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Female rats exhibit less avoidance than male rats of a cocaine-, but not a morphine-paired, saccharin cue

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Abstract

Rats avoid intake of an otherwise palatable taste cue when paired with drugs of abuse (Grigson & Twining, 2002). In male rats, avoidance of drug-paired taste cues is associated with conditioned blunting of dopamine in the nucleus accumbens (Grigson & Hajnal, 2007), conditioned elevation in circulating corticosterone (Gomez, Leo, & Grigson, 2000), and greater avoidance of the drug-paired cue predicts greater drug-taking (Grigson & Twining, 2002; Twining, Bolan, & Grigson, 2009). While female rats generally are more responsive to drug than male rats, in this self-administration model, female rats consume more of a cocaine-paired saccharin cue and take less drug than males (Cason & Grigson, 2013). What is not known, however, is whether the same is true when a saccharin cue predicts availability of an opiate, particularly when the amount of drug experienced is held constant via passive administration by the experimenter. Here, avoidance of a saccharin cue was evaluated following pairings with experimenter delivered cocaine or morphine in male and female rats. Results showed that males and females avoided intake of a taste cue when paired with experimenter administered morphine or cocaine, and individual differences emerged whereby some male and female rats exhibited greater avoidance of the drug-paired cue than others. Female rats did not drink more of the saccharin cue than males when paired with morphine in Experiment 1, however, they did drink more of the saccharin cue than male rats when paired with cocaine in Experiment 2. While no pattern with estrous cycle emerged, avoidance of the cocaine-paired cue, like avoidance of a morphine-paired cue (Gomez et al., 2000), was associated with a conditioned elevation in corticosterone in both male and female rats.

Keywords

female; corticosterone; reward comparison; CTA; sex differences

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1. Introduction

Rats avoid intake of an otherwise palatable taste cue when paired with a drug of abuse (Cappell & LeBlanc, 1971; Grigson & Twining, 2002). This finding was initially interpreted as a conditioned taste aversion (CTA), not unlike that occurring following pairings with the illness-inducing agent LiCl (Ferrari, O'Connor, & Riley, 1991; Nachman, 1970). In 1997, we posed the alternative hypothesis that rats avoid intake of the gustatory cue because it is devalued in anticipation of the highly rewarding properties of the drug (Grigson, 1997). Support has been garnered for this reward comparison hypothesis (Geddes, Han, Baldwin, Norgren, & Grigson, 2008; Gomez & Grigson, 1999; Grigson, Lyuboslavsky, Tanase, & Wheeler, 1999; Schroy et al., 2005; Twining et al., 2016). That said, evidence also suggests that rats are in an aversive state when anticipating drug availability. In male rats, avoidance of the drug-paired taste cue (the conditioned stimulus) is associated with a conditioned blunting of dopamine in the nucleus accumbens (Grigson & Hajnal, 2007) and a conditioned elevation in circulating corticosterone (CORT) (Gomez et al., 2000). Finally, our work, and that of others, have shown the onset of aversive taste reactivity behavior (i.e., gapes) following intraoral delivery of the drug-paired cue (Colechio & Grigson, 2014; Wheeler et al., 2011; Wheeler et al., 2008). The taste cue, then, is not only devalued in the anticipation of drug availability, but elicits the onset of an aversive state possibly involving craving and withdrawal (Grigson, 2008). In accordance, avoidance of the drug-paired cue also is associated with a loss of body weight (Nozaki, 1976; Nyland & Grigson, 2013) and, importantly, greater avoidance of both cocaine- and heroin-paired cues correlates with greater drug self-administration – the best correction for withdrawal (Grigson & Twining, 2002; Imperio & Grigson, 2015).

In humans, while males are more likely than females to abuse drugs (Van Etten, Neumark, & Anthony, 1999), women are just as likely to become addicted (Anthony, 1994). Women begin using cocaine and enter treatment at earlier ages than men, suggesting that women are more sensitive to cocaine’s rewarding properties (Griffin, Weiss, Mirin, & Lange, 1989; Mendelson et al., 1991). Accordingly, women are more likely than men to report greater sensitivity to drugs and increased craving following exposure to cues for alcohol (Rubonis et al., 1994), cocaine (Fox, Morgan, & Sinha, 2014; Kosten et al., 1996; Robbins, Ehrman, Childress, & O'Brien, 1999), or heroin (Kennedy, Epstein, Phillips, & Preston, 2013). Male and female rats, like humans, also respond differently to drugs of abuse. Female rats demonstrate greater behavioral sensitization than male rats in response to both acute and chronic administration of cocaine (Bowman & Kuhn, 1996; Glick & Hinds, 1984), regardless of age (Zakharova, Wade, & Izenwasser, 2009). Female rats acquire cocaine self-administration more rapidly than male rats (Lynch & Carroll, 1999) (but see (Swalve, Smethells, & Carroll, 2016)) and they work harder for an infusion of cocaine on a progressive ratio schedule of reinforcement (Roberts, Bennett, & Vickers, 1989). Further, during reinstatement of extinguished cocaine self-administration behavior, female rats respond more than male rats to priming injections of cocaine (Lynch & Carroll, 2000). Similar results have been found for opioids. In studies of self-administration, female rats show faster rates of acquisition (Carroll, Morgan, Lynch, Campbell, & Dess, 2002; Lynch &

Carroll, 1999), take more of both heroin and morphine, and are more willing to work for drug on a progressive ratio schedule of reinforcement (Cicero, Aylward, & Meyer, 2003).

Although there are many possible reasons for differences between males and females in sensitivity to drugs of abuse, several findings attribute these differences to ovarian hormones. In humans, women in the follicular phase of their menstrual cycle demonstrate higher peak plasma cocaine levels following intranasal administration than women in the luteal phase (Lukas et al., 1996). Fluctuations in estrogen and progesterone levels in female rats influence both cocaine-stimulated locomotor behavior (Walker et al., 2001) and cocaine self-administration behavior (Roberts et al., 1989). For example, Walker et al. (Walker et al., 2001) showed that cocaine-induced horizontal movement is attenuated in ovariectomized female rats placed in an open field, while castrated males demonstrate increased locomotor activity. In female Wistar rats, but not males, progesterone was effective in reducing reinstatement to cocaine-seeking (Swalve, Smethells, Zlebnik, & Carroll, 2016). Others have shown that female rats exhibit not only greater cocaine self-administration but also work harder for cocaine during estrous than in other stages of the estrous cycle (Lynch, Arizzi, & Carroll, 2000; Roberts et al., 1989). The importance of estradiol is further evidenced in experiments where responding for cocaine self-administration was enhanced from control levels in ovariectomized rats with estradiol replacement (Ramoa, Doyle, Naim, & Lynch, 2013; Zhao & Becker, 2010).

Sex differences also have proven a factor with saccharin-cocaine pairings (Cason & Grigson, 2013). Specifically, while female rats generally are more responsive to drug than male rats, as described above, female rats were found to consume more of a palatable saccharin cue and then take less cocaine than their male Sprague Dawley counterparts. In this case, however, because of the use of drug self-administration, it was not possible to determine whether differences in suppression of intake of the cocaine-paired saccharin cue reflected true male-female differences or were, alternatively, a consequence of mere differences in overall amounts of cocaine exposure. Additionally, we do not know whether this effect is specific to cocaine or whether female rats also would exhibit less avoidance of a saccharin cue when paired with, for example, an opiate. Experiment 1, then, evaluated suppression of intake of the saccharin cue in male and female rats when paired with experimenter delivered morphine. Experimenter delivered drug ensured that all rats had similar exposure to morphine. In this study, rats drank saccharin for 5 min and then, after a 5 or 15 min interstimulus interval, were injected with the drug. This manipulation was included to assess the impact of a longer wait period on intake of the drugpaired cue. Experiment 2 used experimenter delivered cocaine to test whether female rats will demonstrate less avoidance of the cocaine-paired saccharin cue than male rats even when the dose of the drug is held constant. Additionally, an earlier study (Gomez et al., 2000) found that greater avoidance of a morphine-paired saccharin cue was associated with elevated circulating CORT. This was one of the first indications that avoidance of the drug-paired cue involved the onset of an aversive state. Circulating CORT, then, was measured to test whether greater avoidance of a cocaine-paired saccharin cue also is associated with higher levels of circulating CORT in male and female rats.

2. Material and Methods

2.1. Experiment 1

2.1.1. Subjects—The subjects were 64 naïve Sprague Dawley rats (Charles River, Raleigh, NC). There were 32 males weighing between 295 and 360 g and 32 females weighing between 183 and 288 g on the first day of testing. All rats were individually housed in hanging stainless steel wire bottom cages in a temperature and humidity controlled animal care facility with a 12 h light-dark cycle (lights on at 0700). Food and water were available ad libitum, except where noted otherwise. All experimental protocols complied with National Institutes of Health Animal Care Guidelines and were approved by the Pennsylvania State University Institutional Animal Care and Use Committee.

2.1.2. Apparatus and Solutions—The solutions were presented in inverted, graduated, Nalgene cylinders with silicone stoppers and stainless steel spouts attached to the front of the cage with springs. Intake was measured to the nearest 0.5 ml. Sodium saccharin (Fischer Scientific, Malvera, PA) was dissolved in filtered water and presented at room temperature.

2.1.3. Drugs—Morphine sulphate was generously provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Morphine was dissolved in sterile physiological saline to a concentration of 15.0 mg/ml and used within 2 h of preparation.

2.1.4. Procedure—After arrival and one-week acclimation, all rats were handled and weighed once a day throughout the experiment. The experiment took place in the home cage from 0830 to 1030. Deprivation state. Following several days of handling, all rats were placed on a water deprivation regimen in which they were given 5 min access to filtered water on the front of the cage each morning and 1 h access each afternoon to maintain proper hydration. Conditioning. Once morning water intake stabilized, the last 2 days of morning intake were averaged for each rat and rats were counterbalanced into eight groups by sex (male or female), interstimulus interval (ISI) (5 min or 15 min), and treatment (morphine or saline). During conditioning, the rats were given 5 min access to 0.15% saccharin and, after a 5 or 15 min ISI, injected intraperitoneally (ip) with saline or 15 mg/kg morphine. There was one such taste-drug pairing every other day for a total of 8 pairings. All rats were given 5 min access to water each morning on the days between conditioning trials and 1 h every afternoon to rehydrate.

2.2. Experiment 2

2.2.1. Subjects—This experiment was conducted in two replications. The first replication used 24 naïve, female, Sprague Dawley rats (Charles River Laboratories, Raleigh, NC) weighing between 200 and 240 g at the beginning of the experiment. The second replication, which assessed the effects of estrous, employed, 24 naïve, male (230 – 320 g) and 24 naïve, female (200 – 240 g) Sprague Dawley rats (Charles River Laboratories, Raleigh, NC). Thus, in total, there were 48 female (24/replication) and 24 male rats, all housed and maintained as described in Experiment 1.

2.2.2. Apparatus and Solutions—The apparatus and solutions were the same as those described in Experiment 1.

2.2.3. Drug—Cocaine hydrochloride was generously provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Cocaine was prepared on the morning of each injection day. To avoid the necrosis that can accompany a sc injection of cocaine (Durazzo, Gauvin, Goulden, Briscoe, & Holloway, 1994), the drug was prepared as a 1.5 mg/ml stock solution in sterile physiologic saline and the volume injected was adjusted by animal weight to obtain a 10 mg/kg dose.

2.2.4. Procedure—All rats were handled and weighed once a day throughout the experiment. The experiment took place in the home cage from 0930 to 1130. Deprivation state. Following several days of handling, all rats were placed on a water deprivation regimen in which they were given 5 min access to filtered water on the front of the cage each morning and 1 h access each afternoon to maintain proper hydration. All rats were maintained on this daily regimen until morning intake stabilized. Saccharin preexposure and pre-conditioning CORT. Twenty-four h following the last 5 min access period to water, and 48 hours prior to the first taste-drug pairing, all rats were pre-exposed to the 0.15% saccharin solution for 5 min. Blood samples (approximately 0.4 ml) were collected by means of a tailcut 15 min after saccharin pre-exposure and stored for later evaluation. This baseline (pre-conditioning) CORT measurement was designed to control for any possible unconditioned effect of saccharin. The 15 min time point replicates the procedure used previously (Gomez et al., 2000) and is approximately how long it takes to detect a rise in circulating levels of CORT (Fluttert, Dalm, & Oitzl, 2000). Conditioning. The rats were then matched on the basis of 5 min water intake on the last day of water training and saccharin intake on the pre-exposure day and divided into 2 drug conditions: saline (n = 24; 16 females, 8 males) or cocaine (n = 48; 32 females, 16 males). Again, more subjects were placed in the cocaine group to allow for an assessment of individual differences. During conditioning, the rats were given 5 min access to 0.15% saccharin and, after a 5 min ISI, injected sc with saline or 10 mg/kg cocaine. There was one such taste-drug pairing every other day for a total of 7 pairings, followed by one saccharin only test. All rats were given 5 min access to water each morning on the days between conditioning trials and 1 h every afternoon to rehydrate. Post-conditioning CORT. A second blood sample (approximately 0.4 ml) was collected from the tail 15 min after access to the saccharin cue on the final Test trial (postconditioning). No injections were given on this day.

2.2.4.1. Estrous tracking: The estrous cycle of females was tracked during the second replication only. Vaginal lavages were used daily following afternoon waters to track females' estrous cycle. The cotton swab method (as opposed to the dropper method) was adopted for this study. First, the cotton tip of a swab was moistened with isotonic saline and then inserted into the vagina. This was then smeared onto a clean microscope slide. A new swab was used for each female and four smears were fit onto a single slide. The slides were air dried and then immersed into absolute methyl alcohol for 5 min. Next, the slides were placed in Giemsa stain (undiluted) for 2 min, rinsed with water, and air dried.

2.2.4.2. CORT Radioimmunoassay: Blood samples were maintained on ice and then centrifuged at 11,000 rpm for 10 min. The serum obtained from each sample was stored at −80 degrees Celsius until the CORT radioimmunoassay was performed. Pre- and post-conditioning CORT concentrations were then determined using a standard radioimmunoassay kit (ICN Biomedicals). All samples were run in duplicate.

2.3. Data analysis

All intake data were analyzed as described above using Statistica 7 (StatSoft, 2004) and mixed factorial analyses of variance (ANOVA) varying group (cocaine, saline), sex (male, female), and trials (1–8). Post hoc tests were conducted, when appropriate, using Newman-Keuls tests with α set at 0.05.

3. Results

3.1. Experiment 1

Rats typically exhibit large individual differences in suppression of intake of a drug-paired taste cue whereby some rats show greater avoidance of the drug-paired cue than others (Grigson & Twining, 2002; Imperio & Grigson, 2015). Consequently, saccharin intake for each sex was averaged across the terminal three days of testing and the morphine-treated rats were separated, via a median split, into two groups: those that suppressed intake of the saccharin taste cue to a larger extent (large suppressers); and, those that avoided intake to a lesser extent (small suppressers). Simple one way ANOVAs revealed significant differences between groups for males, $F(1,15) = 37.82$, $p < 0.001$, and females, $F(1,15) = 18.60$, $p < 0.001$ (Figure 1).

Intake data were then analyzed utilizing a 2 × 2 × 3 × 8 mixed factorial ANOVA varying sex (male, female), ISI (5 min, 15 min), suppresser group (saline, large suppresser, small suppresser), and trial (1–8). Post hoc tests were conducted, where appropriate, using Newman-Keuls tests with α set at 0.05. The results showed that the main effect of ISI was significant, $F(1,52) = 10.79$, $p < 0.01$, as was the sex × ISI interaction, $F(1,52) = 6.92$, $p < 0.05$. Follow up Newman-Keuls tests on the sex × ISI interaction revealed that all male rats (saline and drug) drank more of the saccharin cue in the 15 min ISI condition than the other three groups overall, $ps < 0.001$ (Figure 2). There were no other significant interactions with ISI (neither suppresser × ISI, nor sex × suppresser × ISI, $Fs < 1$), therefore the data from both ISI groups were combined, re-analyzed, and presented accordingly.

Large individual differences in intake of the saccharin cue were present in male and in female morphine-treated rats (Figure 3). This observation was supported by the results of post hoc tests on a significant main effect of group, $F(2,58) = 63.99$, $p < 0.001$, indicating that overall consumption of the saccharin conditioned stimulus (CS) was significantly lower for morphine-treated groups than for the saline-treated rats, $ps < 0.001$, with the large suppressers consuming significantly less than the small suppressers overall, $p < 0.001$. The sex × group × trial interaction also was significant, $F(14,406) = 1.79$, $p < 0.05$. Newman-Keuls post hoc tests indicated that small and large suppresser female rats consumed significantly less saccharin than saline rats starting with trial 2, $ps < 0.01$. Male rats did

likewise, with the exception of small suppressers during trial 7. Female large suppressers consumed significantly less saccharin than female small suppressers during trials 4, 7, and 8, ps < 0.05. Male large suppressers consumed significantly less saccharin than male small suppressers during trials 4 through 8, ps < 0.05. There were no differences between male and female morphine treated groups with the exception of trial 7 where male small suppressers drank significantly more of the saccharin cue than female small suppressers, p < 0.05.

3.2. Experiment 2

As described, greater avoidance of the drug-paired cue is important because it is associated with a shorter latency to take drug, greater load-up on drug, more drug-taking, a strong willingness to work for drug, and greater seeking during extinction and drug-induced reinstatement. This is true for both cocaine and for heroin (Grigson & Twining, 2002; Imperio & Grigson, 2015). In Experiment 1, however, both male and female rats avoided intake of the morphine-paired saccharin cue and no differences were found as a function of sex. As described, sex differences were evident in our cocaine self-administration study where female rats consumed more of the saccharin cue than male rats and took less drug (Cason & Grigson, 2013). This finding may be due to the use of a different drug (i.e., cocaine) or to the use of a different route of administration (i.e., contingent, self-administration). Experiment 2 will revisit the assessment of sex differences in cocaine-induced suppression of saccharin intake when cocaine, like morphine, is held constant (g/kg) by passive administration (non-contingent). Furthermore, in anticipation of possible sex differences, the estrous cycle will be tracked daily.

The impact of replication was assessed for the female rats. The results showed that the main effect of replication was not significant, F < 1, following a 2 × 2 × 8 mixed factorial ANOVA varying replication (1–2), drug group (saline and cocaine), and trial (1–8). Therefore, the female data from both cocaine replications in Experiment 2 were combined, re-analyzed, and presented accordingly.

3.2.1. Saccharin (CS) Intake—Large individual differences in intake of the saccharin cue were present among both male and female cocaine-treated rats. As a result, the cocaine-treated rats were divided into two separate groups (large suppressers and small suppressers) based on a median split of terminal three trials saccharin intake. Simple one-way ANOVAs revealed significant differences between groups for females, F(1,31) =43.16, p < 0.001, and males, F(1,15) = 11.58, p < 0.01 (Figure 4).

The data were then re-graphed and analyzed using a 2 × 3 × 8 mixed factorial ANOVA varying sex (male, female), group (saline, large suppresser, small suppresser), and trial (1–8). The results of this analysis revealed a significant sex × group × trials interaction, F(14,462) = 2.64, p < 0.001. Newman Keuls post hoc tests of this 3-way interaction showed that female large suppresser rats (Figure 5, left panel) consumed significantly less of the saccharin cue than both the saline-treated female rats and the small suppresser female rats on trials 3–8, ps < 0.05. The small suppresser rats exhibited a smaller reduction in intake that attained significance from the saline controls only on trials 5–7, ps < 0.05. Male large suppresser rats (Figure 5, right panel) consumed significantly less of the saccharin cue than

saline-treated male rats on trials 2–8, ps < 0.05, and less than the male small suppresser rats on trials 2 and 4–8, ps < 0.05. The male small suppresser rats still demonstrated a strong reduction in intake compared to the saline group that was significant on trials 3–8, ps < 0.05. Although overall suppression in saccharin intake appeared to be more pronounced in males than in females, this effect was heavily carried by the large suppressers. Indeed, additional post hoc comparisons of the same 3-way ANOVA showed that male large suppressers demonstrated greater avoidance of the saccharin cue than female large suppressers on trials 4–6 and then again on trial 8, while intake by the male small suppressers was significantly reduced compared to female small suppressers only on trial 8, ps < 0.05. Saccharin intake also differed between males and females on the first trial, ps < 0.05.

3.2.2. Corticosterone—The CORT data (Figure 6) were analyzed using a 2 × 3 × 2 mixed factorial ANOVA varying sex (male and female), group (saline, small suppressers, and large suppressers), and trials (pre-and post-conditioning). Although the 3-way sex × group × trials interaction was not significant, post hoc comparisons of a significant group × trials interaction, $F(2,65) = 7.99$, $p < 0.001$, showed that postconditioning CORT levels were significantly elevated from pre-conditioning CORT levels for both small and large suppressers, ps < 0.05, but not for the saline controls, $p > 0.05$. This pattern also was reflected by the significant main effects of group, $F(2,65) = 5.92$, $p < 0.01$, and trial, $F(1,65) = 15.9$, $p < 0.001$, indicating, respectively, that cocaine-treated rats demonstrated higher CORT levels than saline treated controls overall, and post-conditioning CORT levels were higher than pre-conditioning CORT levels overall. These group patterns in CORT were the same for male and female rats, as indicated by the lack of a significant main effect of sex or any interactions thereof, ps > 0.05.

Although results from the above analysis of the CORT data did not indicate any differences between males and females, the behavioral data (saccharin intake) indicated that males and females were different. As a result, the CORT data were re-analyzed separately for males and females using a 3 × 2 repeated measures ANOVA varying group (saline, small suppressers, and large suppressers) and trials (pre- and post-conditioning). For females (Figure 6, left panel), post hoc comparisons of a significant group × trials interaction, $F(2,44) = 5.24$, $p < 0.01$, showed that female large suppressers were the only group that exhibited a significant elevation in CORT from pre- to post-conditioning, $p < 0.05$. Both large and small suppressers, however, demonstrated greater levels of circulating post-conditioning CORT than did the saline group, ps < 0.05. For males (Figure 6, right panel), post hoc comparisons of a significant group × trials interaction, $F(2,21) = 4.95$, $p < 0.05$, showed that both large and small suppressers exhibited a significant elevation in CORT from pre- to post-conditioning, ps < 0.05. Both large and small suppressers also demonstrated greater post-conditioning CORT levels compared with that of the saline control group, ps < 0.05.

Correlation analyses were conducted to determine whether there was a relationship between terminal saccharin intake and post-conditioning CORT. The results (data not shown) revealed that, for females, there was no relationship between saccharin intake and CORT at test ($r = -0.01$, $p > 0.05$, $n = 31$) and, for males, there was a slight negative, but non-

significant, relationship in which greater avoidance of saccharin intake trended with greater post-conditioning CORT levels ($n = 16$, $r = -0.38$, $p > 0.05$).

3.2.3. Estrous—Daily lavage revealed that female rats did not demonstrate synchronous estrous cycling. There also were no apparent patterns in saccharin intake and estrous cycling (data not shown). On trial 1, only six of the sixteen cocaine-treated females were observed to be in estrous. Of those six, only two females went on to become large suppressers. Three females were observed to be in proestrous and only one of those three went on to become a large suppresser. By trial 2, five of the sixteen females were in estrous and three of those five went on to become large suppressers. By the end of the experiment, there were three females that stopped showing any sign of regular cycling and instead, exhibited smaller, abnormal vaginal cells. Two of the three females with seemingly disrupted estrous cycling demonstrated the greatest avoidance of the cocaine-paired saccharin cue.

4. Discussion

The data from Experiment 1 show that female Sprague Dawley rats, like males, are sensitive to the suppressive effects of opioids. Furthermore, small and large suppressers emerged among female rats. These individual differences among female rats, however, were not much different than those demonstrated by males, with the exception that no female demonstrated complete avoidance of saccharin intake. The failure to find a sex difference here is somewhat surprising because, as described, female rats exhibited less avoidance of a saccharin cue when paired with the opportunity to self-administer cocaine than their male counterparts (Cason & Grigson, 2013). Although the reason for this lack of a sex difference is not clear, it is consistent with that reported by Randall-Thompson and Riley (Randall-Thompson & Riley, 2003). In that study, male and female rats were given 20 min access to saccharin followed by a subcutaneous (sc) injection of saline or 10, 18, or 32 mg/kg morphine every fourth day and no sex differences were found based on a percentage change from baseline intake. Our data confirm that earlier report and extend the finding by showing clear and marked individual differences in not only males, but in female rats as well. Individual differences were previously reported in male Sprague Dawley rats using the exact same experimental design with the same dosage of morphine (Gomez et al., 2000), confirming individual differences in taste avoidance among morphine treated male and now female rats.

The data from Experiment 2 show that female Sprague Dawley rats, like males, avoid intake of an otherwise palatable saccharin cue when paired with experimenter administered cocaine. Furthermore, small and large suppressers emerged among female rats. These individual differences among female rats, however, were not as great as those demonstrated by male rats in the present and in past studies using morphine (Gomez et al., 2000). Consistent with our cocaine self-administration study (Cason & Grigson, 2013), females seemed to be more resistant to the suppressive effects of cocaine than males. Indeed, few, if any, female rats demonstrated complete avoidance of the cocaine-paired saccharin cue. Interestingly, similar sex differences have been obtained in a study involving LiClinduced CTA learning (Weinberg, Gunnar, Brett, Gonzalez, & Levine, 1982). In that study, sex differences in CTA learning (using a milk cue and LiCl) were evident only if rats were food

and water deprived. While both males and females suppressed intake of the LiCl-paired saccharin cue, females subsequently recovered intake to pretoxicosis levels faster than males. This finding is consistent with the present results suggesting that females are more resistant than males to suppress intake of a naturally rewarding stimulus such as saccharin or milk. As mentioned in the Introduction, sex differences also have been reported by van Haaren (van Haaren & Hughes, 1990) in a study using a paradigm somewhat similar to the present experimental design. In that study, daily 20 min access to a 0.1% saccharin solution was paired with sc administration of 5, 10 or 20 mg/kg cocaine for different groups of fluid deprived (no rehydration period) male and female Wistar rats. Every third pairing was water and was followed with no injection. The results of that study showed that females were more sensitive than males to the suppressive effects of a 20 mg/kg dose of cocaine and this was the only dose in which a consistent decrease in consumption of the conditioned stimulus was observed. This finding is not consistent with the present results showing that male rats are more sensitive than female rats to the suppressive effects of a 10 mg/kg dose of cocaine. Possible reasons for this discrepancy between studies include the use of different rat strains, the use of different concentrations of saccharin (0.1% vs 0.15%), and the lack of a rehydration period in the van Haaren and Hughes study, as dehydration can override the suppressive effects of morphine, cocaine, and LiCl on intake of a saccharin cue (Twining et al., 2016).

Female rats treated with cocaine also demonstrated conditioned elevations in CORT following presentation of the cocaine-paired saccharin cue at test. Indeed, CORT was elevated for male and female rats in both the large and the small suppresser groups. There was, however, no significant correlation between suppression of saccharin intake and CORT at test for either the male or the female rats. This finding differs from earlier work showing that, in male rats, greater suppression of intake of the morphine-paired saccharin cue was correlated ($n = 12$, $r = -0.84$, $P<0.001$) with higher circulating CORT levels at test (Gomez et al., 2000). It is possible that differences would have been evident at a later time point, but that was not assessed in the present study. Even so, in all cases, presentation of the cocaine-paired saccharin cue was associated with a conditioned elevation in circulating CORT and, in most cases, this effect was more robust in the large suppressor group.

While a few studies report that female rats are sensitive to the suppressive effects of cocaine (Ferrari et al., 1991; Goudie, Dickins, & Thornton, 1978; van Haaren & Hughes, 1990), the present study provides the first report of large individual differences being present in females following taste-drug pairings. Ferrari et al. (Ferrari et al., 1991) found that female Long Evans rats will suppress intake of saccharin when paired with cocaine, but the authors did not report any individual differences in intake, nor did they assess CORT levels in the female rats. One possible reason for the lack of large individual variability among cocaine-treated females in the study conducted by Ferrari et al. (Ferrari et al., 1991) is that they used a higher dose of cocaine (18 vs. 10 mg/kg). In the Van Haaren and Hughes study (van Haaren & Hughes, 1990), suppression in intake was evident only when using a 20 mg/kg dose and not when using a 10 mg/kg dose. As described, they also tested a different strain of rats (Wistar), used a lower concentration of saccharin (0.1%), and, importantly, a more stringent fluid deprivation regimen. Thus, the effect of sex on avoidance of the cocaine-paired cue is evident in the Sprague Dawley strain when pairing saccharin with the sc administration of a

lower 10 mg/kg dose of cocaine in rats given a less restrictive fluid deprivation regimen (5 min a.m., 1 h p.m.).

Although CORT was elevated at test for both cocaine treated groups, the reason for the absence of a significant relationship between CS intake and CORT is not clear. This relationship may have attained significance if more male subjects were tested (e.g., 48 males instead of 24). For males, the absence of the correlation is unusual, given our published data (Gomez et al., 2000), but there was at least a tendency for greater avoidance of the saccharin cue to be associated with greater elevations in CORT in the male rats. This is seen with opioids as well. In a study of heroin self-administration, male Sprague Dawley rats that were the large saccharin suppressers also were the largest heroin takers and showed increased mRNA expression for elements of the corticotropin releasing hormone (CRH) signaling pathway (CRH, CRH receptors and CRH binding protein) in the ventral tegmental area, hippocampus, and medial prefrontal cortex (McFalls et al., 2016). For females, the failure to find a correlation between suppression of intake of the saccharin cue and circulating CORT may or may not be unusual since this is the only report of this particular finding. The estrous cycle was not associated with suppression of CS intake on any trial. One possible reason for this is that the estrous cycle for these females was not synchronized. For this reason, the perceived hedonic value of both stimuli may have been different depending on which phase of the estrous cycle the female was in. Thus, variability in the phase of estrous may have contributed to the variation in cocaine-induced suppression of saccharin intake. In addition, to further complicate matters, vaginal lavages performed to monitor estrous have, themselves, been shown to influence the behavioral response to acute cocaine (Walker, Nelson, Smith, & Kuhn, 2002). In the Walker et al. study, repeated lavage decreased the enhanced cocaine-induced locomotor activity during proestrous and estrous. A separate experiment in the same study showed that a conditioned place preference was acquired for the compartment where vaginal lavages took place. The apparent reinforcing effects of vaginal lavages observed in that study were suggested to be related to a sexual representation of the mating process. Regardless, females in the first replication of Experiment 2 of the present study were not lavaged and still did not demonstrate a relationship between CORT and suppression of saccharin intake at test.

There are at least four possible reasons why female rats are more resistant than male rats to the suppressive effects of cocaine on intake of the saccharin cue. First, sweet cues may be more rewarding for females than for males. This is possible because, while a lack of sex differences in sweet preference has been previously reported (Ackroff & Sclafani, 2004; Konkle et al., 2003), our lab has found that prior access to a sweet saccharin cue is more protective against cocaine self-administration in female rats than males rats (Cason & Grigson, 2013). Second, female rats “protect” their intake of nourishment, when deprived, more than males. In support of this idea, Weinberg et al. (Weinberg et al., 1982) showed that sex differences in CTA performance occur only when rats are deprived. When deprived, females protect intake of a novel milk conditioned stimulus that is paired with the administration of LiCl. Because all rats were fluid deprived in the present study, females may have been protecting their intake of the sweet saccharin. However, this seems an unlikely explanation as the effect also would have occurred in the morphine group, not only with cocaine treated rats. Third, the drug may be less rewarding for the females. This is not

likely, however, because female rats not only acquire cocaine selfadministration more rapidly (Lynch & Carroll, 1999), but also work harder on a progressive ratio schedule of reinforcement (Roberts et al., 1989) for a cocaine infusion than male rats. The fourth explanation is pharmacokinetics.

Sex differences in drug pharmacokinetics have been reported before. Evidence in support of this, in terms of psychostimulants, include Becker et al. (Becker, Robinson, & Lorenz, 1982) who found that the systemic administration of amphetamine (1.0 – 10.0 mg/kg) results in significantly higher drug levels in the female brain than in the male's. This finding is not consistent, however, with that of another study showing that there were no sex differences in the metabolism of cocaine in plasma and in brain tissue following a 15 mg/kg ip injection of cocaine (Bowman et al., 1999). It remains unknown whether brain concentrations of cocaine still would be the same if the rats were given subcutaneous injections as in the present study. Regardless, brain levels of drug did not vary with the estrous cycle or with gonadectomy in either of the published studies. This finding suggests that, regardless of drug concentration, sex differences are more heavily influenced by the effects of gonadal hormones on mesostriatal dopamine activity. There also is evidence in support of a pharmacokinetic influence for opiates. Experiments that examined sex differences in metabolism found that for females, maximal levels of heroin in the brain tissue occurred at 15 min post ip injection, and maximal levels were at 45 min for males (Djurendic-Brenesel, Mimica-Dukic, Pilija, & Tasic, 2010). This evidence of faster circulation of opiates from blood to brain in females may create a situation where the drive to protect intake of the sweet may be offset by increased sensitivity to the morphine in female rats. This suggests a need to examine the opiate effect between males and females with self-administration of heroin to ascertain whether the availability of the sweet cue will reduce or eliminate sex differences in self-administration of opioids.

In sum, both male and female rats avoid intake of a taste cue when paired with experimenter administered morphine or cocaine. Individual differences emerged for both males and females with both drugs. With respect to cocaine, females exhibited less avoidance (greater intake) of the drug-paired saccharin cue than did males. This may be a consequence of the females protecting fluid intake due to testing in a water deprived state. As with saccharin-morphine pairings (Gomez et al., 2000), avoidance of the cocaine-paired cue was associated with a conditioned elevation in circulating CORT in both male and female rats. However, no regular pattern with the estrous cycle emerged. Females usually are more responsive for cocaine and heroin; however, females have been shown to self-administer less cocaine than males when preceded by access to a saccharin cue (Cason & Grigson, 2013). Female rats, however, did not drink more saccharin than male rats when paired with morphine in Experiment 1. The increased drive to consume the sweet in the female rat, then, may have been offset by a greater sensitivity to the opiate. When presented with a saccharin-cocaine pairing, the tendency to drink more saccharin by females may contribute to the increase in intake of the saccharin cue, which in turn, may reduce their subsequent self-administration of cocaine (Lenoir, Serre, Cantin, & Ahmed, 2007). Similar avoidance of the morphine paired cue, on the other hand, might predict similar heroin self-administration between male and female Sprague Dawley rats when access to drug is preceded by access to a palatable sweet. This, however, remains to be tested.

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Abbreviations

CORT	corticosterone
CRH	corticotropin releasing hormone
CS	conditioned stimulus
CTA	conditioned taste aversion
HPA	hypothalamic–pituitary–adrenal axis
ip	intraperitoneal
ISI	interstimulus interval
sc	subcutaneous

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Highlights

- Female rats drink more sweet cue than males when paired with cocaine, not morphine.
- Large individual differences in cue intake emerge with females and males.
- Avoidance of sweet cue was associated with conditioned elevation in corticosterone.

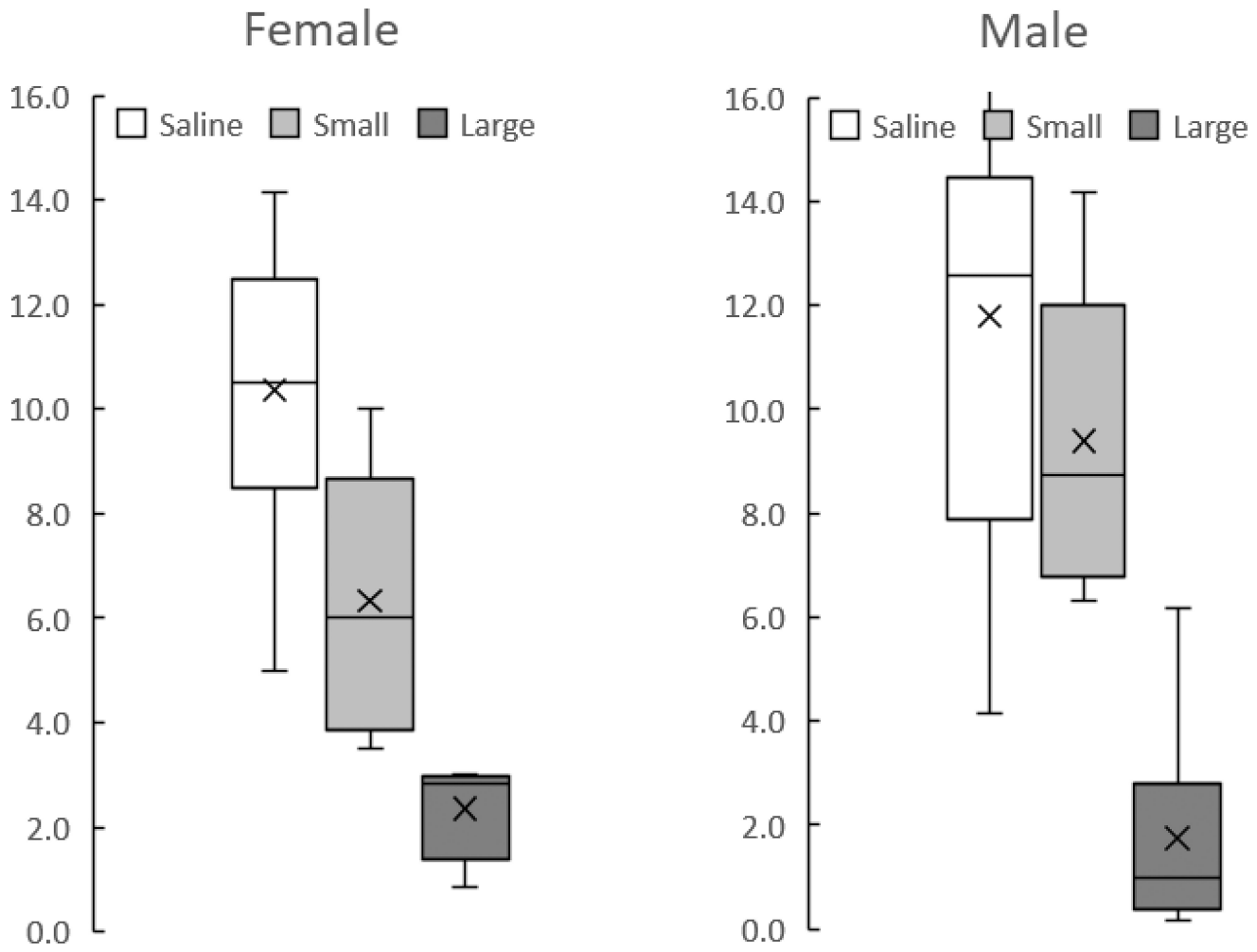

Fig. 1.

Box plots showing increased variability (increased individual differences) of saccharin intake amongst morphine rats averaged across terminal three trials.

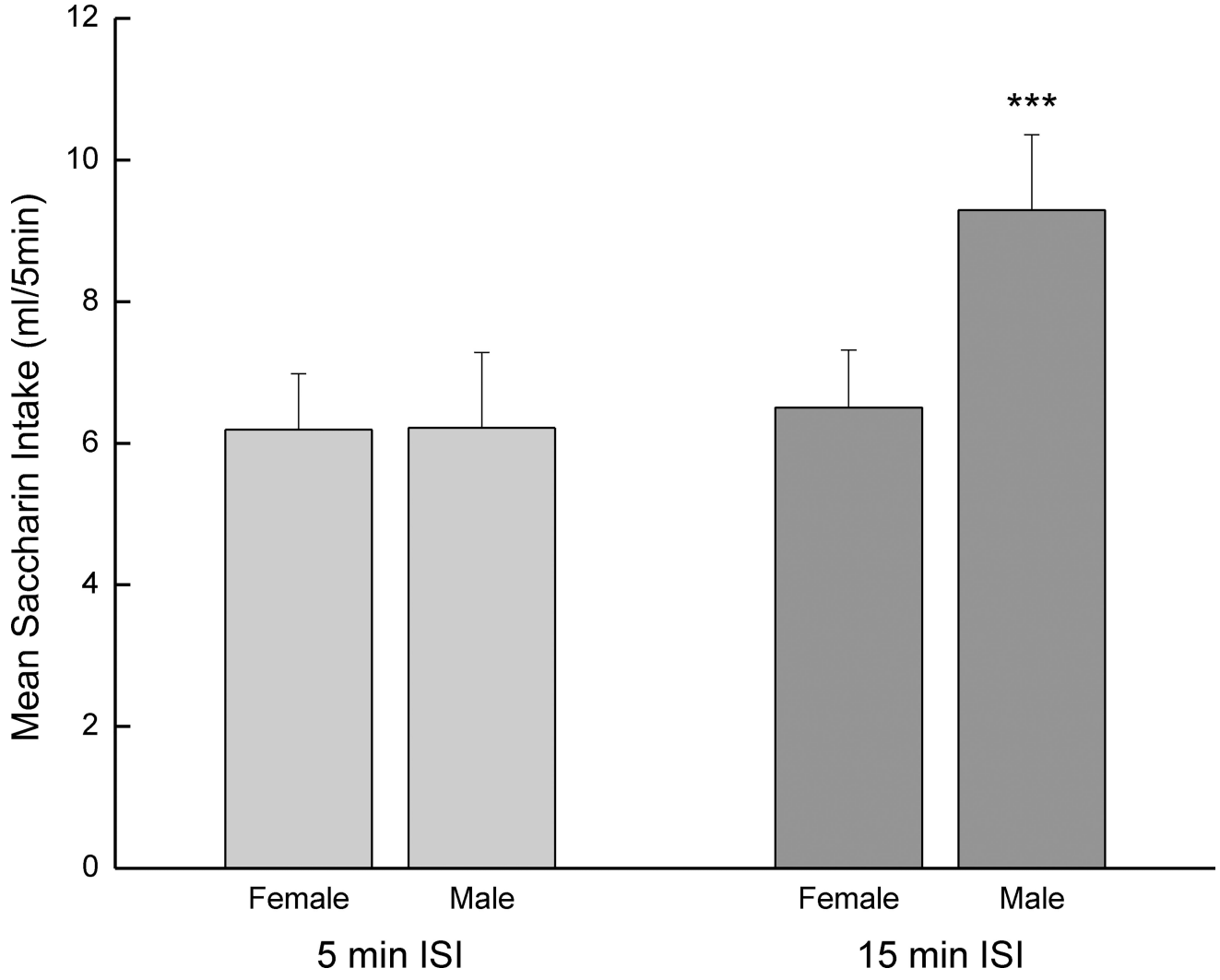

Fig. 2.

Mean (± SEM) intake of 0.15% saccharin (ml/5 min) collapsed across eight pairings (saline and morphine together) separated by either a 5 or 15 min ISI. Male intake prior to the 15 min ISI was different from all others, ***ps < 0.001.

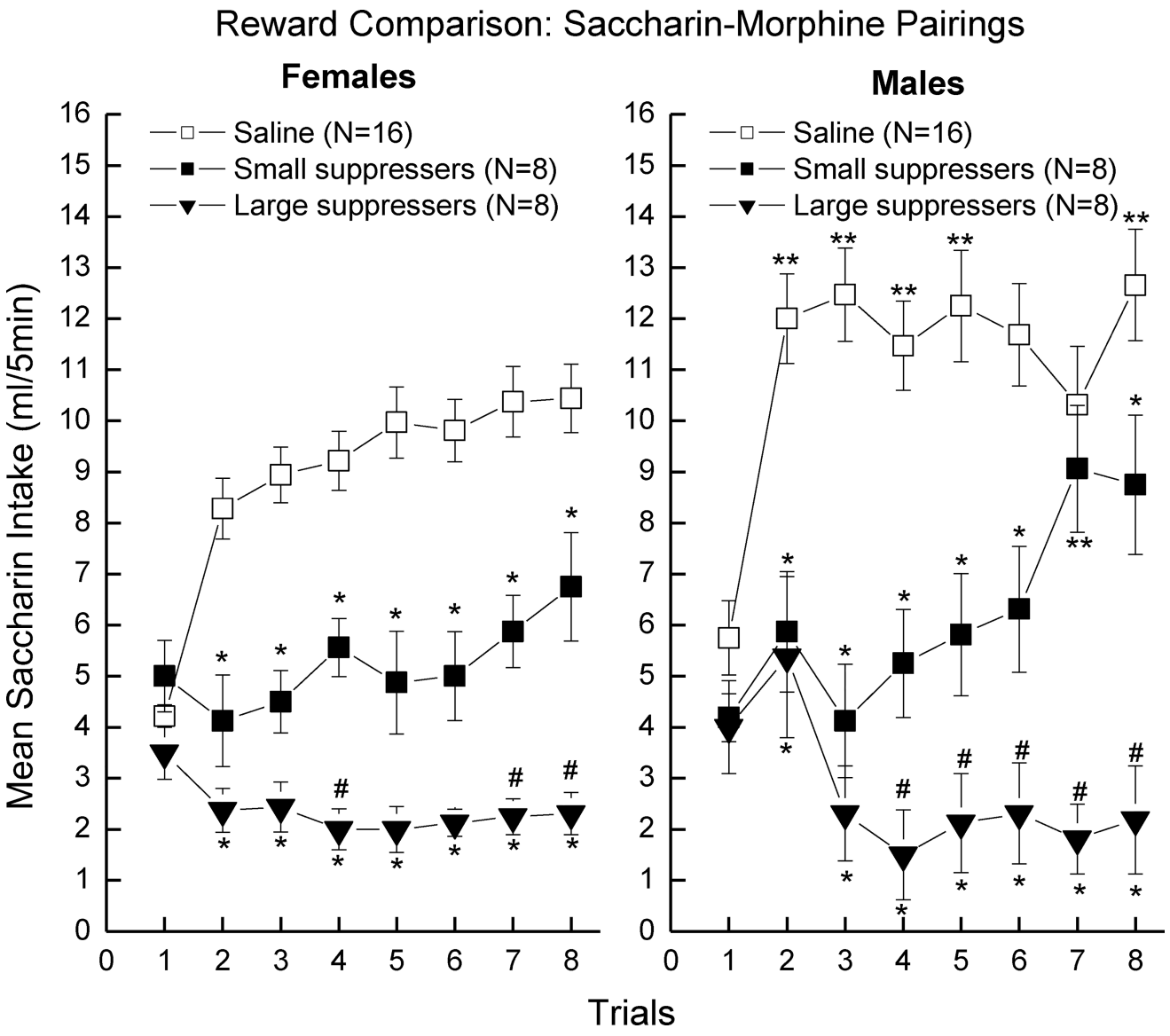

Fig. 3.

Mean (± SEM) intake of 0.15% saccharin (ml/5 min) for saline controls, small suppressers, and large suppressers across eight trials with either saline or morphine (15 mg/kg, ip). Data for female rats are shown in the left panel and data for male rats are shown in the right panel. *Significantly different from saline-injected controls, #different from small suppressers, **different from females, ps < 0.05.

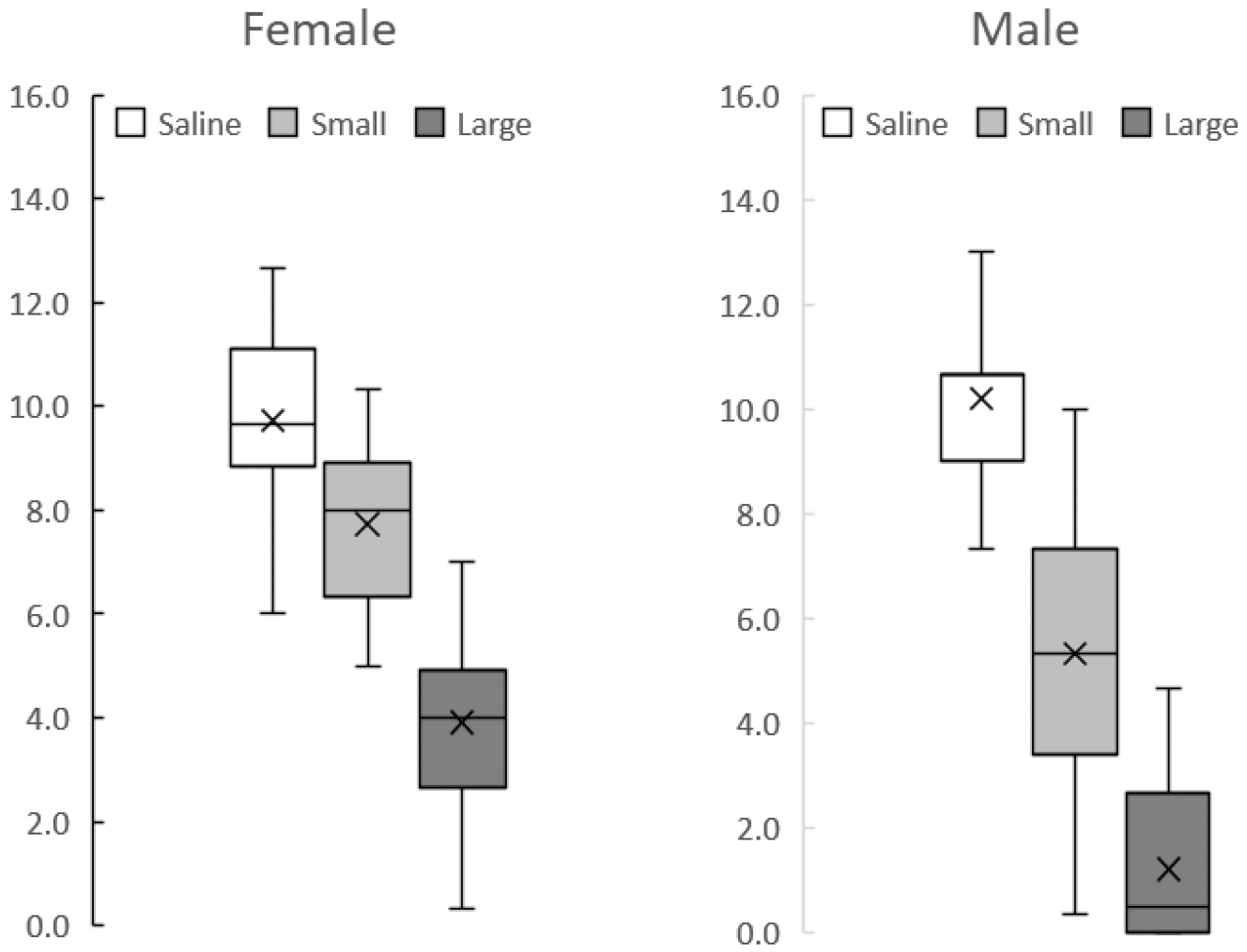

Fig. 4.

Box plots showing increased variability (increased individual differences) of saccharin intake amongst cocaine rats averaged across terminal three trials.

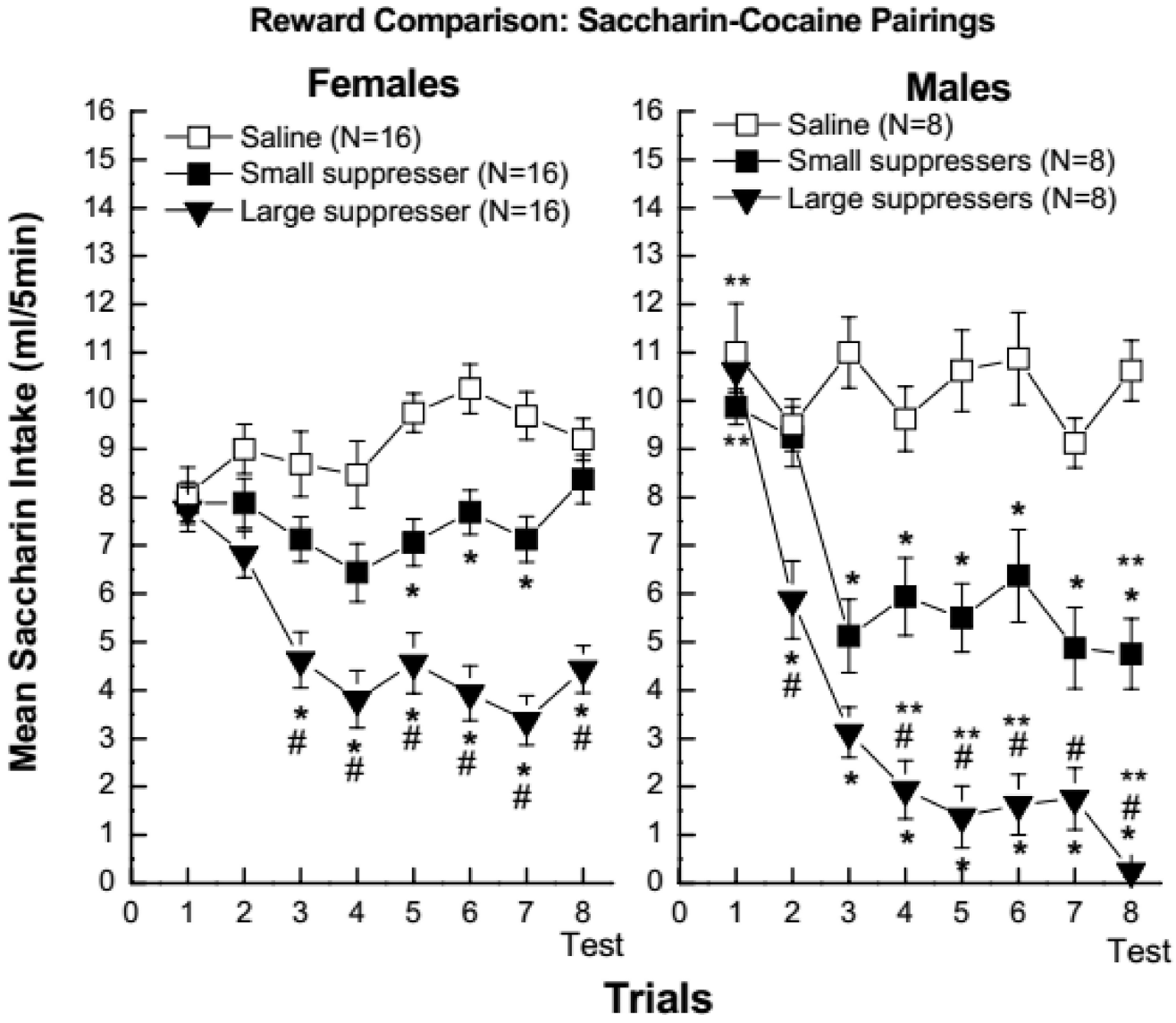

Fig. 5.

Mean (± SEM) intake of 0.15% saccharin (ml/5 min) by saline controls, small suppressers, and large suppressers across 7 pairings with either saline or cocaine (10 mg/kg, sc) followed by a saccharin CS only test trial. Data for female rats are shown in the left panel and data for male rats are shown in the right panel. *Significantly different from saline-injected controls, #different from small suppressers, **different from females, ps < 0.05.

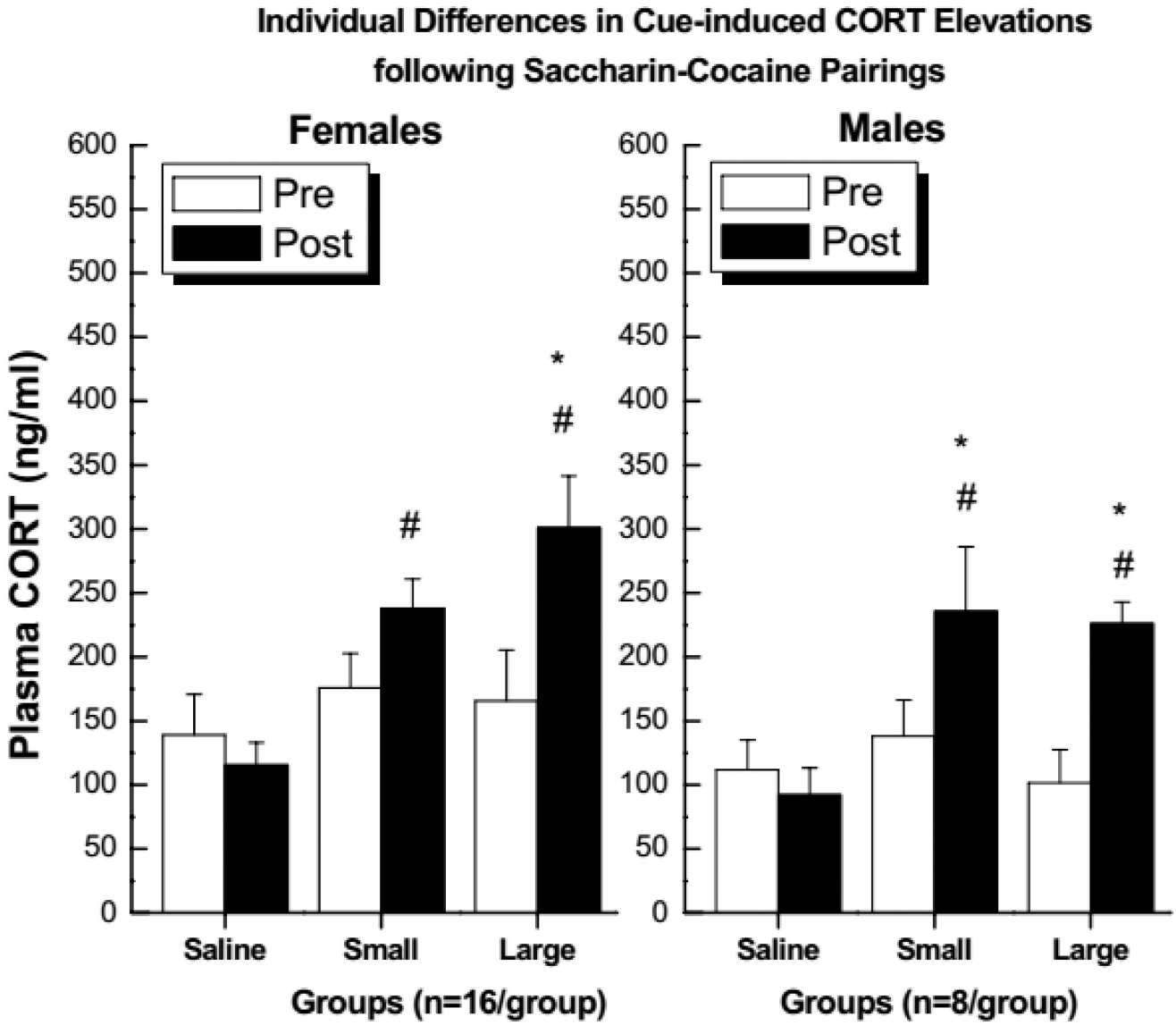

Fig. 6.

Mean (± SEM) pre- and post-conditioning CORT levels (ng/ml) across saline controls, small suppressers, and large suppressers for females (left panel) and males (right panel). #Significantly different from saline group postconditioning CORT levels, *significantly different from pre-conditioning CORT levels within the same group, ps < 0.05.