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Cocaine withdrawal in rats selectively bred for low (LoS) versus high (HiS) saccharin intake

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Abstract

Cocaine use results in anhedonia during withdrawal, but it is not clear how this emotional state interacts with an individual's vulnerability for addiction. Rats selectively bred for high (HiS) or low (LoS) saccharin intake are a well-established model of drug abuse vulnerability, with HiS rats being more likely to consume sweets and drugs of abuse such as cocaine and heroin (Carroll et al. 2002) than LoS rats. This study examined whether the motivational consequences of cocaine withdrawal are differentially expressed in HiS and LoS rats. HiS and LoS rats were trained to respond for a sucrose reward on a progressive ratio (PR) schedule of reinforcement and breakpoints were measured during and after chronic, continuous exposure to cocaine (30 mg/kg/day). Cocaine, but not saline, treatment resulted in lower breakpoints for sucrose during withdrawal in LoS rats only. These results suggest anhedonia during withdrawal is more pronounced in the less vulnerable LoS rats. Fewer motivational deficits during withdrawal may contribute to drug vulnerability in the HiS line.

Keywords

cocaine; rat; motivation; sweet preference; selective breeding; withdrawal

1. Introduction

In humans, cocaine produces acute symptoms that include euphoria, increased energy and alertness, and feelings of extreme confidence (Gawin 1991). Following long-term use of the drug, these symptoms wane and a withdrawal syndrome emerges during periods of abstinence (Gawin 1991). During both short- and long-term abstinence, cocaine addicts experience craving for the drug along with lethargy and anhedonia (Gawin and Kleber, 1986). The lack of motivation and flat affect that accompanies cocaine (Coffey et al. 2000; Goldstein et al. 2009b; Leventhal et al. 2008) withdrawal is sometimes termed “washed-out syndrome” (Goldstein et al. 2009a). In rodent models, withdrawal following chronic cocaine

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exposure produces decreased interest in rewarding stimuli (Harris et al. 2007), including reductions in operant responding for a sucrose reward (Carroll and Lac 1987).

Although the anhedonic signs of cocaine withdrawal are well documented, it is still not clear how withdrawal interacts with an individual's propensity for cocaine abuse. To address this question, this study examined the effects of cocaine on rats selectively bred for high (HiS) or low (LoS) saccharin intake (Carroll et al. 2008). HiS rats consume a variety of sweeteners more avidly (Dess 2000; Dess and Minor 1996; Dess et al. 2005) and respond at higher rates than LoS rats in an operant conditioning paradigm for a sucrose reward (Gosnell et al. 2010) than LoS rats. On measures of cocaine-seeking, HiS rats are more vulnerable to acquisition (Carroll et al. 2002), escalation, and reinstatement (Perry et al. 2006) than their LoS counterparts. Because humans with a preference for sweet substances are also more likely to abuse drugs (Janowsky et al. 2003; Kampov-Polevoy et al. 1997; Kampov-Polevoy et al. 2001; Pomerleau et al. 1991; Weiss 1982), HiS and LoS rats have been used as a model of drug-abuse vulnerability (Carroll et al. 2008).

To study differences in motivation during chronic cocaine exposure and withdrawal we measured motivation to obtain a reward on a progressive ratio (PR) schedule of reinforcement (Hodos 1961), based on a procedure described by Der-Avakian and Markou (2010). PR schedules require a progressive increase in the ratio of responses required to attain a single reward, and the highest ratio completed within a given time allotment is termed the "breakpoint." Psychostimulant exposure has been shown to increase breakpoints for sucrose (Der-Avakian and Markou 2010), while psychostimulant withdrawal results in reductions in responding (Carroll and Lac 1987; Barr and Phillips 1999; Der-Avakian and Markou 2010; LeSage et al. 2006). HiS and LoS rats were trained to lever-press for a sucrose reward, and breakpoints were measured during and after chronic cocaine exposure. We hypothesized that sucrose responding would increase during cocaine exposure and decrease during withdrawal in both HiS and LoS rats, but the magnitude of the motivational effects would differ between the lines.

This study examined whether greater expression of acute cocaine-induced motivational deficits during withdrawal are associated with an increased propensity for drug taking. The results of these experiments are an important step in characterizing the HiS and LoS rat lines that provide information regarding how motivational state after drug exposure may contribute to vulnerability to cocaine abuse.

2. Materials and Methods

2.1 Subjects

Adult male rats selectively bred at the University of Minnesota (Carroll et al. 2002) from Occidental HiS and LoS lines (Occidental College, Los Angeles, CA) were used in this study. The lines were started as outbred lines, defined as no mating closer than second cousins (Dess and Minor 1996; Lohmiller and Swing 2006). To maintain this status, we continued to avoid sibling, half-sibling, and first cousin mating and every four to six generations we purchased rats from the founding stock (i.e. Sprague-Dawley from Harlan, formerly Holtzman), tested them for saccharin preference, and mated both males and

females with our selectively bred rats. Thus, the rats are selectively outbred from Holtzman/Harlan Sprague-Dawley founding stock (Carroll et al. 2008; Dess 2000; Dess and Minor 1996). Rats in this study were selected from a total of 13 different litters (6 HiS and 7 LoS), and drug treatment was balanced across litters.

Rats were bred and housed in plastic cages with *ad libitum* access to rat pellet chow (Purina Mills, Minneapolis, MN, USA) and water until the experiment began. The humidity, temperature (21–23 °C), and light–dark cycle (12 h–12 h; lights on at 6:00 AM) were all regulated. All procedures conformed to the eighth edition of the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (National Academies Press 2011) and were approved by the University of Minnesota Institutional Animal Care and Use Committee under protocol number 1008A87755. All laboratory facilities were approved by the Association for Assessment and Accreditation of Laboratory Animal Care.

2.2 Drugs

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC), dissolved in 0.9% sterile saline and administered subcutaneously through an osmotic minipump (#2ML2, Alzet, Cupertino, CA).

2.3 Surgery

Rats were anesthetized with a combination of ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and administered doxapram (5 mg/kg, i.p.) and atropine (0.4 mg/ml, 0.15 ml, s.c.) to facilitate respiration. For minipump implantation, an incision was made on the left flank, and the minipump was inserted into the subcutaneous space, parallel to the spine. The incision was then sutured and treated with topical antibiotic ointment. Following recovery rats were returned to their home cage. Minipumps were removed two weeks later using the same procedure.

2.4 Operant responding for sucrose

Rats were housed individually in custom-made operant conditioning chambers consisting of alternating stainless steel and Plexiglas walls enclosed in a sound-attenuating box. Each chamber included a drinking spout, a food receptacle, two response levers, two sets of multicolored light-emitting diode stimulus lights located above the levers, a large green stimulus light, and a white house light (4.76 W). MED-PC IV software was used to control stimulation parameters and for data collection. Operant sessions were conducted once a day, 7 days a week during training and testing. During the experiment rats had *ad libitum* access to water and were fed 20 g of food at 3:00 PM.

The operant responding for sucrose paradigm was based on that used by Der-Avakian and Markou (2010). At 12:00 PM each day the green stimulus light turned on and sucrose pellets (45 mg chocolate flavor Sucrose Reward Tablet, TestDiet, St. Louis, MO) were available by pressing on the right lever. Training sessions lasted 3 h and began with a fixed-ratio 1 schedule of reinforcement with a 1 s time-out period (FR1 TO1). After each successful response, the multicolored stimulus lights were illuminated for the duration of the time-out period. After rats acquired this procedure (defined as less than 20% variability in response

rates over 3 sessions), the schedule of reinforcement was increased to FR2 TO10, followed by FR5 TO20 and finally to a progressive ratio (PR) schedule with 20 s time-out period. The progression of response requirements was as follows: 5, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219. This schedule is similar to that used by Roberts et al. (1989) and has been used previously with cocaine self-administration in our laboratory (Anker et al. 2009, Carroll et al. 2011). Once the PR schedule began, sessions lasted until the rats failed to earn a pellet in 60 min or after a maximum of 3 h. Breakpoints were defined as the final ratio attained during the session.

2.5 Experimental timeline

A timeline of experimental events can be found in Figure 1. Once rats acquired the PR task, five days of baseline responding was collected. At the end of the fifth session rats were removed from their chamber and implanted with an osmotic minipump containing 2 ml of sterile saline or cocaine hydrochloride (100 mg/ml). Cocaine was delivered continuously via osmotic minipump to ensure that the drug dose was high enough to produce withdrawal and that exposure levels were equal across lines. The dose of cocaine was calculated to deliver an average of 30 mg/kg/day (based on previous work by King et al. 1993). Importantly, previous work found no evidence of necrotic skin lesions using doses greater than or equal to the one used here (King et al. 1993; Kunko et al. 1998). Sucrose responding under a PR schedule recommenced the following day and was measured for a total of 14 days. At the end of the 14th day the minipump was removed. Sucrose responding recommenced the following day and was measured for another 14 days. At the end of the experiment rats were transferred to individual plastic cages for saccharin preference testing.

2.6 Saccharin preference testing

Phenotype score was derived from a 24 h two-bottle test (see Badia-Elder et al. 1996 for details) in which consumption of 0.1% saccharin solution was assessed relative to previously attained 24 h water intake, divided by body weight to control for sex/age of the rats [saccharin score = (saccharin ml – water baseline ml)/body weight × 100]. Table 1 shows group numbers and saccharin scores that were measured 2 weeks after the final drug exposure. Measuring saccharin preference 2 weeks after drug exposure is standard procedure in our laboratory because it allows adequate time for drug washout and environmental acclimation.

2.6 Data Analysis

Throughout the text and figures all data are expressed as mean ± SEM. Data were analyzed using factorial ANOVA, with repeated measures on within-subject factors, or t-tests where appropriate. For main effects or interactions involving repeated measures, the Huynh-Feldt correction was applied to control for violations of the sphericity assumption. *A priori* (planned) contrasts were performed to assess differences between saline and cocaine groups (HiS-Sal vs. HiS-Coc and LoS-Sal vs. LoS-Coc) and the HiS and LoS lines (HiS-Coc vs LoS-Coc). All statistical analyses were conducted using SPSS (version 17.0) with a Type I error rate of $\alpha = 0.05$ (two-tailed).

3. Results

No differences in weight were observed, but rats in the cocaine group were, on average, a few weeks older than those treated with saline (Table 1). The average dose of cocaine received through the minipumps was 31.88 ± 1.09 mg/kg/day in HiS rats and 31.53 ± 1.08 mg/kg/day in LoS rats, and these values were not significantly different. Additionally, throughout the experiment, no evidence of lesions or other adverse effects of subcutaneous cocaine delivery were observed.

An analysis of raw breakpoint values failed to identify significant effects, though one-way ANOVA revealed a trend toward significance in LoS rats treated with cocaine (main effect of experimental phase, $p = 0.067$) (Fig 2). Data were subsequently expressed as a percentage of baseline breakpoints to minimize variability. Additionally, because no significant effects of day were observed following an initial repeated measures ANOVA (day $\times$ line $\times$ treatment) (Fig 3), data were collapsed across days within each phase of the experiment (cocaine treatment and withdrawal) for further analysis.

A two-way ANOVA (line $\times$ treatment) during the cocaine treatment phase revealed a significant line $\times$ treatment interaction ($F_{1, 18} = 6.66$, $p < 0.05$). *A priori* contrasts revealed a significant difference between saline and cocaine treatment in the LoS ($p < 0.05$) but not HiS rats. A two-way ANOVA (line $\times$ treatment) during the withdrawal phase revealed a significant line $\times$ treatment interaction ($F_{1, 18} = 14.66$, $p < 0.01$). Breakpoints during cocaine withdrawal were significantly lower than during saline treatment in LoS rats ($p < 0.01$), but not HiS rats (Fig 4). Additionally, breakpoints were lower in LoS rats vs HiS rats treated with cocaine ($p < 0.0001$).

A two-way ANOVA (line $\times$ treatment) of saccharin phenotype scores revealed a significant main effect of line ($F_{1, 19} = 19.92$, $p < 0.001$) (Table 1). Additionally, daily water consumption during the PR experiment was higher in HiS rats than LoS rats, regardless of cocaine treatment (HiS-Sal = 46.03 ± 5.39 g, LoS-Sal = 29.24 ± 1.84 g, HiS-Coc = 43.76 ± 2.60 g, LoS-Coc = 29.40 ± 1.47 g; significant main effect of line, $F_{1, 20} = 27.70$, $p < 0.0001$).

4. Discussion

This study found that LoS rats (vs. HiS rats) demonstrate lower breakpoints for a sucrose reward following chronic, continuous cocaine administration. These results suggest that the anhedonic effects of withdrawal are less severe in the HiS line compared with LoS.

While the behaviors of the HiS and LoS lines are well characterized, less is known about what underlies the observed differences. Increased rates of acquisition (Carroll et al. 2002), escalation, and reinstatement (Perry et al. 2006) of cocaine self-administration in the HiS rats could be explained by a number of hypotheses, including increased sensitivity to reward (rats consume more drug because it is more rewarding), decreased sensitivity to reward (rats consume more drug to compensate for a reward deficit), a loss of control in reward seeking, or differences in the severity of withdrawal. Considering recent evidence that reward- and withdrawal-related behaviors require overlapping brain mechanisms (Radke et al. 2011,

Radke and Gewirtz 2012), more than one of these hypotheses may be true. While the current results cannot speak to whether HiS and LoS rats differ in reward-related mechanisms, they do suggest decreased withdrawal severity in the HiS line. Although cocaine was not self-administered in this study, similar effects following cocaine self-administration could explain the increased propensity for cocaine self-administration in HiS rats.

The results of this study may help further define the interaction between motivational signs of cocaine withdrawal and cocaine abuse. Recently, we have found evidence of greater anxiety and aversion (Radke et al. 2013; but see Dess et al. 2005) and reduced anhedonia using ICSS (Holtz et al., unpublished data) in the HiS line during opiate withdrawal. The current results concur with the latter finding and highlight that different emotional withdrawal signs may differentially contribute to the addictive process. Acutely experienced emotions such as anxiety and aversion triggered by drug offset or drug-paired conditioned stimuli may strongly motivate drug seeking while long-term changes in the sensitivity of the reward system could produce the opposite result by decreasing the drive to seek rewards (e.g., sucrose, cocaine). Alternatively, withdrawal signs in the HiS and LoS rats may contribute minimally to drug-seeking, and the phenotypic differences in the lines may be due almost exclusively to differences in the rewarding effects of the drug. More work is needed to characterize the withdrawal responses of the HiS and LoS lines, especially as they relate to self-administration behavior, as well the acutely rewarding effects of cocaine in these rats. Finally, because the relationship between drug, preference and withdrawal may differ across classes of abused drugs (Turene et al. 1996), it would be worth repeating the current study using opiates, ethanol, or other psychostimulants.

Our results are at odds with previous work demonstrating that ICSS threshold elevations during withdrawal predict escalation of cocaine intake (Ahmed et al. 2002), since here increased anhedonia during withdrawal was found in the less vulnerable LoS rats. These disparate results could be due to the method of measuring anhedonia (ICSS vs. PR responding for sucrose) or the method of drug administration (acute self-administration vs. chronic, continuous non-contingent administration). This latter point is an important one since drug self-administration produces multiple drug-associated cues that can trigger signs of withdrawal and affect subsequent intake (Siegel 2005). While use of a non-contingent mode of drug administration allowed us to avoid variable levels of drug exposure in the HiS and LoS rats, we are left with the question of whether similar results would be observed following self-administration of cocaine.

The absence of a difference in baseline breakpoints for sucrose between the lines is notable, especially given that HiS rats have previously been shown to achieve higher breakpoints for a sucrose reward than LoS rats (Gosnell et al. 2010). While the sample size of these experiments yields insufficient power to draw firm conclusions about differences in baseline, LoS rats actually tended to achieve higher breakpoints, and it seems unlikely that additional subject would have reversed this trend. As the rats in this experiment exhibited robust differences in saccharin phenotype, this inconsistency may be due to a difference in the training protocol between the two studies (rats in the Gosnell study received 38 training session on a fixed ratio schedule before being switched to PR).

Furthermore, although we hypothesized that cocaine would increase breakpoints for sucrose, this was not the case, and cocaine treatment actually decreased responding in LoS rats (compared to saline-treated LoS rats, but not cocaine-treated HiS rats). The lack of an increase may have been due to the continuous nature of the treatment, resulting in consistent, low levels of drug and preventing the rapid spikes in drug levels which produce euphoria and reinforcement (Abreu et al. 2001; Woolverton and Wang 2004). Additionally, as others have noted (Allen and Leri 2010), cocaine's effects on operant tasks can be obscured by its effects on activity or food consumption (Balpole et al. 1979; Flagel and Robinson 2007).

Overall, these experiments in HiS and LoS rats suggest that a genetically-mediated propensity for cocaine abuse may be associated with less anhedonia during an extended withdrawal period. It will be important for future studies to determine whether these associations hold true across multiple models of drug abuse vulnerability, in self-administering animals, and whether similar patterns can be found in human populations.

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Highlights

- Rats bred for high and low saccharin intake show differential addiction vulnerability.
- Decreases in progressive ratio responding measure anhedonia during withdrawal.
- Withdrawal from cocaine produced greater anhedonia in addiction-resistant LoS rats.
- Motivational deficits during withdrawal may deter drug taking in LoS rats.

Fig 1. Timeline of experimental events

Fig 2. Raw breakpoints during each phase of the experiment

Breakpoints for sucrose were measured in HiS and LoS rats during and after chronic saline and cocaine (30 mg/kg/day) administration.

Fig 3. Daily sucrose responding during and after chronic saline and cocaine delivery
Breakpoints for sucrose were measured in HiS (*circles*) and LoS (*diamonds*) rats daily during and after chronic saline (a) and cocaine (b) administration and expressed as a percentage of baseline (dotted line).

Fig 4. Average sucrose responding during and after chronic saline and cocaine delivery
 Breakpoints for sucrose were measured in HiS (a) and LoS (b) rats during and after chronic saline and cocaine (*hatched bars*) administration and expressed as a percentage of baseline. Average values for each the treatment phase and withdrawal phase are shown. * $p < 0.05$ compared to saline treated rats; @ $p < 0.001$ compared to HiS rats.

Table 1

Experimental group information

Line	Group	N	Age (days) $\pm$ SEM [†]	Weight (g) $\pm$ SEM	Saccharin Phenotype Score $\pm$ SEM*
HiS	Saline	5	98.8 $\pm$ 2.5	432.0 $\pm$ 8.0	18.89 $\pm$ 1.76
	Cocaine	7	130.1 $\pm$ 13.1	479.0 $\pm$ 18.0	15.92 $\pm$ 4.07
LoS	Saline	5	106.4 $\pm$ 5.8	466.0 $\pm$ 14.0	6.93 $\pm$ 1.60
	Cocaine	6	121.4 $\pm$ 2.7	468.0 $\pm$ 22.0	-0.38 $\pm$ 2.97

* Significant main effect of line, $p < 0.05$

[†] Significant main effect of treatment, $p < 0.05$