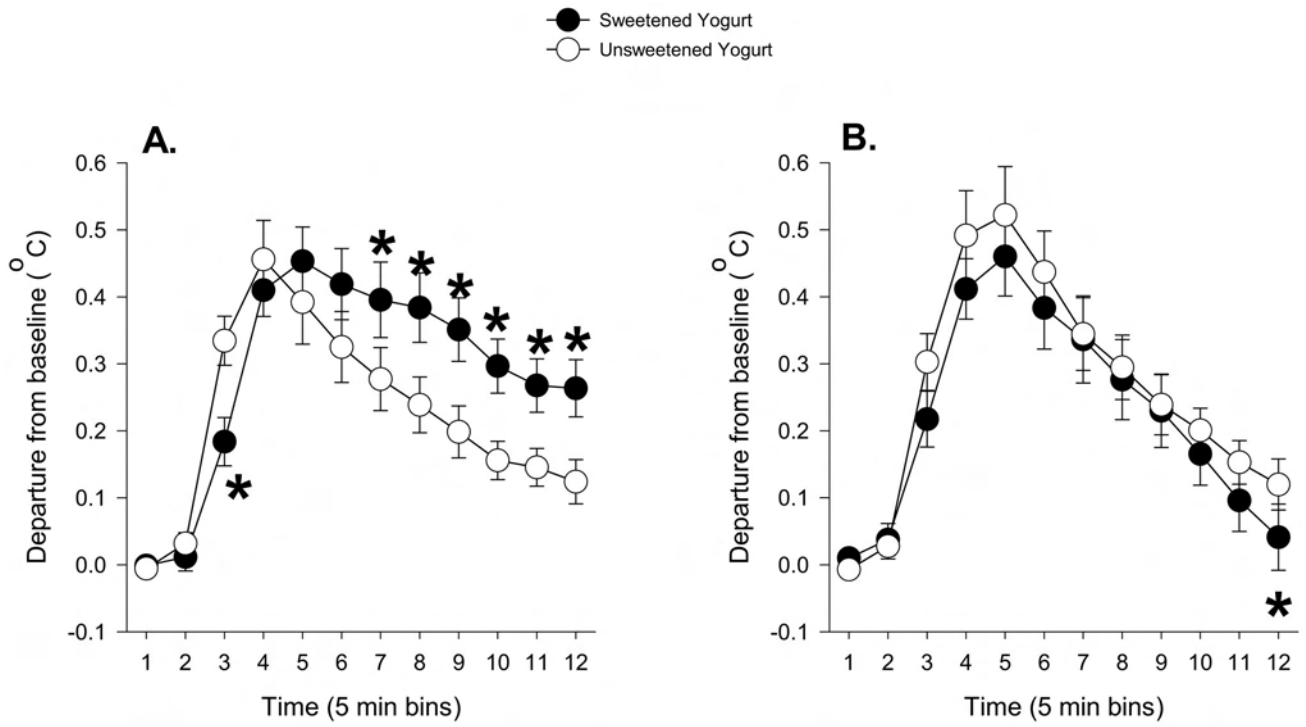

Figure 8. Changes in core body temperature over the first 60 min following yogurt presentation during sweet predictive (A) or sweet nonpredictive (B) training. Error bars represent standard error. $^{*}p < .05$.

$F(11, 132) = 5.83$, $p < .05$; Yogurt Type × Time × Group interaction, $F(11, 132) = 4.29$, $p < .05$. Post hoc analyses revealed that during training in the sweet predictive group, departures from baseline body temperature were significantly higher when the sweetened yogurt was available than they were when the unsweetened yogurt was available for the final 30 min of measurement. In the sweet nonpredictive group, core body temperature was not higher following consumption of the sweetened yogurt than after consumption of the unsweetened yogurt at any time; in fact, the only significant difference was a small increase in body temperature during the final 5-min bin when sweetened yogurt was consumed as compared with body temperature when unsweetened yogurt was consumed.

During testing, when the same novel premeal was provided to both groups, core body temperature changes were significantly affected by the training group and time (see Figure 9)—main effect of group, $F(1, 12) = 5.29$, $p < .05$; main effect of time, $F(5, 60) = 153.11$, $p < .05$, Time × Group Interaction, $F(5, 60) = 4.18$, $p < .05$. Sweet predictive rats showed significantly greater increases in core body temperature than did nonpredictive rats. Activity levels during testing were significantly affected by the time since presentation of the diet (see Figure 10)—main effect of time, $F(5, 60) = 3.15$, $p < .05$. There was a trend for activity level to vary by training group, but neither the main effect of group nor the Group × Time interaction reached statistical significance (see Figure 10)—main effect of group, $F(1, 12) = 3.79$, $p = .075$; Time × Group Interaction, $F(5, 60) = 1.62$, $p = .17$. Although the differences between the groups approached significance, the activity levels of both groups were quite low and did not vary directly across time with core body temperature.

General Discussion

A number of researchers have suggested that Pavlovian conditioning may contribute to the control of energy intake (e.g., Woods, 1991; Woods & Ramsey, 2000) and other types of regulatory processes (e.g., Dworkin & Dworkin, 1995; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). The present research extends these earlier ideas by investigating the possibility that experiences that weaken Pavlovian conditioning also make regulatory mechanisms involved with the control of energy intake and body weight less effective. An idea fundamental to contemporary theories of Pavlovian conditioning is that learning about cues and outcomes is promoted to the extent that these events are embedded in predictive (i.e., contingent) relationships. The strength of a predictive relationship is an increasing function of the number of occasions in which a cue and its outcome occur together and are omitted together. Conversely, this predictive relationship is weakened by increasing the number of occasions in which either the cue or the outcome occur alone (e.g., Escobar & Miller, 2004; Rescorla, 1969).

From a Pavlovian conditioning perspective, sweet tastes can be conceptualized as orosensory cues (i.e., conditioned stimuli) that are normally very valid predictors of the occurrence of postoral caloric or nutritive outcomes (i.e., unconditioned stimuli). The strength of this predictive relationship determines the ability of orosensory cues to evoke a variety of conditioned cephalic-phase reflexes (e.g., hormonal, metabolic, thermogenic) that have been hypothesized to contribute to the tight physiological control of energy regulation. The present experiments assessed the effects of varying the strength of this predictive relationship on the ability of rats to regulate their food intake and body weight. The strength of

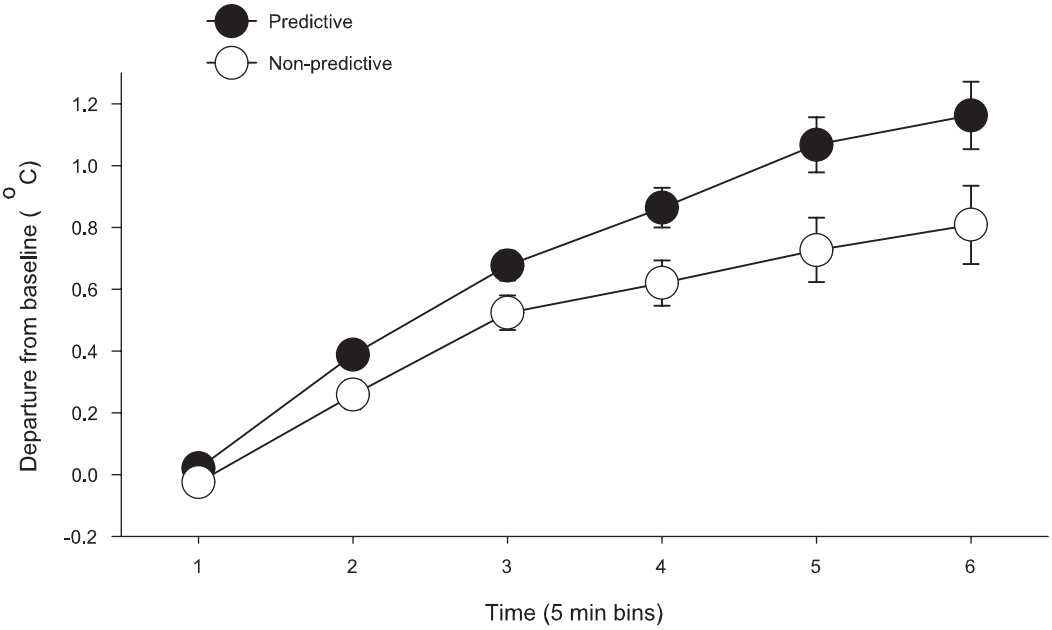

Figure 9. Changes in core body temperature during the first 30 min following presentation of the same novel, sweet premeal to sweet predictive and sweet nonpredictive rats. Sweet predictive rats showed significantly greater increases in core body temperature than did sweet nonpredictive rats.

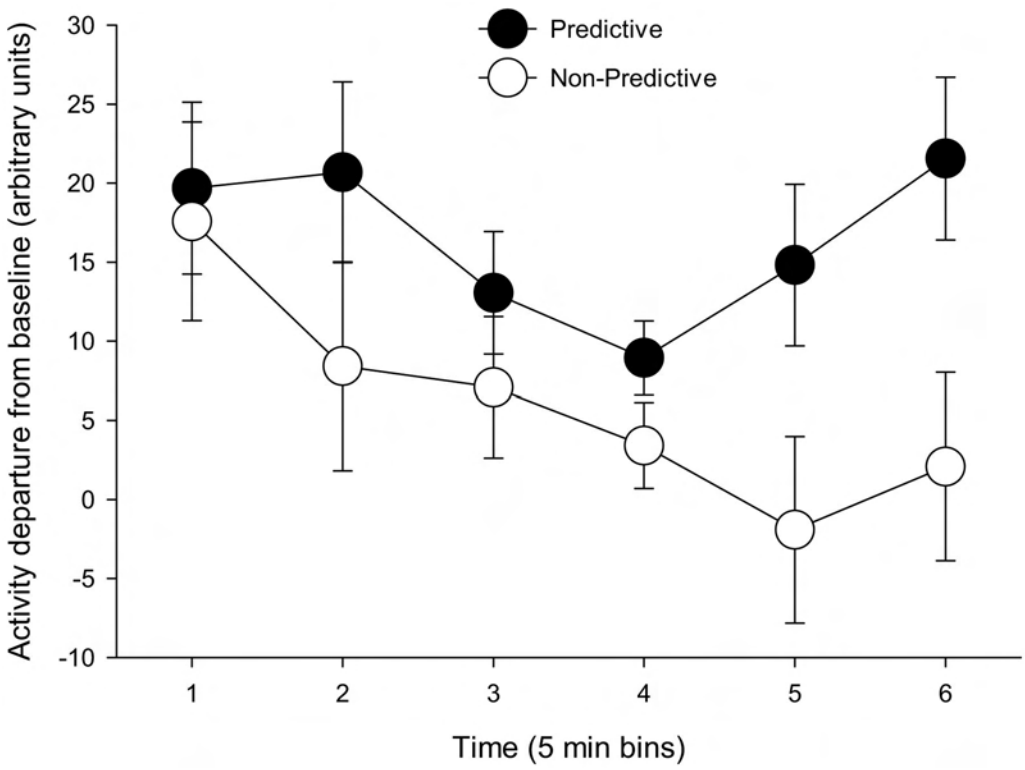

Figure 10. Changes in activity during the first 30 min following presentation of the same novel, sweet premeal to sweet predictive and sweet nonpredictive rats. There were no significant differences in activity across the two training groups.

the sweet-taste/caloric-outcome contingency was manipulated by exposing rats to plain yogurt in which sweet taste was either consistently paired with an increment in calories or not.

The results demonstrated that, in comparison with rats for which sweet taste did predict an increase in calories, rats that received the nonpredictive sweet-taste/calorie relationship exhibited greater caloric intake, greater body weight gain, increased body adiposity, an impaired ability to compensate for the calories contained in a novel sweet food by eating less during a subsequent test meal, and a smaller increment in core body temperature following consumption of a novel, sweetened high-calorie food. In our research, the volume of yogurt (unsweetened and calorically and noncalorically sweetened) eaten and the conditions of access to the yogurt were equated for rats exposed to the respective predictive and nonpredictive relations. Thus, differences in preference for or palatability of the calorically and noncalorically sweetened yogurts cannot explain the observed differences in our dependent measures (body weight gain, adiposity, food intake, core body temperature). In addition, because the amount consumed of each type of yogurt was equated, more calories would have been derived from the glucose sweetened-yogurt consumed by rats in the predictive group than from the saccharin-sweetened yogurt consumed by rats in the nonpredictive groups. However, rather than exhibiting less weight gain and adiposity, the rats in the nonpredictive groups that ate the lower calorie, saccharin-sweetened yogurt gained more weight and body fat than did rats in the predictive groups that ate the higher calorie yogurt sweetened with glucose. The finding that consuming a lower calorie food yielded more weight gain and body adiposity than did consuming an equal amount of a higher calorie version of the same food appears to pose difficulties for views that emphasize the homeostatic aspects of energy regulation (Cummings & Overduin, 2007; Murphy & Bloom, 2006; Seeley & York, 2005).

The results of Experiments 2 and 3 provide one basis for interpreting this outcome. In Experiment 2, rats trained with nonpredictive and predictive sweet-taste/calorie relations were tested for caloric compensation after both groups consumed a common novel, sweet tasting, relatively high-calorie premeal (Chocolate Ensure Plus). In comparison with rats trained with the predictive relationship, rats trained with the nonpredictive relationship were less able to compensate for calories contained in the premeal by reducing their intake of lab chow in the subsequent test meal.

Experiment 3 extended the results of Experiment 2 by showing that eating the Chocolate Ensure premeal also produced a smaller increment in core body temperature for rats trained with the nonpredictive sweet-taste/calorie relationship than was seen in rats trained with the predictive sweet-taste/calorie relationship. If the increments in core body temperature that we observed in Experiment 3 index preabsorptive energy utilization, then consuming the Chocolate Ensure premeal was associated with less energy utilization by rats given prior nonpredictive sweet-taste/calorie training. It may be that caloric compensation during a meal depends not only on the amount of energy consumed but also on the amount of energy utilized prior to the meal. If this is the case, a blunted

thermic response to the premeal might have contributed to impaired caloric compensation.

The mechanisms that link experience with a nonpredictive sweet-taste/calorie relationship to a blunting of the thermic response to food need to be specified. Viewed from the present Pavlovian perspective, preabsorptive increases in core body temperature could index the evocation of a conditioned cephalic-phase response that anticipates and promotes the increased utilization of calories that is normally produced by the nutrient absorption. We assume that the elicitation of these responses depends, at least in part, on the ability of sweet taste to predict these postabsorptive caloric or nutritive consequences. Accordingly, manipulations that disrupt or degrade this predictive relationship would also interfere with the ability of sweet-tasted cues to evoke conditioned thermic and other cephalic-phase responses. This interference could lead to reduced energy utilization and, ultimately, to increased weight gain.

There is little doubt that sweet tastes can evoke responses in addition to the thermic reflexes that we measured in Experiment 3 (Mattes, 1997; Teff, 2000). For example, ingestion of sweet food is also accompanied by preabsorptive or cephalic-phase insulin release (CPIR). It is interesting that both reduced CPIR and cephalic-phase thermic responses have been linked to energy dysregulation in humans. Teff, Mattes, Engelman, and Mattern (1993) reported that the magnitude of the CPIR is diminished in obese humans when expressed as a proportion of basal insulin levels, whereas Hashkes, Gartside, and Blondheim (1997) reported that obese humans exhibited a weaker cephalic-phase thermic response than did nonobese controls following consumption of a palatable (Ensure) test meal. It may be that the magnitude of the thermic response to food is mediated by insulin release (Laville et al., 1993). In keeping with this possibility, Storlien and Bruce (1989) proposed that a primary failure of normal cephalic-phase responses eventually leads to increased postprandial hyperglycemia and decreased thermogenesis. Persistent hyperglycemia leads to insulin resistance (as insulin does not effectively dispose of glucose), and diminished postprandial thermogenesis promotes weight gain based on reduced energy expenditure (Watanabe et al., 2006). This analysis suggests a potential mechanism whereby degrading the predictive relationship between sweet taste and calories could lead to excess food intake and body-weight gain. Previous findings showed that the thermic effect of food was reduced when meal taking occurred on an irregular basis as compared with that seen when meal taking occurred on a regular basis (Farshchi, Taylor, & Macdonald, 2004). In keeping with the present analysis, it may be that temporal cues that are associated with caloric intake are also degraded in their ability to promote the evocation of thermic reflexes when meal times are difficult to predict.

In addition to sweet taste, cephalic-phase responses could be evoked by other types of orosensory cues that are also valid signals of postabsorptive caloric outcomes. For example, the caloric content of a food is typically directly correlated with oiliness or fatty taste. The viscosity of food may also provide a similar signal in that, holding other sensory properties constant, energy-rich foods are more likely to be thick and creamy than thin and watery. Accordingly, from the current theoretical perspective, manipulations that reduce the predictive validity of oily, fatty tastes or of viscosity with respect to caloric outcomes should produce changes in energy regulation similar to those reported with sweet tastes in the present studies.

Recent research in our laboratories supports these predictions. For example, Swithers, Doerflinger, and Davidson (2006) gave rats potato chips as a dietary supplement along with ad-libitum rat chow. For some rats, the potato chips were a consistent source of high fat and high calories (regular potato chips). For other rats, the chips provided high fat and high calories on some occasions (regular potato chips) and provided no digestible fat and fewer calories at other times (reduced calorie chips manufactured with a fat substitute). Thus, the fatty taste of the potato chips was a stronger predictor of high calories for the former group than it was for the latter group. Adult rats that were exposed to the nonpredictive relationship between potato chips and calories exhibited increased intake of a novel high-fat, high calorie corn chip and an impaired ability to compensate for calories contained in a novel, high-fat premeal by reducing intake of lab chow in a subsequent test meal. Considering viscosity cues, Davidson and Swithers, (2005) showed that when adult rats were offered dietary supplements matched on caloric density and both macronutrient and micronutrient composition but differing in viscosity, consumption of a lower viscosity (milklike) supplement was associated with reduced caloric compensation on short-term intake tests and increased long-term body weight gain as compared with rats that consumed a higher viscosity (puddinglike) dietary supplement. In addition, juvenile rats given 9 weeks access to low-viscosity versions of supplemental diets had greater adiposity both immediately following the exposure and up to 3 months after return to chow alone than did rats given 9 weeks access to identical diets given in high-viscosity form (Swithers & Davidson, 2005a).

In our research, increased body weight gain, energy intake, adiposity, decreases in core body temperature, and blunted caloric compensation for sweet-tasting calories were observed in rats that experienced a nonpredictive relationship between sweet tastes and calories. One interpretation of these results is that they are directly related to each other; in other words, increased body weight gain and adiposity result directly from altered physiological changes that reduce preprandial cephalic-phase energy expenditure as indexed by blunted thermic responses to food. However, an alternative possibility is that these outcomes, while linked, are mediated through some other common process. For example, although levels of activity during the premeal test were low, there was a trend for rats in the predictive group to show more activity than did rats in the nonpredictive group. Thus, differences in core body temperature could be related to differences in activity. Whether the activity drives the increased body temperature or increased body temperature drives activity remains to be determined. In addition, it is possible that the changes in temperature do not reflect preabsorptive (e.g., cephalic) responses but are instead related to differences in patterns of intake of the premeal or gastrointestinal handling of the ingested premeal. Each of these possibilities warrants investigation. However, independent of the particular mechanism that produces these changes, the data clearly indicate that consuming a food sweetened with no-calorie saccharin can lead to greater body-weight gain and adiposity than would consuming the same food sweetened with high-calorie sugar.

Such an outcome may seem counterintuitive, if not an anathema, to human clinical researchers and health care practitioners who have long recommended the use of low-and no-calorie sweeteners as a means of weight control (Duffy & Sigman-Grant, 2004). According to the Calorie Control Council (www.caloriecontrol.

org), the number of Americans that consume products containing sugar-free sweeteners grew from fewer than 70 million in 1987 to about 160 million in 2000. These substances are now commonly found in a wide variety of low-calorie, health conscious foods, with increased consumption in the form of diet soft drinks being especially dramatic. Over the same period, the incidence of obesity in the United States increased from about 15% to 30% and continues to increase in the present day (Flegal, 2005). This alarming trend toward weight gain is apparent, in varying degrees, across all age groups, ethnic groups, and social strata in all regions of the country (Flegal, Carroll, Ogden, & Johnson, 2002). Of special concern, findings that overweight or obese children tend to become overweight or obese adults suggests that, unless effective interventions can be developed, the current obesity epidemic is likely to continue (Freedman, Khan, Serdula, Srinivasan, & Berenson, 2001; Freedman et al., 2004).

A common interpretation of the direct correlation between increased use of noncaloric sweeteners and increased incidence of obesity is that people have turned to calorie-free sweeteners as a means of reducing energy intake and controlling body weight. However, our findings and theoretical framework are in closer agreement with the possibility that increased intake of no-calorie sugar substitutes could promote increased intake and body weight gain, which is consistent with recent data from prospective human clinical studies that have documented increased risk for obesity and metabolic syndrome in individuals consuming beverages sweetened with high-intensity sweeteners (e.g., Dhingra et al., 2007; Liebman et al., 2006). Although much research has been directed at selecting among these alternatives, a consensus opinion about the effectiveness of consuming artificially sweetened substances as means of weight control has yet to emerge (see Bellisle & Drewnowski, 2007, and Blundell & Green, 1996, for reviews).

Our data were obtained under the highly controlled experimental conditions that research with a rat model can afford. Furthermore, guided by our Pavlovian framework, we studied the effects of consuming saccharin on intake and body weight regulation under conditions that had not been investigated previously with either humans or animals. Specifically, we assessed the effects of varying the predictive relationship between sweet taste and calories on the ability of rats to regulate their intake of lab chow and to utilize the calories contained in a novel, sweet, high-calorie food. The increases in food intake and body weight we obtained with this approach may be considered to be modest when compared with that seen in animals that have undergone hypothalamic (e.g., lesions, stimulation) or genetic manipulations (King, 2006; Zhang et al., 1994). However, it is also the case that very few humans show dramatic increases in food intake and body weight similar to that seen in hypothalamic-lesioned or genetically altered rodents. Thus, the gradual increases in body weight shown by our rats makes them more similar to the current U.S. human population, which has exhibited about a 10% increase in body weight over the past 10 years (Lewis et al., 2000).

The generality of findings obtained with rats in the laboratory to humans in their much more complex food environments can and should be questioned. However, it is conceivable that just as exposure to nonpredictive sweet taste-calorie relationships in the laboratory appears to promote increased body weight and body adiposity in rats, the widespread use of noncaloric sweeteners in the food environment of humans may have similar effects on the predictive validity of sweet tastes and ultimately on the normal ability of humans to control their intake and body weight.

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