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Prior access to a sweet is more protective against cocaine self-administration in female rats than male rats

Angie M. Cason¹ and Patricia S. Grigson

Department of Neural and Behavioral Sciences, The Pennsylvania State University, College of Medicine, Hershey, PA 17033, United States of America

Abstract

It is well established that female rats are more sensitive than male rats to the reinforcing effects of cocaine (Lynch, 2008 for review). We hypothesized that greater preference for cocaine would support greater avoidance of a cocaine-paired taste cue in female vs. male rats. Moreover, at least in male rats, greater avoidance of the taste cue is associated with greater cocaine self-administration (Grigson & Twining, 2002). Thus, we anticipated that female rats would not only demonstrate greater avoidance of the drug-paired taste cue, but greater drug-taking as well. We tested these hypotheses by examining avoidance of a saccharin cue in male and female rats following several pairings with self-administered saline or cocaine (0.16, 0.33, or 0.66 mg/infusion). Contrary to expectations, the results showed that female rats exhibited less avoidance of the cocaine-associated saccharin cue than male rats and self-administered less, rather than more, cocaine. Thus, while female rats reportedly take more drug than male rats when the drug is presented in the absence of an alternative reward, they take less drug than male rats when the opportunity to self-administer cocaine is preceded by access to a palatable sweet. Females, then, may not simply be more sensitive to the rewarding properties of drug, but also to the reinforcing properties of natural rewards and this increase in sensitivity to sweets may serve to protect against drug-taking behavior.

Keywords

reward; sex differences; drug abuse; conditioning; cocaine; self-administration

1.1 Introduction

Rats suppress intake of a saccharin solution that predicts the administration of a drug of abuse [1–5]. It has long been believed that avoidance of the drug-paired taste cue is due to aversive drug properties and, as such, is mediated by a conditioned taste aversion like that induced by the aversive agent LiCl [6, 7]. Other evidence, however, suggests that the suppressive effects of drugs of abuse can be caused, at least in part, by devaluation of the

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Correspondence to: Angie M. Cason, Ph.D., Medical University of South Carolina, Department of Neuroscience, 173 Ashley Avenue, Suite 403 BSB, Charleston, SC 29425, United States of America, casona@musc.edu, Telephone: (843) 792-5289, Fax: (843) 792-4423¹.

¹Permanent Address: Angie M. Cason, Ph.D. Medical University of South Carolina, Department of Neuroscience, 173 Ashley Avenue, Suite 403 BSB, Charleston, SC 29425 United States of America

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natural reward (i.e., the saccharin cue) in anticipation of the availability of the more potent drug reward. This phenomenon, referred to as reward comparison, was described by Grigson (1997) and is thought to be similar to the anticipatory contrast effect in which rats avoid intake of the same saccharin cue when it predicts the opportunity to consume a highly rewarding sucrose solution [8–10]. In support, reward-sensitive Lewis rats are more sensitive to the suppressive effects of cocaine and sucrose, but not LiCl, than are less sensitive Fischer 344 rats [11–13]. In Sprague-Dawley rats, a history of treatment with chronic morphine leads to greater avoidance of a taste cue paired with cocaine or sucrose, but not the aversive agent, LiCl [14]. Additionally, bilateral lesions centered on the gustatory thalamus or gustatory insular cortex have no effect on a LiCl-induced conditioned taste aversion, but fully prevent the suppressive effects of a rewarding sucrose solution, morphine, and a standard dose of cocaine [2, 15–20]. Anticipation of the rewarding effects of a drug of abuse, then, may contribute to avoidance of the drug-associated taste cue.

In addition to drug-induced devaluation of natural rewards, evidence suggests that a second process is at play and this process involves aversion. For example, some time ago, we reported that avoidance of the drug-paired taste cue is accompanied by elevated levels of circulating corticosterone [21]. Indeed, rats that consume the least of the drug-paired taste cue exhibit the greatest conditioned corticosterone response [21]. Avoidance of the taste cue is also accompanied by reduced levels of dopamine in the nucleus accumbens [22, 23]. Finally, earlier data showed that rats exhibit aversive orofacial responses (e.g., gapes) following the intraoral infusion of a taste cue paired with LiCl [24], but not when paired with passive administration of all manner of drugs of abuse [25–28]. More recent data, however, show that gapes clearly are emitted following the intraoral infusion of a taste cue that has been paired with the opportunity to self-administer cocaine and the greater this aversive taste reactivity behavior, the faster the rats take drug, the greater they load up at the start of a trial, and the faster they acquire stable drug-taking behavior across trials [29].

Taken together, these findings lead us to conclude that cue-induced anticipation of the drug does not only devalue the taste cue, by comparison, but also elicits the development of a conditioned aversive state that involves craving and withdrawal. In accordance, like drug-induced suppression of CS intake, withdrawal is associated with an increase in circulating corticosterone, a blunting of accumbens dopamine, and onset of aversive taste reactivity [21, 22, 29–32]. Withdrawal also is associated with a loss of body weight [33] and we recently showed that consumption of a morphine- or cocaine-paired taste cue was sufficient to elicit naloxone-induced loss of body weight and greater withdrawal (by this index) predicted greater drug taking [34].

It is well known that there are significant gender differences in the development of cocaine addiction, propensity to relapse and response to treatment [35–38]. Females acquire self-administration faster than males, show enhanced locomotor responses to cocaine, and stronger preference for environments paired with cocaine [39–43]. Furthermore, females show greater resistance to extinction [44], greater motivation for cocaine during progressive ratio testing following a period of abstinence [39, 41–43, 45, 46], and enhanced cocaine-primed reinstatement [47, 48]. The biological mechanisms underlying these sex differences are primarily due to circulating gonadal hormones in the female rat [41, 43, 45, 48, 49]. Estrogen promotes drug-taking behavior and locomotor sensitization and progesterone counteracts the effects of estrogen and prevents reinstatement [41, 43, 48–51]. Therefore, whether mediated by reward comparison and/or by cue-induced craving/withdrawal, the greater propensity by female rats to take drug should support greater avoidance of a natural reward cue (i.e., saccharin). In male rats, greater avoidance of the drug-paired taste cue is associated with greater cocaine self-administration [3, 52]. A similar pattern is expected in female rats although other studies have shown minimal sex differences in suppression of CS

intake when paired with experimenter delivered drugs of abuse, including cocaine [53–55]. The present study tested the above hypotheses by examining avoidance of a saccharin cue in male and female rats following several pairings with iv self-administration of saline or a range of doses of cocaine using fixed ratio and progressive ratio schedules of reinforcement.

1.2 Methods

1.2.1 Subjects

The subjects were age-matched, female (n=41) and male (n=43) Sprague–Dawley rats (Charles River Laboratories, Raleigh, NC). Females weighed between 200–225 g and males weighed between 275–300 g at the start of the experiment. Within each sex, rats were divided into 4 conditioning groups. All rats were housed individually in standard hanging wire mesh cages, in a colony room with temperature, humidity, and ventilation automatically controlled. The rats were maintained on a 12-h light–dark cycle with the lights on at 0700 h. All experimental manipulations were conducted over an 8-h period starting 2 h into the light phase of the cycle. Except where otherwise noted, all rats were maintained on ad libitum food and water. All experiments were approved by the Pennsylvania State University, College of Medicine, Institutional Animal Care and Use Committee and conducted in accordance to the National Institutes of Health specifications outlined in their Guide for the Care and Use of Laboratory Animals.

1.2.2 Surgical implantation of jugular catheters

The catheters were custom made in our laboratory using a modified procedure previously described by Koob and colleagues (1987) [3, 56–57].

1.2.3 Catheter implantation

Rats were anesthetized using an intraperitoneal injection of a ketamine (70 mg/kg) and xylazine (16 mg/kg) mixture and then surgically implanted with a jugular catheter into the right jugular vein using a method similar to that described previously and routed subcutaneously to the dorsal surface of the rat [3]. The catheters were flushed daily with 0.2cc of heparinized saline to maintain catheter patency. When necessary, catheter patency was verified using Propofol (0.1 ml) followed by saline. Data were discarded from all rats that failed to show rapid loss of muscle tone during catheter patency testing.

1.2.4 Coupling assembly

Before the start of each self-administration session, a coupling assembly was attached to the catheter assembly. The coupling assembly was attached to a swivel system in the operant chamber that was connected to a syringe pump that allowed computer controlled intravenous infusion of cocaine and saline.

1.2.5 Operant Chambers

Standard operant chambers (MED Associates, St. Albans, VT) that measured 30.5 cm long × 24.0 cm wide × 29.0 cm high and were housed in a light- and sound-attenuating cubicle. All chambers had a combination of clear Plexiglas and aluminum walls and stainless steel rod floors, spaced 1.6 cm apart. Each chamber was equipped with three retractable sipper tubes that entered the chamber through 1.3-cm diameter holes in the front panel. A lickometer circuit was used to monitor licking. A stimulus light was located 6 cm above each tube. Each chamber was also equipped with a houselight (25 W). Cocaine delivery was controlled by an electronic circuit that operated a syringe pump. Events in the chamber and collection of the data were controlled with a Pentium computer that using the Med-PC program (MED Associates).

1.2.6 Water Deprivation

Following one week of recovery from catheter surgery, rats were placed on a water deprivation regimen with 5 min access to water on the home cage in the morning and 1 h access each afternoon. During the last five days of deprivation, rats received the 5-min a.m. access period in the operant chambers via the left spout in order to habituate them to the chamber.

1.2.7 Phase1: Fixed Ratio

During each session, the rat was attached to the catheter coupling assembly and placed in the operant chamber. The left tube advanced, and the rats were given 5 min access to the 0.15% saccharin conditioned stimulus (CS). Then, the CS tube retracted, and two empty tubes advanced, one in the center (inactive) and one on the right (active). A stimulus light was illuminated above the active empty spout on the right. A FR10 schedule of reinforcement was used in which completion of 10 licks on the active empty spout led to an iv infusion of the unconditioned stimulus (US), cocaine (0.16, 0.33 or 0.66 mg/kg) or saline over a 6-s period. Drug or saline delivery was signaled by offset of the stimulus light, retraction of the spout, and onset of the tone and house light, which remained on for a total of 20 s. Further responding during this time was not reinforced; nor was responding on the inactive spout. The total daily access period to cocaine or saline was 1.5 h. Supplemental water was provided for 1 h, no sooner than 45 min after the rats were returned to the home cage. There was one saccharin (CS) – cocaine (US) pairing a day for a total of 16 days under the FR10 schedule of reinforcement.

1.2.8 Phase 2: Progressive Ratio

A single PR session was conducted 1 or 40 days following the final FR10 trial in order to better assess the rewarding efficacy of cocaine in male and female rats. During the PR test, all rats were given 5 min access to the saccharin CS. Thereafter, the rats responded for saline or cocaine as described. The first infusion occurred after 10 licks, but the requirement for each subsequent cocaine infusion was increased by 20 licks. The session ended when 30 min elapsed without having earned an infusion. Break point was operationally defined as the last completed ratio.

1.2.9 Data Analysis

Fixed Ratio. Responding during fixed ratio trials (1–16) was assessed using a mixed factorial analysis of variance (ANOVA) with two between groups factors: sex (male vs. female) and dose (0, 0.16, 0.33, and 0.66 mg/kg); and one repeated measure: trials (1–16). Post hoc tests were conducted, where appropriate using Tukey's tests with alpha set at 0.05. Terminal intake was calculated by averaging the responses made for the CS (saccharin) or the US (saline or cocaine) across trials 15 and 16 and was analyzed using a 2×4 ANOVA varying sex and dose, respectively. These data provided insight on the effect of sex on responding in drug-experienced rats. Progressive Ratio. The timing of the PR test (1 or 40 days following acquisition) had no effect on behavior; thus, the data were combined for analysis. The Progressive Ratio data were then analyzed using a similar 2×4 ANOVA varying sex and dose and post hoc tests were conducted, where appropriate, as described above. Statistica, version 9 software from StatSoft was used for statistical analysis.

1.3 Results

Due to a loss of catheter patency, 4 rats contributed data to less than 16 trials and 11 rats did not contribute PR data. The available data from these rats (4 male; 7 female) were analyzed along with the data from the remaining rats. Despite our efforts to collect data on the estrous

cycle, these measures were complicated by unexpected disruptions in the light cycle. Consequently, these data will not be addressed further.

1.3.1 CS (Saccharin) Intake Across Self-administration Days

As expected, rats self-administering cocaine suppressed intake of the saccharin CS (Fig 1) compared to saline controls. A mixed 3-way ANOVA did not reveal a significant interaction between sex, dose, and test day; however, there was a significant main effect of sex $F(15,1050) = 6.17, p < 0.05$, dose $F(3,70) = 20.59, p < 0.001$, and test day $F(15,1050) = 4.49, p < 0.001$. Therefore, a repeated measure ANOVA was conducted comparing the effect of dose across test days within each sex. The results from the repeated measure ANOVA revealed a significant interaction between dose and test day in females, $F(45,510) = 3.53, p < 0.001$, and in males $F(45,540) = 3.86, p < 0.001$. Female and male rats avoided the saccharin CS when it predicted the high dose (0.66 mg/kg) of the cocaine US. In addition, male rats avoided the saccharin CS when it predicted the low and the medium doses (0.16 and 0.33 mg/kg) of the cocaine US. These same doses were ineffective in suppressing intake of the saccharin CS in female rats (Fig 1).

1.3.2 Terminal CS (Saccharin) Intake

The terminal amount of CS (saccharin) intake was calculated by averaging CS intake on self-administration days 15 and 16 only. A 2-way ANOVA revealed a significant interaction between sex and dose, $F(3,71) = 3.21, p < 0.05$ (see Fig 2A). Overall, the results showed that rats avoided the saccharin CS when it predicted the opportunity to self-administer the cocaine US and the magnitude of this effect varied as a function of dose and was smaller in female rats. Thus, while male rats consumed significantly less of the saccharin cue when paired with either the low, medium, or high dose of cocaine, $ps < .05$, female rats suppressed intake relative to their saline treated controls only when the saccharin cue was paired with the medium or the high dose of the drug, $ps < .05$. The low dose, on the other hand, was without effect, $p > .05$.

1.3.3 Progressive Ratio CS (Saccharin) Intake

The results of a 2-way ANOVA revealed a non-significant interaction between sex and dose (Fig 2B). The main effect of dose was significant, $F(3,63) = 20.14, p < 0.001$, and post hoc test revealed that all three doses of cocaine were effective at suppressing intake of the saccharin cue relative to intake by the saline treated controls, overall, $ps < .05$. The main effect of sex approached but did not reach statistical significance, $F(1,63) = 3.43, p = 0.07$. Thus, as with the terminal CS intake data, there was a strong tendency for the female rats to consume more of the saccharin cue than male rats overall.

1.3.4 US (Cocaine) Intake Across Self-administration Days

As expected rats in the cocaine paired groups took more infusions than saline rats, and cocaine intake increased across test days (Fig 3). A 3-way mixed factorial ANOVA did not reveal a significant interaction between sex, dose, and test day. However, there was a significant main effect of sex, $F(1,69) = 23.14, p < 0.001$, dose, $F(3,69) = 12.10, p < 0.001$, and test day, $F(15,1035) = 5.15, p < 0.001$. Therefore, a repeated measure ANOVA was conducted comparing the effect of dose across test days within each sex. The results revealed a significant interaction between dose and test day in females, $F(45,510) = 1.73, p < 0.01$, and in males, $F(45,525) = 2.66, p < 0.001$ (Fig 3). Post hoc analysis indicated that female and male rats took more infusions of the medium and high doses of cocaine (0.33 or 0.66 mg/kg) than saline ($p < 0.05$). In addition, male rats took more infusions of the lowest cocaine dose (0.16 mg/kg) than saline ($p < 0.05$).

1.3.5 Terminal US (Cocaine) Intake

In general, female rats took fewer terminal infusions of cocaine than male rats (Fig 4). When assessed for terminal US (cocaine) intake, a 2-way ANOVA revealed a significant interaction between sex and dose, $F(3,71) = 4.18$, $p < 0.01$ (Fig 4A). Specifically, at the end of self-administration testing, female rats took significantly more infusions of cocaine than saline, but this effect only attained statistical significance at the 0.33 mg/kg dose of the drug, $p < .05$. Male rats, on the other hand, took more infusions of cocaine than saline at both the 0.16 and 0.33 mg/kg doses, $ps < .05$. Furthermore, males given the 0.16 mg/kg and 0.33 mg/kg dose took more infusions of cocaine than their female counterparts, $ps < .05$.

1.3.6 Progressive Ratio US (Cocaine) Intake

A 2-way ANOVA did not reveal a significant interaction between sex and dose in the number of infusions taken during PR testing (Fig 4B). There was a significant main effect of dose, $F(3,63) = 8.2$, $p < 0.001$, and post hoc tests showed that rats self-administered significantly more infusions of the 0.33 mg/kg and 0.66 mg/kg doses of cocaine than saline, overall, $ps < .05$. The main effect of sex also was significant, $F(3,63) = 7.75$, $p < 0.01$, indicating that, on the whole, female rats took fewer infusions during progressive ratio testing than male rats.

1.3.7 Correlation between CS (saccharin) and US (cocaine) intake

Correlation analysis of terminal CS and US intake were conducted in female and male rats independently (Fig 5). The results of the correlational analyses showed that terminal CS (saccharin) and US (cocaine) intake were significantly correlated in female rats ($r = -0.69$, $p < 0.001$) and in male rats ($r = -0.73$, $p < 0.001$). Thus, as previously shown for male rats [3, 52], greater avoidance of the saccharin cue also is associated with greater cocaine self-administration in female rats.

1.4 Discussion

As has occurred previously in male rats [3, 5, 52], all rats, male and female alike, avoided intake of the saccharin CS when it was paired with the opportunity to self-administer cocaine. The magnitude of this effect, however, was smaller in the female rats. Thus, while male and female rats in the saline condition consumed an equivalent amount of saccharin, female rats consumed more of the cocaine-paired saccharin cue than did similarly treated male rats. Although females consumed more of the cocaine-paired saccharin cue, they responded less for drug than did the male rats. Specifically, female rats took fewer infusions of cocaine than males when tested on a fixed ratio schedule of reinforcement and they were less willing to work for drug on a progressive ratio schedule of reinforcement. In addition, consistent with earlier reports in male rats, greater avoidance of the taste cue also was correlated with greater drug-taking in female rats [3, 52].

As described, this is opposite to that which was expected on the basis of the literature showing that female rats generally take more drug than male rats [58, 59]. So, why might female rats have taken less drug than male rats in this study? Of course, there are several methodological differences between our study and previous studies. For example, our laboratory used an empty spout for the operant instead of a lever or nose poke. It is, however, unlikely that the use of the empty spout operant is responsible for this finding because we have found comparable self-administration data using a FR10 schedule of reinforcement with a lever [3]. Another difference is the length of the access period to cocaine. In our study, rats were given 1.5 hours to self-administer cocaine. This is very different from the 6-hour long-term access period typically used by Carroll and colleagues and others [39, 43, 46, 48, 60]. That said, the access period used in this study was similar to

that used in other studies that also found females to be more susceptible than males to cocaine [41, 45].

Without a doubt, the main methodological difference is that, in the present study, the opportunity to self-administer cocaine was preceded each day by brief access to a sweet saccharin solution. Thus, while we have reported that drugs of abuse can devalue natural rewards, we also have argued that natural rewards (specifically sensitivity to natural rewards) can protect against responding for drug [61], (see Grigson, 2008 for a discussion) [62, 63]. In accordance, there is evidence that the availability of alternative natural rewards can facilitate abstinence in the addicted human [64–66] and can reduce acquisition of drug-taking behavior in rats [64, 67–70]. Furthermore, the findings from a recent study by Dietrich et. al (2012) indicate that increased appetite for food is associated with decreased interest in novelty as well as in cocaine, while on the other hand less interest in food can predict increased interest in cocaine [71]. Taken together with the present data, these findings suggest that alternative natural rewards can be highly protective and, in our study, that the magnitude of this protective effect is accentuated in female rats.

According to the reward comparison hypothesis, rats reduce intake of a taste cue following taste-drug pairings because they are anticipating the availability of a preferred drug reward [8]. By this account, one might conclude that female rats evidenced less suppression of intake of the saccharin cue because they attribute less value to the cocaine US. On the face of it, this seems an unlikely accounting as several studies have shown that females are more, not less, sensitive to the rewarding properties of cocaine than males and they are willing to work harder for the drug [39, 41, 43, 45, 46]. That said, this was not the case in the present experiment. The female rats took less drug, suggesting that, under present conditions, they found the drug less rewarding than did the male rats. Thus, we speculate that the perceived rewarding properties of the drug may have been reduced in female rats by the potent perceived rewarding properties of the sweet cue. As mentioned, this finding is of particular significance as female rats are consistently found to respond more for cocaine than male rats when no sweet cue is provided [50, 51]. Future studies using a neutral CS such as water, and in the absence of water restriction are needed to test the merits of this hypothesis.

So, why are the female rats better protected by the sweet? One explanation is that females simply find the sweet solution more rewarding than their male counterparts. There is, in fact, a great deal of data to support this suggestion. Early studies showed that female rats consumed more glucose and saccharin than male rats. For example, when males were given a choice, they switched their initial preference from saccharin to glucose, while females maintained their initial preference for saccharin [72]. Females also consume more saccharin during two-bottle tests than males [73]. More recently, basic taste reactivity tests have shown that females produce more ingestive responses to sucrose and fewer aversive responses to quinine than male rats [74]. These sex differences in ingestive behavior could explain why the magnitude of CS suppression was reduced in female compared to male rats (but see also Tordoff et al. 2008 [75]). As mentioned, reward-preferring mice with elevated expression of delta-FosB in the nucleus accumbens also exhibit less avoidance of a cocaine-paired saccharin cue [61] as do reward-preferring C57BL/6J mice compared to less-preferring DBA mice [76].

A key point is not necessarily that the female rats consumed more of the cocaine-paired saccharin cue than similarly treated male rats, but that female rats, so treated, actually took fewer infusions of cocaine than male rats on the FR schedule of reinforcement. This is of particular significance as females are consistently found to respond more for cocaine than male rats [58, 59]. Notably, when cocaine intake was compared on a mg/kg basis, male rats took the same amount of cocaine regardless of whether they received the 0.33 mg/kg or 0.66

mg/kg dose of cocaine (i.e. while they took more infusions of the 0.33 mg/kg dose compared to the 0.66 mg/kg, the total mg/kg intake was similar between the groups). Females, on the other hand, took a similar number of infusions of the 0.33 mg/kg dose and the 0.66 mg/kg dose. Therefore, total intake of cocaine in females actually was greater at the 0.66 mg/kg dose than the 0.33 mg/kg dose. Taken together, these data suggest that the amount of cocaine obtained rather than the number of CS/US pairings is critical for producing the associated decrease in CS consumption.

For male rats, greater avoidance of the saccharin cue was associated with greater responding for drug. As stated, this is consistent with our previous findings [3, 52]. Interestingly, although the female rats consumed more of the saccharin cue and less of the drug of abuse than their male counterparts, greater avoidance of the taste cue also was correlated with greater drug-taking in the female rats. In male rats, greater avoidance of the taste cue is correlated with higher levels of circulating corticosterone [21] and the onset of greater conditioned aversive taste reactivity (i.e., gapes) when the cocaine-paired cue is directly infused into the oral cavity. Greater aversive taste reactivity, in turn, predicts a shorter latency to take cocaine, greater load up on drug at the start of a session, and faster acquisition of cocaine self-administration over trials [29]. These findings led us to conclude that, with experience, avoidance of the drug-paired taste cue is due to the onset of an aversive conditioned state involving withdrawal [34]. Were we to extrapolate to females, we would hypothesize that a similar pattern of behavior is evident in female rats, but that presentation of the sweet cue serves to lessen the magnitude of the conditioned aversive state (i.e., to lessen conditioned craving and withdrawal) and, consequently, to lessen subsequent drug-seeking and drug-taking. This is a critical and testable hypothesis.

1.5 Conclusions

In conclusion, rats suppressed intake of the cocaine-paired saccharin cue. The magnitude of this effect was reduced in female rats, indicating that cocaine exerts less of a suppressive effect on intake of the saccharin CS in female rats. These same rats also took less cocaine than did their male counterparts. Thus, while female rats generally are more sensitive than male rats to the rewarding properties of cocaine, this pattern is reversed when drug availability is preceded by even brief access to a saccharin reward cue. Female rats, then, may not simply be more sensitive to the rewarding properties of the drug, but also to the relative reinforcing properties of natural rewards and this increase in sensitivity to sweets, for example, may serve to protect against drug-seeking and drug-taking. If these findings have bearing on human disease, then one might argue that the use of alternative natural rewards may be highly beneficial in prevention and treatment of substance abuse and addiction in females.

References

1. Cappell H, LeBlanc AE. Parametric investigations of the effects of prior exposure to amphetamine and morphine on conditioned gustatory aversion. *Psychopharmacology (Berlin)*. 1977; 51:265–271. [PubMed: 403542]
2. Grigson PS, Twining RC, Carelli RM. Heroin-induced suppression of saccharin intake in water-deprived and free-feeding rats. *Pharmacol Biochem Behav*. 2000; 66:603–608. [PubMed: 10899377]
3. Grigson PS, Twining RC. Cocaine-Induced Suppression of Saccharin Intake: A Model of Drug-Induced Devaluation of Natural Rewards. *Behav Neurosci*. 2002; 116(2):321–333. [PubMed: 11996317]
4. Le Magnen J. Peripheral and systemic actions of food in caloric regulation of intake. *Ann NY Acad Sci*. 1969; 157:1126–1157. [PubMed: 5255624]

5. Wise RA, Yokel RA, DeWit H. Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. *Science*. 1976; 191:1273–1274. [PubMed: 1257748]
6. Davis CM, Riley AL. Conditioned taste aversion learning: implications for animal models of drug abuse. *Ann NY Acad Sc*. 2010; 1187:247–275. [PubMed: 20201857]
7. Garcia J, Koelling RA. A comparison of aversions induced by x-rays, toxins, and drugs in the rat. *Radiation Research Supplement*. 1967; 7:439–450. [PubMed: 6058671]
8. Grigson PS. Conditioned taste aversions and drugs of abuse: a reinterpretation. *Behav Neurosci*. 1997; 111(1):129–136. [PubMed: 9109631]
9. Flaherty, CF. Incentive relativity. New York: Cambridge University Press; 1996.
10. Flaherty CF, Checke S. Anticipation of incentive gain. *Anim Learn Behav*. 1982; 10:177–182.
11. Glowa JR, Shaw AE, Riley AL. Cocaine-induced conditioned taste aversions: comparisons between effects in LEW/N and F344/N rat strains. *Psychopharmacology (Berlin)*. 1994; 114(2): 2299–2232.
12. Grigson PS, Freet CS. The suppressive effects of sucrose and cocaine, but not lithium chloride, are greater in Lewis than in Fischer rats: evidence for the reward comparison hypothesis. *Behav Neurosci*. 2000; 114(2):353–363. [PubMed: 10832796]
13. Verendevev A, Riley AL. Relationship between the rewarding and aversive effects of morphine and amphetamine in individual subjects. *Learn Behav*. 2011; 39(4):399–408. [PubMed: 21710342]
14. Grigson PS, Wheeler RA, Wheeler DS, Ballard SM. Chronic morphine treatment exaggerates the suppressive effects of sucrose and cocaine, but not lithium chloride, on saccharin intake in Sprague-Dawley rats. *Behav Neurosci*. 2001; 115(2):403–416. [PubMed: 11345965]
15. Flynn FW, Schulkin J, Grill HJ, Norgren R. Central gustatory lesions: II. Effects on sodium appetite, taste aversion learning, and feeding behaviors. *Behav Neurosci*. 1991; 105:944–954. [PubMed: 1777107]
16. Geddes RI, Han L, Baldwin AE, Grigson PS. Gustatory insular cortex lesions disrupt drug-induced, but not lithium chloride-induced, suppression of conditioned stimulus intake. *Behav Neurosci*. 2008; 122(5):1038–1050. [PubMed: 18823161]
17. Reilly S, Pritchard TC. Gustatory thalamus lesions in the rat: II. Aversive and appetitive taste conditioning. *Behav Neurosci*. 1996; 110:746–759. [PubMed: 8864266]
18. Reilly S, Trifunovic R. Progressive ratio performance in rats with gustatory thalamic lesions. *Behav Neurosci*. 1999; 113:1008–1019. [PubMed: 10571483]
19. Scalera G, Grigson PS, Norgren R. Gustatory functions, sodium appetite, and conditioned taste aversion survive excitotoxic lesions of the thalamic taste area. *Behav Neurosci*. 1997; 111:633–645. [PubMed: 9189278]
20. Schroy PL, Leuenberger E, Wheeler RA, Grigson PS. Female rats, like male rats, exhibit individual differences in cocaine-induced avoidance of saccharin intake and greater avoidance of the tastant is associated with greater conditioned elevations in circulating corticosterone levels at test. *Appetite*. 2002; 39:98.
21. Gomez F, Leo NA, Grigson PS. Morphine-induced suppression of saccharin intake is correlated with elevated corticosterone levels. *Brain Res*. 2000; 863(1–2):52–58. [PubMed: 10773192]
22. Grigson PS, Hajnal A. Once is too much: conditioned changes in accumbens dopamine following a single saccharin-morphine pairing. *Behav Neurosci*. 2007; 121(6):1234–1242. [PubMed: 18085877]
23. Wheeler RA, Aragona BJ, Fuhrmann KA, Jones JL, Day JJ, Cacciapaglia F, Wightman RM, Carelli RM. Cocaine cues drive opposing contextdependent shifts in reward processing and emotional state. *Biol Psychiatry*. 2011; 69(11):1067–1074. [PubMed: 21481843]
24. Grill HJ, Norgren R. The taste reactivity test: II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. *Brain Res*. 1978; 143:281–297. [PubMed: 630410]
25. Parker LA. Positively reinforcing drugs may produce a different kind of CTA than drugs which are not positively reinforcing. *Learn Motiv*. 1988; 19:207–220.
26. Parker LA. Taste reactivity responses elicited by reinforcing drugs: A dose-response analysis. *Behav Neurosci*. 1991; 105:955–964. [PubMed: 1777108]

27. Parker LA. Taste reactivity responses elicited by cocaine-, phencyclidine-, and methamphetamine-paired sucrose solutions. *Behav Neurosci.* 1993; 107:118–129. [PubMed: 8447949]
28. Parker LA. Rewarding drugs produce taste avoidance, but not taste aversion. *Neurosci Biobehav R.* 1995; 19:143–151.
29. Wheeler RA, Twining RC, Jones JL, Slater JM, Grigson PS, Carelli RM. Behavioral and electrophysical indices of negative affect predict cocaine self-administration. *Neuron.* 2008; 57(5): 774–785. [PubMed: 18341996]
30. McDonald R, Parker L, Siegel S. Conditioned sucrose aversions produced by naloxone-precipitated withdrawal from acutely administered morphine. *Pharmacol Biochem Behav.* 1997; 58(4):1003–1008. [PubMed: 9408206]
31. Nunez C, Foldes A, Laorden M, Milanes M, Kovacs K. Activation of stress-related hypothalamic neuropeptide gene expression during morphine withdrawal. *J Neurochem.* 2007; 101(4):1060–1071. [PubMed: 17286593]
32. Shaham Y, Stewart J. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology (Berl).* 1995; 119(3):334–341. [PubMed: 7675970]
33. Nozaki M. Assessment of morphine-type physical dependence liability: a screening method using the rat. *Psychopharmacology.* 1976; 47:225–235. [PubMed: 823558]
34. Nyland JE, Grigson PS. A drug-paired taste cue elicits withdrawal and predicts cocaine self-administration. *Behav Brain Res.* 2013; 240:87–90. [PubMed: 23174208]
35. Doyle SE, Breslin FJ, Rieger JM, Beauglehole A, Lynch WJ. Time and sex-dependent effects of an adenosine A2A/A1 receptor antagonist on motivation to self-administer cocaine in rats. *Pharmacol Biochem Behav.* 2012; 102(2):257–263. [PubMed: 22579716]
36. Fattore L, Altea S, Fratta W. Sex differences in drug addiction: a review of animal and human studies. *Womens Health (London).* 2008; 4:51–65.
37. Anker JJ, Carroll ME. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. *Curr Top Behav Neurosci.* 2011; 8:73–96. [PubMed: 21769724]
38. Becker JB, Perry AN, Westenbroek C. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. *Biol Sex Differ.* 2012; 3(1):14. [PubMed: 22676718]
39. Carroll ME, Morgan AD, Lynch WJ, Campbell UC, Dess NK. Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. *Psychopharmacology.* 2002; 161(3):304–313. [PubMed: 12021834]
40. Festa ED, Russo SJ, Gazi FM, Niyomchai T, Kemen LM, Lin SN, Foltz R, Jenab S, Quinones-Jenab V. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. *Neuropharmacology.* 2004; 46(50):672–687. [PubMed: 14996545]
41. Jackson LR, Robinson TE, Becker JB. Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. *Neuropsychopharmacology.* 2006; 31(1):129–138. [PubMed: 15920500]
42. Lynch WJ. Acquisition and maintenance of cocaine self-administration in adolescent rats: effects of sex and gonadal hormones. *Psychopharmacology.* 2008; 197:237–246. [PubMed: 18066534]
43. Roberts DC, Bennett SA, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. *Psychopharmacology (Berlin).* 1989; 98(3):408–411. [PubMed: 2501818]
44. Fuchs RA, Evans KA, Mehta RH, Case JM, See RE. Influence of sex and estrous cyclicity on conditioned cue-induced reinstatement of cocaine-seeking behavior in rats. 2005
45. Hu M, Crombag HS, Robinson TE, Becker JB. Biological basis of sex differences in the propensity to self-administer cocaine. *Neuropsychopharmacology.* 2004; 29(1):81–85. [PubMed: 12955098]
46. Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. *Psychopharmacology (Berlin).* 1999; 144(1):77–82. [PubMed: 10379627]
47. Kippin TE, Fuchs RA, Mehta RH, Case JM, Parker MP, Bimonte-Nelson HA, See RE. Potentiation of cocaine-primed reinstatement of drug seeking in female rats during estrus. *Psychopharmacology (Berlin).* 2005; 182(2):245–252. [PubMed: 16001116]

48. Lynch WJ, Arizzi MN, Carroll ME. Effects of sex and the estrous cycle on regulation of intravenously self-administered cocaine in rats. *Psychopharmacology (Berlin)*. 2000; 152(2):132–139. [PubMed: 11057516]
49. Lynch WJ, Roth ME, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. *Psychopharmacology (Berlin)*. 2002; 164(2):121–137. [PubMed: 12404074]
50. Feltenstein M, See R. Plasma progesterone levels and cocaine seeking in freely cycling female rats across the estrous cycle. *Drug Alcohol Depend*. 2007; 89(2–3):183–189. [PubMed: 17240083]
51. Quinones-Jenab V, Jenab S. Progesterone attenuates cocaine-induced responses. *Horm Behav*. 2010; 58(1):22–32. [PubMed: 19819242]
52. Twining RC, Bolan M, Grigson PS. Yoked delivery of cocaine is aversive and protects against the motivation for drug in rats. *Behav Neurosci*. 2009; 123(4):913–925. [PubMed: 19634952]
53. Roma PG, Davis CM, Kohut SJ, Huntsberry ME, Riley AL. Early maternal separation and sex differences in the aversive effects of amphetamine in adult rats. *Physiol Behav*. 2008; 93:897–904. [PubMed: 18230402]
54. Rinker JA, Busse GD, Riley AL. An assessment of sex differences in nicotine-induced conditioned taste aversions. *Pharmacol Biochem Behav*. 2008; 88:427–431. [PubMed: 17945339]
55. Jones JD, Busse GD, Riley AL. Strain-dependent sex differences in the effects of alcohol on cocaine-induced taste aversions. *Pharmacol Biochem Behav*. 2006; 83:554–560. [PubMed: 16650466]
56. Koob GF, Le HT, Creese I. The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neurosci Lett*. 1987; 79(3):315–320. [PubMed: 2958724]
57. Liu C, Grigson PS. Brief access to sweets protect against relapse to cocaine-seeking. *Brain Res*. 2005; 1049(1):128–131. [PubMed: 15935999]
58. Anker JJ, Ziebnik NE, Navin SF, Carroll ME. Responding during signaled availability and nonavailability of iv cocaine and food in rats: age and sex differences. *Psychopharmacology (Berlin)*. 2011; 215(4):785–799. [PubMed: 21301816]
59. Cummings JA, Gowl BA, Westenbroek C, Clinton SM, Becker JB. Effects of a selectively bred novelty-seeking phenotype on the motivation to take cocaine in male and female rats. *Biological Sex Differences*. 2011; 11(2):3.
60. Campbell UC, Morgan AD, Carroll ME. Sex differences in the effects of baclofen on the acquisition of intravenous cocaine self-administration in rats. *Drug Alcohol Depend*. 2002; 66(1):61–69.
61. Freet CS, Tesche JD, Tompers DM, Riegel KE, Grigson PS. Lewis rats are more sensitive than Fischer rats to successive negative contrast, but less sensitive to the anxiolytic and appetite-stimulating effects of chlordiazepoxide. *Pharmacol Biochem Behav*. 2006; 85(2):378–384. [PubMed: 17049372]
62. Grigson PS. The state of the reward comparison hypothesis: theoretical comment on Huang and Hsiao (2008). *Behav Neurosci*. 2008; 122(6):1383–1390. [PubMed: 19045958]
63. Freet CS, Steffen C, Nestler EJ, Grigson PS. Overexpression of DeltaFosB is associated with attenuated cocaine-induced suppression of saccharin in mice. *Behav Neurosci*. 2009; 123(2):397–407. [PubMed: 19331462]
64. Cosgrove KP, Hunter RG, Carroll ME. Wheel-running attenuates intravenous cocaine self-administration in rats: sex differences. *Pharmacol Biochem Behav*. 2002; 73(3):663–671. [PubMed: 12151042]
65. Donny EC, Bigelo GE, Walsh SL. Assessing the initiation of cocaine self-administration in humans during abstinence: effects of dose, alternative reinforcement, and priming. *Psychopharmacology (Berlin)*. 2004; 172(3):316–323. [PubMed: 14647955]
66. Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Badger G. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiat*. 1993; 150:763–769. [PubMed: 8480823]
67. Carroll ME, Lac ST, Nygaard SL. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. *Psychopharmacology (Berlin)*. 1989; 97(1):23–29. [PubMed: 2496421]
68. Carroll ME, Lac ST. Effects of buprenorphine on self-administration of cocaine and a nondrug reinforcer in rats. *Psychopharmacology (Berlin)*. 1992; 106(4):439–446. [PubMed: 1579619]

69. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *Plos One*. 2007; 2(8):e698. [PubMed: 17668074]
70. Vendruscolo LF, Gueye AB, Darnaudéry M, Ahmed SH, Cador M. Sugar overconsumption during adolescence selectively alters motivation and reward function in adult rats. *Plos One*. 2010; 5(2):e9296. [PubMed: 20174565]
71. Dietrich MO, Bober J, Ferreira JG, Tellez LA, Minuer YS, Souza DO, Gao XB, Picciotto MR, Araujo I, Liu ZW, Horvath T. AgRP neurons regulate development of dopamine neuronal plasticity and nonfood-associated behaviors. *Nature Neuroscience*. 2012; 15(8):1108–1110.
72. Valenstein ES, Kakolewski JW, Cox VR. Sex differences in taste preference for glucose and saccharin solutions. *Science*. 1967; 156(3777):942–943. [PubMed: 6023257]
73. Zucker I. Hormonal determinants of sex differences in saccharin preference, food intake and body weight. *Physiol and Behav*. 1969; 4:595–602.
74. Clarke SN, Ossenkopp KP. Taste reactivity responses in rats: influence of sex and the estrous cycle. *Am J Physiol*. 1998; 274(3 Pt 2):R718–R724. [PubMed: 9530238]
75. Tordoff MG, Alarcon LK, Lawler MP. Preferences of 14 rat strains and 17 taste compounds. *Physiol Behav*. 2008; 95:308–332. [PubMed: 18639567]
76. Freet CS, Motter A, Grigson PS. Compared with DBA/2J mice, C57BL/6J mice demonstrate greater preference for saccharin and less avoidance of a cocaine-paired saccharin cue. (Submitted).

Highlights

- Rats suppress intake of cocaine when it is preceded by access to saccharin
- Saccharin-induced suppression of cocaine intake is greater in female rats than males.
- Increased sensitivity to sweets in females may protect against drug-taking behavior.

Figure 1.

Saccharin (CS) intake is attenuated following repeated pairings with cocaine. Data are presented as mean saccharin (0.15%) intake (licks/ 5min) $\pm$ standard error of mean, SEM.. (A-C) illustrate saccharin intake across self-administration days 1–16 in female rats and (D-F) male rats. Solid lines represent saccharin intake of the saline controls; dashed lines represent saccharin intake in the cocaine-paired groups. * = significantly different from saline ($p < 0.05$ to $p < 0.001$).

A. Terminal CS (Saccharin) Intake

B. Progressive Ratio CS (Saccharin) Intake

Figure 2.

Terminal (A) and progressive ratio (B) CS (saccharin) intake is attenuated by pairing with cocaine in female and male rats. Data are presented as mean saccharin (0.15%) intake (licks/5min) $\pm$ standard error of mean, SEM. For terminal saccharin intake, intake was averaged across self-administration days 15 & 16. * = significantly different from saline ($p < 0.05$ to $p < 0.001$); # = significantly different from female ($p < 0.01$).

Figure 3.

US (cocaine) intake increases across self-administration days following repeated pairing with saccharin. Data are presented as mean $\pm$ standard error of mean, SEM. (A-C) represent cocaine intake (# of infusions mg/kg) across self-administration days 1–16 in female rats and (D-F) in male rats. Solid lines represent cocaine intake of the saline controls; dashed lines represent cocaine intake in the saccharin-paired groups. * = significantly different from saline ($p < 0.05$ to $p < 0.001$).

A. Terminal US (Cocaine) Intake **B. Progressive Ratio US (Cocaine) Intake** **Figure 4.**

Terminal (A) and progressive ratio (B) US (cocaine) intake is increased following pairing with saccharin in female and male rats. Data are presented as mean $\pm$ standard error of mean, SEM. Terminal cocaine intake (# of infusions mg/kg) was averaged across self-administration days 15 & 16. * = significantly different from saline, # = significantly different from male at the same dose ($p < 0.05$ to $p < 0.001$).

A. Females **B. Males**

Figure 5. Terminal CS (saccharin) intake versus US (cocaine) intake in female (A) and male (B) rats. Correlation analysis revealed that CS intake was inversely related to US intake in female and male rats. Rats that consumed the least amount of the CS (saccharin) consumed more of the US (cocaine)