Extended Access to Cocaine Self-Administration Enhances Drug-Primed Reinstatement but Not Behavioral Sensitization

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ABSTRACT

Cocaine addicts increase the frequency and amount of drug use over time. This characteristic has been modeled by escalating drug intake in rats that were given extended access to cocaine. However, it remains unclear whether the behavior of escalating drug intake or simply increased drug dose is the relevant aspect of this model. The present study investigated whether the phenomenon of escalated drug-taking enhances cocaine-induced sensitization and reinstatement. Rats were trained to self-administer cocaine during daily 1-h sessions for 7 days. A short-access (ShA) group continued to receive 1-h sessions for 10 days while a group of rats was switched to 6 h of drug access, long-access (ShA-LgA), for 10 days. In addition, a long-access only (LgA-only) group was added that was not pretrained but was only given extended access for 10 days. ShA subjects maintained stable drug intake; ShA-LgA subjects escalated intake while LgA-only subjects decreased drug intake. All groups displayed an inverted-U shaped cocaine dose-response curve in both the sensitization and reinstatement tests. There was no difference in the expression of behavioral sensitization between groups. Whereas both long-access groups showed reinstatement at more doses of cocaine than the ShA group, the presence of escalation did not affect reinstatement. These results indicate that extended access to cocaine self-administration produces behavioral differences relative to traditional short-access animals in reinstatement, but not sensitization. Furthermore, the differences in reinstatement are predicted more by length of cocaine access than by escalation of drug intake.

A major challenge for the field of neuropsychopharmacology is developing predictive animal models of neuropsychiatric disorders. Among the most well characterized models is the drug self-administration model in which subjects learn to perform an operant response to achieve intravenous infusions of drug (Weeks 1962). Initial work conducted with drug self-administration allowed subjects unlimited access to the drug, which often times resulted in death by overdose (e.g., Johanson et al., 1976). Thus, many researchers moved to a “short-access” model that permits limited (1 or 2 h) access to drug infusions. In this situation, animals typically attain a stable level of responding for drug. However, human addicts do not maintain steady intake but instead increase the frequency and/or amount of drug administration over time (Gawin and Kleber, 1981). To more closely mirror the human condition, some researchers have proposed using a “long-access” model of drug self-administration in which rats are given six or more hours of drug access. The gradual increase in drug-taking, which typically results from extended access, is termed “escalation” and is thought to be analogous to the loss of control over drug-taking demonstrated by addicted humans (Ahmed and Koob, 1998; Ahmed et al., 2000; Mantsch et al., 2001; Paterson and Markou, 2003; Ben-Shahar et al., 2004; Ferrario et al., 2005).

Given that extended access protocols are more costly in terms of time and resources, it is important to validate the involvement of escalation in classic behavioral procedures thought to model different aspects of drug addiction. Both behavioral sensitization and reinstatement of drug-seeking in animals withdrawn from drug self-administration have been suggested to model the aspects of addiction. The sensitization of motor behaviors after repeated drug is proposed to be analogous to human addicts attributing progressively greater salience to drugs and the cues that predict drugs (Robinson and Berridge, 2000; Robinson, 2004), and reinstatement is thought to model relapse (de Wit and Stewart, 1981). It should be noted that, although the reinstatement model is viewed as having adequate criterion validity, many would argue that it has weak construct validity (Katz and Higgins, 2003; Epstein et al., 2006).

Previous studies comparing the degree of sensitization after long (LgA) or short access (ShA) to cocaine have yielded conflicting results with some finding that LgA subjects dis-
play tolerance (Ben-Shahar et al., 2004), sensitization (Ferrario et al., 2005), and identical locomotion (Ahmed and Cador, 2006) in comparison with ShA animals. However, it should be noted that Ahmed and Cador (2006) performed sensitization testing only 24 h after the last self-administration session. Although Ferrario et al. (2005) reported a failure of both LgA and ShA animals to sensitize to traditional estimates of locomotion, they identified enhanced sensitization of head movements in the LgA group.

A variety of results have also been reported comparing LgA and ShA subjects on the reinstatement of drug-seeking. This paradigm involves extinction of a previously reinforced response (i.e., lever presses) and subsequent, noncontingent presentation of the reinforcer itself (i.e., drug) or reinforcer-related cues (Stewart and deWit, 1987). Ferrario et al. (2005) reported enhanced reinstatement of cocaine-seeking behavior in LgA animals relative to ShA animals. However, these authors omitted the extinction portion of the reinstatement paradigm and tested animals that had been in withdrawal for 47 days and thus measured abstinence-relapse. Likewise, Ahmed and Cador (2006) reported greater reinstatement in LgA animals while testing after only 24 h of withdrawal and permitting animals just one 45-min extinction session. When the traditional 2 to 3 weeks of extinction training was implemented, De Vries et al. (2005) found no differences in reinstatement behavior between LgA and ShA animals, whereas Mantsch et al. (2004) found that LgA animals displayed enhanced reinstatement relative to ShA subjects. Although Kippin et al. (2006) did not find escalation of drug-taking in their LgA subjects, they found that this group nonetheless displayed enhanced drug-primed reinstatement of cocaine-seeking.

The present study was designed to examine the effects of long access and the relevance of escalating drug intake in the sensitization and reinstatement models of cocaine addiction. In addition to ShA and ShA-LgA treatment groups, a novel long-access group was included that was not pretrained using short access to cocaine (LgA-only). It was predicted that this group would fail to escalate and thus serve as a control for the length of access given to the traditional ShA-LgA group. Thus, by examining a dose-response curve for cocaine-induced sensitization and reinstatement of drug-seeking, it was shown that access duration and escalation were without effect on behavioral sensitization. In contrast, long access resulted in reinstatement to more doses of cocaine, but the increase was independent of the presence of escalated drug intake.

**Materials and Methods**

**Subjects.** Male Sprague-Dawley rats (Charles River Laboratories, Indianapolis, IN) weighing 250 to 275 g were housed individually in a temperature controlled vivarium on a 12-h/12-h light/dark cycle (lights on at 7:00 AM). All experiments were conducted during the light cycle. Animals were provided with food and water ad libitum, with the exception of the 5-day food-training procedure, during which animals only received food during operant training. All experiments were conducted according to specifications of the National Institute of Health (Institute of Laboratory Animal Resources, 1996). A total of 96 rats were used for this study; of which 24 rats were excluded for the following reasons: nine failed to acquire cocaine self-administration, six failed to meet extinction criteria, and nine experienced catheter failure.

**Drugs.** Cocaine hydrochloride was generously donated by the National Institute on Drug Abuse (Bethesda, MD) and was dissolved in 0.9% physiological saline for injection. For the purposes of self-administration, a 5 mg/ml solution was prepared, and subjects received 0.25 mg/injection. Doses of 3, 10, and 30 mg/kg cocaine (i.p.) were administered for both the sensitization and reinstatement studies.

**Self-Administration Procedures.** After 1 week of acclimatization to the colony room and handling procedures, animals were food-deprived and given five 1-h sessions (one session/day) of food training in a two-lever operant chamber (MED Associates, St. Albans, VT). A complete description of operant chambers is described by McFarland et al. (2003). Animals were trained on a fixed ratio-1 schedule of reinforcement in which each press on the active lever (always the right lever) resulted in the delivery of one 45-mg food pellet (P. J. Noyes, Lancaster, NH) and the illumination of the stimulus light above the active lever. The light signified the length of the time-out (TO) period, during which presses on the active lever were recorded but did not result in delivery of the reinforcer. During food training, the TO period was initially 1 s until 100 pellets were earned in one session. After reaching this criterion, subjects experienced one session in which the TO was 10 s, and then the remaining sessions used a TO of 20 s. Three to 7 days after food training, subjects underwent surgery for the implantation of jugular catheters for the delivery of intravenous cocaine as described previously (McFarland et al., 2003). Upon recovery from surgery (3–7 days), animals began cocaine self-administration (fixed ratio-1, 20 s TO) training for 1 h/day, during which active lever presses resulted in a cocaine infusion (0.25 mg in 0.05 ml over 2.7 s). A subset of animals (n = 12) was the yoked-saline control and received an infusion of saline (0.05 ml over 2.7 s) when their yoked counterpart received a cocaine infusion. This acquisition period lasted 7 days, at which point cocaine self-administering subjects were divided into two groups: a ShA (n = 19) group, which continued to receive 1 h of access to cocaine, and a ShA-LgA (n = 19) group, which was permitted 6 h of access to cocaine for the next 10 days (the escalation period). Another group was added at this point, a LgA-only (n = 22) group, which never experienced the 1-h training sessions that the ShA-LgA group received but instead only experienced 10 days of 6-h access to cocaine self-administration. Animals underwent self-administration sessions every day of the week, with no drug-free days until the conclusion of the escalation period. Upon conclusion of the 10-day escalation period, a subset of animals (n = 36) was returned to their home cages for a 2-week withdrawal period, whereas a separate group of animals (n = 36) underwent extinction procedures.

**Reinstatement Testing.** Subjects underwent extinction of the lever-pressing response, during which presses on the active lever no longer resulted in cocaine infusions. Animals received one daily 1-h extinction session for a minimum of 2 weeks. After pressing reached 20% of self-administration levels, animals were tested with 0, 3, 10, or 30 mg/kg cocaine (i.p.). Animals were again subjected to extinction procedures for a minimum of three sessions or until the previous extinction criterion was met, and they were tested with a second dose of cocaine different from the dose used in the first reinstatement trial. The order of doses was randomized.

**Behavioral Sensitization Testing.** Behavioral activity was measured in a photocell apparatus (Omnitech Electronics Inc., Columbus, OH). On the day before the first cocaine sensitization test, subjects were placed into the apparatus for a 60-min acclimation period and then received a saline injection (0.25 ml i.p.), and behavioral activity was recorded for 120 min. The next day, animals were placed in the apparatus for the 60-min acclimation period before receiving an injection of one of three doses of cocaine (3, 10, or 30 mg/kg i.p.). Behavior was recorded in 10-min increments for 120 min after the cocaine injection, as well as for the habituation period. Each rat was tested, with all of the doses of cocaine in random order; each test was separated by 4 to 6 days. Motor activity was quantified as total distance traveled estimated by breaking of adjacent photo-
beams), total horizontal beam breaks, vertical movements, and stereotypy counts (estimated by repetitive breaking of the same photobeam).

**Data Analyses.** The behavioral data were compared using analyses of variance (ANOVA), or when comparing only two groups, a two-tailed Student’s *t* test was used. Because subjects in the reinstatement portion of the experiment were tested with only two challenge doses of cocaine and did not receive all treatment doses, these analyses were done assuming independent groups, because repeated-measures analyses were not possible. When a statistically significant interaction (*p* < 0.05) was obtained with an ANOVA, the least significant differences (LSD) post hoc test was used to assess specific group differences (Milliken and Johnson, 1984). For a one-way ANOVA, a Student’s *t* test with a Bonferroni adjustment was used for post hoc comparisons.

**Results**

**Self-Administration.** A change in cocaine intake during the 10-day escalation period was quantified by comparing the average of the mean number of infusions obtained during the first 3 days of the escalation period (days 1–3) with the last 3 days of the escalation period (days 8–10). This was done to account for the variance that was observed in the day-to-day cocaine intake of both the long-access groups. Most previous studies employing long-access paradigms find that the escalation of drug-taking is most prominent during the 1st h of the self-administration session (Ahmed and Koob, 2004; Ahmed and Cador, 2006). Accordingly, Fig. 1 shows that escalation of cocaine infusions in the ShA-LgA group occurred during the 1st h ([t(18) = 2.510, *p* = 0.022; Fig. 1, B and D]) but not when averaged over the entire 6-h session ([t(18) = 1.287]). In contrast, the ShA subjects maintained stable levels of cocaine intake ([t(18) = 0.490; Fig. 1, A and D]), whereas the LgA-only group significantly decreased intake during the 1st h ([t(20) = 2.128, *p* = 0.045], as well as over the 6-h access period ([t(20) = 3.053, *p* = 0.006; Fig. 1, C and D]).

**Reinstatement of Drug-Seeking.** Whereas the ShA group initially displayed greater responding on the active lever during extinction training, all groups decreased their active lever pressing in a similar manner during the first 10 extinction sessions (Fig. 2A), yielding a significant effect of time ([F(9,18) = 5.236, *p* = 0.001] but not group ([F(2,36) = 0.808]). It should be noted that Fig. 2A only displays the first 10 days of extinction training, because all animals experienced a minimum of 10 extinction sessions (five trials/week for 2 weeks); however, the majority of subjects required additional sessions to meet extinction criteria (20% of active lever pressing achieved during the last 3 days of self-administration). There was no significant difference in the mean number of days to reach extinction criteria among the three groups ([F(2,33) = 0.862; ShA, 12.7 ± 3.4; ShA-LgA, 11.7 ± 2.7; and LgA-only, 11.5 ± 1.6]. Six animals were excluded for

**Fig. 1.** The number of cocaine infusions taken during the 1st h of self-administration and during the entire self-administration session. A, the mean ± S.E.M. number of cocaine infusions taken by the ShA group remained stable over the 10-day escalation period. B, the ShA-LgA group significantly escalated their drug-taking in the 1st h of the session but not over the entire session. C, the LgA-only group significantly decreased their 1st h and entire session of drug-taking. D, when the average of the 1st h intake over the first 3 days of self-administration was compared with the 1st h intake in the last 3 days, the ShA-LgA subjects escalated, whereas the LgA-only subjects decreased drug intake and the ShA subjects remained stable. *, *p* < 0.05, paired two-tailed Student’s *t* test.

**Fig. 2.** Active and inactive lever presses during extinction and reinstatement testing. A, the mean active lever presses during the first 10 days of extinction training. B, mean ± S.E.M. responses made on the active lever during reinstatement induced by an injection of cocaine (3, 10, or 30 mg/kg i.p.). Extinction responding is shown as the mean ± S.E.M. of the last 3 days of extinction training. C, responses made on the inactive lever during extinction and reinstatement testing. Number of determinations is shown on the bar. *, *p* < 0.05, comparing each dose to extinction within each group using a one-way ANOVA; ***, *p* < 0.05, comparing ShA with ShA-LgA and LgA-only, using a two-way ANOVA.
failing to meet criteria by week 3 of extinction training (ShA, 2; ShA-LgA, 3; LgA-only, 1).

Responses on the active lever during a reinstatement test were compared with the average number of responses made during the last 3 days of extinction training. All three groups showed an inverted U-shaped dose-response curve for reinstated cocaine-seeking behavior (Fig. 2B). A two-way ANOVA yielded a significant effect of Group \( F(2,6) = 5.626, p = 0.005 \) and Dose \( F(3,6) = 10.507, p < 0.001 \) but no Group \( \times \) Dose interaction \( F(6,100) = 0.868 \). A LSD post hoc comparison between groups revealed that the LgA-only and the ShA-LgA groups were not different from each other \( (p = 0.498) \) but that the ShA group differed significantly from both the ShA-LgA group \( (p = 0.048) \) and the LgA-only group \( (p = 0.007) \). Although a significant interaction was not measured by the overall ANOVA, if a one-way ANOVA was conducted within each group, all groups displayed significant reinstatement in comparison with extinction responding [ShA, \( F(3,31) = 6.628, p = 0.001 \); ShA-LgA, \( F(3,32) = 4.570, p = 0.009 \); LgA-only: \( F(3,40) = 3.77, p = 0.018 \), and the ShA group \( (p < 0.001) \) displayed significant increases in active lever presses relative to extinction only after the 10 mg/kg injection of cocaine, whereas the LgA-only group reinstated to both the 10 mg/kg \( (p = 0.012) \) and 30 mg/kg doses \( (p = 0.022) \). The ShA-LgA group also significantly reinstated to two challenge doses: the 3 mg/kg \( (p = 0.021) \) dose and the 10 mg/kg dose \( (p < 0.001) \). Figure 2C displays the mean inactive lever responding during extinction and reinstatement testing. A two-way ANOVA revealed no significant Group \( \times \) Dose interaction \( F(6,100) = 0.459 \), nor were there effects of Group \( F(2,6) = 0.099 \) or Dose \( F(3,6) = 0.940 \) on responding for the inactive lever during reinstatement.

Behavioral Sensitization. Four different indices of behavioral sensitization were used: distance traveled, overall horizontal activity, vertical movements, and stereotypy counts. There were no significant effects measured in vertical movements, so these data are not illustrated. Figure 3 displays the time course and dose-response function for all of the behavioral measures that shared a general biphasic character and a peak effect at 10 mg/kg. Figure 3A shows the temporal pattern of distance traveled when rats were injected with 10 mg/kg, and a two-way ANOVA with repeated measures over time revealed a significant Group \( \times \) Time interaction \( F(33,352) = 1.959, p = 0.002 \) and a significant effect of Time \( F(11,33) = 41.484, p < 0.001 \) but not Group. Whereas all three self-administration groups showed significant sensitization compared with the yoked-saline controls during the first 40 min after cocaine administration, they did not differ between each other. The dose-response function for total distance traveled over the 30 min after the injection reveals that all self-administration groups displayed similar behavior relative to yoked-saline controls. A two-way ANOVA with repeated measures indicates that there is a significant effect of Dose \( F(2,6) = 17.701, p < 0.001 \) but not Group and no significant Dose \( \times \) Group interaction. Although there was not a significant interaction, a one-way ANOVA conducted between treatment groups at the 10 mg/kg dose revealed a significant effect \( F(3,32) = 2.906, p = 0.05 \), and a post hoc analysis (LSD) revealed that this effect was due to the saline group being significantly different from all cocaine groups.

A similar pattern was observed for horizontal activity (Fig.

![Fig. 3. Cocaine-induced motor behavior. Each animal was injected with 3, 10, or 30 mg/kg (i.p.) in random order separated by a 4 to 6-day interval. A, time course data for distance traveled during the 60 min before the 10 mg/kg cocaine injection and 60 min after the injection (left). The dose-response curve for the mean ± S.E.M. distance traveled over the first 30 min after injection is also shown (right). B, time course and dose-response curve for horizontal photobeam breaks. C, time course and dose-response curve for stereotypy. *, \( p < 0.05 \), compared with yoked saline at each dose using a one-way repeated measures ANOVA.](image-url)
Elevated Freezing. Escalated versus Nonescalated Subjects. To further evaluate sensitization and reinstatement relative to escalating drug intake during the training period, a median split was conducted on the 1st-h self-administration data to divide the ShA-LgA subjects into escalated and nonescalated subjects. Again, the mean number of infusions attained in days 1 to 3 was compared with the mean number attained in days 8 to 10. The nonescalated subjects either decreased mean infusions over the course of the experiment or only increased a maximum of three infusions (median: 1.3; range: –15 to 3). All escalated subjects increased the number of infusions (median: 13.7; range: 3.3 to 20.7). As shown in Fig. 4A, escalated subjects clearly increased the mean number of infusions obtained in the 1st h of the self-administration session over the course of the escalation period ($t(9) = 4.137, p = 0.003$), whereas the nonescalated subjects did not ($t(8) = 0.430$).

Re-examination of the data shown in Figs. 2 and 3 after dividing the groups into escalated and nonescalated ShA-LgA subjects revealed no effect of Group and no Group × Dose interaction on the measures of sensitization and reinstatement (Fig. 4B and C). A significant effect of Dose was measured in the sensitization experiment ($F(1,6) = 4.607, p = 0.033$).

Discussion

When given the opportunity to self-administer cocaine for an extended period of time, the ShA-LgA subjects significantly escalated the intake of drug in the 1st h of the self-administration session over the course of 10 days. This was in contrast with the ShA subjects that remained stable in their drug consumption and the LgA-only subjects that showed a decrease in cocaine self-administration. Thus, three populations of subjects were generated: a stable group, a group that escalated its drug intake, and a “decelerated” group (see Fig. 1). It is possible that the deceleration was an artifact of food-training in that this group alone was not initially given 1-h sessions, but rather its first experience with cocaine self-administration was during a 6 h session. Thus, the high level of cocaine attained on the 1st day of self-administration may have been aversive and resulted in deceleration of self-administration. The ShA group displayed significantly different reinstatement from either of the LgA groups, and the LgA groups did not differ from each other in the reinstatement of drug-seeking. Thus, regardless of acceleration or deceleration of cocaine self-administration, training with 6 h of cocaine access caused subjects to reinstate to more doses of cocaine than the ShA subjects. Despite the different patterns of self-administration behavior, all groups expressed similar dose-response curves for behavioral sensitization. Further supporting the idea that escalated drug intake itself does not underlie differences in subsequent cocaine-induced behavior, dividing animals into escalating and nonescalating groups revealed no differences in the reinstatement of drug-seeking or expression of sensitization. Furthermore, the modest escalation seen in these rats and the fact that only 50% of ShA-LgA subjects escalated over the course of the experiment raised the question of whether escalation is truly a robust phenomenon in Sprague-Dawley rats.

Reinstatement of Drug-Seeking. The present data show that long-access training caused animals to reinstate to more doses of cocaine but that the augmentation was independent of escalating drug intake. This was revealed both by using a cocaine dose-response comparison between self-administration groups, as well as by dividing animals into escalating and nonescalating subgroups. To date, four publications report testing for reinstatement of drug-seeking in long-access versus short-access subjects (Mantsch et al., 2004; Ferrario et al., 2005; Ahmed and Cador, 2006; Kippin et al., 2006). Similar to the present experiment, all four studies found enhanced reinstatement in long-access relative to short-access subjects.

Comparing the experimental details and results of these four reinstatement studies in combination with the present article points to a conclusion that the main factors influencing reinstatement behavior are the length of access to self-administration and potentially the dose of cocaine attained. The presence of escalated drug intake, strain of rats, withdrawal period, and extinction training has not been shown to enhance reinstatement in rats trained on a long-access regimen of cocaine self-administration. For example, whereas the long-access animals in the Kippin et al. (2006) study did not show escalated intake, these subjects nonetheless demonstrated the same enhancement in reinstatement displayed by the subjects in three other published studies (Mantsch et al., 2004; Ferrario et al., 2005; Ahmed and Cador, 2006). Mantsch et al. (2004) showed that long-access training at higher doses of cocaine was more likely to induce escalating drug intake and found that augmented reinstatement to a

Fig. 4. Using a median split to separate the ShA-LgA group into escalated and nonescalated subjects shows no effect of escalation on reinstatement or sensitization. A, mean ± S.E.M. average number of infusions on the first 3 versus last 3 days of self-administration training; derived from data shown in Fig. 1D. B, distance traveled between the escalated and nonescalated subjects derived from Fig. 3A. C, active lever presses induced by a cocaine-priming injection derived from data in Fig. 2B. Number of determinations is shown in the bar, and all of the data are shown as mean ± S.E.M. *p < 0.05, comparing days 1 to 3 with days 8 to 10, using a two-tailed paired Student’s t test.
cocaine-priming injection was dependent on the long-access training dose. Thus, although the long-access rats trained on a low dose of cocaine showed increased reinstatement compared with the short-access group, long-access rats trained on the high dose demonstrated even more robust reinstatement. Although strain may play a role in propensity to escalate cocaine-seeking (C. Ferrario, personal communication), it has no apparent effect on the augmented reinstatement in the published studies because both Wistar (Ferrario et al., 2005; Ahmed and Cador, 2006) and Sprague-Dawley rats (Mantsch et al., 2004; present data) showed increased reinstatement after long-access training. Finally, the augmented reinstatement measured by Ferrario et al. (2005) was found in animals that did not undergo extinction training but were placed in abstinence for 45 days after discontinuing daily training sessions. Likewise, Ahmed and Cador (2006) tested for reinstatement after only 24 h of withdrawal and used only one extinction training session, which took place immediately before reinstatement testing. Thus, even though extinction training is known to induce neurobiological adaptations in cocaine-trained animals (Sutton et al., 2003), this factor has not been shown to significantly influence the augmented reinstatement accompanying long-access training.

Behavioral Sensitization. Similar to previous studies (Hooks et al., 1994; Phillips and Di Ciano, 1996), animals trained to self-administer cocaine using a short-access paradigm demonstrated behavioral sensitization. However, similar to observations by Ahmed and Cador (2006), sensitization was not augmented by long-access training. Moreover, there was no difference in sensitization between escalating and nonescalating long-access subjects. In contrast, other studies report enhanced (Ferrario et al., 2005) and diminished (Ben-Shahar et al., 2004, 2005) expression of behavioral sensitization in escalated subjects when testing at least 2 weeks after the last self-administration session. Although many parameters (e.g., the strain of rats used and the dose of cocaine self-administered) in the present study were identical to those in the Ben-Shahar et al. (2004, 2005) studies, over a range of challenge doses, sensitization was equivalent between the short- and long-access subjects. However, it should be noted that the report of decreased sensitization in long-access animals may be due to the intravenous administration of the challenge dose of cocaine (Ben-Shahar et al., 2004). When these investigators administered a 15 mg/kg challenge injection via the i.p. route 14 days after discontinuing cocaine self-administration, they no longer found sensitization in either short-access or long-access subjects relative to saline subjects, and the motor response between the short-access and long-access groups was equivalent. It is interesting that testing these subjects again at 60 days post-self-administration yielded a reduced locomotor response in long-access subjects, whereas the short-access subjects showed behavioral sensitization (Ben-Shahar et al., 2005). Similar to Ben-Shahar et al. (2005), Ferrario et al. (2005) reported no differences in the mean number of beam breaks (analogous to the “horizontal activity” measure used in the present article) among long-access, short-access, and control subjects that were administered cocaine after 30 days of withdrawal from cocaine self-administration. Although these animals did not show evidence of sensitization estimated by standard automated measures of motor activity, when Ferrario et al. (2005) visually quantified “head movements”, they found evidence that both short-access and long-access subjects were sensitized relative to saline control subjects and that the response was augmented in long-access compared with short-access subjects. Given that some studies did not find augmented sensitization in rats trained on long-access protocols (Ben-Shahar et al., 2004, 2005; present data) and that the one study showing enhanced sensitization after long access to cocaine did not find sensitized behavior in measures known to reliably manifest sensitization (Kalivas and Stewart, 1991), escalation of cocaine intake may have less impact on sensitization than other experimental variables, such as dose, timing, or route of the test injection of cocaine, or how the behavioral profile is quantified.

Conclusions

Taken together with the studies outlined above, the present data make a clear statement that escalation of drug intake is not critical for long-access training to augment cocaine-induced reinstatement, nor is it related to changes in behavioral sensitization. It is possible that, after other doses of cocaine or durations of self-administration, there may be a greater correlation between the presence of escalated intake and reinstatement or sensitization. However, the present study clearly shows dissociation between these behaviors and casts doubt on the utility of escalating drug intake in rats as an important influence on traditional models of cocaine-induced behavioral plasticity. Nonetheless, it remains important to contrast the biological effects of higher doses of self-administered cocaine, regardless of whether escalating drug intake is a meaningful correlate of addiction in rodents. Studies to date that make neurochemical or morphological comparisons between animals trained on different cocaine access paradigms find that both access conditions produce the same direction of changes but that the long-access subjects show an enhancement of these changes relative to the short-access subjects, including increased dopamine 2 receptor and preproenkephalin mRNA in the striatal complex (Mantsch et al., 2004). Increases in dendritic spine density in both the shell and core of the nucleus accumbens of short-access rats relative to yoked-saline controls (Robinson et al., 2001) are augmented by long-access training only in the core (Ferrario et al., 2005). Other changes, including relatively reduced activation of c-fos in a number of brain regions in long-access subjects, indicate that in some measures, higher drug intake results in tolerance (Ben-Shahar et al., 2005). Based upon present findings, these comparisons between long and short access in terms of biological changes may be more readily interpreted as correlates of access duration and dose and not escalated intake.

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