CONDITIONED TASTE AVOIDANCE PREDICTS MORPHINE,

BUT NOT COCAINE, SELF-ADMINISTRATION: A ROLE

OF DRUG AVERSION IN DRUG TAKING

By

Andrey Verendeev

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Chair:

Anthony L. Riley, Ph.D.

Terry L. Davidson, Ph.D.

Kevin B. Freeman, Ph.D.

David N. Kearns, Ph.D.

Dean of the College of Arts and Sciences

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ABSTRACT

Drugs of abuse are complex pharmacological compounds that produce multiple effects, not all of which are rewarding or positively reinforcing. Drugs of abuse have also been described in terms of their aversive effects, evidenced by their ability to suppress consumption of a taste stimulus with which they were previously paired. This ability to condition taste avoidance has been described for all major drugs of abuse, including morphine and cocaine. In the present series of experiments, the relationship between the ability of morphine and cocaine to condition taste avoidance or place preference and support self-administration was assessed. There was a significant negative relationship between the aversive effects of morphine and morphine self-administration, such that rats most sensitive to the aversive effects of morphine self-administered less drug than rats least sensitive to morphine's aversive effects. Interestingly, no such relationship was found with cocaine. Moreover, there was no relationship between the ability of either morphine or cocaine to produce place preference and support self-administration. The present results are discussed in the context of the theoretical position that the balance of drug reward and aversion determines drug self-administration.

ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION

Drugs of abuse are complex pharmacological compounds that produce multiple interoceptive stimulus effects, not all of which are rewarding (Koob and LeMoal, 2006; Stolerman, 1992; Verendeev and Riley, 2012; Wise et al., 1976). Specifically, drugs of abuse have also been shown to produce aversive effects, as evidenced by their ability to support conditioned taste avoidance (CTA) learning, i.e., suppress consumption of a taste stimulus with which they have been previously paired (Cunningham et al., 2009; Riley, 2011; Verendeev and Riley, 2011, 2012). This ability to produce avoidance has now been demonstrated for a variety of drugs of abuse, including morphine and cocaine (for review, see Verendeev and Riley, 2012).

Although these opposing motivational effects are usually examined separately in different groups of subjects and often in different experiments, several studies have assessed the ability of drugs to produce both rewarding and aversive effects at the same time and in the same animal (Reicher and Holman, 1977; Simpson and Riley, 2005; Turenne et al., 1996; White et al., 1977; Wise et al., 1976). In one such study (Verendeev and Riley, 2011), the rewarding and aversive effects (as well as their relationship to each other) were examined. Using a combined CTA/CPP procedure, Verendeev and Riley (2011) assessed the ability of either morphine or amphetamine to produce rewarding and aversive effects in individual subjects. Specifically, rats were given a novel saccharin solution to drink, injected with either a low or high dose of morphine (5 and 10

mg/kg) or amphetamine (3 and 5 mg/kg) and immediately placed in a distinctive environment of a conditioned place preference (CPP) apparatus. Thus, a single injection of a drug was used to condition both taste avoidance (saccharin – drug association) and place preference (drug – environment association; see Verendeev and Riley, 2011, for more detail). The authors found that both morphine and amphetamine (at both doses) conditioned both taste avoidance and place preference.

Two other interesting findings emerged from this work. First, there was considerable variability in the sensitivity of individual subjects to the rewarding and aversive effects of morphine and amphetamine. For example, individual subjects were sensitive to either one or the other, or to both, or to neither of these effects. Second, the ability of either drug to condition a place preference was not dependent on its ability to condition a taste avoidance and vice versa. That the presence of one effect was not related to the presence of the other suggested that the mechanisms underlying drug reward and drug aversion are independent (Verendeev and Riley, 2011).

If drugs of abuse are complex pharmacological compounds with rewarding and aversive effects, both of these effects should be taken into account in our attempt to model drug-taking behavior (Meyer and Quenzer, 2005). Clearly, the rewarding effects of a drug have been well implicated in the initiation and maintenance of drug use (Bozarth, 1987; Koob and Le Moal, 2006; Wise, 1998). The aversive effects of drugs, however, have been less studied. Although it has been suggested that drug taking may be a function of the balance between the

rewarding and aversive effects of a drug, with its aversive effects playing a role of a limiting factor in drug self-administration (Gaiardi et al., 1991; Riley and Simpson, 2001; Shabani et al., 2011; Stolerman and D'Mello, 1981; Riley, 2011), the actual role of drug aversion in drug self-administration has not been systematically examined.

Such an attempt to examine the relationship between drug aversion and drug self-administration was recently conducted by Cunningham and his colleagues in an analysis of ethanol-induced taste avoidance and ethanol intake across different strains of mice (Cunningham et al., 2009). Specifically, using the CTA preparation, the authors examined the sensitivity to the aversive effects of 2 mg/kg ethanol in 15 different inbred mouse strains (Broadbent et al., 2002) and correlated these strain differences with previously reported strain differences in the intake of 10% ethanol (from Belknap et al., 1993). They found a significant negative relationship between the sensitivity to the aversive effects of ethanol and ethanol consumption, such that strains of mice more sensitive to the aversive effects of the drug (i.e., those showing greater taste avoidance) consumed less ethanol and vice versa (see also Cannon et al., 1994 and Risinger and Cunningham, 1998). Interestingly, the evidence for the relationship between ethanol reward (as measured by ethanol CPP) and ethanol intake is mixed. Cunningham (1995), for example, found no relationship between ethanol CPP and ethanol intake. A later study by this same group, however, showed that mice that have been selectively bred for high vs. low ethanol consumption

demonstrated significant ethanol place preference after four, but not the first two, generations of selection (Phillips et al., 2005).

It should be noted, however, that these assessments were done in different strains of mice and across different experiments. Although supportive of the position that drug aversion plays a limiting role in drug intake, it would be interesting to examine whether sensitivity to the aversive effects of a drug could predict drug self-administration *in the same animal*. Doing so will allow one to make more direct predictions regarding the role of drug reward and aversion in drug taking. This was the purpose of the present series of studies. Specifically, using a within-subject design, rats were first trained with either 5 mg/kg morphine (Experiment 1) or 20 mg/kg cocaine (Experiment 2) in the combined CTA/CPP procedure and their conditioned preference and avoidance were measured. They were then trained to lever press for intravenous infusions of either 0.56 mg/kg morphine or 0.75 mg/kg cocaine, respectively. We then examined whether the sensitivity to either the rewarding and/or aversive effects of morphine or cocaine predicted later drug self-administration.

CHAPTER 2

METHODS

All the procedures were the same for both experiments, except where specifically noted.

Subjects and Housing

Twenty naive adult male Sprague-Dawley rats at approximately 90 days of age (Harlan, Indianapolis) served as subjects in each experiment. They were individually housed in hanging wire-mesh cages with *ad libitum* access to food and restricted access to water during the CTA/CPP conditioning phase (see below). During the self-administration phase (see below), they were housed in plastic cages (21 X 19 X 20 cm) with wood chip bedding and metal wire tops and were given *ad libitum* water but food restricted to maintain them at 85% of free-feeding weights (approximately 280-340 g for Experiment 1 and 300-370 g for Experiment 2). For both studies, the subjects were maintained on a 12-h light-dark cycle (lights on at 0800h) and at ambient temperature of approximately 23°C. All procedures were conducted under the guidelines established by the Institutional Animal Care and Use Committee at American University and were in compliance with the Guidelines for the Care and Use of Laboratory Animals (National Research Council, 2011).

Apparatus

A total of eight identical CPP apparatuses were used for place preference conditioning. Each CPP apparatus (San Diego Instruments Place Preference

System, San Diego, CA) consisted of two main conditioning chambers (28 X 21 X 34.5 cm) joined by a smaller middle chamber (14 X 21 X 34.5 cm) and featured a 16 x 4 photobeam array for recording time in each chamber (in seconds). One of the conditioning chambers featured a white aluminum diamond plate floor with white walls; the other conditioning chamber featured a haircell-textured black plastic floor with black walls; the smaller middle chamber was outfitted with a steel rod floor and gray walls. Each individual chamber in each apparatus had its own white LED lights, and the lights were set on minimum. The CPP room was illuminated by a 25-w red light mounted to the ceiling, and a white noise generator was used to mask background noise.

A total of 10 identical self-administration apparatuses were used for morphine self-administration. Each self-administration apparatus (Coulbourn Instruments, Whitehall, PA) measured 24 x 29 x 29 cm and had aluminum front and rear walls and ceiling, clear Plexiglas side walls and a grid floor. Each apparatus was housed within a sound- and light- attenuating chamber (Coulbourn Instruments). Each apparatus was equipped with two non-retractable levers (3.4 X 1.7 cm) positioned approximately 6 cm above the grid floor on both sides of a food cup. Pellet dispensers were located behind the front wall of the apparatus. All self-administration testing equipment and data acquisition were controlled by a desktop personal computer running Med Associates software (MED-PC for Windows). A swivel was located above the center of each self-administration chamber from which a spring-arm leash was suspended. The terminal end of the leash had a nylon wing nut that screwed onto a threaded

nylon post embedded in a dental acrylic plate on the subject's skull. This permitted the animals to move about the chamber freely without putting strain on the polyethylene (PE) drug-delivery tubing. For drug delivery, the terminal end of the PE tubing was connected to the external portion of the animal's catheter tubing where it exited between the scapulae. Outside the self-administration chamber, the swivel was connected with PE tubing (Plastics One; 0.044 mm ID, 0.814 mm OD) to a 10-ml syringe containing either morphine or cocaine solution which was driven by a Med-Associates (St. Albans, VT) syringe pump. A white-noise generator was used in the self-administration room to mask background noise.

Drugs and Solutions

Morphine sulfate (generously provided by NIDA) was prepared as a 5 mg/ml solution in 0.9% physiological saline and administered subcutaneously for CTA/CPP conditioning at a dose of 5 mg/kg and intravenously for self-administration at 0.56 mg/kg per infusion. Cocaine hydrochloride (generously provided by NIDA) was prepared as a 10 mg/ml solution in 0.9% physiological saline and administered intraperitoneally for CTA/CPP conditioning at a dose of 20 mg/kg and intravenously for self-administration at 0.75 mg/kg per infusion. The doses of drugs used for taste avoidance and place preference conditioning were based on earlier reports from our laboratory that showed intermediate avoidance and preference (Ferrari et al., 1991; Verendeev and Riley, 2011). Self-administration doses of morphine and cocaine were based on earlier work in our

lab and others' that demonstrated reliable self-administration (Mantsch et al., 2001; Mierzejewski et al., 2003). Saccharin (0.1% sodium saccharin, Sigma Chemical Co.) was prepared as a 1 g/l solution in tap water.

Procedure

Habituation and CPP pretest. Subjects were restricted to 20-min water access each day until body weights and fluid consumption stabilized and all subjects were approaching and drinking water from the tube within 2 s of its presentation. On the day before conditioning, each animal was allowed 15-min access to the entire place conditioning apparatus to obtain individual baseline times spent in each chamber (pretest). Analysis of side preference during the pretest in each experiment revealed no apparatus bias for either Experiment 1 ($t(19)=1.108$; $p>0.05$) or Experiment 2 ($t(16)=0.625$; $p>0.05$). Change in time spent on the drug-paired side (DPS) was later calculated for individual subjects by subtracting the time spent on the DPS during pretest from the time spent on the DPS during the post-conditioning test (posttest, see below).

Conditioning and CTA/CPP testing. Subjects were run between 0900 and 1200 h daily, and each subject was run at the same time throughout conditioning. On the first conditioning day, all animals were given access to a novel saccharin solution in their home cages during their normal daily 20-min fluid access period. Five minutes after the removal of saccharin, the animals were injected with either morphine (Experiment 1) or cocaine (Experiment 2) and immediately restricted to the white chamber (DPS) of the CPP apparatus for 30 min (see Verendeev and

Riley, 2011). On the next day, all animals received 20-min access to water, followed by an injection of saline and then restricted to the black chamber (non-drug-paired side [NDPS]). This cycle (saccharin-drug-DPS and water-vehicle-NDPS) was repeated twice for conditioning with morphine and four times for conditioning with cocaine (see below). On the day following the last conditioning day, all animals were given a test for CPP (posttest), during which they were placed in the middle gray compartment and given 15-min access to the entire apparatus in a drug-free state. On the day following this test, all subjects were given a one-bottle avoidance test in which they received 20-min access to the saccharin solution in the home cage. No injections were given following this avoidance test.

Surgery. Following the CTA test, animals were left undisturbed for one week during which food and water were provided *ad libitum*. Subjects were then transferred to plastic cages with wood chip bedding and maintained at 85% free-feeding weight with restricted food and *ad libitum* water. After several days, rats were surgically prepared with chronic indwelling jugular vein catheters, using a modification of the procedure originally developed by Weeks (1962). Briefly, under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia, approximately 3 cm of Silastic tubing (0.044 mm i.d., 0.814 mm o.d.) was inserted into the right jugular vein. This Silastic tubing was connected to 8 cm of vinyl tubing (Dural Plastics; 0.5 mm i.d., 1.0 mm o.d.) that was passed under the skin around the shoulder and exited the back at the level of the shoulder blades. The vinyl tubing was threaded through a section of Tygon tubing (10 mm long, 4 mm diameter)

that served as a subcutaneous anchor. Six stainless steel jeweler's screws were implanted in the skull to which a 20-mm plastic screw was cemented with dental acrylic. Catheters were flushed daily with 0.1 ml of a saline solution containing 1.25 U/ml heparin and 0.08 mg/ml gentamycin.

Operant training for food reinforcement. Subjects were initially trained to respond on the right (active) lever for a food reinforcer (one 45-mg pellet) on a fixed-ratio 1 (FR1) schedule during 1-h sessions. During food training, the house light was turned on and the cue light above the lever was turned off. Each lever press resulted in the delivery of a food pellet. The maximum number of pellets was set at 100, and free pellets were dispensed on a variable-time (VT) 2-min schedule if no responses occurred. Subjects were trained on this procedure until they earned at least 95 pellets of 100 possible for 3 consecutive days (3-5 days of training).

Assessment of morphine and cocaine self-administration. The day following the last food reinforcement session, all subjects were switched to intravenous drug self-administration, wherein a lever press on the active lever resulted in delivery of either 0.56 mg/kg/infusion morphine (Experiment 1) or 0.75 mg/kg/infusion cocaine (Experiment 2). During the session, the house light was turned on and the cue light was turned off. A lever press resulted in a drug infusion immediately followed by a 20-s timeout period during which the house light turned off and the cue light above the active lever was illuminated. Lever presses during the timeout period were recorded but had no programmed consequences. Once the timeout period was over, the house-light was turned

back on, the cue light was turned off and subsequent lever presses again resulted in drug delivery. Each drug self-administration session lasted for 2 h, and each subject was trained daily. All subjects completed eight sessions in total. Catheters were flushed daily and were confirmed for patency at the end of the self-administration phase by aspirating blood through the catheter. If patency could not be confirmed by drawing blood back, 0.1 ml of a saline solution containing 0.3 mg ketamine and 0.4 mg xylazine was infused into the catheter at the end of the study and patency was assumed if rapid ataxia (loss of motor control within 10 s) was observed. Subjects discovered to have non-patent catheters were excluded from the study. Three rats were removed from Experiment 2 due to failed catheters, and their data were removed from all statistical analyses. This resulted in 20 animals for Experiment 1 and 17 animals for Experiment 2 that completed the experiment.

Statistical Analyses

The relationship between place preference or taste avoidance and drug self-administration was determined using separate Spearman correlation coefficients by comparing either change in time spent on the DPS from pretest to the posttest (place preference) or change from baseline in amount of saccharin consumed (taste avoidance) in individual subjects and the number of either morphine or cocaine infusions averaged over the last 4 days of drug self-administration. To further explore the ability of either CPP or CTA to predict subsequent drug self-administration, subjects were divided into high (top 7) and

low (bottom 7) responders for both change in time spent on the DPS and change in saccharin consumption. We then compared drug intake (number of morphine or cocaine infusions averaged over the last 4 days of drug self-administration) in both high and low responders for both CPP and CTA using independent-samples t-test. Statistical significance for all analyses was set at $\alpha = 0.5$.

CHAPTER 3

RESULTS

Morphine

Figure 1 shows the relationship between morphine infusions (averaged over the last 4 days of morphine self-administration) and change in saccharin consumption (i.e., CTA; Panel A) or change in time spent on the DPS (i.e., CPP; Panel B). Spearman correlation analyses revealed a significant relationship between change from baseline in amount of saccharin consumed and the average number of morphine infusions taken by individual subjects (ρ= 0.517; p< 0.05). On the other hand, there was no significant relationship between change in time spent on the DPS and the average number of morphine infusions taken by individual subjects (ρ= -0.330; p> 0.05; see Figure 1).

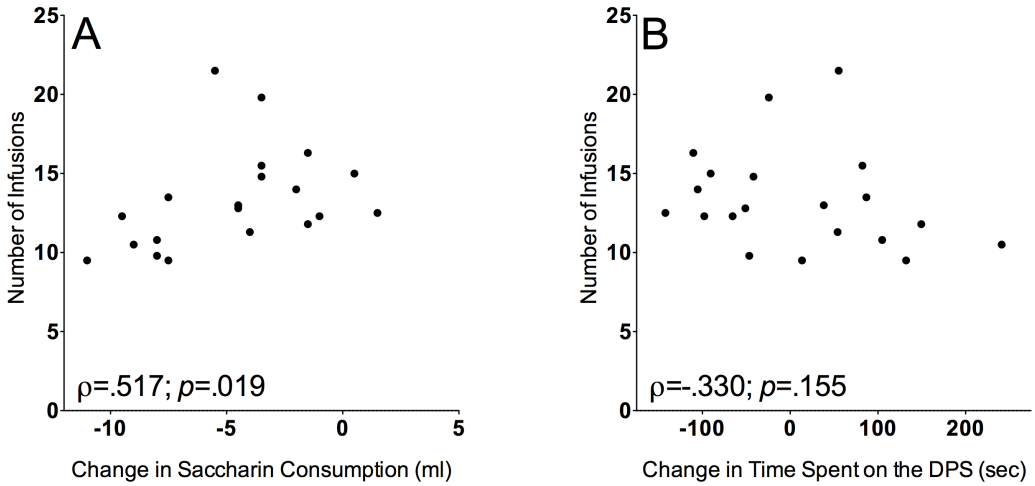

Figure 1. Relationship between morphine infusions (averaged over the last four days of morphine self-administration) and change in saccharin consumption (panel A) and change in time spent on the DPS (panel B). Spearman correlation coefficient revealed a significant relationship between the number of morphine infusions and CTA, but not between morphine infusions and CPP (see text for more detail).

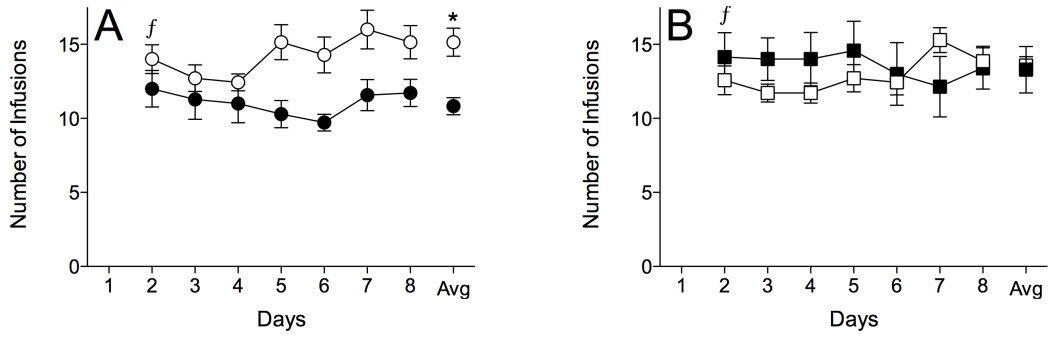

Figure 2. The number of morphine infusions (mean ± SEM) taken by high (filled) and low (empty) responders for CTA (panel A) and CPP (panel B). When the number of infusions (averaged over the last four days of morphine self-administration) were compared between the high and low responders for CTA, independent-samples t-test revealed a significant difference between the two ($t(12)= -3.493$; $p< 0.01$), such that animals displaying greatest morphine-induced taste aversions took less morphine than animals displaying weakest taste aversions (see text for more detail). When the number of infusions (averaged over the last four days of morphine self-administration) were compared between the high and low responders for CPP, independent-samples t-test revealed no significant difference between the two ($t(12)= -0.179$; $p> 0.05$; see text for more detail).

[f]Due to power outage during the first self-administration session, half of the rats (that included both high and low responders for CTA and CPP) experienced a prematurely terminated self-administration session, in which the drug was available for 1.5 hours instead of 2. Analysis of individual data revealed that rats showed responding comparable to that of the second self-administration session. Because of this technical difficulty, however, we have not included the data from the first self-administration session in Figure 2, panels A and B.

Given the significant correlation between change in saccharin consumption (i.e., taste avoidance) and the number of morphine infusions, we further analyzed this relationship between drug aversion and morphine self-administration by comparing the average number of drug infusions between the high and low responders for CTA over the last 4 days of morphine self-administration. An independent-samples t-test revealed a significant difference between high and low CTA responders in the average number of morphine

infusions taken (10.8 vs. 15.1 infusions on average; $t(12)= -3.493$; $p< 0.01$), such that subjects most sensitive to the aversive effects of morphine (i.e., larger reductions from baseline in saccharin intake) took less morphine than subjects least sensitive to the aversive effects of the drug (see Figure 2). When morphine infusions were compared between the high and low CPP responders over the last 4 days of morphine self-administration, an independent-samples t-test revealed no significant difference between the two (13.3 vs. 13.6 infusions on average; $t(12)= -0.179$; $p> 0.05$ see Figure 2).

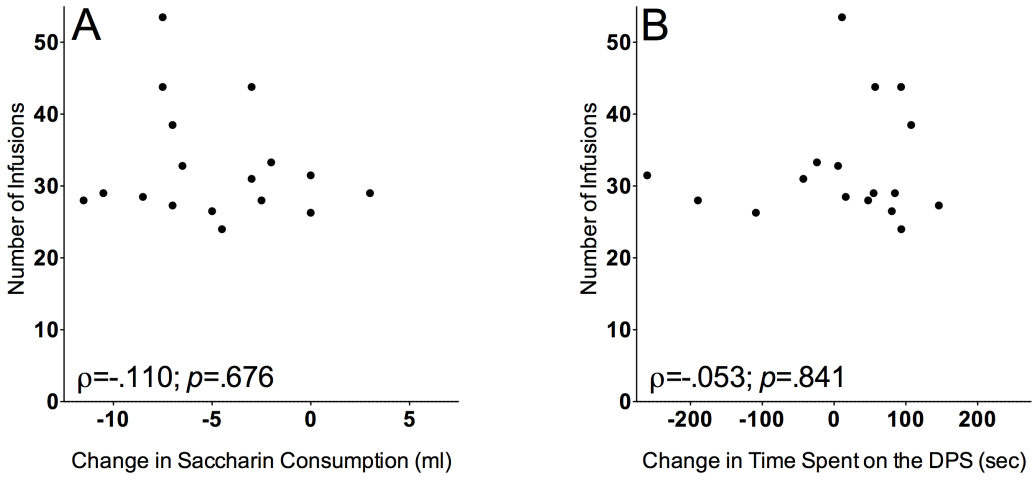

Figure 3. Relationship between cocaine infusions (averaged over the last four days of cocaine self-administration) and change in saccharin consumption (panel A) and change in time spent on the DPS (panel B). Spearman correlation coefficient revealed no significant relationship between the number of cocaine infusions and either CTA or CPP (see text for more detail).

Cocaine

Figure 3 shows the relationship between cocaine infusions (averaged over the last 4 days of cocaine self-administration) and change in saccharin consumption (Panel A) or change in time spent on the DPS (Panel B). Spearman

correlation analyses revealed no significant relationship between the average number of cocaine infusions taken by individual subjects and either change from baseline in amount of saccharin consumed (ρ= -0.110; *p*>0.05) or change from baseline in time spent on the DPS (ρ= -0.053; *p*> 0.05; see Figure 3).

When the relationship between cocaine self-administration and avoidance or preference was analyzed by comparing the number of drug infusions between the high and low responders for both CTA and CPP over the last 4 days of cocaine self-administration, independent-samples t-tests revealed no significant difference in the average number of cocaine infusions taken between high and low CTA responders (35.5 vs. 31.8 infusions on average; *t*(12)= 0.833; *p*> 0.05) or high and low CPP responders (33.3 vs. 33.8 infusions on average; *t*(12)= -0.106; *p*> 0.05; see Figure 4).

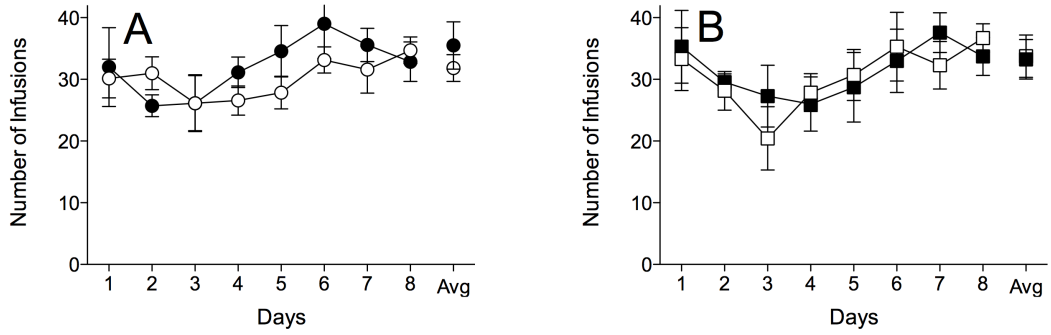

Figure 4. The number of cocaine infusions (mean ± SEM) taken by high (filled) and low (empty) responders for CTA (panel A) and CPP (panel B). When the number of infusions (averaged over the last four days of cocaine self-administration) were compared between the high and low responders for CTA, independent-samples t-test revealed no significant difference between the two (t(12)= 0.833; p> 0.05). When the number of infusions (averaged over the last four days of morphine self-administration) were compared between the high and low responders for CPP, independent-samples t-test revealed no significant difference between the two (t(12)= -0.106; p> 0.05; see text for more detail).

CHAPTER 4

DISCUSSION

The results of the present study show that the aversive effects of morphine, as measured by the CTA preparation, predict morphine self-administration. As described above, when initially trained in the combined CTA/CPP procedure, individual rats that showed greater reductions in saccharin intake were less likely to subsequently self-administer morphine than subjects that showed minimal or no decrease in saccharin consumption. This relationship was further confirmed when the number of self-administered morphine infusions was directly compared between the highest and lowest CTA responders, such that the high CTA group had significantly fewer morphine infusions compared to the low CTA group. Interestingly, the rewarding effects of morphine, as measured by change in time spent on the DPS, did not correlate with morphine self-administration, i.e., there was no significant relationship between change in time spent on the DPS and the number of morphine infusions in individual subjects; moreover, there was no difference in the number of infusions between high and low CPP responders. When the relationship between the aversive effects of cocaine, as measured by change in saccharin intake, and the number of cocaine infusions taken during self-administration were assessed, there was no significant correlation between the two. This lack of relationship was further reflected in no difference in the number of cocaine infusions between high and low CTA responders. The rewarding effects of cocaine, measured by change in time spent on the DPS, were also not predictive of the number of cocaine

infusions, and there was no difference in the number of infusions taken by high and low CPP responders.

Taken together these findings suggest that 1) sensitivity to the aversive effects of morphine predicts morphine self-administration, 2) sensitivity to the aversive effects of cocaine does not predict cocaine self-administration; there is a difference between morphine and cocaine in the ability of the aversive effects of the drug to predict drug taking and 3) the rewarding effects of either drug, as measured by the CPP preparation, are not predictive of the drug self-administration.

Regarding the first finding, the present data show a negative relationship between the sensitivity to the aversive effect of morphine and morphine self-administration. That individual subjects most sensitive to the aversive effects of morphine take less of the drug than the subjects least sensitive to its aversive effects suggests that the aversive effects play an important role in its self-administration. Indeed, as discussed earlier, it has been suggested that drug taking is a function of the balance between a drug's rewarding and aversive effects, with the drug's rewarding effects driving, and the drug's aversive effects limiting, drug intake (see Gaiardi et al., 1991; Riley and Simpson, 2001; Shabani et al., 2011; Stolerman and D'Mello, 1981; Riley, 2011). The present finding supports this position.

That drug aversion is important in our attempts to understand drug-taking behavior is further corroborated by the evidence from work done on different strains of mice and rats differentially sensitive to the aversive effects of drugs of

abuse. As described above, for example, mice strains that exhibit greater ethanol-induced CTA show less ethanol consumption and vice versa (Cunningham, 2009). Similar findings have been reported in other selectively bred mouse strains. For example, Chester et al. (2003) found that high alcohol preferring (HAP) mice show greater ethanol consumption than low alcohol preferring (LAP) mice. HAP mice, however, are less sensitive to the aversive effects of 2 and 4 g/kg ethanol than their LAP counterparts as measured by CTA procedure (see also Horowitz and Whitney 1975; Risinger and Cunningham 1992, 1995, 1998). Further, mice selectively bred for high sensitivity to the aversive effects of ethanol (high taste avoidance [HTA]) consume less ethanol and had a lower overall ethanol preference ratio than mice selectively bred for low sensitivity to the aversive effects of the drug (low taste avoidance [LTA]). It is interesting to note that although some of the above-mentioned studies were done using well-established lines of selectively bred mouse strains (C57BL/6J and DBA/2J; Horowitz and Whitney 1975; Risinger and Cunningham 1992, 1995, 1998), others used short-term selective breeding to create mouse lines that differed in their preference for ethanol (Chester et al., 2003) or sensitivity to ethanol's aversive effects (Phillips et al., 2005). Moreover, analysis of ethanol-induced CTA in selectively bred rats presents a similar picture as well. For example, Froehlich (1988) showed that selectively-bred ethanol preferring (P) rats show weaker CTA than ethanol non-preferring (NP) rats. Moreover, Wistar Kyoto (WKY) rats that consume less ethanol than Marshall (M520) rats acquire

taste avoidance at lower dose compared to M520 rats (i.e., show higher sensitivity to the aversive effects of ethanol; Cannon and Carrell, 1987).

Although most of the work in selectively bred lines of mice and rats has been done with alcohol, several studies examined this relationship using other drugs, including morphine and cocaine (see below). For example, studies done in F344 and LEW inbred rat strains with morphine provide further support for the position that drug aversion plays a role in drug-taking behavior. For example, F344 rats have been described as less sensitive to the rewarding effects of morphine (as measured by CPP; Guitart et al., 1992; although see Davis et al., 2007) and more sensitive to its aversive effects (as measured by CTA; Lancellotti et al., 2001) than inbred LEW rats. When compared in self-administration, F344 rats take less morphine (Ambrosio et al., 1995) and show lower break points on progressive ratio schedule (Martin et al., 1999, 2003; Sanchez-Cardoso, 2007) than LEW rats, a pattern consistent with our present finding (see Riley et al., 2009 for a discussion on drug-induced CTAs and their relation to self-administration in selectively bred mouse and rat strains).

Our second finding is that there is no direct relationship between the sensitivity to cocaine's aversive effects and cocaine self-administration. As described above, the analyses within individual subjects revealed that rats most sensitive and least sensitive to the aversive effects of cocaine did not differ in their pattern of cocaine self-administration. However, it is important to note that although we found no relationship between the sensitivity to cocaine's aversive effects and cocaine self-administration, this does not argue that cocaine does not

produce aversive effects – it clearly does, evidenced by its ability to support CTA learning. Our data, however, show that cocaine's aversive effects do not appear to be a rate-limiting factor in cocaine self-administration.

When the role of the rewarding and aversive effects of cocaine on self-administration is examined in LEW and F344 rats, the available data present a less consistent picture than that with morphine. For example, LEW rats show a greater taste avoidance response (i.e., greater sensitivity to the aversive effects of cocaine; Glowa et al., 1994; Grigson and Freet, 2000) than F344 rats. At the same time, however, LEW rats appear to be more sensitive to the rewarding effects of cocaine as well. LEW rats, for example, show more robust cocaine-induced CPP compared to F344 rats (Guitart et al., 1992) or show place preferences at doses that produce no place preference in F344 rats or produce conditioned place avoidance (Kosten et al., 1994). When cocaine self-administration is examined in these strains, the results are mixed with some studies showing faster acquisition in LEW rats (Kosten et al., 1997) and others showing greater responding for the drug in F344 rats (Haile and Kosten, 2001; Haile et al., 2005). Thus, the available data with these strains do not yet allow direct predictions regarding cocaine self-administration and its relation to the aversive or rewarding effects of the drug. The pattern of differential sensitivity of these strains to both the rewarding and aversive effects of cocaine underlines the importance of considering the relative sensitivity to both the rewarding and aversive effects of drugs rather than sensitivity to either of these effects alone.

The present data with morphine and cocaine add to the existing literature showing differences between opiates and psychostimulants in a number of factors pertaining to drug use and addiction (see Badiani et al., 2011 for a review). For example, rats given unlimited access to heroin steadily increase drug intake, whereas rats with unlimited cocaine access alternate between binge intake and reduced intake (Bozarth and Wise, 1985). Also, the escalation of heroin and cocaine self-administration is independent, i.e., in the same animals, escalation of heroin self-administration does not predict escalation of cocaine self-administration and vice versa (Lenoir et al., 2012). Further, rats with prolonged access to heroin, but not cocaine, show resistance to extinction (Ahmed, 2011). Finally, escalation of cocaine, but not heroin, self-administration is predicted by impulsivity (Anker et al., 2009; McNamara et al., 2010; Schippers et al., 2012;) and anxiety (Dilleen et al., 2012; see Badiani et al., 2011 for more detail). These behavioral differences between opiates and psychostimulants are further exemplified by different neurochemical and neurophysiological effects, as well as epidemiological and clinical data showing differences in genetic and environmental factors in the vulnerability to, and patterns of, use of both drugs (see Badiani et al., 2011 for further discussion). The present results add a further difference between an opiate (morphine) and a psychostimulant (cocaine) in that the sensitivity to the aversive effects of the drug predicts morphine, but not cocaine, self-administration.

Of particular interest to the present discussion is a series of studies done by Ettenberg and Geist (1991; 1993) that examined heroin and cocaine self-

administration in a runway model of drug reinforcement (see also Su et al., 2011). In this runway model, rats were trained to run down a straight alley for five intravenous injections of either 0.06 mg/kg heroin or 0.75 mg/kg cocaine. During training, the latency to leave the start box and the time to reach the goal box were recorded for each subject. The analysis of runway behavior in two groups of rats revealed important differences between animals receiving heroin vs. cocaine injections. Specifically, rats receiving heroin injections showed a decrease in both the time it took to leave the start box and the time it took to reach the goal box over the course of the experiment. Rats receiving cocaine, however, were slower to leave the start box and over training sessions *increased* the time it took to reach the goal box. This increased latency in time was a function of the frequency of stops and retreats as the animals approached the goal box, which increased over trials. The authors interpreted this approach/avoidance conflict behavior in terms of cocaine's rewarding and anxiogenic effects, respectively. Although consistent with the position that drugs of abuse possess both positive and negative elements, as well as showing a difference between an opiate and a psychostimulant in the motivational state underlying drug seeking, their data are seemingly in opposition to our present results showing that morphine's aversive effects, but not those of cocaine, limit drug self-administration. The obvious difference between our study and theirs, however, may explain the discrepancy in the results. Ettenberg and Geist (1993), for example, did not allow the subjects to self-administer the drug in a free-operant situation over a fixed period of time, as is usual in self-administration studies. Instead, their rats could only make one

drug-taking response per session, precluding the possibility of examining the role of approach/avoidance behavior in the actual drug intake (i.e., amount of drug self-administered). Thus, although cocaine, unlike heroin, may induce approach-avoidance behavior, which may lead to a longer latency to the first drug infusion, this measure may not be an accurate reflection of how much drug an animal will self-administer over time. Unlike Ettenberg and Geist, in the present study we examined the role of the aversive effects of drugs on the amount of drug self-administered by individual animals, rather than the latency to initiate drug taking.

Our third finding is that the rewarding effects of morphine and cocaine, as measured by the CPP procedure, did not predict drug self-administration. These results may seem surprising at first (although see Cunningham et al., 2009), since CPP has been commonly used as a measure of drug reward (Bardo and Bevins, 2000) and the rewarding effects of drugs have been clearly implicated in drug self-administration (Koob and Le Moal, 2006). Indeed, there appears to be a common concordance in the ability of various drugs of abuse to produce CPP and support self-administration (reviewed in Bardo and Bevins, 2000). For example, both morphine (Bardo et al., 1984; Glick et al., 1992) and cocaine (Nomikos and Spyraki, 1988; Caine and Koob, 1994), as well as other opiates and psychostimulants, have been shown to produce both CPPs and support self-administration. Conversely, several compounds, such as opiate and dopamine antagonists, that don't support self-administration (Weeks and Collins, 1987) also have been shown ineffective in producing CPPs (Di Scala and Sandner, 1989) or

have been shown to actually produce conditioned place avoidance (Shippenberg and Bals-Kubik 1995).

Although generally concordant, the relationship between CPP and self-administration is not perfect (Bardo and Bevins, 2000). For example, pentobarbital (Collins et al., 1984; Lew and Parker, 1998) and phencyclidine (Marquis et al., 1989; Aquas et al., 1990) that support self-administration have nonetheless been found ineffective in the CPP preparation. On the other hand, LSD (Meehan and Schechter, 1998), buspirone (Balster, 1990; Neisewander et al., 1990) and pentylenetetrazole (Gauvin et al., 1991) that have been reported to produce place preferences do not engender self-administration (Balster, 1990; Gauvin et al., 1991; Meehan and Schechter, 1998; Neisewander et al. 1990).

Interestingly, one study that examined the ability of amphetamine to produce place preference and engender self-administration in the same individual subjects found no relationship between the two. The authors (Bardo et al., 1999) first examined the ability of intravenous amphetamine to establish place preferences in individual subjects. They found that different doses of amphetamine (1.0 and 3.0 mg/kg) produced CPPs in a dose-dependent manner, with the larger dose producing stronger place preference than the medium dose, while two lower doses (0.1 and 0.3 mg/kg) were not effective in producing place preference at all. Using the intermediate dose of 1.0 mg/kg amphetamine, a new set of drug-naive rats was given a one-trial CPP conditioning session, following which they were allowed to self-administer 30 μg/infusion amphetamine. Place preferences were then correlated with the number of amphetamine infusions.

The authors reported no significant relationship between place preference scores and the number of infusions taken by individual subjects.

Although these results (and those of the present study) may at first seem contradictory in that place preference, which is generally thought as a measure of reward, and self-administration are not directly related when examined in the same subjects, it is important to stress that self-administration may not be a function of drug reward only but instead is dependent on the balance of a drug's rewarding and aversive effects (Gaiardi et al., 1991; Riley and Simpson, 2001; Shabani et al., 2011; Stolerman and D'Mello, 1981; Riley, 2011; Verendeev and Riley, 2012). According to this position, the rewarding effects of drugs drive self-administration while drugs' aversive effects limit drug taking. Previous work has demonstrated that individual animals are differentially sensitive to the rewarding and aversive effects of drugs (Verendeev and Riley, 2011). Consequently, drug-taking behavior will differ from one individual subject to another, with the specific pattern of drug intake dependent on the overall drug experience of the individual.

One of the possible limitations of the present analysis of the relationship between drug-induced CPP and self-administration in both morphine and cocaine experiments is that individual subjects exhibited a wide range of change in time spent on the drug-paired side with some animals showing negative place preference scores, meaning that the individual subject actually *decreased* time spent on the DPS following drug-environment pairing. Although both Bardo et al. (1999) and the present study included these animals in statistical analyses, it may be argued that given negative preference scores the analysis between CPP

and self-administration may not be a meaningful one. To avoid misinterpretation, for a follow-up analyses we excluded all animals spending more than a minute (60 seconds) less on the DPS on the test compared to the pre-test. This manipulation resulted in excluding six subjects from Experiment 1 (morphine) and three subjects from Experiment 2 (cocaine) resulting in 14 subjects for both experiments. When the relationship between CPP and self-administration was examined in this subset of subjects, there was no difference from the initial analyses in the patterns revealed for either animals receiving morphine or cocaine (data not shown). In subjects receiving morphine, we found no significant relationship between change in time spent on the DPS (CPP) and the number of infusions taken (ρ= -0.198; p> 0.5) but a significant relationship between change in saccharin consumption (CTA) and the number of morphine infusions taken by individual subjects (ρ= 0.646; p< 0.5). In rats receiving cocaine, we found no significant relationship between the number of infusions taken by individual subjects and either change in time spent on the DPS (ρ= -0.284; p> 0.5) or change in the amount of saccharin consumed (ρ= 0.051; p> 0.5).

Another important caveat of the analyses described above is that CTAs and CPPs seemed to be of different strengths. In other words, overall both morphine and cocaine seemed to produce greater taste avoidance than place preference. Visual analysis of figures 1 and 3, for example, reveals that most individual subjects decreased their saccharin intake following its pairing with either morphine or cocaine (i.e., exhibited taste avoidance), but only about half of subjects in both conditions increased their time spent on the DPS (i.e., exhibited

place preference). Given this inequality between the ability of either drug to produce taste avoidance and its ability to produce place preference at any particular dose, it may be argued that the assessments of the relationship between self-administration and either taste avoidance or place preference may not reflect the existing (if any) relationship. This is a valid criticism and future studies should seek doses that produce taste avoidance and place preference of comparable strength.

That sensitivity to the aversive effects of morphine predicts morphine self-administration in individual subjects confirms the view that any complete account of drug use and abuse must incorporate the effects of the aversive properties of drugs upon drug-taking behavior. This position is further reinforced by the findings from selectively bred mouse and rat strains that demonstrate a negative relationship between drug aversion and drug intake. Although this opposite relationship was not observed with cocaine in the present study and is yet to be examined in all drugs of abuse, the available evidence suggests that drugs of abuse are not simple pharmacological compounds that produce rewarding effects only. That drugs of abuse are complex pharmacological stimuli with both positive and negative elements demands consideration of both of these effects in our ongoing attempts to understand drug-taking behavior.

REFERENCES

Ahmed, S. H. (2011). Escalation of drug use. Neuromethods, 53, 267–292.

Ambrosio, E., Goldberg, S. R., & Elmer, G. I. (1995). Behavior genetic investigation of the relationship between spontaneous locomotor activity and the acquisition of morphine self-administration behavior. Behavioural Pharmacology 6, 229–237.

Anker, J. J., Perry, J. L., Gliddon, L. A., & Carroll, M. E. (2009). Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacology Biochemistry, and Behavior, 93, 343-348.

Aquas, E., Carboni, E., Garau, L., & Di Chiara, G. (1990). Blockade of acquisition of drug-conditioned place aversion by 5HT3 antagonists. Psychopharmacology, 100, 459–463.

Badiani, A., Belin, D., Epstein, D., Calu, D., & Shaham, Y. (2011). Opiate versus psychostimulant addiction: the differences do matter. Nature Reviews Neuroscience, 12, 685-700.

Balster, R. L. (1990). Abuse potential of buspirone and related drugs. Journal of Clinical Psychopharmacology, 10, 31S–37S.

Bardo, M. T., & Bevins, R. A. (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology, 153, 31-43.

Bardo, M. T., Miller, J. S., & Neisewander, J. L. (1984). Conditioned place preference with morphine: the effect of extinction training on the reinforcing CR. Pharmacology, Biochemistry, and Behavior, 21, 545–549.

Bardo, M. T., Valone, J. M., & Bevins, R. A. (1999). Locomotion and conditioned place preference produced by acute intravenous amphetamine: role of dopamine receptors and individual differences in amphetamine self-administration. Psychopharmacology, 143, 39-46.

Belknap, J. K., Crabbe, J. C., & Young, E. R. (1993). Voluntary consumption of ethanol in 15 inbred mouse strains. Psychopharmacology, 112, 503-510.

Bozarth, M. A., & Wise, R. A. (1985). Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. Journal of the American Medical Association, 254, 81-83.

Broadbent, J., Muccino, K. J., & Cunningham, C. L. (2002). Ethanol-induced conditioned taste aversion in 15 inbred mouse strains. Behavioral neuroscience, 116, 138- 148.

Caine, S. B., & Koob, G. F. (1994). Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. Journal of Pharmacology and Experimental Therapeutics, 270, 209–218.

Cannon, D. S., & Carrell, L. E. (1987). Rat strain differences in ethanol self-administration and taste aversion learning. Pharmacology, Biochemistry, and Behavior, 28, 57-63.

Cannon, D. S., Leeka, J. K., & Block, A. K. (1994). Ethanol self-administration patterns and taste aversion learning across inbred rat strains. Pharmacology, Biochemistry, and Behavior, 47, 795-802.

Chester, J. A., Lumeng, L., Li, T. K., & Grahame, N. J. (2003). High–and low–alcohol‐preferring mice show differences in conditioned taste aversion to alcohol. Alcoholism: Clinical and Experimental Research, 27, 12-18.

Collins, R. J., Weeks, J. R., Cooper, M. M., Good, P. I., & Russell, R. R. (1984). Prediction of abuse liability of drugs using IV self-administration in rats. Psychopharmacology, 82, 6–13.

Cunningham, C. L. (1995). Localization of genes influencing ethanol-induced conditioned place preference and locomotor activity in BXD recombinant inbred mice. Psychopharmacology, 120, 28-41.

Cunningham, C. L., Gremel, C. M., & Groblewski, P. A. (2009). Genetic influences on conditioned taste aversion. In S. Reilly & T. R. Schachtman (Eds.), Conditioned taste aversion: behavioral and neural processes (pp. 387-421). New York: Oxford University Press.

Davis, C. M., Roma, P. G., Dominguez, J. M., & Riley, A. L. (2007). Morphine-induced place conditioning in Fischer and Lewis rats: acquisition and dose-response in a fully biased procedure. Pharmacology, Biochemistry, and Behavior, 86, 516-523.

Dilleen, R., Pelloux, Y., Mar, A. C., Molander, A., Robbins, T. W., Everitt, B. J., Dalley, J. W., & Belin, D. (2012). High anxiety is a predisposing endophenotype for loss of control over cocaine, but not heroin, self-administration in rats. Psychopharmacology, 222, 89-97.

Di Scala, G., & Sandner, G. (1989). Conditioned place aversion produced by FG 7142 is attenuated by haloperidol. Brain Research, 483, 91–97.

Ettenberg, A., & Geist, T. D. (1991). Animal model for investigating the anxiogenic effects of self-administered cocaine. Psychopharmacology, 103, 455–461.

Ettenberg, A., & Geist, T. D. (1993). Qualitative and quantitative differences in the operant runway behavior of rats working for cocaine and heroin reinforcement. Pharmacology, Biochemistry, and Behavior, 44, 191–198.

Ferrari, C. M., O'Connor, D. A., & Riley, A. L. (1991). Cocaine-induced taste aversions: effect of route of administration. Pharmacology, Biochemistry, and Behavior, 38, 267–271.

Froehlich, J. C., Harts, J., Lumeng, L., & Li, T. K. (1988). Differences in response to the aversive properties of ethanol in rats selectively bred for oral ethanol preference. Pharmacology, Biochemistry, and Behavior, 31, 215-222.

Gaiardi, M., Bartoletti, M., Bacchi, A., Gubellini, C., Costa, M., & Babbini, M. (1991). Role of repeated exposure to morphine in determining its affective properties: place and taste conditioning studies in rats. Psychopharmacology, 103, 183–186.

Gaiardi, M., Bartoletti, M., Bacchi, A., Gubellini, C., Costa, M., & Babbini, M. (1991). Role of repeated exposure to morphine in determining its affective properties: place and taste conditioning studies in rats. Psychopharmacology, 103, 183–186.

Gauvin, D. V., Dormer, K. N., & Holloway, F. A. (1991). Pentylenetetrazole can induce a conditioned place preference. Pharmacology, Biochemistry, and Behavior, 40, 987–990.

Glick, S. D., Merski, C., Steindorf, S., Wang, S., Keller, R. W., & Carlson, J. N. (1992). Neurochemical predisposition to self-administer morphine in rats. Brain Reseasrch, 578, 215–220.

Glowa, J. R., Shaw, A. E., & Riley, A. L. (1994). Cocaine-induced conditioned taste aversions: comparisons between effects in LEW/N and F344/N rat strains. Psychopharmacology, 114, 229–232.

Grigson, P. S., & Freet, C. S. (2000). 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. Behavioral Neuroscience, 114, 353–363.

Guitart, X., Beitner-Johnson, D., Marby, D. W., Kosten, T. A., & Nestler, E. J. (1992). Fischer and Lewis rat strains differ in basal levels of neurofilament proteins and their regulation by chronic morphine in the mesolimbic dopamine system. Synapse, 12, 242–253.

Haile, C. N., & Kosten, T. A. (2001). Differential effects of D1-and D2-like compounds on cocaine self-administration in Lewis and Fischer 344 inbred rats. Journal of Pharmacology and Experimental Therapeutics, 299, 509-518.

Haile, C. N., Zhang, X. Y., Carroll, F., & Kosten, T. A. (2005). Cocaine self-administration and locomotor activity are altered in Lewis and F344 inbred rats by RTI 336, a 3-phenyltropane analog that binds to the dopamine transporter. Brain Research, 1055, 186-195.

Horowitz, G. P., & Whitney, G. (1975). Alcohol-induced conditioned aversion: Genotypic specificity in mice (Mus musculus). Journal of Comparative and Physiological Psychology, 89, 340-346.

Koob, G. F., & Le Moal, M. (2006). Neurobiology of addiction. Amsterdam/Boston: Elsevier/Academic Press.

Kosten, T. A., Miserendino, M. J. D., Chi, S., & Nestler, E. J. (1994). Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. Journal of Pharmcology and Experimental Therapeutics, 269, 137–144.

Lancellotti, D., Bayer, B. M., Glowa, J. R., Houghtling, R. A., & Riley, A. L. (2001). Morphine-induced conditioned taste aversions in the LEW/N and F344/N rat strains. Pharmacology, Biochemistry, and Behavior, 68, 603–610.

Lenoir, M., Guillem, K., Koob, G. F., & Ahmed, S. H. (2012). Drug specificity in extended access cocaine and heroin self‐administration. Addiction Biology, 17, 964-976.

Lew, G., & Parker, L. A. (1998). Pentobarbital-induced place aversion learning. Animal Learning and Behavior, 26, 219–224.

Mantsch, J. R., Ho, A., Schlussman, S. D., & Kreek, M. (2001). Predictable individual differences in the initiation of cocaine self-administration by rats under extended-access conditions are dose-dependent. Psychopharmacology, 157, 31-39.

Marquis, K. L., Webb, M. G., & Moreton, J. E. (1989). Effects of fixed ratio size and dose on phencyclidine self-administration by rats. Psychopharmacology, 97,179–182.

Martin, S., Lyupina, Y., Crespo, J. A., Gonzalez, B., Garcia-Lecumberri, C., & Ambrosio, E. (2003). Genetic differences in NMDA and D1 receptor levels, and operant responding for food and morphine in Lewis and Fischer 344 rats. Brain Research, 973, 205–213.

Martin, S., Manzanares, J., Corchero, J., Garcia-Lecumberri, C., Crespo, J. A., Fuentes, J. A., & et al (1999). Differential basal proenkephalin gene expression in dorsal striatum and nucleus accumbens, and vulnerability to morphine self-administration in Fischer 344 and Lewis rats. Brain Research, 821, 350–355.

McNamara, R., Dalley, J. W., Robbins, T. W., Everitt, B. J., & Belin, D. (2010). Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. Psychopharmacology, 212, 453–464.

Meehan, S. M., & Schechter, M. D. (1998). LSD produces conditioned place preference in male but not female fawn hooded rats. Pharmacology, Biochemistry, and Behavior, 59, 105–108.

Meyer, J. S., & Quenzer, L. F. (2005). Psychopharmacology: drugs, the brain, and behavior. Sunderland, Massachusetts: Sinauer Associates.

Mierzejewski, P., Koros, E., Goldberg, S. R., Kostowski, W., & Stefañski, R. (2003). Intravenous self-administration of morphine and cocaine: a comparative study. Polish Journal of Pharmacology, 55, 713-726.

Neisewander, J. L., McDougall, S. A., Bowling, S. L., & Bardo, M. T. (1990). Conditioned taste aversion and place preference with buspirone and gepirone. Psychopharmacology, 100, 485–490.

Nomikos, G. G., & Spyraki, C. (1988). Cocaine-induced place conditioning: importance of route of administration and other procedural variables. Psychopharmacology, 94, 119–125.

Phillips, T. J., Broadbent, J., Burkhart-Kasch, S., Henderson, C., Wenger, C. D., McMullin, C., & Cunningham, C. L. (2005). Genetic correlational analyses of ethanol reward and aversion phenotypes in short-term selected mouse lines bred for ethanol drinking or ethanol-induced conditioned taste aversion. Behavioral Neuroscience, 119, 892-910.

Reicher, M. A., & Holman, E. W. (1977). Location preference and flavor aversion reinforced by amphetamine in rats. Animal Learning Behavior, 5, 343–346.

Riley, A. L. (2011). The paradox of drug taking: the role of the aversive effects of drugs. Physiology and Behavior, 103, 69-78.

Riley, A. L., Davis, C. M., & Roma, P. G. (2009). Strain differences in taste aversion learning: implications for animal models of drug abuse. In S. Reilly & T. R. Schachtman (Eds.), Conditioned taste aversion: behavioral and neural processes (pp. 226-261). New York: Oxford University Press.

Riley, A. L., & Simpson, G. R. (2001). The attenuating effects of drug preexposure on taste aversion conditioning: generality, experimental parameters, underlying mechanisms and implications for drug use and abuse. In: R. R. Mowrer & S. B. Klein (Eds.), Contemporary learning theory, second edition (pp. 505-559). Hillsdale, NJ: Lawrence Erlbaum Associates.

Risinger, F. O., & Cunningham, C. L. (1992). Genetic differences in ethanol-induced hyperglycemia and conditioned taste aversion. Life Sciences, 50, PL113-PL118.

Risinger, F. O., & Cunningham, C. L. (1995). Genetic differences in ethanol-induced conditioned taste aversion after ethanol preexposure. Alcohol, 12, 535-539.

Risinger, F. O., & Cunningham, C. L. (1998). Ethanol‐Induced conditioned taste aversion in BXD recombinant inbred mice. Alcoholism: Clinical and Experimental Research, 22, 1234-1244.

Sanchez-Cardoso, P., Higuera-Matas, A., Martin, S., del Olmo, N., Miguens, M., Garcia-Lecumberri, C., & et al. (2007). Modulation of the endogenous opioid system after morphine self-administration and during its extinction: A study in Lewis and Fischer 344 rats. Neuropharmacology, 52, 931–948.

Schippers, M. C., Binnekade, R., Schoffelmeer, A. N., Pattij, T., & De Vries, T. J. (2012). Unidirectional relationship between heroin self-administration and impulsive decision-making in rats. Psychopharmacology, 219, 443-452.

Shabani, S., McKinnon, C. S., Reed, C., Cunningham, C. L., & Phillips, T. J. (2011). Sensitivity to rewarding or aversive effects of methamphetamine determines methamphetamine intake. Genes, Brain, and Behavior, 10, 625-636.

Shippenberg, T. S., & Bals-Kubik, R. (1995). Involvement of the mesolimbic dopamine system in mediating the aversive effects of opioid antagonists in the rat. Behavioral Pharmacology, 6, 99–106.

Simpson, G. R., & Riley, A. L. (2005). Morphine preexposure facilitates morphine place preference and attenuates morphine taste aversion. Pharmacology, Biochemistry, and Behavior, 80, 471–479.

Stolerman, I. P. (1992). Drugs of abuse: behavioural principles, methods and terms. Trends in Pharmacological Science, 13, 170–176.

Stolerman, I. P., & D'Mello, G. D. (1981). Oral self-administration and the relevance of conditioned taste aversions. In: T. Thompson, P. B., Dews, & W. A. McKim (Eds.). Advances in behavioral pharmacology (pp. 169-214). Hillsdale, NJ: Lawrence Erlbaum.

Su, Z. I., Wenzel, J., Baird, R., & Ettenberg, A. (2011). Comparisons of self-administration behavior and responsiveness to drug-paired cues in rats running an alley for intravenous heroin and cocaine. Psychopharmacology, 214, 769-778.

Turenne, S. D., Miles, C., Parker, L. A., & Siegel, S. (1996). Individual differences in reactivity to the rewarding/aversive properties of drugs: assessment by taste and place conditioning. Pharmacology, Biochemistry, and Behavior, 53, 511– 516.

Verendeev, A., & Riley, A. L. (2011). Relationship between the rewarding and aversive effects of morphine and amphetamine in individual subjects. Learning and Behavior, 39, 399–408.

Verendeev, A., & Riley, A. L. (2012). Conditioned taste aversion and drugs of abuse: history and interpretation. Neuroscience and Biobehavioral Reviews, 36, 2193-2205.

Weeks, J. R. (1962). Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science 138, 143-144.

Weeks, J. R., & Collins, R. J. (1987). Screening for drug reinforcement using intravenous self-administration in the rat. In: M. A. Bozarth (Ed), Methods of assessing the reinforcing properties of abused drugs (pp. 35-43). New York: Springer.

White, N., Sklar, L., & Amit, Z. (1977). The reinforcing action of morphine and its paradoxical side effect. Psychopharmacology, 52, 63–66.

Wise, R. A., Yokel, R. A., DeWit, H. (1976). Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science, 191, 1273–1275.