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Prepulse inhibition of the acoustic startle response in cocaine-withdrawn rats

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Abstract

Prepulse inhibition (PPI) of startle is a sensorimotor gating task in which a low-intensity acoustic stimulus presented prior to a high-intensity, startle-eliciting stimulus can attenuate the acoustic startle response (ASR). Previous studies on startle reactivity in cocaine-withdrawn rats have found minimal changes; the present study extends this work to the gating of ASR. In Experiment 1, rats were injected daily with either saline or cocaine (30 mg/kg ip) for 2 weeks. ASR and PPI were measured prior to, and at 3- and 14-day withdrawal from, the chronic treatment. No effect of cocaine treatment was found on either measure. In Experiment 2, treatment was extended to 8 weeks, and an earlier withdrawal time point (1 day) was added. Rats treated with cocaine for 8 weeks exhibited lower startle reactivity during withdrawal compared with saline-treated controls. PPI did not differ between treatment groups. Thus, extended chronic treatment with cocaine rendered significant effects on startle responsivity. Further, this finding mirrors the blunted ASR exhibited in chronic cocaine users [Neuropsychopharmacology 22 (2000) 89.].

Keywords: Cocaine; Withdrawal; Startle reaction; Prepulse inhibition; Sensory gating; Rats

1. Introduction

Termination of chronic cocaine use does not induce obvious physiological symptoms like those seen upon withdrawal of opioids or ethanol. Still, a multiphasic abstinence syndrome has been described clinically (Gawin and Kleber, 1986). Behavioral research in animals has provided further support for a cocaine withdrawal syndrome. Within 1 week of terminating chronic cocaine administration, disruptions in spontaneous activity and operant responding have been observed both in rats and monkeys (Carroll and Lac, 1987; Fung and Richard, 1994; Woolverton and Kleven, 1988). During the same time frame, behaviors associated with anxiety have been demonstrated in various rodent models, including generalization to a pentylenetetrazol-discriminative stimulus (Wood and Lal, 1987), decreased time on the open arms of an elevated plus maze (Sarnyai et al., 1995), and increased conditioned defensive burying (Harris and Aston-Jones, 1993). Also, increased thresholds for intracranial self-stimulation have been observed and hypothesized to reflect a state of "anhedonia" in cocaine-withdrawn rats (Markou and Koob, 1991). Animal behavioral models have thus provided sensitive measures of cocaine dependence.

The prepulse inhibition (PPI) of the acoustic startle response (ASR) is a sensorimotor gating task in which a low intensity acoustic stimulus, presented 30–120 ms prior to a high-intensity, startle-eliciting stimulus, can attenuate the startle response. Both PPI and ASR are modulated by a variety of neurotransmitter systems including dopamine, acetylcholine, serotonin, and glutamate (Davis, 1980; Swerdlow et al., 1993) and are altered in certain neuropathological states (Braff and Geyer, 1990). Thus, startle reactivity and the gating of that response may serve as sensitive functional correlates of changes that occur with chronic cocaine administration and its withdrawal. Indeed, chronic cocaine users exhibit marked impairment in acoustic startle reactivity and, under certain conditions, increased inhibition by presentation of prepulses (Efferen et al., 2000). These deficits were deemed to be consistent with a putative functional state of reduced dopaminergic neuro-

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transmission during cocaine withdrawal (Kuhar and Pilotte, 1996). A few investigators have looked at startle responsivity to acoustic or tactile stimuli during cocaine withdrawal in rats and reported largely negative results (Barros and Miczek, 1996; Mansbach et al., 1994; Martinez et al., 1999, but see Mutschler and Miczek, 1998). Only one study has examined PPI under these conditions. Martinez et al. (1999) observed no change in PPI 10 days after cessation of continuous cocaine administration. Other withdrawal time points were not assessed, so it is unknown whether changes might have been detected. One objective of the present study was to test PPI in rats during earlier phases of withdrawal.

Animal studies have used widely different methods of chronic cocaine administration with which to study withdrawal symptomatology, but treatment schedules have seldom extended beyond 2-week duration. One striking parameter in the clinical study cited above (Efferen et al., 2000) was the long duration of drug use (mean of 17 years). Thus, a second objective of the present study was to test whether extending the duration of cocaine treatment in rats would translate into measurable changes in ASR and/or PPI.

2. Methods

2.1. Subjects

Fifty-six male Sprague–Dawley rats weighed 150–175 g upon arrival from Charles River Labs (Kingston, NY). They were housed in pairs in standard cages lined with hardwood bedding. Food and water were available at all times, and a 12:12 light–dark cycle was maintained. Experiments began after animals had acclimated to the animal facility for 1 week and had been handled on at least three separate occasions. All animal procedures were reviewed and approved by the Animal Studies Subcommittee and the Research and Development Committee at the New York Veterans Affairs Medical Center and were in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Animals."

2.2. Apparatus

Experiments were conducted using a commercially available startle analysis system (SR-LAB, San Diego Instruments; San Diego, CA), which was located in a sound-attenuating room. Briefly, a Plexiglas cylinder, 8.5 cm in diameter and 20.5-cm long, rested on a 12.5×20.8-cm base. Each cylinder and base were housed in separate sound-attenuating chambers. A sealed piezoelectric transducer was affixed to the underside of the base. Movement within the cylinder resulted in flexion of the transducer, which induced a voltage change. These voltage changes were recorded and analyzed by computer, with 250 1-ms samples collected from stimulus onset.

2.3. Acoustic startle procedure

For an acoustic startle test session, animals were transported to the laboratory, weighed, and allowed to habituate for at least 1 h. The startle session began by placing a rat in the cylinder and closing the chamber. After a 4-min period during which continuous white noise (63 dB) was present, subjects were exposed to four blocks of 12 trials presented in random order: a 115-dB broadband, 50-ms pulse alone (PA; three trials); a 75-dB, 25-ms prepulse followed 100 ms later by a 115-dB, 50-ms pulse (75 PP, three trials); an 85-dB, 25-ms prepulse followed 100 ms later by a 115-dB pulse (85 PP, three trials); a 75-dB, 25-ms PA (one trial); an 85-dB, 25-ms PA (1 trial); and white noise alone (no stimulus, one trial). Trials were separated by an average of 30 s; actual intertrial intervals varied randomly between 20 and 40 s. The duration of the entire test session was approximately 28 min.

2.3.1. Experiment 1

Three acoustic startle sessions were conducted with each of 16 rats. The first was a baseline session occurring prior to chronic drug administration; no injections were administered. The other two were test sessions that took place 3 and 14 days after cessation of drug treatment and were otherwise identical to the baseline session.

Animals were divided into two groups ($n = 8$/group) for chronic drug administration (i.e., saline or cocaine). Group assignment was based on startle amplitudes averaged across the baseline session, such that the mean (and variance) of the groups' startle responses were matched as closely as possible. Rats were weighed and injected intraperitoneally (ip) with either 30 mg/kg cocaine or saline (1 ml/kg) 7 days/week for 2 weeks. Injections were administered between 09:00 and 12:00 h.

2.3.2. Experiment 2

Four acoustic startle test sessions, as described above, were conducted in each of 40 rats. The first (baseline session) occurred prior to chronic drug administration. The other three test sessions took place after cessation of drug treatment at 1, 3, and 14 days after the last injection. Based on average startle amplitudes from the baseline session, animals were divided into two matched groups. Rats were weighed and injected intraperitoneally with either 30-mg/kg cocaine or saline (1 ml/kg) 5 days/week (Mon–Fri) for either 2 or 8 weeks (four groups of 10 rats each). Injections were administered between 09:00 and 12:00 h.

2.4. Drugs

Cocaine hydrochloride (Sigma; St. Louis, MO) was dissolved in saline and doses are reported in terms of the salt. All injections were administered intraperitoneally in a volume of 1 ml/kg.

2.5. Data analysis

Startle amplitude for each trial was recorded. It is expressed herein as the average change over a 250-ms interval; the units are arbitrary. Like trials across a session block or the entire test session were averaged for each subject. PPI is calculated by: 100%*(PA − PP)/PA, where PA is the startle amplitude of 115-dB PA trials and PP is the startle amplitude of prepulse + pulse trials. Two-way (treatment group × test day) and three-way ANOVAs (treatment group × test day × session block) with repeated measures (test day and session block) were performed on startle amplitude and PPI data. When significant main effects were found, Student–Newman–Keuls post-hoc tests were conducted.

3. Results

3.1. Experiment 1

3.1.1. Baseline measures

Table 1 displays the mean ASR to PA trials by session block (each block lasted approximately 6 min and contained three of these PA trials presented randomly among 12 trials total) for all 16 animals in Experiment 1 prior to chronic drug administration. No significant effect of block ($P > .05$) was observed over the duration of the session, i.e., rats did not habituate to the startle stimuli under these conditions. Mean startle amplitudes averaged across the entire session were 217 ± 22 (arbitrary units). Table 1 also exhibits the mean PPI that occurred when startle-eliciting stimuli were preceded by lower-intensity stimuli. Again, data are presented by session block. As was the case with PA responses, there was no main effect of block ($P > .1$) on PPI. A 75-dB prepulse inhibited the startle response by a mean of 38 ± 3% and a 85-dB prepulse by 69 ± 2% averaged across the entire session.

3.1.2. Withdrawal measures

Fig. 1 shows the results from startle sessions held 3 and 14 days after the last treatment injection. A two-way ANOVA with repeated measures (treatment × withdrawal day) was performed using the mean ASR (each rat's PA trials averaged across the entire test session). A significant effect of day ($P < .01$, $df = 1$, $F = 13.2$) was found, with increased startle responses observed in both treatment groups on withdrawal day 14 (Fig. 1, top panel). However, there were no significant difference between treatment groups and no significant interaction between the two factors (both $P > .1$). There was an apparent trend towards reduced startle amplitude in cocaine-treated rats on withdrawal day 14. Further analysis of these data including the block factor also failed to show a significant main effect of treatment or interaction between treatment and any other factor (all $P > .1$), although there was a significant effect of block itself ($P < .01$, $df = 3$, $F = 4.67$; by-block data not shown). PPI of startle, whether by 75- or 85-dB prepulses, was plainly unaffected by treatment condition (Fig. 1, middle and bottom panels; both $P > .1$).

3.1.3. Body weight

All rats gained weight over the course of chronic treatment (Table 2). There was no difference in mean body weight between treatment groups at any time point ($P > .1$).

3.2. Experiment 2

One rat in the 8-week cocaine treatment group died within minutes after receiving its daily cocaine dose during the fifth week of treatment.

Table 1
Baseline measures for each experimental group by session block

	Block 1	Block 2	Block 3	Block 4
Experiment 1 (n = 16)				
Startle amplitude	243 ± 32	192 ± 20	209 ± 23	222 ± 24
% Inhibition (75-dB prepulse)	37 ± 4	42 ± 4	33 ± 8	41 ± 5
% Inhibition (85-dB prepulse)	69 ± 5	68 ± 4	67 ± 4	71 ± 3
Experiment 2 (2-week groups; n = 20)				
Startle amplitude	226 ± 21	198 ± 20	200 ± 19	187 ± 21
% Inhibition (75-dB prepulse)	39 ± 5	28 ± 5	27 ± 6	27 ± 11
% Inhibition (85-dB prepulse)[a]	52 ± 11	54 ± 6	48 ± 5	25 ± 32
Experiment 2 (8-week groups; n = 19)				
Startle amplitude	248 ± 20	214 ± 18	195 ± 15	208 ± 28
% Inhibition (75-dB prepulse)	43 ± 5	32 ± 9	25 ± 12	31 ± 7
% Inhibition (85-dB prepulse)	67 ± 5	72 ± 4	66 ± 4	68 ± 5

Values are expressed as the mean ± S.E. No significant effect of block for any measure in any experimental group.
[a] Experimental group significantly different than others on this measure.

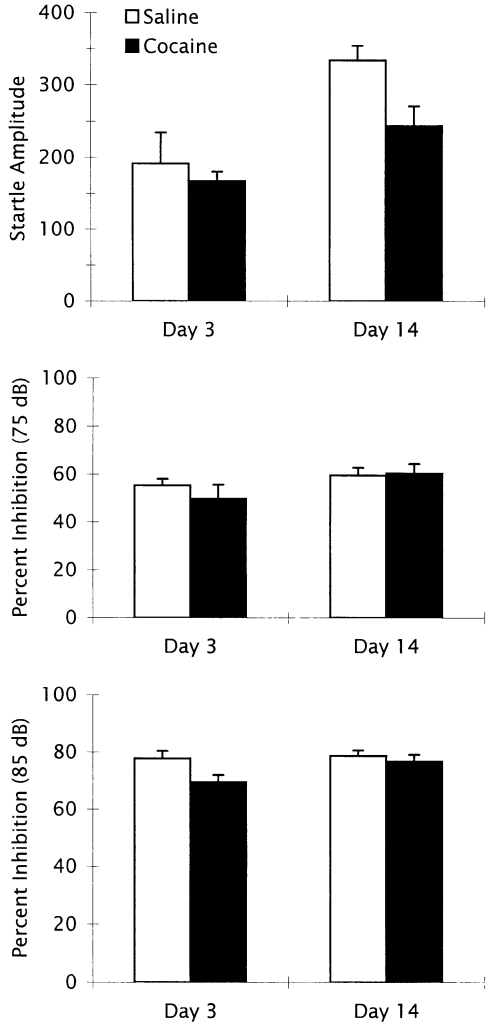

Fig. 1. Effects of treatment condition on ASR and PPI in Experiment 1. Data shown are averages across the entire test session on each withdrawal day. Top panel displays mean ± S.E. startle amplitude (arbitrary units), middle panel plots mean ± S.E. percent inhibition of startle in 75-dB prepulse trials, and bottom panel plots mean ± S.E. percent inhibition in 85-dB prepulse trials for each treatment group. $N = 8$ rats/group. Significant main effect of day ($P < .01$) but not treatment ($P > .1$).

3.2.1. Baseline measures

The ASR (to PA trials analyzed by session block) for rats that completed Experiment 2 are quite comparable to those obtained in Experiment 1 (Table 1). For the 20 rats in the 2-week group, no significant habituation occurred over the session (effect of block: $P > .1$) and the mean startle amplitude averaged across the session was 203 ± 17. Likewise for the 19 rats in the 8-week group, no significant habituation occurred (effect of block: $P > .1$), and mean startle amplitude averaged across the session was 217 ± 16. In terms of mean PPI that occurred with 75- and 85-dB prepulses by session block, these measures did not change significantly over the four blocks (all $P > .1$). Data for 75-dB PPI were also consistent with those of Experiment 1 (Table 1). Trials with 75-dB prepulses inhibited the startle response by a mean of 35 ± 4% in the 2-week group and a mean of 37 ± 5% in the 8-week group (data averaged across entire session). However, trials with 85-dB prepulses resulted in 57 ± 3% inhibition in the 2-week group, which was statistically different from each the 8-week group and the group from Experiment 1 (Student–Newman–Keuls post-hoc test at $P < .05$). Percent inhibition by 85-dB prepulses was 70 ± 3% in the 8-week group.

3.2.2. Withdrawal measures

The mean ASR for each test day is plotted in Fig. 2. Statistical analysis of the 2-week data (Fig. 2, top left panel) found a significant effect of test day ($P < .001$, $df = 2$, $F = 11.4$) but no difference between treatment groups and no interaction between these two factors (both $P > .1$). The 8-week data (Fig. 2, top right panel) showed an apparently consistent trend towards lower startle amplitudes in the cocaine-treated rats; however, this did not reach statistical significance ($P = .1$, $df = 1$, $F = 2.13$). Like the 2-week data, there was a significant test day effect ($P < .05$, $df = 2$, $F = 3.62$) and no interaction effect ($P > .1$). The significant day effect in both groups represents a chronological increase in startle amplitudes.

A more detailed analysis was performed on the 8-week groups data to determine if within session variables were affected differentially by drug treatment (Fig. 3). A three-way ANOVA with repeated measures (treatment group × withdrawal day × session block) resulted in significant main effects of day ($P < .05$, $df = 2$, $F = 3.61$) and block ($P < .005$, $df = 3$, $F = 6.63$), and a significant interaction

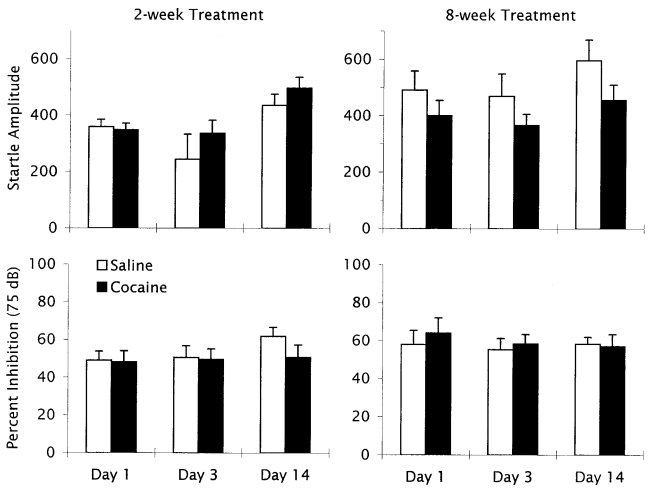

Fig. 2. Effects of treatment condition on ASR and PPI in Experiment 2. Data shown are averages across the entire test session on each withdrawal day. Top panels display mean ± S.E. startle amplitude, and bottom panels plot mean ± S.E. percent inhibition of startle in 75-dB prepulse trials; left panels show results from 2-week treatment groups, and right panels show results from 8-week treatment groups. $N = 9–10$ rats/group. Significant main effect of day ($P < .001$) but not treatment ($P > .1$).

Table 2
Mean body weights (g) for each experimental group by test day

	Pre	Withdrawal day 1	Withdrawal day 3	Withdrawal day 14
Experiment 1				
Saline ($n=8$)	240 ± 3	–	351 ± 6	387 ± 8
Cocaine ($n=8$)	249 ± 3	–	345 ± 13	381 ± 21
Experiment 2 (2-week groups)				
Saline ($n=10$)	250 ± 5	350 ± 8	369 ± 9	412 ± 10
Cocaine ($n=10$)	251 ± 6	351 ± 8	370 ± 8	425 ± 8
Experiment 2 (8-week groups)				
Saline ($n=10$)	262 ± 3	461 ± 10	462 ± 10	476 ± 10
Cocaine ($n=9$)	269 ± 2	488 ± 15	490 ± 15	509 ± 14

S.E. are also shown. No significant effect of treatment group in any experiment.

between block and treatment group ($P<.05$, $df=3$, $F=2.91$). This interaction can be seen in Fig. 3 with significant within-session decreases in startle amplitude in the saline-treated group but not the cocaine-treated group. A Student–Newman–Keuls post-hoc test showed that this interaction is significant for Block 1 ($P<.005$) where the difference between treatment groups is the greatest. When this same analysis was applied to the 2-week groups data, no significant effect of, nor interaction with, treatment group was found (all $P>.1$), consistent with the results from Experiment 1.

PPI of startle, whether by 75-dB (Fig. 2: 2-week data shown in bottom left panel; 8-week data in bottom right) or 85-dB prepulses (data not shown), was unaffected by treatment condition (all $P>.1$).

3.2.3. Body weight

All rats gained weight over the course of chronic treatment (Table 2). There was no difference between treatment groups at any time point ($P>.1$ for each 2- and 8-week treatments). A correlation was found between rats' body weight and startle amplitude (correlation coefficient = .8).

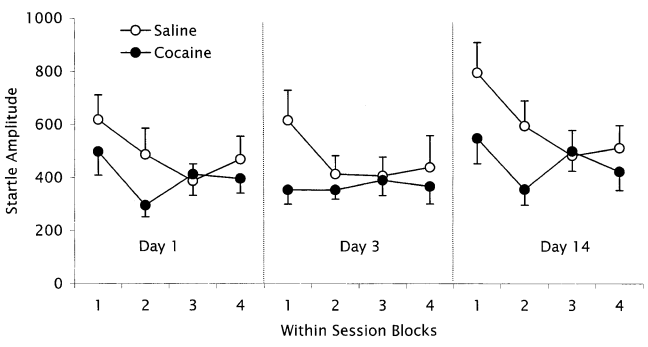

Fig. 3. Effect of 8-week treatment condition on ASR within-session analysis (Experiment 2). Data are shown for each of four consecutive 6-min blocks of the startle session on each withdrawal day. Mean ± S.E. startle amplitudes (by block) are plotted for each treatment group. $N=9-10$ rats/group. Significant main effects of day ($P<.05$) and block ($P<.005$) and interaction effect of block × treatment group ($P<.05$).

4. Discussion

Acoustic startle amplitudes were reduced, particularly early in the test session, but PPI of startle was not significantly altered, after withdrawal from 8 weeks of chronic cocaine treatment as compared to saline treatment (Experiment 2). No differences in startle or PPI were observed after cessation of daily cocaine administration for 2 weeks (Experiments 1 and 2).

In a clinical study (Efferen et al., 2000), cocaine users abstinent for less than 1 week and for as long as 6 months exhibited markedly reduced ASR and slightly enhanced PPI as compared to normal controls. The present study was designed in an attempt to model this clinical study. After collecting the data in Experiment 1 and finding no effect of drug treatment, we chose to extend the duration of chronic treatment in part because of the long duration (mean of 17 years) of drug use recorded in the clinical sample. Experiment 2 included a replication of the 2-week treatment, albeit without weekend injections, and the results were identical: no main treatment effect on ASR or on PPI. However, after 8-week chronic drug administration, there was a trend towards lower startle amplitudes in the experimental group, and within-session analysis indicated that significant differences occurred early in the session. These differences were observed as early as 1 day after the last cocaine dose and for up to 14 days. Thus, long-term cocaine treatment induced significant albeit modest withdrawal effects in the same direction as the clinical finding (Efferen et al., 2000). Reduced startle amplitude would be consistent with the general pattern of withdrawal changes being opposite in direction to the acute effects of a drug. Acute doses of cocaine clearly increase the ASR in rats (Davis, 1985). Moreover, these data suggest that duration of chronic cocaine treatment is a critical factor in determining withdrawal effects.

Previous studies on startle reactivity in rats have reported little to no effect during withdrawal from cocaine (Barros and Miczek, 1996; Mansbach et al., 1994; Martinez et al., 1999). Chronic regimens in these studies ranged from 12-h intravenous self-administration binges, 2-week noncontingent continuous infusion, to 60-day oral self-administration. Withdrawal measures were assessed as early as 3 h and as long as 1 month after termination of treatment. Thus, despite extensive differences in dose, frequency, duration, route, and contingency of cocaine administration, as well as in the observed period of withdrawal, the lack of significant effects on startle responsivity has been a fairly consistent finding. One exception is an investigation by Mutschler and Miczek (1998), who studied withdrawal from intravenous self-administration "binges" (doses taken ranged from 67 mg/kg/12 h to 270 mg/kg/48 h). Increased startle and ultrasonic vocalizations were found as early as 6 h and up to 24-h postbinge in response to both high- and moderate-intensity tactile stimuli. These authors attribute the significant results (as compared to Barros and Miczek, 1996) in part to the "binge" pattern of self-administration, allowing remarkably high doses of drug to be delivered, and to the use of a lower-intensity stimuli, which may be more sensitive in revealing subtle effects. The differing result in our study (i.e., decreased startle) may be due to any number of procedural differences, most notably dose, dosing pattern, and duration of chronic treatment, but it was curious that, if anything, it was opposite in direction to that of Mutschler and Miczek (1998).

The present study found no significant effect of cocaine treatment on sensorimotor gating as measured by PPI as early as 1 day and as long as 14 days after termination of treatment. Martinez et al. (1999) reported a disruption of PPI of acoustic startle both with acute administration and during chronic administration (3 days into a 5-day continuous infusion of cocaine via subcutaneous pellet). Ten days (the only withdrawal time point used) after the pellet was removed, PPI had returned to normal. Thus, we extended the negative findings on PPI to the early withdrawal period (1–3 days) in which some of the significant findings on startle reactivity were reported as discussed above (Mutschler and Miczek, 1998). Further, we extended the negative findings on PPI to withdrawal from long-term cocaine treatment, in which significant findings on startle reactivity were observed herein. Two studies using a quite different measure of sensory gating, the inhibition of the auditory event-related potential, showed decreased inhibition when rats were tested during treatment with daily injections of cocaine but complete recovery of this deficit after 1 week of withdrawal (Boutros et al., 1994; Salamy et al., 1997). To summarize across sensory-gating paradigms, the effects of cocaine during chronic treatment were in the same direction as acute effects (Boutros et al., 1994; Martinez et al., 1999; Salamy et al., 1997). These effects did not last for very long after discontinuing cocaine, and opposite effects were never observed (present results included). In humans, an increase in PPI was reported during withdrawal from cocaine (Efferen et al., 2000).

The parameters of chronic cocaine administration, namely dose, frequency, duration, route, and contingency, most certainly influence the degree and perhaps direction of withdrawal effects. Our study used a relatively high dose for single injection methods, 30 mg/kg. While higher acute doses can be tolerated, sensitization that occurs with repeated administration limits their use. In our study, one rat died during chronic cocaine treatment, suggesting we may have been near the threshold of tolerability. Higher daily doses can be obtained with continuous infusion (e.g., (Mansbach et al., 1994; Mutschler and Miczek, 1998)). However, experimental outcomes differ radically depending on whether stimulant administration is intermittent or continuous, e.g., sensitization vs. tolerance to stimulant effects, respectively (Post, 1980; Reith et al., 1987). Withdrawal effects differ as well (King et al., 1994). Intermittent injections would seem to have greater face validity than continuous infusion as a model of long-term human use with a repeated phasic pattern of circulating cocaine levels and their resultant neurobiological effects. Indeed, our regimen did induce a modest effect on acoustic startle qualitatively similar to that observed in human cocaine addicts (Efferen et al., 2000). There are intermittent chronic dosing paradigms that use multiple injections per day, temporally clustered to model human "binges" or "runs" of stimulant use; these methods also allow higher daily doses to be achieved (Segal and Kuczenski, 1997; Unterwald et al., 1994). It remains to be seen whether such a regimen would render significant effects on startle responsivity (and in what direction they might be).

The present results consistently showed a significant effect of test day on startle amplitude. The increased startle amplitudes were observed in both saline- and cocaine-treated rats in every experiment and were especially dramatic when compared to baseline session data. The increase was correlated with increased body weights over the duration of the experiments. No difference in body weight gain was observed between cocaine- and saline-treated groups, thus this potential variable did not contribute to any difference in startle amplitudes on any particular test day. The startle apparatus is designed to be relatively unaffected by small differences in weight; however, this early does not extend to the 150–200-g increases in weight that occurred in the present study. Preliminary experiments repeatedly testing rats (using the identical startle session) over a 5-week period also revealed this gradual increase in startle amplitudes (unpublished observations).

In conclusion, neither ASR nor PPI of startle was significantly altered after withdrawal from 2-week cocaine treatment. After 8-week treatment, startle responsiveness was modestly but significantly decreased compared to saline controls at each withdrawal time point observed. Conversely, PPI of startle did not differ between treatment groups at any time point.

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