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Prolonged daily exposure to IV cocaine results in tolerance to its stimulant effects

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Abstract

We have previously shown that 1 h, but not 6 h, of daily access to IV cocaine induces a sensitized response to IV cocaine challenge after 14 days of withdrawal. Here we tried to replicate these results using an IP cocaine challenge and adding a group of animals that had 1 h daily access to cocaine, but maintained levels of administration comparable to that of saline animals (i.e. a Coc group). Since addiction-associated neuroadaptations are particularly long lasting, we also tested the response to cocaine challenge after a longer withdrawal period of 60 days. Rats had daily access to IV self-administered saline or cocaine for 1 h (Coc1h), or to cocaine for 6 h (Coc6h) over 8 days. Subsequently, after 14 days of withdrawal only Coc animals showed a sensitized locomotor response to cocaine challenge administered IP. After 60 days of withdrawal, IP cocaine failed to produce a sensitized response in Coc1h animals and produced a tolerant response in Coc6h animals. The present data support the notion that 6 h of daily access to cocaine leads to different neuroadaptations than those resulting from 1 h of daily access to the drug. In addition, these data further demonstrate a dissociation between sensitization and addiction to cocaine.

Keywords: Cocaine; Tolerance; Addiction; Self-administration; Rat

1. Introduction

It is well established that chronic administration of cocaine leads to lasting changes in brain function (Jentsch and Taylor, 1999; Koob and Le Moal, 1997; Robinson and Berridge, 1993; Self and Nestler, 1998; White and Kalivas, 1998; Wolf, 1998). However, the specific changes found after chronic treatment with cocaine are very much dependent on the route of, schedule of, and control over, drug administration (Davidson et al., 2000; Hemby et al., 1997; King et al., 1994; Porrino, 1993). It follows, then, that in order to identify the neuroadaptations that are relevant to drug abuse in humans (Gawin, 1991; Kramer et al., 1967), one should employ an animal model that closely mimics patterns of drug administration in human addicts. One such model was developed by Ahmed and Koob (1998). This model employs two different self administration protocols – one in which rats are allowed to self-administer IV cocaine for 1 h a day and another in which rats self-administer IV cocaine for 6 h a day. While the first condition leads to stable controlled patterns of self-administration, the second condition produces an escalating pattern of self-administration similar to that exhibited by human addicts (Ahmed and Koob, 1998; Ben-Shahar et al., 2004).

Using this model, and adding a control condition in which rats self-administered IV saline, we found that after 14 days of withdrawal locomotor activity and c-Fos induction in response to one self-administered infusion of cocaine were higher in rats from the 1-h condition compared to both the saline animals and the 6 h animals (Ben-Shahar et al., 2004). We concluded that, while short-term daily access to cocaine can sensitize the neural responses to the drug, more prolonged daily access to cocaine produces a compensatory reduction in sensitivity that may reflect an aspect of the "addictive" process. The current experiment was devised to assess: whether this differential response to cocaine would be apparent using an IP cocaine challenge, whether animals that self-administer cocaine at levels comparable to saline administration will also show a sensitized response to cocaine and, finally, whether the reduced response to cocaine challenge observed in the long-access cocaine condition will still be apparent after a longer

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withdrawal period of 60 days – a point at which the sensitized locomotor response to cocaine was found to dissipate (Henry and White, 1991, 1995).

2. Materials and methods

2.1. Subjects

The subjects ($n=71$) were male albino Sprague–Dawley rats weighing 300–350 g at the beginning of the experiment obtained from Charles River Laboratories (Hollister, CA). Animals were housed individually in wire-hanging cages located within a temperature-controlled (22 °C), 12/12 h light/dark cycle (lights on at 0700) vivarium located in the Psychology Department at UCSB. Subjects had ad libitum access to food and water, except during operant training for food reinforcement (see Food training below). All procedures were conducted in strict adherence to the NIH *Guide for the Care and Use of Laboratory Animals* and were reviewed and approved by the UCSB Institutional Animal Care and Use Committee.

2.2. Surgery

Rats were implanted with chronic intravenous silastic catheters in the right jugular vein under Isoflurane gas anesthesia (Abbott Laboratories, North Chicago, IL; 4% for induction; 2.0–2.5% for maintenance). A single dose of atropine (0.04 mg/kg IM) was administered to minimize respiratory congestion during anesthesia. Banamine (2 mg/kg SC), a non-opiate analgesic, was provided to treat post-surgical pain. Catheters were 13 cm long (0.3 mm inner diameter, 0.64 mm outer diameter; Dow Corning Corporation, Midland, MI), and cemented to a 22-gauge guide cannula (Plastics One, Roanoke, VA) that was in turn secured with Bard Mesh (C.R. Bard Inc., Cranston, RI) to the animals' back. The other end of the catheter was passed subcutaneously around the shoulder to the neck where it was inserted into the jugular vein and secured in place by suture. Animals were allowed 10 days for recovery. Catheter patency was maintained by flushing the IV system with 0.1 ml of a sterile heparin/saline solution each day. Catheter patency was confirmed in all animals with the fast acting anesthetic Brevital (1 mg/0.1 ml saline), once a week and at the end of the last session of cocaine self-administration.

2.3. Apparatus

2.3.1. Self-administration

Six standard (29 cm wide × 25 cm long × 30 cm high) operant chambers were used for all behavioral training and testing. Each chamber was equipped with a non-retractable (fixed) lever and a retractable lever, each positioned 7.0 cm above the grid floor on either side of a food pellet trough that was situated 2 cm above the grid floor. Food dispensers were located outside the chambers. A center house light (2.8 W) was situated 28 cm above the grid floor in the center of the back panel. Two cue lights (2.8 W) were located 6–7 cm above each lever. In the current study, only the right cue light was used. All behavioral testing equipment and data acquisition were controlled by a desktop personal computer running Med Associates software (MED-PC for Windows, Version 1.17). A custom-made liquid swivel was located above the center of each operant chamber permitting the animals to freely move about the chamber without strain on the PE tubing. The inlet of the liquid swivel was connected with polyethylene tubing (Plastic One; outer diameter 0.127 cm, inner diameter 0.058 cm) to a 10-ml syringe containing the self-administration solutions and seated in a syringe pump (Med Associates Inc., St. Albans, VT). An additional length of PE tubing passed through a cannula connector (C313CT Plastic One) from the swivel overhead to the animal where it was connected to the external cannula on the animal's back. Intravenous infusions were administered by activation of the syringe pump.

2.3.2. Locomotor activity

Sixteen identical wire hanging cages (26 cm W × 35 cm L × 20 cm H) were used to monitor locomotor activity. Each cage was equipped with two pairs of infrared emitter-detector photocells that were positioned along the long axis 1 cm from the floor and 8 cm from the front and back of the cage. Photocell interruptions served as a measure of locomotor activity and were recorded by a PC equipped with a John Bell Engineering Universal I/O board, and controlled by custom software written in Turbo Pascal by Stephen Fowler (University of Kansas).

2.4. Drug

Cocaine hydrochloride (provided by the National Institute of Drug Abuse) was dissolved in 0.9% physiological saline. The concentration used for intravenous (IV) administration was 0.25 mg/0.1 ml that was infused at a volume of 0.1 ml over a 4-s period. For IP administration the concentration used was 15 mg/ml/kg.

2.5. Procedure

All training and testing were conducted during the light phase of the light/dark cycle at the same time each day. To facilitate acquisition of operant responding for cocaine, rats were initially trained to lever press for food prior to catheter implantation. Rats were food deprived for 24 h before the initiation of training and maintained on a restricted diet (approximately 15 g of Purina chow/per day) for the duration of food training (one week on average).

2.5.1. Food training

Rats were given daily 1-h sessions in the operant boxes with both levers available. Each right-lever press resulted in a delivery of one 45-mg food pellet (Noyes; FR-1 schedule) followed by a time-out (TO) period. The TO period was signaled by illumination of the right cue light (above the right lever) and initially lasted 1 s. Once a rat had earned 100 pellets

in a session, the TO period was lengthened to 10 s for one session followed by 3 daily sessions in which the TO period was 20 s. After the last session of food training, food again was made available ad libitum in the animals' home cage. Surgical implantation of catheters was performed one to two days after a rat completed the food-training regimen.

2.5.2. Self-administration training

Ten days after surgery, cocaine self-administration training began. Training consisted of 1-h daily sessions that were initiated by extending the right lever into the operant chamber and terminated by withdrawal of the lever. Each right-lever press resulted in infusion of either 0.1 ml physiological saline or 0.25 mg cocaine in 0.1 ml physiological saline, and in the illumination of the right cue light for 20 s. During the TO, additional right-lever presses were recorded but produced no scheduled consequences. Responses at the left lever were recorded throughout the session but had no effects. Once a rat exhibited a stable response rate for cocaine (i.e., no more than 15% variability over 3 consecutive days) and had experienced at least seven self-administration sessions, self-administration training ended and the rat was assigned to one of two groups corresponding to a "short access condition" or a "long access condition". At this point in the experiment, a saline-control rat would also be assigned to the "short access condition". Animals that administered less than ten infusions per hour during training were also assigned to the short access condition.

2.5.3. Self-administration post-training

Self-administration post-training lasted for eight days. During this period the short access groups continued to have 1 h daily access to the same IV compound as during training: cocaine for both the low self-administration animals (i.e., less then 10 infusions per hour, Coc group) as well as the animals that self-administered cocaine at "normal" levels (Coc1h group) or saline. The long access group was now provided with 6-h daily access to cocaine (Coc6h group). At the end of this eight-day period, rats were given 14 or 60 days of withdrawal during which they had no access to cocaine (or saline) and were never placed in the operant boxes.

2.5.4. Locomotor activity

Rats were acclimated to a locomotor chamber for 2 h on either the 12th or 58th day of withdrawal. Rats returned to the locomotor chamber for 2 additional hours on the 13th or 59th day of withdrawal, respectively. One hour into this session subjects received a saline injection (1 ml/kg IP) and locomotor activity was monitored over the course of the remaining 60 min (Baseline). On the 14th or 60th day of withdrawal, a subset of the saline control group was again tested for their locomotor response to saline (1 ml/kg IP; designated as SalS group) during their second hour in the locomotor chambers. The remaining saline control subjects (designated as SalC group) and all of the cocaine animals (i.e., Coc, Coc1h, and Coc6h groups) were tested for their locomotor response to cocaine (15 mg/1 ml/kg IP) administered 60 min into the 2-h session.

3. Results

3.1. Self-administration behavior during the "post-training" period

There were no differences in weights between the different experimental groups. Saline control animals ($n=30$) exhibited low response rates (mean ± S.E.M of 3.5 ± 0.5 infusions per session). Coc animals self-administered low levels of cocaine that were comparable to rates of saline self-administration and significantly lower than those of Coc1h ($n=8$; mean ± S.E.M infusions 5 ± 0.8; two-tailed *T*-test yielding $p<00001$). At the beginning of the post-training period Coc1h and Coc6h animals showed the same levels of cocaine self-administration (see Fig. 1 Panel A). Coc1h ($n=18$) animals exhibited stable self-administration patterns and showed no change in self-administration rates between the first and last day of the eight-day period (See Fig. 1 Panel A or B). Coc6h ($n=17$) animals showed increased rates of self-administration (i.e., escalation) from the first to the last day of the eight-day period. This was true for rates of self-administration during the first hour or the whole session (See Fig. 2 Panel A and B, respectively). Thus two-way ANOVA's yielded significant main effects for Day ($F(1,33)=33.707$, $p<0001$–first hour; $F(1,33)=55.591$, $p<0.0001$–whole session), and significant day × group interactions ($F(1,33)=19.1$, $p<0001$–first hour; $F(1,33)=48.761$, $p<0.0001$–whole session). A one-way ANOVA revealed no difference between day 1 and day 8 for the Coc1h group, but a significant difference for the Coc6h group ($F(1,16)=29.963$, $p<0001$–first hour; $F(1,16)=50.147$, $p<0001$–whole session).

3.2. Locomotor activity

The locomotor response to saline injection on the 13th day of withdrawal (i.e. baseline) was similar in all groups (i.e., SalS $n=9$; SalC $n=7$, Coc $n=8$; Coc1h $n=7$; and Coc6h $n=6$). However, locomotion in response to cocaine challenge on the 14th day of withdrawal (i.e., Test) differed between groups.

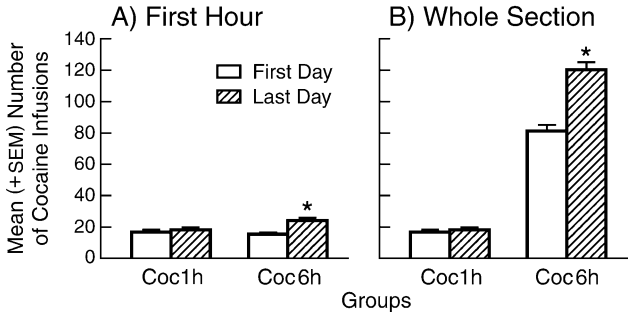

Fig. 1. Mean (+SEM) number of cocaine self-administered infusions on the first (light bars) and eighth (striped bars) day of testing for groups having experienced daily 1 h and 6 h of access to IV cocaine. Panel A depicts data for the first hour of testing and Panel B for the entire 1-h or 6-h sessions. * Represents a significant difference between the first and eighth day of testing ($p<0.001$). Coc1h animals are animals that had daily 1 h access to cocaine during the "Post-Training" period. Coc6h animals are animals that had daily 6 h access to cocaine during the "Post-Training" period.

These data are illustrated in Fig. 2. Two-way ANOVA yielded a significant main effect for Day ($F(1,33)=26.19$, $p<0001$), and a significant day × group interaction ($F(4,33)=4.986$, $p<003$). Simple effects analyses revealed no differences between groups on Baseline, but a significant difference between groups on Test ($F(4,33)=4.908$, $p<003$). Post-hoc analyses showed that this effect was due to differences between the saline animals' response to saline on Test and the Coc animals' ($p<0001$), the Coc1h animals'($p<0.005$), and the Coc6h animals' ($p<014$) response to cocaine on that same day. This significant main effect of Group on Test was also due to the significant difference between the Coc group and the SalC group ($p<046$).

Similarly, on the 59th day of withdrawal, animals from all groups exhibited similar activity rates in response to saline administration (i.e., baseline activity) (i.e., SalS $n=6$; SalC $n=8$, Coc1h $n=11$; and Coc6h $n=11$). However, the response to cocaine administration on the 60th day of withdrawal (i.e., test day) was significantly higher in the Coc1h and SalC subjects compared to the Coc6h subjects (see Fig. 3). Indeed, the locomotor response to cocaine exhibited by the Coc6h animals was very similar to the locomotor response to saline exhibited by the SalS animals. A 2 × 4 factor (day × group) mixed ANOVA computed on these data revealed significant main effects for Group ($F(3,31)=4.326$, $p<012$), for Day ($F(1,31)=48.055$, $p<0001$), and a significant day × group interaction ($F(3,31)=3.986$, $p<016$). To reveal the source of this interaction, two one-way ANOVAs were computed on baseline data and on test data. The one-way ANOVA analyzing baseline activity levels revealed no difference between the four groups. In contrast, the one-way ANOVA analyzing activity following cocaine or saline challenge on day 60 of withdrawal revealed a significant difference between the groups ($F(3,34)=5.317$, $p<.004$). Subsequent LSD Post-hoc tests revealed no difference between Coc6h and SalS group, or between the Coc1h and SalC groups, but did identify significant differences between the Coc1h group and both the SalS group ($p<003$) and the Coc6h group ($p<007$), as well as significant differences between the SalC group and both the SalS group ($p<012$) and the Coc6h group ($p<034$).

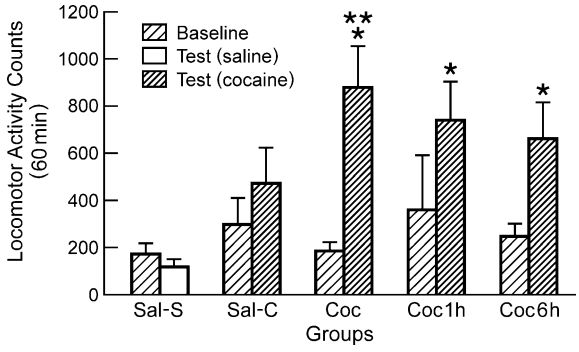

Fig. 2. Mean (+SEM) total group locomotor counts on baseline (light bars) and test (dark bars) sessions. SalS and SalC animals self-administered saline for 1 h a day throughout the training and post-training period. Coc animals self-administered cocaine for 1 h a day throughout the training and post-training period but maintained low rates of self-administration (i.e., an average of 5 infusions per hour). Coc1h animals had daily 1-h access to cocaine during the "Post-Training" period and were tested for their locomotor response to cocaine injection. Coc6h animals had daily 6 h access to cocaine during the "Post-Training" period. Test session data reflect activity produced by a single 15 mg/ml/kg IP injection of cocaine (or single IP injection of 1 ml/kg saline for the Sal-S; white open bars). All data were collected thirteen (baseline) or fourteen (test) days after termination of daily self-administration. * Represents a significant difference on test day compared the Sal-S group ($p<0.05$). ** Represents a significant difference on test day compared to the Sal-C group ($p<0.05$).

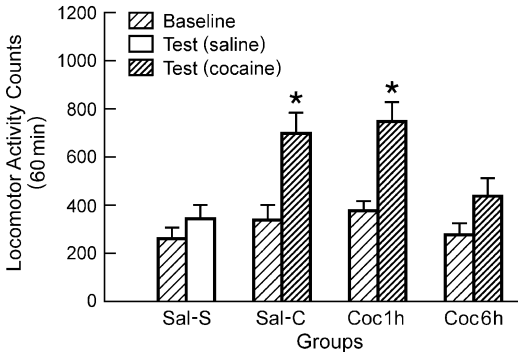

Fig. 3. Mean (+SEM) total group locomotor counts on baseline (light bars) and test (dark bars) sessions. SalS and SalC animals self-administered saline for 1 h a day throughout the training and post-training period. Coc1h animals had daily 1-h access to cocaine during the "Post-Training" period and were tested for their locomotor response to cocaine injection. Coc6h animals had daily 6 h access to cocaine during the "Post-Training" period. Test session data reflect activity produced by a single 15 mg/ml/kg IP injection of cocaine (or single IP injection of 1 ml/kg saline for the Sal-S; white open bars). All data were collected fifty-nine (baseline) or sixty (test) days after termination of daily self-administration. * Represents a significant difference on test day compared to both the Sal-S and the Coc6h groups ($p<0.05$).

4. Discussion

As previously shown, rats given 1-h daily access to cocaine (Coc1h) exhibited stable patterns of self-administration, while rats given 6 h of daily access (Coc6h) exhibited escalating levels of cocaine self-administration over days (Ahmed and Koob, 1998; Ben-Shahar et al., 2004). In the current study, the locomotor counts of Coc1h animals and saline controls (SalC) were not significantly different when both groups were challenged with IP cocaine after 14 or 60 days of withdrawal. In other words, 14 or 60 days after the termination of cocaine self-administration the Coc1h animals showed a "non-sensitized" response to the drug. A sensitized locomotor response to cocaine was found only in the Coc subjects; that is, animals that received the same access to cocaine as the Coc1h animals, yet displayed significantly lower rates of cocaine self administration that were comparable to those of animals reinforced only with saline.

One might argue that, because locomotor sensitization is partially context dependent, the lack of a sensitized locomotor response in the Coc1h animals was due to the fact that cocaine self-administration occurred in a different environment than the one in which locomotor activity was tested. However, the very same procedure was used previously when the locomotor

response to self-administered IV cocaine was examined by us (Ben-Shahar et al., 2004), and in that study Coc1h subjects did indeed show a sensitized response. More specifically, the environment in which the locomotor response to cocaine was tested was different from the environment in which animals self-administered cocaine, in both studies (Ben-Shahar et al., 2004 and the current study). However, a sensitized response to cocaine was found in these animals only in the previous study. This suggests that in order to understand the source of these differing results (i.e., the lack of sensitized response to cocaine in the Coc1h animals of the current study but not the prior one), we should look at the differences between the two studies. Since the only difference was the route of and control over cocaine administration (IP vs. IV self-administration), it is reasonable to assume that the change of route and control over administration was the critical factor that led to the lack of sensitization in the Coc1h group in the current study.

The difference between our previous study (Ben-Shahar et al., 2004), in which we found sensitized responding to cocaine challenge in the Coc1h group at 14 days of withdrawal, and our current study, in which we did not see this effect, is that previously the cocaine challenge was self-administered IV, while in the current study it was administered IP by the experimenter. These differential results further highlight the importance of the control over and route of cocaine administration for its effects (Davidson et al., 2000; Hemby et al., 1997; King et al., 1994; Porrino, 1993). Therefore, as we have previously argued, it is critical that animal models of cocaine addiction mimic the human situation as closely as possible.

Finally, it is important to note that in the current study only the Coc animals exhibited a sensitized locomotor response to cocaine. These animals, though having the same amount of access to cocaine as the Coc1h group, self-administered significantly less cocaine than Coc1h animals. More precisely, these animals self-administered cocaine in the same amounts *and temporal patterns* that saline animals self-administered saline. It is reasonable to argue, then, that cocaine was weakly, if at all, reinforcing to these subjects. Since the reinforcing potential of a drug is highly predictive of its abuse potential (Foltin and Fischman, 1991), we can reasonably conclude that, in the current study, cocaine induced sensitization only in the group showing the lowest abuse liability, i.e. the Coc group. Therefore, these data are consistent with our argument that cocaine-induced sensitization and addiction are independent dissociable processes. This argument is further supported by the observation that cocaine-induced reinstatement, but not locomotor sensitization, is much more pronounced in animals that had long daily access to the drug (Mantsch et al., 2004; Ahmed and Cador, 2005). Indeed, Ahmed and Cador (2005) concluded that psychomotor sensitization is dissociated from the motivational changes that underlie the transition to compulsive cocaine use.

After 60 days of withdrawal, administration of cocaine challenge to the Coc6h animals resulted in a significantly lowered locomotor activation compared to either the SalC, or the Coc1h groups. Indeed, the responses of Coc6h subjects to cocaine were not reliably different than saline control animals that responded to saline challenge (SalS group). Hence, the 6-h animals exhibited a tolerant response to cocaine 60 days after withdrawal from drug self-administration. One might argue that the Coc6h animals were in fact hyper-responsive to cocaine on test day but exhibited low locomotor rates because of drug induced stereotypy. This seems unlikely since we used a low dose of cocaine that would have to be enhanced several fold to mimic the doses necessary to induce stereotypy. In fact, the dose we used is the one most commonly used to induce locomotor sensitization (For example see: Chambers and Taylor, 2004; Crombag et al., 2002; Ghasemzadeh et al., 2003; Ricci et al., 2004; Schroeder et al., 2004). In our view, the most parsimonious explanation is that, after 60 days of withdrawal, cocaine challenge resulted in a reduced or tolerant locomotor response in the Coc6h animals. We further note that this tolerant response was not observed after 14 days of withdrawal (Ben-Shahar et al., 2004), suggesting that the development of this phenomenon occurs over a period longer than two weeks.

In summary, the current results confirm our previous conclusions that short vs. long daily access to cocaine leads to qualitatively different adaptations. Here, after 60 days of withdrawal, short duration access to cocaine resulted in a "normal" increase in locomotor activity, while more prolonged daily access was associated with a tolerant locomotor response to cocaine. The current results further demonstrate dissociation between cocaine induced sensitization and addiction. We therefore conclude that our data are consistent with the notion that the transition from recreational to compulsive drug use is accompanied by the development of tolerance to cocaine that may underlie the need for the increasing consumption of the drug with repeated use.

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