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Cocaine Euphoria, Dysphoria, and Tolerance Assessed Using Drug-Induced Changes in Brain-Stimulation Reward

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FRANK, R. A., P. Z. MANDERSCHEID, S. PANICKER, H. P. WILLIAMS AND D. KOKORIS. *Cocaine euphoria, dysphoria, and tolerance assessed using drug-induced changes in brain-stimulation reward.* PHARMACOL BIOCHEM BEHAV **42**(4) 771–779, 1992.—The time course of cocaine-induced changes in self-stimulation thresholds were used to evaluate cocaine euphoria and dysphoria as a function of the chronicity of drug treatment, dosage level, and the spacing of injections. It was assumed that cocaine-induced decreases in thresholds were indicative of cocaine euphoria, while increases in thresholds reflected rebound dysphoric responses to cocaine administration. Three experiments were performed using self-stimulating rats implanted with ventral tegmental area electrodes. Cocaine's threshold-lowering effects were evident 15 min postinjection (IP) with thresholds returning to baseline by approximately 3.0 h after treatment. Little evidence for cocaine-induced *increases* in thresholds was observed during periods of chronic cocaine treatment. However, thresholds were slightly elevated upon withdrawal from chronic cocaine treatment in Experiments 2 and 3. No evidence of tolerance or sensitization to cocaine-induced shifts in thresholds was noted with single daily injections, while multiple daily injections produced tolerance to cocaine's threshold-lowering effects. It is concluded that cocaine's ability to enhance brain-stimulation reward is highly reliable and robust, while *decreases* in brain-stimulation reward associated with chronic cocaine treatment are less reliable and difficult to demonstrate. The possible influence of drug dosage on the induction of cocaine dysphoria and the ability of various self-stimulation procedures to measure dysphoric effects are discussed.

Brain stimulation reward Euphoria Dysphoria Chronic cocaine Self-stimulation threshold Drug abuse Cocaine tolerance

OVER the past several years, there has been increasing interest in developing pharmacotherapies for substance abuse, particularly drug therapies for cocaine abuse (19,24).The main rationale for this approach is that habitual cocaine use produces alterations in central neurochemistry that are responsible for drug craving and dysphoria in the abstinent user (9). If drugs could be found that reverse the effects of cocaine, such compounds could be used during the initial stages of treatment to mitigate craving and rebound dysphoria, thus allowing the other components of a treatment strategy to be more effective.

Animal models have been employed to evaluate the behavioral pharmacology of cocaine abuse (2,4,11,38) and assess the therapeutic potential of a number of "anticocaine" agents (22,29). One model that offers a number of attractive features involves the assessment of a drug's effects on intracranial self-stimulation. Self-stimulation thresholds and maximal response rates can be measured using a curve shift paradigm that has been rigorously validated in a number of laboratories (13,27,40). It has been demonstrated that thresholds are sensitive to changes in brain-stimulation reward while maximal response rates are altered by manipulation of performance capacity (13). Since euphorigenic drugs decrease self-stimulation thresholds and drugs that blunt reward increase thresholds (17), it is possible to evaluate whether a drug's ability to reduce or block cocaine self-administration is due to a drug-induced reversal of cocaine's effects, the deactivation of the reward substrate, or the drug's own euphorigenic effects. Thus, self-stimulation threshold experiments can provide information concerning the mechanism(s) by which a compound modifies drug self-administration (15).

It is necessary to understand how cocaine influences rewarding brain stimulation when administered alone if one

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The results of Experiment 2 were presented in preliminary form at the Nineteenth Annual Meeting of the Society for Neuroscience in Phoenix, Arizona, November 1989.

wishes to assess an agent's ability to reverse these effects. It is well established that cocaine lowers thresholds for self-stimulation in the period immediately following drug administration (10,14-16,25,26,30). This finding is taken as evidence that cocaine sensitizes the neural circuitry that mediates the rewarding aspects of the stimulation, and it is presumed that cocaine's effects on this substrate are responsible for the drug's euphorigenic effects. It has been hypothesized that a dysphoric, rebound reaction may follow the positive affective changes induced by cocaine, especially with chronic drug use (24). If this dysphoric reaction is related to a hypoactive central reward substrate, rebound dysphoria should produce an elevation of self-stimulation thresholds. Postcocaine elevation of self-stimulation thresholds has been reported recently by several investigators (5,25,28), suggesting that self-stimulation paradigms may be used to assess both the euphoric and dysphoric responses induced by cocaine. In addition, the ability of potential pharmacotherapies to reverse these effects could be explored.

Previous self-stimulation experiments focused on either cocaine-induced increases *or* decreases in brain-stimulation reward but not on the transition from one to the other. If cocaine administration leads to activation, and then depression of neural reward substrates, it should be possible to follow the expression of this pattern by measuring self-stimulation thresholds with multiple daily postinjection tests. In addition, since the elevation of thresholds may only emerge following chronic cocaine treatment it may be necessary to trace the development of rebound dysphoria over days of drug administration. In the first of three experiments, self-stimulation train-duration thresholds were measured from 15-195 min postinjection over 18 days of cocaine treatment. Testing was also performed for 6 days following chronic drug administration. It was predicted that cocaine would lower self-stimulation thresholds during the initial postinjection period, followed by increases in thresholds above baseline, saline levels. It was also predicted that the increases in thresholds would become larger over the days of chronic cocaine treatment, reflecting the development of a rebound, dysphoric response.

EXPERIMENT 1

METHOD

Subjects and Surgery

Male Sprague-Dawley rats (Zivic Miller Labs, Pittsburgh, PA) weighing between 300-400 g (at the time of surgery) served as subjects. Animals were individually housed in stainless steel wire hanging cages and had continuous access to food (Purina Lab Chow) and water except during testing. They were maintained on a reversed 12 L:12 D cycle at a temperature of 70°F. All testing was performed during the dark cycle. Each rat was implanted with a bipolar stainless steel electrode (Plastics One, Roanoke, VA, electrode diameter = 0.5 mm) under sodium pentobarbital anesthesia (55 mg/kg). The electrodes were aimed at the ventral tegmental area using the coordinates 4.5 mm posterior from bregma, 1.5 mm lateral from the midline, and 8.5 mm ventral from the skull surface, with the skull held level between lambda and bregma.

Apparatus

All training and testing took place in six metal and Plexiglas chambers (23 × 21 × 19 cm) with a floor constructed of aluminum rods spaced 1.0 cm apart. One wall of the chamber had a 3.5-cm square hole positioned 5.0 cm above the floor. The hole opened into a 5 × 5 × 4 cm chamber that contained a photocell beam. A 1.0-cm excursion of an object such as a rat's nose into the chamber initiated a signal pulse that was registered as a response by the computer.

Brain stimulation was delivered by Grass (Quincy, MA) SD9 square-wave stimulators. These stimulators delivered constant-current bipolar square-wave stimulation through a high-impedance stimulation circuit. Stimulation frequency and pulse width were set at 100 Hz and 5.0 ms, respectively. Currents were selected such that train-duration response functions were centered around 50-100 ms (see below). Train duration was timed with an Advanced Logic Research 80286 computer. The computer also handled all other timing and logic functions.

Procedure

Animals were screened for self-stimulation following a 10-day postoperative recovery period. The most reliable rats (n = 12) were selected for further study. These animals were trained to self-stimulate during 75-s trials separated by 15-s time-out periods. Each trial was broken down into a 15-s warm-up period and a 60-s test. The train duration of the stimulation was set at 250 ms during this phase of the experiment. Once subjects were responding reliably during test trials, but not during time-outs, the train duration available during each trial was varied from 0-140 ms in 10 ms-intervals. The order of presentation of these different train durations was randomized across trials. Current levels were then adjusted so that the train duration that supported no responding and that which supported maximal response rates fell between 50-100 ms. One training session was run for all animals each day until appropriate currents had been selected for all subjects.

In the next phase of the experiment, rats were injected (IP) with isotonic saline (0.25 ml) 15 min prior to testing for 3 consecutive days. Next, half the animals were injected with 15 mg/kg cocaine HCl (IP) 15 min prior to testing, while the remaining rats received 30 mg/kg. Animals were subsequently tested at 45, 135, and 195 min postinjection. This procedure was maintained for 18 consecutive days. At the end of this period, subjects were tested for 6 additional days with saline as described previously.

Histology

At the conclusion of testing, rats were sacrificed with an overdose of sodium pentobarbital and then perfused through the heart with a 10% formal-saline solution. Brains were subsequently sectioned at 60 μm using the frozen method and sections were examined to determine locations of the electrode tips.

RESULTS AND DISCUSSION

Train-duration response functions were generated for each animal for the saline and cocaine conditions by calculating the median response rate for each train duration across 3-day blocks of testing. (An example of a train duration response function is shown in Fig. 1.) This produced nine functions for each animal (one for predrug baseline, six for cocaine treatment, and two for postdrug saline testing) at each of the four test times. Self-stimulation thresholds were calculated from these functions by determining the shortest train duration that supported 50% of the maximal response rate ob-

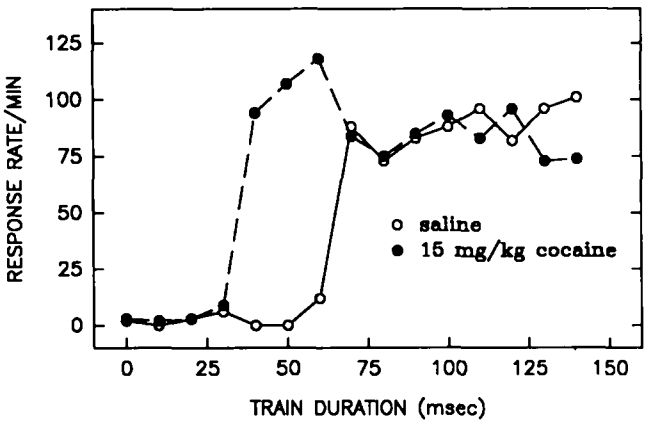

FIG. 1. Train-duration response functions for an individual rat following saline or 15 mg/kg cocaine HCl (IP). Each data point is the median of 3 days of testing.

served for each of these functions. Thresholds were typically found by interpolating between two train durations. Mean thresholds were then calculated for the saline and cocaine conditions across the four testing times for the 15- and 30-mg/kg doses of cocaine. These means are shown in Figs. 2 and 3.

The cross-hatched areas shown in each of the graphs delineate ± two SEM around the mean of the predrug and second postdrug saline blocks of trials. Means that fall outside these confidence intervals are significantly different from saline threshold. As can be seen, cocaine generally lowered thresholds for both dosage levels at 15, 45, and 135 min postinjection. By 195 min postinjection, animals in both groups had begun to return to saline baseline.

The thresholds showed no pattern of tolerance or sensitization over the period of cocaine treatment as evaluated by a repeated-measures analysis of variance (ANOVA) performed at each testing time across blocks of trials. This finding replicates an earlier report from our lab (14). Since there were no significant effects across days of testing, the data were collapsed across days. These collapsed threshold data are shown in Fig. 4, expressed as percentages of saline baseline (defined as the average of the first and final saline tests for each testing period).

Inspection of Fig. 4 suggests cocaine's effects were more pronounced at 30 mg/kg, lowering thresholds more and lasting a longer time at the higher dosage level. This impression was tested by assessing the difference between the cocaine means for the two doses to see if they were significantly different at each time interval. Repeated-measures student's *t*-tests revealed that the threshold changes were larger for the 30-mg/kg dose than for the 15-mg/kg dose at 15, 45, and 135 min postinjection ($p < 0.05$).

Finally, the effects of withdrawal from chronic cocaine treatment were evaluated. A repeated-measures ANOVA was used to compare the thresholds from predrug saline testing to the two postdrug saline tests. This analysis revealed no significant differences among the three saline test periods. The return of thresholds to predrug levels following cocaine treatment replicates our previous findings (14).

The results of Experiment 1 can be summarized as follows. Cocaine lowered thresholds for brain-stimulation reward during the period that immediately followed drug administration. Thresholds returned to baseline approximately 3 h postinjection. The higher dose produced a larger and longer-lasting effect, and there was no evidence for tolerance or sensitization to cocaine's effects over the 18 days of drug treatment. In addition, rats returned to predrug saline baselines following the period of chronic drug administration. Thus, there was no evidence of a "cocaine crash" after a period of chronic drug treatment.

The histological analyses revealed that the electrode tips were located in the medial forebrain bundle at the level of the ventral tegmental area and substantia nigra. The distribution of the electrode placements was essentially identical to the distributions of placements we have reported previously (13).

EXPERIMENT 2

No evidence of cocaine-induced dysphoria was found in Experiment 1. However, since self-stimulation thresholds were returning to baseline at the last postinjection test it is possible that an elevation of thresholds would have been observed if postinjection testing had been extended. In Experiment 2, testing was extended to 435 min postinjection to test the hypothesis that self-stimulation thresholds would be elevated during these later testing periods.

METHOD

Subjects

Ten male Sprague-Dawley rats served as subjects for the experiment. They were implanted with ventral tegmental area electrodes as described previously. Details of their housing, etc. are described in Experiment 1.

Procedure

The procedures used in Experiment 2 were identical to Experiment 1 with the following exceptions. Tests were 45 min in length and consisted of three blocks of 15 trials each. Each trial began with a 15-s self-stimulation warm-up period followed by a 30-s test. A different train duration ranging between 0–140 ms was available during each trial. Each test period was followed by a 15-s time-out. This procedure allowed us to calculate median response rates for each train duration for each day of testing and thereby calculate daily thresholds. Animals were tested in two groups of five animals each. One group was tested at 15, 135, 255, and 375 min postinjection. The other group was tested 75, 195, 315, and 435 min postinjection. Cocaine HCl was injected (IP) at a dosage of 25 mg/kg. Animals were tested following saline injections for 3 days, then tested with cocaine for 18 consecutive days. Immediately following the cocaine phase, rats were tested for 3 additional days with saline. Finally, after a 14-day hiatus 3 days of saline testing were performed.

RESULTS AND DISCUSSION

Train-duration response functions were generated for all testing times each day by calculating median response rates across the three blocks of trials at each testing time. Self-stimulation thresholds were determined using these functions and mean daily thresholds were calculated from these data. Saline baseline was determined by averaging the mean daily thresholds across the predrug saline test and the final 3 days of saline testing [repeated-measures ANOVA revealed that thresholds for these two periods did not differ across testing times ($p < 0.05$)]. Daily mean thresholds from the cocaine tests and from the saline testing that immediately followed

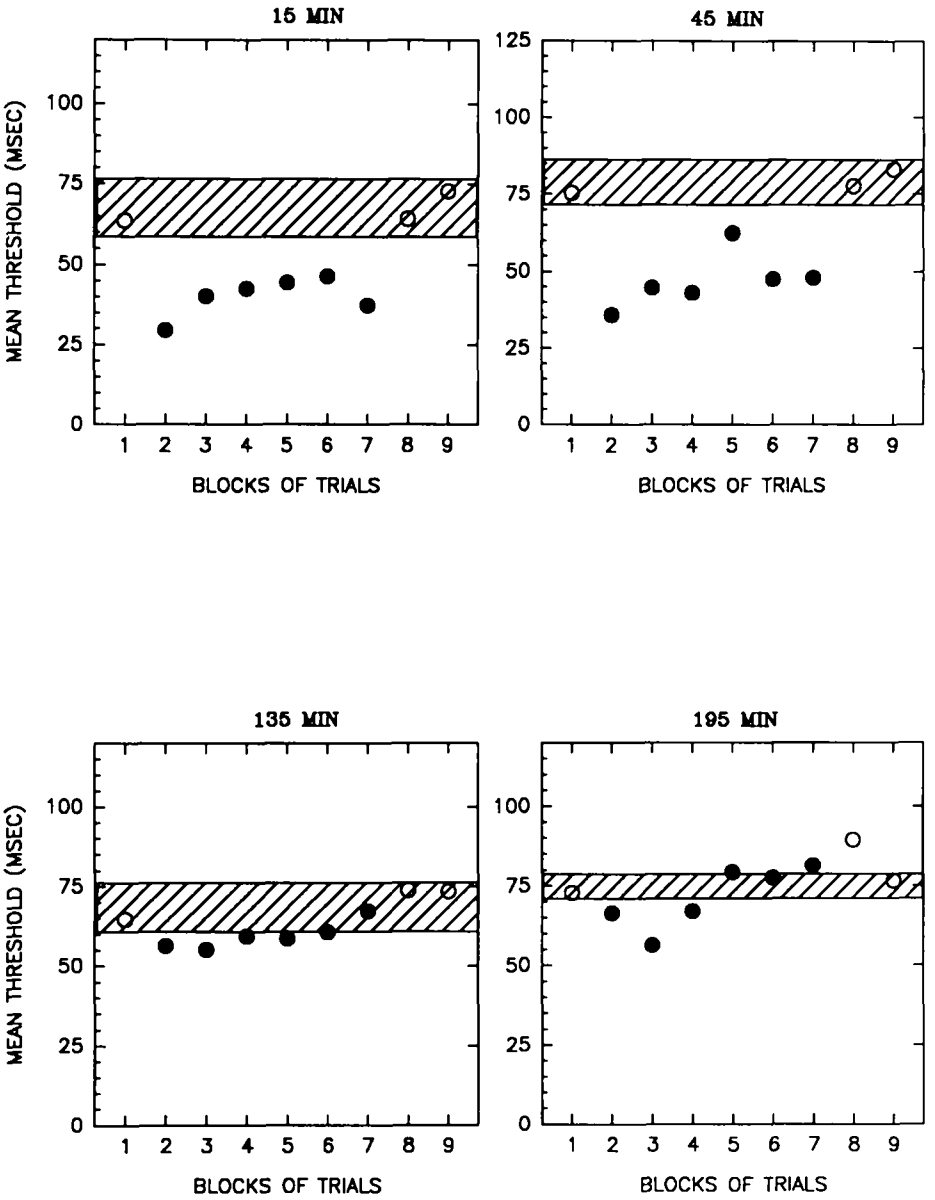

FIG. 2. Mean train-duration thresholds for 3-day blocks of trials following saline (○) or 15 mg/kg cocaine HCl (●). The hatched areas in each panel show ±two SEM from the mean of the first and last saline test blocks.

chronic cocaine treatment were collapsed into 3-day blocks of trials. These data were then analyzed with a repeated-measures ANOVA to assess changes in thresholds across the blocks of chronic cocaine treatment. As found in Experiment 1 and previously (14), cocaine's threshold-lowering effect did not change across the 18 days of testing. Therefore, the data were collapsed across days of testing. The threshold data from Experiment 2 are shown in Fig. 5, expressed as percentages of saline baseline.

As observed in Experiment 1, cocaine significantly lowered thresholds up to 195 min postinjection (repeated-measures t-tests, $p < 0.05$). Then, however, there is a trend toward increases in thresholds. However, these increases in thresholds were not significant (repeated-measures t-tests, $p > 0.05$).

A repeated-measures t-test was also used to evaluate the changes in postdrug saline thresholds for the test block that immediately followed chronic cocaine treatment. The percent change from saline baseline was calculated for this test at each of the eight test times, these scores were averaged, and the mean percent change was assessed to determine whether it differed from zero. Thresholds increased an average of 28%, a significant increase in thresholds for this period (repeated-measures t-test, $p < 0.05$). The finding that rats failed to return to saline baseline in the period that immediately followed

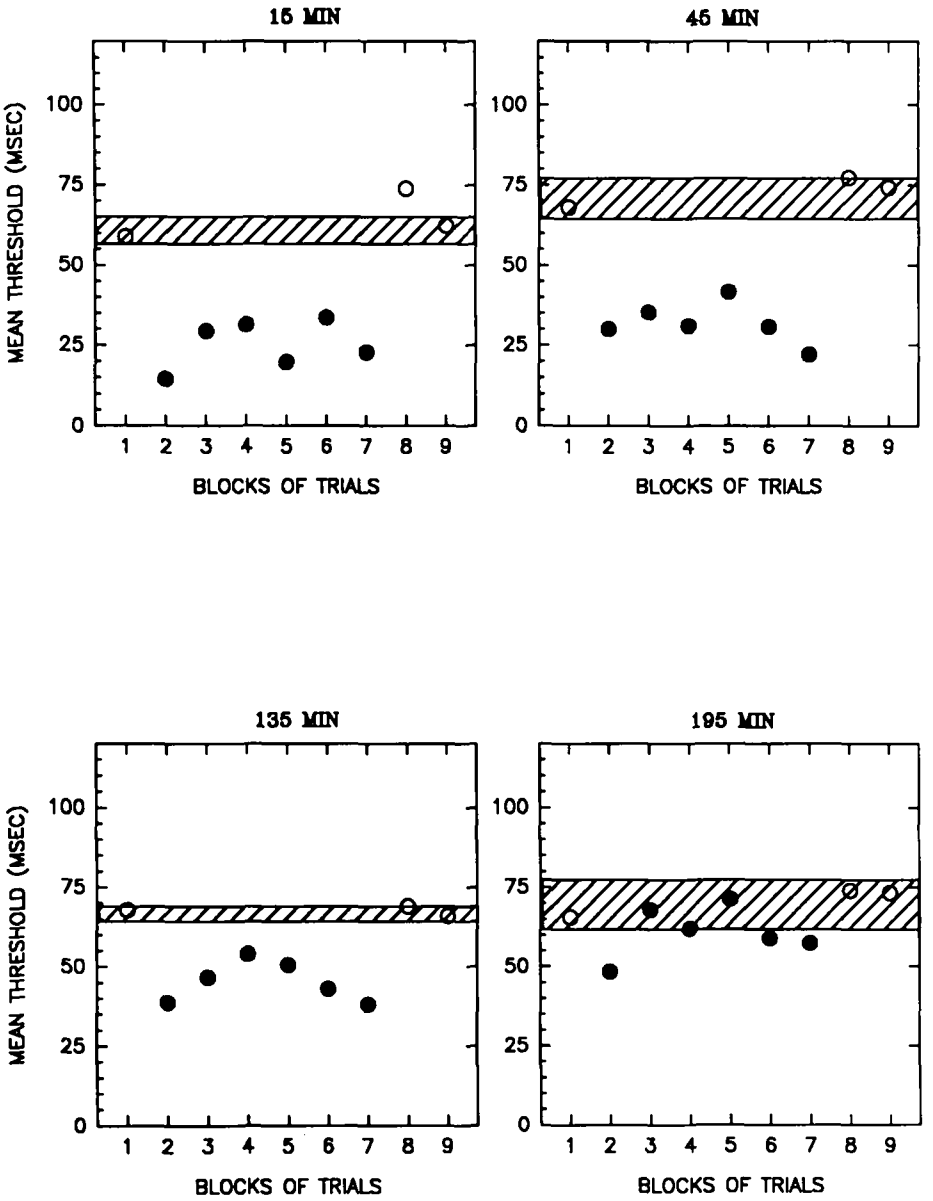

FIG. 3. Mean train-duration thresholds for 3-day blocks of trials following saline (○) or 30 mg/kg cocaine HCl (●). The hatched areas in each panel show ± two SEM from the mean of the first and last saline test blocks.

chronic cocaine administration may be taken as evidence for a dysphoric reaction associated with cocaine withdrawal. A similar effect has been reported by others (5,25,28). However, this effect was not observed in Experiment 1, nor was it observed in a previous experiment from our laboratory (14).

EXPERIMENT 3

Although postcocaine rebound dysphoria has been reported by researchers from three different self-stimulation laboratories (5,25,28), little evidence for such an effect was observed in Experiments 1 and 2. A comparison of the procedures used in Experiments 1 and 2 and the other studies reveals differences in the doses employed and the spacing of cocaine injections. These factors have been shown to have a substantial impact upon the behavioral effects of cocaine and other psychomotor stimulants (12,19). Experiment 3 was designed to assess the influences of multiple daily injections of cocaine on cocaine-induced changes in self-stimulation. Markou and Koob (28) examined self-stimulation thresholds in rats that had been self-administering cocaine from 3–48 h prior to self-stimulation testing. They reported that self-stimulation thresholds were not significantly elevated when animals were given 3 or 6 h of prior cocaine self-administration. However, 12–48 h of prior cocaine self-administration resulted in significant elevations in thresholds. The authors found that the amount

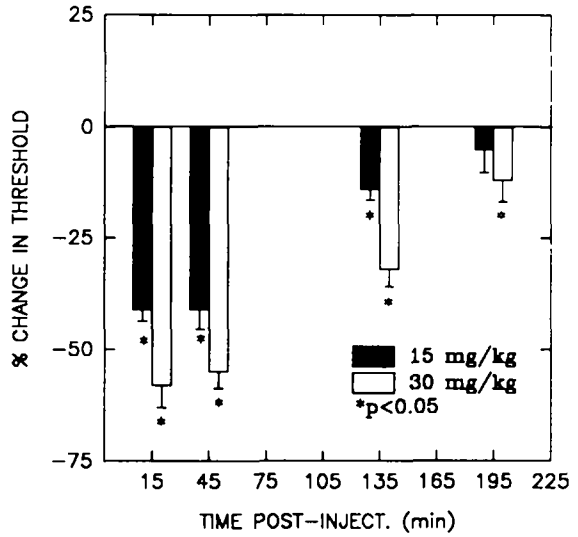

FIG. 4. Mean changes in thresholds across the four postinjection testing times for both the 15- and 30-mg/kg groups of Experiment 1. The data have been collapsed across blocks of trials and are expressed as % changes from the mean of the first and final saline tests. *significant difference from saline baseline (repeated-measures t-test, $p < 0.05$).

of cocaine consumed during the self-administration period was positively and significantly correlated with the extent to which self-stimulation thresholds were increased. The average dose of cocaine associated with a significant increase in thresholds was 110 mg/kg/self-administration session. The procedure used by Markou and Koob (23) was approximated in Experiment 3 by injecting rats with 30 mg/kg cocaine at 3.0-h intervals over a 12-h period and then giving self-stimulation tests 0.5, 3.0, 6.0, and 13.0 h following final injection.

METHOD

Subjects

Twelve male Long-Evans rats (Harlan, Indianapolis, IN) were implanted with electrodes and maintained as described in the previous experiments.

Procedure

The details of the experimental procedure were identical to those described in Experiment 2 with the following exceptions. Each self-stimulation test period was 1.0 min in length. Testing began with a 3-day predrug saline condition. Isotonic saline was injected at 3.0-h intervals over a 12.0-h period for a total of four injections. The effects of saline treatment were assessed at 0.5, 3.0, 6.0, and 13.0 h following final injection. One group of rats ($n = 6$) was tested at 0.5 and 6.0 h postinjection, while the other group ($n = 6$) was tested at 3.0 and 13.0 h postinjection. In the next phase, saline injections were replaced with 30 mg/kg cocaine HCl (IP). Following 3 days of testing with the cocaine schedule, a postdrug saline test was performed that was the same as the predrug saline testing except only a single test was performed 24.5, 27.0, and 30.0 h following the last cocaine injection.

Following a 14-day hiatus, saline testing resumed for 3 days. A single saline injection was given 30 min prior to testing, and only one test was performed each day. Next, rats were tested for 3 consecutive days following a single injection of 30 mg/kg cocaine HCl. Finally, a postdrug saline test was performed that was identical to predrug saline testing.

RESULTS AND DISCUSSION

Self-stimulation thresholds were calculated as described in Experiment 2. Mean thresholds were calculated across days of testing for those conditions run for more than 1 day. A one-between (testing time), one-within (first and second predrug test) ANOVA performed on the predrug saline thresholds showed no significant difference among any of the predrug tests ($p > 0.05$) so predrug saline thresholds were averaged to create a single predrug saline baseline for each rat.

Each subject's predrug saline baseline was then divided into the thresholds collected 0.5, 3.0, 6.0, and 13.0 h following cocaine treatment so that these conditions were expressed as percentages of predrug saline baseline. The resulting percentages are shown in Fig. 6.

Cocaine failed to lower self-stimulation thresholds at any of the postdrug testing intervals (repeated-measures t-tests, $p > 0.05$). This finding is especially interesting in the case of the 30-min postinjection test since a substantial reduction in thresholds was noted during this time period in Experiments 1 and 2. It appears that tolerance developed to cocaine's rewarding effects as a result of the multiple-injection procedure. Frank et al. (14) found no evidence of tolerance to cocaine-induced reductions in thresholds when three 25-mg/kg injections were separated by an 8.0-h interinjection interval. This suggests that the critical interinjection interval for inducing tolerance (with doses of 25–30 mg/kg) lies between 3.0–8.0 h.

Self-stimulation thresholds were elevated (15–61%) for tests conducted at 24.5, 27.0, and 30.0 h following final cocaine injection, but the increases in thresholds were not statis-

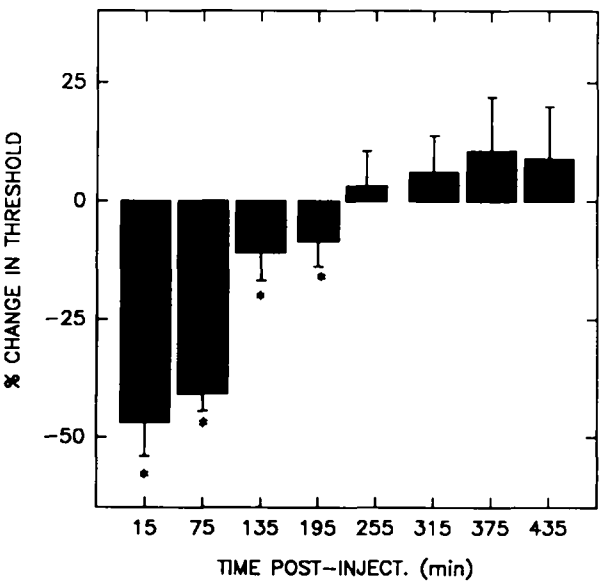

FIG. 5. Mean changes in thresholds across the eight postinjection testing times of Experiment 2. The data have been collapsed across blocks of trials and are expressed as % changes from the mean of the first and final saline tests. *significant changes from baseline saline thresholds (repeated-measures t-test, $p < 0.05$).

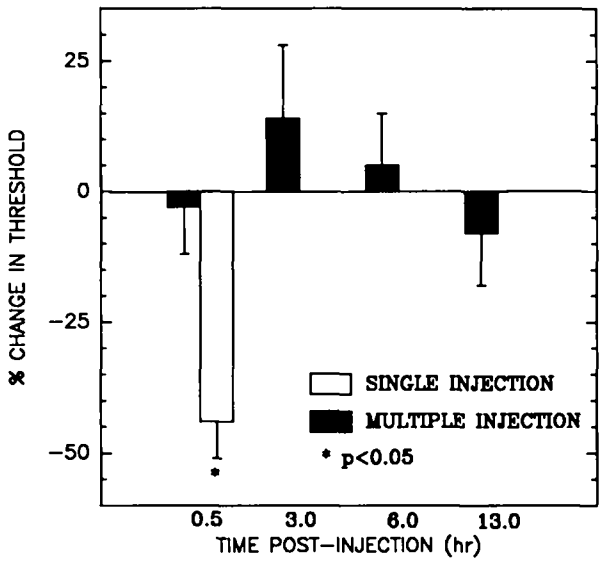

FIG. 6. Mean changes in thresholds across testing times for Experiment 3. The solid bars show data collected following multiple injections of cocaine while the open bar shows data following a single pretreatment injection. *significant changes from baseline saline thresholds (repeated-measures t-test, $p < 0.05$).

tically significant (repeated-measures t-tests, $p > 0.05$). The failure of these increases in threshold to reach significance was related to the increased variability observed among subjects during postdrug saline testing. While some subjects returned to predrug saline levels of responding, others exhibited substantial declines in self-stimulation behavior.

Finally, thresholds returned to predrug saline levels once testing resumed 14 days following the first phase of the experiment. In the next phase of the experiment, single daily injections of 30.0 mg/kg cocaine produced a significant threshold decrease (−44%) when animals were tested 30 min postinjection [repeated-measures t-test comparing the average of all saline testing to cocaine, $t(5) = 6.3$, $p < 0.05$]. The 44% reduction is comparable to that seen in Experiments 1 and 2 in the present series of experiments and other experiments performed in our lab (14,15). The same group of animals showed a 3% decrease in thresholds following multiple daily injections. Two conclusions can be drawn from these observations. First, the subjects tested in Experiment 3 exhibited normal sensitivity to cocaine's threshold-lowering effects following single (rather than multiple) injections of cocaine; second, there was full recovery from the tolerance that was produced by the multiple daily injection procedure.

GENERAL DISCUSSION

Consistent with previous reports (10,14-16,25,26), cocaine significantly lowered self-stimulation thresholds following single daily injections. The threshold-lowering effect was evident for approximately 3.0 h postinjection and exhibited no evidence of tolerance or sensitization over days of testing. However, tolerance to cocaine's effects *was* noted when multiple injections spaced at 3.0-h intervals preceded testing. During periods of chronic cocaine treatment, self-stimulation thresholds returned to saline baseline levels when either single or multiple daily injections were given. Thus, there was no evidence for rebound dysphoria *within* a period of chronic cocaine administration. Evidence for elevation of self-stimulation thresholds *following* a period of cocaine treatment was mixed. While statistically significant increases in thresholds were observed in Experiment 2 (mean = 28%), the increases noted in Experiments 1 (mean = 11%) and 3 (mean = 35%) did not reach statistical significance.

Studies of human cocaine abusers indicate that abstinence from cocaine following a period of prolonged use can be associated with intense depression, agitation, anxiety, and dysphoria (9,24). There has been a substantial effort made to understand the biological basis of this "withdrawal" response, and a number of investigators have reported alterations in brain neurochemistry as a result of chronic cocaine treatment (1,6,20,21,23,32,34,41). In addition, there have been attempts to develop animal models of the cocaine abstinence syndrome so, among other things, drugs may be developed that block or attenuate cocaine's mood-altering effects (8,39,44). Several investigators reported elevations in self-stimulation thresholds follow chronic cocaine treatment and suggested these increases reflect postcocaine rebound dysphoria (5,25,28). However, the postcocaine increases in self-stimulation thresholds observed in Experiments 1-3 tended to be small and were usually nonsignificant.

Differences in the doses of cocaine employed by other investigators and in Experiments 1-3 may account for the differences in experimental outcomes. Two other studies (5,25) used higher doses of cocaine than were used in Experiments 1-3 (40 vs. 25-30 mg/kg) and rats self-administered the drug in a third study (28). Lower doses of cocaine were used in the present experiments because we have found that doses over 30 mg/kg induced severe stereotypy, which interferes with the initial self-stimulation testing, thus precluding an assessment of the time course of cocaine's effects after each injection. In addition, we have found that doses over 30 mg/kg can induce brachycardia and death in a significant number of rats. Perhaps such toxic levels of cocaine are required to produce the neurochemical changes associated with rebound dysphoria, while more moderate doses produce euphoria without a subsequent dysphoric response. Dysphoric reactions to cocaine use may not follow euphoric responses at more moderate dosage levels. In a recent human study reported by Weddington et al. (42), the researchers found little evidence for a cocaine crash and subsequent withdrawal syndrome in their patient population, suggesting that rebound dysphoria is not universally reported by cocaine users. In fact, prior to the 1980s it was widely believed that cocaine was nonaddicting, producing a "high" without the abstinence syndrome associated with alcohol or heroin (24). The conditions under which cocaine-induced dysphoria are observed are not well defined in either animal or human experiments. Given the theoretical importance of rebound dysphoria to some conceptions of cocaine abuse (9), it is important to elucidate the conditions under which rebound dysphoria emerges. Some cocaine abusers may rarely or never experience rebound dysphoria due to their patterns of drug use. Treatment strategies that assume that rebound dysphoria plays a central role in a patient's motivation for drug use may not be effective for this group of users.

The assumption made in Experiments 1-3 was that cocaine dysphoria is associated with hypoactivity in the neural substrate(s) that mediate brain-stimulation reward. This hypoactivity should have been reflected in the elevation of self-stimulation thresholds. However, it is possible that cocaine dysphoria may be mediated by neural substrates independent of the substrate associated with brain-stimulation reward, in which case dysphoria would not produce increases in thresh-

olds. Dysphoria may be reflected in changes in performance rather than changes in reward (27). Therefore, indices of brain-stimulation reward that are more sensitive to the confounding effects of performance-altering manipulations would more readily detect cocaine-induced dysphoria. Different self-stimulation procedures have been employed in the self-stimulation/cocaine dysphoria experiments that have been reported. Markou and Koob (28) used a discrete-trial, current threshold procedure. Bozarth and Podiak (5) used a threshold tracking method. Although Kokkinidis and McCarter (25) used a procedure similar to the curve shift approach used in Experiments 1-3, they used ascending and descending changes in current to generate their curves and their methods for analyzing the data were different from those employed in the present experiments. The measures of brain-stimulation reward used in these experiments may differ regarding their sensitivity to reward and performance manipulations. Perhaps a series of experiments should evaluate the sensitivity of different self-stimulation procedures to drugs known to produce withdrawal syndromes. Although the withdrawal effects that accompany cocaine abstinence may differ from those produced by other drugs of abuse (e.g., ethanol or opiates), these studies would provide some basis for comparison among the measures generated by various self-stimulation procedures regarding their sensitivity to drug-induced dysphoria.

Several investigators, using measures as diverse as human reports of euphoria to dopamine release in nucleus accumbens, have reported that cocaine's effects peak and disappear within 60 min postinjection (7,18,33,35,37). However, in the present studies cocaine's threshold-lowering effect was observed up to 195 min postinjection. Two factors seem to account for the difference in cocaine's time course: dose and route of administration. Most of the previous experiments used intravenous injections and lower doses of cocaine (0.25-10.0 mg/kg), while intraperitoneal injections and higher doses were used in the present study. Several experiments that used intraperitoneal injections and doses of 10-20 mg/kg demonstrated substantial cocaine effects that extended past 90 (36) and 150 min (31) postinjection. Pettit et al. (34) reported that cocaine-stimulated dopamine release in nucleus accumbens had not returned to predrug baseline by 150 min postinjection following administration of 30 mg/kg cocaine (IP).

Tolerance to cocaine's ability to lower thresholds was noted following massed (every 3.0 h) but not spaced (every 24 h) injections. The stimulus properties of cocaine showed tolerance using a dose of 20 mg/kg/8.0 h over a period of 7 days, while a dose of 5.0 mg/kg/8.0 h produced no evidence of tolerance even after 14 days of drug treatment (43). In addition, Ambre et al. (3) found that human subjects' reports of a drug-induced high showed complete tolerance within 4.0 h when blood levels of cocaine were held constant over the 4.0-h test period. These data indicate that the pattern of cocaine administration has an important influence on the drug's mood-altering effects. It seems likely that different patterns of use (e.g., occasional recreational vs. binge use) influence the magnitude and duration of the cocaine-induced high and that further study of the parameters associated with the tolerance of cocaine euphoria may contribute to a better understanding of binge behavior.

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