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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.

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

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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, led 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 ± 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 2 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 cm × 24 cm × 21 cm) housed within sound-attenuating cabinets (Med Associates, Incorporated; St. Albans, VT), described previously (Allen et al., 2007a,b). 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 (2900 Hz)-houselight (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.

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

[a] Statistical outlier for baseline cocaine intake (mg/kg).
[b] Catheter failure.
[c] Weight loss.
[d] Urinary tract complications.
[e] Stopped responding.

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 7 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 ± standard deviation; 2 h/vehicle, $n = 1$, 40 mg/kg; 2 h/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.