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BRIEF COMMUNICATION

Cocaine Facilitates Prefrontal Cortex Self-Stimulation

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MOODY, C. A. AND R. A. FRANK. *Cocaine facilitates prefrontal cortex self-stimulation.* PHARMACOL BIOCHEM BEHAV **35**(3) 743–746, 1990.—It has been demonstrated that cocaine HCl lowers thresholds for and increases rates of medial forebrain bundle intracranial self-stimulation. The influence of cocaine on prefrontal cortex self-stimulation was assessed in the present experiment. The prefrontal cortex was chosen because evidence indicates that the neuroanatomical and pharmacological substrate for intracranial self-stimulation at this site may differ from the substrate for medial forebrain bundle self-stimulation. Cocaine significantly decreased train-duration thresholds and increased the rate of prefrontal cortex self-stimulation. It was concluded that cocaine facilitates both prefrontal cortex and medial forebrain bundle self-stimulation, perhaps by influencing neural activity in the mesocorticolimbic dopamine system. However, the role of dopamine in cocaine's effects at both sites remains speculative.

Cocaine Prefrontal cortex Self-stimulation Drug abuse Dopamine

IT is well established that cocaine facilitates medial forebrain bundle (MFB) self-stimulation (3, 4, 6, 7, 10, 17). Although data from self-administration experiments suggest that cocaine's euphoric effects may be mediated by mesolimbic dopamine neurons projecting to the nucleus accumbens (13), the mechanism of cocaine-induced facilitation of intracranial self-stimulation is unknown. In addition, it is not known if cocaine facilitates self-stimulation at all electrode loci. An assessment of cocaine's effects at multiple self-stimulation sites could provide insights into the anatomy and pharmacology that underlie cocaine-induced euphoria.

Cocaine's influence on prefrontal cortex self-stimulation was assessed in the present experiment. This site ws selected for several reasons. Autoradiographic, neurophysiologic and lesion studies support the hypothesis that different neuronal substrates mediate prefrontal cortex and MFB self-stimulation [see (12) and (15) for recent reviews]. Although rats will self-administer cocaine directly into prefrontal cortex (9), destruction of dopamine terminals in the prefrontal cortex had no effect on intravenous self-administration of cocaine (11). In addition, the behaviors associated with the acquisition and maintenance of self-stimulation differ dramatically for the two sites (1, 2, 14). A differential effect of cocaine on intracranial self-stimulation in the MFB and prefrontal cortex would suggest that different neuroanatomical/neuropharmacological systems may mediate cocaine's effects at these two loci. If cocaine facilitates self-stimulation at both of these sites, the common elements of these two loci (e.g., the mesocorticolimbic dopamine system) or elements independent of both may be implicated in cocaine's euphorigenic effects.

METHOD

Subjects

Male Sprague-Dawley rats (Zivic Miller Labs, Pittsburgh, PA) weighing between 300–750 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 (65 mg/kg). The electrodes were aimed at the prefrontal cortex using the coordinates 4.5 mm anterior from bregma, 0.6 mm lateral from the midline and 3.2 mm ventral from the brain surface, with the incisor bar set at +5.0 mm.

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

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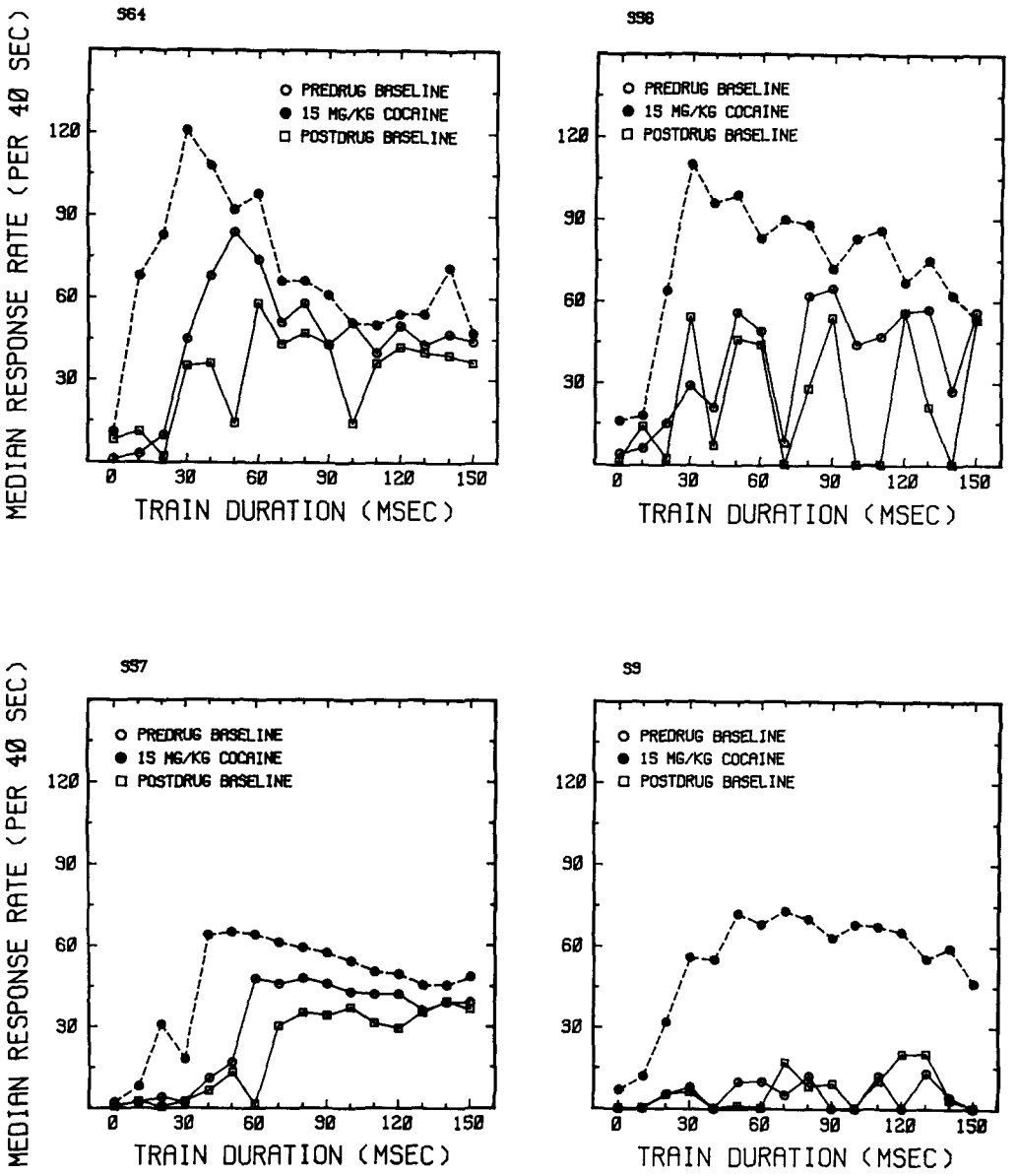

FIG. 1. Train duration response functions for the saline and cocaine conditions for four rats.

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 a 1.0 msec. Train duration was timed with a microcomputer. The computer also handled all the timing and logic functions including data storage and formatting.

Procedure

The rats were allowed at least 10 days for postoperative recovery, and then trained to nose poke for brain stimulation using a stimulation train duration of 350 msec and current intensity of 100 μA. Rats that reliably produced an average of 100 responses/min were retained for further study. Seven of 20 rats met this criterion.

In the next phase of the experiment, the rats were tested with train durations that ranged from 0 to 150 msec, with test durations spaced every 10 msec (i.e., test durations of 0, 10, 20, 30 msec, etc., were used). The order of the train durations was randomly varied across sixteen 1.0-min test trials, and a 20-sec time-out separated the tests. The time-outs were signalled by the illumination of a small light bulb on each test cage, and during the time-outs, responding had no consequence.

Once the rats were acclimated to the variable train duration procedure, they were injected with isotonic saline (0.25 ml) 15 min prior to testing on three consecutive days. These tests were used to establish a predrug baseline. In the next phase, the animals were injected with 15 mg/kg cocaine HCl (IP) 15 min prior to testing for three consecutive days. This dose was selected because

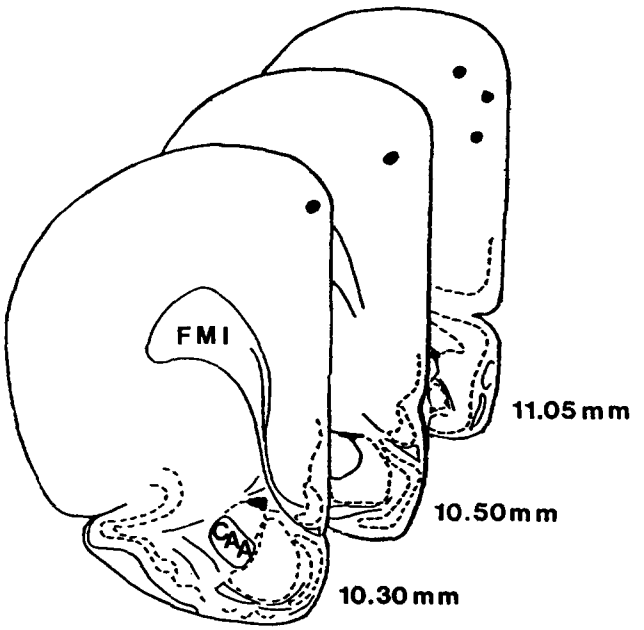

FIG. 2. Locations of the electrode tips for five of the seven subjects in the experiment.

it is in the mid-range of doses that facilitate ventral tegmental area self-stimulation (6,7). Postdrug saline baseline was assessed 6 days after the final cocaine injection by injecting isotonic saline (0.25 ml) prior to testing on 3 consecutive days.

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 initial 20 sec of each train duration test trial was considered a warm-up/sampling period and responses made during this time were not analyzed in detail. Median response rates from the final 40 sec of testing were calculated for each train duration for the saline and cocaine conditions for each rat. The data of four representative subjects are shown in Fig. 1. Notice that the cocaine enhanced responding for nearly all the train durations that were tested. This pattern was observed in all seven rats. The irregular train duration response functions associated with prefrontal cortex self-stimulation (e.g., see No. S56) made it difficult to calculate self-stimulation thresholds [e.g., see (6–8)]. Nevertheless, train duration thresholds were calculated to assess whether cocaine shifted self-stimulation response functions to the left. Such a shift would suggest a cocaine-induced increase in brain stimulation reward. Train duration threshold was defined as the shortest train duration that supported 50% of the median maximal response rate [see (8)]. Thresholds were determined for each rat in each condition, and then the pre- and postsaline thresholds were averaged and compared to the thresholds associated with the cocaine condition. It was found that self-stimulation thresholds averaged 65.6 msec after treatment with saline, and 26.6 msec following cocaine administration. This difference was found to be statistically significant [repeated measures t-test; $t(6)=4.0$, $p<0.01$]. Changes in maximal response rates were also assessed to evaluate cocaine's performance effects (8). The median maximal response rates were determined for each rat in each condition, and then averaged across the two saline conditions. The mean maximal response rate following saline treatment was 42 responses/40 sec, whereas the mean maximal rate after cocaine was 88 responses/40 sec. The difference between the cocaine and saline rates was statistically significant [repeated measures t-test; $t(6)=8.8$, $p<0.01$]. Histological analyses revealed that the electrode tips were located within prefrontal cortex for five of the seven rats (see Fig. 2). The location of electrode tip could not be determined for two of the subjects.

DISCUSSION

The goal of the present study was to compare cocaine's effects on MFB and prefrontal cortex self-stimulation. Cocaine clearly facilitated responding for prefrontal cortex stimulation, just as has been reported for MFB sites (3,17). Although, due to unstable saline baseline responding, it was difficult to measure prefrontal-cortex self-stimulation thresholds, self-stimulation thresholds were reduced by cocaine treatment. This is indicative of an increase in brain stimulation reward (8). Cocaine-induced decreases in self-stimulation thresholds have also been reported for MFB self-stimulation (4, 6, 7, 10). Therefore, it would appear that cocaine does not differentially affect MFB and prefrontal cortex self-stimulation. In addition, cocaine induced an increase in maximal response rates, an effect not found at MFB sites (6,7). Although the explanation for this effect is unclear, it may be related to the generally lower rates of self-stimulation observed with prefrontal cortex stimulation. The lower rates may facilitate the expression of a cocaine rate effect by avoiding a performance ceiling associated with high rates of self-stimulation.

It is well established that cocaine blocks the reuptake of dopamine (5) and this neurotransmitter has been implicated in cocaine self-administration (13). Since mesocorticolimbic dopamine neurons project to self-stimulation sites in the MFB and prefrontal cortex (12), this system may represent the critical anatomical link to cocaine's effects on self-stimulation at these two sites. However, the role of dopamine in mediating self-stimulation at either site is controversial (12,16), and in any case, considerable evidence suggests that the directly stimulated neurons underlying self-stimulation are probably *not* dopaminergic (15). Therefore, the role of dopamine in general and the mesocorticolimbic dopamine system in particular in cocaine-induced facilitation of self-stimulation remains unclear. It would be interesting to know if dopamine depletion of either the nucleus accumbens or prefrontal cortex affects cocaine-induced facilitation of self-stimulation. This information could add significantly to our understanding of the neuroanatomy and pharmacology of cocaine's euphorigenic effects.

REFERENCES

1. Corbett, D.; Silva, L. R.; Stellar, J. R. An investigation of the factors affecting development of frontal cortex self-stimulation. Physiol. Behav. 34:89–95; 1985.

2. Corbett, D.; Laferriere, A.; Milner, P. M. Plasticity of the medial prefrontal cortex: Facilitated acquisition of intracranial self-stimulation by pretraining stimulation. Physiol. Behav. 28:531–534; 1982.

3. Crow, T. J. Enhancement by cocaine of intra-cranial self-stimulation in the rat. Life Sci. 9:375–381; 1970.
4. Esposito, R. U.; Motola, A. H. D.; Kornetsky, C. Cocaine: Acute effects on reinforcement thresholds for self-stimulation behavior to the medial forebrain bundle. Pharmacol. Biochem. Behav. 8:437–439; 1978.
5. Fischman, M. W. Cocaine and the amphetamines. In: Meltzer, H. Y., ed. Psychopharmacology: The third generation of progress. New York: Raven Press; 1987:1543–1554.
6. Frank, R. A.; Martz, S.; Pommering, T. The effect of chronic cocaine on self-stimulation brain duration thresholds. Pharmacol. Biochem. Behav. 29:755–758; 1988.
7. 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.
8. Frank, R. A.; Markou, A.; Wiggins, L. L. A systematic evaluation of the properties of self-stimulation train duration response functions. Behav. Neurosci. 101:546–559; 1987.
9. Goeders, N. E.; Smith, J. E. Cortical dopaminergic involvement in cocaine reinforcement. Science 221:773–775; 1983.
10. Kornetsky, C.; Esposito, R. V. Reward and detection thresholds for brain stimulation: dissociative effects of cocaine. Brain Res. 209: 496–500; 1981.
11. Martin-Iverson, M. T.; Szostak, C.; Fibiger, H. C. 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administration of cocaine. Psychopharmacology (Berlin) 88:310–314; 1986.
12. Phillips, A. G.; Fibiger, H. C. Neuroanatomical bases of intracranial self-stimulation: untangling the Gordian Knot. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. Oxford: Clarendon Press; 1989:66–105.
13. Roberts, D. C. S.; Koob, G. F.; Klonoff, P.; Fibiger, H. C. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol. Biochem. Behav. 12:781–787; 1980.
14. Robertson, A.; Laferriere, A.; Milner, P. Development of brain stimulation reward in the medial prefrontal cortex: facilitation by prior electrical stimulation of the medial prefrontal cortex. Physiol. Behav. 28:869–872; 1982.
15. Shizgal, P.; Murray, B. Neuronal basis of intracranial self-stimulation. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. Oxford: Clarendon Press; 1989:106–163.
16. Stellar, J. R.; Rice, M. B. Pharmacological basis of intracranial self-stimulation reward. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. Oxford: Clarendon Press; 1989:14–65.
17. Wauguier, A.; Niemegeers, C. J. E. Intracranial self-stimulation in rats as a function of various stimulus parameters V. Influence of cocaine on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 38:201–210; 1974.