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Continuous exposure to dizocilpine facilitates escalation of cocaine consumption in male Sprague-Dawley rats

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Abstract

Background—Although the escalation of cocaine consumption is a hallmark of cocaine dependence, the neurobiological mechanisms that underlie this change in behavior are not well understood.

Methods—This study used an extended access version of the drug self-administration procedure to explore how N-methyl-D-aspartate (NMDA) receptors are involved in escalation of cocaine consumption. Male Sprague-Dawley rats ($n = 59$) were first trained to self-administer cocaine (0.33 mg/infusion, i.v.) under a fixed-ratio 1 (FR1) schedule of reinforcement. After training, rats were implanted with subcutaneous osmotic minipumps filled with vehicle or the non-competitive NMDAR antagonist, dizocilpine (0.2 or 0.4 mg/kg/d), and subsequently allowed to self-administer cocaine in 2 h or 6 h self-administration sessions.

Results—In the 6 h groups, vehicle-treated rats escalated cocaine self-administration across 15 self-administration sessions; rats treated with dizocilpine escalated cocaine self-administration at a greater rate and to a greater degree. Rats that self-administered cocaine during 2 h sessions did not escalate consumption of cocaine under any treatment condition. Discontinuation of dizocilpine treatment in the 6 h access condition led to a substantial decrease in cocaine consumption, down to pre-escalation levels, and then control rates of escalation thereafter. Despite large differences in intake under the FR1 schedule, post-escalation break point under a progressive ratio schedule of reinforcement did not differ between groups.

Conclusion—These data suggest that glutamate tone through NMDA receptors can play a dynamic role in regulating cocaine intake and escalation of consumption.

Keywords

escalation; self-administration; cocaine; NMDA; dizocilpine

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The author of this paper designed the study, wrote the protocol, collected and oversaw collection of the data, completed the statistical analyses, and wrote the manuscript.

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1. INTRODUCTION

Cocaine addiction remains a persistent public health problem. It is estimated that 37.2 million persons aged 12 and older living in United States households have consumed cocaine at least once in their lifetime. Based upon their survey responses, approximately one million of those people might qualify for a DSM-IV diagnosis of cocaine dependence or abuse (Substance Abuse and Mental Health Services Administration, 2011). Of the seven criteria listed for a diagnosis of cocaine dependence, most are defined or are exacerbated by an increase in cocaine consumption (e.g., tolerance; withdrawal; substance taken in larger amounts or over a longer period than was intended; persistent desire or unsuccessful attempts to cut down or control substance use; American Psychiatric Association, 2000). Thus, understanding the mechanisms that control escalation of consumption is critical to understanding cocaine dependence.

Humans increase cocaine consumption by increasing both the amount of cocaine consumed on any given episode and their frequency of use (Gawin, 1991). Rodent drug self-administration procedures have been modified to model this important aspect of cocaine dependence (e.g., Ahmed and Koob, 1998; Fitch and Roberts, 1993; Mantsch et al., 2001; Tornatzky and Miczek, 2000). In one such model, rats that are given long daily access to cocaine (6 h) gradually increase their rate of intake over sessions, an effect not observed in rats given short, 1 h daily access to cocaine (Ahmed and Koob, 1998).

Despite cocaine's efficacy as a dopamine transport inhibitor, large or long-lasting escalation-specific changes in dopamine function have not been observed with this long-access procedure (i.e., Ahmed and Koob, 1998). For example, rats given short and long access to cocaine show no differences in the direct threshold-lowering effect of an acute infusion of cocaine in an intracranial self-stimulation procedure (Ahmed et al., 2002) or basal and cocaine-elicited changes in dopamine levels measured via microdialysis (Ahmed et al., 2003). Relative to cocaine naïve rats, rats with long access to cocaine are *less* likely than rats with short access to show significant changes in transporter density or dopamine receptor number (Ben-Shahar et al., 2006, 2007). Although rats with long access, but not short access, show a large (~70%) reduction in D2 receptor mRNA in the medial prefrontal cortex, protein is reduced by only ~10% under these conditions (Briand et al., 2008).

We have been interested in the role of glutamate in escalation of cocaine consumption, in particular the role of the N-methyl-D-aspartate (NMDA) glutamate receptor subtype. Consistent with reports of N-methyl-D-aspartate receptor (NMDAR) antagonist disruption of acquisition of cocaine self-administration (Schenk et al., 1993) and prevention of cocaine conditioned place preference (Cervo and Samanin, 1995) and locomotor sensitization (Karler et al., 1989), we initially hypothesized that continuous administration of an NMDAR antagonist during cocaine self-administration would prevent escalation of cocaine consumption. Surprisingly, continuous infusion of the competitive NMDAR antagonist, LY235959, facilitated escalation of cocaine consumption in rats with 6 h access to cocaine, lead to apparent "upward" shifts in the cocaine dose-response curve (Allen et al., 2007a) and increased responding for cocaine under a PR schedule of reinforcement (Allen et al., 2007b).

The present study had two aims. The first aim was to provide convergent evidence for a role of the NMDAR in the escalation of cocaine self-administration by treating rats with a different NMDAR antagonist during the escalation phase of the experiment, here the non-competitive NMDAR antagonist, dizocilpine. The second aim was to determine the consequence of discontinuation of continuous NMDAR blockade on escalated cocaine self-administration. The results reported here demonstrate that NMDARs can play a dynamic role in regulating cocaine intake and escalation of consumption.

2. MATERIALS AND METHODS

2.1 Animals

Fifty-nine male, Sprague-Dawley rats trained to self-administer cocaine for an average of 15.3 ± 0.2 sessions (mean $\pm$ standard error of the mean, throughout, unless otherwise noted; range, 14 – 18 sessions) were used in the first experiment. Rats were purchased from Harlan (Indianapolis, IN) and housed at the University of Colorado, Denver. Rats weighed 275 – 324 g upon arrival. A 12 h light/dark cycle was programmed in each colony, with lights on at 7:30 AM. Rats lived in the animal colony for at least one week before intravenous catheters were surgically implanted. Food and water were available *ad libitum* during this habituation period and for one week following catheter implantation. Water was restricted to 30 mL/d during training in the self-administration procedure and the subsequent experiments. An additional eight rats were used in a dizocilpine discontinuation experiment (see below). These rats were similar to the other rats used in the study in all ways with the exception that they had prior exposure to acute intravenous infusions of butorphanol tartrate during a conditioned place preference experiment (3.2 mg/kg, 2 – 4 infusions). All experiments described herein were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

2.2 Catheter Placement and Cocaine Self-Administration Training

Intravenous catheters constructed in the laboratory were surgically implanted under ketamine (100 mg/kg, i.m.)/xylazine (10 mg/kg, i.m.) anesthesia. Rats received acetaminophen in their drinking water (20 mg/ml) for two days post-surgery. Rats recovered from surgery for at least one week before self-administration training. Catheters were flushed with 0.3 ml of bacteriostatic 0.9% sodium chloride solution containing 16.7 USP units/ml heparin, before and after each self-administration session and during recovery.

Rats self-administered cocaine in Plexiglas and metal experimental chambers (29×24×21 cm) housed within sound-attenuating cabinets (Med Associates, Incorporated; St. Albans, VT), described previously (Allen et al., 2007a; 2007b). All behavioral events were monitored and controlled by a personal computer using MED-PC for Windows software (Med Associates, Incorporated; St. Albans, Vermont). Rats were trained in 2 h sessions, 5 days/week. Each session began with the onset of a stimulus light located over a lever on the right side of the operant chamber and the extension of two retractable levers. Responses on the right side lever produced an intravenous infusion of cocaine (0.33 mg over 6 s) according to a fixed ratio (FR) 1 schedule of reinforcement. The simultaneous onset of a tone (2,900 Hz)-house light (100 mA) conditioned stimulus complex (20 s) signaled the initiation of drug delivery. During the 20 s post reinforcement interval, responses on the right lever did not activate the pump. Responses on the left lever had no programmed consequences.

2.3 Progressive Ratio Schedule of Reinforcement

Rats responded for cocaine under a PR schedule of reinforcement (Richardson and Roberts, 1996) twice during training, the latter of which (after all FR1 training sessions) served as the pre-escalation PR baseline session. Under this schedule, the delivery of each cocaine infusion resulted in an increase in the response requirement for a subsequent infusion, such that the response requirements for the first 30 infusions were 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, 1102, 1347, 1646, and 2012. Sessions ended when rats reached the “break point,” defined as the last response requirement completed prior to a one h period in which no cocaine infusions were earned.

2.4 Alzet osmotic minipump procedure

For the escalation experiment, model 2ML4 Alzet osmotic pumps (Alza Corporation, Palo Alto, CA) were prepared to deliver vehicle, 0.2, or 0.4 mg/kg/d dizocilpine for 28 days. After self-administration training and the PR baseline, osmotic pumps were surgically implanted subcutaneously at each rat's left dorsal flank under ketamine (50 mg/kg, i.m.)/xylazine (10 mg/kg, i.m.) anesthesia. Forty-eight hours later, rats began the escalation phase of the experiment in which they self-administered cocaine during 15 weekday sessions for either 2 or 6 h. The day after escalation session 15, responding under the PR schedule was measured in all rats. For the dizocilpine discontinuation experiment, an additional eight rats trained to self-administer cocaine (14 – 16 training sessions) were implanted with model 2ML1 osmotic pumps (Alza Corporation, Palo Alto, CA) prepared to deliver 0.4 mg/kg/d dizocilpine for seven days. These rats completed the same escalation procedure as rats implanted with 2ML4 osmotic pumps with the exception that responding under the PR schedule of reinforcement was measured after escalation sessions 5, 10 and 15.

2.5 Data Analysis

Data was analyzed using SPSS for Windows, version 21.0. Repeated measures analysis of variance (ANOVA) was used throughout. When the assumption of sphericity was violated for a particular repeated measures analysis, as revealed by Mauchly's test statistic, tests of significance were based on the more conservative Huynh-Feldt corrected degrees of freedom. The symbol, ^a, indicates Huynh-Feldt corrected values throughout the text. When significant main and interaction effects were revealed by repeated-measures ANOVA, tests for between-groups significance were made using one-way ANOVA and/or t-tests. For the escalation data, mg/kg cocaine intake was used as the dependent measure. The number of infusions associated with break point was also used as a dependent measure (PR schedule). Table 1 lists the number of subjects included in each statistical analysis.

2.6 Exclusions and exceptions

Two of the 59 rats implanted with 2ML4 osmotic pumps (escalation experiment) had baseline cocaine intake rates greater than three standard deviations above mean baseline cocaine intake for this group of rats (25.2 ± 4.0 mg/kg for $n=59$, mean $\pm$ standard deviation; 2 h/vehicle, $n=1$, 40 mg/kg; 2h/0.4 DZ, $n=1$, 37.2 mg/kg), and they were excluded from the final data analysis. Only the rats that completed a particular phase of the experiment were included in the statistical analysis of that experimental phase. Table 1 lists the number of subjects included in each statistical analysis.

2.7 Drugs

The National Institute on Drug Abuse generously supplied cocaine hydrochloride. Cocaine was dissolved in a 0.9% sodium chloride solution and filtered through a disposable Nalgene filtration unit (0.2 μ m surfactant-free cellulose acetate membrane). Heparin sodium was then added to the filtered solution to produce a final concentration of 1.67 USP units heparin /ml. Dizocilpine hydrogen maleate (the (+) isomer of MK-801) was purchased from Sigma-Aldrich (St. Louis, MO) and dissolved in sterile water.

3. RESULTS

3.1 Baseline

Body weight, baseline cocaine intake (FR1 schedule), and baseline break point-associated infusions earned under the PR schedule are presented, by experimental condition, in table 2. There were no statistically significant between group differences revealed by ANOVA for any of the variables.

3.2 Access condition

As previously reported, vehicle-treated rats that self-administered cocaine in 6 h sessions gradually escalated consumption of cocaine whereas vehicle-treated rats in the 2 h access condition did not (figure 1). The 6 h/vehicle-treated rats increased their consumption of cocaine by approximately 36% over 15 6 h sessions, from 60.9 ± 1.4 mg/kg to 82.7 ± 3.3 mg/kg. RMANOVA revealed a significant main effect of session [$F(14,112) = 9.932$, $P < 0.001$] and post hoc pair wise comparisons revealed that cocaine intake at session one was significantly lower than cocaine intake at all sessions except 2, 6, 7, and 11 ($p < 0.05 - 0.001$). Repeated measures ANOVA for the 2 h/vehicle group also revealed a main effect of session [$F(14,84) = 2.447$, $P < 0.05$], however, post hoc pair wise comparisons revealed that intake at session one was significantly lower than intake at sessions 3, 5, and 10 only. Further, there were no significant differences in intake between the baseline 2 h session (26.4 ± 1.1 mg/kg) and any escalation session (range = $24.1 \pm 0.8 - 28.3 \pm 1.6$ mg/kg) for this group of rats.

3.3 Dizocilpine treatment

Figure 1 (top panel) shows daily intake data from rats that self-administered cocaine during 6 h sessions while exposed to continuous subcutaneous infusion of vehicle, 0.2, or 0.4 mg/kg/d dizocilpine (open symbols). Rats treated with 0.4 mg/kg/d dizocilpine increased cocaine intake by approximately 38% after only five escalation sessions, from 71.5 ± 3.4 mg/kg to 98.9 ± 6.9 mg/kg. Repeated measures ANOVA revealed significant main effects of session, dose, and a session by dose interaction [$F(8, 84) = 2.060$, $P < 0.05$] when data from sessions 1 – 15 were analyzed. Significant between-group differences in cocaine intake at each session, including session one, were revealed by one-way ANOVA. Post-hoc comparisons revealed that the 0.4 mg/kg/d dizocilpine-treated rats self-administered significantly more cocaine each session than the other two groups ($p < 0.01 - p < 0.001$).

Dizocilpine did not affect the rate of cocaine consumption in the same way under 2 h access conditions (figure 1, top panel, filled symbols). A repeated measures ANOVA of cocaine intake data from the 2 h access groups revealed a main effect of session [$F(9,170) = 9.429$, $P < 0.001$], but no main effect of dose or session by dose interaction. The results of post-hoc pair wise comparisons for session seemed to reflect the observation that rate of intake tended to vary around the mean control rate of intake (i.e., the rate during the baseline session) in all groups.

The bottom panel of figure 1 presents cumulative intake data for rats in the 2 h and 6 h conditions. A repeated measures ANOVA of cumulative intake data from rats in the 2 h condition revealed a main effect of session [$F(1,22) = 653.3$, $P < 0.001$], but no main effect of dose or dose by session interaction. In contrast, the same analysis for rats in the 6 h condition revealed main effects of session [$F(1,30) = 1708.136$, $P < 0.001$], dose [$F(2,21) = 16.521$, $P < 0.001$], and a dose by session interaction [$F(3,30) = 14.0$, $P < 0.001$]. One-way ANOVAs revealed significant differences in intake between groups at each session. Subsequent post hoc comparisons revealed that cumulative intake in the vehicle and 0.2 mg/kg/d dizocilpine conditions did not differ significantly at any session, but the 0.4 mg/kg/d dizocilpine treated group differed significant from vehicle treated rats at every session, and from 0.2 mg/kg/d dizocilpine treated rats at every session after session 2 ($p < 0.05 - p < 0.001$).

3.4 Dizocilpine discontinuation

Figure 2 (top panel) shows data from rats treated with 0.4 mg/kg/d dizocilpine through model 2ML1 (filled inverted triangles; $n=5$) or 2ML4 osmotic pumps ($n=5$, from previous experiment; open circles). Both groups showed a similar increase in the rate of escalation

during the first six escalation sessions. However, cocaine intake decreased from escalation session six to eight (i.e., one to three days beyond the expected life of the 2ML1 osmotic pumps) only in rats with a 2ML1 pump (i.e., when dizocilpine infusion expired). Repeated measures ANOVA with revealed a significant pump model by session interaction [$F(5,38) = 4.701$, $P < 0.01$] and significant between group differences were revealed for most sessions beyond session 7. Further, at session seven, cocaine intake in the 2ML1/6 h/0.4 mg/kg/d dizocilpine group did not differ significantly from session one cocaine intake in 2ML4/vehicle-treated rats [66.6 ± 8.2 mg/kg vs. 60.9 ± 1.4 mg/kg; two-tailed t-test] and the post-dizocilpine exposure rate of escalation in this group was indistinguishable from the rate of escalation in 2ML4/vehicle-treated rats (figure 2, bottom panel).

3.5 PR Schedule

A three-way repeated measures ANOVA (session by access by treatment) did not reveal any significant main or interaction effects when pre- and post-escalation break point associated infusions were analyzed as the dependent measure (data not shown).

3.6 Other variables

There were no significant effects of access condition, dizocilpine treatment, or session on responding during the CS or on the inactive lever revealed by repeated measures ANOVA of data from the escalation phase of the experiment. In addition, despite the significant increase in cocaine consumption, there was no change in mean body weight for rats that completed the study in the 2ML4 or 2ML1 6 h/0.4 mg/kg/d dizocilpine treatment conditions (e.g., for $n=5$ in the 2ML4/0.4 mg/kg/d dizocilpine group, body weight = 355.6 ± 4.5 g at baseline and 358.4 ± 4.7 g at escalation day 15).

4. DISCUSSION

In the present study, continuous infusion of 0.4 mg/kg/d dizocilpine facilitated escalation of cocaine consumption when rats self-administered cocaine in 6 h, but not 2 h sessions. The current data set extends our findings with the competitive NMDAR antagonist, LY235959, in important ways (Allen et al., 2007a; 2007b). First, we replicated our initial results with another class of NMDAR antagonist, here the non-competitive NMDAR antagonist, dizocilpine, providing convergent evidence for a role of the NMDAR in the facilitation of escalation of cocaine consumption. Second, we demonstrate the effect of discontinuing antagonist treatment after facilitation of escalation, revealing a dynamic role for the NMDAR in this process.

Together with our published data using the competitive NMDAR antagonist, LY235959 (Allen et al., 2007a; 2007b), these data demonstrate that two functionally-distinct, high affinity NMDAR antagonists can facilitate escalation of consumption, strongly implicating the NMDAR in this process. Continuous receptor blockade with compounds that have affinity for other glutamate receptors during escalation has not been examined to date. Thus, it is not known whether this effect is specific to the NMDAR or extends to inhibition of glutamate function more generally.

Rats injected with a bolus dose of dizocilpine self-administer cocaine at a lower rate under an FR1 schedule of reinforcement (with longer, but regular inter-infusion intervals) and attain a higher break point when responding under a progressive ratio (PR) schedule of cocaine reinforcement when compared with vehicle-injected controls (Allen et al., 2005, 2007b; Pierce et al., 1997; Hyttia et al., 1999). Thus, it was unexpected that dizocilpine treatment did not lead to increases in break point when rats responded under a progressive ratio schedule after the escalation phase of the experiment, an effect observed after

continuous treatment with LY235959, also (Allen et al, 2007b). Although no significant changes in break point were revealed by the statistical analysis performed in the present study, 0.4 mg/kg/d dizocilpine treated rats (in both the 2 and 6 h conditions) were the only groups to show mean increases in break point after the escalation session (data not shown). Given the reduced number of rats in these conditions by the time post-escalation break point was determined, and the variability in this measure, it is possible that we did not have enough power to detect this difference. Alternatively, it is possible that chronic NMDAR blockade does not reliably alter break point after escalation under these conditions. Indeed, increases in break point under extended access conditions in the absence of NMDAR blockade have been observed under some (Paterson and Markou, 2003), but not all (Liu et al., 2005) conditions, including negative findings from our own laboratory (present study and Allen et al., 2007b).

The decreased responding under an FR schedule and increased responding under a PR schedule of cocaine reinforcement produced by dizocilpine is a change that would be expected to occur by simply increasing the self-administered dose of cocaine (Allen et al., 2005; Richardson and Roberts, 1996). Cocaine dose can affect the rate and/or magnitude of escalation as well, with greater escalation produced when animals self-administer higher doses of cocaine (Mandt et al., 2012; Mantsch et al., 2001; Wee et al., 2007). These findings suggest the hypothesis that dizocilpine facilitates escalation by producing a condition functionally equivalent to increasing cocaine dose.

In addition to effects at the NMDAR, there is some evidence that dizocilpine can bind with high affinity to the high affinity state of the dopamine D2 receptor (Seeman et al., 2005). An agonist action of dizocilpine at D2 receptors would potentiate cocaine's effects (Caine et al., 1999; Barrett et al., 2004). However, LY235959 is a selective and competitive NMDAR antagonist from a different functional class (Schoepp et al., 1991) and also produces this same facilitation of escalation. Thus, although an action at D2 receptors might contribute to effects observed with dizocilpine, the most parsimonious explanation for our data is that facilitation of escalation is mediated by an antagonist action at NMDARs.

It is also noteworthy that a significant interaction between escalation session and dizocilpine dose was observed in the present study: that is, rats treated with 0.4 mg/kg/d dizocilpine in the 6 h access group escalated consumption of cocaine at a greater rate than vehicle-treated rats. We have argued that this differential rate of escalation, as was also observed with LY235959 (Allen et al., 2007a), suggests that blockade of NMDARs engages or mimics a mechanism that underlies escalation of cocaine consumption. Further supporting this idea, when dizocilpine treatment was discontinued during the 6 h phase of the experiment, cocaine self-administration rates fell to a level *below* those measured in the 6 h vehicle control group after an equivalent number of escalation sessions (i.e., escalation session 8).

Several laboratories have published data that show blocking NMDARs during repeated experimenter-administered injections of cocaine can block the development of locomotor sensitization and its neurobiological correlates (Li et al., 1999; Scheggi et al., 2002), yet sensitization may still develop to the combination (i.e., cocaine + dizocilpine; Gambarana et al., 1998). Interestingly, in rats that are already sensitized to cocaine, repeated treatment with a cocaine/dizocilpine combination (but not dizocilpine alone) can reverse the pre-established sensitization to cocaine (De Montis et al., 1995; Gambarana et al., 1998; Li et al., 2000), again, even when the locomotor response to the cocaine/dizocilpine combination remains sensitized (Gambarana et al., 1998). The findings from the present study are consistent with these locomotor data: escalation of cocaine intake increased dramatically during continuous NMDAR blockade, but was reduced to pre-escalation levels when cocaine was self-administered again in the absence of dizocilpine.

Despite these similarities to models that employ experimenter-administered doses of cocaine, it appears that the NMDAR can play a fundamentally different role in cocaine self-administration. A recent study with “addict” rats (i.e., rats that reveal greater motivation to seek and/or respond for cocaine across several behavioral measures than “non-addict” rats; Kasanetz et al., 2010) revealed impaired accumbal NMDAR-dependent LTD (but normal pre-synaptic mGluR2/3-mediated LTD). These authors argue that a hallmark of addiction, inflexible drug-seeking insensitive to current environmental contingencies, may be mediated by an *impairment* of this mechanism of synaptic plasticity. The data from the present study are consistent with this hypothesis and further suggest that NMDAR availability and/or functionality may serve as a mechanism that controls the rate of cocaine intake.

The data from the present study are in some ways also consistent with a report showing that injections of dizocilpine prior to the start of daily self-administration sessions “blocked” acquisition of cocaine self-administration in rats (Schenk et al., 1993). Although dizocilpine treated rats did not discriminate the active from inactive lever in that study, rats treated with dizocilpine appeared to consume greater amounts of cocaine than the vehicle-control group, and did so at early sessions (Schenk et al., 1993). Thus, while blockade of NMDARs may prevent learning related to the elicited effects of cocaine (e.g., locomotor sensitization), NMDAR blockade might have the opposite effect on cocaine self-administration.

The rebound to pre-escalation levels of cocaine consumption when dizocilpine treatment was discontinued and the normal rate of escalation thereafter is one of the most striking findings in the present study. Both repeated exposure to cocaine and continuous NMDAR blockade can increase expression of NMDAR subunit mRNA and/or protein under some conditions (Oh et al., 2001; Scheggi et al., 2002; Tang et al., 2004). Consistent with the hypothesis that NMDAR level controls rate of intake, it is possible that in the present study continuous blockade of NMDARs with dizocilpine produced an upregulation of NMDARs that was revealed when dizocilpine treatment expired. In addition, behavioral dependence, revealed as a decrease in operant responding during withdrawal from continuous NMDAR blockade, may also have developed in these animals and may explain the decrease in responding observed here (Beardsley and Balster, 1987; Bessalov et al., 1999). These are not mutually exclusive possibilities, and may have been additive in determining response rate in the present study. Additional work is necessary to clarify the mechanisms by which continuous NMDAR blockade so profoundly alters cocaine self-administration.

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Figure 1.

Effect of vehicle or dizocilpine (0.2 mg/kg/d or 0.4 mg/kg/d) on cocaine self-administration under 2 h (closed symbols) or 6 h (open symbols) access conditions under an FR1 schedule of cocaine reinforcement (0.33 mg/6 s infusion). Vehicle and dizocilpine were continuously infused via surgically implanted subcutaneous osmotic minipumps (Alzet® model 2ML4, 28 day infusion life). Top panel: Ordinate, cocaine intake, mg/kg. Abscissa, escalation session. Bottom panel: Ordinate, cumulative cocaine intake, mg/kg. Abscissa, escalation session. Sessions marked -4 to -1 on the top panel represent data from the final four days of training to self-administer cocaine in daily 2 h sessions (i.e., the training baseline level of intake.) Statistical analyses are described in the text. DZ, dizocilpine. V, vehicle.

Figure 2.

Top panel: Effect of 0.4 mg/kg/d dizocilpine delivered through Alzet® model 2ML4 osmotic minipumps (28 day infusion life, open triangles) or model 2ML1 osmotic minipumps (7 day infusion life, open inverted triangles) on responding for cocaine (0.33 mg/6 sec infusion) during 15 6 h self-administration sessions. Ordinate, cocaine intake, mg/kg. Abscissa, escalation session. *, $p < 0.05$ between groups. **, $p < 0.01$ between groups. DZ, dizocilpine. V, vehicle. Bottom panel: Escalation of cocaine consumption by rats in the 6 h – vehicle group (open circles) beginning at escalation session 1 (x) and rats treated with 0.4 mg/kg/d dizocilpine through model 2ML1 osmotic minipumps beginning at escalation session 7 (x) (open inverted triangles.) Escalation session seven was the first session at

which cocaine intake in the 0.4 mg/kg/d dizocilpine 2ML1 group did not differ significantly from the 6 h vehicle control group at escalation session 1. Ordinate, cocaine intake, mg/kg. Abscissa, escalation session, relative to x. DZ, dizocilpine.

Table 1

Total number of subjects (n) that completed each phase of the experiment, and reasons for exclusion. BL, final baseline session; E5, escalation session 5; E15, escalation session 15; PR, post-escalation behavior under the PR schedule of reinforcement.

Access	Tx	n (BL)	n (E5)	n (E15)	n (PR)
2	vehicle	10	9 ^a	7 ^{b,b}	7
2	0.2 DZ	10	10	8 ^{b,b}	8
2	0.4 DZ	10	8 ^{a,b}	7 ^b	7
6	vehicle	9	9	9	9
6	0.2 DZ	10	10	10	10
6	0.4 DZ	10	9 ^b	5 ^{b,c,c,d}	4 ^d
6	2ML1	8	8	5 ^{b,c,e}	5

^aStatistical outlier for baseline cocaine intake (mg/kg)

^bCatheter failure

^cWeight loss

^dUrinary tract complications

^eStopped responding

Body weight ("weight"; g) and cocaine intake ("FR intake"; mg/kg) measured during the final FR1 baseline session, break point-associated infusions earned under the pre-escalation PR session, and number of pre-escalation training sessions (Training) for all rats included in the statistical analysis. All values represent the mean $\pm$ standard error.

Table 2

Access	Tx	n	Weight (g)	FR intake	PR infusions	Training
2	vehicle	9	350.6 $\pm$ 5.3	26.4 $\pm$ 1.1	17.9 $\pm$ 0.7	15.1 $\pm$ 0.3
2	0.2 DZ	10	346.7 $\pm$ 5.8	24.6 $\pm$ 1.1	17.2 $\pm$ 0.5	14.9 $\pm$ 0.3
2	0.4 DZ	8	356.0 $\pm$ 9.6	22.9 $\pm$ 1.0	17.8 $\pm$ 1.5	17.6 $\pm$ 0.4
6	vehicle	9	338.0 $\pm$ 2.6	24.2 $\pm$ 1.3	17.4 $\pm$ 1.0	15.0 $\pm$ 0.2
6	0.2 DZ	10	340.2 $\pm$ 6.0	24.6 $\pm$ 0.9	16.6 $\pm$ 1.4	14.7 $\pm$ 0.2
6	0.4 DZ	9	361.0 $\pm$ 4.2	25.8 $\pm$ 0.8	18.3 $\pm$ 0.9	14.4 $\pm$ 0.2