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Lack of Altered Startle Responding in Rats Following Termination of Self-Administered or Noncontingently Infused Cocaine

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MANSBACH, R. S., A. MARKOU AND G. A. PATRICK. *Lack of altered startle responding in rats following termination of self-administered or noncontingently infused cocaine.* PHARMACOL BIOCHEM BEHAV **48**(2) 453–458, 1994.—The effect of cocaine on the acoustic startle response was assessed in rats trained to intravenously self-administer cocaine (0.25 mg/injection) and in rats continuously infused through an intraperitoneal catheter with up to 170 mg/kg/day of cocaine. Neither a 12-h self-administration "binge" nor 13 days' continuous infusion produced significant effects on the startle response as compared to controls up to 24 h after termination of drug exposure. These findings suggest that prolonged cocaine administration may result in a dependence syndrome dissimilar to that observed with CNS depressant drugs or alcohol.

Cocaine Rat Withdrawal Startle Self-administration

THE highly reinforcing effect of cocaine is regarded to play a principal role in its widespread abuse (28). Unlike opiates, alcohol, barbiturates, or benzodiazepines, however, the discontinuation of chronic cocaine use does not result in typical manifestations of a withdrawal syndrome, long considered an important factor in persistent drug use and relapse. Despite the absence of classical withdrawal signs, several studies have described a cocaine abstinence syndrome in humans, which is reportedly characterized by anxiety, dysphoria, lethargy, drug craving, depression, and anhedonia (11,24,26).

Attempts to produce behavioral dependence in animals—a behavioral effect in response to cocaine removal (2)—have resulted in mixed findings. Using schedule-controlled responding, some investigators have reported that chronic or repeated cocaine administration produces tolerance, and that discontinuation of the drug results in behavioral disruptions that diminish with time (4,15,29). However, these changes in behavior are not typically accompanied by overt manifestations of withdrawal, and sometimes occur only under extreme dosing conditions (15).

Another reported consequence of acute cocaine administration is a lowering in thresholds for intracranial self-stimulation (ICSS). In contrast, upon discontinuation of noncontingently administered (16) or self-administered cocaine (20), marked elevations in ICSS thresholds have been observed in rats. This decreased sensitivity to the reinforcing effects of electrical stimulation—opposite to the acute effect of the drug—occurs primarily in the first 24 h after discontinuation of cocaine, and has been proposed as a model of postcocaine depression or anhedonia following a cocaine "binge" (20).

Previous work has demonstrated that alterations in the startle response occur during withdrawal from ethanol and morphine (19,22). In the present study, the effects of startle-inducing acoustic and tactile stimuli were examined in rats immediately following an extended period of self-administration or noncontingent infusion of cocaine. Because increases in startle have been reported following acute administration of cocaine (6), it was hypothesized that startle reactivity would decrease during withdrawal. There were two reasons for employing both contingent and noncontingent methods of cocaine administration. First, there is evidence that the effects of self-administered cocaine can be markedly different from those produced by the same dosages administered noncontingently (9). Second, a chronic infusion paradigm allowed exam-

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ination of the effects of constant, high-dose cocaine exposure. In previous experiments, this method of drug delivery has been shown to produce physical dependence upon opiates and barbiturates (25,30). Because post-cocaine increases in ICSS thresholds apparently begin and disappear much sooner after drug discontinuation than do the disruptions in operant behavior discussed above, the present study focussed on possible behavioral changes in the first 24 h after cessation of cocaine exposure.

METHOD

Experiment 1: Self-Administration Study

Subjects. Fourteen male albino Wistar rats (260–300 g at the beginning of the experiment) were obtained from Charles River (Kingston, NY), housed in groups of three, and maintained in a temperature- and light-controlled environment (The Scripps Research Institute). The animals had free access to laboratory chow and water except during testing sessions less than 12 h in duration. They were maintained on a 12 L : 12 D cycle (lights on at 0600 and off at 1800 h), and tested during the light phase.

Startle apparatus. For both experiments, startle response studies were conducted using San Diego Instruments (San Diego, CA) startle chambers and associated interface equipment, as previously described (16). An IBM-compatible personal computer delivered stimuli and collected data, which were stored on magnetic media. Acoustic stimuli were delivered by a Radio Shack Supertweeter located in the chamber's ceiling. Tactile (air puff) stimuli (chronic infusion experiment only) were delivered to the animal's dorsal surface via flexible polyethylene tubing. One tube exited an air regulator with a pressure of 50 p.s.i. The tube then split into two branches, each connected to a solenoid-controlled valve. Each branch split again after passing through the valve for a total of four branches, each supplying one chamber. Responses were collected by a sealed accelerometer device. Data were collected as 100 1-ms voltage readings which began immediately after the onset of stimuli. Responses were rectified, digitized, and stored on microcomputer. The average of the 100 readings was selected as the dependent measure.

Self-administration apparatus. Training and testing on cocaine self-administration took place in sound-attenuated operant chambers constructed of metal and Plexiglas (24.5 × 24 × 24 cm). One wall contained a metal retractable lever mounted 5 cm above the floor that required a 10 *g* force for switch closure. Plastic Products swivels (Plastic One Inc., Roanoke, VA) connected the animals to pump-driven syringes (Razel, Stamford, CT).

Surgery. Rats were anesthetized with halothane and a silastic catheter was implanted in the jugular vein as previously described (23). The catheter was passed subcutaneously to a polyethylene assembly mounted on the animal's back. This assembly consisted of a Plastics One guide cannula (C313G) attached with epoxy to a 3 cm^2 piece of marlex mesh. The marlex mesh was positioned under the skin on the rat's back and the skin was sutured around the guide cannula. A stylet was inserted into the guide cannula, which protruded from the rat's back.

Self-administration procedure. Each self-administration session began with two priming injections. The retractable lever was then extended into the operant chamber. Rats were trained under a fixed ratio 1 schedule and reinforced with an intravenous injection of 0.1 ml saline solution of cocaine HCl (Sigma Chemical Co., St. Louis, MO; 0.25 mg/injection, approximately 0.65 mg/kg/injection calculated as the salt) administered over a period of 4 s. A signal light located above the lever indicated the onset of an injection and remained lit for 20 s, during which time the lever was inactive. The session duration was 3 h during training and 12 h in the final testing session.

Startle testing. Startle sessions began with 5 min of background noise [67 dB(A)]. After this acclimation period, 21 122 dB[A] acoustic startle stimuli (80 ms in duration) were presented at varying intervals (range 20–40 s). The mean startle amplitude of the first trial was analyzed separately from that of the remaining 20 trials, because responses to the first stimulus presentation are considered to reflect initial reactivity [e.g., (1)].

Rats were tested in the startle apparatus 1–2 days prior to the surgical implantation of catheters. Results from the presurgery startle test served as a measure for the assignment of subjects into cocaine (n = 7) and control (n = 7) groups with nearly equivalent mean startle responses. Because the control group received no surgery or cocaine treatments, it was important to assess potential effects of these manipulations on startle response magnitude. Hence, all subjects were tested in the startle apparatus 1–2 days after the cocaine animals underwent surgery (postsurgery test). Then, subjects in the cocaine group were trained to self-administer cocaine during 3-h daily sessions. After stable responding for cocaine was established (+10% variation over 3 consecutive days), rats in both groups were tested in the startle apparatus 24 h after a 3-h cocaine self-administration session (posttraining test). All rats were then tested immediately after the cocaine group received a 3-h self-administration session (acute cocaine). The control animals received no cocaine before this test. The purpose for conducting these two startle sessions 24 h apart was to assess the potential effects of short-term (acute) and repeated (6–15 days) cocaine self-administration on startle response magnitude. Subsequently, cocaine-trained rats were allowed to continuously self-administer cocaine for 12 h (2100–0900 h; cocaine binge). Finally, all rats were tested in the startle apparatus at 0, 1, 3, 6, 12, and 24 h after the cocaine rats had performed the 12-h self-administration session.

Data analysis. The BMDP (8) and SYSTAT (27) statistical packages were used for all statistical analyses. The level of significance was set at $p < 0.05$. The Greenhouse-Geisser (12) corrected degrees of freedom were used in repeated-measures analyses of variance (ANOVAs) when the sphericity test indicated nonhomogeneity of variance. Newman-Keuls post hoc comparisons were made when the ANOVAs indicated statistically significant effects.

Experiment 2: Chronic Infusion Study

Subjects. Twenty-four adult male Sprague-Dawley rats (Charles River), weighing 300–350 g, were singly housed in a temperature- and light-controlled (on 0700, off 1900) animal facility (Medical College of Virginia) with free access to water and laboratory chow.

Surgery. Rats were surgically prepared with chronically implanted intraperitoneal cannulae as described by Teiger (25). Rats were anesthetized with methoxyflurane (Pitman-Moore Inc.), the abdomen incised, and a PE50 cannula was anchored into the peritoneal space and the free end was advanced, subcutaneously, to exit at the nape of the neck. Cannulae and instruments were sterilized in a benzalkonium chloride (Zephiran) 1 : 750 solution prior to use.

Infusion procedure. Upon recovery from surgery, rats were secured into specially designed harnesses (30) and re-

turned to their home cages. The indwelling cannula was connected to a flow-through swivel which, in turn, was connected to a 10 ml syringe placed on a Harvard infusion pump. Cocaine HCl (National Institute on Drug Abuse) was dissolved into physiological saline in a concentration to deliver the appropriate dosage in a volume of 8 ml/24 h (Monday through Friday) or 4 ml/24 h (Saturday to Sunday). Dosages were calculated as the salt.

Prior to the administration of cocaine, all rats in the study were acclimated to the infusion paradigm for a period of 48 h, during which saline was administered. Control rats continued with the continuous saline infusion while drug-treated rats received a continuous infusion of cocaine on an escalating dosage schedule for the following 13 days. Rats were initially infused with cocaine at a dose of 80 mg/kg/24 h. Subsequently, the dosage was increased by 10 mg/kg per day (except for Sunday). At the time of discontinuation, cocaine-treated rats were receiving a dosage of 170 mg/kg/24 h. Body weight was measured daily during the infusion period.

Startle testing. All rats were tested in the startle apparatus 8 days prior to the surgical implantation of IP catheters, and again at 3, 6, 12, and 24 h after the termination of cocaine or saline infusions. Results from the presurgery startle test served as a baseline measure for the assignment of subjects into cocaine and saline infusion groups. An effort was made to match the mean startle scores on both acoustic and tactile trials as closely as possible in the two groups. The same session design was used in withdrawal tests as in the baseline test.

The session consisted of a 5 min of background noise [67 dB(A)] followed by a series of 40 trials from which stabilimeter readings were recorded. Three different types of trials were defined for this session: a 40-ms, 122 dB[A] broad-band auditory pulse (acoustic stimulus), a 60-ms air puff (tactile stimulus), and a period during which no change in stimulus conditions occurred (no stimulus). In addition to an initial acoustic trial, each of the trial types was presented 13 times over the course of the session. Trials were presented in a mixed order and separated by 30-s intertrial intervals, during which only background noise was present.

Data analysis. The average stabilimeter readings for each trial type were used in subsequent statistical analyses (SAS Institute, Cary, NC). As in the self-administration experiment, results from the first trial were analyzed separately from the remaining trials. Two-way ANOVAs were performed on acoustic and tactile results with time point as a repeated measure.

TABLE 1

STARTLE RESPONSES (±SEM) BEFORE SURGERY, AFTER SURGERY, AFTER COCAINE SELF-ADMINISTRATION TRAINING AND AFTER A 3-H COCAINE SELF-ADMINISTRATION SESSION (ACUTE COCAINE)

	Control* (SEM) (n = 7)	Cocaine (SEM) (n = 7)
Presurgery	†307.1 (49.9)	333.9 (59.9)
Postsurgery	498.5 (86.4)	‡387.9 (93.4)
Posttraining (Baseline)	†637.2 (103.5)	516.6 (93.7)
Acute cocaine	577.7 (105.3)	‡§353.1 (45.1)

*Control subjects were tested on the same occasions as cocaine subjects but received no surgery or cocaine treatments.
†Significantly different from postsurgery.
‡Significantly different from posttraining.
§Significantly different from control.

RESULTS

Experiment 1: Self-Administration Study

Effects of catheter implantation. The implantation of the self-administration catheter did not have a significant effect on startle response magnitude in the cocaine group (Table 1). A two-factor ANOVA with one repeated-measures factor on these data indicated a significant increase in startle response magnitude from the first to the second startle session, $F(1, 12) = 7.55$, $p < 0.05$. This increase was statistically significant only for the control group ($p < 0.05$) and not for the cocaine group. Neither the group factor, $F(1, 12) = 0.19$, NS, nor the interaction term, $F(1, 12) = 2.37$, NS, however, was statistically significant. Thus, in the subsequent ANOVA that assessed the effects of repeated testing and the effects of a recently completed self-administration session on startle response magnitude, the postsurgery startle values were used as the control.

Effects of self-administration training and acute cocaine. A three-factor ANOVA with one repeated-measures factor showed no differences between the two groups on any of the three startle sessions (postsurgery, posttraining, acute cocaine), $F(1, 12) = 1.78$, interaction, $F(2, 24) = 0.82$, NS. However, as in the analysis above, there was a significant effect of the repeated-measures factor, $F(2, 24) = 4.2$, $p < 0.05$, reflecting increased startle responding from the postsurgery session to the posttraining session in both groups, and reduced startle responding during the acute cocaine session as compared to the posttraining session for the cocaine group only ($p < 0.05$). This decrease in startle produced by recently self-administered cocaine was also significant when compared to responding in time-matched control rats.

Effects of termination of a cocaine binge. In light of the results presented above, the posttraining baseline was selected as a comparison measure for assessing the effects of discontinuation of cocaine self-administration. Mean intake (±SEM) of cocaine during the final 12-h session was 107.9 (±7.5) mg/kg, ranging from 67–129 mg/kg in individual subjects. Mean startle amplitudes in the cocaine group were lower than in the

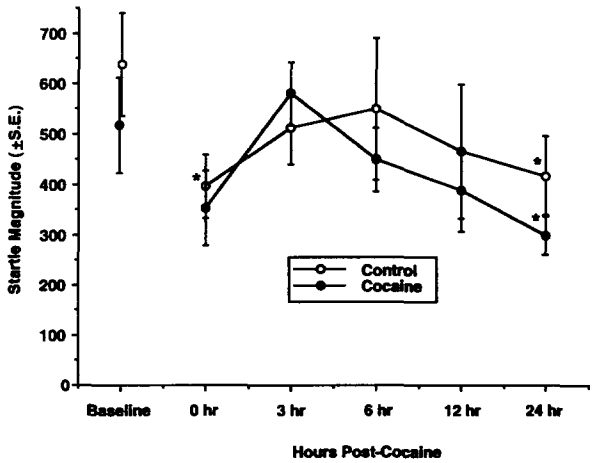

FIG. 1. Acoustic startle response magnitude at different time points after a 12-h session of IV cocaine self-administration (cocaine group) or no treatment (control group). There were no significant differences between control and cocaine groups (n = 7/group) at any time point. Baseline refers to the results of a startle test session conducted in both groups after the cocaine rats were trained to self-administer cocaine (see text). Asterisks indicate significant differences from each group's own baseline, Newman-Keuls following ANOVA ($p < 0.05$).

control group at most time points after cocaine discontinuation (Fig. 1). However, this effect was not statistically significant at any time point during withdrawal, as indicated by a two-factor ANOVA [group factor, $F(1, 12) = 0.63$, and group × time interaction, $F(5, 60) = 0.9$, NS). However, as in earlier testing in these subjects, startle responses changed with repeated testing, $F(5, 65) = 5.96$, $p < 0.01$]. Although there were no statistically significant differences between the two groups over the period of withdrawal testing, startle amplitudes in the cocaine group were significantly decreased relative to the baseline test at 24 h postcocaine. In the control group, startle was decreased relative to baseline at the 0 and 24 h time points ($p < 0.05$).

The withdrawal data were also transformed to percentage scores, using as baseline the postsurgery results, or the collapsed mean resulting from the presurgery and postsurgery sessions. ANOVAs on the percentage data further confirmed a lack of significant changes in startle responding during cocaine withdrawal. In addition, analyses of the data by blocks of startle trials (trial 1, trials 2–6, trials 7–11, trials 12–16, trials 17–21) also yielded no statistically significant differences between the two treatment groups.

Finally, correlation coefficients were calculated on the amount of cocaine self-administered during the 12-h session vs. startle response magnitude at 0, 3, 6, 12, and 24 h postcocaine. None of the correlations, which ranged from 0.00 to −0.483, was statistically significant, indicating that varying exposure to cocaine was not likely to have contributed to the lack of observed behavioral dependence.

Experiment 2: Chronic Infusion Study

One subject assigned to the cocaine group died during surgery. Baseline (presurgery test) and subsequent startle measures are presented in Figs.2 and 3 for the remaining 11 subjects in the cocaine group and 12 subjects in the saline infusion group. On the baseline matching day, mean startle scores following tactile stimuli (± SEM) were 248.6 (± 21.2) startle units in the designated saline group and 247.4 (± 36.2) units in the designated cocaine group. For acoustic stimuli, mean scores were 178.1 (± 21.4) units in the saline group and 199.8 (± 47.8) units in the cocaine group. With subjects assigned in this way, there were no statistically significant differences between the two groups for either stimulus modality. Stabilimeter readings were uniformly low (< 10) during trials in which no stimulus was delivered, and this measure was not affected by the treatment conditions or time points (data not shown).

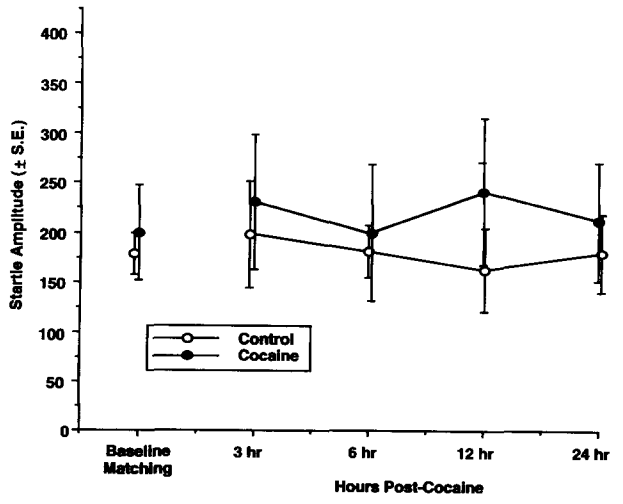

FIG. 2. Acoustic startle responding following the termination of chronic intraperitoneal infusions of cocaine ($n = 11$) or saline ($n = 12$). Baseline Matching refers to the results of a startle test prior to surgery after which subjects were assigned to groups to produce nearly equivalent mean scores.

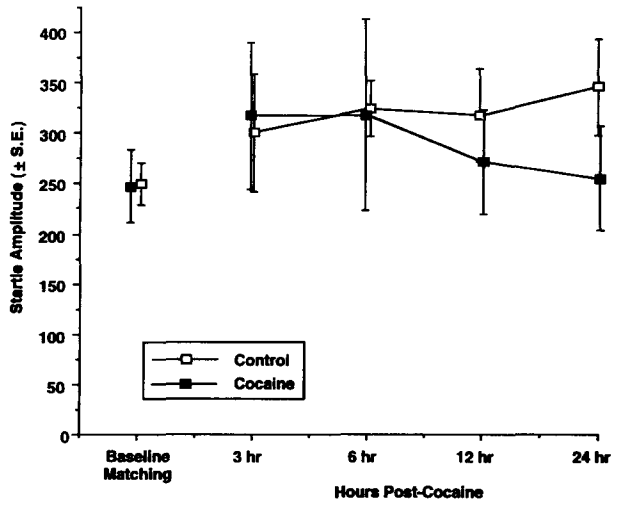

FIG. 3. Tactile startle responding following the termination of chronic intraperitoneal infusions of cocaine ($n = 11$) or saline ($n = 12$). Details are as in Fig. 2.

On the acoustic measure, startle responding was largely unchanged from baseline measures in control animals over the course of withdrawal testing. Startle magnitude was higher in rats having undergone chronic cocaine infusion than in controls, with the group difference greatest at the 12 h time point. However, there were no main effects of infusion condition, $F(1, 21) = 0.3$, or time point, $F(3, 63) = 0.2$, and no interaction, $F(3, 63) = 0.7$, indicating a lack of evidence for cocaine withdrawal using the acoustic modality.

Startle responses to tactile stimuli were slightly but nonsignificantly decreased during withdrawal tests in the cocaine group as compared to the control group at the 12 and 24 h time points. As with the acoustic measure, however, there were no main effects of infusion condition, $F(1, 21) = 0.2$, or time point, $F(3, 63) = 0.25$, and no treatment-by-time-point interaction, $F(3, 63) = 1.0$. Finally, effects on the first trial were not systematically different from those of the remaining trials for either stimulus modality.

DISCUSSION

The results of the present study do not provide evidence of dependence upon cocaine as measured by the startle response in rats. In light of earlier published results (6,13), it was expected that short sessions of cocaine self-administration would increase startle scores when measured immediately afterward. However, there was a statistically significant decrease in startle following a 3-h session of cocaine self-administration in Experiment 1. This unexpected finding may be explained, in part, by differences in the route and time course of drug administration, and the inability to conduct a full dose-response curve in the present study. In fact, previous research has shown that acute effects of stimulants on startle can be bipha-

sic, consisting of an early excitatory phase followed by a later depressive phase (7). After the initial startle tests, rats were allowed to intravenously self-administer cocaine for a period of 12 h, and then drug access was terminated. While startle responding in cocaine-treated animals tended to be lower than in controls at most postdrug time points, none of these differences achieved significance. There was some evidence that repeated testing influenced startle magnitude, as when progressive decreases were observed from 3–24 h postcocaine (Fig. 1), but these effects occurred in both groups and were unlikely to have masked the expression of dependence. In Experiment 2, when repeated startle tests were given at the same postcocaine times as in the self-administration study, scores remained relatively constant or slightly increased. In previous studies of morphine withdrawal, significant differences between the startle scores of withdrawn and nondependent subjects were still observable after four or more startle tests (19), suggesting that repeated testing does not necessarily mask withdrawal effects.

Although not statistically significant, the decreased startle scores in cocaine animals at the 0 h time point in Experiment 1 may have been indicative of the effects of recently self-administered cocaine or the effects of a lengthy period of operant responding. However, it is unclear why control scores should also have been decreased. Consequently, this pattern of results makes difficult any comparison of the first time point with baseline measures or with subsequent time points during withdrawal. However, the observed startle decreases at the 24-h time point were significant in comparison to baseline observations in both groups. Comparisons between the two groups at different time points, and additional analyses that transformed scores to percentages of baseline and examined trial blocks within sessions yielded no statistically significant differences. Thus, there was no evidence to support the existence of a withdrawal effect after the extended period of cocaine self-administration.

As in the study of self-administered cocaine, no significant disruptions of startle responding were observed following discontinuation of noncontingently administered cocaine. The study of passively infused cocaine was intended to determine whether the failure to observe behavioral dependence in self-administering animals was due to insufficient exposure to the drug, unequal dosages among animals, or to inconstant drug offset times. The results showed that while mean cocaine dosage was similar for the two experiments over the final 12 h of administration (107.9 mg/kg for Experiment 1 and 85 mg/kg for Experiment 2), the additional cocaine exposure in the passive infusion study and the more constant drug delivery was not more effective than the self-administration technique in demonstrating abstinence. It is, therefore, clear that our failure to observe a withdrawal effect using the startle response was not due to an inadequate dosing regimen. Experiment 2 also assessed whether the modality of startle stimulus (acoustic vs. tactile) would influence the expression of dependence as measured by the startle response. Although neither modality yielded evidence of cocaine withdrawal, the opposite trends in startle responding observed after cocaine discontinuation suggest that stimulus modality could be an important factor in future drug-dependence studies utilizing this behavior.

In humans, cocaine abstinence appears to manifest itself as a predominantly motivational state, which includes only a mild form of the more familiar physical component of withdrawal. These characteristics may help to explain why cocaine abstinence is not easily detected by the startle response or by procedures designed to assess performance deficits. For instance, in operant studies observing the effects of cocaine discontinuation, behavioral disruptions (usually response-rate decreases) have been reported (4,29), but these decreases do not always occur in the first 24 h, the period during which the vast majority of cocaine is metabolized or excreted (21). Moreover, several other experiments failed to reveal evidence of behavioral dependence upon cocaine as measured by disruptions of schedule-controlled responding (3,5,14). Thus, while the discontinuation of cocaine administration does produce clear consequences, these consequences may be qualitatively different from the sequelae of withdrawal from opiates or other CNS depressants when these methods are used as dependent measures.

The findings of Experiment 1 differ from the results of a nearly identical study in which significant and time-dependent elevations in ICSS thresholds occurred in the first 24 h following discontinuation of cocaine self-administration in rats (20). The early onset of the elevation in reward thresholds was suggested to parallel a similar phenomenon in humans (crash) following an extended period of cocaine-taking behavior (binge). This postcocaine crash (10,11) has been proposed to represent an early phase of cocaine abstinence during which subjects experience decreased interest in normally pleasurable activities or stimuli. The lack of changes in startle amplitude in the present study provides further evidence that the increases in ICSS thresholds observed by Markou and Koob (20) can be dissociated from nonspecific behavioral disruption which might also have occurred during the first 24 h of withdrawal.

Using the startle measure, evidence of dependence has been observed following termination of ethanol and morphine administration (19,22). Interestingly, the withdrawal syndromes produced by both alcohol and morphine are usually characterized as excitatory in nature, but the startle experiments yielded opposite results, with ethanol abstinence resulting in startle increases and morphine abstinence resulting in startle decreases. Because both effects on startle were opposite to those observed during chronic administration, it is tempting to suggest that the behavioral expression of drug abstinence as measured by startle may be reflective of an opponent process (17). Acutely administered cocaine has been reported to increase startle (6,13), while, in the present study, there was evidence for decreases in acoustic startle immediately after 3 and 12 h cocaine self-administration sessions. Because the acute effects of cocaine appear to vary across experiments, it would be difficult to predict based on available data whether changes in startle during cocaine withdrawal should be represented by increases or decreases in magnitude.

In conclusion, currently available data suggest that the discontinuation of high-dose cocaine results in an abstinence syndrome clearly different from that produced by CNS depressants. Abstinence after exposure to CNS depressants is characterized by severe somatic signs, while cocaine abstinence is typified by motivational signs which are apparently not reflected by changes in startle response magnitude. Future experiments will be necessary to more fully characterize the cocaine abstinence syndrome and how it differs from abstinence syndromes associated with other drugs of abuse.

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