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Operant Responding for Sucrose by Rats Bred for High or Low Saccharin Consumption

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Abstract

The use of rats differing in the intake of sweet substances has highlighted some interesting parallels between taste preferences and drug self-administration. For example, rats selectively bred to consume high (HiS) or low (LoS) amounts of a 0.1% saccharin solution (when compared to water consumption), show corresponding differences across several measures of cocaine self-administration (HiS > LoS). In this study, we measured whether the two strains also differ when response requirements are imposed for obtaining a sucrose reinforcer. Male HiS and LoS rats were measured for operant responding for sucrose pellets under fixed-ratio (FR) schedules of 1, 3, 5 and 10 and under a progressive-ratio (PR) schedule, during which the response requirement for each successive pellet increased exponentially. The effect of systemic naltrexone (0.3, 1 and 3 mg/kg) on PR responding for sucrose pellets was also tested. Under all FR and PR schedules, the numbers of pellets obtained by the LoS rats were significantly lower than those obtained by the HiS rats. Although the LoS weighed more than the HiS rats, this difference does not appear to explain differences in operant behavior. No strain differences in the effect of naltrexone were observed; the 3 mg/kg dose reduced the number of pellets obtained in both strains. Measures of locomotor activity taken prior to operant trials suggest that the differences in responding were not due to differences in general activity levels. These studies provide further characterization of the HiS and LoS rat lines by demonstrating that motivation to consume sucrose is greater in HiS than in LoS rats.

Keywords

Saccharin; Sucrose; Reward; Naltrexone; Opioid; Locomotor Activity

1. Introduction

Studies which compare experimental subjects that have been selected or bred for a particular behavior may be informative of the nature of co-occurring behaviors. For example, the alcohol-preferring (P) and alcohol non-preferring (NP) rat lines were developed on the basis of their voluntary intake of ethanol [1]. Numerous studies have compared the two rat lines on many different variables, such as gene expression, neurotransmitter levels, and other ethanol-related

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behaviors [2,3]. Interestingly, P rats also consume more saccharin and sucrose than NP rats [4-6]. Conversely, animals selected for high or low saccharin intake have correspondingly different ethanol intakes [7-9]. These studies have provided support for the idea that food/taste reward and drug reward are mediated by similar or overlapping brain mechanisms. Other studies, including those that investigated drugs other than ethanol, support this view [see 10-12]. For example, rats selected on the basis of saccharin or sucrose intake have been found to differ in the self-administration of morphine, amphetamine, and in the acquisition of cocaine self-administration [13-15]. In 1996, Dess and colleagues reported the development of lines of rats selectively bred for high or low saccharin intake, termed HiS and LoS rats, respectively [16,17]. Subsequently, these rats were also found to differ in ethanol intake (HiS > LoS), thus providing a finding complementary to the results described above based on rats bred for differences in ethanol intake [18]. General differences in size or ingestive behavior do not apparently account for differences in saccharin or ethanol intake, as the two lines do not consistently differ in body weight or food or water intake [17,19,20]. Furthermore, in HiS and LoS rats, body weight was not correlated with food intake, wheel running, or meal patterning [20], and sucrose preference and avidity did not significantly covary with body weight [17]. Carroll and colleagues have continued breeding these lines and reported line differences in several stages of the animal model of the human drug abuse process. In several studies, HiS and LoS were found to differ (HiS > LoS) in the acquisition, maintenance, escalation and reinstatement of cocaine-seeking behavior (see [21] for review). Studies of the HiS and LoS rat lines, therefore, may be useful in studies of both drug-seeking and ingestive behaviors, as well as in studies of the relationship between these behaviors.

The present study was intended to provide a further characterization of the HiS and LoS rat lines. In addition to differences in saccharin intake (the basis of selective breeding), the two lines have also been shown to differ in a similar direction in the preference, intake or avidity of sucrose, Polycose and sodium chloride solutions, as well as other non-caloric sweeteners [19,22]; they do not appear to differ in their aversion or avidity for sour (quinine and sucrose octaacetate) or bitter (citric acid) tastes [22]. To determine whether HiS and LoS rats differ in sweet intake when a response requirement was imposed, they were tested for operant responding for sucrose pellets under fixed- and progressive-ratio (PR) schedules of reinforcement. The PR schedule is thought to measure reinforcing efficacy and/or the motivation to consume food or drugs [23-25]. It was hypothesized that HiS rats would obtain more sucrose pellets than LoS rats under all schedules of reinforcement. Prior to operant measures, HiS and LoS rats were also measured for locomotor activity. The rationale was to determine whether the expected differences in operant responding for sucrose could be attributed simply to differences in general activity levels. This was considered unlikely, however, as prior research on activity levels in a circular open field or with running wheels indicated that LoS rats have a higher level of activity than HiS rats, though the circular open field difference appeared to be transient [20,26,27]. Finally, we tested the effect of the opioid antagonist naltrexone on progressive-ratio responding in the two rat lines. Opioids are thought to play a role in mediating the rewarding aspects of sweet taste [see (28)], and differential responsiveness to naltrexone would suggest the possibility that differences in saccharin and sucrose intake in HiS and LoS rats are due to differences in endogenous opioid activity.

2. Materials and methods

2.1. Animals and Housing

Male rats were obtained from a selective breeding program at the University of Minnesota. The HiS and LoS strains have been bred for their high or low saccharin intake [21]. Due to the limited availability of these rats and of the testing chambers, this study was conducted in three separate cohorts over a total of approximately 36 weeks. Both phenotypes were represented in

each cohort, and the data from all cohorts were combined for analysis and presentation. Activity and operant testing for each cohort lasted approximately 14.5 – 16 weeks. Testing on the second and third cohorts began approximately 7 and 22 weeks, respectively, after the start of testing on the first cohort. Before experimental testing, saccharin phenotype status was computed as described by Carroll *et al.* [21]. Briefly, 24 hr water intake was compared to 24 hr 0.1% saccharin intake (with water also available). This difference was then expressed as a percentage of body weight (g) and multiplied by 100. At the time the saccharin phenotype status was determined in the present study, the HiS (n=12) and LoS (n=11) groups weighed 378 ± 11 and 428 ± 14 g ($t[21] = 2.884$, $p < 0.01$), and had saccharin scores of 24.3 ± 2.0 and 4.6 ± 1.8 , respectively ($t(21) = 7.19$, $p < 0.001$). They were given *ad libitum* food and water except as noted below, and were individually housed in stainless steel cages (rats were transferred to plastic cages with wood chip bedding if body weight reached 600 g). They were maintained on a 12:12 light-dark schedule, and all tests were performed during the light phase. On the first day of operant behavior measurement, the rats' ages were 97 – 116 days for HiS rats and 90 – 114 days for LoS rats. This study was approved by the University of Minnesota Institutional Animal Care and Use Committee.

2.2. Activity Measurement

Activity was measured in eight 43.2×43.2 cm chambers with clear plastic walls and a solid, smooth floor (Med Associates, St. Albans, VT). The chambers were individually housed in sound-attenuating cubicles equipped with a house light and a ventilation fan. Two banks of 16 infrared photobeams and detectors, mounted at right angles 3.5 cm above the floor, detected horizontal activity. An additional 16-beam array mounted 12.5 cm above the floor detected vertical activity. After a period of adaptation to the animal facility, rats were transported to the lab and placed in the activity chambers for a 90 min session. During this period, food and water were not available; they were returned to their home cages after the session. Activity Monitor software (Med Associates, St. Albans, VT) was used to count and analyze photobeam breaks. This software subdivides total photocell interruptions in the X and Y axes into stereotypic and ambulatory counts according to the repetitive (stereotypic) vs. sequential (ambulatory) patterning of the beam-breaks. Briefly, a box-shaped zone (10.2×10.2 cm) is constructed around the computed center of the rat. Beam-breaks within this zone are considered as stereotypic counts. The rat is considered ambulatory when three beam-breaks are counted outside the zone that occur in less than 500 ms; these and other beam-breaks are classified as ambulatory counts until the rat stops for at least 500 ms, at which time the box-shaped zone is re-centered on the rat. The primary measures were distance travelled and ambulatory, stereotypic and vertical counts. Rat groups were compared on each activity measure with *t*-tests.

2.3. Operant Procedures

Operant behavior was measured in chambers (Med Associates, Georgia, VT) equipped with two levers, lights above each lever, house light, ventilation fan, and a feeder that dispenses 45 mg pellets. On the day following activity measurements, rats were tested 4 – 7 days per week in operant sessions; food and water were not available during these sessions. In all sessions, the right and left levers were considered the active and inactive levers, respectively. Presses of the inactive lever were counted but had no programmed consequences; differences in presses of the inactive lever-presses may be related to differences in general activity, and are typically measured to support or rule out this potential confound. Immediately after a rat was placed into a chamber, the session was initiated when the investigator pressed the active lever. This lever-press turned on the houselight for the duration of the session. It also caused the delivery of one “free” sucrose pellet and initiated a 20 sec timeout period, during which the light above the active lever was illuminated. The initial pellet was not counted as an earned or delivered pellet. A 20 sec timeout period was also initiated by all pellet deliveries during the sessions. During

timeouts, active lever-presses were counted, but did not count toward the response requirement to obtain the next pellet. All sessions except those using the progressive-ratio schedule were 90 min in duration.

In the first 19 sessions, the schedule of reinforcement was fixed-ratio 1 (FR1), during which each press of the active lever delivered one 45 mg sucrose pellet into a feeding tray, provided the lever-press did not occur during a timeout period. After the first FR1 session, rats were food-deprived overnight once to facilitate acquisition of lever pressing. Food was returned to the home cage immediately after the next session. After a total of seven sessions, three rats failed to acquire lever pressing behavior and were retested in the next session in the food deprived condition (one HiS and two LoS rats). No rat experienced more than two overnight periods of deprivation in the entire study. In addition to the limited use of food deprivation during the FR1 sessions, the chambers were programmed to evaluate the cumulative number of pellets acquired every 15 min and deliver one “free” pellet if the total number of pellets earned during the session up to that point was five or less. This added condition was only in effect during sessions 4 – 13. After a total of 19 sessions at FR1, the response requirement for pellet delivery was increased such that 3, 5 or 10 presses were required to obtain each sucrose pellet (FR3, FR5 and FR10, respectively). Rats were tested at FR3 and FR5 for seven sessions each, and at FR10 for five sessions. One HiS rat never acquired more than two pellets during any of the first 33 sessions; all data from this rat were excluded from the results. Following the FR sessions, a progressive-ratio (PR) schedule was used for 56 additional sessions. During the PR sessions, the response requirement for each successive pellet delivery increased according to the exponential formula described by Richardson and Roberts [23]. Under this schedule, the response requirements for each of the first 10 pellets were 1, 2, 4, 6, 9, 12, 15, 20, 25 and 32. Unlike the FR sessions (90 min in duration), each PR session ended when 60 min elapsed without a pellet delivery; the breakpoint was defined as the number of pellets earned during the session. This definition was used because the actual values of the highest ratios completed are not interval-scaled (see [23]).

For analysis, the means of the final four sessions at each FR schedule were computed for active lever-presses, inactive lever-presses, and pellets earned. The group means of these values were compared with a two-factor analysis of variance (ANOVA), with the FR schedule treated as a repeated measures factor; *t*-tests were used to compare the strains at each FR schedule. PR results were compared with *t*-tests.

2.4. Naltrexone Study

During the final 13 PR sessions, the effect of naltrexone hydrochloride (NTX) on PR responding was measured. Rats were tested a total of four times and received s.c. injections of NaCl, 0.3, 1 or 3 mg/kg 15 min before being placed in the operant chambers. The order of testing the four doses was counterbalanced across rats, such that approximately equal numbers of rats received each dose on each test day. Three PR sessions (without injections) were interposed between each test session. The naltrexone data were analyzed with a two-factor ANOVA, with dose treated as a repeated-measures factor and strain (HiS and LoS) as a between-groups factor.

3. Results

For all activity measures, the means for the HiS and LoS rats were did not significantly differ ($p > 0.05$, see Fig. 1). As a secondary analysis, we analyzed the activity data in terms of time spent in the middle of the open field vs. that spent on the periphery. A 22.9 cm × 22.9 cm zone was defined in the center of the open field, and the time spent in this zone and in the remaining area was calculated. As with the other activity measures, the HiS and LoS rats did not

significantly differ (20.2 ± 4.7 vs. 10.8 ± 2.5 min for the LoS and HiS groups, respectively) ($t(21) = 1.83$, $p = 0.082$).

Figure 2 shows the number of pellets earned under the FR and PR schedules. There were significant main effects of phenotype ($F(1,21) = 24.55$, $p < 0.001$) and FR schedule ($F(3,63) = 33.38$, $p < 0.001$); the phenotype $\times$ schedule interaction was not significant ($p = 0.96$). In all cases, the HiS rats earned significantly more pellets than the LoS rats (t -tests, all p 's ≤ 0.001). As expected, the numbers of pellets earned decreased as work requirement increased. Under reinforcement schedules of FR 1 to FR10, HiS rats earned 77 to 185% more sucrose pellets than LoS rats; higher FR ratios produced larger percentage increases than lower FR ratios. The rat groups differed in presses of the active lever in a manner similar to the differences in the number of pellets earned. However, the phenotype $\times$ schedule interaction was also significant ($F(3,63) = 13.69$, $p < 0.001$). At FR1, LoS and HiS rats had 40.4 ± 7.2 and 66.6 ± 3.2 presses, respectively (a 65% increase); at FR10, the corresponding values were 113.5 ± 23.6 and 332.9 ± 42.9 (a 193% increase). Presses of the inactive lever were low, with the mean values never exceeding 4 presses. There were no significant differences in inactive lever presses between the groups under any reinforcement schedule (active and inactive lever data not shown).

On the PR schedule, the LoS and HiS groups differed by only 1.7 pellets obtained (6.3 ± 0.4 vs. 8.0 ± 0.5). Nevertheless, this difference was significant ($t(21) = 2.56$, $p = 0.018$). The median highest completed ratio was 12 for the LoS rats and 20 for the HiS rats. Because of the accelerating nature of the PR schedule, completion of these final ratios requires a minimum of 34 and 69 active lever-presses, respectively. The actual numbers of presses over the final four days prior to NTX testing were 54.4 ± 8.0 and 100.4 ± 15.0 for the LoS and HiS groups ($t(21) = 2.63$, $p = 0.016$). The increases above the minimum required are due to lever-presses during the time-out periods and presses that occurred after the highest completed ratio.

The results of the naltrexone trials are shown in Figure 3. An ANOVA indicated a significant effect of dose ($F(3,63) = 4.63$, $p = .005$) and of group ($F(1,21) = 7.23$, $p = .014$); however, the dose $\times$ group interaction was not significant ($p = .917$). *Post hoc* comparisons (Bonferroni, two-tailed) indicated that only the 3 mg/kg condition significantly reduced breakpoints compared to the NaCl condition ($p = 0.002$). This difference was also confirmed with repeated-measures t -tests applied separately to each rat group.

Because the present experiment was conducted in three partially overlapping cohorts, we visually inspected the operant data for the possibility of differences between cohorts. For the data represented in Figs. 2 and 3, which represent the effects of different reinforcement schedules and of multiple doses of naltrexone, the means of the HiS rats within each cohort are greater than the corresponding means of the LoS rats tested at the same time. The overall results, therefore, do not appear to be confounded by the use of multiple overlapping groups of HiS and LoS rats.

The differences in body weight are likely the consequence of the limited availability of the animals rather than a phenotype difference (see Introduction). To help rule out the influence of body weight in the present study, we examined the correlations within each group (HiS and LoS) between the various measures of operant responding (average of the final four sessions under each reinforcement schedule, and performance after injections of saline and naltrexone) and the average body weights taken on the days the trials were conducted. Operant performance was not significantly correlated with body weight in either group for any of the operant measures (all p 's > 0.05). Weight differences, therefore, do not appear to have systematically influenced the results.

4. Discussion

As predicted, HiS and LoS rats, selectively bred on the basis of *ad libitum* drinking of saccharin and water, also differed correspondingly when a work requirement was imposed for obtaining a sucrose reward. Also as expected, differences in general activity do not appear to account for this difference. Differences in operant responding for sucrose might be expected, given that the reinforcer (sucrose) is similar in taste to saccharin, that HiS – LoS differences in sucrose intake have previously been reported, and that the two lines have been shown to differ in operant responding for cocaine. However, it is not always the case that the results of free-drinking (or free-eating) tests and operant tests show similar results. For example, mice lacking either β -endorphin or enkephalin showed reduced responding for chow or sucrose pellets on a PR schedule, but did not differ from wild-type mice in two-bottle free-choice tests with water and saccharin or sucrose solution [29]. Similarly, methadone is more effective at increasing food intake in free-feeding trials than in trials in which a lever press is required to obtain food [30]. This difference may be response-dependent, however, as methadone was more effective when the response requirement was a nosepoke rather than a lever press. Finally, Lewis rats were observed to have a greater preference for 10% ethanol than Sprague Dawley (SD) rats in two-bottle free-drinking tests, but in operant self-administration tests, SD rats showed greater intake of 8% ethanol than Lewis rats [31]. Hayward *et al.* [29,32] interpret two-bottle free-choice and PR responding procedures as indicators of consummatory and appetitive behavior, respectively. In the present study, the HiS and LoS rat lines, which were selectively bred on the basis of a saccharin consummatory behavior, also differed in sucrose appetitive behavior. To our knowledge, these rat lines have not been tested for appetitive behavior for other highly palatable foods or tastes.

In measures of locomotor activity in a circular open field, LoS rats have been observed to have higher activity than HiS rats [26,27]. This difference was more pronounced in females than males, and was not seen on the next exposure to the same apparatus [27]. Carroll *et al.* [21] suggested this difference (LoS > HiS) was due more to greater response to novelty by the LoS rats than to an innate difference in activity levels. Similarly, Dess and Minor [17] found that latency to emerge into a novel open field was longer in LoS than in HiS rats, but the lines did not differ in a subsequent brief open field test. When rats were housed in cages with attached running wheels, LoS rats exceeded HiS in wheel-running activity, particularly during nocturnal testing [20]. In the present study, LoS rats did not significantly differ from HiS rats on any measure of activity. These results suggest that differences in sucrose-seeking behavior are not simply due to overall differences in activity.

Endogenous opioids and their receptors are thought to play a role in mediating the rewarding or hedonic aspects of sweet taste (see [28] for review). It was therefore reasoned that HiS and LoS rats may differ in their response to an opioid antagonist. However, both groups responded approximately equally to NTX, and only the highest dose (3 mg/kg) caused a significant reduction in the PR breakpoint. In food-restricted or food-deprived rats, naloxone has been found to be more effective in reducing intake of a preferred diet compared to a non-preferred diet [33], and more effective at reducing the intake of sweetened diets than that of non-sweet diets; doses as low as 0.3 mg/kg were found to have significant effects [34,35]. When rats were responding for sucrose pellets on a FR40 schedule, the lowest naloxone dose to significantly reduce the number of reinforcer deliveries was 3.0 mg/kg for rats maintained on a grain-based diet, and 0.3 mg/kg for rats maintained on a sucrose-based diet [36]. Cleary *et al.* [37] compared the effect of naloxone on the intake of a sucrose solution in free-drinking trials to its effect when rats responded for the solution under on a PR schedule of reinforcement. In free-drinking trials, naloxone doses as low as 0.3 mg/kg significantly reduced the intake of 5 and 10% solutions. However, under the PR schedule, the effect of naloxone was dependent on the sucrose concentration; doses from 1 – 10 mg/kg reduced the breakpoint for 5% sucrose, yet

doses as high as 10 mg/kg had no significant effect on the breakpoint for 10% sucrose. The results of the current study are in general agreement with the aforementioned studies, in that a relatively large dose of naltrexone was required to significantly reduce breakpoints. Although opioids appear to be involved in mediating food and taste reward, these results do not offer any evidence that differences in the activity of endogenous opioid systems contribute to the differences between HiS and LoS rats in sucrose consumption. However, additional comparisons with other feeding/drinking tests and conditions may provide additional information in this regard.

In summary, rats selectively bred for high or low saccharin intake also displayed corresponding differences in appetitive behavior for sucrose. The differences could not be accounted for by differences in general locomotor activity, and the two lines do not appear to differ in endogenous opioid tone. However, additional research is required to definitively rule these possibilities out. These studies provide further characterization of the HiS and LoS rat lines which may be useful in additional studies on the relationship between food and drug reward.

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Fig. 1.

Locomotor activity of LoS and HiS rats ($n = 11$ and 12 , respectively) in a 90 min trial conducted on the day before operant trials began. The vertical axis on the left (photocell counts) applies to measurements of ambulatory, stereotypic and vertical activity (bars and lines represent means and standard errors). The right vertical axis applies to distance traveled. There were no significant group differences (t -tests, all p -values > 0.05).

Fig. 2. Number of sucrose pellets earned by LoS and HiS rats under fixed-ratio (FR) and progressive ratio (PR) schedules of reinforcement. For all schedules, the groups were significantly different (*t*-tests, * $p < 0.02$).

Fig. 3.

The effect of naltrexone on responding for sucrose pellets on a PR schedule. There were significant overall effects of group and dose ($p = 0.014$ and 0.005 , respectively); the interaction was not significant ($p > 0.9$). The 3 mg/kg condition was significantly different from the control (NaCl) condition (Bonferroni *post hoc* comparison (* $p = 0.002$)).