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BRIEF COMMUNICATION

Chronic Imipramine Does Not Block Cocaine-Induced Increases in Brain Stimulation Reward

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FRANK, R. A. AND E. ZUBRYCKI. *Chronic imipramine does not block cocaine-induced increases in brain stimulation reward.* PHARMACOL BIOCHEM BEHAV **33**(3) 725–727, 1989.—Self-stimulating rats implanted with ventral tegmental area electrodes were tested with 15 mg/kg cocaine HCl before and after chronic imipramine treatment. Chronic imipramine had no influence on cocaine's ability to lower brain stimulation reward thresholds, suggesting that tricyclic antidepressant treatment does not block cocaine-induced euphoria.

Cocaine Imipramine Self-stimulation Brain stimulation reward Tricyclic antidepressants

IT has been known for sometime that chronic tricyclic antidepressant treatment can be used to control depression (6). More recently, the tricyclics have been used to treat cocaine dependence under the assumption that these drugs block cocaine euphoria and/or reduce cravings associated with abstinence (1, 2, 5, 7, 9, 10, 12). However, little empirical research has assessed the interaction of cocaine and the tricyclics. In one of the few studies of this type, Frank, Pommering and Nitz (4) demonstrated that imipramine enhanced rather than blocked cocaine's facilitative effect on brain stimulation reward when the two drugs are coadministered. This finding suggests that the tricyclics increase cocaine euphoria.

The present study was designed to more closely model the regimen of tricyclic treatment that would be used with cocaine abusers. The effects of cocaine were examined before and after a period of chronic imipramine administration. Chronic imipramine treatment was used since the antidepressant effects of the tricyclics require 7–14 days to become evident (6) and because short-term administration does not facilitate cocaine abstinence in humans (12). The finding that chronic tricyclic antidepressant treatment blocks or reduced cocaine-induced facilitation of brain stimulation reward would suggest that these drugs block cocaine euphoria. This could make the tricyclics especially useful in the treatment of cocaine abuse.

METHOD

Subjects

Six 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 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. 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 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 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 pulse width was set at 1.0 msec. Train duration was 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 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 response 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 received 15 mg/kg cocaine HCl (IP) 15 min prior to testing for three consecutive days. In the chronic imipramine treatment phase that followed, the rats were injected with 10 mg/kg imipramine 30 min prior to testing on 18 consecutive days. Next, the rats received an additional three days of cocaine injections at the original dose. At the conclusion of this phase, the animals were injected with saline for three days during a final, postdrug baseline period.

Histology

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

RESULTS

The first 60 sec of each stimulation trial were considered a warm-up/sampling period and responses obtained during this time were not analyzed in detail. Data from the final 30 sec of each trial were used to generate train duration response functions. This was accomplished by calculating median response rates for each train duration in each phase of the experiment. Response functions were generated for each animal for the pre- and postdrug saline phases, the pre- and postimipramine cocaine phases and in three-day blocks for the imipramine phase of the experiment.

Self-stimulation train duration thresholds were calculated from the response functions by determining the shortest train duration that supported 50% of the maximal median rate of responding. The threshold was usually found by interpolating between two train durations. Thresholds were calculated for each response function. Previous research [e.g., (3)] has shown that train duration thresholds are sensitive to changes in brain stimulation reward. The mean thresholds for each condition are shown in Fig. 1.

The train duration thresholds were statistically analyzed with repeated measures *t*-tests. Since the pre- and postdrug saline thresholds did not differ, $t(5)=1.14$, $p<0.05$, the two saline conditions were collapsed into a single, no-drug baseline. Thresholds were lowered significantly during the first cocaine phase of the experiment, $t(5)=2.67$, $p<0.05$. However, imipramine had no effect on thresholds [saline vs. imipramine collapsed across blocks, $t(5)=1.0$, $p<0.05$]. Following imipramine treatment, cocaine continued to lower thresholds, $t(5)=2.24$, $p<0.05$ (one-tailed). Cocaine's threshold lowering effects averaged 21 msec prior to imipramine treatment and 26 msec after chronic imipramine. The difference in these threshold lowering effects was not significant, $t(5)=0.05$, $p>0.05$.

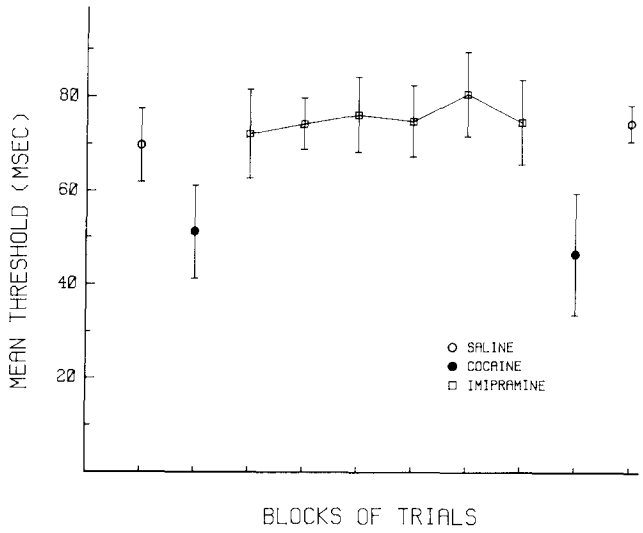

FIG. 1. Mean thresholds for each condition and three-day blocks of imipramine treatment. The lines above and below each data point show one standard error above and below each mean.

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. The loci were similar to those reported by Frank *et al.* (3).

DISCUSSION

Chronic imipramine pretreatment had no effect on cocaine's ability to lower self-stimulation train duration thresholds. This result, together with previous findings, suggest that imipramine does not block or reduce cocaine euphoria. This may limit the usefulness of the tricyclics as a drug treatment for cocaine abuse since incentive approach is seen as a major determinant of psychomotor stimulant self-administration (5,11). Of course, imipramine and other tricyclics may reduce cravings for cocaine or cocaine-induced dysphoria (5,7) independent of these drugs' effects on cocaine-induced euphoria. The reduction of the negative effects would recommend tricyclic antidepressant treatment for the recovering cocaine user. However, the dangers of coadministering cocaine and the tricyclics (4), and the failure of these drugs to influence cocaine euphoria, suggest they be used with caution.

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REFERENCES

1. Blum, K. Depressive states induced by drugs of abuse: Clinical evidence, theoretical mechanisms and proposed-treatment. J. Psychedelic Drugs 8:235–262; 1976.
2. Ellinwood, E. H. Amphetamine and cocaine. In: Jarvik, M. E., ed. Psychopharmacology in the practice of medicine. New York: Appleton-Century-Crofts; 1977:467–436.
3. Frank, R. A.; Markou, A.; Wiggins, L. A systematic evaluation of the properties of self-stimulation train-duration response functions. Behav. Neurosci. 101:546–559; 1987.
4. Frank, R. A.; Pommering, T.; Nitz, D. The interactive effects of cocaine and imipramine on self-stimulation train-duration thresholds. Pharmacol. Biochem. Behav. 30:1–4; 1988.
5. Gawin, F. H.; Ellinwood, E. H., Jr. Cocaine and other stimulants: Actions, Abuse and treatment. N. Engl. J. Med. 318:1173–1182; 1988.
6. Heninger, G. R.; Charney, D. S. Mechanism of action of antidepressant treatments: Implications for the etiology and treatment of depressive disorders. In: Meltzer, H. Y., ed. Psychopharmacology: A third generation of progress. New York: Raven; 1987:535–544.
7. Kleber, H. D.; Gawin, F. H. Cocaine abuse: A review of current and experimental treatments. In: Grabowski, J., ed. Cocaine: Pharmacology, effects and treatment of abuse. NIDA Research Monograph, 50. Rockville, MD: U.S. Government Printing Office; 1984:111–129.
8. Kleber, F. H.; Gawin, H. Issues in cocaine abuse treatment research. In: Fisher, S.; Raskin, A.; Vhlenhuth, E. H., eds. Cocaine: Clinical and biobehavioral aspects. New York: Oxford University Press; 1987:174–192.
9. Siegel, R. K. Cocaine smoking. J. Psychedelic Drugs 14:271–359; 1982.
10. Smith, D. E.; Wesson, D. R. Cocaine. In: Jeri, F. R., ed. Cocaine, 1980. Lima, Peru: Pacific Press; 1980:49–61.
11. Stewart, J.; deWit, H.; Eikelboom, R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol. Rev. 91:251–268; 1984.
12. Tennant, F. S.; Tarver, A. L. Double-blind comparison of desipramine and placebo in withdrawal from cocaine dependence. Presented at Proceedings of the 46th Annual Scientific Meeting, Committee on Problems of Drug Dependence, 1984.