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Reinstatement of MDMA (ecstasy) seeking by exposure to discrete drug-conditioned cues

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Abstract

The widely used recreational drug MDMA (ecstasy) supports self-administration in animals, but it is not known whether MDMA-associated cues are able to reinstate drug seeking in a relapse model of drug addiction. To assess this possibility, drug-naïve rats were trained to press a lever for MDMA infusions (0.30 mg/kg/infusion, i.v.) paired with a compound cue (light and tone) in daily 2 h sessions. Responding was reinforced contingent on a modified fixed-ratio 5 schedule of reinforcement. Conditioned cue-induced reinstatement tests were conducted after lever pressing was extinguished in the absence of MDMA and the conditioned cues. Conditioned cues reinstated lever pressing after extinction, and the magnitude of reinstatement was positively correlated with the level of responding during MDMA self-administration. These results show for the first time that conditioned cues can trigger reinstatement of MDMA-seeking behavior in rats, and that individual differences in the pattern of MDMA self-administration can predict the magnitude of reinstatement responding.

Keywords: Addiction; Cue; MDMA; Reinstatement; Relapse; Self-administration

1. Introduction

The widely used amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) is a so-called "club" or "designer" drug that has an amphetamine-like action at monoamine transporters (Nash and Brodkin, 1991), resulting in increased synaptic levels of serotonin and dopamine (Gough et al., 1991). Although the neurobehavioral effects of MDMA can be distinguished from those of amphetamine, MDMA appears to share several important properties with other highly addictive psychostimulants. In fact, several animal models of drug reinforcement and addiction, including conditioned place preference (Marona-Lewicka et al., 1996; Meyer et al., 2002), a rat runway procedure (Wakonigg et al., 2003), behavioral sensitization (Ball et al., 2006; Kalivas et al., 1998), and drug self-administration (Beardsley et al., 1986; Ratzenboeck et al., 2001), have provided evidence of MDMA's positive reinforcing properties and potential for abuse.

In contrast, human MDMA use appears to be, for the most part, recreational or casual (Meilman et al., 1990; Solowij et al., 1992). It is not surprising, therefore, that many users believe MDMA is a safe drug with relatively low abuse potential (Murphy et al., 2006). Indeed, progressive-ratio self-administration studies in rhesus monkeys have shown that MDMA is a weaker reinforcer compared to the psychomotor stimulants methamphetamine and cocaine (Lile et al., 2005; Wang and Woolverton, 2007). Nonetheless, there are data to suggest that a minority of individuals find their MDMA use problematic (Topp et al., 1999) or meet the *Diagnostic and Statistical Manual of Mental Disorders* criteria for dependence (Cottler et al., 2001). Furthermore, recent reports suggest that, for a subgroup of users, MDMA is consumed in large amounts (Gouzoulis-Mayfrank et al., 2005; McCann et al., 2005), sometimes as much as 25 pills in a single session (Parrott, 2005). Taken together, these data suggest that although many MDMA users do not fit the profile of a compulsive user,

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there is a high degree of individual variability in the pattern of MDMA use and in the drug's potential for abuse (Soar et al., 2006).

To explore further the addictive potential of MDMA, we used an animal model of drug addiction known as the reinstatement model (Stewart and de Wit, 1987). This paradigm models the most challenging problem in clinical drug treatment—the high rate of relapse among addicts (Mendelson and Mello, 1996). In this model, the same stimuli that induce craving and relapse in humans, such as exposure to the drug, drug-associated cues, or a stressor (Jaffe et al., 1989;O'Brien et al., 1992; Sinha et al., 1999), are used to reinstate extinguished drug-seeking behavior in animals with a history of drug self-administration. Although these stimuli have been reported to reinstate responding for several drugs of abuse (Lê and Shaham, 2002; Shalev et al., 2002), no studies to date have assessed whether this holds true for MDMA. To test this possibility, we used the reinstatement model to assess whether discrete cues previously paired with intravenously self-administered MDMA would reinstate extinguished MDMA-seeking behavior in rats. In addition, we assessed how individual rats' self-administration behavior was related to subsequent relapse vulnerability.

2. Materials and methods

2.1. Animals

Data were collected from experimentally naïve adult (3–4 months of age) male Sprague–Dawley rats ($n=14$), bred from animals supplied by Harlan Industries (Indianapolis, IN), and housed individually in a colony room maintained on a 12 h light cycle from 7:30 AM to 7:30 PM. Animals were allowed free access to water and were maintained at ~85% of free-feeding body weight via restricted diet throughout experiments with the exception of a period before and after surgery during which animals were given free access to food. Free-feeding body weight of the animals at the commencement of procedures was 270–385 g. All experiments were conducted during the light cycle. All procedures were performed in compliance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council of the National Academies, 2003), and approved by the Indiana University Institutional Animal Care and Use Committee.

2.2. Sucrose training

Experimental sessions were conducted in an operant box (area = 30 × 30 cm) containing one response lever, a food well, one house light, two cue lights, and a tone generator, housed within a sound-attenuating chamber. Rats were first trained to press the lever for 0.075 ml of a 10% sucrose solution contingent upon a fixed-ratio 1 (FR1) schedule of reinforcement in daily 30 min sessions. No programmed stimuli accompanied the delivery of the sucrose solution. After lever-pressing behavior was established, the reinforcement schedule gradually increased to FR5. An FR5 schedule was used because we have found it to be effective in eliciting CS-induced cocaine reinstatement (e.g., Sun and Rebec, 2003). When rats received 60 reinforcements in one session on the FR5 schedule they progressed to surgery. This criterion was met following three to eight sessions for all rats.

2.3. Surgery

Following a subcutaneous (s.c.) injection of atropine sulfate (0.05 mg/kg), animals were anesthetized with intramuscular injections of ketamine HCl (90 mg/kg) and xylazine HCl (10 mg/kg), with supplemental injections as needed. Animals were implanted with a jugular catheter constructed from polyethylene tubing (PE10, PE50, and PE160; Fisher Scientific, Pittsburgh, PA) and a 22 gauge cannula-guide connector assembly (Plastics One, Roanoke, VA). The catheter was routed subcutaneously and mounted to the skull with dental cement. Animals were allowed a minimum of 3 days of free feeding following surgery. Catheters were flushed with 3 USP units of heparin sodium twice daily, and 1.0 mg of gentamycin was administered once daily for 10 days following surgery to prevent infection. During the period of MDMA self-administration, catheter patency was evaluated by injecting 0.1 ml Brevital (1%) as necessary. Loss of muscle tone within 5 s after injection indicates a patent catheter. Seven animals that began self-administration training were subsequently removed from the experiment due to catheter-related problems before completion of 14 sessions.

2.4. MDMA self-administration sessions

Following recovery from surgery, rats began a series of 14 daily, 2 h MDMA self-administration sessions, parameters that are within a standard range for drug self-administration studies in rats (Lê and Shaham, 2002; Shalev et al., 2002). (±)-MDMA (National Institute on Drug Abuse, Bethesda, MD) was dissolved in 0.9% saline at a concentration of 1.0 mg/ml (salt). Rats were placed on a modified FR5 schedule under which the first lever press resulted in an intravenous infusion of 0.075 mg of MDMA delivered over 4 s in a volume of 0.075 ml accompanied by conditioned stimuli (CS), which consisted of a tone + light compound stimulus presented for 4 s. Delivery of the drug and CS was followed by a 6 s time-out period signaled by illumination of the house light. During MDMA infusions and time-outs responding was recorded but had no programmed consequences. After the first infusion, MDMA infusions and presentations of the CS were contingent upon an FR5 schedule of reinforcement. Based on the body weight that was maintained throughout self-administration sessions, the mean dose for all rats was 0.30 mg/kg/infusion. The largest and smallest rats deviated by only ~0.04 mg/kg/infusion from this mean. This self-administration dose of MDMA was chosen because it is within a range of doses reported to support the highest levels of operant responding (Cornish et al., 2003; Ratzenboeck et al., 2001; Schenk et al., 2003). Although the daily self-administration sessions were not consecutive [mean (±S.E.M.) sessions/week = 5.10 (±0.36)], we found no relationship between peak responding and time after the last session.

2.5. Extinction sessions

Extinction sessions began on the day following the last self-administration session. During each daily 1 h extinction session, there were no programmed consequences for lever pressing. Extinction sessions continued until the total presses for a session were ≤20% of the mean number of total presses during self-administration sessions 9–14. If this ≤20% value was greater than five total presses, lever pressing was extinguished to five or fewer total presses. This criterion was met within five sessions for all animals.

2.6. Reinstatement sessions

Following extinction, animals ($n=7$) underwent 1 h CS-induced reinstatement sessions. Reinstatement sessions began with a 4 s non-contingent presentation of the CS and subsequent 6 s time-out marked by the house light. Thereafter, CS presentations were contingent upon an FR1 schedule of reinforcement. Following any 10 min time interval without a lever press, an additional non-contingent CS was presented. At no time during the session did animals receive MDMA. Lever presses during CS-induced reinstatement sessions were compared to the preceding extinction session by means of a one-tailed repeated measures *t*-test.

3. Results

3.1. MDMA self-administration

Fig. 1A shows the mean response rates for each of the 14 self-administration sessions. Animals acquired MDMA self-administration as determined by means of a one-tailed repeated measures *t*-test comparing responses/hour during the last self-administration session with responses during the last extinction session [$t(6)=2.00$, $p<0.05$]. Nonetheless, there was considerable variability in self-administration behavior both between animals and within individual animals across sessions. Mean (±S.E.M.) infusions earned on the last five consecutive self-administration sessions were 6.43 (±3.54), 10 (±4.92), 7.57 (±3.43), 7.57 (±3.39), and 9.71 (±4.72), respectively. The median number of infusions earned for each of the last five self-administration sessions remained constant at 3. The ranges between smallest and largest number of infusions for the last five consecutive self-administration sessions were 26, 29, 22, 26, and 31, respectively.

3.2. CS-induced reinstatement

The mean (±S.E.M.) response rate during the extinction session prior to CS-induced reinstatement sessions was 1.29

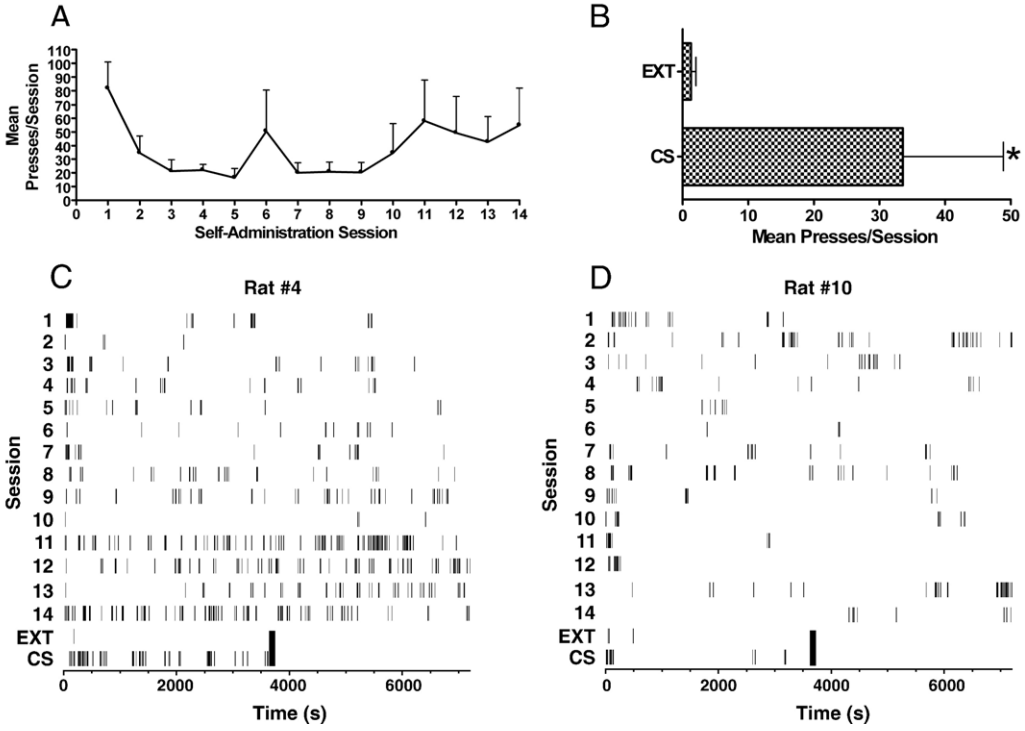

Fig. 1. (A) Mean lever presses for each of 14 daily 2 h MDMA self-administration sessions. Rats ($n=7$) were responding for intravenous infusions of 0.075 mg of MDMA on a modified FR5 schedule of reinforcement. Error bars represent S.E.M. (B) Mean lever presses during CS-induced reinstatement session (CS) compared to the prior extinction session (EXT). Extinction and reinstatement sessions were 1 h in length. CS-induced reinstatement sessions began with an initial non-contingent presentation of the CS; thereafter, responding was reinforced only by the CS contingent upon an FR1 schedule of reinforcement. Following any 10 min time interval without a lever press, an additional non-contingent CS was presented. Error bars represent S.E.M. *$p<0.05$ compared to prior extinction session. (C and D) Raster displays of lever pressing in two rats with different rates and patterns of responding. Each short vertical line above the time axis represents a lever press. Labels to the left of the raster indicate self-administration day (1–14) and extinction session (EXT) prior to CS-induced reinstatement session (CS). The thick vertical lines mark the end of extinction and reinstatement sessions.

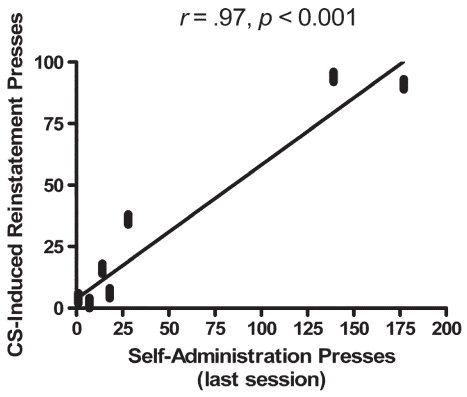

Fig. 2. Regression slope for the correlation between MDMA self-administration and CS-induced responding in individual rats. There was a very strong positive correlation between the response rate of rats during the last self-administration session and their total presses during CS-induced reinstatement sessions ($r=0.97$, $p<0.001$).

(±0.75). As Fig. 1B illustrates, the response rate increased significantly to 33.57 (±15.33) during CS-induced reinstatement sessions [$t(6)=2.17$, $p<0.05$]. Fig. 1C and D shows raster displays of lever pressing in two rats with different rates and patterns of responding for MDMA and their subsequent extinction and reinstatement responding. Despite variability in the level of responding between individual animals during CS-induced reinstatement sessions, there was a strong positive correlation between the mean response rate of rats during the last five self-administration sessions and their responding during CS-induced reinstatement sessions ($r=0.88$, $p<0.01$). As Fig. 2 illustrates, a comparison of response rates on the last self-administration day to responding during reinstatement sessions showed a nearly perfect positive correlation ($r=0.97$, $p<0.001$). Thus, relapse-related variability was directly related to magnitude of responding during self-administration.

3.3. Additional analyses

On the last self-administration day, we compared time-out responding following the first MDMA infusion to time-out responding following the last MDMA infusion and found no significant difference [$t(6)=0.00$, $p=1.00$], arguing against non-specific behavioral activation as a cause of lever pressing. In addition, we injected a subset of rats ($n=6$) with 5.0 mg/kg MDMA, a dose known to elicit behavioral activation (Ball et al., 2003, 2006; Ball and Rebec, 2005), two days after CS-induced reinstatement and monitored lever pressing (lever presses had no programmed consequences during these sessions). This procedure did not induce lever-pressing behavior [no significant difference from the level of responding during extinction; $t(5)=0.67$, $p=0.27$], further supporting our conclusion.

4. Discussion

These results not only support and extend earlier studies showing that rats will intravenously self-administer MDMA (for review, see De La Garza et al., 2007), but also indicate that discrete MDMA-paired cues can reinstate extinguished MDMA-seeking behavior. Although the majority of previous MDMA self-administration studies in rats used either FR1 or FR2 schedules of reinforcement, the overall drug intake we report is very similar to these studies, which noted average infusion rates between 3 and 13 infusions/session at doses similar to ours (Cornish et al., 2003; De La Garza et al., 2007; Ratzenboeck et al., 2001; but see Daniela et al., 2004; Schenk et al., 2003). Thus, the increase in operant requirements did not appear to diminish responding for MDMA.

Because of the large between-subject variability in responding that we observed, one could argue that all subjects did not acquire MDMA self-administration. It is noteworthy, however, that despite this variability, all rats showed a decrease in responding during extinction sessions and an increase in responding during CS-induced reinstatement sessions. Further, all animals met our extinction criteria, and there was a significant decrease in responding during extinction compared to the last self-administration session (see Results). Thus, even in the lowest responder (mean=4 presses/session for the last 6 sessions), presses during extinction decreased to 0. The highest responder (mean=145 presses/session for the last 6 sessions) decreased to 5 presses/session during extinction. In both cases, reinstatement responding was at least 50%. In other words, the same pattern of responding (i.e., a decrease during extinction and an increase during reinstatement) was evident in all subjects, only the magnitude differed. Because we used a within-subjects design, which accounts for individual differences, we were able to demonstrate a significant effect of both extinction and CS exposure on MDMA seeking, despite large between-subject variability.

In contrast to CS presentations, passive MDMA injections (5 mg/kg) did not significantly increase lever pressing during extinction. This result provides strong evidence that the lever pressing during CS-induced reinstatement sessions does not reflect non-specific behavioral activation (as opposed to goal-directed behavior), because this dose of MDMA induces robust locomotor activation (present results; Ball et al., 2003, 2006; Ball and Rebec, 2005). Interestingly, this finding also suggests that, in contrast to other drugs of abuse (Lê and Shaham, 2002; Shalev et al., 2002), drug exposure may not reinstate MDMA seeking following extinction. Although no previous MDMA reinstatement studies have been reported, De La Garza and colleagues (De La Garza et al., 2007) found that when saline was substituted for MDMA on two consecutive daily self-administration sessions, responding decreased and did not return to pre-saline levels during subsequent sessions when MDMA was again available for self-administration. In contrast to this finding, Schenk and colleagues (Daniela et al., 2006; Schenk et al., 2003) reported that, following decreased responding during saline-substitution sessions, re-exposure to MDMA reinstated lever pressing. Several important methodological differences between these latter studies and our test for non-specific lever pressing preclude direct comparison of the results, most notably, in the Schenk studies: 1) a passive I.V. drug infusion was the reinstating stimulus, and subsequent responding was maintained with I.V. infusions of MDMA and 2) all self-administration sessions commenced with a passive infusion of MDMA. Thus, it is clear that future testing with a

range of MDMA doses will be necessary to determine whether drug exposure can reinstate MDMA seeking, especially given the variability in MDMA self-administration that we (present results) and others (De La Garza et al., 2007) have observed.

It was recently reported that animals' responding during cocaine-primed reinstatement sessions was positively related to several addiction-like behaviors, including persistence in responding for cocaine during preceding self-administration sessions (Deroche-Gamonet et al., 2004). Similarly, our correlational results suggest that the propensity to self-administer MDMA is a very good predictor of the magnitude of responding during CS-induced reinstatement sessions. In agreement with these results, rats that display higher rates of cocaine self-administration are more vulnerable to both drug- (Baker et al., 2001; Sutton et al., 2000) and CS- (Sutton et al., 2000) induced reinstatement of cocaine seeking. Importantly, differential responding for MDMA in the present study does not appear to be due to a global difference in hyperactivity or impulsivity, because extinction responding was similarly low in all animals. Additionally, the especially high rates of lever pressing in two animals occurred mainly in the last four to five self-administration sessions, suggesting that differential neurobehavioral alterations developed over the course of several sessions (see Fig. 1C). Because our experimental procedures included tests of catheter patency and maintenance of body weight, this latter result was not due to decreased catheter viability or an increase in body weight across self-administration sessions. De La Garza et al. (2007) reported a remarkably similar phenomenon, in which only 1 of 5 rats displayed a large acceleration of lever pressing for MDMA that began on the 13th day of daily MDMA self-administration sessions. Together with our results, this suggests that, compared to the majority of subjects that display relatively low rates of MDMA self-administration, a few are especially vulnerable to the reinforcing and incentive motivational effects of MDMA, a conclusion that appears consistent with reports in the human literature (see Introduction).

Although it now becomes important to investigate the neural mechanisms underlying MDMA relapse, inactivation of any one of several interconnected limbic regions, including amygdala, nucleus accumbens, hippocampus, medial prefrontal cortex, or orbitofrontal cortex has been shown to block either discrete or contextual cue-induced reinstatement of cocaine seeking or both in rats (Fuchs et al., 2004a,b, 2005; McLaughlin and See, 2003; Sun and Rebec, 2003). Recently, this circuitry has been extended to dorsal striatum, an area shown to be critical for both discrete and contextual cue-induced cocaine seeking after extinction, as well as contextual cue-induced cocaine seeking following abstinence (Fuchs et al., 2006). Future studies will be necessary to determine the extent to which striatal and related limbic regions are involved in CS-induced relapse to MDMA and their overlap with the circuits driving cocaine relapse.

5. Conclusion

The present results provide the first evidence that discrete MDMA-associated cues reinstate extinguished MDMA-seeking behavior in animals. In addition, these findings show remarkable homology with two important observations in the clinical literature: 1) a minority of individuals are more vulnerable to compulsive drug use than most following recreational exposure to drugs and 2) the longer an individual uses drugs, the more prominent these differences become (Uhl, 2004). In this regard, MDMA may be a useful drug for the study of individual differences in vulnerability to drug abuse, and in particular, to conditioned cue-induced relapse.

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