Pharmacology Biochemistry and Behavior, Vol. 43, pp. 111–115, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Prazosin Attenuates the Effects of Cocaine on Motor Activity but Not on Schedule-Controlled Behavior in the Rat

CHARLES W. BERTHOLD III,
REUBEN A. GONZALES AND JOSEPH M. MOERSCHBAECHER[1]

Department of Pharmacology, Louisiana State University Medical Center, New Orleans, LA 70112

Received 3 May 1989

BERTHOLD III, C. W., R. A. GONZALES AND J. M. MOERSCHBAECHER. *Prazosin attenuates the effects of cocaine on motor activity but not on schedule-controlled behavior in the rat.* PHARMACOL BIOCHEM BEHAV **43**(1) 111–115, 1992.—The spontaneous motor activity of rats was measured following administration of cocaine alone and in combination with the centrally acting α_1-antagonist prazosin. Cocaine alone (18–42 mg/kg) increased motor activity in a dose-related manner. At doses of 1 and 1.8 mg/kg, prazosin attenuated the increases in motor activity produced by cocaine. In rats responding under a fixed-ratio discrimination procedure, cocaine (10–32 mg/kg) produced dose-dependent increases in percent errors and decreases in overall response rate. Across a range of doses (0.32–3.2 mg/kg), prazosin failed to antagonize the effects of cocaine on responding under the discrimination procedure. Rather, the combined effects were frequently greater than those obtained with cocaine alone. The data suggest that in rats activation of α_1-adrenergic systems may mediate the effects of cocaine on motor activity but not on schedule-controlled behavior.

Antagonism Cocaine Discrimination Fixed-ratio schedule Motor activity Prazosin Rats

STIMULANTS such as amphetamine and cocaine are known to have significant abuse potential and exert pronounced behavioral effects (3,22). In the rat, blockade of dopamine reuptake systems in the nucleus accumbens is generally thought to mediate the reinforcing properties of cocaine (13,21). In contrast, the neuronal mechanisms underlying many of the other behavioral effects of cocaine remain more controversial. For example, dopamine has also been implicated in mediating both the discriminative stimulus properties (4,6) and locomotor effects (5,11,12) of cocaine. The role of the noradrenergic system in mediating some of these same behavioral effects of cocaine and other stimulants has, however, also received some attention (2,19,20). For example, Snoddy and Tessel (15,16) reported that in mice prazosin, but not pimozide or propranolol, blocks the discriminative stimulus properties of both amphetamine and nisoxetine. In that same study (16), prazosin was also found to antagonize the increases in locomotor activity produced by amphetamine and cocaine but not those produced by the dopamine uptake blocker bupropion, More recently, Tessel and Barrett (17) examined the effects of prazosin in combination with *d*-amphetamine and cocaine on schedule-controlled responding in pigeons and squirrel monkeys. They found that prazosin antagonized, in a dose-dependent manner, the rate-decreasing effects of *d*-amphetamine and cocaine, but not those of bupropion, in pigeons responding under a fixed-ratio (FR) schedule. Similarly, prazosin antagonized both rate-increasing and decreasing effects of *d*-amphetamine in squirrel monkeys responding under a fixed-interval (FI) schedule. Consistent with these observations, it has recently been reported that cocaine will enhance norepinephrine (NE)-stimulated phosphatidylinositol (PI) hydrolysis in vitro and that this effect may be blocked by prazosin (10).

Together, these studies would support the notion that some of the behavioral effects of amphetamine and cocaine might, in part, be mediated by central α_1-adrenergic systems. However, the data base supporting this notion is relatively small, particularly with regard to schedule-controlled behavior. Therefore, the purpose of the present study was to expand this data base and determine the generality of these findings in another species. To this end, the effects of cocaine and prazosin, alone and in combination, on spontaneous motor activity and schedule-controlled behavior in the rat were investigated.

[1] Requests for reprints should be addressed to J. M. Moerschbaecher, Ph.D., Department of Pharmacology, LSU Medical Center, 1901 Perdido Street, New Orleans, LA 70112-1393.

METHOD

Schedule-Controlled Behavior

Subjects. Five experimentally naive, adult, male Long-Evans hooded rats were maintained at 80% (350–400 ± 10 g) of their free-feeding body weights by food presented during the session and by supplemental postsession feeding (Purina Rat Chow) throughout the experiment. Water was available continuously in individual home cages. The home cages were kept in a temperature-controlled room under a 12 L:12 D cycle.

Apparatus. A standard experimental chamber (Lehigh Valley Electronics, Lehigh Valley, PA: model 132-04) measuring 23.5 × 30 × 26.5 cm was used. Three response levers were aligned horizontally on the rear wall 9 cm apart, center to center, and 5 cm above the grid floor. Each lever required a minimum force of 0.22 N for activation. A white pilot lamp (no. 1820) was located 5 cm above each lever. A food cup was mounted in the center of the opposite wall 2 cm above the grid floor. A houselight was located 23 cm above the food cup. Each chamber was housed in a larger insulated shell equipped with a ventilation fan. Events were scheduled and recorded by means of solid-state circuitry, counters, running-time meters, and a cumulative recorder.

Procedure. Rats responded under a FR discrimination procedure (9). Under this procedure, the stimulus above the center lever was illuminated and the subject was required to complete a FR on the center lever. Either an FR 16 or FR 8 was required. Completion of the ratio turned off the stimulus above the center lever and illuminated the stimulus above each side lever. If the ratio completed was high (e.g., FR 16), a response on the left lever was reinforced. If, however, the ratio was low (e.g., FR 8), a response on the right lever was reinforced. A correct response turned off the stimulus above each lever, produced a 45-mg food pellet (Bio-Serv, no. 0021) and illuminated the houselight for 2.5 s. Incorrect responses produced a brief (2 s) time-out during which all stimuli were off and responses had no programmed consequences. After either food delivery or a time-out, the stimulus above the center lever was illuminated and the subsequent ratio was programmed with equal probability (i.e., noncorrection). Session durations were 30 min and were conducted 5 days/week. The data for each session were analyzed in terms of a) the FR response rate (total center-lever responses/time center-lever stimulus was on) and b) the overall accuracy or percentage of errors {[incorrect/(correct + incorrect responses)] × 100}. The data for each subject were analyzed by comparing drug sessions with the control range of variability (saline). A drug

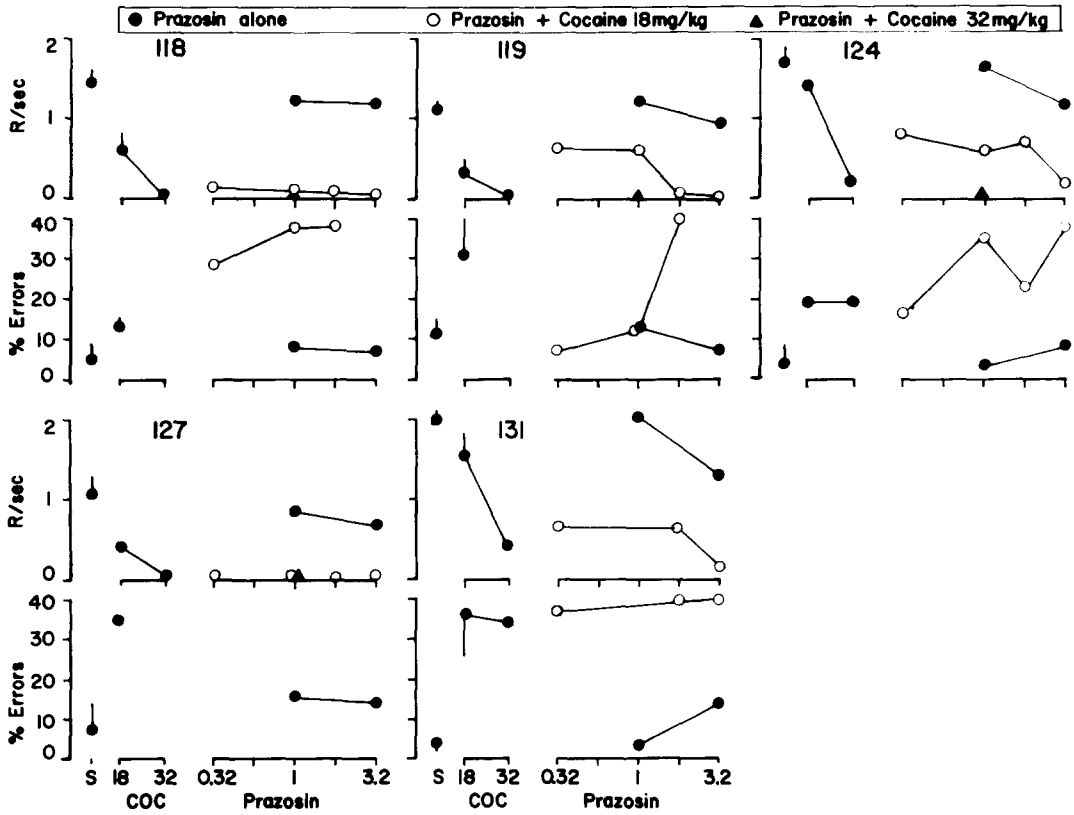

FIG. 1. Effects of cocaine and prazosin, both alone and in combination, on overall response rate and percent errors in each subject responding under the FR discrimination procedure. The points and vertical lines above S indicate the mean and range of at least six sessions that were preceded by saline injections. The points with vertical lines in the dose-response curves indicate the mean and range for at least two determinations. The points without vertical lines indicate either a single determination or an instance in which the range is encompassed by the point. The data plotted above COC represent the effects of cocaine alone, while the other points represent the effects of prazosin either alone or in combination with cocaine (see captions at top of figure). No data point for percent errors are shown in those cases where response rate was zero.

was considered to have an effect to the extent that the dose data fell outside the control range.

Motor Activity

Subjects. Five adult, male Long-Evans hooded rats served as subjects. Food (Purina Rat Chow) and water were available continuously in individual home cages. The home cages were kept in a temperature-controlled room under a 12 L:12 D cycle.

Apparatus. Motor activity was measured using a photocell system (PLK Instruments, Carborro, NC). Each photocell apparatus in this system consisted of a clear Plexiglas cage (25 × 50 cm; 35 cm high) with a wire mesh floor. Each cage had two horizontal photocells mounted front to back 12 cm above the cage floor and two horizontal photocells mounted side to side 4.5 cm above the cage floor. The photocell consisted of a narrow beam (4) IR emitter (Fairchild Camera and Instrument Corp., Mountain View, CA) coupled with a general purpose N-P-N silicon phototransistor (Texas Instruments, Dallas, TX). Eight such photocell cages were interfaced to a Rockwell (Anaheim, CA) AIM-65 microprocessor, and the entire system was located in a isolated room.

Procedure. Each subject was placed in a photocell cage at approximately 10 a.m. Motor activity was measured in 10-min bins over the course of a 60-min session 5 days/week. Counts were summed for the session, where each count represented one interruption of a photobeam by the animal. Data for drug sessions were calculated relative to saline sessions and expressed as a percentage of the control counts.

Drugs. Cocaine hydrochloride was dissolved in a 0.9% sterile saline and prazosin hydrochloride was dissolved by sonicating the drug in sterile water. Drug and control injections were given IP either 15 min (prazosin) or 10 min (cocaine) presession. The volume of injection for each drug was 2 ml/kg body weight. The doses of each drug were tested in a mixed order. Drug sessions were generally conducted on Tuesdays and Fridays, with control injections on Thursdays. At higher doses, however, drug injections were given only once a week.

RESULTS

The effects of cocaine and prazosin, alone and in combination, on overall response rate and percent errors under the FR discrimination procedure are shown in Fig. 1. When administered alone, cocaine generally produced dose-related decreases in response rate and increases in percent errors. These effects on response rate were, however, somewhat variable among subjects. For example, at a dose of 18 mg/kg cocaine produced only small rate-decreasing effects in two subjects (124 & 131) while in three subjects large rate-decreasing effects obtained. Note that this same dose increased percent errors in each subject tested. In general, at a dose of 1 mg/kg prazosin alone had little or no effect on either overall response rate or

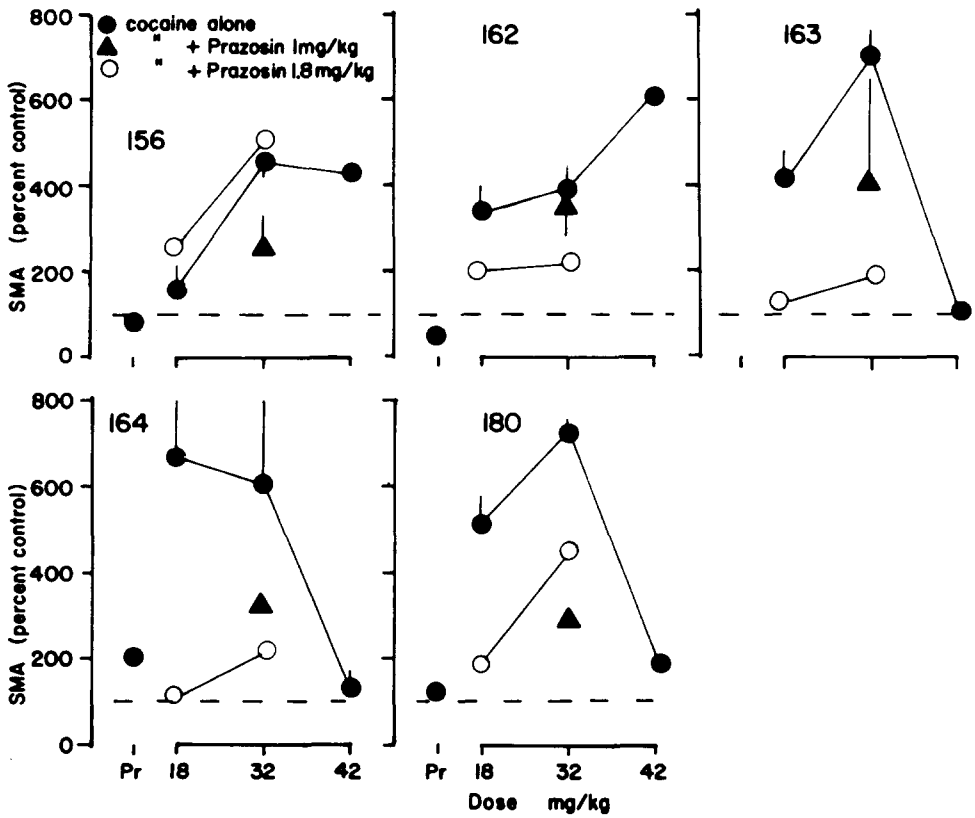

FIG. 2. Effects of cocaine and prazosin, both alone and in combination, on spontaneous motor activity. The point above Pr represents the effects of prazosin 1.8 mg/kg alone (not tested in 163). The points with vertical lines in the dose-response curves indicate the mean and range for at least two determinations. The points without vertical lines indicate either a single determination or an instance in which the range is encompassed by the point.

percent errors. At a dose of 3.2 mg/kg, however, prazosin produced small decreases in overall response rate in three (124, 127, and 131) subjects tested. This same dose generally had no effect on percent errors.

Across the range of doses tested, prazosin (0.32–3.2 mg/kg) failed to antagonize the effects of cocaine at a dose of 18 mg/kg. Rather, the combined effects were often greater than those obtained when the same dose of cocaine was administered alone. This was especially true in relation to the rate-decreasing effects of the drugs. For example, note that in subjects 118 and 127 the combined effects of prazosin and cocaine (18 mg/kg) were clearly greater than those that might be expected based upon the effects of each drug administered alone. The only exception to this finding was in subject 119, where prazosin at doses of 0.32 and 1 mg/kg antagonized the error-increasing effects of cocaine 18 mg/kg. Prazosin, 1 mg/kg, also failed to antagonize the large rate-decreasing effects produced by cocaine 32 mg/kg.

The effects of cocaine and prazosin, alone and in combination, on spontaneous motor activity are shown in Fig. 2. When administered alone at a dose of 1.8 mg/kg, prazosin had little or no effect on motor activity. Lower doses of prazosin were also without effect (data not shown). In contrast, cocaine produced large increases in motor activity at doses of 18 and 32 mg/kg in four of five subjects. In two subjects (156 and 162), activity was also increased at a dose of 42 mg/kg, while in three subjects (163, 164, and 180) this same dose decreased activity relative to doses of 18 and 32 mg/kg. In general, prazosin antagonized the effects of cocaine on spontaneous motor activity. At a dose of 1 mg/kg, prazosin attenuated the increases in motor activity produced by cocaine 32 mg/kg in four of five subjects tested. Similarly, at a dose of 1.8 mg/kg prazosin attenuated the effects of 18 and 32 mg/kg cocaine in four of five subjects. Following the combined drug administration, the effects of cocaine (18 and 32 mg/kg) were redetermined in each subject. The effects generally replicated, indicating that the combined effects were not simply due to the development of tolerance to cocaine.

DISCUSSION

The present data are in good agreement with previous reports of the acute effects of cocaine on spontaneous motor activity (1,5,16). Similarly, the FR discrimination data are also consistent with previous reports of the disruptive effects of cocaine on the acquisition and performance of discriminations in a variety of species (7,14,18). When administered alone, the effects of cocaine were somewhat variable among subjects under both procedures. Such variability in terms of cocaine's effects in rats following IP administration has been previously reported and may, in part, reflect individual differences in brain levels of cocaine (1).

In the present study, prazosin antagonized the effects of cocaine on spontaneous motor activity but not on schedule-controlled behavior. Thus, it would appear that, in the rat, the behavior under study may determine whether or not antagonism will obtain. Several alternative explanations might, however, be offered to this conclusion. For example, when administered alone cocaine produced an inverted V-shaped dose–effect curve on motor activity. Based upon this curve, it might be argued that prazosin rather than antagonizing actually potentiated the effects of cocaine (i.e., shifted the cocaine dose–effect curve to the left). Alternatively, it might be argued that prazosin will antagonize a cocaine-induced increase in behavior, as was obtained in motor activity, but not a decrease, as was obtained in response rate. Two pieces of evidence detract from this argument. First, cocaine increased percent errors yet prazosin failed to attenuate this increase. It has been demonstrated (8,9) that errors may be affected independent of response rate under this procedure. Second, in a previous study (17) prazosin was found to antagonize the rate-decreasing effects of cocaine in pigeons responding under an FR schedule of food presentation. Thus, it would seem unlikely that prazosin's efficacy as an antagonist is limited only to those instances in which cocaine produces an increase in some aspect of behavior.

The results obtained under the FR discrimination procedure differ from those previously reported by Tessel and Barrett (17), who found that prazosin antagonized the effects of cocaine on schedule-controlled behavior in the pigeon. The reason for the discrepancy between that and the present study is unclear but may be related to a species difference. The attenuation of cocaine's effect on motor activity by prazosin is, however, consistent with results obtained by Snoddy and Tessel (16) in mice. It has been suggested that some of the central effects of cocaine may be mediated, in part, through the enhancement of α_1-stimulated PI hydrolysis by NE (10). Interestingly, the in vitro concentrations of cocaine that enhanced PI hydrolysis correspond well with those used in the present study. In summary, the data suggest that, in rats, activation of α_1-adrenergic systems may mediate at least in part the effects of cocaine on motor activity but not on schedule-controlled behavior.

ACKNOWLEDGEMENTS

This research was supported by U.S. Public Health Service Grants DA 03573, DA 04775, and AA 07297.

A preliminary report of this work appears in FASEB J. 2:A1803; 1988.

REFERENCES

1. Benuck, M.; Lajtha, A.; Reith, M. E. A. Pharmacokinetics of systemically administered cocaine and locomotor stimulation in mice. J. Pharmacol. Exp. Ther. 243:144–149; 1987.
2. Calligaro, D. A.; Eldefrawi, M. E. Central and peripheral cocaine receptors. J. Pharmacol. Exp. Ther. 243:61–68; 1987.
3. Fischman, M. W. Cocaine and the amphetamines. In: Meltzer, H. Y., ed. Psychopharmacology: The third generation of progress. New York: Raven Press; 1987:1543–1553.
4. Jarbe, T. U. Discriminative stimulus properties of cocaine: Effects of apomorphine, haloperidol, cocaine and other drugs. Neuropharmacology 23:899–907; 1984.
5. Kalivas, P. W.; Duffy, P.; DuMars, L. A.; Skinner, C. Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J. Pharmacol. Exp. Ther. 245:485–492; 1988.
6. McKenna, M. L.; Ho, B. T. The role of dopamine in the discriminative stimulus properties of cocaine. Neuropharmacology 19: 279–303; 1980.
7. Moerschbaecher, J. M.; Boren, J. J.; Schrot, J.; Simoes Fontes, J. C. Effects of cocaine and *d*-amphetamine on the repeated acquisition and performance of conditional discriminations. J. Exp. Anal. Behav. 31:127–140; 1979.
8. Moerschbaecher, J. M.; Devia, C.; Brocklehurst, C. Differential antagonism by naltrexone of the effects of opioids on a fixed-

ratio discrimination in rats. J. Pharmacol. Exp. Ther. 244:237–246; 1988.
9. Moerschbaecher, J. M.; Mastropaolo, J.; Winsauer, P. J.; Thompson, D. M. Effects of opioids on accuracy of a fixed-ratio discrimination in monkeys and rats. J. Pharmacol. Exp. Ther. 230:541–549; 1984.
10. Mosaddeghi, M.; Moerschbaecher, J. M.; Gonzales, R. A. Effect of monoamine uptake inhibitors on norepinephrine stimulated phosphatidylinositol hydrolysis in rat cortex. Biochem. Pharmacol. 38:257–262; 1989.
11. Reith, M. E. A.; Lajtha, A. Locomotor depression in mice by norcocaine does not involve central α_2-adrenergic or presynaptic dopamine receptors. Pharmacol. Biochem. Behav. 24:305–307; 1986.
12. Reith, M. E. A.; Meisler, B. E.; Lajtha, A. Locomotor effects of cocaine, cocaine congeners, and local anesthetics in mice. Pharmacol. Biochem. Behav. 23:831–836; 1985.
13. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
14. Schrot, J.; Boren, J. J.; Moerschbaecher, J. M.; Símoes Fontes, J. C. Effects of *d*-amphetamine and cocaine on repeated acquisition with timeout from avoidance. Pharmacol. Biochem. Behav. 9:659–663 1978.
15. Snoddy, A. M.; Tessel, R. E. Nisoxetine and amphetamine share discriminative stimulus properties in mice. Pharmacol. Biochem. Behav. 19:205–210; 1983.
16. Snoddy, A. M.; Tessel, R. E. Prazosin: Effect on psychomotor-stimulant cues and locomotor activity in mice. Eur. J. Pharmacol. 116:221–228; 1985.
17. Tessel, R. E.; Barrett, J. E. Antagonism of the behavioral effects of cocaine and *d*-amphetamine by prazosin. Psychopharmacology (Berl.) 90:436–440; 1986.
18. Thompson, D. M.; Moerschbaecher, J. M. An experimental analysis of the effects of *d*-amphetamine and cocaine on the acquisition and performance of response chains in monkeys. J. Exp. Anal. Behav. 32:433–444; 1979.
19. Tyler, T. D.; Tessel, R. E. Amphetamine's locomotor-stimulant and norepinephrine-releasing effects: Evidence for selective antagonism by nisoxetine. Psychopharmacology (Berl.) 64:291–296; 1979.
20. Tyler, T. D.; Tessel, R. E. Norepinephrine uptake inhibitors as biochemically and behaviorally selective antagonists of the locomotor stimulation induced by indirectly acting sympathomimetic amines in mice. Psychopharmacology (Berl.) 69:27; 1980.
21. Wise, R. A. Neural mechanisms of the reinforcing action of cocaine. In: Grabowski, J., ed. Cocaine: Pharmacology, effects and treatment of abuse. NIDA Monograph 50. Washington, DC: U.S. Government Printing Office; 1984:15–33.
22. Woods, J. H. Behavioral effects of cocaine in animals. In: Petersen, R. C.; Stillman, R. C., eds. Cocaine: 1977. NIDA Monograph 13. Washington, DC: U.S. Government Printing Office; 1977:63–95.