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Effect of opioid antagonism on conditioned place preferences to snack foods

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Abstract

Previous research has shown that food-deprived rats acquire conditioned place preferences (CPPs) to sweet liquids that are largely attenuated by the opioid antagonist naltrexone (NAL). This study determined if ad libitum Chow-fed rats can learn CPPs when given relatively brief exposures to different solid snack foods (SFs)—one high in sugar (Froot Loops cereal: FL®) vs. one high in fat (Cheetos®: C). Two groups of 16 male rats were trained during 20-min sessions to eat either FL or C in one side of a three-chambered CPP apparatus vs. Chow in the opposite side on alternating days for 20 days. Rats ate considerably more SFs of both types than Chow during the conditioning sessions (SFs: about 23 kcal versus Chow: about 7 kcal). Ten-minute tests for CPPs in the absence of SFs showed that the time spent on SF-conditioned sides increased significantly compared to pre-conditioning tests. Analyses of variance for re-tested CCPs after 0.1, 1.0, 2.5, and 5.0 mg/kg NAL showed dose-dependent suppressions of CPPs to both SFs. These data show that consuming sweet or fatty SFs can become reliably associated with environmental cues in the non-deprived state. The endogenous opioid system, which mediates hedonic aspects of palatable food intake, appears to mediate these learned associations.

Keywords: Conditioned place preference; Snack foods; Palatability; Learning; Opioid; Naltrexone; Rat

1. Introduction

Foods are natural reinforcers of both appetitive and consummatory behaviors that apparently have evolved to insure survival of the species that eat them. However, some foods, because of their taste, texture and/or palatability, are more rewarding than others. For that reason, their initial consumption increases the probability they will be selected over other foods in the future. One category of such preferred foods in humans are "snack foods". While there has been some debate about the exact definition of the term "snack" (Chamontin et al., 2003), we refer to it here as commercially prepared foods that are not main staples of normal diets and are typically of high caloric value. Intake of snack foods has increased substantially over the past decade (Zizza et al., 2001; Nielsen et al., 2002) and has been suggested to be one contributing factor to the increased prevalence of obesity (Jacobson and Brownell, 2000; McCrory et al., 2002). Recent work in humans (see Volkow and Wise, 2005) confirms past animal work (e.g., Hoebel, 1985; Wise, 1989) showing that the same brain regions and neurochemical processes that mediate reward associated with illicit drug use can also mediate the rewarding properties of food. The brain's opioid system is one of those neural substrates (Kelley and Berridge, 2002). This study aimed to explore the rewarding properties of brief periodic snack food (SF) intake in rats through the use of the conditioned place preference (CPP) paradigm, as well as the potential role of the opioid system in mediating this process.

The experimental animal literature shows a rich history of using the CPP paradigm to understand how various drugs influence learning, reward and brain neurochemical processes (e.g., Bardo, 1998; Bardo and Bevins, 2000; Wise, 1989). CPPs have also been produced in response to food reward, primarily by using sucrose in aqueous solutions, as an additive to rodent chow in mash form, or in commercially formulated sucrose pellets (Agmo et al., 1995; Delamater et al., 2000; Guyon et al., 1993; Perks and Clifton, 1997). The incentive to learn such CPPs has, for the most part, been motivated by restricting animals' food or water intake. One problem with this approach

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is that hunger or thirst may increase the hedonic and/or incentive value of these substances, contributing to motivational states that are not necessarily parallel to those seen in humans, who often consume snack foods in the absence of physiological hunger or thirst because they "taste good".

Based on these considerations, we sought to determine if non-deprived rats provided periodic access to a solid high-calorie sucrose-based food sometimes used as a snack by humans (Froot Loops® cereal; FL) could generate a CPP. In addition, since solid high-calorie fat-based snack foods have, to the best of our knowledge, not been studied in the same fashion, we also sought to determine if Cheetos® (C) would generate CPPs in non-deprived rats. Finally, since CPPs were, in fact, demonstrated to both types of SF, we determined if such learning could be reversed by the opioid antagonist, naltrexone (NAL). The unique aspects of these studies over those previously reported were: (a) rats were not food or water deprived in order to condition a CPP, and (b) different forms of food reward (sweet vs. fatty) were used under the same experimental conditions. This seemed important to examine in order to determine the relative strength of CPPs to foods of different macronutrient types, as well as to allow a comparison of the effect of opioid receptor blockade in mediating the CPPs observed.

2. Method

2.1. Animals

Thirty-two experimentally naïve adult male Sprague-Dawley rats (8 weeks old, Harlan, Indianapolis, IN) were housed in single wire-mesh hanging cages within a temperature-controlled colony room illuminated 09:00–21:00 h each day. Animals were given free access to standard Purina Rodent Chow (#5001) and water at all times in their home cages. All experimental sessions occurred between 13:00 and 17:00 h. Rats were habituated to home cage housing conditions, standard laboratory rodent diet, lighting cycle and human handling for 10 days prior to initiating experimental procedures. All procedures were approved by the Wayne State University Animal Investigation Committee as complying with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Apparatus

Four rectangular three-chambered CPP apparatuses were used (Med Associates, Georgia, VT). The two end chambers were identical in size (27.5 cm long × 20.6 cm wide × 21.5 cm tall). The middle chamber was half the horizontal size (11.9 cm long × 20.6 cm wide × 21.5 cm tall) of the two end chambers. Each compartment was separated by a Plexiglas barrier that could be raised or lowered manually. The walls of one end chamber were black, with stainless steel rod flooring (rods arranged 1 cm apart); the other was white, with 1.3 cm square wire mesh flooring. During conditioning with SF, a smaller (0.6 cm × 0.6 cm) wire mesh sub-floor was inserted into each assigned chamber to prevent substantial food spillage. An outside source of light (25 W) was placed 56.5 in. above the chambers in between each set of two apparatuses to serve as room lighting as well as an external environmental cue. Data were electronically recorded by photo beam breaks within each chamber and collected by a computer using Med PC software. Data collected included: activity counts (any beam break within a given chamber), number of chamber entrances (multiple beams broken as animals entered each chamber), explorations (single beam breaks in an adjacent chamber without entry into that chamber), and zone time in each chamber.

2.3. Procedure

Our experimental design was based on the previous work of Delamater et al. (2000) who demonstrated that CPPs learned by food-deprived rats to sucrose solutions could be blocked by NAL. The procedure consisted of 3 phases: pretesting, conditioning, and the CPP test. The effect of opioid antagonism on SF-induced CPPs consisted of injecting various systemic doses of NAL separated by two 2-day reconditioning blocks.

2.3.1. Pretest of initial chamber preference

Animals were pretested on the first day of the experiment. They were placed in the middle chamber of the 3-chamber apparatus with the doors open, then given 10 min access to all chambers of the apparatus without food available while data was recorded to determine baseline chamber preferences. Based on these preferences and animals' bodyweights, two equivalent groups of 16 rats were formed.

2.3.2. Conditioning phase

Over a 20-day period, rats were placed individually on one side of an apparatus with food for a 20-min session. Sixteen of the 32 rats received FL (3.75 kcal/g; 89.6% carbohydrate, 7.2% fat, 3.2% protein) in the non-preferred side, determined from initial preference testing; the other 16 received C (5.64 kcal/g; 37.5% carbohydrate, 56.3% fat, 5.0% protein) in the same fashion. Half of the animals in each group received their designated SF during each conditioning session. The rest of the animals received their standard rodent Chow on the side opposite to where they were conditioned to receive their SF. On alternate days, Chow was replaced by the SF and vise versa. SF and Chow intakes were recorded for each session. During the last four sessions, rats received subcutaneous (SC) saline (0.9%; 1 ml/kg) injections 15 min before each training session to acclimate them to this procedure.

2.3.3. Testing phase

After conditioning, CPP testing was conducted using the same procedure as in the *pretest* phase. Rats were given 1 ml/kg saline SC 15 min prior to testing, then placed in the apparatus without food and given 10 min access to all 3 chambers while data were collected.

2.3.4. Effect of opioid antagonism on place preference

A second sequence of preference testing was conducted. After 4 additional reconditioning sessions (alternating days of

SF vs. Chow as during the *Conditioning* phase), animals were retested as they were in their initial preference tests, except they were injected SC 15 min before hand with the non-specific opioid antagonist NAL (Sigma-Aldrich, St. Louis, MO) at doses of 1.0, 0.1, 2.5, and 5.0 mg/kg. Each dose tested was separated by 4 reconditioning sessions. A second preference test with saline only was conducted between the 2.5 and 5.0 mg/kg doses to reassess the existence of CPPs in the absence of NAL.

2.3.5. Statistical analysis

Intake data during conditioning and reconditioning trials were recorded in g and converted to kcal. Measures of CPP acquisition and CPP-related behaviors examined were: zone time(s), activity counts, entrance counts, and explorations. A CPP was defined as having occurred if groups spent significantly more time in the SF-trained chamber than in the Chow-trained chamber compared to the day they were first exposed to all chambers in the absence of food. Zone time was analyzed in two ways: (a) time spent in the SF-trained chamber divided by time spent in both SF-trained plus Chow-trained chambers, and (b) a preference score, tabulated by subtracting the time spent in the Chow-trained chamber from the time spent in the SF-trained chamber (see Torrella et al., 2004, for the rationale for this measure). On CPP test days, rats were placed in the smaller middle gray zone that separated the two conditioning chambers. Previous studies with 3-chamber CPP systems (Bechara and van der Kooy, 1992; Bechara et al., 1992) have shown that the amount of time spent in gray zones is small and similar for different groups of rats. Since that was also the case in this study, CPP scores presented did not attempt to interpret the meaning of times spent in these neutral (unconditioned) zones.

To examine the acquisition of CPPs, repeated measures analyses of variance (ANOVAs) employing within-subjects contrasts and SF type as a between-subjects factor were applied to both pretest and testing data. To examine the effect of NAL injections on the expression of CPPs, repeated measures ANOVAs with within-subjects contrasts and SF type as a between-subjects factor were used with all doses of NAL compared to initial CPP (saline) testing.

3. Results

Rats consumed considerably more SF of both types than they did Chow during the initial conditioning sessions (Fig. 1). During this conditioning, SF intake gradually increased over training sessions, plateauing at 23–26 kcal consumed for both SFs. In contrast, a minimal amount of Chow was consumed over the course of initial conditioning (6–7 kcal/session). After initial CPP testing, reconditioning sessions between NAL drug tests showed that these strong SF preferences continued ($F_{(1,30)}$ = 2.4, $p < 0.01$). In fact, comparing the last four sessions of intake during initial conditioning with the intake seen during reconditioning revealed even higher SF consumption than that seen during initial training ($F_{(1,30)} = 10.7$, $p < 0.01$).

Fig. 2 shows the percentage of time spent on the SF-trained sides before vs. after conditioning. All changes were statistically significant. Rats consuming FL showed the most pronounced change, from 44% before conditioning to 59% after conditioning.

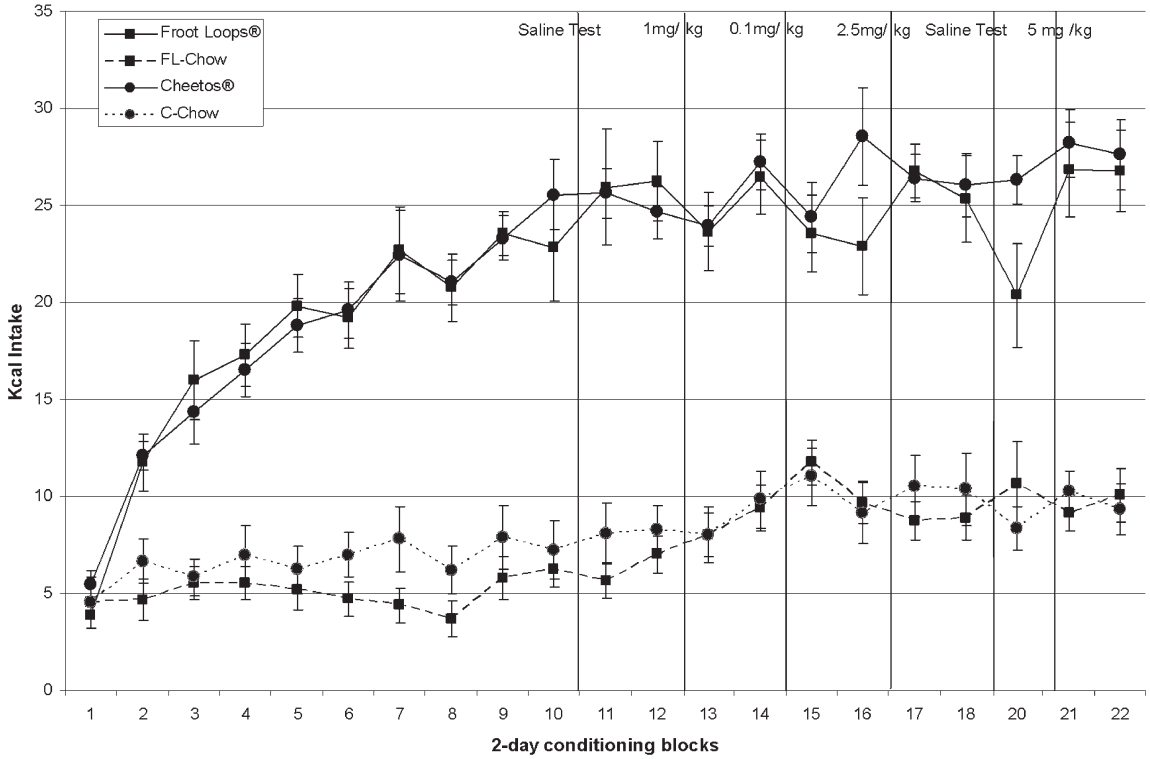

Fig. 1. Mean intake in kilocalories consumed by rats during 20-min sessions every other day. Each day represents a 2-day conditioning block (SF one day, chow the other). 1–10 is the period of initial conditioning; 11–21 are periods of reconditioning between testing sessions. CPP testing occurred at each of the vertical lines.

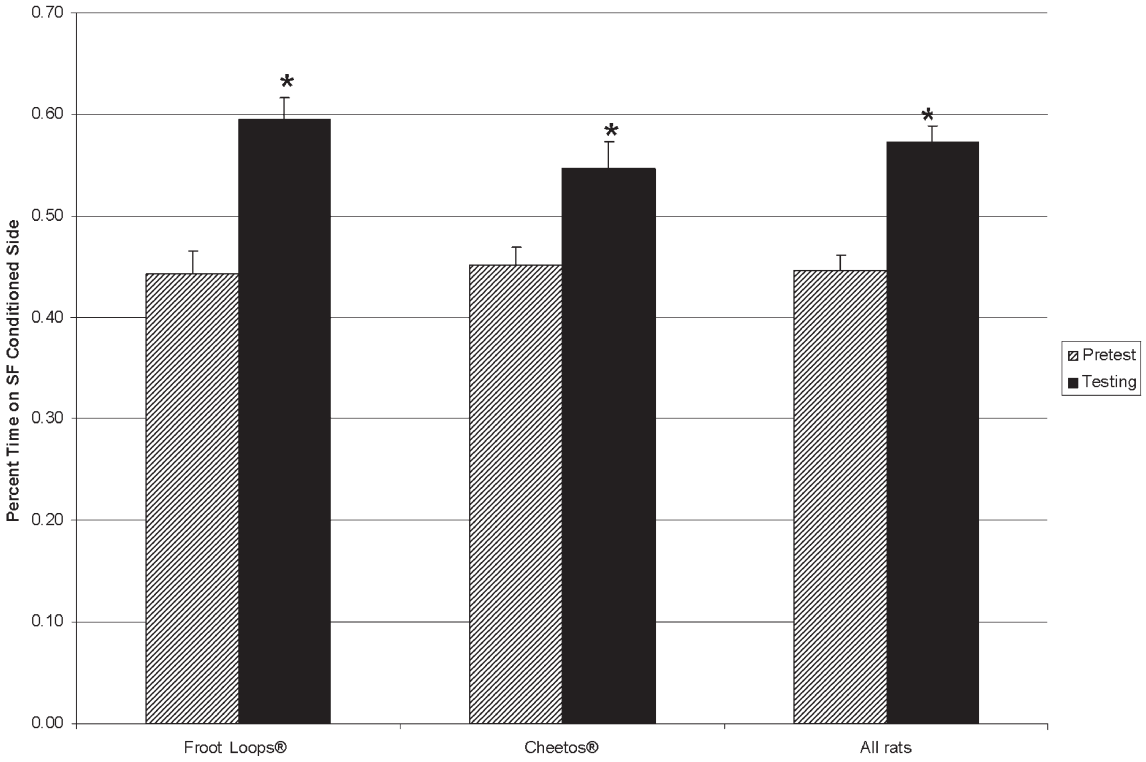

Fig. 2. Percent time in SF conditioned chamber. * indicates $p<0.001$.

Among rats consuming C, time spent on the SF-trained side increased more modestly (47% at baseline to almost 55% after conditioning). Since the ANOVA showed that the between-subjects factor of SF type was not significantly different, data were collapsed across SF conditions. After that was done, the time spent on SF-conditioned sides was shown to have increased significantly from 44.7% before conditioning to 57.2% after conditioning ($F_{(1,30)}=21.1$, $p<0.001$).

Fig. 3 shows the preference scores recorded during initial apparatus exposure vs. testing after conditioning. Rats consuming

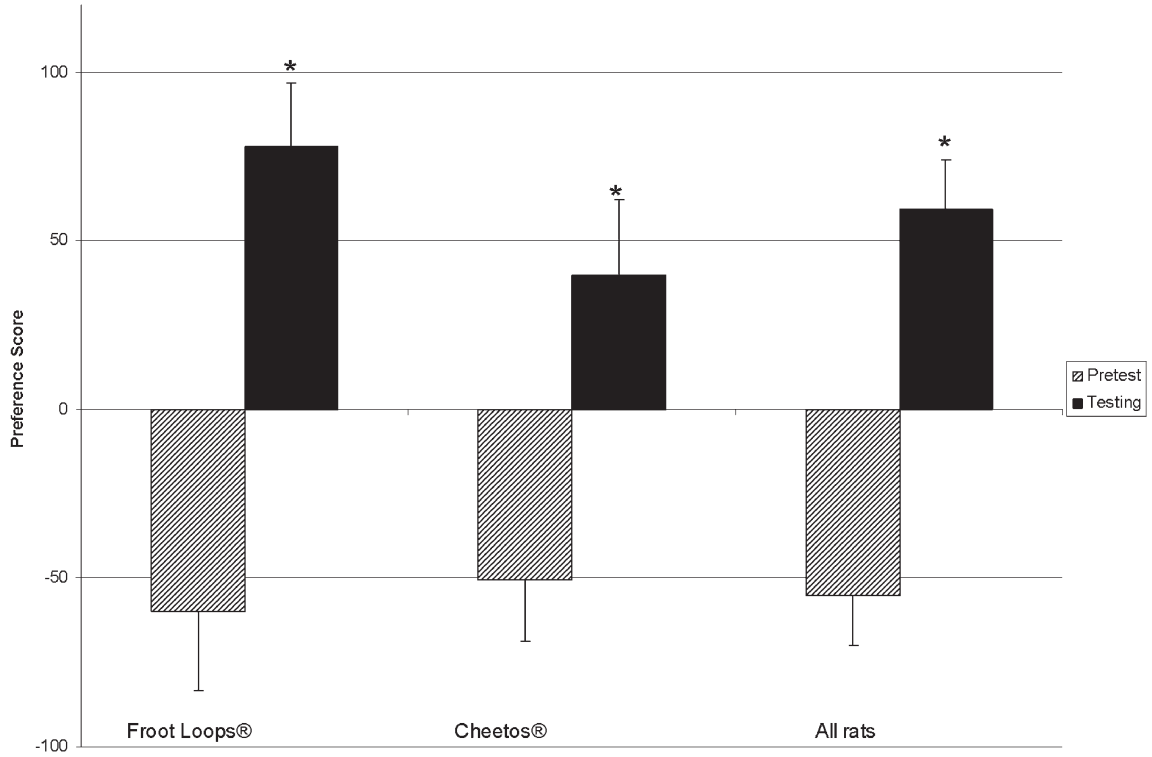

Fig. 3. CPP scores measured at baseline and after conditioning. * indicates $p<0.001$.

Table 1
CPP-related activity measures; CPP testing measures are compared with Pretest

	Entrances SF Side	Explorations SF Side	Activity SF Side	Total activity (3 chambers)
Pretest	46.6 (3.4)	33.0 (3.2)	389.3 (20.8)	981.3 (35.1)
CPP testing	55.3 (3.4)	45.8 (3.4)**	476.3 (38.0)*	993.2 (42.7)
Dose response				
CPP testing (saline)	55.3 (3.4)	45.8 (3.4)	476.3 (38.0)	993.2 (42.7)
0.1 mg/kg	43.4 (2.4)**	39.7 (2.7)	432.1 (70.0)	915.1 (65.7)
1 mg/kg	43.7 (2.4)**	41.7 (2.5)	378.1 (23.0)**	903.1 (34.0)*
2.5 mg/kg	43.5 (4.9)*	39.9 (3.2)	407.4 (57.8)	905.5 (59.0)
Saline 2	46.8 (4.5)	41.5 (3.4)	391.2 (45.5)*	917.9(50.7)
5 mg/kg	31.3 (1.8)***	32.8 (2.9)**	311.9 (79.3)	757.0 (69.9)**

All doses of NAL are compared to CPP testing. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

FL showed reliable increases in preference scores for the SF-trained side from −59.7±20.9 to 77.8±20.2. Rats consuming C showed a smaller yet reliable increase from −50.6±21.6 to 39.8±20.9. Since ANOVA showed no differences between SF type and change in preference scores, data again were collapsed across this factor. This yielded a highly reliable increase ($F_{(1,30)}=19.5$, $p<0.001$) from −55.3±14.8 to 59.4±14.7 on this measure.

Since no differences in either SF intake or CPP learning were found as a function of SF type, subsequent analyses of activity measures were performed on data collapsed across SF groupings. As shown in Table 1, entrance counts, explorations, and activity counts on the SF conditioned side all increased from baseline levels during CPP testing (Table 1). Activity counts and explorations increased significantly ($F_{(1,30)}=5.6$, $p<0.05$ and $F_{(1,30)}=1.3$, $p<0.01$, respectively), while there was a tendency ($p=0.06$) for an increase in entrance counts. However, overall activity (the sum of movement in all 3 chambers) was not significantly different after conditioning. But, as depicted in Fig. 4, activity counts in both the SF-conditioned chambers as well as in the middle (neutral) chamber were both significantly increased after CPP training, while activity in the Chow-conditioned chamber actually decreased.

Fig. 5 shows that NAL was effective in diminishing CPPs during retests of such learning. The reduction in percentage time spent on the SF-conditioned side after 0.1 mg/kg was not significant, but significant reductions in CPP scores were seen after 1.0, 2.5, and 5.0 mg/kg doses ($F_{(1,30)}=5.3$, $p<0.05$; $F_{(1,30)}=7.9$, $p<0.01$; and $F_{(1,30)}=6.6$, $p<0.05$, respectively). Since the between-subjects factor SF type was not significantly different, FL and C data were combined in this graph. CPP scores (not shown) also decreased significantly as dose of NAL increased (after 0.1 mg/kg, ($F_{(1,30)}=6.1$, $p<0.05$; after 2.5 mg/kg, ($F_{(1,30)}=7.1$, $p<0.05$; and after 5 mg/kg, ($F_{(1,30)}=4.7$, $p<0.05$).

As also shown in Table 1, there was a dose-dependent effect of NAL on CPP-related activity measures. Entrance counts, explorations, and activity counts decreased as doses of NAL increased. Entrance counts were reduced significantly after 0.1, 1.0, 2.5, and 5.0 mg/kg doses ($F_{(1,30)}=12.2$, $p<0.01$, $F_{(1,30)}$

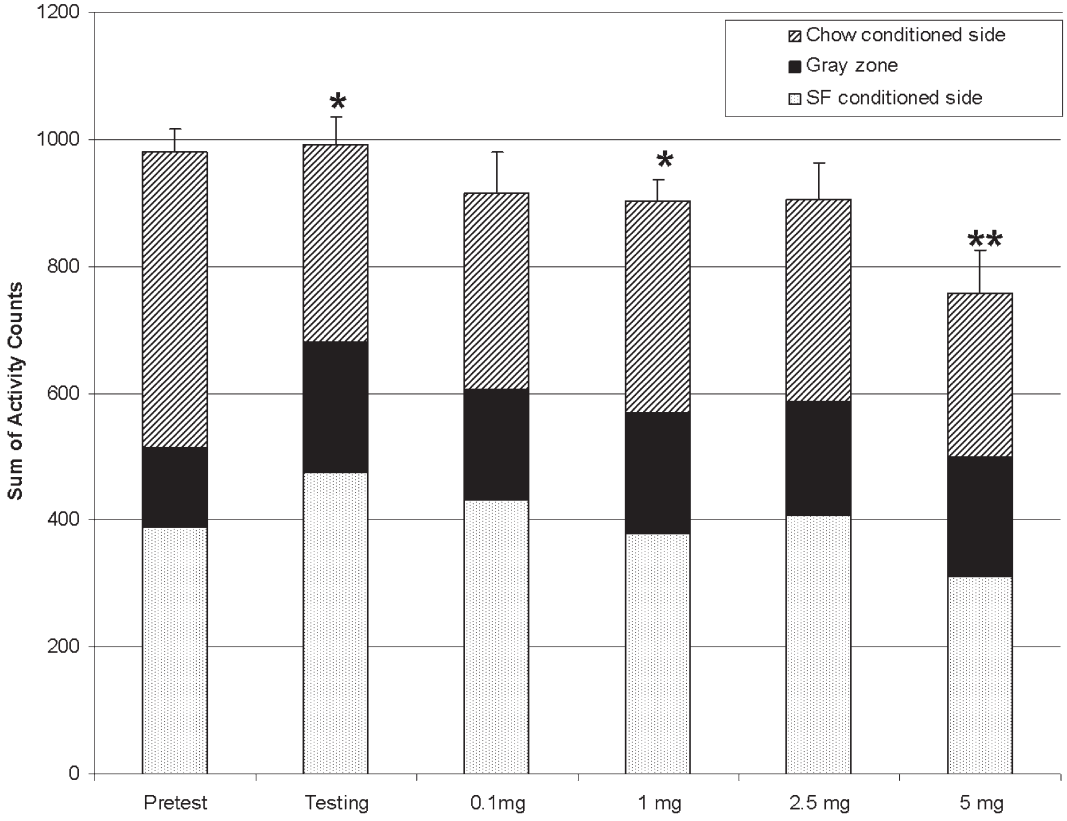

Fig. 4. Sum of activity counts in the 3 chambers. *$p<0.05$, **$p<0.01$.

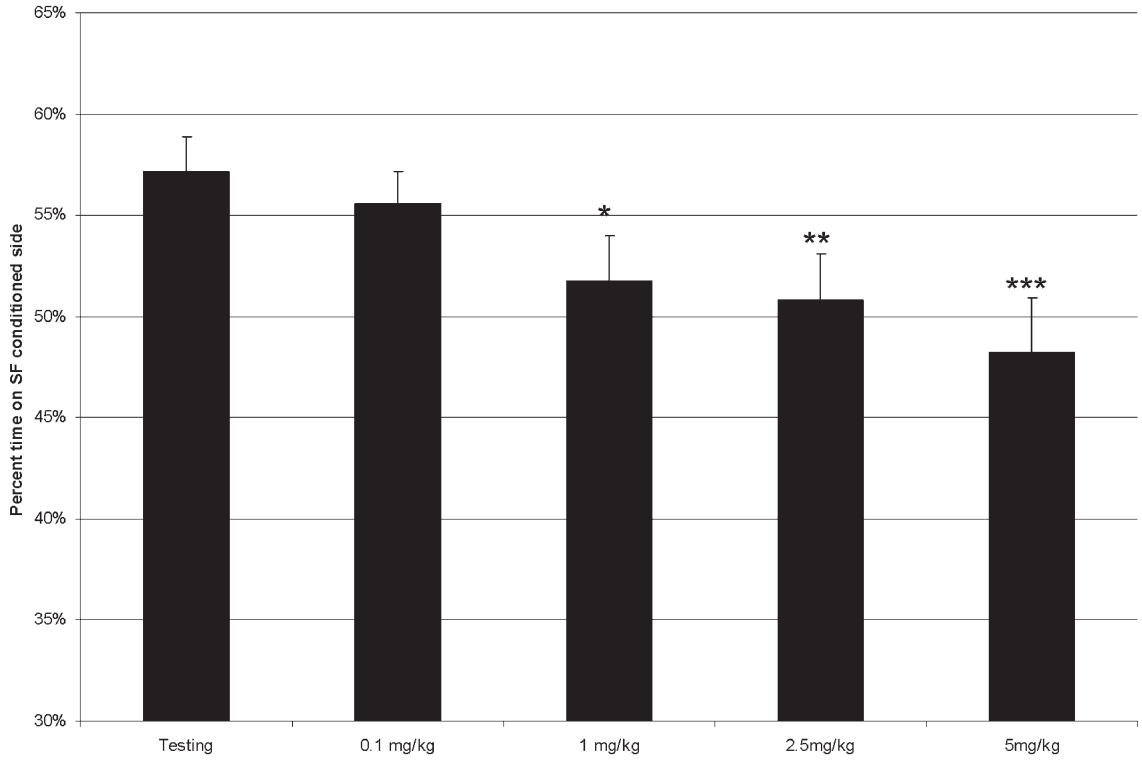

Fig. 5. Naltrexone, dose-dependently antagonizes the conditioned place preference produced by palatable foods. Rats were tested after being injected with saline, and 0.1, 1.0, 2.5, 5.0 mg/kg naltrexone doses; *$p<0.05$, **$p<0.01$, ***$p<0.001$.

$=11.0$, $p<0.01$, $F_{(1,30)}=4.7$, $p<0.05$, $F_{(1,30)}=57.0$, $p<0.001$, respectively). Reductions in explorations were only significant after 5.0 mg/kg ($F_{(1,30)}=11.2$, $p<0.01$) while the reductions in activity on the SF side were significant after 1 mg/kg ($F_{(1,30)}=10.3$, $p<0.01$). Total activity counts were reduced after 1 and 5 mg/kg doses ($F_{(1,30)}=4.5$, $p<0.05$ and $F_{(1,30)}=9.9$, $p<0.01$).

4. Discussion

The current findings demonstrate that rats never exposed to food deprivation can nonetheless learn reliable CPPs in response to brief, repeated exposures to solid palatable foods. This occurred in an equivalent caloric manner whether those foods were high in sucrose (i.e., sweet FL) or fat (i.e., greasy C). Such a finding is perhaps not surprising. Stimuli of various sorts that have rewarding properties elicit strong approach responses and generate secondary associative learning (Agmo and Gomez, 1993; Delamater et al., 2000; Torrella et al., 2004). This phenomenon has been studied most extensively in the field of drug addiction to better understand the "cravings" that occur in addicts (Bardo and Bevins, 2000). The high consumption of both SFs displayed by our rats during CPP conditioning (at least 25% of normal daily kcal consumption on standard rat chow) provides operationalized evidence that such foods are naturally rewarding. The avidity of our animals for these foods was demonstrated by the fact that after only 1 day of initial training, the amount of SFs consumed on the second conditioning day was significantly greater than that seen during Chow exposure. This intake pattern increased steadily throughout conditioning and grew slightly more during reconditioning. The power of very brief (20 min) SF exposures every other day to elicit such substantial intake was all the more impressive considering that such training occurred during the daylight hours—a time when rats would otherwise have been quiescent and eaten very little regular Chow.

The existence of CPPs learned to both SFs was reflected in several measures. During preference tests in the absence of food, rats exhibited significant increases in time spent in the SF-conditioned chamber vs. the Chow-conditioned chamber. When CPPs were defined as preference scores for SF-conditioned sides, CPPs were also apparent. In addition, locomotor activity (entrance counts, explorations, and activity counts) all increased in SF-conditioned chambers.

Our finding that the solid high-sucrose food, FL, can motivate CPP learning in non-deprived rats is consistent with earlier reports in deprived rats showing that sucrose presented in solution or as an additive to Chow mash or food pellets can also induce such associative learning (Delamater et al., 2000; Guyon et al., 1993; Perks and Clifton, 1997). But, to our knowledge, this is the first study to demonstrate that a solid high-fat food (C) can produce equivalent CPPs in non-deprived rats. Corwin (2004) has previously shown that exposing Chow-fed rats to 2 h of dietary fat only 3 times per week produces high intakes equivalent to those seen with continuous 24 h access. Our findings can be interpreted as extending these observations by showing that exposure to a palatable fatty food (as well as one containing sugar) for one-sixth this amount of time also produces substantial increments in intake that are sufficient to

produce a CPP. This suggests that palatable foods, regardless of their macronutrient type, produce associative learning as long as they are rewarding. Recently, Imaizumi et al. (2000) reported that corn oil consumption in non-deprived mice can also produce CPPs. Interestingly, they also found that oral corn oil injections 60 min prior to CPP training did not produce such learned preferences. They concluded that the post-ingestive effects of corn oil alone were insufficient to support CPP learning. Rather, the flavor/taste/feel of corn oil in the oral cavity was hypothesized to have contributed to this effect. Although this study was conducted in mice using a different form of fatty food, it appears to generally support our current finding that CPPs can develop to fat-based foods in non-deprived animals.

During our first test of CPPs in non-deprived SF-trained rats, animals spent 55–60% of their time on the conditioned sides of the apparatus. This was less than the 64–70% preference times observed by Delamater et al. (2000) in deprived rats trained to consume sucrose solutions. Such a difference may represent the stronger physiological cues (e.g., low levels of blood glucose and free fatty acids) present in deprived animals which, when combined with the naturally reinforcing properties of a sweet taste, gave rise to stronger associative learning. Nevertheless, our findings demonstrate that even in the absence of such energetic challenges, the properties of our SFs were apparently sufficient to support reliable CPP learning. But another factor that may have contributed to why we observed lower CPP percentage changes than Delamater et al. (2000) could be our use of a 3-chambered apparatus vs. their 2-chambered one. As a result, our rats had an additional chamber to explore in CPP tests in the absence of food. In other words, the lower percentage score may in part reflect the choice of the SF-conditioned chamber over the Chow-conditioned chamber and a third (novel) neutral chamber.

A variety of past research has demonstrated that highly palatable foods can produce reward by activating the brain's endogenous opioid system (e.g., Glass et al., 1999). Of particular importance is the report that the opiate agonist, morphine, increases the intake of foods that have been previously shown to be "preferred" by rats (Gosnell et al., 1990; Welch et al., 1994). Such findings suggest an important role for this system in modulating the expression of the CPPs we observed to both forms of SF, which were "trained" to be preferred in our paradigm. In keeping with that possibility, Delamater et al. (2000) showed that NAL doses of 2.5 and 5.0 mg/kg reduced the expression such learning in their food-deprived rats. In the present study, CPPs to both SF in our non-deprived rats were also reduced by NAL in a similar dose range (1.0, 2.5 and 5.0 mg/kg). However, the fact that overall activity was more depressed during CPP tests at the 5.0 mg dose suggests that its reduction may have in part been due to non-specific motivational effects (Leventhal et al., 1996). Additional work will be needed to clarify that possibility, as well as the more complex role that opioid receptor blockade may play in such learning (see important considerations of this by Levine et al., 2002; Levine and Billington, 2004). That issue aside, the efficacy of lower doses of NAL to disrupt CPPs learned to SF supports the important role of the opioid system in mediating reward to these forms of highly palatable food.

Kelley and Berridge (2002) have contended that rewards are important hedonic incentives, not merely habit reinforcers. The data from our study are in agreement with this proposition. Eating can reduce the negative experience of hunger. But eating in the sated state (which is often how snacking occurs) is clearly not due to reducing the aversiveness of hunger. Consuming palatable SF is often a motivated, goal-directed learned behavior, sometimes associated with intense food cravings (Greeno et al., 2000). These same foods are sometimes viewed as "comfort foods" that are consumed to reduce stress or negative affective states (Dallman et al., 2003). Thus, food intake behaviors reflect not only the influence of hunger and satiety, but also the learned preferences for specific foods they have experienced to be rewarding. In support of this view, exposure to palatable food has been shown to activate brain reward pathways. Human subjects exposed to the taste and smells of foods they consider to be palatable have been documented to exhibit a 24% increase in brain metabolism (Wang et al., 2004). In particular, one of the areas activated was the orbitofrontal cortex, a somatosensory area of the brain involved in taste perception. Increased activity in this same brain region has been linked to drug cravings in cocaine addicted subjects (Volkow et al., 1999). Perhaps related to both findings is the fact that women that have recovered from bulimia nervosa displayed subnormal binding of serotonin (5-HT) 2A agonists in the medial orbital frontal cortex (Kaye et al., 2001).

In conclusion, our data demonstrate that solid SF, like addictive drugs, can become linked with environmental cues in the absence of any "deprivation" state, perhaps because of their naturally rewarding properties. It is now well established that excess consumption of high-calorie foods containing sugar and/or fats has contributed to the obesity epidemic occurring in industrialized countries (Hill et al., 2003). To the extent that CPPs to such foods represent strong "cravings" to continue consuming them, and that endogenous opioids mediate such "reward", this may help explain why reducing the intake of those foods in humans can be so difficult. To the extent that drugs of abuse and certain foods both activate common brain reward circuits, appropriate pharmacological interventions may offer one means to both identify this circuitry and better understand both normal and aberrant eating behaviors (Volkow and Wise, 2005).

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