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ORIGINAL INVESTIGATION

Social defeat stress, sensitization, and intravenous cocaine self-administration in mice

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Abstract
Rationale Behavioral sensitization has been proposed as a process that is important in compulsive drug use and in psychotic disorders.
Objective The present experiments examine the relationship between behavioral sensitization, induced by either social defeat or amphetamine, and intravenous cocaine self-administration in mice.
Materials and methods Male CFW mice were exposed either to defeat experiences, amphetamine (2.5 mg/kg, i.p.) or saline (i.p.) every day for 10 days. Ten days after the last defeat or injection, mice were challenged with varying doses of amphetamine (1.0–2.5 mg/kg i.p). Mice were then trained to nose poke for intravenous cocaine (1.0 mg/kg/inf) during daily 3-h sessions. Following this acquisition phase, the animals self-administered varying doses of cocaine (0.3–1.8 mg/kg/inf) or were allowed to self-administer cocaine (0.3 mg/kg/inf) according to a progressive ratio schedule of reinforcement.
Results Repeated social defeat produced a sensitized motor response to a single challenge of 1.5 mg/kg amphetamine and to a cumulative dosing of amphetamine. Amphetamine-pretreated mice exhibited increased cocaine self-administration during acquisition and elevated break points during performance on a progressive ratio schedule of reinforcement relative to stress-sensitized and control animals.
Conclusions These data extend the evidence from rats to mice for the process of sensitization leading to more cocaine taking. Contrary to what is seen in rats, increased levels of cocaine self-administration were seen only in the amphetamine-pretreated mice and not after repeated defeat stress, suggesting that the sensitized response to defeat stress may not be as robust as it is in rats in this particular strain of mice.

Keywords Amphetamine · Cocaine · Social stress · Defeat · Mouse · Sensitization · Intravenous self-administration

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Introduction

There is a strong connection between certain stress experiences and drug addiction. Adverse life events, chronic distress, and environmental stressors can correlate with increased drug abuse in humans (Kosten et al. 1986; Dembo et al. 1988; Brown et al. 1995; Harrison et al. 1997; Jacobsen et al. 2001; Sinha 2001). Rats self-administer more psychomotor stimulants and heroin after exposure to footshock (Piazza et al. 1990; Goeders and Guerin 1994; Shaham and Stewart 1994) and social stress (Ramsey and Van Ree 1993; Haney et al. 1995; Miczek and Mutschler 1996; Kosten et al. 2000; Covington and Miczek 2001, 2005). Corticosterone, a hormone released in response to many types of stress, is also orally self-

administered by rats (Deroche et al. 1993). Adrenalectomy and corticosterone synthesis inhibitors have been found to reduce self-administration of psychostimulants (Piazza et al. 1994; Goeders and Guerin 1996). In humans, acute administration of cortisol produces significant increases in craving in cocaine-dependent individuals, suggesting that cortisol can induce a state that is associated with drug abuse (Elman et al. 2003). Given the correlative relationship stress experience has with drug abuse, the mechanisms underlying the role stress plays in the development of drug addiction can be investigated using rodent models.

One such model involves the process of sensitization, which is thought to be important in the transition from recreational drug user to compulsive drug addict. Repeated, intermittent administration of psychomotor stimulants leads to a progressively increasing, or sensitized, locomotor response to the drug (Shuster et al. 1977; Karler et al. 1989). Certain repeated stress experiences can also result in cross-sensitization to psychostimulants, where previously stressed animals show an augmented locomotor response to a later challenge with a psychostimulant. Sensitized behavioral responses have been observed after repeated footshock (Kalivas and Duffy 1989; Sorg and Kalivas 1991), restraint (Hahn et al. 1986), food restriction (Cabib et al. 2000), and maternal separation (Meaney et al. 2002). Increasing activity in the mesocorticolimbic dopamine system is seen after stress manipulations, including increases in the metabolic responses of dopamine neurons and changes in dopamine activity (Kalivas and Duffy 1989; Piazza et al. 1989). Intermittent exposure to footshock or social defeat stress results in increased dopamine levels in the nucleus accumbens (NAC), up to 65% above baseline (Abercrombie et al. 1989; Puglisi-Allegra et al. 1991; Imperato et al. 1992; Tidey and Miczek 1996). Various stressors, including handling stress, swim stress, footshock, and social defeat stress increase dopaminergic activity in the mesocorticolimbic brain regions (Thierry et al. 1976; Claustre et al. 1986), particularly in the NAC and prefrontal cortex (PFC) (Bannon and Roth 1983; Abercrombie et al. 1989; Imperato et al. 1990; Deutch et al. 1991; Dazzi et al. 1995; Feenstra et al. 1995; Tidey and Miczek 1996). While several stressors induce behavioral sensitization and changes in the mesocorticolimbic dopamine system, it is useful to validate these stress effects with more ethologically valid stressors.

Most stressors affecting humans are of a social nature, and episodes of social defeat in rodents have been shown to modulate changes in circadian rhythmicity (Tornatzky and Miczek 1993; Meerlo et al. 1999), produce long-lasting neural adaptations in immediate early gene expression in the mesocorticolimbic structures (Covington et al. 2005), induce behavioral cross-sensitization to psychostimulants (Nikulina et al. 1998, 2004; Miczek et al. 1999; Covington and Miczek 2001; Yap et al. 2005), and lead to decreased cell proliferation in the dentate gyrus of the hippocampus (Yap et al. 2006). Brief episodic social stress is sufficient to induce profound changes in defensive behavior and long-lasting depression of circadian rhythmicity that persist for weeks (Tornatzky and Miczek 1993; Meerlo et al. 1999). In rats, the autonomic, behavioral, and ultrasonic vocal response pattern before and during repeated weekly confrontations show no evidence for habituation for the following 10 weeks (Tornatzky and Miczek 1994). A single defeat is sufficient to disrupt daily temperature rhythm, and this disruption lasts up to 4 days (Meerlo et al. 1996). Unlike continuous subordination stress, which produce chronic pathophysiological consequences and often require the rescue of the stressed animal (Barnett et al. 1975; Blanchard et al. 1985; Von Holst 1985, 1998), animals are behaviorally activated by brief episodes of social defeat stress and show enduring functional activation in mesocorticolimbic systems (Mos and van Valkenburg 1979; Louilot et al. 1986; Puglisi-Allegra and Cabib 1990; Tidey and Miczek 1996). Up until this point, the impact social defeat stress-induced sensitization has on later cocaine taking had not been investigated in mice.

In the following experiments, we sought to demonstrate the relationship between social defeat stress-induced sensitization and intravenous cocaine self-administration in mice and compare this to the cocaine taking of amphetamine-pretreated mice. An advantage of using mice is the availability of numerous inbred strains and the possibility of using transgenic "knockout" mice when pharmacological manipulations to examine a specific mechanism are not possible. Given the similarities both brief stress episodes and psychostimulants have on the mesocorticolimbic dopamine system, it is expected that amphetamine-induced and stress-induced sensitization will have parallel effects on drug taking.

Materials and methods

Animals

Adult male CFW mice (Charles River Breeding Laboratories; Wilmington, MA) were at least 55–60 days old and weighed ca 25 g upon arrival. Intruder mice were housed individually in clear polycarbonate cages (28 cm×17 cm×14 cm^3) covered by a stainless steel wire lid. Male resident mice were housed in pairs with a female mouse for at least 3 weeks before any experimentation to facilitate the display of aggression in the male resident. Under these housing conditions, the resident always wins the fight, either by having the intruder show the defeat posture or by fighting

with the intruder for the full 5 min allotted. Food and water were available ad libitum, except during a brief conditioning phase of the experiment. When conditioned by food reinforcement, mice were fed 3.2 g of Purina rodent chow per day, which reduced weight gain. A 12-h light/dark photocycle was used with lights on at 08:00 hours. The procedures followed the "Principles of Laboratory Animal Care" (NIH publication No. 86-23 1996) and were approved by the Institutional Care and Use Committee (IACUC) of Tufts University.

Video tracking of locomotor behavior

Video tracking and motion analysis of the mouse was performed via a PC-based data acquisition system (Ethovision, VTMAS v 1.80, Noldus, Wageningen, Netherlands) that receives video input from a camera (Cohu, Model 4815-211/A209) placed 164 cm above the 52×36×32 cm open fields (Rubbermaid).

Experiment 1: amphetamine sensitization

Mice were injected (i.p.) with either 2.5 mg/kg D-amphetamine sulfate (n=18) or saline (n=18) for 10 consecutive days. During the induction phase of sensitization, locomotor activity was assessed on days 1, 4, 7, and 10 for 15 min before the amphetamine or saline injection and for 30 min postinjection in an open field (Fig. 1a). On the days between locomotor testing, injections were given in the home cage. Expression of sensitization was tested on day 20 (10 days after the last amphetamine or saline treatment during the induction phase). The mice were placed into an open field for habituation for 15 min, and locomotor activity was recorded during this period, after saline injection (15 min), and after a challenge with 1.0 mg/kg amphetamine (30 min).

Social defeat stress protocol

For 10 days (days 1–10), subjects (n=24) for both stress and control groups were weighed and injected with saline daily. After the saline injection, animals in the stress group were subjected to social defeat stress. A social defeat episode consisted of three phases: *instigation*, *defeat*, and *threat* (Tornatzky and Miczek 1993). During the instigation phase, the intruder mouse was placed in a transparent polycarbonate protective cage with perforated walls (6×6×17.5 cm^3) within the resident's home cage for 5 min. This protective cage allowed unrestricted auditory, olfactory, and visual contact between the two animals but protected the intruder from potentially injurious bites. During the next phase, the defeat, the intruder was removed from the protective cage and was placed back into the resident's cage. The resident continued to attack the intruder until the intruder assumed the defeat posture, where the mouse stood upright on its hind legs with ears pulled back, head angled upward, retracted ears, and forepaws limp (Miczek et al. 1982). When the intruder held this posture for 3 s, the defeat phase ended, and the threat phase began. The intruder was placed back into the protective cage, and the protective cage was placed back into the resident's cage for 5 min. The social defeat episode consisted of three phases in an attempt to reduce the variability of the stress experience for each animal. Stressed mice were defeated everyday for 10 days. This 10-day period was chosen because our preliminary data had shown that this protocol produces a reliable stress-sensitized response to subsequent psychostimulant challenge (Yap et al. 2005).

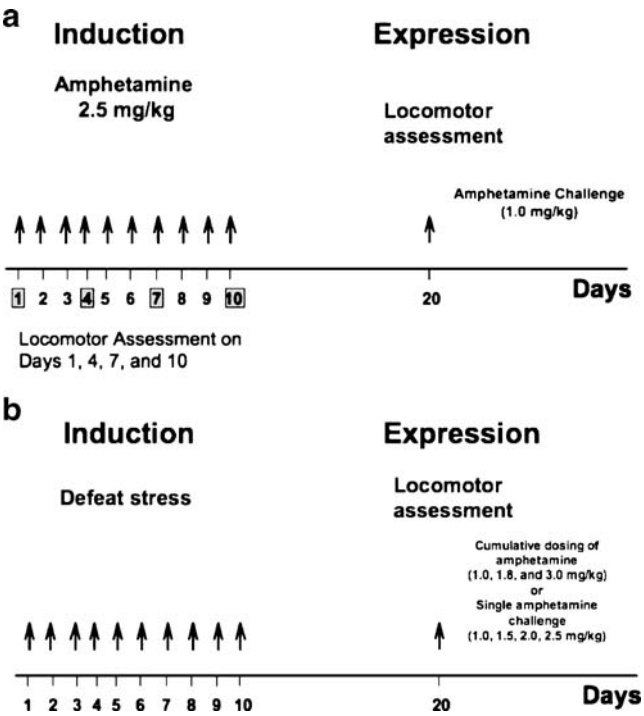

Fig. 1 Induction of sensitization. **a** Induction of amphetamine sensitization. Mice were injected with either amphetamine (2.5 mg/kg, i.p.) or saline every day for 10 days. Locomotor activity was recorded on days 1, 4, 7, 10, and 20. All mice were challenged with 1.0 mg/kg amphetamine on day 20. **b** Induction of defeat stress sensitization. Mice were defeated every day for 10 days. All mice were challenged either with accumulating doses of amphetamine (1.0, 1.8, and 3.0 mg/kg) or a single dose of amphetamine (1.0, 1.5, 2.0, or 2.5 mg/kg) on day 20, 10 days after the last defeat experience

Intravenous self-administration

Procedures similar to those outlined by Caine et al. (1999) and Caine et al. (2002) were used. One day after the amphetamine challenge, mice were conditioned to nose poke, with each response being reinforced by delivery of a

17-μl bolus of liquid food (Ensure, Abbott Laboratories, Columbus, OH) as reinforcement according to a fixed-ratio 1 (FR-1) schedule. The duration of this training period was 5 days. Training sessions ended after 2 h or when the animal received 100 deliveries of liquid food. At the start of the session, the houselight and a green light in the active nose poke hole were illuminated. When the active hole was poked, the green light in the hole turned off, and the food was delivered over 2 s. The green light stays off for an additional 28 s. Pokes in the inactive hole were of no consequence.

The day after the last day of food training, mice were implanted with jugular catheters using sterile procedures. Mice were anesthetized with 2-2-2 tribromoethanol (Avertin®, Sigma-Aldrich Chemical, 40 mg/kg, i.p.). A 7.0-cm length of Micro-Renathane® tubing (0.36 mm ID, 0.84 mm OD; Braintree Scientific, Braintree, MA) was inserted 1.2 cm into the right jugular vein of the mouse, was flushed with sterile saline, and was fixed in place with silk sutures and tissue adhesive (VetBond). The other end of the catheter ran subcutaneously over the shoulder and was fitted to a 22-gauge back-mount cannula connector pedestal (Plastics One, Roanoke, VA), which was placed between the shoulder blades, under the skin. After surgery, the animals were weighed, and their health was evaluated daily for 5 days before beginning cocaine self-administration training. Heparinized saline (0.02 ml of 30 IU/ml solution) was used daily to flush the catheter and maintain patency. The patency of the catheter was evaluated periodically (approximately every 10 days) and whenever drug self-administration behavior appeared to deviate dramatically from previous behavior. Approximately 0.02 ml of a cocktail containing 15% ketamine, 15% midazolam and 70% saline was flushed through the catheter. If signs of anesthesia were not apparent within 10 s of infusion, the mouse was removed from the experiment.

After 5 days of recovery postsurgery, mice nose poked to receive cocaine (1 mg/kg/inf) on a fixed-ratio 2 (FR-2) schedule of reinforcement. A 28-s time-out period was selected to avoid possible cocaine overdosing and overly rapid infusions. Sessions were initiated with an infusion that fills the catheter volume (ca 7 μl). Self-administration sessions were conducted daily for 3 h (50 infusion max). The 50-infusion limit was chosen to prevent overdose. Once the animal reached a stable baseline level of responding (which was reached in 5 days), mice were tested for responding under varying doses of cocaine. The criteria for baseline were stable daily responding (within 20% across two consecutive sessions) and at least 70% of responses on the active poke. The doses used were: 0.30, 0.56, 1.00, and 1.78 mg/kg/inf of cocaine. The order in which the doses were self-administered was counterbalanced, with the mice administering each dose for 2–3 days.

Experiment 2: social defeat stress, aggression, and cumulative dosing of amphetamine

Upon arrival in the facility, male CFW mice were placed in one of four groups: intruder stress, intruder control, resident stress, or resident control. The resident mice were housed with a female mouse and remained undisturbed for 3 weeks. Intruder mice were singly housed. The social stress manipulations—defeat or aggression—began 3 weeks later. Figure 1b visually depicts the design of this experiment. Every day for 10 days, intruder mice were subjected to an encounter with an aggressive stimulus resident mouse. The stimulus mice (residents and intruders) were rotated every day to maintain a comparable level of aggressive behavior. Everyday for 10 days, resident stress and intruder stress mice encountered a stimulus intruder or resident, respectively, using the three phases of social defeat stress described previously (instigation, fight/defeat, and threat). Ten days after the last aggressive encounter (day 20 of experiment), mice were given a habituation period in the open field for 45 min. Then, mice were given a saline injection, and motor activity was recorded for 20 min. This was followed by a cumulative dosing (1.0, 1.8, 3.0 mg/kg i.p.) of amphetamine, and locomotor activity was assessed for 20 min after each injection.

Experiment 3: social defeat stress and single challenges of amphetamine

One week after arrival to the facility, mice were defeated in the manner previously described over the course of 10 days (Fig. 1b). Ten days after the last defeat episode, separate groups of animals were challenged with various doses of amphetamine (1.0, 1.5, 2.0, 2.5 mg/kg, i.p). Locomotor activity was assessed during a 45-min habituation period, for 15 min after a saline injection, and for 45 min after amphetamine injection.

Experiment 4: social defeat stress and day 40 amphetamine challenge

Procedure for this experiment is the same as experiment 2, except the amphetamine challenge (1.5 mg/kg i.p.) is given on day 40 (30 days after the last defeat). Locomotor activity is assessed in the same manner on the challenge day as described in experiment 2.

Experiment 5: social defeat stress-induced sensitization, amphetamine-induced sensitization, and intravenous self-administration of varying doses of cocaine

Mice are exposed to either ten daily defeats or ten daily injections of amphetamine (2.5 mg/kg, i.p.). Ten days after

the last defeat or injection, mice were challenged with 1.0 or 1.5 mg/kg to check for behavioral sensitization. The 1.5 dose of amphetamine was chosen to challenge the stressed mice because it is the dose found to most reliably show a sensitized locomotor response, relative to controls. The day after this expression test, animals were conditioned to nose poke (as described above) for 5 days and then were implanted with jugular catheters. Mice were allowed to recover for 5 days and then were allowed to acquire cocaine self-administration for 5 days. After this acquisition phase, mice were allowed to self-administer varying doses of cocaine. Figure 2a illustrates the timeline for this experiment.

Experiment 6: social defeat stress-induced sensitization, amphetamine-induced sensitization and intravenous cocaine self-administration on a progressive ratio schedule

Intruder mice were defeated every day for 10 days. As the sensitized locomotor response to amphetamine is diminished by day 40 (30 days after the last defeat) in socially defeated mice, we shortened our protocol from experiment 4 by food training the mice before the start of the defeats, and jugular vein catheterization was performed 5 days after the last defeat, allowing the start of the acquisition of cocaine self-administration to begin on day 20 (Fig. 2b). This way, the self-administration phase commences during a time period of known cross-sensitization to psychostimulants. The acquisition phase lasted 5 days. After this period, mice were allowed to self-administer 0.3 mg/kg/inf cocaine on a progressive ratio (PR) schedule of reinforcement for 3 days. Between each PR session, mice self-administered 1.0 mg/kg/inf cocaine on an FR-2 schedule during 3-h sessions, just as they did during the acquisition phase. These FR sessions were added to prevent full extinction of the cocaine-seeking behavior during the PR days. The algorithm used for the progression was previously derived by Richardson and Roberts (1996). The ratio progression was: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178.... The last completed ratio, which resulted in the final infusion, was defined as the breaking point. The PR session ended when the mouse failed to receive an infusion of cocaine during a 60-min period. The average number of break points and completed ratios (i.e., total infusions) over the last two PR sessions for each individual mouse were

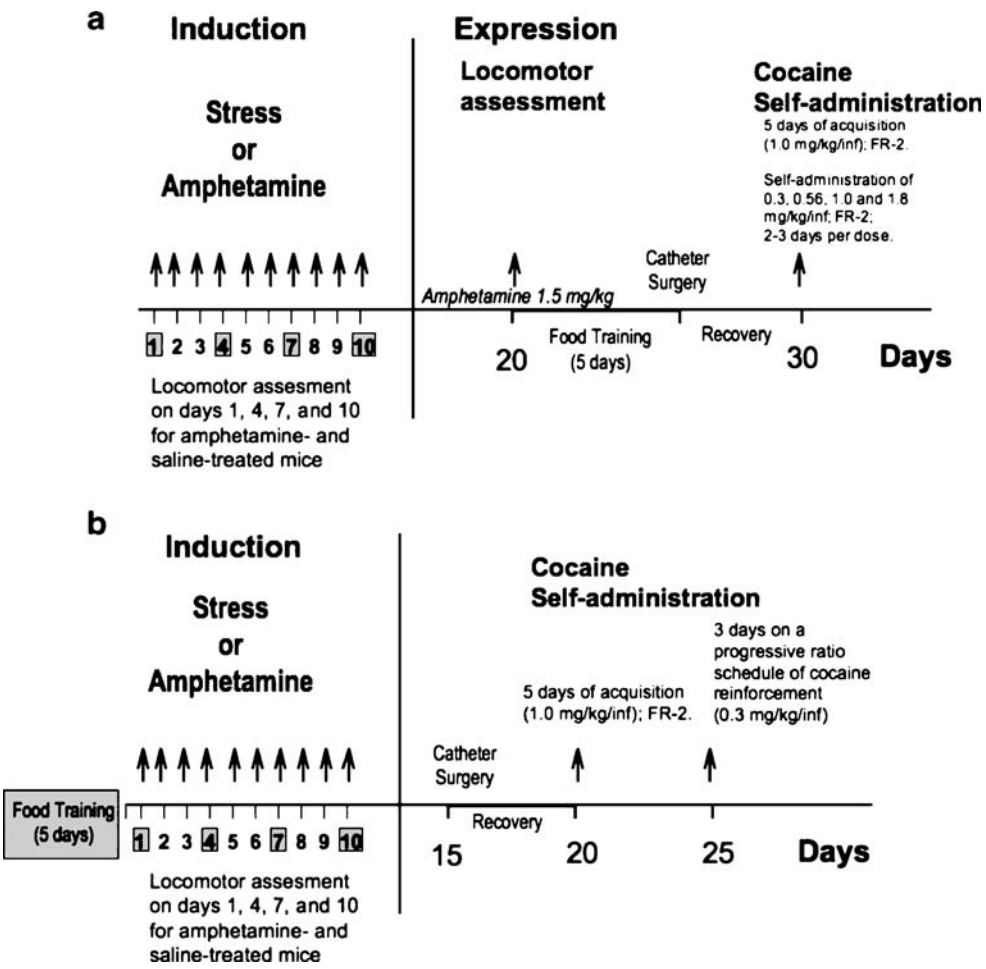

Fig. 2 Sensitization and cocaine self-administration. **a** Amphetamine or stress sensitization and intravenous cocaine self-administration of varying doses (0.3, 0.56, 1.0, and 1.8 mg/kg/inf) on a fixed-ratio 2 schedule of reinforcement. **b** Amphetamine or stress sensitization and intravenous cocaine self-administration (0.3 mg/kg/inf) on a progressive ratio schedule of reinforcement

used as the dependent variables, as data from the first PR day are highly variable, and the break point values are much higher than subsequent days.

Drugs

D-Amphetamine sulfate (0.8–2.5 mg/kg; NIDA Research Technology Branch) and cocaine HCl (0.3–1.8 mg/kg; NIDA Research Technology Branch) were dissolved in 0.9% saline. D-Amphetamine was administered intraperitoneally at a volume of 0.1 ml/kg body weight. Cocaine was self-administered intravenously at a volume of 18 μl over 2 s.

Nose-poke apparatus

An aluminum panel is inserted into the center of the home cage of the mouse and is affixed to the side walls of the cage with thumb screws. The panel contains two nose-poke sensors, each on opposite sides of the panel and stimulus lights in the nose-poke holes (Fig. 3). During food training, a fluid delivery cup is placed in the center of the panel, and during cocaine self-administration, the delivery cup is replaced with a flat metal plate. A spring-supported arm holding a liquid swivel (Instech Laboratories, Plymouth Meeting, PA) is affixed to the top of the panel directly above the center metal plate. The 22-gauge cannula is connected to a liquid swivel with PE-50 tubing. The swivel is connected to a 3-ml syringe attached to the infusion pump. All responses were recorded automatically using a computer interface and software from Med Associates (St. Albans, VT, USA).

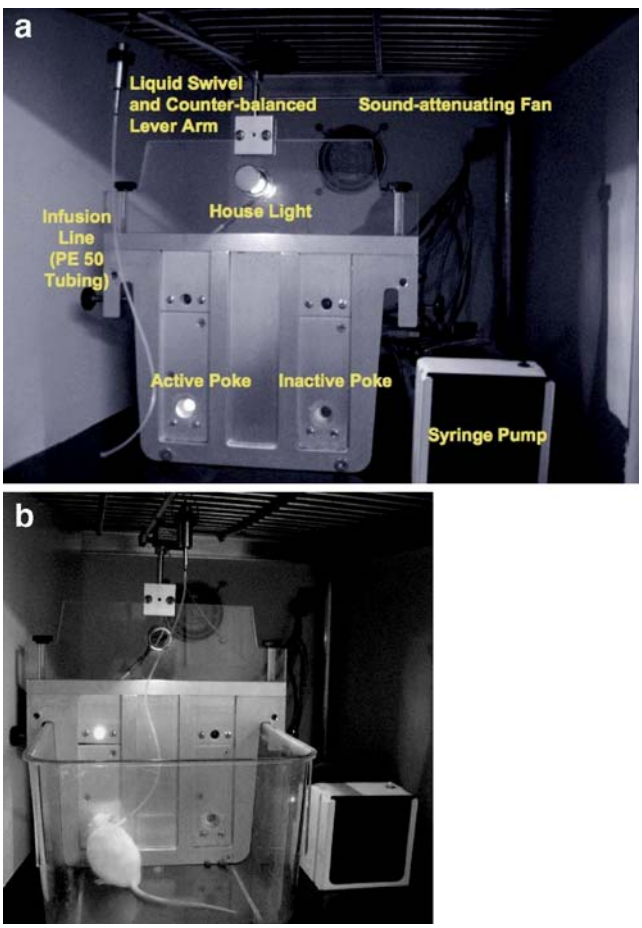

Fig. 3 Nose-poke apparatus. **a** Photograph of nose-poke apparatus. **b** Photograph of mouse poking for I.V. cocaine

Statistical analyses

To determine behavioral sensitization to social defeat stress, the distance traveled during each 5-min increment of behavioral analysis, before and after psychostimulant injections, were analyzed using two-way analyses of variance (ANOVAs) (group x treatment). Post hoc comparisons were made using Student Newman–Keuls tests. Data collected during the acquisition phase of cocaine self-administration were analyzed using *t*-tests. All subsequent self-administration data were analyzed using repeated measures ANOVAs in a between-groups and within-groups design. Progressive ratio data (break points and infusions) were analyzed using one-way ANOVA (sensitization group). Post hoc comparisons were made with Dunnett's tests when significant *F* values were attained. Alpha was set at 0.05.

Results

Experiment 1: amphetamine-induced sensitization

Repeated amphetamine injections led to a progressive increase in locomotor activity during the induction phase, as seen through a significant main effect of day [$F_{(3,\ 102)}$= 40.54, P<0.0001] and a significant main effect of drug treatment [$F_{(1,\ 102)}$=170.28, P<0.0001], and no increases were seen in the saline-treated animals (Fig. 4a). Post hoc tests revealed that mice traveled a greater distance on days 4, 7, and 10 compared to day 1 (P<0.001). On day 20, amphetamine-injected animals showed a sensitized response to a low dose of amphetamine compared to saline controls that received this same challenge [$F_{(1,\ 272)}$=9.28, P<0.005] (Fig. 4b). Post hoc tests revealed that mice given amphetamine during induction showed significantly higher distance traveled during the first 25 min after the amphetamine challenge (P<0.05).

Experiments 2–4: defeated mice show a sensitized response to amphetamine

Mice with a history of repeated defeat show a sensitized locomotor response to increasing, accumulating doses of

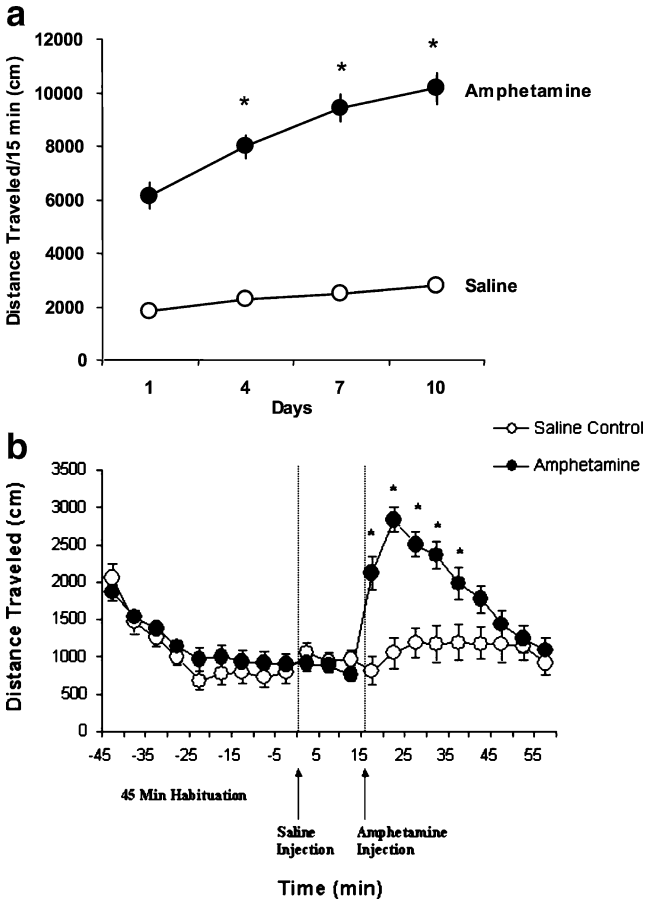

Fig. 4 Amphetamine-induced sensitization. **a** Induction phase. The effect of repeated amphetamine injections on locomotor behavior. Locomotor activity is expressed as the mean distance traveled in 15 min by each group as a function of time. Mice were injected with either amphetamine (2.5 mg/kg, i.p.) or saline every day for 10 days. *asterisks*: $P<0.001$ compared to day 1 value for amphetamine-treated mice. **b** Expression test. Mice were challenged with 1.0 mg/kg amphetamine (i.p.) on day 20, 10 days after the last amphetamine or saline injection. Locomotor activity is expressed as the mean distance traveled in 5 min by each group as a function of time. *asterisks*: $P<0.05$ compared to control mice

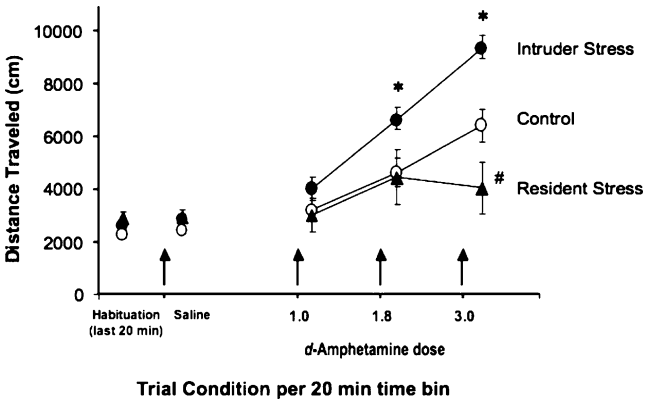

Fig. 5 Day 20 expression test for intruder, resident, and control mice. Locomotor activity is represented as points indicating the average distance traveled in 20 min by each group. Stressed mice were previously exposed to ten daily aggressive encounters where they were either the defeated mice or the aggressors. Ten days after the last aggressive experience, mice were challenged with accumulating doses of amphetamine (1.0, 1.8, and 3.0 mg/kg, i.p.). Intruder mice show a sensitized locomotor response to amphetamine at the 1.8 and 3.0 doses (*asterisks*: $P<0.05$ compared to controls). Resident mice show a blunted response to 3.0 mg/kg amphetamine (*number signs*: $P<0.001$ compared to both intruders and controls)

amphetamine [$F_{(2,\ 215)}=12.99$, $P<0.001$] (Fig. 5). Post hoc tests show that intruder mice differ significantly from control mice at the 1.8 and 3.0 doses of cocaine ($P<0.001$ for both doses). Aggressive resident mice that fought for 10 consecutive days actually show a blunted response to cocaine at the highest dose, compared to both intruders and controls ($P<0.001$).

On day 20, defeat-stressed mice show a sensitized response to a 1.5-mg/kg challenge of amphetamine compared to non-stressed control mice [$F_{(1,\ 368)}=11.02$, $P<0.005$]. Post hoc comparisons revealed that defeat-stressed mice showed a significantly higher distance traveled from 10–45 min after amphetamine injection ($P<0.05$, Fig. 6). Defeat-stressed mice did not differ significantly from control mice when challenged with other doses of amphetamine (1.0, 2.0, and 2.5). This is unlikely due to stereotypy. Video footage was recorded with a videocassette recorder (VCR) simultaneously with the Ethovision analysis, and there were no classic signs of stereotypy (e.g., circling, sniffing, head bobbing, repetitive head movements, etc). This sensitized locomotor response seen on day 20, after defeat stress, diminishes by day 40 (i.e., 30 days after the last defeat).

Experiment 5: amphetamine-pretreated mice show facilitated cocaine taking during the acquisition phase

Defeat-stressed mice and non-stressed controls did not differ in the cocaine self-administration behavior, neither during acquisition nor during determination of the cocaine dose–response curve (Fig. 7a,b).

Amphetamine-pretreated mice show increased drug taking during the acquisition phase of cocaine self-administration (1.0 mg/kg/inf) compared to control mice ($t=2.52$, $P<0.05$; Fig. 8a). Both amphetamine-sensitized and control mice self-administer cocaine dose-dependently, as seen by a significant effect of dose [$F_{(3,\ 49)}=6.05$, $P<0.005$] (Fig. 8b). However, there is no difference between the two groups at any of the doses of cocaine that were available, during the dose–effect determination.

Experiment 6: amphetamine-pretreated mice attain higher break points on a progressive ratio schedule of reinforcement

Amphetamine-sensitized mice attained slightly, but not significantly, higher levels of cocaine intake during the last

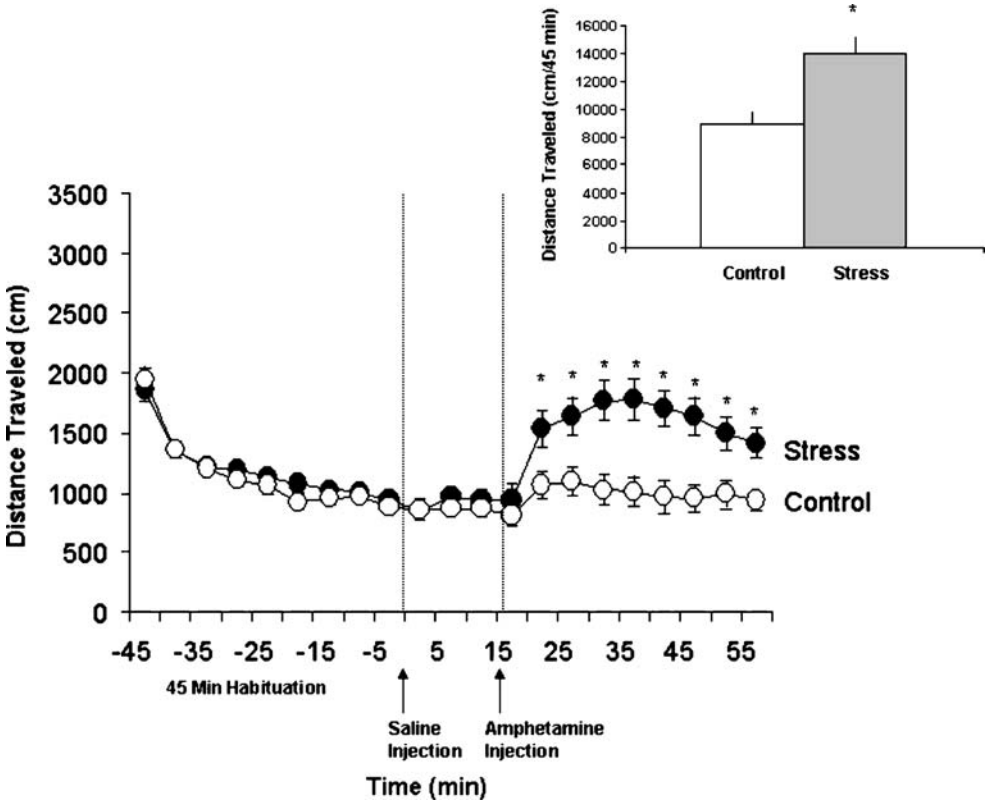

Fig. 6 Day 20 expression test for stressed and non-stressed mice. Locomotor activity is expressed as the average distance traveled in 5 min. *Inset* shows the average distance traveled during the full 45 min following amphetamine injection for both stress and control mice. Ten days following the last defeat episode, mice were challenged with amphetamine (1.5 mg/kg, i.p.). *asterisks*: $P<0.05$ compared to controls

2 days on a progressive ratio schedule of reinforcement relative to stressed and control mice (Fig. 9a). Amphetamine sensitization leads to higher break points on this schedule of reinforcement ($F_{(2,\ 16)}=3.98$, $P=0.039$, Fig. 9b). Dunnet's test analysis reveals a significant difference between amphetamine-sensitized mice and control mice ($P<0.05$) on this measure.

Discussion

The present results indicate that repeated, intermittent social defeat stress in mice is sufficient to induce behavioral cross-sensitization to amphetamine, extending our findings from the rat to outbred mice. The magnitude of the sensitized amphetamine response after social defeat stress is comparable to that seen in mice with a history of repeated low-dose (1.0 mg/kg) amphetamine administration (Yap et al. 2005). A more intense defeat protocol may produce results more equivalent to those seen with repeated injections of 2.5 mg/kg of amphetamine. Locomotor sensitization to an amphetamine challenge after the intermittent administration of a stressor is seen in several species and across various stress protocols (Antelman et al. 1980; Hahn et al. 1986; Kalivas and Stewart 1991; Covington and Miczek 2001; Pacchioni et al. 2002) and persists undiminished for at least 1 year in the rat (Paulson et al. 1991).

Repeated, intermittent defeat experiences produce more persistent behavioral cross-sensitization. A single exposure to social defeat stress in mice is sufficient to induce a sensitized behavioral response to future challenges with a psychomotor stimulant (Nikulina et al. 1998; Miczek et al. 1999). However, a single defeat in mice, contrary to rats, was found to produce no significant Fos expression in the ventral tegmental area (VTA), a critical site for the induction of neural sensitization in rats (Vezina 1993; Cador et al. 1995; Nikulina et al. 1998). Repeated social defeat stress increases Fos expression in subsets of neurons in the mesocorticolimbic system, including the VTA, prelimbic, and infralimbic cortical areas, NAC shell and core, and the medial, central, and basolateral amygdala, 7 days after the last stress episode in rats (Nikulina et al. 2004). This neuronal sensitization is still seen 60 days after the last defeat in the VTA and the amygdala when the animals are challenged with amphetamine (Miczek et al. 2004; Nikulina et al. 2004). In addition, *zif268* mRNA expression is decreased in the PFC and increased in the central and basolateral amygdala, 60 days after the last stress exposure (Covington et al. 2005). Taken together, these immediate early gene data suggest that the VTA, PFC, and amygdala are critical sites for the mediation of social defeat stress-induced sensitization, and these genomic changes due to stress may play a role in the transition to compulsive drug taking.

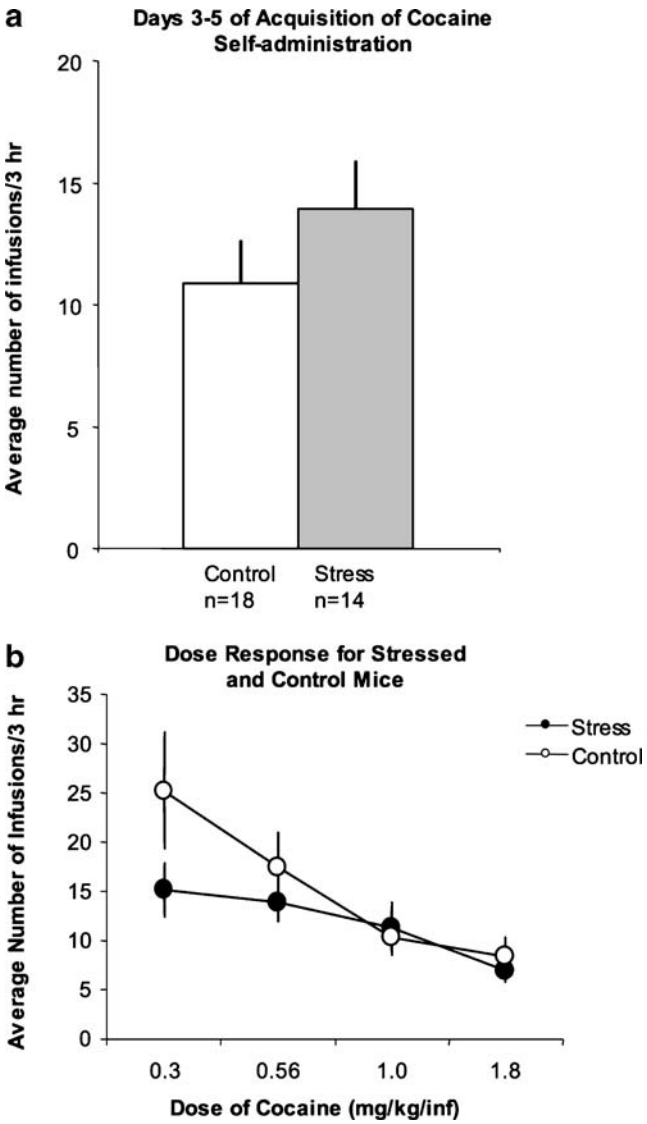

Fig. 7 Intravenous self-administration of cocaine by stressed and control mice. **a** Acquisition phase. The effect of repeated social defeat on the acquisition of cocaine self-administration. Defeated and control mice do not significantly differ in their self-administration behavior during this phase. *Bars* represent average number of infusions of 1.0 mg/kg/inf cocaine per 3-h session. **b** Self-administration of varying doses. Defeated and control mice self-administer cocaine dose-dependently. *Points* indicate average number of infusions of each dose of cocaine per 3-h session

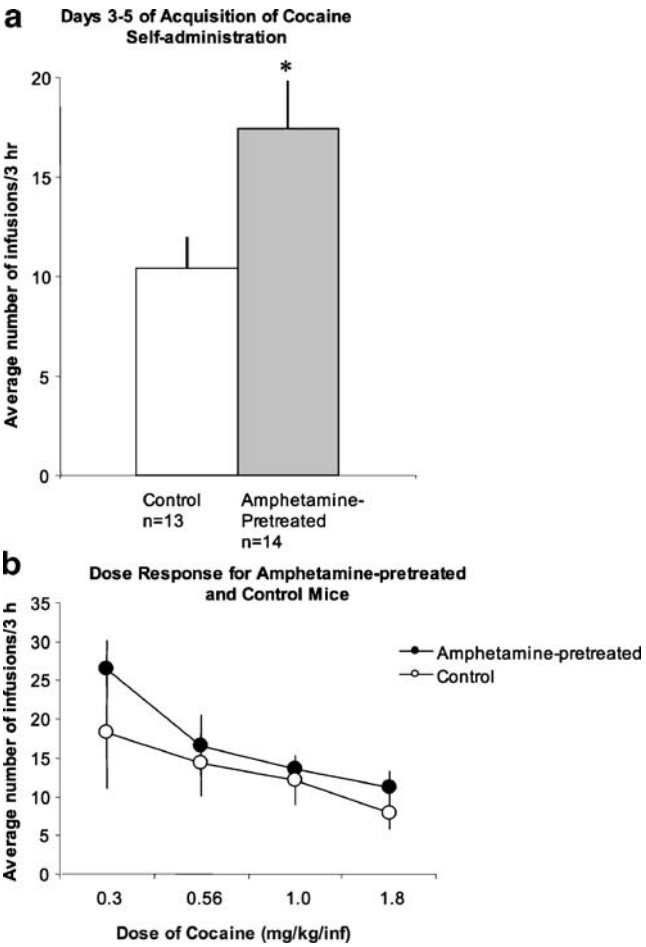

Fig. 8 Intravenous self-administration of cocaine by amphetamine-pretreated and control mice. **a** Acquisition phase. Amphetamine-pretreated mice take significantly more cocaine than control mice during this phase. *Bars* represent average number of infusions of 1.0 mg/kg/inf cocaine during a 3-h session. *asterisk*: $P<0.05$ compared to controls. **b** Self-administration of varying doses. Cocaine self-administration is represented as the mean number of infusions of each dose of cocaine per 3-h session. Amphetamine-pretreated and control mice self-administer cocaine dose-dependently

Other neurotransmitters, in addition to dopamine, may also be involved in the long-term neural adaptations that occur as a consequence of repeated stress. Glutamate is critical in the development of stress-induced sensitization, through its actions on the mesolimbic dopamine system, primarily via activation of *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The afferent and efferent connections between the basolateral amygdala and PFC are glutamatergic, and the PFC sends glutamatergic efferents to the dopamine cell bodies in the VTA (Kelley et al. 1982; Christie et al. 1987; Groenewegen et al. 1987, 1996; Gorelova and Yang 1997). Glutamatergic input to the VTA increases the activity of dopaminergic cells and enhances dopamine release in the NAC (Tzschentke and Schmidt 2000; Tzschentke 2001). Antagonism of the NMDA and mGlu5 receptors prevents the induction of sensitization by repeated social defeat, suggesting that social defeat stress is mediated by glutamatergic activity, possibly in the amygdala and PFC, which in turn, affects dopamine cells in the VTA and dopamine release in the NAC (Yap et al. 2005).

Repeated stress in rats and mice has also been shown to increase baseline plasma corticosterone levels (Covington and Miczek 2001; Keeney et al. 2001), and corticosterone may play a role in sensitization. Adrenalectomy (Rivet et al. 1989) and antibody inactivation of corticotropin releasing

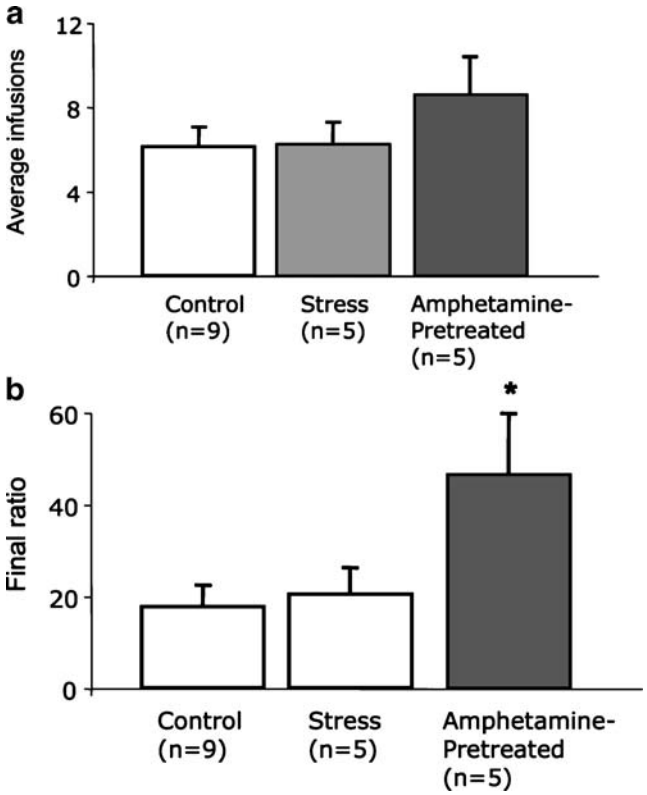

Fig. 9 Intravenous cocaine self-administration performance on a progressive ratio schedule of reinforcement. **a** Average infusions during the last 2 days on a PR schedule. *Bars* represent average number of infusions as a function of treatment during self-administration of cocaine on a PR schedule. Amphetamine-pretreated mice show slightly higher levels of cocaine intake relative to stress and control mice, although this effect is not significant. **b** Average "break point" reached during the last 2 days on a PR schedule. *Bars* represent the mean final ratio achieved while self-administering cocaine on a progressive ratio schedule. Amphetamine-pretreated mice have significantly higher break points than stress and control mice (*asterisks*: $P<0.05$)

factor (CRF) (Cole et al. 1990) prevent sensitization to amphetamine, while administration of CRF (Cador et al. 1993) or corticosterone (Deroche et al. 1992) produces sensitization. Corticosterone enhances glutamate-induced burst firing in rat midbrain dopaminergic neurons, whereas adrenalectomy significantly reduces the firing rate of dopaminergic cells in the VTA (Overton et al. 1996). It is plausible that corticosterone released during social defeat stress may affect the physiological reactivity of dopamine neurons by changing the response elicited by glutamate. However, resident rats and mice also show large increases in corticosterone after an aggressive confrontation, and their locomotor activity neither becomes sensitized nor do they self-administer cocaine more frequently (Covington et al. 2005), suggesting that while corticosterone may play a role in sensitization, it may not be as critical as suspected. While fighting is stressful for both the winner and the loser of the fight, losing leads to increased c-*fos* activation in many more brain areas associated with behavioral arousal, stress, and anxiety than winning (Kollack-Walker et al. 1997).

Repeated exposure to experimenter-administered amphetamine resulted in increased cocaine self-administration during the acquisition phase, confirming previous findings in cocaine, amphetamine, and nicotine pretreated animals (Horger et al. 1990, 1992; Piazza et al. 1990). However, this potentiated drug-taking behavior diminishes after the acquisition phase, when the doses of cocaine are varied. It may be that after several days of cocaine self-administration, the control animals also undergo various neural adaptations and become sensitized, thereby, possibly increasing their drug intake to levels similar to amphetamine pretreated mice. The present data also show that amphetamine-pretreated mice have higher break points on a progressive ratio schedule of cocaine reinforcement, confirming and extending the current findings in the rat (Mendrek et al. 1998; Suto et al. 2003).

In rats that previously experienced social defeat, exposure to olfactory, visual, and auditory cues increases nucleus accumbens dopamine release, and previously defeated rats acquire intravenous cocaine self-administration in half the time than non-stressed rats do (Tidey and Miczek 1997). Defeat stress-induced sensitization increases cocaine self-administration and intake in rats (Covington and Miczek 2001). Rats that experience four social defeat episodes separated by 72 h show increased drug intake when compared to non-stressed control animals during a 24-h continuous access session. Defeat stress-sensitized rats also show higher "break points" to a low dose of cocaine when placed on a progressive ratio schedule of reinforcement (Covington and Miczek 2001). Surprisingly, repeated intermittent social defeat stress did not lead to increased cocaine self-administration, contrary to what is seen in socially stressed rats (Miczek and Mutschler 1996; Tidey and Miczek 1997; Covington and Miczek 2001; Covington et al. 2005). It seems that the effects of social defeat stress in this particular strain of mice are more subtle than they are in rats. It is also interesting to note that defeat stressed rats do *not* show higher levels of cocaine self-administration during acquisition, under a variable dose protocol, or under a progressive ratio schedule with 0.75 mg/kg/infusion of cocaine (Covington and Miczek 2001). Differences between stressed and non-stressed rats are only seen during a 24-h binge and during a progressive ratio with a low dose of cocaine (0.3 mg/kg/inf) (Covington and Miczek 2005). The difference seen between mice who show amphetamine-induced sensitization and mice that show defeat-induced sensitization during acquisition of cocaine taking may be attributed to differential processes governing the sensitized response, with possible points of divergence along the long and complicated neuronal cascade after repeated amphetamine and social defeat stress. It is only recently that we are

starting to see differences between psychostimulant- and stress-induced sensitization. The induction of sensitization due to social defeat is prevented by 2-methyl-6-(phenylethynyl)pyridine (MPEP), a non-competitive mglu5 receptor antagonist, yet MPEP does not inhibit the development of behavioral sensitization to amphetamine (Yap et al. 2005).

Outbred CFW mice may cope differently with stress than inbred mice. On the measure of social defeat-induced tolerance, there is a considerable degree of variability across mouse strains (Miczek and Thompson 1984). Genetic lines with the highest levels of intermale attack (i.e., wild and Swiss-CD1) have also been shown to have the highest levels of infanticide, interfemale attack, and maternal aggression, but also the lowest levels of anxiety-like behavior, compared to DBA/2 and C57/BL6N mice (Parmigiani et al. 1999). Exploratory behavior is lower and risk assessment behavior is markedly higher in DBA/2 and C57/BL6N mice compared to Swiss and wild genetic lines. The strain of mice used in the current study (CFW) is derived from the Swiss Webster line and are genetically similar to CD-1 mice. It may be that the CFW strain of mice does not perceive being defeated as being so intensely "stressful" compared to inbred strains. Previous work showing long-term tolerance after social defeat was done in $B6AF_1$ (Miczek et al. 1982) and DBA/2 (Rodgers and Randall 1985) mice [i.e., inbred strains that are less aggressive and possibly more anxious (Parmigiani et al. 1999)], thereby, possibly showing a more robust stress response. Parallel to the long-lasting analgesic effects in $B6AF_1$ and DBA/2 mice, enduring sensitization after defeat may be observed in these mice, comparable to what is seen in Long–Evans rats (Nikulina et al. 2004; Covington et al. 2005). The sensitized response in CFW mice disappears 30 days after the last defeat, coinciding with the time period in which these mice intravenously self-administer cocaine.

The present findings indicate that both amphetamine and social defeat stress can result in behavioral sensitization to the locomotor-stimulating effects of amphetamine in mice, and amphetamine sensitization leads to increased drug taking, as evidenced by potentiated cocaine intake during acquisition and higher "break points" on a PR schedule. Mice are an ideal species for studying the relationship between sensitization and subsequent intravenous drug self-administration, as transgenic mice can be used in situations where there are no pharmacological tools available for a particular mechanism of study. Further investigation of the cocaine self-administration behavior of various strains of mice after repeated social defeat stress would lend more light on the relationship between defeat stress sensitization and subsequent drug taking and would clarify to what degree interstrain variability is involved in the changes in cocaine-taking behavior after psychostimulant- and stress-induced sensitization.

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