Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 2, pp. 511–514, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0006-4

Effects of Cocaine on Fixed-Ratio Responding of Rats: Modulation by Required Response Force

MALATH MAKHAY, KEN ALLING AND ALAN POLING[1]

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

Received 23 July 1993

MAKHAY, M., K. ALLING AND A. POLING. *Effects of cocaine on fixed-ratio responding of rats: Modulation by required response force.* PHARMACOL BIOCHEM BEHAV 48(2) 511–514, 1994.—The effects of acute cocaine administrations (5.6–32 mg/kg) were determined in rats responding under a multiple fixed-ratio 15 (FR 15) FR 15 schedule of food delivery. The minimum response effort required in one schedule component was 25 g, whereas in the other component it was 200 g. Cocaine produced generally dose-dependent decreases in rate of responding and increases in preratio pause time under each component. There was, however, a significant interaction between force and drug dose, and drug effects were larger in the component requiring 200 g for lever operation. Although a number of other parameters have been shown previously to modulate the effects of cocaine on schedule-controlled responding, the present data constitute the first demonstration that minimum response effort does so.

Cocaine Schedule-controlled behavior Fixed-ratio schedule Response force

STUDIES of drug effects on schedule-controlled responding have played a significant role in behavioral pharmacology, and these studies have shown that the schedule of reinforcement under which behavior is maintained powerfully influences the effects of a wide range of drugs [e.g., (12,13,18,20)]. One schedule aspect that has been essentially ignored as a possible determinant of drug action is the amount of force, or effort, required to emit a response. In the characteristic preparation for examining drug effects on schedule-controlled responding, the operant response (e.g., key pecking by pigeons, lever pressing by rats) requires minimal physical effort, and the effort required does not change through the course of the study. Although some studies have examined how drugs and other environmental variables influence the force of responses [e.g., (4,7,8,15)], as Fowler (7) pointed out, "little is known about the effects of behavior-controlling variables on force and duration of operant response" (p. 83). Even less is known concerning how the effects of these variables, including drugs, are modulated by required response force. Put simply, response force has been largely ignored as a dependent variable in behavioral pharmacology, and completely ignored as an independent variable.

To provide an indication as to whether required response force modulates drug action, the present study examined the effects of cocaine in rats responding under fixed-ratio 15 (FR 15) schedules of food delivery that differed with respect to the minimum amount of effort required for lever operation (25 g vs. 200 g). Previous investigations have shown that the drug produces generally dose-dependent rate reductions under FR schedules (2,7,10,11,20), but whether this action is affected by response effort has not been determined.

METHOD

Subjects

Six Long–Evans strain male rats, maintained at 80% of their free-feeding weights, served as subjects. Subjects were approximately 270 days old and experimentally naive at the onset of training. They were individually housed with unlimited access to water in a room with controlled lighting (16 h light and 8 h dark cycle), temperature (22–24°C), and humidity (60–70%). The study was approved by the Institutional Animal Care and Use Committee of Western Michigan University.

Apparatus

Four aluminum operant conditioning chambers, measuring 20 cm long, 13 cm wide, and 15 cm high, were used. The front (13 × 15 cm) wall of each chamber was equipped with two response levers that were separated by 3.5 cm and centered

[1] To whom requests for reprints should be addressed.

horizontally 7.5 cm above the floor. Only the left lever was used in this study. A 7-W yellow light was located 6 cm above each lever, and a dipper through which 0.1 ml sweetened condensed milk diluted with water (50/50 ratio) could be delivered was centered 3 cm below the levers. When the dipper was raised, the dipper aperture was illuminated by a 7-W white light. A buzzer (Sonalert, Mallory Inc., New York) mounted on the rear wall of the chamber allowed for tone presentation when desired. An exhaust fan supplied masking noise and ventilation.

A rheostatically controlled electromagnet allowed the minimum force requirement for operation of the left lever to be adjusted from 25 g to 200 g. With this arrangement the lever had to be pressed with a force greater than the specified minimum to initiate movement, which proceeded through a downward arc of approximately 0.2 cm so long as at least 25 g of pressure was applied. At the end of this arc, microswitch operation terminated lever movement and a response was recorded. Control of experimental events and data recording were accomplished through the use of a PDP8/e minicomputer equipped with interfacing and software obtained from State Systems (Kalamazoo, MI).

Behavioral Procedure

During training sessions, which ended after 40 food deliveries, subjects received response-independent deliveries of food (4-s access to sweetened condensed milk) on average every 60 s (i.e., under a random-time 60-s schedule). An FR 1 schedule of food delivery for left-lever presses also was in effect. These conditions engendered lever pressing in all rats. Once each rat lever pressed reliably, the random-time 60-s schedule terminated and the FR value was gradually increased over sessions to 15. Under the FR 15 schedule, every 15th lever press was immediately followed by a 4-s food delivery. When subjects completed 10 sessions under the FR 15 schedule, the force requirement for lever pressing was gradually increased over sessions from 25 g to 200 g. The FR 15 schedule with 200 g required response force remained in effect until the rate of responding of each individual rat showed no visually evident trend over 10 consecutive sessions. When this occurred, the experiment proper began.

In the experiment proper, a multiple FR 15 FR 15 schedule of food delivery was arranged. The components differed with respect to minimum force requirement. In one FR 15 component, the minimum force requirement was 25 g. In the other FR 15 component, the minimum force requirement was 200 g. For three rats, selected at random, the stimulus lights above the levers were constantly illuminated and the tone remained on throughout the FR 15 component with the 25-g force requirement. For those animals, the lights flashed and the tone came on and went off at 1-s intervals during the FR 15 component with the 200-g force requirement. Relations between stimuli and the two FR 15 components were reversed for the other three subjects. Each FR 15 component was in effect until the programmed ratio was completed five times or until no responding occurred during 5 consecutive min, whichever occurred first. At that time, the other component was arranged. Components continued to alternate until each was arranged on four occasions, after which the session ended. Throughout the study, sessions were arranged seven days per week at about the same time each day.

Pharmacological Procedures

Drug injection began after mean response rates and preratio (or postreinforcement) pause times for an individual rat showed no visually evident trend over 10 consecutive sessions. During the drug regimen each subject received four doses (5.6, 10, 17.8, and 32 mg/kg) of cocaine hydrochloride (Sigma Chemical Co., St. Louis) dissolved in isotonic saline solution and prepared at an injection volume of 1 mg/kg. Drug injections were given according to a BBCD design, where B represents baseline (no injections), C represents vehicle control, and D represents drug sessions. Drug and vehicle injections were administered IP 10 min prior to behavioral testing. All doses were administered twice, in two ascending series.

RESULTS

For each session, mean response rates and mean preratio pause times under the two different FR 15 components were recorded for each animal. The former measure was calculated by dividing total responses by total time in the appropriate component. The latter measure was calculated by determining the time elapsed from the offset of each food delivery to the first subsequent response (an individual preratio pause), then finding the mean of these values.

During vehicle control sessions, the mean response rate for the six rats during the FR 15 component with the lower (25 g) required effort was 2.07 responses/s; the range across individual animals was 1.62–2.52 responses/s. For the FR 15 component with the higher (200 g) required effort, the mean group rate was 0.83 responses/s and the range across rats was 0.40–1.32 responses/s.

Statistical analysis (two-factor repeated-measures analysis of variance) revealed a significant interaction between minimum force requirement and drug dose for response rate (interaction $F = 8.47$, $p < .05$). This effect is evident in Fig. 1, which shows the effects of cocaine on response rates under the two FR 15 components. In this figure, response rates in the presence of drug are expressed as a percentage of the vehicle control rate. Regardless of whether the minimum force requirement in the FR 15 component was 25 g or 200 g, cocaine produced generally dose-dependent rate reductions relative to control levels. The magnitude of the rate reduction at a particular dose, however, was always greater in the component with the higher force requirement. Under this component, mean response rates were

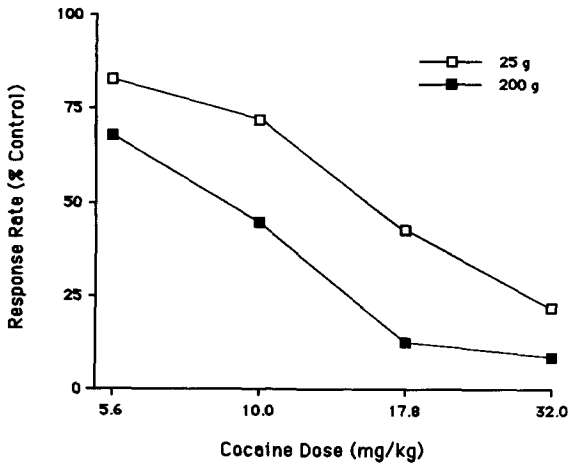

FIG. 1. The effects of cocaine on the rate of responding of rats exposed to a multiple FR 15 FR 15 schedule of food delivery in which the minimum force requirement for a lever press was 25 g in one component and 200 g in the other component. Drug data, which represent means for two administrations of each dose to six rats, are expressed as percent of the vehicle control rate.

0.55, 0.36, 0.09, and 0.06 responses/s at cocaine doses of 5.6, 10, 17.8, and 32 mg/kg, respectively. In contrast, mean response rates under the other component were 1.68, 1.44, 0.85, and 0.41 responses/s at these same doses.

During vehicle control sessions, the mean preratio pause time for the six rats during the FR 15 component with the lower (25 g) required effort was 2.32 s; the range across individual animals was 1.03–3.63 s. For the FR 15 component with the higher (200 g) required effort, the mean pause time was 6.69 s and the range across rats was 4.19–12.82 s.

Statistical analysis (two-factor repeated-measures analysis of variance) revealed a significant interaction between minimum force requirement and drug dose for preratio pause data (interaction $F = 8.34$, $p < .05$). This effect is evident in Fig. 2, which shows the effects of cocaine on preratio pause time under the two FR 15 components. As in Fig. 1, drug data are expressed as a percentage of vehicle control data. Cocaine produced generally dose-dependent increases in pause time in both FR components, although the magnitude of this effect was always greater in the component with the higher force requirement. Under this component, mean pause times were 13.37, 267.60, 1069.13, and 1214.43 s at cocaine doses of 5.6, 10, 17.8, and 32 mg/kg, respectively. In contrast, mean pause times under the other component were 2.34, 4.25, 21.38, and 45.73 s at these same doses. The very large increases in mean pause time at high doses (i.e., 17.8 and 32 mg/kg) under both components reflect, in part, the occurrence of sessions in which animals failed to complete a single ratio. Although failures to complete a single ratio were observed under both components, they occurred more often under the component with the higher force requirement. Unfortunately, data were not recorded in a manner that allowed pause times to be calculated separately for ratios that were actually completed.

DISCUSSION

As in previous investigations (1,3), increasing required response effort decreased response rate and increased preratio pause time in the present study. Also consistent with the results of earlier studies (2,9,10,11,20), cocaine produced generally dose-dependent rate reductions under both FR components. At high doses, the effects of the drug on both dependent measures were pronounced.

Although the *qualitative* effects of cocaine did not depend on the minimum force requirement, this variable significantly affected the *quantitative* effects of the drug. At all doses and with both dependent variables, the relative effects of cocaine were greater under the FR 15 component that required more force. To our knowledge, the present data represent the first demonstration of an effect of this kind.

Previous studies have shown, however, that required response effort in another sense (viz., FR size) can modulate the acute effects of cocaine [e.g., (10,11,14)]. In those investigations, the magnitude of the rate reduction produced by a given dose of cocaine was directly related to the size of the FR schedule of food delivery in effect. For example, Hughes and Branch (11) found that cocaine doses of 0.3 and 1.0 mg/kg reduced the response rates of squirrel monkeys to 40–57% of control rates under the smallest FR to which they were exposed (FR 5 for all four animals), whereas the same doses reduced rates to 8–12% of control rates under larger FRs (i.e., those ranging from 17 to 125 across components and animals).

Like other psychomotor stimulants, cocaine has rate-dependent effects: Low to moderate doses characteristically reduce high-rate operants and increase low-rate operants (17,19). The magnitude of the relative rate reduction observed at a given dose characteristically is directly related to the control rate (i.e., higher rates are reduced more than lower rates relative to control values). Such an effect was not observed in the present study, where greater rate reductions were observed under the FR component that required more effort and engendered lower rates of responding in the absence of drug. Therefore, the present findings cannot be explained in terms of the usual rate-dependent effects of cocaine.

Previous studies have shown that preratio pause size is directly related to FR size (5,6,16), and a similar relation was observed when minimum force requirement was observed in the present study. This effect was very prononuced in the present study, due in large part to the fact that we considered pause time to be equivalent to component length for components in which animals failed to complete a single ratio. Such components rarely occured when the minimum required lever force was 25 g, but occured rather frequently when it was 200 g.

Although FR size and minimum response force appear to produce similar behavioral effects and to modulate the rate-reducing effects of cocaine in comparable fashion, it is unclear whether these variables actually are symmetrical in their actions, how they interact, and what the neuropharmacological mechanisms are through which they modulate the behavioral effects of cocaine.

Interestingly, tolerance develops more readily to the effects of cocaine under relatively short FR schedules than under longer schedules (10,11,14), although why this occurs remains to be determined. No one has ascertained whether a similar relation obtains when effort is manipulated in terms of the actual physical force required to emit each response under same-sized FRs, but this could be easily accomplished using the procedures employed in the present investigation coupled with a chronic drug regimen.

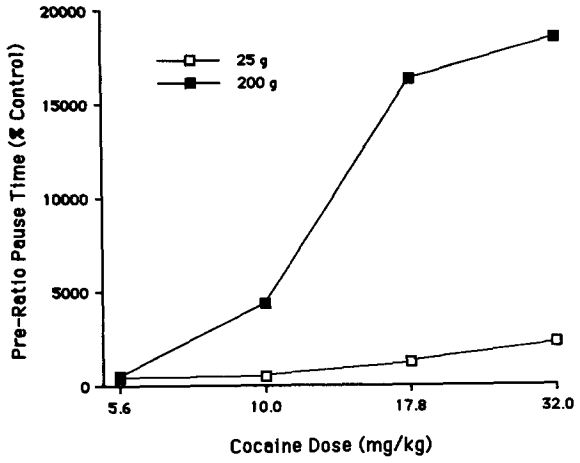

FIG. 2. The effects of cocaine on mean preratio pause time in rats exposed to a multiple FR 15, FR 15 schedule of food delivery in which the minimum force requirement for a lever press was 25 g in one component and 200 g in the other component. Drug data, which represent means for two administrations of each dose to six rats, are expressed as percent of the vehicle control rate.

ACKNOWLEDGEMENTS

The reported research was conducted as part of the M.A. thesis of Malath Makhay and was supported by a grant from the Faculty Research and Creative Activities Support Fund, Western Michigan University.

REFERENCES

1. Armus, H. L. Effect of response effort requirement on frequency of short interresponse times. Bull. Psychonom. Soc. 24:284–285; 1986.
2. Branch, M. N.; Dearing, M. E. Effects of acute and daily cocaine administration on performance under a delayed-matching-to-sample procedure. Pharmacol. Biochem. Behav. 16:713–718; 1982.
3. Chung, S.-H. Effects of effort on response rate. J. Exp. Anal. Behav. 8:1–7; 1965.
4. Falk, J. L. Drug effects on discriminative motor control. Physiol. Behav. 4:421–427; 1969.
5. Felton, M.; Lyon, D. O. The postreinforcement pause. J. Exp. Anal. Behav. 9:131–134; 1966.
6. Ferster, C. B.; Skinner, B. F. Schedules of reinforcement. Englewood Cliffs, NJ: Prentice Hall; 1968.
7. Fowler, S. C. Force and duration of operant response as dependent variables in behavioral pharmacology. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Neurobehavioral pharmacology. Hillsdale, NJ: Erlbaum; 1987:83–127.
8. Fowler, S. C.; Filewich, R. J.; Beberer, M. R. Drug effects upon force and duration of response during fixed-ratio performance in rats. Pharmacol. Biochem. Behav. 6:421–426; 1976.
9. Gonzales, F. A.; Goldberg, S. R. Effects of cocaine and *d*-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. J. Pharmacol. Exp. Ther. 201:33–43; 1977.
10. Hoffman, S. H.; Branch, M. N.; Sizemore, G. M. Cocaine tolerance: Acute vs. chronic effects as dependent upon fixed-ratio size. J. Exp. Anal. Behav. 47:363–376; 1987.
11. Hughes, C. E.; Branch, M. N. Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. J. Exp. Anal. Behav. 56:345–360; 1991.
12. Kelleher, R. T.; Morse, W. H. Determinants of the specificity of the behavioral effects of drugs. Ergeb. Physiol. 60:1–56; 1968.
13. McKearney, J. W.; Barrett, J. E. Schedule-controlled behavior and the effects of drugs. In: Blackman, D. E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:1–68.
14. Nickel, M.; Alling, A.; Kleiner, M.; Poling, A. Fixed-ratio size as a determinant of tolerance to cocaine: Is relative or absolute size important? Behav. Pharmacol. 4:471–478, 1993.
15. Notterman, J. M.; Mintz, D. E. Dynamics of response. New York: Wiley; 1965.
16. Powell, R. W. The effect of small sequential changes in fixed-ratio size upon the postreinforcement pause. J. Exp. Anal. Behav. 11:589–593; 1968.
17. Sanger, D. J.; Blackman, D. E. Rate-dependent effects of drugs: A review of the literature. Pharmacol. Biochem. Behav. 32: 267–274.
18. Seiden, L. S.; Dykstra, L. A. Psychopharmacology: A biochemical and behavioral approach. New York: van Nostrand Reinhold; 1977.
19. van Haaren, F. Schedule-controlled behavior: Positive reinforcement. In: van Haaren, F., ed. Methods in behavioral pharmacology. New York: Elsevier; 1993:81–99.
20. Woolverton, W. L.; Kandel, D.; Schuster, C. R. Effects of repeated administration of cocaine on schedule-controlled behavior of rats. Pharmacol. Biochem. Behav. 9:327–337; 1978.