Psychopharmacology (2006) 186: 235–245
DOI 10.1007/s00213-006-0371-x

ORIGINAL INVESTIGATION

Jennifer L. Perry · Andrew D. Morgan · Justin J. Anker · Nancy K. Dess · Marilyn E. Carroll

Escalation of i.v. cocaine self-administration and reinstatement of cocaine-seeking behavior in rats bred for high and low saccharin intake

Received: 30 December 2005 / Accepted: 2 March 2006 / Published online: 5 April 2006

Abstract *Rationale:* Rats selectively bred for high saccharin (HiS) intake consume more alcohol, acquire intravenous (i.v.) cocaine self-administration more rapidly, and show more dysregulated patterns of cocaine self-administration than their low saccharin-consuming (LoS) counterparts. *Objectives:* The purpose of the present study was to determine whether HiS and LoS rats also differ in the escalation, maintenance, extinction, and reinstatement of i.v. cocaine self-administration. *Materials and methods:* Two experiments were conducted in separate groups of rats. In the first experiment, HiS and LoS female rats were allowed to self-administer cocaine [0.4 mg/kg; fixed ratio (FR) 1] under short (ShA, 2 h per day) or long (LgA, 12 h per day) access conditions for 21 days. Session lengths were subsequently equated (2 h), and FR1-maintained cocaine self-administration was examined. In the second experiment, additional groups of HiS and LoS female rats were given access to cocaine (0.4 mg/kg; FR 1) self-administration during 2-h sessions for 10 days. Subsequently, saline was substituted for cocaine, and responding was extinguished. After a 14-day extinction period, saline- and cocaine-[5, 10, and 15 mg/kg, intraperitoneal (i.p.)] induced reinstatement of drug-seeking behavior was measured. *Results:* HiS LgA rats escalated their cocaine intake more rapidly than LoS rats, and during the 2 h sessions after escalation cocaine self-administration was significantly higher in HiS LgA rats, compared to LoS LgA rats. HiS rats responded on the cocaine-paired lever more than LoS rats during maintenance, extinction, and cocaine-(15 mg/kg) induced reinstatement. *Conclusions:* These results suggest that HiS and LoS rats have distinct drug-seeking and drug-taking profiles. The HiS and LoS rats differ along a wide range of behavioral dimensions and represent an important model to study the interactions of excessive intake of dietary substances and vulnerability to drug abuse.

Keywords Cocaine · Escalation · Extinction · Genetic · Intravenous · Maintenance · Reinstatement · Selective breeding · Self-administration

J. L. Perry (✉) · A. D. Morgan · J. J. Anker · M. E. Carroll
Department of Psychiatry,
University of Minnesota Medical School,
MMC 392, Minneapolis, MN 55455, USA
e-mail: perry050@umn.edu
Tel.: +1-612-6247813
Fax: +1-612-6248935

N. K. Dess
Department of Psychology, Occidental College,
1600 Campus Road, Los Angeles, CA 90041, USA

Introduction

Individual differences in the effects of drugs of abuse and/or vulnerability to self-administer these drugs are well-established in humans and animals (Crabbe 2002; Nestler 2000). In animal models, differences in behavioral reactivity have been used as one factor that is related to vulnerability to drug abuse. For example, rats that show high novelty-induced locomotor activity (high responders, HR) acquired intravenous (i.v.) amphetamine (Piazza et al. 1989, 1990) and cocaine (Mantsch et al. 2001; Piazza et al. 1998) self-administration faster than those that show low novelty-induced locomotor activity (low responders, LR). Female HR rats also show greater reinstatement of drug-seeking behavior than female LR rats (Larson and Carroll 2005); however, there were no HR/LR differences in reinstatement of drug-seeking behavior in males (Sutton et al. 2000). The elevated response to novelty and corresponding drug self-administration in HR rats has been suggested, in part, to be analogous to high sensation-seeking behaviors in humans (Dellu et al. 1996).

While elevated novelty-seeking behavior in rats is generally predictive of increased vulnerability to acquire drug self-administration and reinstate drug-seeking behavior after a period of abstinence, it does not consistently predict self-administration performance during steady-state or maintenance phases of drug self-administration (e.g., Carroll and Campbell 2000; Kosten et al. 1997). In contrast to novelty-induced locomotor activity, stress-induced self-grooming behavior has been associated with drug self-

administration performance during maintenance under a PR, but not with the rate of acquisition. Homburg et al. (2002) reported no differences in the rate of acquisition of cocaine self-administration in rats selected for high stress-induced self-grooming (HG), compared with those selected for low stress-induced self-grooming (LG); however, HG rats were more motivated to respond for cocaine under a PR schedule during the maintenance phase than LG rats. In another study of maintenance phase performance, rats selected for high levels of wheel running (HiR) self-administered more cocaine infusions than those selected for low levels of wheel running (LoR, Larson and Carroll 2005). Thus, examining several phases of drug self-administration in rodent populations with distinct behavioral phenotypes might further our understanding of factors that confer vulnerability not only to the initiation of drug use, but also to continued drug use.

Individual differences in the consumption of sweetened dietary substances (e.g., saccharin and sucrose) have predicted drug self-administration in rats (Carroll 1993, 1999; Gosnell and Krahn 1998; Levine et al. 2003a,b). Additionally, rats that were selectively bred for high saccharin (HiS) intake consumed more alcohol (Dess et al. 1998), acquired i.v. cocaine self-administration more rapidly (Carroll et al. 2002), and regulated their cocaine intake less precisely (Carroll et al. unpublished data) than their low (LoS) saccharin-consuming counterparts. Rats that are selectively bred for high and low alcohol consumption often show a corresponding increase or decrease in sweet intake, respectively (Kampov-Polevoy et al. 1999; Le et al. 2006), and they have distinct drug-seeking and drug-taking profiles. For example, rats that were selectively bred for high ethanol consumption (P) self-administered more nicotine during maintenance than those bred for low ethanol consumption (NP), and they responded more during extinction and after a nicotine priming injection (Le et al. 2006). Additionally, despite self-administering similar levels of cocaine, lever responding was higher in P rats during subsequent tests of extinction and cocaine-primed reinstatement than in NP rats (Le et al. 2006). These data suggest that genetic factors mediate the association between excessive consumption of sweetened dietary substances and drug abuse.

Previous work in rats has established the importance of drug availability in determining whether drug intake is regulated or whether it will progress toward a loss of control and dysregulation (Fitch and Roberts 1993; Johanson et al. 1976). Differential access conditions can model the escalation of drug intake by allowing rats to self-administer drug during short access (ShA; 1–2 h per day) or long access (LgA; ≥6 h per day) conditions (Ahmed and Koob 1998, 1999). Escalation under extended access conditions is sensitive to subtle individual differences that may be less pronounced during stable (i.e., short access) self-administration periods. For example, female rats (Roth and Carroll 2004) and monkeys (Carroll et al. 2005) escalated their drug intake (cocaine and phencyclidine, respectively) to a greater extent than males under long access conditions; however, no sex differences were found in either species under short access conditions. Thus, one goal of the present study was to determine whether HiS and LoS rats show different patterns of escalation of cocaine intake using differential access conditions similar to those described by Ahmed and Koob (1998, 1999). Based on the acquisition results (Carroll et al. 2002), it was hypothesized that HiS rats would show greater escalation of cocaine self-administration than LoS rats.

A second goal of the present study was to compare the maintenance and extinction of cocaine self-administration and subsequent cocaine-induced reinstatement of drug-seeking behavior in HiS and LoS rats. Using a procedure similar to that reported by De Vries et al. (1998), the reinstatement of cocaine-seeking behavior was examined in HiS and LoS rats after extinction. This procedure has been used to measure reinstatement of drug-seeking behavior in other rodent models with differential reactivity to rewards, namely, rats screened for high (HiR) and low (LoR) levels of wheel running (Larson and Carroll 2005). HiR rats self-administered more cocaine than LoR rats, and after an extinction period, HiR rats displayed more cocaine-seeking behavior in response to a cocaine injection (10 mg/kg) than LoR rats. The reinstatement model has direct clinical relevance, as similar factors that precipitate relapse and craving in humans (e.g., drug-associated cues, stress, drugs) can reinstate extinguished drug-seeking behavior in rats (see reviews by Carroll and Comer 1996; Goeders 2002; Shaham et al. 2003).

The purpose of the present study was to determine whether HiS and LoS rats differ in the escalation of cocaine self-administration and in the reinstatement of cocaine-seeking behavior after maintenance and extinction of cocaine self-administration. Based on previous reports suggesting that HiS rats were more vulnerable to abuse drugs than LoS rats (Carroll et al. 2002), we hypothesized that HiS rats would show greater escalation of cocaine intake and higher levels of responding for cocaine during maintenance, extinction, and reinstatement. In the first experiment, groups of female HiS and LoS rats were compared in a procedure similar to that reported by Ahmed and Koob (1998, 1999). After acquisition and stable drug-taking behavior under a FR 1 schedule, HiS and LoS rats were separated into short access (ShA; 2 h per day) or long access (LgA; 12 h per day) conditions and allowed to self-administer cocaine (0.4 mg/kg) during a 21-day differential access period. Subsequently, session lengths were equated across groups (2 h) and FR 1-maintained cocaine self-administration before and after differential access was compared. In a second experiment using female HiS and LoS rats, the reinstatement of cocaine-seeking behavior after extinction was compared with a procedure similar to that described by de Vries et al. (1998). After acquisition, rats were allowed to self-administer cocaine (0.4 mg/kg) during 2-h sessions under a FR 1 schedule for 10 days. Cocaine was then replaced by saline, and drug-seeking behavior extinguished over the next 14 days. After a 3-day period (cue extinction), in which no conditioned stimuli were presented (i.e., no house light, stimulus lights, or pump) contingent upon a lever press response, the

reinstatement of cocaine-seeking behavior was examined after administration of saline (S) or cocaine (C; 5, 10, and 15 mg/kg) priming injections that occurred on alternating days (S, C, S, C, S, C).

Materials and methods

Animals

Forty-four experimentally naïve adult female HiS and LoS rats were used as subjects in the present study. Twenty-four rats from the 20th to 23rd generations of selective breeding were used for the escalation experiment, and 20 rats from the 24th to 27th generations were used for the reinstatement experiment. At the beginning of each experiment, rats weighed between 200 and 300 g. The HiS and LoS lines have been propagated through pairings of rats with extreme HiS or LoS phenotype scores, including no sibling, half-sibling, or first cousin matings (Badia-Elder et al. 1996). Several progenitor LoS and HiS rats were obtained from the Occidental stock (Occidental College, Los Angeles, CA, USA) to maintain an adequate breeding population, and all rats used in the present study were bred from the Minnesota stock (Carroll et al. 2002). Occasional out-breeding (every 4–6 generations) with rats from the original breeding stock (Sprague–Dawley, Harlan Sprague–Dawley, Indianapolis, IN, USA) was used to maintain the vigor of both lines.

Rats were bred and pair-housed in plastic cages with ad libitum access to food and water before the experiments. During the experiments, rats were fed 16 g of food per day, an amount that maintains female rats at approximately 85% of their free-feeding body weight, and water was freely available. The breeding and experimental rooms were temperature- (24°C) and humidity-controlled with a 12-h light/dark schedule (lights on at 6:00 A.M.). The use of the rats for the studies detailed below was approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC Protocol #0112A13581 and #0410A64760). Laboratory facilities were accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), and recommended principles of laboratory animal care were followed (National Research Council 2003). Table 1 summarizes mean body weights, daily food and water intake during the experiments, and saccharin phenotype scores for each group.

Apparatus

During the experiments, rats were housed in octagonal operant conditioning chambers with alternating Plexiglas and stainless steel walls. Stainless-steel walls contained an attachment for a recessed food jar, water bottle, and two standard response levers (Coulbourn Instruments, Lehigh Valley, PA, USA). Three colored 4.6-W stimulus lights (red, yellow, green) were located directly above each lever, and a white house light (4.6 W) was located at the top of the operant conditioning chamber. Each operant conditioning chamber was housed in a melamine-coated wooden sound-attenuating cubicle that was equipped with a fan for ventilation and white noise. Reservoir drug infusion pumps (model RHSYOCKC, Fluid Metering, Oyster Bay, NY, USA) were used for the escalation experiment, and syringe pumps (PHM-100 Med Associates, St. Albans, VT, USA) were used for the reinstatement experiment. A 500-ml glass reservoir was mounted on the outside of each cubicle for the escalation experiment, and 30-ml syringes and syringe pumps were mounted on the inside of each cubicle for the reinstatement experiment. Each of these was connected to a swivel (050–0022, Alice King Chathum, Hawthorne, CA, USA) via Tygon tubing (1.52 mm o.d., 0.51 mm i.d., Fisher Scientific, Springfield, NJ, USA). A spring-covered tether (C313CS, Plastics One, Roanoke, VA, USA) attached the swivel to the rat's cannula connector and i.v. catheter (0.94 mm o.d., 0.508 mm i.d., Plastics One, Roanoke, VA, USA), which was held in place by a covance infusion harness (Harvard Apparatus, Holliston, MA, USA). Experiments were programmed and data were collected using Med-PC software (Med Associates, St. Albans, VT, USA) running on PCs.

Table 1 Group information

Group	*n*	Weight (g)(±SEM)	Daily food intake (g)(±SEM)	Daily water intake (g)(±SEM)	Saccharin phenotype score (±SEM)
Experiment 1. Escalation					
HiS ShA	7	329 (±11)	16.1 (±0.1)	41.8 (±1.0)	33.7 (±8.4)
LoS ShA	5	289 (±8)	16.1 (±0.2)	38.8 (±1.7)	21.5 (±9.1)
HiS LgA	5	315 (±13)	16.1 (±0.1)	43.1 (±1.3)	39.0 (±8.5)
LoS LgA	7	319 (±12)	16.2 (±0.1)	33.1 (±1.8)	9.0 (±8.2)
Experiment 2. Reinstatement					
HiS	10	253 (±10)	16.0 (±0.1)	38.4 (±1.8)	32.9 (±3.2)
LoS	10	264 (±10)	15.9 (±0.1)	37.8 (±1.9)	17.6 (±3.3)

Procedure

Surgery

After the administration of ketamine (90 mg/kg, i.p.), pentobarbital (10 mg/kg, i.p.), and atropine (0.02 mg/kg, s.c.) in Experiment 1 or ketamine (60 mg/kg, i.p.), xylazine (10 mg/kg, i.p.), dopram (5 mg/kg, s.c.), and atropine (0.02 mg/kg, s.c.) in Experiment 2, rats were implanted with a chronic indwelling silastic catheter in the right external jugular vein as recently described (Carroll et al. 2002; Perry et al. 2005). The anesthesia protocol was altered for Experiment 2 to accommodate the heightened sensitivity of these animals to the anesthesia used in Experiment 1. Briefly, one end of the catheter terminated near the opening of the right atrium, and the free end was led subcutaneously to a medial incision 1 cm caudal to the scapulae. The free end of the catheter was then connected to the harness via a cannula connector. During a 3-day post-surgical recovery period, rats were administered gentamycin (2 mg/kg, i.v.) and heparinized saline (10 IU/kg, i.v.) daily to prevent infection and catheter blockage. In Experiment 2, buprenorphine (0.05 mg/kg, s.c.) was also administered every 12 h for 48 h after surgery.

Experimental sessions were conducted 7 days per week beginning at 9:00 A.M. 3 days after surgery. Food and water solutions were measured, changed, and replenished daily from 8:00 A.M. to 9:00 A.M., drug solutions were measured, changed, and replenished as necessary, and body weights were monitored weekly. Catheter patency was confirmed approximately every 7 days with an injection of sodium methohexital (5 mg/kg, i.v.) in Experiment 1, or an injection of a solution containing 30 mg/ml ketamine and 1.5 mg/ml midazolam (Caine et al. 1999) in Experiment 2. Patency was assumed with an immediate loss of the righting reflex. If the catheter was not patent, rats were anesthetized, a catheter was implanted in the left jugular vein, and they were returned to the experiment after a 3-day recovery period.

Ten to 14 days after drug self-administration measures were completed, a saccharin consumption phenotype score (Table 1) was calculated for each rat to verify the selective breeding (Carroll et al. 2002; Dess et al. 1998). The following equation was used to calculate a score, which indicated a saccharin preference if it was positive, no preference if it was zero, and an aversion to saccharin if it was negative:

$$\textit{Saccharin Phenotype Score} = \frac{24\,h\,\textit{saccharin intake}\,(ml) - 24\,h\,\textit{water intake}\,(ml)}{\textit{body weight}} \times 100$$

Experiment 1. Escalation of cocaine self-administration

Acquisition

To limit differences in cocaine exposure due to differential acquisition rates between groups (Carroll et al. 2002), rats were rapidly trained to self-administer cocaine (0.8 mg/kg) during two daily 2-h sessions (9:00–11:00 A.M. and 3:00–5:00 P.M.) under a FR1 schedule. Throughout the experiment, the left lever was designated as the active lever and the right one was the inactive lever. Responses on the left lever during an infusion were counted, but not reinforced. To facilitate acquisition of the lever press-drug delivery contingency, a small amount of peanut butter (0.5–1.0 g) was placed above the active lever and one noncontingent cocaine infusion was given at the start of each of the first three to five sessions. Acquisition of cocaine self-administration was defined as 2 consecutive days (four sessions) of at least a 3:1 active:inactive lever responding ratio and cocaine intake of at least 15 infusions (12 mg/kg) per session.

ShA before differential access

After acquisition, rats were maintained on the two daily 2-h session (9:00–11:00 A.M. and 3:00–5:00 P.M.) schedule, but the dose of cocaine was decreased from 0.8 mg/kg used in acquisition to 0.4 mg/kg. Rats proceeded to the differential access phase once their self-administration was stable. Stability was defined as no increasing or decreasing trend in infusions over at least three consecutive sessions. The last three sessions of stable responding for each rat served as the ShA baseline.

Differential access

The HiS and LoS rats were randomly divided into short (ShA; 2-h) or long (LgA; 12-h) access to cocaine (0.4 mg/kg) self-administration groups. The ShA and LgA rats were allowed to self-administer cocaine under an FR1 schedule for 21 days between 9:00 A.M. and 11:00 A.M. or 9:00 A.M. and 9:00 P.M. daily, respectively.

ShA after differential access

The effects of ShA or LgA during the differential access period were investigated by subsequent tests of FR1-maintained cocaine self-administration. Rats were returned to the two daily 2-h session (9:00–11:00 A.M. and 3:00–5:00 P.M.) schedule until the stability criterion (no increasing or decreasing trend of infusions over three sessions) was met. The last three sessions of stable responding served as the ShA measure of post-differential access responding. The ShA periods from before and after

differential access were subsequently compared across phenotypes and access conditions.

Data analysis

The main dependent measures were the mean number of cocaine infusions self-administered before, during, and after differential access. The number of cocaine infusions self-administered during the differential access period was compared using a three-way mixed factorial analysis of variance (ANOVA; GB Stat, Dynamic Microsystems, Silver Spring, MD, USA) with repeated measures (phenotype×access×day). The mean number of cocaine infusions self-administered over three stable sessions before and after the differential access period was compared using a three-way mixed factorial ANOVA with repeated measures (phenotype×access×before/after). In addition, mean food and water intake, body weights, and days to acquisition of cocaine self-administration were compared using a two-way ANOVA (phenotype×access). The number of infusions self-administered during the 4-day acquisition period was compared using a three-way mixed factorial ANOVA with repeated measures (phenotype×access×day). Fisher's LSD Protected *t* tests were used for post hoc comparisons. Additionally, saccharin score, and the mean number of infusions self-administered before, during, and after differential access were analyzed for correlations using a Pearson Product Moment Correlation. Results were considered statistically significant if $p<0.05$.

Experiment 2. Reinstatement of cocaine-seeking behavior

Acquisition

To facilitate rapid acquisition in HiS and LoS groups, and to eliminate group differences in acquisition reported previously (Carroll et al. 2002), rats were allowed to self-administer cocaine (0.8 mg/kg) under a FR1 schedule in 6-h sessions. Peanut butter (0.5–1.0 g) was placed above the active lever, and three noncontingent infusions were given every 2 h (9:00 A.M., 11:00 A.M., and 1:00 P.M.). Again, the left lever was designated as the active lever and the right lever was designated as the inactive lever. Responding during infusions was counted but not reinforced throughout the experiment. Acquisition was defined as three consecutive sessions in which the rat self-administered approximately 30 infusions.

Maintenance

After acquisition, the dose of cocaine self-administered was decreased from 0.8 to 0.4 mg/kg. The session length was decreased from 6 (9:00 A.M.–3:00 P.M.) to 2 h (9:00–11:00 A.M.), and session times remained the same throughout the duration of the experiment. Three noncontingent infusions were given at the beginning of each session, and the maintenance phase consisted of 10 days of stable responding.

Extinction

Cocaine was replaced by saline for a 14-day extinction period immediately after the maintenance period. All aspects of the experimental sessions remained the same as in the maintenance phase, except the noncontingent infusions were discontinued.

Pre-reinstatement

After the extinction period, a 3-day pre-reinstatement period took place, in which the house light remained off. Additionally, there were no programmed consequences for lever press responses (i.e., stimulus lights and pump remained off after a lever press response).

Cocaine-induced reinstatement

The reinstatement of cocaine-seeking behavior was examined over 6 days. The drug pump, house light, and stimulus lights remained off through the duration of the experiment to eliminate their influence as conditioned stimuli. For the next 6 days, a daily injection of either saline (S) or cocaine (C; 5, 10, and 15 mg/kg, presented in random order) was administered at 9:00 A.M. (S_1, C_1, S_2, C_2, S_3, C_3), and lever pressed responses were monitored for 2 h thereafter. Reinstatement of cocaine-seeking behavior was measured as the mean number of responses on the previously active (vs inactive) lever after saline and cocaine priming injections.

Data analyses

Dependent measures were the mean number of lever presses during the maintenance, extinction, and reinstatement phases; these were analyzed using a two-way mixed factorial ANOVA with repeated measures (phenotype×day) for each phase. The mean number of cocaine infusions during the maintenance phase were also analyzed using a two-way mixed factorial ANOVA with repeated measures (phenotype×day). Fisher's LSD Protected *t* tests were used for post hoc comparisons. The mean food and water intake, body weights, number of days to acquire cocaine self-administration, and the mean number of cocaine infusions self-administered during acquisition of cocaine self-administration were compared using a Students *t* test (Sigma Stat, SPSS, Chicago, IL, USA). Saccharin score, mean number of infusions during maintenance, responding on the first day of extinction, and responding after 5, 10, and 15 mg/kg cocaine were analyzed to determine whether any of these measures were correlated using a Pearson

Product Moment Correlation. Results were considered statistically significant if $p<0.05$.

Drugs

Cocaine HCl was provided by the National Institute of Drug Abuse (Research Triangle Institute, Research Triangle Park, NC, USA), and it was dissolved in sterile physiological saline. The cocaine dose was varied by changing the concentration of the cocaine/saline solution. Cocaine (0.4, 0.8 mg/kg) and saline were infused at a rate of 0.025 ml/s. The infusion duration was 1 s/100 g body weight, and it was recalibrated weekly on the basis of the most recent body weight.

Results

In the present experiments, rats were food-restricted, and mean body weight and food and water intake during the experiment did not significantly differ across the groups (see Table 1). Additionally, there was little or no responding on the inactive lever in all groups; thus, these data are not shown.

Experiment 1. Escalation of cocaine self-administration

Acquisition

There were no significant differences among the four groups in the number of days to meet the criterion for the acquisition of cocaine self-administration. The mean (±SEM) number of days to acquisition for the LoS ShA rats was 27.40(±4.93), and it was 18.66(±4.15) for the LoS LgA rats. The HiS ShA rats acquired cocaine self-administration in 16.43(±3.37) days, and the HiS LgA rats acquired in 18.40(±4.01) days. Additionally, there were no differences among the groups in the number of infusions self-administered per 2-h session during acquisition. The LoS ShA rats self-administered an average of 23.20(±3.04) infusions, and the LoS LgA rats self-administered 29.71(±6.29) infusions during acquisition. HiS ShA rats self-administered 37.14(±5.35) infusions and HiS LgA rats self-administered 27.00 (±1.51) infusions during acquisition.

Differential access

Figure 1 displays the mean number of cocaine infusions self-administered over the 21-day differential access period in HiS ShA, HiS LgA, LoS ShA, and LoS LgA rats. There was a main effect of access condition ($F_{1,\ 503}=134.61$, $p<0.0001$), with HiS LgA rats self-administering more cocaine than both HiS and LoS ShA rats on days 1–21 ($p<0.05$), and LoS LgA rats self-administering more cocaine than HiS and LoS ShA on days 3–21 ($p<0.05$). There was also a main effect of day ($F_{20,\ 503}=7.40$, $p<0.0001$), a phenotype×day interaction ($F_{20,\ 503}=2.53$, $p<0.01$), an access condition×day interaction ($F_{20,\ 503}=5.84$, $p<0.0001$), and a phenotype×access condition×day interaction ($F_{20,\ 503}=2.91$, $p<0.0001$). HiS ShA and LoS ShA both escalated their cocaine intake slightly, but not significantly. HiS LgA rats escalated their intake over the first 10 days of the escalation period (intake during days 1–3 was significantly less than intake on days 6–10, $p<0.05$), and during days 11–20, HiS LgA rats had stable levels of intake (there were no significant differences in cocaine intake over days 11–20). LoS LgA rats were slower to escalate their cocaine intake than HiS LgA rats, and their cocaine intake peaked on days 13 and 14 (days 1–10 were significantly less than days 12–14, $p<0.05$) compared to day 10 in HiS LgA rats. Additionally, HiS LgA rats self-administered significantly more cocaine than LoS LgA rats on days 1, 2, 4, 6, 7, 9, 10, and 16 ($p<0.05$), while LoS LgA rats self-administered more cocaine than HiS LgA rats on days 13 and 14 ($p<0.05$).

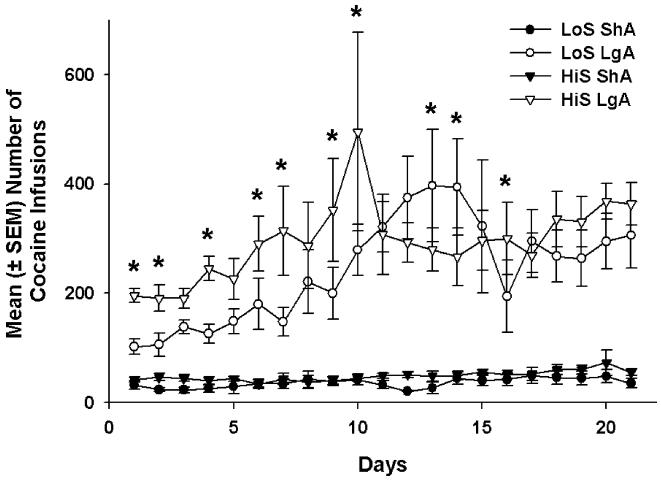

Fig. 1 Effect of short (ShA) or long (LgA) access condition in Experiment 1 on the mean (±SEM) number of cocaine (0.4 g/kg) infusions self-administered in HiS and LoS female rats during the 21-day differential access phase. *Filled circles* refer to LoS ShA; *open circles* refer to LoS LgA; *filled triangles* refer to HiS ShA; and *open triangles* refer to HiS LgA rats. *Asterisks* indicate post-hoc comparisons of LoS LgA v HiS LgA at $p<0.05$

The HiS LgA rats increased their intake more rapidly and self-administered more cocaine than the LoS LgA rats; however, there was no HiS vs LoS difference in the number of cocaine infusions self-administered by the end of the 21-day period. The LoS LgA rats displayed a proportionally greater increase in the number of cocaine infusions self-administered from days 1 to 21 (300%), compared to HiS rats (186%), most likely due to elevated intake in the HiS rats at the beginning of the escalation period.

ShA before and after differential access

Figure 2 shows the mean number of cocaine (0.4 mg/kg) infusions self-administered under an FR 1 schedule in the four groups immediately before and after the 21-day differential access period. There was an overall effect of phenotype ($F_{1,\ 47}$=12.68, p<0.01), with HiS rats self-administering more cocaine than LoS rats. Given that the groups had equal levels of self-administration during acquisition, the between-group differences are most likely due to the change in dose of cocaine self-administered, as it has been reported previously that subtle group differences appear when lower doses are used (Carroll et al. 2002). Additionally, all groups self-administered significantly more cocaine after the 21-day differential access period ($F_{1,\ 47}$=44.38, p<0.0001) compared to before the differential access period. There was also a phenotype×access condition (ShA vs LgA)×before/after differential access interaction ($F_{1,\ 47}$=6.39, p<0.05). HiS ShA rats self-administered more cocaine than LoS ShA rats before the differential access period (p<0.05); however, both groups self-administered similar amounts of cocaine after differential access. HiS LgA and LoS LgA self-administered similar amounts of cocaine before differential access; however, after differential access, HiS LgA rats self-administered significantly more cocaine infusions than LoS LgA rats (p<0.05). There were no significant differences between HiS ShA and HiS LgA or LoS ShA and LoS LgA either before or after differential access, and there were no group differences in the number of days to reach stable responding after differential access. Additionally, saccharin score was not correlated with the number of infusions self-administered before, during, or after differential access.

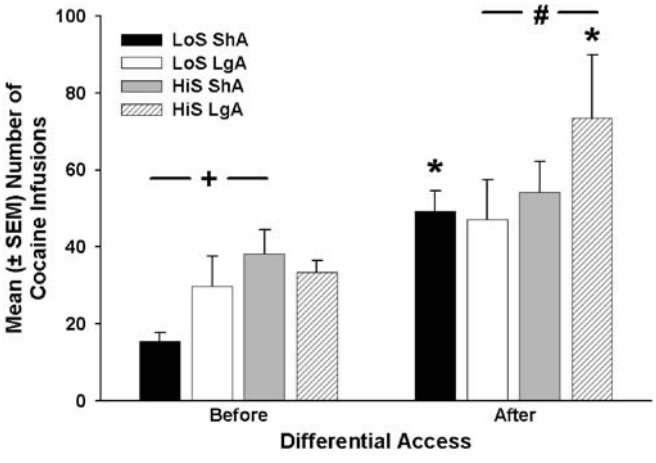

Fig. 2 Mean (±SEM) number of cocaine (0.4 mg/kg) infusions self-administered under a FR 1 schedule during the last three stable self-administration sessions before and after the 21-day differential access phase. The four groups from *left to right* are: LoS ShA (*filled bar*), LoS LgA (*open bar*), HiS ShA (*shaded bar*), and HiS LgA (*hatched bar*). Significant within-group increases in the number of cocaine infusions self-administered before vs after differential access were identified only in the LoS ShA and HiS LgA groups (as indicated by *asterisk*). + represents a significantly higher intake in HiS ShA v LoS ShA rats, and # represents significantly higher intake in HiS LgA v LoS LgA

Overall, HiS rats showed increased levels of cocaine intake after LgA access, while LoS rats did not, indicating that they may be more vulnerable to escalated patterns of drug abuse.

Experiment 2. Reinstatement of cocaine-seeking behavior

Acquisition

There were no between-group differences in the rate of acquisition in HiS and LoS rats, and both groups self-administered approximately the same number of cocaine infusions in the acquisition phase. The HiS rats acquired cocaine self-administration in an average (±SEM) of 9.21 (±1.41) days, while the LoS rats acquired in 14.20 (±2.87) days. During acquisition, the mean (±SEM) number of cocaine infusions self-administered by the HiS rats was 49.03(±4.70), and for the LoS rats, it was 47.30 (±3.38).

Maintenance

Figure 3 indicates that HiS rats responded more for cocaine than LoS rats ($F_{1,199}$=5.76, p<0.05) over the entire 10-day maintenance phase. Post hoc tests revealed that HiS rats made more lever press responses than LoS rats on days 1 and 5–10 (p<0.05). There were no within-group differences in responding over the 10-day maintenance phase.

Figure 4 shows that HiS rats received significantly more cocaine (0.4 mg/kg) infusions than LoS rats ($F_{1,199}$=4.51, p=0.05) over the entire maintenance phase. There was also a phenotype×day interaction ($F_{9,199}$=2.18, p<0.05), with HiS rats self-administering more cocaine infusions than LoS rats on days 4 and 7–10 (p<0.05). Additionally, HiS

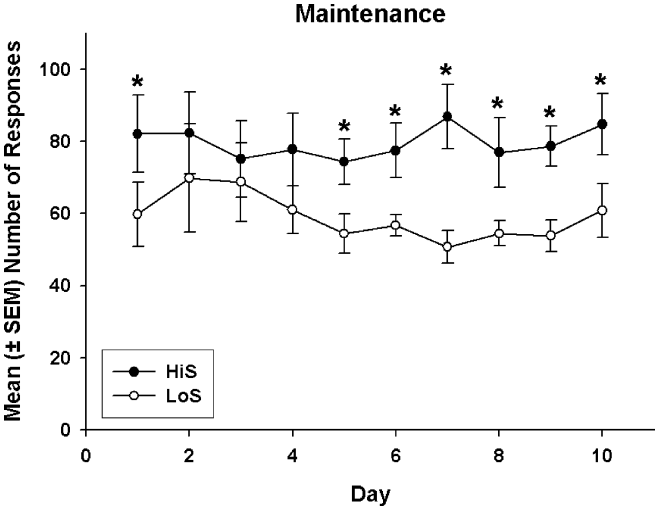

Fig. 3 Mean (±SEM) number of responses on the cocaine-paired lever during the maintenance period. *Closed circles* represent HiS rats, and *open circles* represent LoS rats. Asterisks represent significant HiS/LoS differences at p<0.05

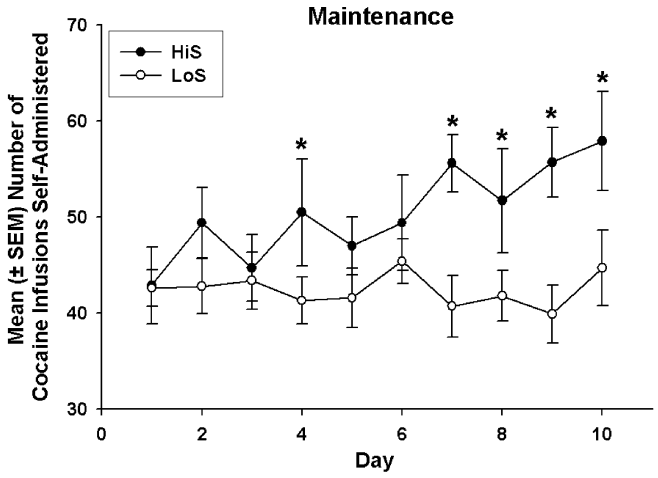

Fig. 4 Mean (±SEM) number of cocaine (0.4 mg/kg) infusions self-administered during the maintenance phase in Experiment 2. Overall, HiS rats (*closed circles*) self-administered more cocaine infusions than LoS rats (*open circles*). *Asterisks* represent significant HiS/LoS differences at $p<0.05$

rats escalated their intake over the 10-day period (days 1–6 were significantly less than day 10, and day 1 was significantly less than days 7–10, $p<0.05$), while LoS rats maintained stable patterns of cocaine intake.

Extinction

When saline was substituted for cocaine, HiS rats maintained more active lever presses than LoS rats (see Fig. 5; $F_{1,279}=7.72$, $p<0.05$). There was a significant effect of day ($F_{13,279}=8.60$, $p<0.05$) and a significant phenotype×day interaction ($F_{13,279}=5.14$, $p<0.05$). Post hoc tests revealed that HiS rats responded more than LoS rats during the first 4 days of extinction ($p<0.01$). Additionally, HiS responding on days 1–3 was significantly higher than their responding on days 5–14 ($p<0.05$), and day 4 responding was significantly less than day 1 ($p<0.01$) and significantly more than days 5–6 and 8–14 ($p<0.05$). There were no significant differences in responding due to day in LoS rats.

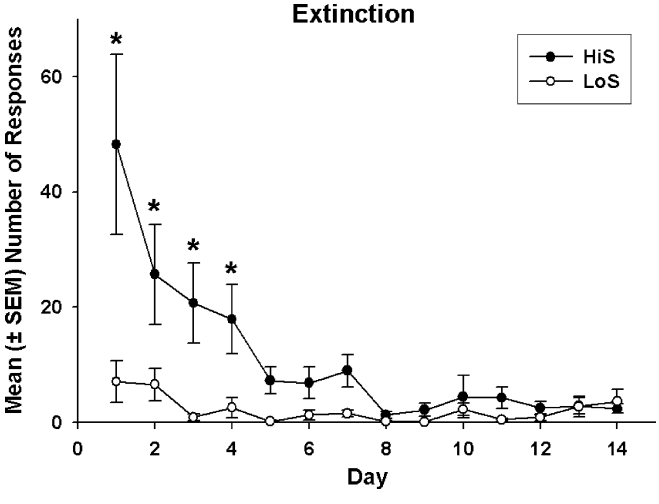

Fig. 5 Mean (±SEM) number of responses on the previously cocaine-associated lever during the extinction phase. *Closed circles* represent HiS rats, and *open circles* represent LoS rats. During the first 4 days of extinction, HiS rats made significantly more responses on the previously active (cocaine-associated) lever than LoS rats (*$p<0.05$)

Reinstatement

As shown in Fig. 6, there was a significant effect of day ($F_{5,119}=7.53$, $p<0.05$) and a significant day×phenotype interaction ($F_{5,119}=3.36$, $p<0.05$) in the reinstatement phase. HiS and LoS rats responded more to 5 mg/kg cocaine than saline, but post hoc tests revealed no significant differences. Priming injections of 10 mg/kg cocaine resulted in significantly higher responding than saline injections in both HiS and LoS rats ($p<0.05$). However, LoS rats did not show significantly higher responding to 15 mg/kg cocaine (vs saline) injections, while HiS rats' responding significantly increased after 15 mg/kg cocaine injections ($p<0.01$). HiS rats responded significantly more than LoS rats after administration of 15 mg/kg cocaine ($p<0.01$). Additionally, HiS rats responded significantly more to 15 mg/kg than to 5 or 10 mg/kg cocaine injections ($p<0.01$), and the mean number of responses in all rats during maintenance was significantly correlated with responding after administration of 15 mg/kg cocaine ($r=0.498$, $p<0.01$).

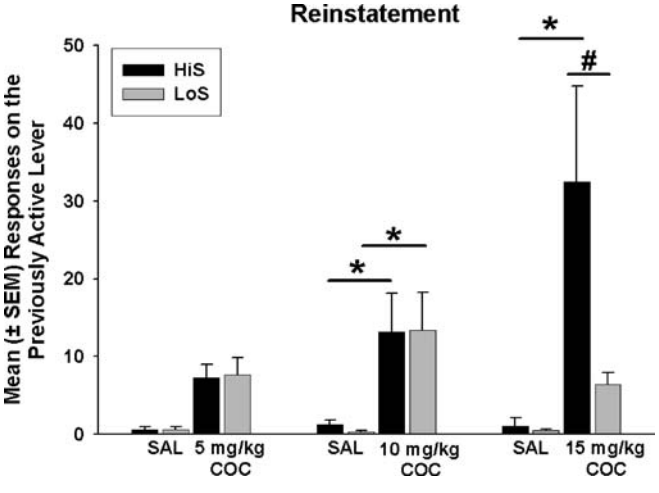

Fig. 6 Mean (±SEM) number of responses on the previously cocaine-associated lever following saline or cocaine (5, 10, and 15 mg/kg, i.p.) injections. Both HiS (*black bars*) and LoS (*gray bars*) rats responded more following a 10 mg/kg cocaine injection compared to saline (as indicated by asterisk, $p<0.05$). After a 15-mg/kg injection, HiS rats responded significantly more than when they were given saline (indicated by *, $p<0.05$), and they responded more than LoS rats (indicated by #, $p<0.05$)

Discussion

Experiment 1. Escalation of cocaine self-administration

In this experiment, a differential access paradigm similar to that described by Ahmed and Koob (1998, 1999) was used to investigate escalation of cocaine intake in female HiS and LoS rats. This experiment extended previous work in the HiS and LoS lines that showed HiS rats consumed more ethanol (Dess et al. 1998) and acquired i.v. cocaine self-administration more rapidly (Carroll et al. 2002) than LoS rats. Consistent with previous escalation studies (see review by Koob et al. 2004), both the HiS and LoS rats escalated their cocaine intake under daily LgA self-administration conditions. The escalation patterns in the HiS and LoS LgA rats were similar to those reported previously (Ahmed and Koob 1999; Mantsch et al. 2001), with an overall increase in cocaine intake over the 21 days in the LgA group; however, there were phenotype differences during this period. The HiS rats displayed a large and immediate escalation of cocaine intake that remained relatively stable after day 10, while LoS rats gradually increased their cocaine intake, and they reached peak levels of intake on days 13 and 14. Both the HiS and LoS LgA rats self-administered the same amount of cocaine by the end of the differential access period, indicating that the rate, but not the amount of escalation was sensitive to the saccharin phenotype.

It should be noted that HiS and LoS LgA rats might have continued to escalate their cocaine self-administration beyond the levels seen in the present study; however, the intake may have been limited by the length of the extended access sessions. In support of this interpretation, the hourly cocaine intake of HiS LgA rats during sessions 1–10 was approximately twice that (i.e., 10 vs 5 mg/kg/h, respectively) of LgA rats in a previous study (Ahmed and Koob 1999), and the session length (12 h) was twice that of the extended access session length used in the previous study (6 h). Perhaps if the extended access sessions were longer, there would have been increases in cocaine intake throughout the 21-day period.

A finding in the present study that was not consistent with previous results (Ahmed and Koob 1998, 1999) was that both the LoS and HiS ShA rats showed a slight escalation in their cocaine self-administration over the 21-day period. In previous studies, escalation was not reported in the ShA (1 h) condition; however, this might have been due to procedural differences between the studies such as rat strain, sex, and/or length of ShA (1 vs 2 h). Specifically, previous reports of stable self-administration patterns under ShA conditions have been shown in male rats from outbred strains (e.g., Spargue–Dawley and Wistar), while the rats in the present study were selectively bred female Sprague–Dawley rats. This difference might also have been due to sex, as female rats were used in the present study. Roth and Carroll (2004) examined sex differences in a differential access paradigm similar to that used in the present study, and female Wistar rats escalated their cocaine self-administration to a greater extent than male rats. The female LgA rats' subsequent responding under an FR 1 schedule at several doses was shifted upward with respect to the LgA males. Roth and Carroll (2004) did not find escalation in the ShA rats; however, a slightly higher dose of cocaine (0.5 mg/kg) was available for self-administration, compared to the present study (0.4 mg/kg), and they used 1 h sessions compared with 2 h sessions in the present study. Similarly, Ahmed and Koob (1999) did not find escalation in the ShA rats using a slightly higher cocaine dose (0.60–0.75 mg/kg) and 1-h sessions.

There was some variability in the LgA female rats' cocaine self-administration patterns in the present study. It has previously been reported that phase of estrous cycle can modify cocaine-reinforced responding (Roberts et al. 1989). Because estrous phase was not monitored in the present study and allowed to vary randomly, the variability in cocaine intake across subjects may have been mediated by fluctuations in ovarian hormones associated with each rat's estrous cycle. There did not appear to be any systematic patterns in each rat's cocaine intake; however, future studies using HiS and LoS rats may benefit from examination of the hormonal fluctuations associated with phases of the estrous cycle in relation to the variability in cocaine intake.

In summary, HiS LgA female rats made the transition from low to high levels of cocaine self-administration more quickly than LoS LgA rats. Additionally, in 2-h sessions after the differential access period, HiS LgA rats self-administered more cocaine (mg/kg) than the LoS rats. Thus, HiS rats were more vulnerable than LoS rats to increases in cocaine intake (mg/kg) due to LgA.

Experiment 2. Reinstatement of cocaine-seeking behavior

In the maintenance phase, HiS rats responded more for cocaine, and they had higher levels of cocaine intake than LoS rats. This is consistent with previous reports that HiS rats acquired cocaine self-administration faster and self-administered more cocaine infusions than their LoS counterparts (Carroll et al. 2002); however, it appears inconsistent with the escalation experiment presented here in which there were no significant HiS/LoS differences in responding under a FR 1 schedule during 2-h sessions. Consistent with the day 1 data from the escalation experiment, there were no HiS/LoS differences in the number of cocaine infusions self-administered on day 1 of the maintenance phase in the reinstatement experiment. In contrast, by day 10 of the reinstatement experiment, HiS rats were self-administering significantly more infusions than LoS rats.

HiS rats escalated their cocaine intake over the 10-day maintenance period, which is consistent with escalation of cocaine intake in HiS ShA rats. HiS rats maintained stable levels of responding for cocaine, yet they increased the number of infusions self-administered over the maintenance phase. This indicates that HiS rats were responding

during infusions, when responses are measured but not reinforced, and that over the maintenance phase, they gradually learned to inhibit their inappropriate responding such that they no longer responded as much during infusions. This may suggest that HiS rats are more impulsive than LoS rats, as failure to inhibit inappropriate responding has been used as a measure of impulsivity (see reviews by de Wit and Richards 2004; Fillmore 2003; Mitchell 2004). Indeed, preliminary data from our laboratory suggest that HiS rats score higher on delay discounting measures of impulsivity for food rewards than LoS rats (Perry et al. unpublished data).

The HiS/LoS differences in cocaine self-administration during the maintenance phase is consistent with reports from investigations of the maintenance phase in other phenotypes that exhibit a vulnerability to drug abuse, such as rats selected for high (HG) and low (LG) stress-induced self-grooming (Homburg et al. 2002) and rats selected for high (HiR) and low (LoR) levels of wheel running (Larson and Carroll 2005). HG rats were more motivated to respond for cocaine than LG rats under a PR schedule (Homburg et al. 2002). Similarly, during maintenance, HiR rats responded more for cocaine than LoR rats (Larson and Carroll 2005), and P rats responded more for nicotine than NP rats (Le et al. 2006).

HiS rats responded more during the first 4 days of extinction than LoS rats. This could also be indicative of higher levels of impulsivity in HiS (v. LoS) rats, as responding during extinction could be viewed as "inappropriate" because it is no longer drug-reinforced. It is also possible that higher levels of responding and cocaine intake in the maintenance phase led to higher levels of responding during extinction. However, in a previous study in which HiR rats responded more than LoR rats during a maintenance phase, no differences were found in responding during extinction (Larson and Carroll 2005). Conversely, Lynch and Carroll (2000) and Le et al. (2006) reported that responding in the maintenance phase did not differ between males and females or ethanol preferring (P) and non-preferring (NP) rats, respectively; however, females and P rats responded more than males and NP rats when cocaine was replaced by saline. Together, these results indicate that the higher levels of cocaine intake in the maintenance phase in HiS rats may not be related to higher levels of responding during extinction.

During the reinstatement phase, HiS rats also showed greater cocaine-induced drug-seeking behavior than LoS rats at the highest dose tested (15 mg/kg). Results from other studies have indicated that group differences are revealed when higher doses are given in the reinstatement phase. For example, females reinstated cocaine-seeking behavior to a greater extent than males, but only at the highest doses tested (Lynch and Carroll 2000). Additionally, there was a correlation between the average number of responses made during the 10-day maintenance period and 15 mg/kg cocaine-primed reinstatement. This is not surprising, given previous reports that increased levels of cocaine self-administration correspond to increases in psychostimulant-primed reinstatement (Baker et al. 2001; Sutton et al. 2000). Because responding in the reinstatement phase is not reinforced by drug or drug-associated cues, responding under reinstatement conditions may also be a measure of drug-induced impulsive behavior. It could be hypothesized that after cocaine administration (especially at higher doses), HiS rats are unable to stop the prepotent responding that occurred under maintenance conditions, when rats could readily self-administer cocaine.

The results of the present experiment extend results from previous reinstatement studies to another model of vulnerability to drug abuse. Previously, differences in reinstatement have been shown in rats selected for high and low levels of wheel running (HiR>LoR, Larson and Carroll 2005) and locomotor activity in a novel environment (HR>LR, Larson and Carroll 2005), and in rats selectively bred for high and low levels of ethanol intake (P>NP, Le et al. 2006). Additionally, females exceeded males in the reinstatement of drug-seeking behavior (Lynch and Carroll 2000), and estrogen plays a role in this enhanced response (Larson et al. 2005). Future studies of the enhanced vulnerability to reinstatement of drug-seeking behavior will add to our understanding of factors that lead to relapse.

In conclusion, HiS rats more rapidly made the transition from low to high cocaine self-administration than LoS rats, and they self-administered more cocaine (mg/kg) after differential access than the LoS rats. Thus, in an escalation model of cocaine abuse, HiS rats were more vulnerable than LoS rats to increases in cocaine intake (mg/kg) due to LgA. Similarly, in the reinstatement experiment, HiS rats responded more for cocaine and had higher cocaine intake during maintenance than LoS rats, and HiS rats escalated their intake despite having a short period (2 h) in which they were allowed access to cocaine. HiS rats also responded more than LoS rats when cocaine was replaced with saline (extinction), and HiS rats showed greater reinstatement of cocaine-seeking behavior than LoS rats after a 15-mg/kg i.p. cocaine priming dose. Combined, these data suggest that HiS and LoS rats have distinct drug-seeking and drug-taking profiles. Selective breeding for differential saccharin intake offers an important model to study the interactions between excessive intake of dietary substances and vulnerability to drug abuse.

Acknowledgements The authors would like to thank Erin B. Larson, Jennifer Newman, Ph.D., and Jason T. Ross, M.A., for careful reading of this manuscript, and Annemarie K. Loth, Sarah E. Nelson, and Marissa M. Anderson for their technical assistance. This work was supported by NIH grants T32 DA07097 (ADM), R01 DA03240 (MEC), and K05 DA15267 (MEC).

References

Ahmed SH, Koob GF (1998) Transition from moderate to excessive drug intake: change in hedonic set point. Science 282:298–300

Ahmed SH, Koob GF (1999) Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology (Berl) 146:303–312

Badia-Elder NE, Kiefer SW, Dess NK (1996) Taste reactivity in rats selectively bred for high versus low saccharin consumption. Physiol Behav 59:749–755

Baker DA, Tran-Nguyen LT, Fuchs RA, Neisewander JL (2001) Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. Psychopharmacology (Berl) 155:18–26

Caine SB, Negus SS, Mellow NK, Bergman J (1999) Effects of dopamine D(1-like) and D(2-like) agonists in rats that self-administer cocaine. J Pharmacol Exp Ther 291:353–360

Carroll ME (1993) The economic context of drug and non-drug reinforcers affects acquisition and maintenance of drug-reinforced behavior and withdrawal effects. Drug Alcohol Depend 33:201–210

Carroll ME (1999) Interactions between food and addiction. In: Boobis S (ed) Neurobehavioral toxicology and addiction: food, drugs and environment. CRC, Boca Raton, Florida, pp 286–311

Carroll ME, Campbell UC (2000) A behavioral economic analysis of the reinforcing effects of drugs: transition states of addiction. In: Vuchinich RE (ed) Reframing health behavior change with behavioral economics. Lawrence Erlbaum, Mahwah, pp 63–87

Carroll ME, Comer S (1996) Animal models of relapse. Exp Clin Psychopharmacol 4:11–18

Carroll ME, Batulis D, Landry K, Morgan AD (2005) Sex differences in the escalation of oral phencyclidine (PCP) self-administration under FR and PR schedules in rhesus monkeys. Psychopharmacology (Berl) 180:414–426

Carroll ME, Morgan AD, Lynch WJ, Campbell UC, Dess NK (2002) Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology (Berl) 161:304–313

Crabbe J (2002) Genetic contributions to addiction. Annu Rev Psychol 53:435–462

de Vries T, Schoffelmeer A, Binnekade R, Mulder A, Vanderschuren L (1998) Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. Eur J Neurosci 10:3565–3571

de Wit H, Richards JB (2004) Dual determinants of drug use in humans: reward and impulsivity. Neb Symp Motiv 50:19–55

Dellu F, Piazza PV, Mayo W, Le Moal M, Simon H (1996) Novelty-seeking in rats—biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. Neuropsychobiology 34:136–145

Dess NK, Badia-Elder NE, Thiele TE, Kiefer SW, Blizard DA (1998) Ethanol consumption in rats selectively bred for differential saccharin intake. Alcohol 16:275–278

Fillmore MT (2003) Drug abuse as a problem of impaired control: current approaches and findings. Behav Cogn Neurosci Rev 2:179–197

Fitch T, Roberts DC (1993) The effects of dose and access restrictions on the periodicity of cocaine self-administration in the rat. Drug Alcohol Depend 33:119–128

Goeders N (2002) Stress and cocaine addiction. J Pharmacol Exp Ther 301:785–789

Gosnell BA, Krahn DD (1998) Taste and diet preferences as predictors of drug self-administration. NIDA Res Monogr 169:154–175

Homburg J, van den Akker M, Raaso H, Wardeh G, Binnekade R, Schoffelmeer A, de Vries T (2002) Enhanced motivation to self-administer cocaine is predicted by self-grooming behavior and related to dopamine release in the rat medial prefrontal cortex and amygdala. Eur J Neurosci 15:1542–1550

Johanson CE, Balster RL, Bonese K (1976) Self-administration of psychomotor stimulant drugs: the effects of unlimited access. Pharmacol Biochem Behav 4:45–51

Kampov-Polevoy A, Garbutt J, Janowsky D (1999) Association between preference for sweets and excessive alcohol intake: a review of animal and human studies. Alcohol 34:386–395

Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, O'Dell LE, Parsons L, Sanna PP (2004) Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev 27:739–749

Kosten T, Miserendino M, Haile C, DeCaprio J, Jatlow P, Nestler EJ (1997) Acquisition and maintenance of intravenous cocaine self-administration in Lewis and Fischer inbred rat strains. Brain Res 778:418–429

Larson EB, Carroll ME (2005) Wheel running as a predictor of cocaine self-administration and reinstatement in rats. Pharmacol Biochem Behav 82:590–600

Larson EB, Roth ME, Anker JJ, Carroll ME (2005) Effect of short- vs. long-term estrogen on reinstatement of cocaine-seeking behavior in female rats. Pharmacol Biochem Behav 82:98–108

Le AD, Li Z, Funk D, Shram M, Li TK, Shaham Y (2006) Increased vulnerability to nicotine self-administration and relapse in alcohol-naive offspring of rats selectively bred for high alcohol intake. J Neurosci 26:1872–1879

Levine AS, Kotz CM, Gosnell BA (2003a) Sugars and fats: the neurobiology of preference. J Nutr 133:831S–834S

Levine AS, Kotz CM, Gosnell BA (2003b) Sugars: hedonic aspects, neuroregulation, and energy balance. Am J Clin Nutr 78:834S–842S

Lynch WJ, Carroll ME (2000) Reinstatement of cocaine self-administration in rats: sex differences. Psychopharmacology (Berl) 148:196–200

Mantsch JR, Ho A, Schlussman SD, Kreek MJ (2001) Predictable individual differences in the initiation of cocaine self-administration by rats under extended-access conditions are dose-dependent. Psychopharmacology (Berl) 157:31–39

Mitchell SH (2004) Measuring impulsivity and modeling its association with cigarette smoking. Behav Cogn Neurosci Rev 3:261–275

National Research Council (2003) Guidelines for the care and use of mammals in neuroscience and behavioral research. The National Academies, Washington, District of Columbia, p 209

Nestler EJ (2000) Genes and addiction. Nat Genet 26:277–281

Perry JL, Larson EB, German JP, Madden GJ, Carroll ME (2005) Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology (Berl) 178:193–201

Piazza PV, Deminiere JM, Le Moal M, Simon H (1989) Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511–1513

Piazza PV, Deminiere JM, Maccari S, Mormede P, Le Moal M, Simon H (1990) Individual reactivity to novelty predicts probability of amphetamine self-administration. Behav Pharmacol 1:339–345

Piazza PV, Deroche V, Rouge-Pont F, Le Moal M (1998) Behavioral and biological factors associated with individual vulnerability to psychostimulant abuse. NIDA Res Monogr 169:105–133

Roberts DC, Bennett SA, Vickers GJ (1989) The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology (Berl) 98:408–411

Roth ME, Carroll ME (2004) Sex differences in the escalation of intravenous cocaine intake following long- or short-access to cocaine self-administration. Pharmacol Biochem Behav 78:199–207

Shaham Y, Shalev U, Lu L, de Wit H, Stewart J (2003) The reinstatement model of drug relapse: history, methodology and major findings. Alcohol 168:3–20

Sutton M, Karanian D, Self D (2000) Factors that determine a propensity of cocaine-seeking behavior during abstinence in rats. Neuropsychopharmacology 22:626–641