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Baclofen has opposite effects on escalation of cocaine self-administration: Increased intake in rats selectively bred for high (HiS) saccharin intake and decreased intake in those selected for low (LoS) saccharin intake

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ABSTRACT

Rats selectively bred for high saccharin intake (HiS) self-administer more cocaine, escalate their cocaine intake during long access, and reinstate cocaine seeking at higher levels than those bred for low saccharin intake (LoS). The present study was conducted to determine if baclofen, an agonist at the $GABA_b$ receptor, has differential effects on the escalation of i.v. cocaine intake and reinstatement of cocaine-seeking in HiS and LoS rats. HiS and LoS rats self-administered cocaine during a 2-h daily short-access (ShA) phase for 3 days and then long-access (LgA) sessions for 21 days followed by a second ShA phase. One group of HiS and LoS rats received i.p. injections of 2.5 mg/kg baclofen (HiS + B and LoS + B, respectively), and other groups of HiS and LoS rats received saline (HiS + Sal and LoS + Sal) before each daily session. In a second experiment, HiS and LoS rats self-administered i.v. cocaine during 2-h sessions for 14 days followed by a 21-day extinction period. Baclofen (2.5 mg/kg, i.p.) or saline was administered before saline- or cocaine-primed reinstatement sessions. The HiS + B group escalated their cocaine self-administration and had increased cocaine infusions in the post-LgA ShA phase. The LoS + B group self-administered less cocaine throughout the entire LgA period compared to the LoS + Sal or HiS groups. Baclofen attenuated reinstatement of cocaine seeking in both the HiS and LoS rats with no phenotype differences. Thus, baclofen had opposite effects on cocaine intake in HiS and LoS rats during escalation; but similar effects during reinstatement. These results suggest that treatment effects might vary with individual differences (HiS vs. LoS) and the phase of drug-motivated behavior that is modeled.

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1. Introduction

The association of preference for sweetened dietary substances with drug abuse liability has been investigated with rats selectively bred for high (HiS) and low (LoS) saccharin intake (Carroll et al., 2008; Dess et al., 1998), and these studies have characterized HiS rats as drug-prone and LoS rats as drug-resistant. For instance, HiS rats acquire cocaine, heroin (Carroll et al., 2002), and ethanol (Dess et al., 1998) self-administration at faster rates, show greater resistance to the extinction of cocaine-seeking behavior (Perry et al., 2006), have higher cocaine-induced locomotor activity and behavioral sensitization (Carroll et al., 2007), and show more reinstatement of drug-seeking following cocaine priming injections compared to LoS rats (Perry et al., 2006). Additionally, the HiS line displays higher measures of impulsive choice (Perry et al., 2007) and motor impulsivity (Anker et al., 2009b) relative to the LoS rats. Rats screened for high impulsivity using measures such as the five-choice serial reaction time task or the delay discounting procedure are more vulnerable to addictive behaviors across multiple aspects of animal models of human drug addiction relative to rats screened for low impulsivity (Anker et al., 2009b; Belin et al., 2008; Perry et al., 2005). Taken together, the overlap of reciprocal behavioral traits shown by HiS and LoS rats with other phenotypes exhibiting high and low proclivity for drug self-administration suggests that the HiS and LoS rats are ideal models of genetically-mediated drug addiction-prone and -resistant behavior, respectively, in the human population.

While a number of rodent behavioral phenotypes have been developed and tested for their drug abuse liability across several critical phases of the addiction process, little attention has been given to the responsiveness of rats with these individual differences to treatments for drug abuse. Phenotypic behavioral markers such as sweet preference may be predictive of addiction treatment receptivity in humans. Therefore, a potential utility of the HiS and LoS lines is in investigating treatment models during critical phases of drug abuse such as

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escalation (bingeing). During periods of short access (ShA, 1–2 h per day) rats maintain stable intake, while under long access conditions (LgA, ≥6 h per day) they typically increase daily drug intake over extended periods. Self-administration under conditions of LgA is sensitive to individual differences such as sex (Carroll et al., 2005; Roth and Carroll, 2004), impulsivity (Anker et al., 2009b), and sweet intake, such as that displayed by the HiS vs. LoS rats (Perry et al., 2006) that will be used in the present study. For example, HiS rats escalated their drug intake during LgA to cocaine relative to the LoS rats, while there were no phenotype differences during ShA. This gradual increase in consumption is proposed to be a critical component that accounts for the transition of controlled drug use to uncontrolled binge use and addiction, and it is thought to be mediated by dramatic shifts in mesolimbic reward system functioning (Koob and Volkow, 2010). The escalation model is invaluable for understanding one of the most important aspects of addiction, yet only a few studies have addressed the use of treatment agents during this phase (e.g., Hansen and Mark, 2007; Specio et al., 2008), and none have evaluated individual differences using selective breeding models.

Similar to the escalation model, reinstatement (relapse) is another phase of human drug addiction that has yielded individual differences in responding. For example, female (vs. male) rats (Lynch and Carroll, 2000), rats screened for high (vs. low) measures of impulsivity using a delay discounting procedure (Perry et al., 2008), and HiS (vs. LoS) rats (Perry et al., 2006) showed elevated reinstatement of cocaine-seeking behavior compared to their low-performing counterparts. Also, like escalation, reinstatement models a critical phase of human drug addiction in which individual differences in treatment receptivity have not yet been assessed.

In the present studies, HiS and LoS rats were compared on escalation of cocaine intake and during the reinstatement of cocaine-seeking behavior while treated with a pharmacological intervention, baclofen, a potent agonist at the $GABA_B$ receptor that has been used for alcohol and cocaine dependence (for review, see Karila et al., 2008; Leggio et al., 2010; Roberts, 2005; Smith et al., 2004). In rats, baclofen dose--dependently attenuated discrete contextual cue- and cocaine-primed reinstatement (Campbell et al., 1999; Filip and Frankowska, 2007), cocaine sensitization (Frankowska et al., 2009), maintenance of i.v. cocaine self-administration (Campbell et al., 1999), and cocaine-induced dopamine release in the nucleus accumbens (Fadda et al., 2003). In another study, baclofen pretreatment reduced the reinstatement of cocaine-primed behavior in baboons (Weerts et al., 2007).

The effectiveness of baclofen in human populations, however, has been mixed. In a preliminary open-label trial, baclofen (20 mg, t.i.d) reduced cocaine craving and use compared to placebo (Ling et al., 1998). In another study baclofen (60 mg/day) reduced cocaine self-administration, but it failed to alter cocaine's positive subjective effects in non-opioid dependent volunteers (Haney et al., 2006). Despite the mainly promising results of these earlier studies, a recent multi-site, double-blind trial failed to show an effect of baclofen (60 mg/day) on self-reported abstinence or negative urine screens compared to placebo in individuals suffering from severe cocaine addiction (Kahn et al., 2009).

One possible reason for incongruent results from experiments that test treatment drugs for stimulant addiction, like baclofen, is that treatment receptivity may be genetically mediated. Individual differences (male vs. female) have been found in baclofen treatment receptivity, with female rats showing a greater baclofen-induced decrease in the acquisition of cocaine self-administration relative to treated males (Campbell et al., 2002). This is of particular interest, as female rats generally have faster rates of cocaine acquisition relative to males (Lynch and Carroll, 1999). Additional clinical and preclinical research has further identified females as generally more drug prone than males (Becker and Hu, 2008), yet initial results suggest that females are more receptive to treatment than males, possibly due to a rate-dependent effect (Carroll and Anker, 2010).

The goal of this study was to determine if baclofen differentially affects escalation and reinstatement of cocaine-seeking behavior in HiS and LoS rats. These two models of drug abuse represent transition states of drug-taking (escalation) and drug-seeking (reinstatement) aspects of behavior, and are differentiated by high vs. low levels of baseline intake, respectively. As the HiS rats are more prone to drug seeking than LoS rats, and based on initial findings with male and female animals and enhanced treatment effects in females vs. males, it was hypothesized that HiS rats would show a greater decrease in escalation and reinstatement of cocaine seeking following baclofen administration compared to LoS rats. Also, previous research has shown that, following a prolonged period of LgA, rats earn more infusions during a subsequent ShA period relative to the ShA phase that preceded it (Perry et al., 2006). Therefore, HiS rats treated with baclofen were expected to show a greater reduction in post-LgA ShA cocaine intake compared to LoS rats treated with baclofen. Another hypothesis was that baclofen would reduce cocaine-primed reinstatement responding more in the HiS relative to the LoS rats.

2. Methods

2.1. Subjects

Sixty-two experimentally naïve adult female 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. Male rats were initially included in this study; however, as previously shown in Carroll et al. (2002), all but one male LoS rat failed to acquire cocaine self-administration. Phenotypic differences were the primary interest in the present study, and HiS and LoS females were used exclusively because they display a wider range of saccharin intake and behavioral measures compared to HiS and LoS males (Carroll et al., 2008). Rats weighed between 278 and 326 g at the start of the experiment and were between 90 and 120 days old. The HiS and LoS lines were cultivated through breeding pairs based on extreme saccharin phenotype scores with no sibling, half-sibling, or first cousin matings. 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 and body weight [saccharin score = (saccharin ml − water baseline ml, divided by body weight, × 100)]. Table 1 shows group numbers, body weights at the beginning of study, daily food and water intake, and saccharin scores.

Rats were bred and pair-housed in plastic cages with ad libitum access to rat pellet chow (Purina Mills, Minneapolis, MN, USA) and water prior to the experiment. The humidity, temperature (21–23 °C), and light–dark cycle (12 h–12 h; lights on at 6:00 a.m.) were all regulated.

Table 1
Experimental group information.

Group	*n*	Weight (g) (±*SEM*)	Daily food intake (g) (±*SEM*)	Daily water intake (g) (±*SEM*)	Saccharin phenotype score[a] (±*SEM*)
Escalation					
HiS + B	8	326 (±11)	16.1 (±0.1)	41.3 (±2.9)	22.8 (±4.6)[b]
LoS + B	9	284 (±11)	15.9 (±0.1)	36.1 (±1.8)	11.6 (±6.3)
HiS + Sal	8	285 (±8)	15.8 (±0.1)	43.3 (±5.2)	25.4 (±10.2)[b]
LoS + Sal	10	282 (±10)	15.9 (±0.1)	34.4 (±1.5)	9.2 (±7.2)
Reinstatement					
HiS	14	283 (±5)	15.9 (±0.1)	42.0 (±3.3)	18.1 (±3.3)[b]
LoS	13	278 (±6)	15.9 (±0.1)	37.7 (±5.6)	0.9 (±3.6)

[a] Saccharin phenotype score = {[24-h saccharin intake (ml) − average water intake (ml)/weight (g)] × 100} (Dess et al., 1998).
[b] Indicates that after combining saccharin phenotype scores between both experiments HiS rats had significantly higher scores compared to LoS rats ($p < .01$).

Following surgery and throughout housing in operant chambers, rats were given access to 16 g of ground rat chow (Purina Mills) between 3:00 p.m. and 8:00 a.m. the following day. Daily food restriction was based on the amount required to maintain rats at 85% of their free-feeding body weight, compared to age-matched controls that had unlimited food access. Mild food restriction facilitates drug self-administration and reduces intersubject variability (Carroll et al., 1984). Rats had continuous access to water throughout the experiment. Following the cocaine self-administration procedure, and 14 days prior to saccharin testing rats were again individually housed in plastic cages and given free access to pellet chow (Purina Mills). All experimental procedures were approved by The University of Minnesota Institutional Care and Use Committee under Protocol 1008A87754, and they complied with the *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (National Research Council, 2003).

2.2. Apparatus

Following surgery and throughout the experiment, rats were individually housed in custom-made octagonal operant conditioning chambers with alternating Plexiglas and stainless steel walls. Every operant chamber had an active lever that delivered an i.v. cocaine infusion when pressed during session and an inactive lever not associated with cocaine. Above each lever (Coulborn Instruments, Lehigh Valley, PA, USA) were corresponding 4.6-W, tri-colored (red, green, yellow) stimulus lights, and one white 4.6-W house light was positioned at the top of the chamber to signal the start of session. Special inserts in the chamber walls allowed access to a food receptacle and a drinking spout. All operant chambers were enclosed in melamine-coated, wooden sound-attenuating boxes that included a fan for ventilation. During the experimental sessions, response-contingent cocaine infusions were delivered by an infusion system consisting of a syringe pump (PHM-100; Med Associates, St. Albans, VT, USA) and a 30-ml syringe with a blunted 22-gage needle. The syringe was connected to a swivel (050-0022, Alice King Chatham, Hawthorne, CA) that was attached to the top of the operant chamber via Tygon tubing line (1.52 mm o.d., 0.52 mm i.d.; Fischer Scientific, Springfield, NJ). The swivel was connected to a tether (C31CS; Plastics One, Roanoke, VA), enclosed in a protective metal spring that extended into the operant chamber, and attached to a cannula affixed atop an infusion harness (Instech Laboratories, Plymouth Meeting, PA) that was placed on the rat directly following surgery. The bottom end of the cannula that was imbedded within the infusion harness connected to an i.v. catheter implanted in the rat's jugular vein. Programming, data collection, and data storage for all experimental sessions were handled by Med-PC software and PCs equipped with a Med-PC interface (Med Associates).

2.3. Drugs

The cocaine solution (1.6 mg/ml) was prepared by dissolving cocaine HCL (National Institute of Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) in sterile saline (0.9% NaCl) and adding heparin (5 USP units/ml) to prevent catheter thrombus formation. The cocaine infusion rate was 0.025 ml/s, and the solution was dispensed at an interval of 1 s/100 g body weight resulting in 0.4 mg/kg per infusion (i.v.). Baclofen (Sigma Aldrich, St. Louis, MO) was dissolved in saline and administered at a dose of 2.5 mg/kg (i.p.). This dose was chosen because it was previously shown to reveal individual differences in treatment effects (Campbell et al., 2002). Equivalent volumes of saline (0.9% NaCl) were administered as a control.

2.4. Surgery

Rats were anesthetized with i.p. injections of both ketamine (60 mg/kg) and xylazine (10 mg/kg). Atropine (0.15 ml/rat i.p.) and doxapram (5 mg/kg i.p.) were also administered to prevent bradycardia and to assist respiration. The surgical procedure involved implanting one end of a polyurethane catheter in the rat's right jugular vein and subcutaneously tunneling the other end dorsally before exiting through a medial incision approximately 1 cm rostral to the scapulae. The free end of the catheter was connected to the bottom of a cannula embedded in the infusion harness which remained capped off throughout the 3-day post surgical recovery period in which the animals were housed in their operant conditioning chambers. Over the recovery period, 4 subcutaneous injections of buprenorphine (0.05 mg/kg) were administered approximately every 12-h for analgesia along with heparinized saline (20 USP units/ml, 0.3 ml/rat) and gentamicin (2 mg/kg i.v.) to prevent catheter occlusion and infection. The same dose of heparinized saline was administered daily 15-min prior to experimental sessions to further ensure catheter patency. Catheter patency was assessed weekly with a combination of ketamine (100 mg/ml), midazolam (5 mg/ml), and saline (3:3:14 ratio, 0.10 ml/rat) and was established by loss of the righting reflex following injection of this combination. If catheters were not patent, a second catheter was implanted in the left jugular vein following the surgical procedures described above, and the rat was allowed to recover for 3 days before resuming experimental sessions.

3. Procedure

3.1. Escalation of cocaine self-administration

3.1.1. Cocaine self-administration training

Rats were trained to self-administer cocaine infusions (0.4 mg/kg, i.v.) 3 days following surgery under an FR 1 schedule of reinforcement. At the beginning of every daily 2 h training session (9:00 a.m. to 11:00 a.m.), rats were given 3 non-contingent cocaine infusions and the left, active (cocaine-associated) lever was baited with a small amount of peanut butter (0.5–1.0 g). Rats were considered to have achieved self-administration acquisition if they administered $\geq$25 infusions for 3 consecutive days without priming infusions or peanut butter, and they were required to have an active to inactive (right) lever response ratio of at least 2:1. The ratio requirement was established to confirm drug-seeking behavior as opposed to non-drug conditioned reinforcement (i.e., responding for stimulus lights) or incidental lever responses due to cocaine-induced locomotor activity.

3.1.2. Pre-LgA phase (ShA)

Following the acquisition phase, rats were allowed to self-administer cocaine (0.4 mg/kg/inf) under an FR 1 schedule for 3 sessions from 9:00 a.m. to 11:00 a.m. to establish baseline rates of stable responding (no increasing or decreasing trend) prior to the LgA phase.

3.1.3. LgA phase

During this phase of extended access, rats self-administered cocaine (0.4 mg/kg/inf) under an FR 1 schedule for 21 consecutive days. Session length was increased to 6 h (9:00 a.m. to 3:00 p.m.). On the first day of LgA, rats were randomly assigned within each phenotype group to receive either baclofen (2.5 mg/kg) or saline i.p. injections at 8:30 before every session. Thus, there was one HiS ($n=8$) and one LoS ($n=9$) group treated with baclofen (HiS + B and LoS + B, respectively), and one HiS ($n=8$) and one LoS ($n=10$) group treated with saline (HiS + Sal and LoS + Sal, respectively).

3.1.4. Post-LgA phase (ShA)

To investigate the effects of baclofen treatment and phenotype differences during extended access during post LgA self-administration (FR 1, 0.4 mg/kg/inf) on subsequent ShA, presession baclofen and saline injections were discontinued, and session length was returned to 2 h (9:00 a.m. to 11:00 a.m.) for 3 days following LgA.

3.1.5. Saccharin phenotype score

Following the last session of post-LgA ShA, rats were removed from the operant chambers for 14 days before the HiS and LoS phenotype scores were confirmed using the saccharin preference test described previously. Positive scores indicated a saccharin preference, negative scores indicated saccharin aversion, and scores of zero (or near zero) indicated no preference.

3.2. Reinstatement of cocaine-seeking behavior

3.2.1. Maintenance

Rats were trained to self-administer cocaine using the same training procedure in experiment one. Once the same stability criteria were met, rats began a maintenance period in which they self-administered cocaine (0.4 mg/kg, i.v.) under an FR 1 schedule for 14 daily 2-h sessions (9:00 a.m. to 11:00 a.m.).

3.2.2. Extinction

Following the maintenance phase, a 21-day extinction phase began where the same procedure described in the maintenance phase was followed with the exception that cocaine was replaced with saline. After the extinction period, a 3-day pre-reinstatement phase began in which the house light and lever-paired lights were unplugged and remained unplugged for the remainder of the experiment.

3.2.3. Cocaine-induced reinstatement

The effects of baclofen on the reinstatement of cocaine-seeking behavior were investigated during daily 2-h sessions (9:00 a.m.–11:00 a.m.) over a 13-day period. Baclofen (2.5 mg/kg, i.p.) or saline was administered one-half hour before session, and 3 doses of cocaine primes were administered (C; 5, 10, and 15 mg/kg, presented in random order) at the beginning of each session. Each dose of cocaine was administered twice for each animal; once following saline and once following baclofen pretreatment. These cocaine priming sessions were alternated by days in which the animals received i.p. saline injections one-half hour before and saline again at the onset of session. There was also an additional session in which animals received a baclofen injection as a priming injection at the beginning of the session.

3.2.4. Saccharin phenotype score

Following the last day of reinstatement, rats were removed from their operant chambers for 14 days and were then tested for saccharin phenotype scores using the same procedure described in Section 3.1.5.

3.3. Statistical analyses

For the escalation experiment, cocaine infusions and responses on the infusion-paired lever and non-infusion paired lever served as the dependent measures for the LgA and ShA periods. Responses and infusions earned during LgA were averaged into 3 blocks of 7 days and were subsequently analyzed using three-way mixed factor analyses of variance (ANOVA; treatment × phenotype × block) with block as a repeated measure. Three-way, repeated measures ANOVAs (treatment × phenotype × phase) were used to analyze comparisons of the 3-day average of infusions self-administered during the pre- and post-ShA periods for the HiS and LoS groups. Mean number of days to reach acquisition criteria were compared using a two-way ANOVA (treatment × phenotype).

For the reinstatement experiment, dependent measures were the mean number of lever presses made during maintenance, extinction, and reinstatement. For maintenance and extinction, mean responses were analyzed using a two-way, mixed factorial ANOVA (phenotype × day) with day as a repeated measure. Cocaine infusions achieved during maintenance were also examined using a two-way, mixed factorial ANOVA (phenotype × day) with day as the repeated measure. For reinstatement, mean responses were analyzed using a three-way, mixed factorial ANOVA (phenotype × pre-treatment × cocaine dose) with cocaine dose being a repeated measure. They were subsequently analyzed with a two-way, mixed factorial ANOVA (pre-treatment × cocaine dose) with pre-treatment being a repeated measure. Saccharin scores were combined within groups across both experiments and analyzed using a one-way ANOVA (phenotype). All post hoc analyses were made using Fischer's least-significant-difference *t* tests. Results were considered significant if $p<0.05$. All statistical analyses were performed with GB Stat software (Dynamic Microsystems, Silver Spring, MD).

4. Results

4.1. Escalation of cocaine self-administration

4.1.1. Training

All rats were trained to administer cocaine (0.4 mg/kg) during daily 2-h sessions. Baclofen was not administered during training for any of the rats. The LoS + Sal rats had the most mean (±*SEM*) days to reach acquisition criteria (38.50 ± 6.19), followed by the LoS + B (26.37 ± 3.10), HiS + Sal (24.85 ± 7.39), and HiS + B (19.57 ± 3.38); however, these differences were not significant.

4.1.2. LgA phase

There were significant main effects of phenotype, ($F_{1,30}=10.581$, $p<.01$) and block, ($F_{2,60}=6.785$, $p<.01$) in responses during this phase. There were also significant interactions between phenotype and treatment, ($F_{1,68}=12.421$, $p<.005$) as well as treatment and block, ($F_{2,60}=7.714$, $p<.005$). Post hoc comparisons indicated that the first 7-day block of responses for the HiS + B group was significantly less than the second ($ps<.01$) and third 7-day blocks ($ps<.01$) for that same group. The second 7-day block of responses for the HiS + B group were also significantly less ($ps<.01$) than the third block of responses for that group. The third 7-day block of responses for the HiS + B group were significantly greater than the HiS + Sal group ($ps<.01$), while LoS + Sal responses were greater than the LoS + B group across all 7-day blocks ($ps<.01$). There were no significant differences in responses made between the HiS + Sal and LoS + Sal groups across any of the 7-day blocks.

Fig. 1 shows the mean (±*SEM*) number of cocaine infusions (0.4 mg/kg) under a FR 1 schedule of reinforcement for each daily session (6 h/day) during LgA (panel A shows LoS, panel B shows HiS). On day 1 of LgA, mean infusions ranged from 34 to 108 infusions per 6-h session across the four groups. The cocaine infusions self-administered for the HiS + B group increased 113% by the last day of LgA; whereas, the HiS + Sal and the LoS + B groups increased by 28% and 49%, respectively. There were significant main effects of treatment, ($F_{1,29}=2.105$, $p<.001$), and block, ($F_{1,30}=10.581$, $p<.0014$). There were also significant interactions in infusions between phenotype and treatment, ($F_{1,66}=6.933$, $p<.02$), block and phenotype, ($F_{2,58}=4.446$, $p<.02$), as well as block and treatment, ($F_{2,58}=3.789$, $p<0.03$). Post hoc comparisons showed that the LoS + B group earned significantly fewer infusions than the LoS + Sal group across all 7-day blocks ($ps<.01$, Fig. 1a). The LoS + Sal group did not increase infusions when comparing block 1 with block 3 (Fig. 1a). Post hoc comparisons also showed that the HiS + B group was the only one to show a significant increase (escalation) in the number of cocaine infusions from the first block of 7 days to the last ($ps<.01$), and during the last block of 7 days (Fig. 1b), the HiS + B group self-administered significantly more cocaine infusions compared to the HiS + Sal group ($ps<0.01$). Baclofen treatment was associated with escalation of cocaine intake in the HiS group and overall attenuation of cocaine self-administration in the LoS group. The HiS phenotype was associated with greater cocaine intake in the last block of LgA compared to the LoS phenotype.

Fig. 2 shows that the LoS + Sal group also self-administered fewer cocaine infusions during the last 7-day block compared to the HiS + Sal group ($ps<0.05$); however, there were no significant differences

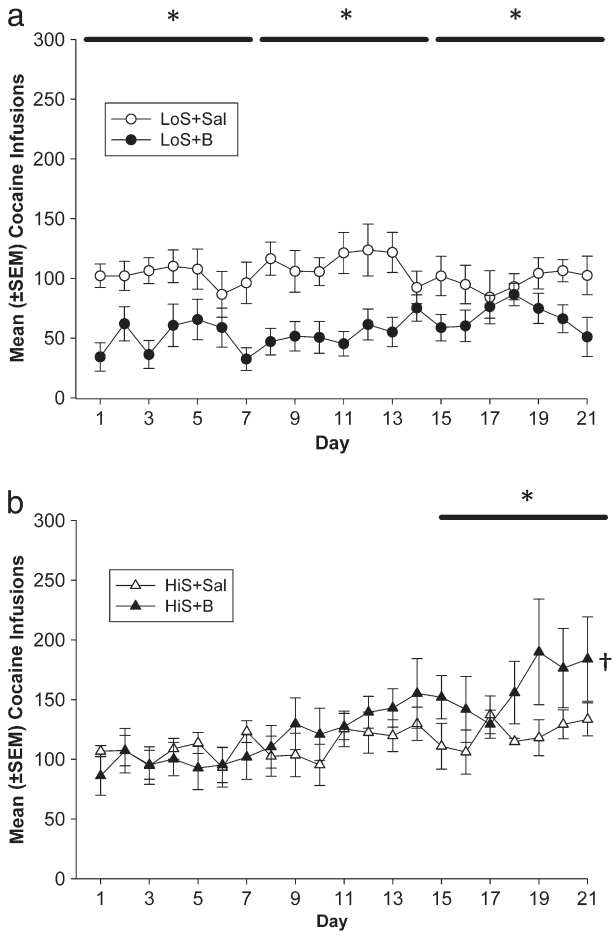

Fig. 1. Panels a and b show infusions self-administered by the LoS and HiS rats (respectively) each day throughout the LgA (6-h sessions) period. Open circles represent the saline-treated LoS rats (LoS + Sal) and filled circles indicate baclofen-treated LoS rats (LoS + B). Open triangles represent the saline treated HiS rats and filled triangles indicate baclofen (B) treated HiS rats. The * indicates that there was a significant difference in infusions between treatment groups ($p<.05$) for the HiS (HiS + B > HiS + Sal) in last 7-day interval and throughout all 3 7-day intervals for the LoS rats (LoS + Sal > LoS + B). Infusions earned by the HiS + B group were significantly higher during the last 7-day block than the first and second blocks ($p<.05$), as indicated by the †.

between these groups for the first and second blocks of 7 days. There were no significant differences in inactive lever responses across groups during the LgA phase.

4.1.3. ShA cocaine self-administration pre- versus post-LgA

Fig. 3 shows the mean (±*SEM*) cocaine infusions self-administered by all groups during the ShA phases before and after the LgA period. There was a main effect of phenotype, ($F_{1,31}=13.226$, $p<.01$) and significant interactions between phenotype and treatment, ($F_{1,31}=4.545$, $p<.05$) as well as phenotype and phase (pre- or post-LgA) ($F_{1,31}=13.250$, $p<.005$). Post hoc comparisons showed no significant differences in infusions administered between any of the groups during the pre-LgA phase. The HiS + B group was the only one to show a significant difference in infusions when comparing the pre-LgA and post-LgA phases ($ps<.05$). Specifically, the HiS + B group earned more infusions during the post-LgA phase.

4.2. Reinstatement of cocaine-seeking behavior

4.2.1. Maintenance

Fig. 4a shows the mean responses made (±*SEM*) on the cocaine-paired lever during the maintenance phase. There was a significant

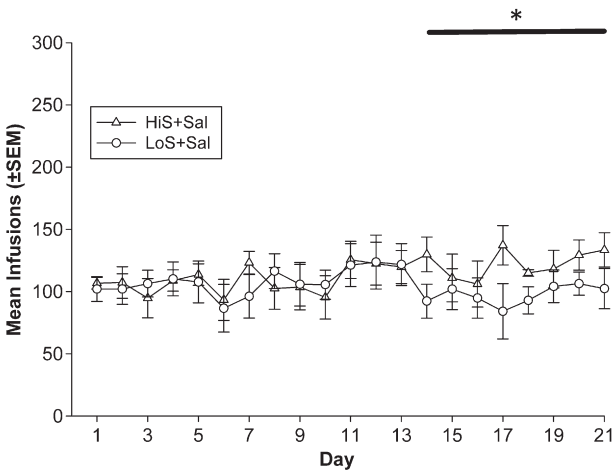

Fig. 2. Mean (±*SEM*) cocaine infusions are presented for the LoS + Sal (open circles) and HiS + Sal groups (open triangles) during the LgA (6-h sessions) period. The * indicates that there was a significant difference in infusions between groups (HiS + Sal > LoS + Sal) in the last 7-day interval ($p<.05$).

main effect of phenotype, ($F_{1,403}=10.719$, $p<.05$), and an interaction between phenotype and day, ($F_{13,403}=8.423$, $p<.05$). Post hoc analysis revealed that the HiS group made significantly more responses than the LoS group during days 3, 5, 7, and 9–14 ($ps<.05$). Fig. 4b shows the mean infusions self-administered (±*SEM*) during maintenance. There was a significant main effect of phenotype, ($F_{1,403}=11.887$, $p<.01$), and an interaction between phenotype and day, ($F_{13,403}=9.086$, $p<.05$), with more infusions in days 3, 5, 9, 10, and 12–14 ($ps<.05$).

4.2.2. Extinction

Fig. 5 shows the mean responses (±*SEM*) on the previously cocaine-paired lever during the extinction phase when saline was replaced with cocaine. There were no significant phenotype differences in responding during this phase.

4.2.3. Reinstatement

Fig. 6 shows responses (±*SEM*) on the previously cocaine-paired lever during the reinstatement phase. These responses were originally analyzed with a three-way, mixed factorial ANOVA (phenotype × pretreatment × cocaine dose); however, no significant three-way interaction was found. Responses were then combined between the HiS and LoS rats and analyzed using a two-way, mixed factorial ANOVA (pretreatment × cocaine dose). There were significant main effects of

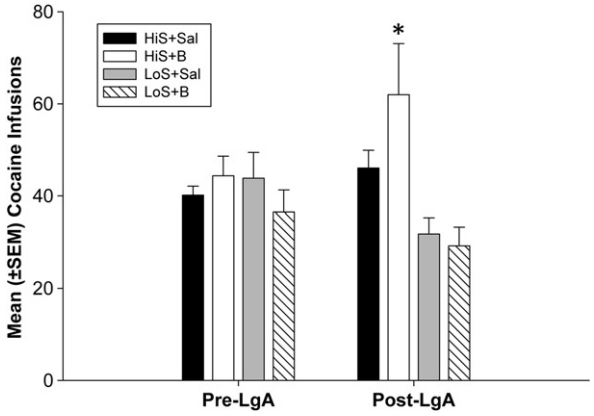

Fig. 3. Mean (±*SEM*) cocaine infusions are presented for the 4 experimental groups, HiS + Sal (filled bar), HiS + B (open bar), LoS + Sal (gray bar), and LoS + B (hatched bar) during ShA (2-h sessions) pre- (left) and post-LgA (right). The * indicates a significant increase ($p<.01$) of cocaine infusions self-administered for the HiS + B group between pre-LgA and post-LgA.

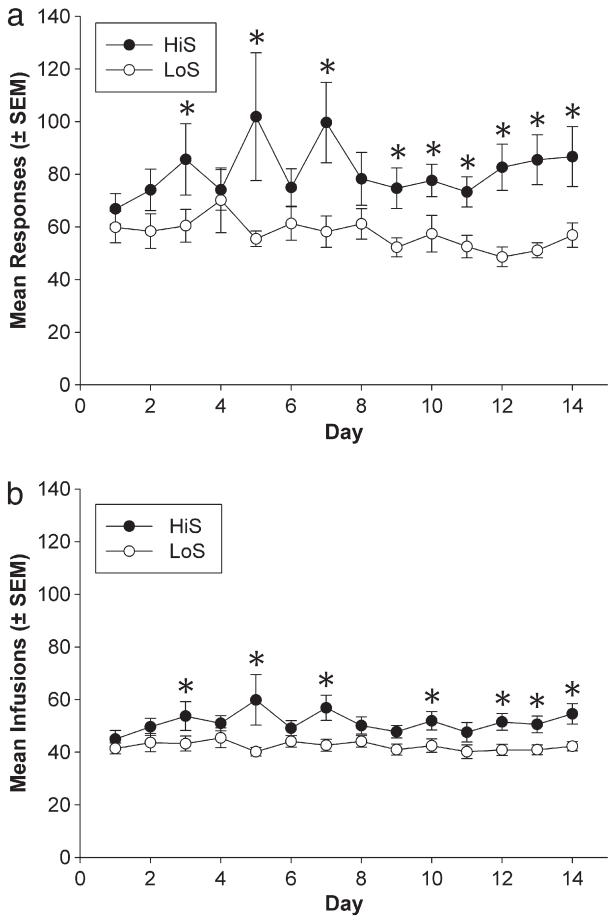

Fig. 4. Mean (±*SEM*) cocaine-paired lever responses (left panel) and cocaine infusions self-administered (right panel) are presented for the 2 experimental groups, HiS (filled circles), and LoS (open circles) during the maintenance phase. The * indicates that the HiS group made more responses or self-administered more cocaine infusions than the LoS group on that day ($p<.05$).

treatment ($F_{1,162}=15.720, p<.001$), dose ($F_{3,156}=10.452, p<.001$), and a significant interaction between treatment and dose ($F_{3,156}=4.175$, $p<.01$). Post hoc analyses showed that rats receiving 5, 10, and 15 mg/kg cocaine priming injections following vehicle pretreatment had significantly more responses than when they received a saline priming injection following vehicle pretreatment, ($ps<.01$). Rats made

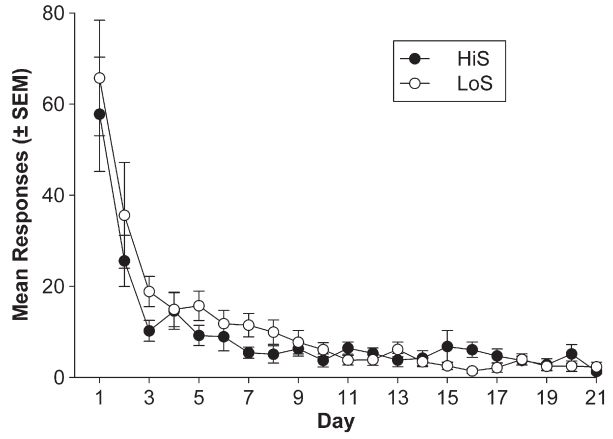

Fig. 5. Mean (±*SEM*) responses on the previously cocaine-paired lever are presented for the 2 experimental groups, HiS (filled circles), and LoS (open circles) during the extinction phase. There were no significant differences between groups during this phase.

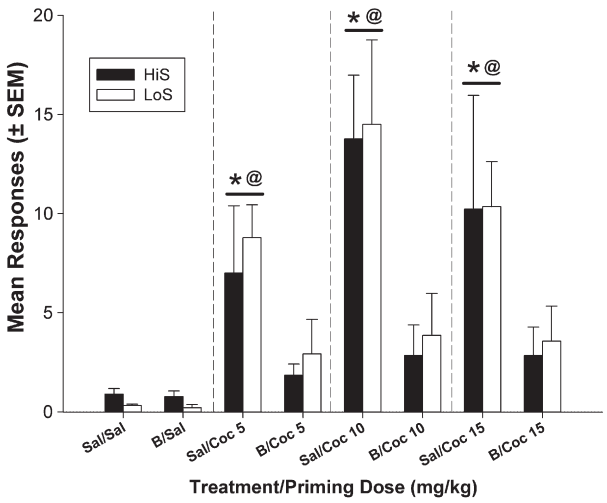

Fig. 6. Responses made on the previously cocaine-paired lever were combined between groups as indicated by the bars during the reinstatement phase. The * indicates a significant ($p<.05$) difference between the 5, 10, and 15 mg/kg dose priming injections that were preceded by Sal injections and saline priming injections that were preceded by Sal treatment. The @ indicates a significant ($p<.05$) difference between the 5, 10, and 15 mg/kg dose cocaine priming injections preceded by Sal treatment and the corresponding 5, 10, and 15 mg/kg dose cocaine priming injections preceded by B treatment.

significantly more responses when they were pretreated with vehicle compared with baclofen following the 5 ($ps<.05$), 10 ($ps<.01$), and 15 ($ps<.01$) mg/kg cocaine doses. When administered alone as a priming injection, baclofen did not induce significantly more responding than after saline priming injections.

5. Discussion

The purpose of these experiments was to examine the effects of baclofen treatment on the escalation and reinstatement of cocaine-seeking behavior in HiS and LoS rats. With a procedure modified from Ahmed and Koob (1998, 1999) and previously used in our laboratory, we showed that baclofen potentiated the escalation of cocaine-seeking in HiS rats and decreased responding in the non-escalating LoS rats throughout LgA. Also, when comparing within-subject infusions earned between ShA periods pre- and post-LgA, only the HiS + B group increased intake. While the HiS + Sal group administered more cocaine during the last 7 days of the LgA phase compared to the LoS + Sal group, neither group escalated intake during this phase. This finding is inconsistent with a previous study in which HiS and LoS rats escalated their intake over a 21-day period (Perry et al., 2006). However, in the previous study, 12-h (vs. 6-h) sessions were used. Six-hour sessions were chosen because we have previously found this length to be appropriate for determining treatment effects (Larson et al., 2007). Further, baclofen is rapidly metabolized (Wuis et al., 1990), and supplemental injections necessitated by 12-h sessions may have disrupted the experiment and introduced stress or other confounds. It is important to note that the novel aspect of this experiment was to provide a setting in which differential treatment effects may be found during LgA to cocaine. Consequently, we demonstrated that baclofen treatment exaggerated the latent traits of high- and low-vulnerable animals and that baseline rates had minimal effects on the differential outcome. This novel finding is an initial step that needs further study, such as investigating the effects of baclofen on HiS and LoS rats with longer access conditions and over protracted periods.

Previously, Carroll et al. (2002) showed phenotypic differences in acquisition rates of cocaine self-administration (HiS > LoS). However, in the present study there were no significant effects of phenotype or treatment grouping. This was likely due to procedural differences

compared to those used in Carroll et al. (2002), such as autoshaping, increased session length, and different acquisition criteria. Further, since baclofen was not administered until the reinstatement or LgA phases, similar HiS vs. LoS acquisition rates may have resulted from procedures taken to facilitate rapid acquisition and eliminate group differences during training, such as lever-baiting, administration of priming infusions, and food restriction.

The attenuating effects of baclofen on cocaine-induced reinstatement of drug-seeking behavior in both the HiS and LoS rats corroborates previous research investigating baclofen's effects on the rodent model of relapse (Campbell et al., 1999; Filip and Frankowska, 2007). In contrast to its differential effects on LgA responding, baclofen attenuated cocaine-primed reinstatement in both the HiS and LoS animals during the reinstatement condition, supporting its efficacy in preventing relapse despite individual differences in vulnerability. The differential results between escalation and reinstatement paradigms may be because intermittent baclofen injections were acutely administered during reinstatement at much lower overall doses, while cocaine was chronically self-administered throughout the LgA phase of the escalation study. These results illustrate the importance of considering acute vs. chronic treatment effects. Also, it is possible that the animal model of escalation is more sensitive to divergent treatment effects compared to reinstatement due to the large amounts of cocaine that are consumed (e.g., a rate-dependent effect). Phenotype differences may be subtle and more or less sensitive to different behavioral assays, and further research comparing the two phases may support the utility of investigating treatments during escalation.

One result of the present reinstatement experiment that is at odds with Perry et al. (2006) is that HiS rats responded more than LoS rats during extinction and following a 15 mg/kg cocaine injection. Repeated exposure to the same cocaine dose in the present experiment may have produced a floor effect and obscured phenotype differences in responding following cocaine-priming injections. Further, in the latter study there were 10 days of maintenance and 14 days of extinction compared to 14 days of maintenance and 21 days of extinction used in the former. This extended protocol was used because Anker et al. (2009a) found individual (sex) differences in treatment effects during cocaine-primed reinstatement using a similar design. However, it is possible that differences in cocaine-primed reinstatement and baclofen treatment effects might exist under reinstatement that would reduce the occurrence of floor effects.

Variation in hormone levels during the estrous cycle has been shown to influence responding for cocaine in female rats (Roberts et al., 1989). While it is possible that there is an interaction between phenotype, baclofen treatment, and cycle phase with regard to cocaine-seeking behavior, estrus was not monitored in the present experiments, and cycle phase was allowed to vary randomly. The number of animals per group did not afford the statistical power to analyze cycle phase as a mediating factor. Further, extended periods of cocaine self-administration may disrupt normal cycling in some female rats (Larson et al., 2007), which would limit the interpretation of the results. The main aim of the present experiment was to provide novel evidence for an animal model of differential treatment receptivity across high and low drug-seeking phenotypes. The inclusion of estrous cycle as a mediating factor, while an important question, was not within the scope of this experiment.

One interpretation of the differential effects of baclofen on LgA responding between the lines relates to the inhibitive action of baclofen on the mesolimbic dopamine reward system through $GABA_B$ agonist activity. The rewarding effects of cocaine are primarily attributed to its inhibition of the dopamine transporter and consequent increase in synaptic dopamine (Ritz et al., 1987), and the elevated proclivity for cocaine in the HiS rats may have propelled them to surmount the inhibitory effects of baclofen on this increase in dopamine by self-administering more cocaine. Such an increase in intake in the HiS + B rats, compared to the HiS + Sal rats, may have potentiated the upward shift of hedonic set point, a process proposed to be fundamental in the transition from regulated drug use to binge-patterns and addiction (Koob and Kreek, 2007). This concept is supported by the finding that only HiS + B rats showed an increase in post-LgA responding when treatment was discontinued compared to HiS + Sal rats, reflecting a potential deviation from baseline reward functioning. To further investigate this phenomenon, baseline intracranial self-stimulation reward thresholds between the phenotypes could be compared to thresholds following chronic baclofen treatment.

The genetically-determined neurobiological differences between the HiS and LoS rats and their contribution to the differential drug-seeking and treatment receptivity patterns in the present and previous studies are not yet well understood. One possible explanation for the successful attenuation of cocaine self-administration throughout the LgA period in the LoS rats but not HiS rats could be attributed, in part, to a differential functionality of GABAergic neurons and thus variable inhibitory action of baclofen on cocaine-induced reward. A recent study has supported this by replicating the present results with progesterone treatment during escalation instead of baclofen (Anker et al., under review). This is particularly relevant because the attenuating effects of progesterone have been attributed to its metabolite allopregnanolone, a positive allosteric $GABA_A$ modulator (Frye et al., 2007). Human genetic studies have established associations between genes encoding for multiple GABAergic neuron subtypes and alcoholism (Enoch et al., 2009; Parsian and Zhang, 1999). While the mechanism of these genes on GABA functioning is not yet known, it is interesting to note that HiS rats consume more alcohol than LoS rats (Dess et al., 1998). Future studies more directly investigating variations in GABAergic functioning is necessary to better characterize the behavioral differences seen in these lines, such as using in vivo microdialysis to assess GABA and dopamine in mesolimbic areas during chronic baclofen and cocaine treatment in the HiS and LoS animals.

Baclofen and other GABA receptor agonists have been shown to decrease the locomotor activity associated with cocaine (Frankowska et al., 2009). Thus, the differential treatment receptivity between the HiS and LoS rats during escalation may have been due to genetic variability in baclofen's effects on cocaine-induced locomotor activity. However, there were no differences in inactive lever pressing during this phase, suggesting similar locomotor activity between the groups. Further, previous studies have shown no effect of baclofen on food-maintained lever responding up to two times the dose used in the present study (Brebner et al., 2000; Roberts and Andrews, 1997), suggesting that 2.5 mg/kg baclofen is unlikely to elicit differential rate-decreasing effects in locomotor activity between the HiS and LoS rats.

The present findings in our HiS rats are in contrast to results of other experiments using pharmacological interventions during escalation on outbred rats that have largely been successful in reducing drug intake. For example, Specio et al. (2008) showed that corticotropin-releasing factor antagonists block the escalation of cocaine self-administration under periods of extended access. Hansen and Mark (2007) found similar results with the nicotinic acetylcholine receptor antagonist, mecamylamine. However, the application of a mutant albumin-butyrylcholinesterase in rats potentiated responding for cocaine during the first 4 days of extended access (Carroll et al., 2010). The results of the present escalation study suggest that treatment success may vary with underlying drug-abuse vulnerability. Experiments investigating pharmaceutical treatments using the animal model of escalation may produce more generalizable results if high- and low-vulnerability lines are included.

Our results may provide valuable insight into the current lack of available treatment drugs for cocaine addiction and for preventing one of its most critical phases, escalation. Future genetic investigations into the HiS and LoS lines could inform recent pharmacogenetic research regarding treatment agents for stimulant abuse (Haile and Kosten, 2009). Data that point to homologous human genetic markers indicative of phenotypic vulnerability differences and projected clinical

responsiveness to pharmacological agents could provide more informative clinical trials. In agreement with the present results, recent efforts in alcoholism research have suggested that genes encoding for GABA receptor subtypes are possible areas of focus. Ooteman et al. (2009) showed that alcoholics with a polymorphism in the GABRA6 gene displayed greater reduction in craving with acamprosate treatment, a drug that facilitates $GABA_A$ transmission and reduces alcohol intake (McNeely and Sherman, 2011). The opposite effects of baclofen in HiS vs. LoS rats may explain the relatively small effect, if any, of baclofen in human cocaine addicts, as it might be expected that the recruited participants had considerable genetic diversity.

The present escalation study emphasizes the utility of animal models of drug abuse that employ bidirectional breeding methodologies based on extreme behavioral phenotypes and illuminates the necessity of investigating possible divergent treatment effects with other selected lines. Subsequent genetic characterization of the HiS and LoS rats, along with the other lines, could reveal divergent mechanisms within the high- or low-vulnerable models. As the genetic contribution to human drug addiction vulnerability is complex and the result of a combination of many genes with small effect (Uhl et al., 2009), a thorough exploration of the genomes in the available selected lines is further justified. Such research, coupled with behavioral procedures that assess the differential effects of pharmacological interventions, could provide valuable guidance in clinical testing and development of new agents aimed at combating human drug abuse.

In conclusion, the present results showed opposite treatment effects for baclofen in HiS and LoS rats in the escalation phase, but similar effects in preventing reinstatement. Baclofen potentiated the escalation of cocaine intake in HiS rats, but attenuated intake in LoS rats during periods of extended drug access. Further, baclofen was equally effective at decreasing the reinstatement of cocaine-seeking behavior in HiS and LoS rats.

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