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BRIEF COMMUNICATION

The Effect of Chronic Cocaine on Self-Stimulation Train-Duration Thresholds[1]

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FRANK, R. A., S. MARTZ AND T. POMMERING. *The effect of chronic cocaine on self-stimulation train-duration thresholds.* PHARMACOL BIOCHEM BEHAV **29**(4) 755–758, 1988.—The effect of chronic cocaine treatment on brain stimulation reward was assessed by examining self-stimulation train-duration thresholds. Following a predrug, saline injection period, cocaine hydrochloride (10 or 15 mg/kg) was injected (IP) across 18 consecutive days of testing. Cocaine lowered thresholds across the entire period of drug administration, with the magnitude of cocaine's effect remaining stable during this time. The subjects returned to predrug, saline levels during a postdrug test conducted immediately following chronic cocaine treatment. In a final attempt to modify cocaine's effects, the subjects received 25 mg/kg cocaine HCl three times/day for three consecutive days. Subsequent testing at the original dosage levels revealed no change in the magnitude of cocaine's effect. It was concluded that cocaine's effect on brain stimulation reward does not show tolerance or sensitization with chronic use. Similar effects have been reported for morphine and amphetamine's effect on brain stimulation reward.

Self-stimulation Cocaine Brain stimulation reward

IT is well established that acutely administered cocaine increases self-stimulation rates and reduces current thresholds, and it has been hypothesized that these effects reflect cocaine-induced sensitization of central reward mechanisms [4, 7, 9, 15]. The effects of chronic cocaine on self-stimulation have not been examined. Such a study would be valuable because it would allow one to track the magnitude of cocaine-induced euphoria over time, and this information might provide insight into the mechanisms that contribute to chronic cocaine abuse. For example, it has been suggested that prolonged cocaine use leads to depletion of synaptic dopamine and a loss of cocaine reward [3,5]. Since dopamine appears to make an important contribution to brain stimulation reward (see [13] for a recent review), one might expect to observe changes in self-stimulation across a period of chronic cocaine administration.

Cocaine-induced behavioral sensitization has been found to accompany chronic drug administration when motor activity has been studied [11]. Therefore, it is important to examine cocaine-induced changes in brain stimulation reward with a behavioral paradigm that permits one to separate cocaine's reward and performance effects. This was accomplished by examining cocaine's influence on self-stimulation train-duration thresholds and maximal response rates. It has been demonstrated that the former measure is mainly sensitive to reward effects, while the latter is sensitive to performance manipulations [8].

METHOD

Subjects

Male Sprague-Dawley rats (Zivic-Miller Labs, Pittsburgh, PA) weighing between 300–400 g (at the time of surgery) served as subjects. These animals were housed in stainless steel hanging wire cages and had continuous access to food (Purina Lab Chow) and tap water. They were maintained on a 12 hr light/dark cycle at a temperature of 70°F in the animal colony rooms of the Psychology Department.

The subjects were implanted with bipolar stainless steel electrodes (Plastic Products Co., 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 midline and 8.5 mm ventral from the skull's surface (with the skull held level between bregma and lambda).

Apparatus

All training and testing took place in six metal and Plexi-

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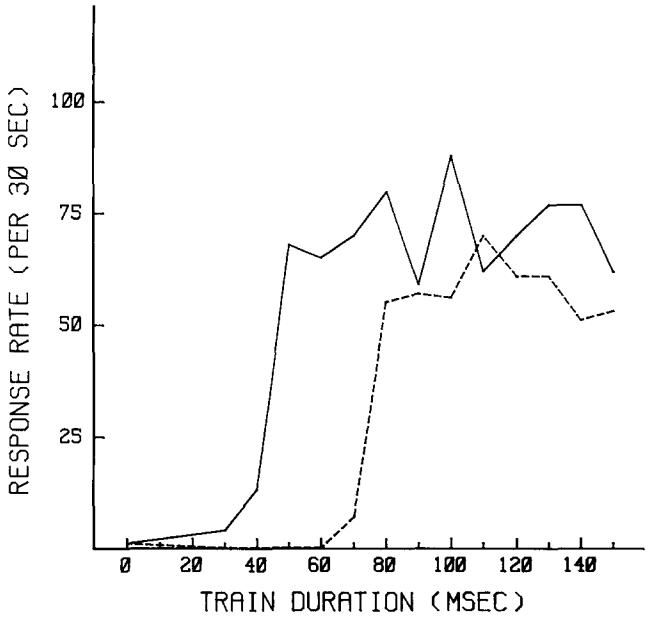

FIG. 1. Train duration response functions for the predrug saline phase (dashed lines) and the first three days of cocaine treatment (solid lines) in a representative subject.

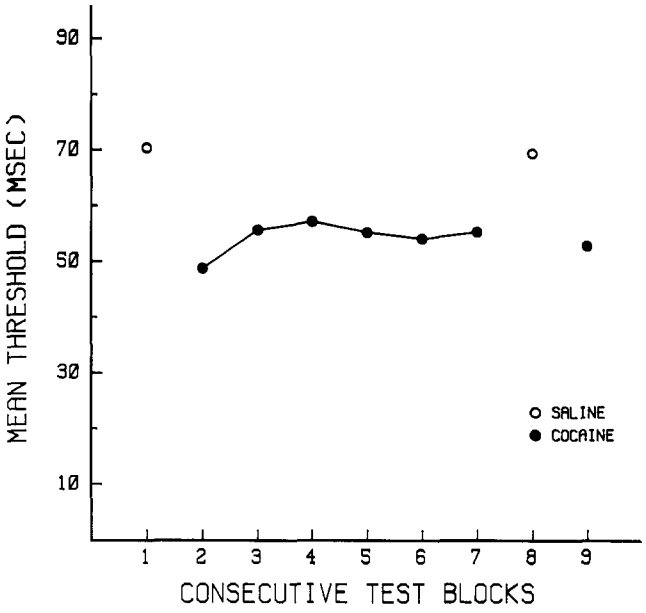

FIG. 2. Mean thresholds for each condition across three-day blocks of testing. Block 1=predrug saline; Blocks 2–7=cocaine (10–15); Block 8=postdrug saline; Block 9=test with original cocaine dose following the multiple daily injection period with 25 mg/kg.

glas chambers measuring 21×21×19 cm with floors constructed of aluminum rods spaced 1.0 cm apart. Each chamber had a metal lever mounted 5.0 cm above the floor. Mercury swivel commutators and bipolar electrode leads allowed the animals to be connected to the stimulation curcuit.

Brain stimulation was delivered by Grass SD9 square wave stimulators. These stimulators delivered constant-current bipolar square-wave stimulation through a high impedance stimulation curcuit. Stimulation frequency was maintained at 100 Hz and pulse width was set at 1.0 msec. Train durations were timed with an Ohio Scientific CIP microcomputer. The computer also handled all other timing and logic functions including data storage and formatting.

Procedure

Subjects were trained to self-stimulate following a 10 day, postoperative recovery period. Stimulation train duration was set at 250 msec for these tests. The 11 most reliable and vigorous self-stimulators were selected for further study. Next the subjects were trained to discriminate between 90 sec stimulation periods, separated by 30 sec time-outs. During time-outs, a small house light attached to each cage was illuminated and no brain stimulation was available. Response rates were collected in 30 sec blocks during each session.

Once the animals had learned to discriminate between the stimulation and time-out periods, the train duration that was available during the stimulation period was randomly varied between 30 and 150 msec. A 10 msec spacing between test durations was used (i.e., train durations of 30, 40, 50 etc., were employed). A train duration of 0 msec was included to assess the effects of cocaine on free operant rates. Once the rats became acclimated to this new procedure, the stimulation current of each animal was adjusted so that the steep portion of each subject's train duration function fell between 60 and 90 msec. Each daily session lasted 28.0 min (i.e., fourteen 90 sec stimulation periods separated by 30 sec time-outs).

In the next phase, the animals were injected (IP) with isotonic saline (0.25 ml) 15 min prior to testing for three consecutive days. Following this predrug baseline phases the subjects were divided into two groups that were matched for their train duration thresholds (with threshold defined as the shortest train duration that supported 50% of the median maximal response rate). Next, animals were injected (IP) with 10 (n=5) or 15 (n=6) mg/kg cocaine HCl for 18 consecutive days. Testing began 15 min post-injection. A postdrug baseline phase immediately followed the drug phase of the experiment. During this phase, the animals were injected with saline 15 min prior to testing on three consecutive days. The rats received injections at the same time of day throughout testing.

During the last phase of the experiment, the rats were injected with 25 mg/kg cocaine HCl three times a day (8:00 a.m., 4:00 p.m., 12:00 a.m.) for three consecutive days. Finally, the subjects were tested at their original dosage levels for three consecutive days using the one injection/day regimen.

Histology

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

RESULTS

The first 60 sec of each stimulation trial was considered a warm-up/sampling period and response rates obtained during

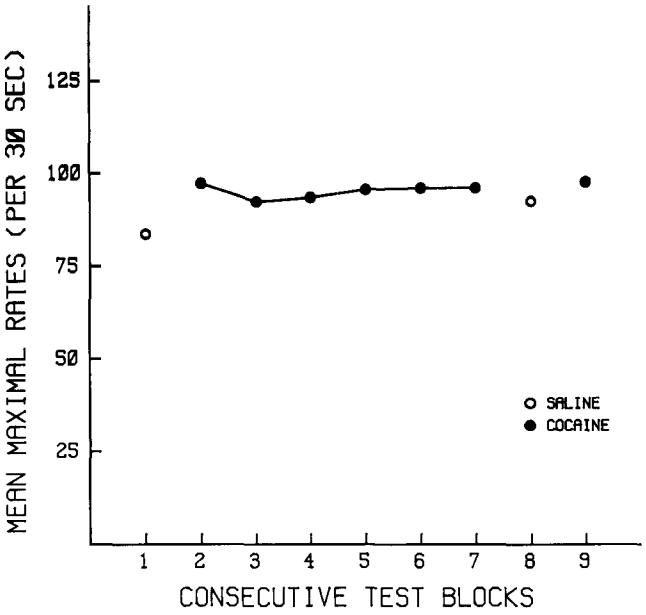

FIG. 3. Mean of the median maximal rates across three-day blocks of testing. Block 1=predrug saline; Blocks 2–7=cocaine (10–15 mg/kg); Block 8=postdrug saline; Block 9=test with original cocaine dose following the multiple daily injection period with 25 mg/kg.

this time were not analyzed in detail. Data from the final 30 sec of each stimulation trial were used to generate train duration response functions for each animal in each condition of the experiment. This was accomplished by calculating median response rates for each train duration in each phase of the experiment. Median rates were determined for three day blocks of trials across the predrug, chronic cocaine, postdrug and final cocaine phases of testing. Train duration response functions of a representative subject are shown in Fig. 1.

Two statistics were derived from these functions; maximal median response rates and train duration thresholds. Train duration threshold was defined as the shortest train duration that supported 50% of the maximal median response rate. The mean thresholds and maximal rates of each condition are shown in Figs. 2 and 3. Notice that the data have been collapsed across dosage level because the rates and thresholds of the 10 and 15 mg/kg groups were not significantly different for any phase of the experiment (independent t-tests, all $p>0.05$).

It was found that maximal rates did not vary significantly across the conditions, $F(1,10)=2.29$, $p<0.05$; conservation *df*. (Conservative degrees of freedom were used because the variance/covariance matrix of the ANOVA was not homogeneous ([11], p. 173).) Changes in train duration thresholds were evaluated in the following manner. Correlated t-tests were used to demonstrate that cocaine treatment significantly lowered thresholds [predrug baseline vs. the first block of cocaine treatment, $t(10)=6.79$, $p<0.01$; last block of cocaine treatment vs. postdrug baseline, $t(10)=-6.21$, $p<0.01$; postdrug baseline vs. final cocaine treatment, $t(10)=4.26$, $p<0.01$].

Changes in the effect of cocaine over time were evaluated with a one-within ANOVA. It was found that the mean thresholds observed across the six blocks of cocaine treatment did not vary significantly [$F(1,10)=2.66$, $p>0.05$, conservative *df*]. Finally, the mean threshold for the first block of cocaine treatment was compared to the mean threshold observed following the period of multiple daily injections. The thresholds produced by these conditions did not differ significantly, $t(10)=0.6$, $p<0.05$.

Histological analyses revealed that the electrode tips were located along the course of the medial forebrain bundle from the level of the ventral tegmental area to the posterior hypothalamus.

DISCUSSION

Cocaine treatment lowered train duration thresholds across the 18 days of drug administration. The magnitude of cocaine's effect on thresholds remained constant across time, even following a series of multiple daily injections. There was no evidence of tolerance or sensitization to cocaine's effects. This finding is consistent with research that has shown no tolerance or sensitization to amphetamine and morphine's facilitative effects on self-stimulation [2, 6, 10]. It is also consistent with the finding that animals that are self-administering cocaine to escalate the amount of cocaine they consume over days of testing [1]. The persistence of cocaine's euphorigenic properties can be taken as support for an incentive approach view of drug dependence [14]. The findings of the present study do not support the hypothesis that cocaine users increase their dosage level to overcome the tolerance that develops to the drug's euphoric effects. The stability of cocaine's effects on thresholds also provides no support for cocaine-induced dopamine depletion [3,5].

Maximal rates were not influenced by cocaine. This may seem paradoxical given cocaine's well established psychomotor stimulant effects [12]. However, it is consistent with previous findings in our laboratory that have shown that amphetamine and changes in stimulation current do not alter maximal rates [8]. It appears that animals respond at near asymptotic rates due to the short train durations and therefore cannot increase their rates in response to the activating effects of cocaine. This interpretation is supported by the high response rates observed for the saline conditions. It is also supported by the observation that changing the effort associated with responding reduces maximal rates [8]. This pattern of results suggests that maximal rates generated with the train duration paradigm are sensitive to manipulations that inhibit responding, but insensitive to those that facilitate responding.

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