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Conditioned place preferences (CPPs) to high-caloric "snack foods" in rat strains genetically prone vs. resistant to diet-induced obesity: Resistance to naltrexone blockade

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Abstract

A previous study in our laboratory using Sprague–Dawley (SD) male rats showed that conditioned place preferences (CPPs) can be learned to two different high-caloric "snack foods" — one high in sugar (Froot Loops cereal: FL) vs. one high in fat (Cheetos: C), and that both preferences were mediated by endogenous opioids. Using the same CPP apparatus and procedures, two genetic sub-strains of SD rats, one selectively bred for diet-induced obesity (DIO) vs. another bred for diet resistance to obesity (DR), were used in this investigation. The experiment determined if (a) CPPs can be created in both strains using the same high-caloric "snack foods" and, (b) if CPPs existed, were they opioid dependent. Four non-deprived groups of eight male rats, half being of each strain, were given 20 min sessions to eat either FL or C in one side of a three-chamber CPP apparatus vs. chow on the opposite side over alternating days of a 20 day period. Each predetermined side had distinctly different environmental cues. Following conditioning, rats were tested during 10 min sessions to see if CPPs existed to the "snack food" trained sides. During conditioning and testing, bodyweights, intakes of foods, and activity were measured. Both FL and C generated strong CPPs that were equivalent in both strains. In contrast to our previous study in the parent strain, doses of 0, 0.50, 1.0, 2.5, and 5.0 mg/kg of the opioid antagonist, naltrexone, had no effect on blocking these CPPs. These results show that (a) DIO and DR rats can learn CPPs (i.e., "exhibit food cravings") as well as their parent strain after periodic access to high-caloric palatable foods, but imply that (b) some physiological system other than the endogenous opioid system mediates such learning.

Keywords: Conditioned place preference; Snack foods; Palatability; Learning; Opioid; Naltrexone; Rat; Dietary induced obesity; Dietary resistance to obesity

Food intake behavior involves not only hunger and satiety but also learned preferences that are reinforced by repetitive reward. Some foods are more rewarding than others and, for that reason, may be overconsumed even in the physiologically sated state. One category of such preferred foods in humans are "snack foods". Previous research in our laboratory has shown that sated Sprague–Dawley (SD) rats acquire conditioned place preferences (CPPs) after brief exposures to highly palatable "snack foods" (Jarosz et al., 2006). The CPP paradigm is a commonly used method for measuring the rewarding properties of addictive drugs. The secondary reinforcement that CPPs measure provides one index of "drug craving". Investigators interested in "food cravings" have also employed the CPP model. We found that the consumption of sweet or fatty snack foods became associated with environmental cues (i.e., CPPs were acquired) and the endogenous opioid system, which is one mediator of the hedonic aspects of palatable foods, appeared to modulate those learned associations.

Outbred SD rats gain weight somewhat homogeneously when fed a low fat, low energy diet. When fed a diet of moderate fat, however, some display a propensity to develop diet-induced obesity (DIO) while others are diet resistant (DR) to obesity development (Berthoud et al., 1981; Levin et al., 1983). Levin et al. (1997) have selectively bred SD rats when exposed to a high energy (sweet, low fat) diet into these weight

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gain phenotypes. DIOs show greater feeding efficiency and weight gain than DRs. Body weight is increased due to increased caloric intake even though DIOs display an early and marked increase in leptin levels (Levin et al., 2003). They have a reduction in hypothalamic leptin signaling from an early age, suggesting that this may be an inherent trait in this model (Levin et al., 2004). Before onset of their obesity, chow-fed DIO-prone rats also show other characteristics associated with obesity development, including reduced sympathetic activity and increased expression of hypothalamic neuropeptide Y mRNA (Levin, 1995, 1996; Levin and Dunn-Meynell, 1997).

Using the same paradigm as in our previous study of the parent SD strain, we determined if (a) DIO and DR sub-strains could learn CPPs after brief exposure to highly palatable snack foods, as well as (b) if CPP learning was mediated by endogenous opioids. Given the greater feeding efficiency and weight gain of DIO rats, the experimental questions posed were: (1) Will DIO rats show greater CPP learning than DR rats? And (2) if they do, might the learning be more resistant to blockade by opioid receptor antagonism? As in our previous work, this study was unique in that animals were never food-deprived, human "snack foods" were used to induce a CPP, and both "high sugar" and "high fat" foods served as primary reinforcers of behavior.

1. Method

1.1. Subjects and experimental procedures

Subjects were experimentally naïve adult male rats, 16 of DIO SD strain (Crl:CD(SD)DIO) and 16 of the DR SD strain (Crl:CD(SD)DR). Animals were 7 weeks old at the time of purchase from Charles River Laboratories, Kingston, NY, in May, 2005. Rats were housed in single wire-mesh hanging cages within a temperature-controlled colony room illuminated 0900–2100 h each day and had unlimited access to standard chow and water. All experimental sessions occurred between 1300 and 1700 h, approximately 4 h into the rats' light cycle. Rats were first familiarized to home cage and colony conditions, as well as human handling for 10 days prior to initiating the experiments. 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.

1.2. CPP pretesting

The study design used in this and in our previous study was based on the work of Delamater et al. (2000) who demonstrated that CPPs learned by food-deprived rats to sucrose solutions in a 2-compartment CPP apparatus could be blocked by naltrexone (NAL). Four 3-compartment CPP apparatuses were used in our study (Med Associates, Georgia, VT). The two end chambers of each apparatus were identical in size (27.5 cm long × 20.6 cm wide × 21.5 cm tall), while 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 (see Jarosz et al., 2006 for further description of apparatus). Pretesting was conducted on the first day. Rats were placed in the middle chamber of the 3-chamber apparatus with the doors open and were then given 10 min access to all chambers without food available. Data were electronically recorded by photo beam breaks within each chamber to determine baseline chamber preferences (time in seconds). In addition to time in each chamber, activity data collected included: activity counts (any beam break within a given chamber), number of entrances (multiple beams broken as animals entered a chamber), and explorations (single beam breaks in an adjacent chamber without entry into that chamber). Based on their chamber preferences (time spent in a chamber) and animals' bodyweights, four equivalent groups of 8 rats were formed.

1.3. CPP conditioning and testing

On alternating days of a 20-day conditioning period, rats were placed on one side of an apparatus with one of two snack foods for 20 min sessions. One group each of DIOs and DRs received Froot Loops® (FL) while the other groups received Cheetos® (C). FL provides 3.75 kcal/g (89.6% carbohydrate, 7.2% fat, and 3.2% protein) while C provides 5.64 kcal/g (37.5% carbohydrate, 56.3% fat, and 5.0% protein). In one end chamber, rats received their snack food, while on the next day they received chow in the opposite end chamber. Half of each group received their designated snack food during each conditioning session in the non-preferred chamber as determined from initial preference testing, while the other half received chow. Intakes of snack food and chow were measured for each session. Fifteen minutes prior to the last four conditioning sessions, rats received subcutaneous (SC) saline (0.9%; 1 ml/kg) injections to become accustomed to this procedure.

On the test day, the same procedure was used as in pretesting, except that rats were given 1 ml/kg SC saline injections 15 min prior to testing. They were then placed into the apparatus without food and given 10 min access to all 3 chambers while data was collected.

1.4. Effect of opioid receptor antagonism on place preference

The effect of opioid antagonism on snack food-induced CPPs was examined by injecting various single SC doses of NAL separated by 4 additional reconditioning sessions (alternating days of snack food vs. chow as during the conditioning sessions). During these drug trials, the procedure followed was the same as in initial preference testing, except rats were injected SC 15 min before hand with NAL (Sigma-Aldrich, St. Louis, MO) at doses of 0.5, 1.0, 2.5, and 5.0 mg/kg sessions.

1.5. Statistical analysis

Intake data during conditioning and reconditioning trials were recorded in grams and converted to kcals. Measures of CPP acquisition and CPP-related behaviors examined were: zone time(s), activity counts, entrance counts, and explorations.

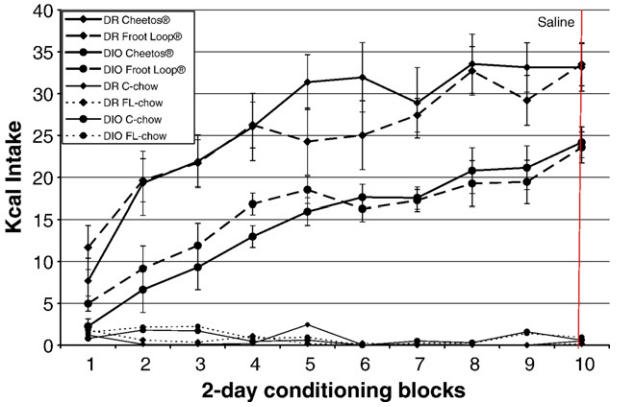

Fig. 1. Mean intake in kilocalories consumed by rats during 20-minute sessions every other day. Each day represents a 2-day conditioning block (snack food one day, chow the other).

Zone time was analyzed in two ways: (a) time spent in the snack food-trained chamber and (b) a percentage of time spent in the snack food-conditioned chamber compared to the chow-paired chamber before and after conditioning excluding the neutral grey chamber. A CPP was defined as having occurred if groups spent significantly more time in the snack food-trained chamber than in the chow-trained chamber compared to the initial test day.

Repeated measures analyses of variance (RM ANOVA), employing within-subjects contrasts with snack food type and sub-strain as between-subjects factors, were applied to both pretest and testing data. To examine the effect of NAL injections on the expression of CPPs, RM ANOVAs with within-subjects contrasts with snack food type and sub-strain type as between-subjects factors were also used including all doses of NAL compared to initial CPP testing.

2. Results

There was a significant increase in snack food intake over the 10 day conditioning period ($F_{(1,28)}=57.1$, $p<0.001$) (see Fig. 1). Both DIO and DR rats consumed substantial amounts of both snack foods vs. minimal amounts of chow (0–2 kcal/session). Snack food intake gradually increased over the conditioning sessions, reaching 23–25 kcal in the DIO rats and reaching 30–33 kcal in the DR rats. There was no effect of snack food type or sub-strain on snack food intake across the groups. However, DR rats ate significantly more than DIOs, ($F_{(1,28)}=19.9$, $p<0.001$). The between-subjects factor snack food type was not significant and there was no snack food by sub-strain interaction.

Table 1
Mean chow intake in kilocalories consumed by rats examined at 3 time points during the study

	9 weeks	12–13 weeks	16 weeks
DIO	30.3 (0.7)	27.7 (2.2)	29.3 (1.6)
DR	26.7 (0.7)	21.1 (1.4)	24.4 (1.3)
Ind. *t*-test	0.008	0.01	0.041
	$p<0.01$	$p<0.05$	$p<0.01$

Fig. 2 shows the differences in the body weights of these rats. DIO rats were nearly 36 g heavier than DR rats at 7 weeks of age and this difference increased over the 8 weeks of the study. While DR rats consumed more snack food than the DIO rats, 24-h kcal intake of chow was significantly greater in the DIO rats than in the DR rats when examined at 3 time points: before conditioning, after 10 2-day conditioning sessions, and at the end of the study (see Table 1).

The acquisition of a CPP occurred in both DR and DIO rats. Fig. 3 shows the zone time changes in each chamber side before vs. after conditioning. RM ANOVA tests of within-subjects contrasts indicated that time spent in the snack food-conditioned chamber increased significantly ($F_{(1,28)}=32.9$, $p<0.001$). There were no significant interactions among the variables across the groups. The RM ANOVA tests of between-subjects effects indicated a significant sub-strain difference between groups ($F_{(1,28)}=9.0$, $p<0.01$, DR>DIO). DR rats spent an average of 50 s more time in the snack food-conditioned chamber while DIO rats spent an average of 45 s more. While the increase in seconds is similar, DR rats began at a lower number of seconds (174.2±8.9 increased to 224.8±6.6) and DIO rats began at a

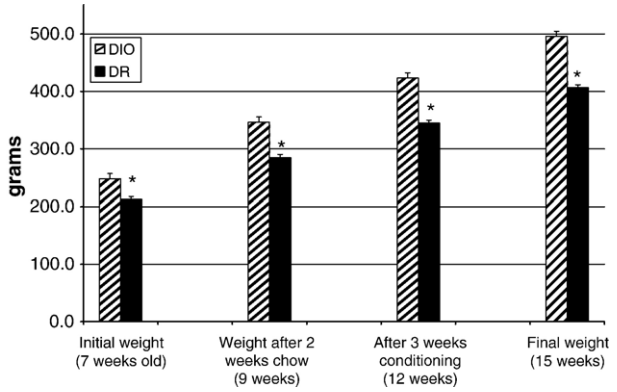

Fig. 2. Mean body weights (±SEM); initial weight: DIO significantly heavier than DR, $t(30)=6.9$, $p<0.001$; weight after 2 weeks chow intake: $t(30)=8.5$, $p<0.0001$; weight after 3 weeks conditioning intake (snack food every other day): $t(30)=8.7$, $p<0.0001$; final weight: $t(30)=8.7$, $p<0.0001$.

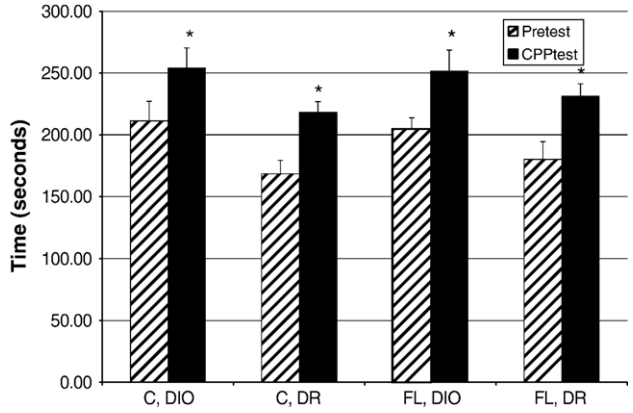

Fig. 3. Time spent in the snack food-conditioned chamber before and after conditioning. C represents Cheetos, FL represents Froot Loops, DIO represents diet-induced obesity, DR represents diet resistant to obesity. * indicates $p<0.001$.

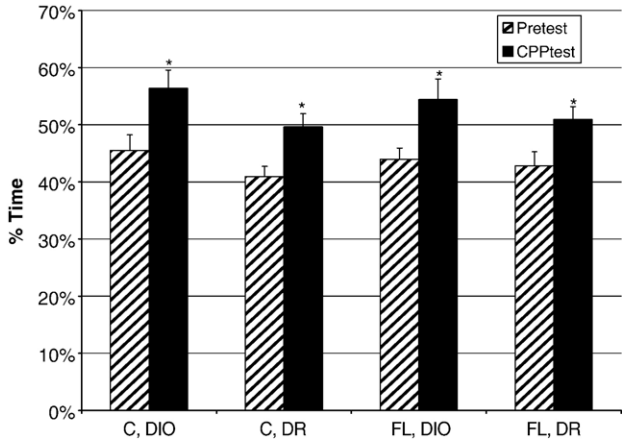

Fig. 4. Percentage time spent in the snack food-conditioned chamber at baseline and after conditioning. * indicates $p<0.001$.

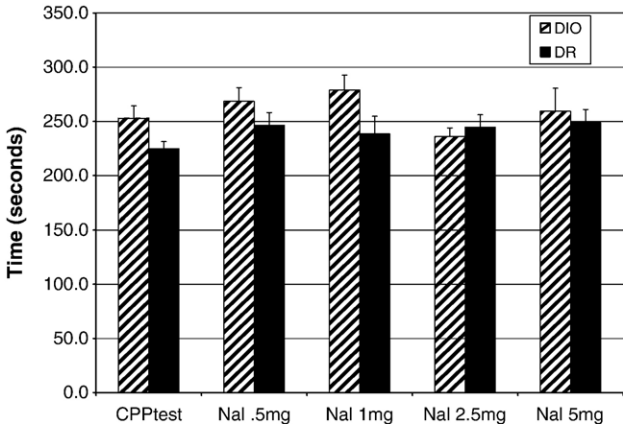

Fig. 5. Naltrexone did not depress the conditioned place preference produced by palatable foods. Rats were tested after being injected with saline, and 0.5, 1.0, 2.5, 5.0 mg/kg naltrexone doses.

higher zone time (207.8±9.0 increased to 252.8±10.4). Snack food type and snack food type × sub-strain interactions were not significant. CPP learning when defined as a percent of time spent in the snack food-conditioned chamber compared to the chow-paired chamber before and after conditioning (the ratio does not include time spent in the neutral grey chamber) was also significant ($F_{(1,28)}=30.7$, $p<0.001$). Both DR and DIO rats spent significantly more time in the snack food-conditioned than the chow-paired chamber (Fig. 4). DIO spent a little more time in the snack food-paired chamber than the DR rats (10% vs. 8%) but this was not significantly different (see Fig. 4).

Since the ANOVA showed that the between-subjects factor, snack food type, was not significantly different in either snack food intake or CPP learning, subsequent analyses of activity measures were performed on data collapsed across snack food groupings. Entrance counts, explorations, and activity counts on the snack food-conditioned side all increased from baseline levels during CPP testing (Table 2). With regard to entrance counts, there was a tendency toward significance ($F_{(1,30)}=3.3$, $p=0.08$) and no between group differences. There was a highly significant change in activity in the conditioned chamber from pretest to CPP testing, ($F_{(1,30)}=48.7$, $p<0.001$). Activity in the conditioned chamber increased in both groups. Total activity within all 3 chambers increased significantly, ($F_{(1,30)}=19.5$, $p<0.001$). This was due primarily to an increase in activity of the DR rats, ($F_{(1,30)}=9.1$, $p<0.01$).

Table 2
CPP-related activity measures

	Entrances	Explorations	Activity	Total activity
Pretest	64.3 (3.5)	49.2 (3.0)	421.3 (3.0)	1141.3 (33.8)
CPP test	71.5 (3.7)	53.3 (2.9)	601.2 (25.1)**	1315.2 (43.6)**
Dose response				
CPP test	71.5 (3.7)	53.3 (2.9)	601.2 (25.1)	1315.2 (43.6)
Nal 0.5 mg/kg	56.3 (3.3)**	44.2 (3.3)**	563.7 (22.0)	1219.9 (34.2)*
Nal 1 mg/kg	73.1 (11.9)	51.1 (3.7)	627.9 (35.7)	1261.5 (37.2)
Nal 2.5 mg/kg	64.2 (3.7)	49.3 (2.8)	597.7 (21.6)	1273.8 (36.1)
Nal 5 mg/kg	59.0 (3.9)*	48.5 (3.4)	487.1 (23.0)**	1091.8 (41.5)***

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

Snack food intake in both groups was more variable during reconditioning between NAL drug tests ($F_{(1,28)}=2.1$, $p<0.05$), but remained for the most part between 20–25 kcal/session for both snack foods in the DIO rats. DR rats continued to consume 30–40 kcal/session of C over the reconditioning sessions, while consumption of FL declined but remained over 20 kcal/session. Tests of within-subjects effects also indicated there was a significant intake by snack food type interaction, ($F_{(1,28)}=2.2$, $p<0.05$) — that is FL intake declined in DR rats. Overall, DR rats continued to consume significantly more snack foods than DIO rats, ($F_{(1,28)}=13.0$, $p<0.01$).

RM ANOVA using within-subjects contrasts, with snack food type and sub-strain as between-subjects factors, was applied to time spent in the snack food-conditioned chamber after various doses of NAL. Time spent in the snack food-conditioned chamber after each dose is compared to CPP testing. Fig. 5 shows that NAL was not effective in diminishing CPPs during retests of this learning. Furthermore, the examination of % time spent in the snack food-conditioned chamber also did not show significant reductions after NAL administration.

Table 2 also summarizes CPP-related activity measures after NAL. A significant reduction in entrance counts, explorations, and total activity was noted after 0.5 mg/kg NAL ($F_{(1,28)}=13.0$, $p<0.01$; $F_{(1,28)}=11.5$, $p<0.01$; $F_{(1,28)}=4.8$, $p<0.05$). There were no between-subjects effects. A significant reduction in entrance counts, activity on the snack food side, and total activity in all 3 chambers was also observed after 5.0 mg/kg NAL ($F_{(1,28)}=6.8$, $p<0.05$; $F_{(1,28)}=8.6$, $p<0.01$; $F_{(1,28)}=16.4$, $p<0.001$). There were no between-subjects effects.

While NAL was not effective in diminishing a previously established CPP, the highest dose, 5 mg/kg, was associated with

a reduction in total activity during CPP testing. In addition, analysis of home cage food consumption showed that chow intake was significantly reduced both the first (33.8±2.2 vs. 28.1±0.9, $F_{(1,26)}=5.6$, $p<0.5$) and the second day (33.8±2.2 vs. 23.3±0.6, $F_{(1,26)}=21.7$, $p<0.001$) after that dose. There were no between-subjects effects for strain. Therefore it does appear that while NAL did not diminish the presence of CPP, the drug was indeed active.

3. Discussion

In this study we have again demonstrated that non food-deprived rats can acquire reliable CPPs after brief, repeated exposures to palatable, solid sweet or fatty snack foods. As in our previous study (Jarosz et al., 2006), FL and C were equally rewarding. This finding that the solid high-sucrose food, FL, can motivate CPP learning in non-deprived rats is consistent with our previous work as well as 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). In addition, our finding here that the solid high-fat food, C, can motivate CPP learning is also consistent with our previous study as well as with earlier reports that fat in the form of corn oil or semisolid mash was associated with CPP learning (Figlewicz et al., 2004; Imaizumi et al., 2000; Jarosz et al., 2006). Thus the incentive to learn CPPs can be demonstrated in rats lacking a physiological need for nutrients as well as in rats motivated by food restriction. While DR rats ate significantly more snack foods during the 20-minute training sessions, DIO rats consumed significantly more grams of chow than DRs during a 24 h period. Overall the DIO rats appeared to be more "feeding efficient" than the DR rats, gaining more body weight per kcal consumed.

The existence of CPPs learned to both snack foods was reflected in several distinct measures. During preference tests in the absence of food, rats exhibited significant increases in time spent in the snack food-conditioned chamber vs. the chow-conditioned chamber. Because of their greater feeding efficiency and weight gain compared to DR rats (Levin et al., 1997; Levin and Keesey, 1998), we suspected that DIO animals might show stronger CPP learning. While DIO rats displayed a slightly greater CPP preference than DR animals, this difference was not statistically significant. In fact, contrary to our expectations, snack food intake was significantly greater in DR rats, even though that enhanced intake was not associated with significantly greater CPP learning. Compared to our previous study using the parent SD strain, the snack food intake of DR rats was significantly greater, while snack food intake in DIO rats was comparable to that of their parent strain.

As with the parent strain, the derivative strains explored the snack food-paired chamber and displayed a greater preference for it over the chow-paired chamber. With respect to percentage time spent in the snack food-paired chamber before vs. after conditioning, the parent SD strain displayed the greatest increase (+12%), followed by the DIO rats (+10%), and then the DR rats (+8%). These small differences, which were not statistically different from one another, indicate that the different amounts of snack foods eaten by these three strains did not translate into robust differences in the strength of CPP learning.

Of particular interest was the fact that, unlike the parent SD strain, the derivative DIO and DR strains did not show suppressed CPP learning under the influence of NAL. Both DIO and DR rats were comparable in their resistance to extinction of their snack food-induced place preferences. The reduction of percentage time in the snack food conditioning chamber in our previous study was approximately 6% for SD rats at a NAL dose of 2.5 mg/kg and approximately 9% at a NAL dose of 5 mg/kg.

There are a number of possibilities that can be considered in attempting to understand why NAL did not impede CPP performance in the current study. Both DIO and DR rats displayed the same reduction in locomotor responses at the highest dose of NAL as was observed in our previous study. This suggests while the NAL was having an effect on locomotor activity the selective breeding process may have had additional unrecognized effects in both derivative strains with respect to learning. For example, both lines may have experienced "genetic drift" that was unrelated to the intended phenotypic selections for which each strain was intended. Should that have occurred, it may, in some way, have rendered both DIO and DR rats less sensitive to NAL's effects on the neural reward processes related to CPP but had no effect on NAL's ability to impede locomotor activity at high doses. Genetic drift occurs when spontaneous neutral mutations disappear or become fixed in a population at random (Silver, 1995). This type of drift can occur in cases of selective breeding in populations of small sizes because of the random fixation of alleles that can result. If such fixation occurred on an allele that influences NAL sensitivity to biological mechanisms mediating reward (possibly by increasing the relevance of another reward system), then the decreased sensitivity could be independent of rats' DIO vs. DR status.

A second possibility perhaps related to the first is that while the endogenous opioid system may have contributed to both DIO and DR rats learning the location of snack food rewards, other neurochemical pathways may have played equal or even more important roles in this process, particularly under the influence of opioid receptor blockade. Cholinergic, GABAergic, and dopaminergic systems have all been shown to modulate reward in addition to opioid systems (Wise, 2002). Other evidence suggests that serotonin and cannabinoid systems may also be involved (Saper et al., 2002). In the present study, CPP learning and/or its expression may have been more strongly influenced by one or more of these other chemical pathways, while the endogenous opioid system played a weaker role. It would be interesting to test the relevance of other reward systems possibly involved in the CPPs learning in future experiments should these rats become available again.

A third possibility, again potentially related to the first, is that although endogenous opioids may have been involved in the initial acquisition of snack food-conditioned CPPs by both SD sub-strains, other systems may have modulated the learning and memory of those rewarding events. The current dominant hypothesis in the literature is that opioids influence the hedonic

evaluation or palatability aspects of food. However, the exact mechanism(s) by which palatability-induced intake occurs remains unclear. Recently, Barbano and Cador (2006) reported that naloxone reduced food intake of palatable food in sated rats but did not modify the intake of food restricted rats. This supports the notion that the opioid system mediates the hedonic value of food when overpowering signals of deprivation are not operating. According to the Incentive Salience theory of Berridge (1996), the rewarding or "pleasing" aspects of consuming palatable food ("liking") can be dissociated from food seeking as a motivational state ("wanting"). Opioids systems may be associated with "liking" food while the dopaminergic system may be associated more with motivation and food seeking. It has been further hypothesized that, in addition to "liking" and "wanting", "learning" may also play a prominent role in such complex forms of behavior (Robinson et al., 2005). Thus, the opioid system may be influencing the hedonic aspects of this complex goal directed behavior while other systems may be influencing reward-related associative learning and wanting of the rewarding stimulus. Both DIO and DR sub-strains as well as their SD parent strain exhibited reward consumption, reward seeking, and learned the location of the snack food-reward. However, the opioid system of DIO/DR rats may have played a less powerful role in the hedonic components of our CPP paradigm than it did in the parent SD stain, thus contributing to the lack of NAL's effects in blunting CPPs in those sub-strains.

In conclusion, we have demonstrated that rats either genetically prone vs. resistant to obesity, much like their parent SD strain, can acquire reliable CPPs after brief, repeated exposures to palatable, solid sweet or fatty snack foods in the absence of food deprivation. However, the reductions in this form of associative learning that were observed after NAL injections in the parent SD train were not observed in these sub-strains. Rewards can be considered environmental incentives we return to after having had contact with them (Wise, 2002). The consumption of foods in the sated as well as in the deprived states clearly qualifies as meeting such rewarding incentives. The naturally rewarding, every day experience of eating good food entails sensory pleasure, associative learning, memory of the events related to eating, and the motivation to seek those experiences again. The complex and interrelated nature of these phenomena insures that a wide variety of neural pathways participate in these events. Therefore, the likelihood of finding a single animal model that embodies all of these components is probably remote.

Author note

After this research was completed, there were problems found with the phenotypic expression of diet-induced obesity in the DIOs and these rats are no longer available commercially from Charles River.

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