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The Interactive Effects of Cocaine and Imipramine on Self-Stimulation Train-Duration Thresholds

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FRANK, R. A., T. POMMERING AND D. NITZ. *The interactive effects of cocaine and imipramine on self-stimulation train-duration thresholds.* PHARMACOL BIOCHEM BEHAV **30**(1) 1–4, 1988.—The present experiment examined the ability of the tricyclic antidepressant imipramine to influence cocaine's effect on intracranial self-stimulation. Following a predrug, saline injection period, cocaine hydrochloride (10, 20 or 30 mg/kg) was injected (IP) in 19 rats implanted with ventral tegmental area electrodes. Cocaine treatment uniformly decreased self-stimulation train-duration thresholds. In the next phase, the subjects were divided into two groups. One group received cocaine (as in the previous phase) and the other received cocaine plus imipramine (10 mg/kg, IP). Imipramine doubled cocaine's effect on self-stimulation train-duration thresholds. In addition, several other effects of cocaine (e.g., bradycardia, rear-limb dyskinesia) were potentiated by imipramine treatment. The results suggest that care must be exercised when treating cocaine abuse with tricyclic antidepressants since coadministration of these drugs intensifies cocaine's effects.

Cocaine Imipramine Self-stimulation Brain stimulation reward Tricyclic antidepressants

TRICYCLIC antidepressants have been used to treat cocaine dependence under the assumption that these drugs block cocaine euphoria and/or reduce the dysphoria and craving associated with abstinence [1, 7, 15, 22, 23, 27]. Several researchers have speculated that changes in brain dopamine are responsible for cocaine's mood altering effects, and the tricyclics produce their therapeutic effects by "normalizing" dopaminergic neurotransmission [3, 6, 15]. However, the effectiveness of tricyclic treatments for cocaine abusers has not been subjected to rigorous testing [15], nor has there been a systematic study of the interaction of tricyclics and cocaine-induced changes in affect in animals. The value of tricyclic antidepressant treatments for cocaine dependence should be evaluated with human and animal studies of this kind.

It is well established that cocaine facilitates self-stimulation, both increasing response rates and lowering thresholds [5, 8, 11, 18, 28]. It has been hypothesized that this effect reflects the ability of cocaine (and other euphorigenic drugs) to sensitize central reward mechanisms [14, 17, 20].

The present experiment evaluated the influence of the tricyclic antidepressant imipramine on cocaine-induced euphoria by examining imipramine's ability to modify cocaine's effect on intracranial self-stimulation.

One would predict that some recovering cocaine abusers who undergo tricyclic antidepressant therapy would relapse, potentially resulting in the coadministration of the antidepressant and cocaine. What effect would this have on cocaine-induced euphoria? Schenkel and Boff [21] demonstrated that imipramine enhanced cocaine's stimulant effects on active avoidance. The present experiment compared the effect of cocaine on intracranial self-stimulation when injected alone or in combination with imipramine. If, as is often the case, cocaine's effects are similar to those of amphetamine, one would predict that imipramine would potentiate cocaine-induced facilitation of brain stimulation reward [2, 13, 19, 25].

METHOD

Subjects

Male Sprague-Dawley rats (Zivic-Miller Labs, Pittsburgh, PA) weighing between 300–400 g (at the time of surgery) served as subjects. The animals were housed individually in stainless steel wire hanging cases, 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. Each subject was implanted with a bipolar stainless steel electrode (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 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 Plexi-

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glas 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 hole positioned 5.0 cm above the floor. The hole opened into a 5×5×4 cm chamber which contained a photocell beam. A 1.0 cm excursion of an object (e.g., a rat's nose) into the chamber initiated a signal pulse that was registered as a response by a computer.

Brain stimulation was delivered by Grass SD9 square wave stimulators. These stimulators delivered constant-current bipolar square-wave stimulation through a high impedance stimulation circuit. Stimulation frequency was maintained at 100 Hz and pluse width was set at 1.0 msec. Train duration as timed with an Ohio Scientific C1P 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 19 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 20 and 140 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 50 and 100 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 with isotonic saline (0.25 ml) 15 min prior to testing for five consecutive days. Following this predrug baseline phase, the subjects were divided into three groups that received 10 (n=7), 20 (n=6) or 30 (n=6) mg/kg cocaine HCl (IP) for three days. Self-stimulation testing began 15 min post-injection. In the next phase, rats in each dosage group were assigned to either a cocaine/imipramine or cocaine alone condition. During a subsequent three-day test phase, the cocaine alone group received the same treatment administered during the initial drug phase of the experiment, except that saline was injected 15 min prior to the cocaine injections. The cocaine/imipramine group received 10 mg/kg imipramine (IP) 15 min prior to the cocaine injection. This test regimen was used for daily testing on six consecutive days. A postdrug baseline phase brought the experiment to a conclusion 10 days after the final day of drug administration. During this phase, the rats were injected with isotonic saline 15 min prior to testing on three consecutive days.

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. The brains were subsequently sectioned at 60 μm and examined to determine the locations of the electrode tips.

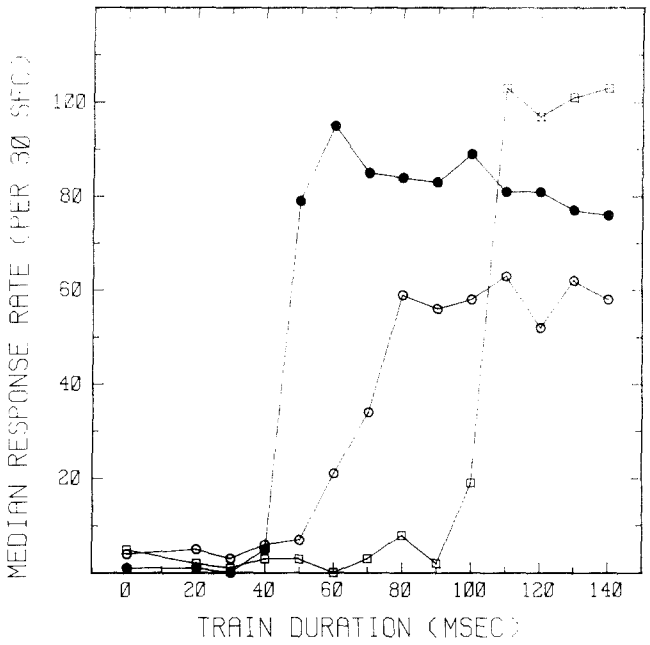

FIG. 1. Train-duration response functions for three representative animals. The data are from the predrug, saline phase of the experiment.

RESULTS

The first 60 sec of each stimulation trial was considered a warm-up and sampling period and response rates obtained during 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. The train duration response functions of several representative subjects are shown in Fig. 1.

Two statistics were used to analyze these functions. The maximal median response rate generated in each phase of the experiment was determined, as was the shortest train duration to support 25, 50 and 75% of the maximal median rate. Train duration threshold was taken as the mean of the 25, 50 and 75% values . (Previous research [10] has shown that the slope of the train duration response function does not change as the function shifts to the left or right, and that the mean of the 25, 50 and 75% values provides a more stable estimate of threshold than any one value alone.)

Two-between (treatment group and dose), one-within (treatment condition) analyses of variance were used to assess the effects of the drugs on thresholds and maximal rates. These analyses revealed that the main effect for treatment condition (i.e., predrug baseline vs. cocaine treatment vs. cocaine/imipramine treatment vs. postdrug baseline) was significant for both the threshold, $F(3,39)=42.7$, $p<0.001$, and maximal rate measures, $F(3,39)=3.9$, $p<0.05$. In addition, the treatment group (cocaine only vs. cocaine/imipramine) by treatment condition interaction was significant for the threshold measure, $F(3,39)=3.1$, $p<0.05$.

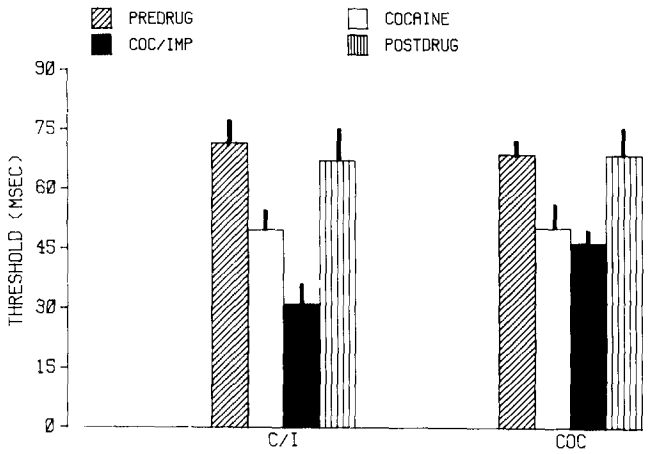

FIG. 2. Mean thresholds for the four experimental conditions in the cocaine/imipramine (C/I) and cocaine only (COC) groups. Predrug=saline; Cocaine=cocaine only; COC/IMP=cocaine plus imipramine or cocaine only, depending on group; Postdrug=saline. The lines above each bar show one standard error of the mean.

No other main effects or interactions were significant.

The mean threshold values for both treatment groups are plotted against treatment condition in Fig. 2. (Notice that the data have been collapsed across dose.)

The treatment groups are similar in two respects; cocaine significantly lowered thresholds in both groups, $t(9)=8.6$, $p>0.01$, $t(8)=4.9$, $p<0.01$, and thresholds returned to predrug levels during postdrug, saline testing, $t(9)=1.09$, $p<0.05$, $t(8)=0.01$, $p>0.05$. However, the two groups differed when the two drug phases of the experiment were compared. The group tested twice with cocaine produced the same mean threshold for the two tests, $t(8)=0.9$, $p>0.05$, whereas the group tested first with cocaine and then with cocaine plus imipramine showed a significant lowering of thresholds from the first to the second drug test, $t(9)=4.5$, $p<0.01$.

Maximal rates were significantly lower for the second phase of drug testing (mean=83 responses/30 sec) vs. the average rate of the other conditions combined (mean=95 responses/30 sec), $t(18)=3.0$, $p<0.01$.

Histological analyses showed that the electrode tips were located along the course of the medial forebrain bundle from the ventral tegmental area to the posterior hypothalamus. The loci were similar to those we have reported in previous work (e.g., see [10]).

DISCUSSION

Research in our laboratory has demonstrated that like stimulation frequency and current thresholds, shifts in train duration thresholds are associated with changes in brain stimulation reward [10]. Consistent with previous findings, cocaine lowered thresholds in the present study [8, 11, 18]. In addition, imipramine enhanced cocaine's threshold lowering effects. This result is consistent with the finding that imipramine facilitates cocaine's effects on active avoidance [21] and other work on the interactive effects of the tricyclics and amphetamine [2, 16, 25]. The interactive effects of cocaine and imipramine are especially interesting given that the tricyclics alone have very little or no effect on self-stimulation thresholds ([9,24], unpublished observations). The most likely explanation for the imipramine/cocaine interaction is that imipramine increases brain levels of cocaine by slowing cocaine catabolism. This interpretation is supported by the findings that coadministration of amphetamine and tricyclics lead to higher levels of amphetamine in the brain [4, 12, 13, 19, 26]. The ability of imipramine to increase brain levels of cocaine should be verified in future research.

The results of the present study suggest that the coadministration of tricyclics and cocaine may intensify cocaine euphoria, thereby increasing the incentive value of the drug. Thus, a relapse episode in a cocaine abuser who is receiving tricyclic treatment would be more likely to lead to the reinstatement of a stable pattern of drug use. In addition, the tricyclics probably potentiate other behavioral and physiological effects of cocaine [21]. In fact, the present experiment was terminated after six days of imipramine/cocaine treatment because the rats receiving both drugs showed increasing problems with bradycardia and rear-limb dyskinesia on consecutive days. This pattern of results indicates that one should exercise extreme care when treating cocaine abusers with the tricyclic antidepressants.

Maximal rates tended to be lower during the second phase of drug testing, dropping from mean predrug baseline, cocaine only and postdrug baseline levels of 93, 95 and 96 responses/30 sec to 83 responses/30 sec. Part of this decrease can be attributed to the stereotypy and rear-limb dyskinesia observed with coadministration of cocaine and imipramine. We have seen a similar drop in rates with high doses of amphetamine [10]. However, the animals who were treated twice with cocaine only also showed this effect. It is unlikely that this finding is related to sensitization to cocaine treatment since previous work in our laboratory found no changes in maximal rates over 18 consecutive days of cocaine treatment [11]. Although the explanation for this effect is unclear, it does demonstrate that changes in self-stimulation rates do not necessarily predict changes in thresholds.

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