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Cocaine's Effects on Rate of Intracranial Self-Stimulation

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WILLIAMS, H. P., P. Z. MANDERSCHEID, M. SCHWARTZ AND R. A. FRANK. *Cocaine's effects on rate of intracranial self-stimulation*. PHARMACOL BIOCHEM BEHAV **40**(2) 273–277, 1991.—While some investigators have reported that cocaine increases response rates for brain stimulation reward, others have failed to demonstrate this effect. The present study was designed to evaluate the influence of stimulation parameters, dose of cocaine and operant-dependent response requirements on cocaine's ability to alter self-stimulation rates. Self-stimulation rates were collected on a minute by minute basis for 45 min following IP injections of 0, 5, 15 or 30 mg/kg cocaine HCl. All doses were tested using both nose-poking and lever-pressing operants. It was found that mean lever-pressing rates were significantly increased by 5 mg/kg cocaine, while nose-poking rates were significantly increased by 15 and 30 mg/kg cocaine. Further examination of the pattern of results indicated that the cocaine-induced increases in lever-pressing rate were mainly due to an increase in the time spent self-stimulating, whereas increases in nose-poking were mainly due to increases in nose-poking rate/min within self-stimulation bouts. It was hypothesized that 5 mg/kg cocaine increased lever-pressing by producing response perseveration, while the higher doses increased nose-poking mainly due to the compatibility of the nose-poking response topography with cocaine-induced stereotypies.

Cocaine Response requirements Brain stimulation reward Drugs of abuse Self-stimulation

INTRACRANIAL self-stimulation has been used to study the behavioral effects of abused drugs such as cocaine in an attempt to elucidate the neurobiology of addiction (14). The interpretation of such experiments can be controversial, however, owing to ambiguity in interpreting some measures of self-stimulation. While it is generally agreed that shifts in self-stimulation thresholds reflect alterations in brain stimulation reward (4, 9, 15, 16), changes in self-stimulation response rates may indicate changes in stimulation reward value *or* alteration in the response capacity of the subject (16,23). For some purposes, then, threshold measures are preferable for their lack of ambiguity. However, response rate data are valuable in providing information that cannot be obtained with threshold measures. For example, self-stimulation rates might assess a drug's ability to induce hyperactivity, catalepsy, or stereotypy (9, 16, 23). The goal of the present study was to clarify some of the factors that influence cocaine's effects on self-stimulation rates.

It has been reported that cocaine lowers intracranial self-stimulation thresholds (4,15) and facilitates self-stimulation rates (1, 3, 24). While Frank and colleagues were able to replicate the effects of cocaine on thresholds, they found no evidence of cocaine-induced facilitation of maximal response rate, using medial forebrain bundle electrodes (6–8).

Differences in the stimulation parameters used in these various studies may account for the discrepant results. Relatively short train durations (20–150 ms) were used in the studies by Frank et al. (6–8), while train durations of over 200 ms were used by other investigators. Since rats produce very high response rates at short train durations, it is possible that response rate ceiling effects limited the Frank et al. results. Therefore, the train duration used in the present experiment was lengthened to 350 ms.

It is also possible that the differences in the findings of the previous experiments were related to the manner in which response rates were calculated. Crow (3) and Wauquier and Niemegeers (24) used perithreshold levels of stimulation and assessed changes in response rate by summing responses across 1.0-h sessions, while Frank and colleagues (6–8) used a curve-shift paradigm to assess changes in asymptotic response rates during relatively short (e.g., 1.0 min) test intervals. The method used by Crow (3) and Wauquier and Niemegeers (24) confounds changes in response rate caused by threshold shifts with those due to factors such as response preservation or drug-induced stereotypies. In addition, summing responses across a lengthy test session makes it impossible to discriminate between drug-induced increases within a self-stimulation bout from increases in responding due to longer self-stimulation bouts. In the present experiment, self-stimulation response rates were collected on a minute by minute basis so session response rate could be compared to the distribution of minute by minute rates. In addition, perithreshold levels of stimulation were avoided to minimize the influence of threshold shifts on the response rate measures.

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Finally, since operant requirements influence rate of self-stimulation and may interact with a drug's effects (5, 10, 18), cocaine's effects were evaluated with both lever-pressing and nose-poking operants. The comparison between the operants was of special interest since some of the stereotypic behaviors induced by cocaine resemble nose-poking behavior (21,22), raising the possibility that cocaine's rate-enhancing effects might be operant dependent.

METHOD

Subjects

Twenty (20) male Sprague-Dawley rats, weighing between 300–400 g at the time of surgery, served as subjects. Animals were individually housed in stainless steel wire hanging cages with continuous access to food (Purina Lab Chow) and water except during times of testing. They were maintained on a reversed 12-h light/dark cycle in the animal colony rooms at the University of Cincinnati Psychology Department.

Surgery

Bipolar stainless steel electrodes (Plastics One, electrode diameter = 0.5 mm) were implanted under sodium pentobarbital anesthesia (65 mg/kg) supplemented with 0.1 ml atropine to alleviate respiratory congestion. The electrodes were aimed at the ventral tegmental area using the coordinates 4.4 mm posterior to bregma, 1.5 mm lateral from the midline and 8.5 mm ventral from the skull surface, with the skull level between lambda and bregma.

Apparatus

Training and testing took place in twelve aluminum and Plexiglas chambers measuring $23 \times 20 \times 19$ cm with floors constructed of stainless steel rods spaced 1.5 cm apart. Each chamber had a stainless steel lever mounted 5.0 cm above the floor in one wall. The opposite wall contained a 4×4 cm hole centered 5 cm above the floor. The animal could interrupt a light beam by poking its nose 1.0 cm into the hole. Each lever-press or nose-poke response delivered a single train of brain stimulation pulses. Responses during a pulse train were recorded but not reinforced. Only one operant was visible or accessible to the animal during a session. A mercury swivel commutator and a bipolar electrode lead allowed the animal to move freely within the box while connected to the stimulation circuit.

Constant current bipolar square wave stimulation was delivered by a Grass SD9 stimulator through a high-impedance, capacitance-coupled circuit. Stimulation frequency was 100 Hz and pulse width was 5.0 ms. An Advanced Logic Research microcomputer controlled all timing and logic functions including data storage and formatting.

Procedure

Self-stimulation training began after a two-week postoperative period. Current intensity was set individually for each animal to the highest level which did not produce disruptive motor effects. Current intensities ranged from 40 to 70 μA. Train-duration was set at 350 ms, and animals were trained on each operant in 45-minute sessions, one session per day. Animals received at least ten training sessions on each operant.

After the initial training period, animals were tested once per day, every other day. Test sessions lasted 45 min and train-durations remained at 350 ms. The number of responses for each of the 45 one-minute trials was recorded by the computer. After the animals acclimated to the every other day testing schedule, the experiment was begun. Each rat received every treatment condition, starting with a predrug, saline condition. Fifteen minutes prior to testing, animals were injected with isotonic saline (IP, 1.0 ml/kg injection volume). Two saline test sessions were conducted on each operant, with the operant alternated between sessions. Half of the animals began testing on the nose-poking operant and half on lever-pressing. After baseline testing was completed, each of three cocaine dosages (5, 15, and 30 mg/kg, IP) was tested with both operants so that a total of six cocaine tests were performed. All animals were tested once under each drug condition. The order of the dose-by-operant testing was randomized across subjects. Testing began 15 min postinjection. Once the subjects had experienced all the dose-by-operant conditions, postdrug, saline tests were conducted using the procedure described for the predrug testing period.

At the conclusion of behavioral testing, the animals were sacrificed with an overdose of sodium pentobarbital, and perfused through the heart with saline followed by a 10% formal-saline solution. The brains were subsequently frozen and sliced (at 60 μm) to determine the locations of the electrode tips.

RESULTS

For each subject, responses were totalled across the 45 one-min test periods for each of the conditions. Repeated-measures *t*-tests revealed that the mean total responses for the pre- and postdrug saline periods were not different for nose-poking and lever-pressing, $t(19) = 1.3$ and 1.39, respectively, $p > 0.05$, so the data from the pre- and postdrug tests were combined into single nose-poking and lever-pressing baselines for further statistical analyses. The mean total responses across the saline and cocaine tests for both operants are shown in Fig. 1. Cocaine significantly increased lever-pressing responses at 5 mg/kg, $t(19) = 1.97$, $p < 0.05$ (one-tailed), but failed to show this effect at 15 or 30 mg/kg. [Since our interest was in whether *any* dose of cocaine produced an effect different from control conditions, and since we were not primarily interested in differences between the doses of cocaine or a direct comparison of the operants, repeated measures *t*-tests (rather than ANOVAs) were used for the statistical analyses.] Nose-poking responses were significantly increased by cocaine at both 15 and 30 mg/kg, $t(19) = 2.81$ and 2.42, respectively, $p < 0.05$ (one-tailed), but not at 5 mg/kg.

Cocaine-induced changes in self-stimulation responding were further investigated by evaluating the influence of cocaine on one-minute response rates across the various combinations of operants and dosage levels. This was accomplished by calculating mean response rates for one-minute intervals during which responses occurred (i.e., by eliminating one-minute trials with response rates of zero). The mean response rates calculated in this manner are shown in Fig. 2. Cocaine significantly increased nose-poking rates at 15 and 30 mg/kg, $t(19) = 2.03$ and 1.95, respectively, $p < 0.05$ (one-tailed). No other effects were significant.

The patterns of results shown in Figs. 1 and 2 are similar, but not identical. In particular, 5 mg/kg cocaine significantly increased the total number of self-stimulation lever-presses, but not the rate of lever-pressing after correction for nonresponding trials. This pattern of results could be accounted for by changes in the number of nonresponding trials. If 5 mg/kg cocaine decreased the number of nonresponding trials but did not influence the rate of lever-pressing within a self-stimulation bout, an increase in total session lever-presses would not be accompanied by a change in the minute by minute lever-pressing rate. This hypothesis was assessed by comparing the number of nonresponding trials across experimental conditions.

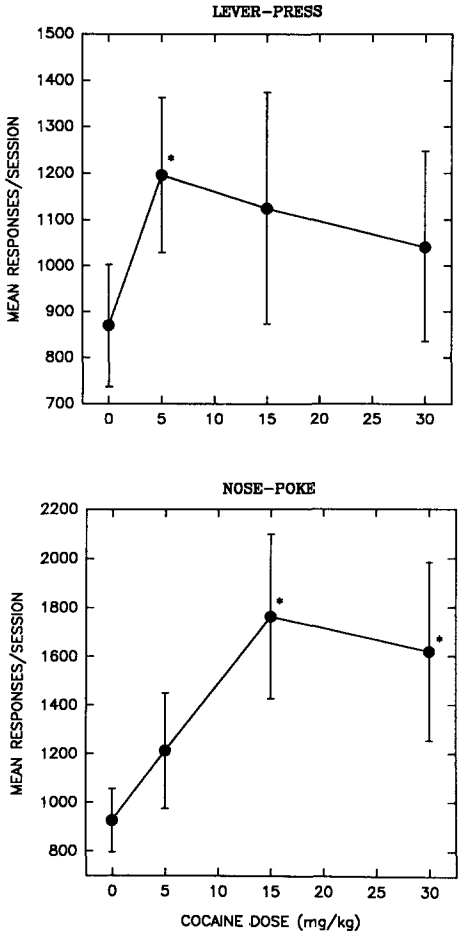

FIG. 1. Mean self-stimulation responses/testing session as a function of operant and dose of cocaine. The points marked with asterisks are significantly different from saline baseline ($p<0.05$). The bars extending from each point show plus and minus one standard error of the mean.

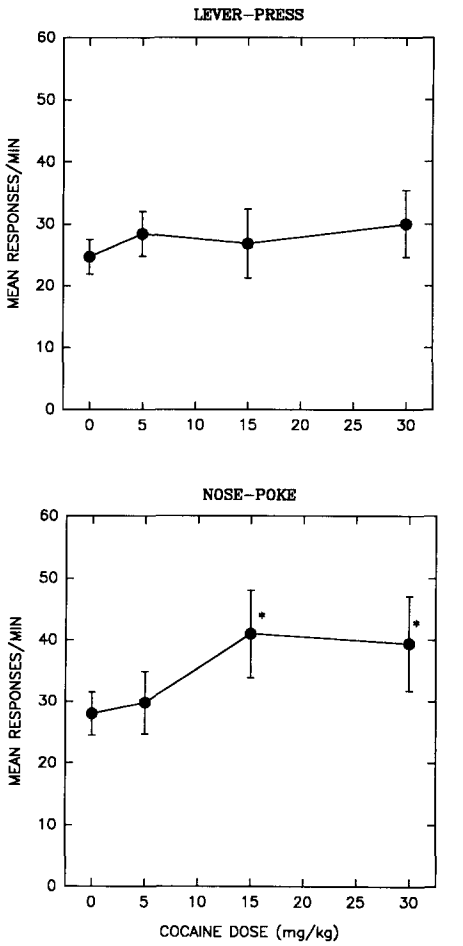

FIG. 2. Mean self-stimulation responses/min (after correction for nonresponding trials) for the eight operant/dosage combinations. The points marked with asterisks are significantly different from saline baseline ($p<0.05$). The bars extending from each point show plus and minus one standard error of the mean.

Figure 3 shows the distribution of subject responding across drug conditions for lever-pressing, and Fig. 4 shows the distribution for nose-poking. A score of 45 means that a rat responded at least once on each of the 45 one-minute trials, while a score of 0 indicates that the subject made no responses on any of the 45 one-minute tests. The lowest dose of cocaine (5 mg/kg) decreased the number of no responding trials for both operants, with the effect being somewhat larger for lever-pressing. This would account for the difference in statistical significance for the 5 mg/kg conditions when total number of responses and response rate/min on responding trials are compared. The failure of higher doses of cocaine to facilitate lever-pressing responses is also clarified by examining Figs. 2 and 3. The two higher doses of cocaine had little effect on lever-pressing rate/min (see Fig. 2), and while these doses increased the number of responding trials for some rats, others showed a large reduction in responding trials (see Fig. 3). This resulted in increases in variance for the total number of lever-presses in the 15 and 30 mg/kg testing sessions (see Fig. 1), and the lack of a statistically significant cocaine effect.

A slightly different pattern was noted for the effects of 15 and 30 mg/kg cocaine on nose-poking. Although a result that was similar to lever-pressing was observed for the number of responding trials (see Fig. 4), unlike lever-pressing, the two higher doses of cocaine substantially increased the nose-poking rate/min on trials where responding occurred (see Fig. 2). This translated into a significant increase in the total number of responses/testing session (see Fig. 1).

Changes in the distribution of responding trials were evaluated statistically using Kolmogorov-Smirnoff tests (19). This test assesses whether two frequency distributions are significantly different. It was found that the distribution of responding trials differed between saline and the 5 and 15 mg/kg cocaine conditions for both operants (all $p<0.05$). This was also true for the 30 mg/kg nose-poking condition, while the difference between saline and 30 mg/kg with lever-pressing produced a statistical result that was marginal ($0.1>p>0.05$).

Histological analyses of 15 of the 20 subjects' electrode placements revealed that the electrode tips were located in or near the medial forebrain bundle at the level of the ventral tegmental area and substantia nigra. No consistent relationship was noted between the location of the electrode tips and the pattern of the behavioral results. Electrode placements could not be verified for five subjects that dislodged their electrodes prior to sacrifice.

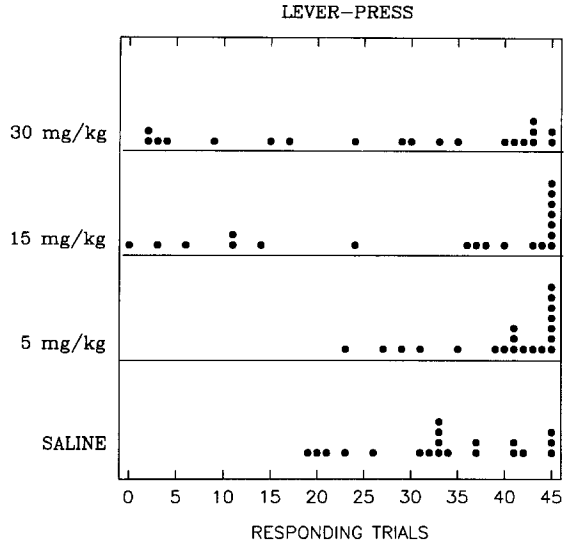

FIG. 3. Distribution of responding trials for lever-pressing as a function of dose of cocaine. Each point shows the data of a single subject.

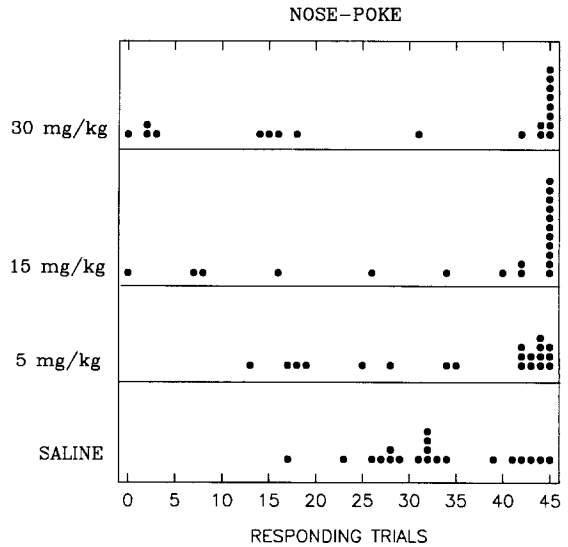

FIG. 4. Distribution of responding trials for nose-poking as a function of dose of cocaine. Each point shows the data of a single subject.

DISCUSSION

In several previous studies conducted in our laboratory, no evidence of cocaine-induced increases in the rate of self-stimulation were observed (6–8). However, a rate-enhancing effect of cocaine has been reported by others (1, 3, 24). The results of the present experiment indicate that differences in the parameters of stimulation, operant response requirements and methods of data analysis probably contributed to differences in the outcomes of these studies.

The short train durations used in previous experiments by Frank and colleagues may have contributed to the failure to find a rate effect of cocaine, since cocaine-induced increases in nose-poking and lever-pressing were observed with longer train durations in the present study. The short train durations used in our previous research (ranging from 10 to 150 ms) elicit very high rates of self-stimulation, often averaging over 100 responses/min. This rate of responding is probably near the maximal response capacity of the rats, making it difficult for any drug to increase response rates. A recent study from our lab (20) supports this interpretation. Here prefrontal cortex self-stimulation rates were facilitated by cocaine. Since prefrontal cortex self-stimulation rates are generally lower than those associated with medial forebrain bundle self-stimulation, limits on response capacity would be less of a problem.

Cocaine-induced increases in lever-pressing at 5 mg/kg seemed to relate to the drug's ability to increase the amount of time self-stimulating rather than the rate of lever-pressing within a self-stimulation bout. It seems likely that this effect is related to cocaine-induced response perseveration. At higher doses, some subjects exhibited more consistent responding while others showed less consistent responding (see Fig. 3). It is likely that this pattern of results relates to individual differences in the subject's sensitivity to cocaine-induced stereotypies (12).

It might be argued that the failure of the higher doses of cocaine to enhance lever-pressing response rates was due to response ceiling effects related to the use of stimulation parameters that support asymptotic rates of self-stimulation. However, it is important to realize that asymptotic response rates do not necessarily provide a measure of maximal response capacity. For example, at suprathreshold levels of stimulation, decreasing train duration can dramatically increase response rates (2). It is unlikely that the lever-pressing rates observed in the present experiment (mean rates averaging between 20 and 30 responses/min) represent the maximal response capacity of the subjects. Much higher rates of lever-pressing have been observed when shorter (but suprathreshold) train durations are employed [mean maximal rates of over 100 responses/min are common, e.g., see (9)].

Nose-poking response rates were facilitated by 15 and 30 mg/kg cocaine, an effect that appears to reflect an increase in the rate of self-stimulation within stimulation bouts. It is hypothesized that the increases in nose-poking rate are related to the characteristics of cocaine-induced stereotypy. Post and Rose (22) reported that cocaine produced hyperactivity and stereotypic head movements in rats, and Post and Contel (21) found that stereotypic nose-poking occurred spontaneously following cocaine administration. It seems likely that nose-poking rates were preferentially increased by cocaine due to the compatibility of the response requirements of this operant with the stereotyped movements induced by cocaine.

Another factor that may account for the operant-dependent effects of cocaine relates to the free operant rates of nose-poking and lever-pressing. Nose-poking is emitted at a higher free operant rate than lever-pressing, perhaps because it is a simple and innate exploratory behavior (16). According to a theory of amphetamine's behavioral effects proposed by Lyon and Robbins (17), "The action of amphetamine is such that as the dose response within the central nervous system increases, the repetition rate of all motor activities will increase with the result that the organism will tend to exhibit increasing response rates within decreasing numbers of response categories" (p. 85). Iversen and Iversen (11) proposed that response simplicity and probability of occurrence determine which responses will remain. Since cocaine's and amphetamine's behavioral effects are similar, one might expect Lyon and Robbins' theory to apply to cocaine. If it does, their analysis could explain the differential effects of cocaine on nose-poking and lever-pressing rates. Nose-poking rates would be facilitated more than lever-pressing because nose-poking is an innate, simple, high probability behavior.

Given the complexity of the findings of the present experiment, it is not surprising that some investigators report cocaine-induced facilitation of self-stimulation rates while others do not.

The effects of cocaine on self-stimulation rate seem to depend on the stimulation parameters, methods of data analysis, and operants that are used. Investigators with interests in cocaine's influence on self-stimulation response rates would be well advised to attend to these factors when designing experiments to elucidate cocaine's behavioral effects.

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