Pharmacology Biochemistry and Behavior, Vol. 42, pp. 849–853, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Effects of Cocaine Alone and in Combination With Prazosin or Ondansetron on Multiple Fixed-Interval Fixed-Ratio Performance in Pigeons

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Received 9 January 1992

VAN HAAREN, F. *Effects of cocaine alone and in combination with prazosin or ondansetron on multiple fixed-interval fixed-ratio performance in pigeons.* PHARMACOL BIOCHEM BEHAV **42**(4) 849–853, 1992.—Three pigeons were trained to respond on a two-component multiple schedule in which the components alternated regularly. In one component of the schedule, food was presented when the pigeon successfully completed a fixed-interval 120-s schedule within 150 s. In the other component of the schedule, food presentation occurred when the pigeon managed to complete a fixed-ratio 30 schedule within 30 s. Once responding had stabilized under both components of the schedule, pigeons were challenged with different doses of cocaine alone or cocaine in combination with 1.0 mg/kg prazosin (a selective α_1-adrenergic antagonist) or 0.10 or 0.50 mg/kg ondansetron (a selective 5-hydroxytryptamine$_3$ antagonist). All drugs were injected intramuscularly 5 min before the start of selected experimental sessions. For two subjects, low doses of cocaine increased the low response rates maintained by the fixed-interval schedule while decreasing the high rates maintained by the fixed-ratio schedule. At intermediate doses, both high and low rates decreased but higher rates were more susceptible to disruption than low rates. The highest doses of cocaine completely eliminated responding in both schedule components. The high-rate behavior of the third subject was not affected by low or intermediate doses of cocaine, while low rates decreased at doses up to 5.6 mg/kg. The higher doses of cocaine eliminated responding in this subject as well. Prazosin and both doses of ondansetron antagonized the behavioral effects of cocaine at doses that ranged from 1.0–3.0 mg/kg. Redetermination of the dose-effect curve for cocaine at the conclusion of the experiment revealed that the curve had significantly shifted to the right.

Multiple schedule Fixed interval Fixed ratio Cocaine hydrochloride Prazosin
Ondansetron Key-peck Pigeons

COCAINE and other psychomotor stimulant drugs enhance dopaminergic (DA), serotonergic (5-HT), and noradrenergic (NA) transmission in the CNS by blocking the reuptake of these neurotransmitters. It has been well established that the mesolimbic DA system plays an important role in mediating cocaine's reinforcing effects, as well as those of other drugs of abuse (8). Drugs that interfere with DA functioning such as SCH 39166, a selective D_1 antagonist, YM 09151-2, a selective D_2 receptor blocker, and flupenthixol, a nonselective blocker of both DA receptor subtypes, have been shown to antagonize cocaine's effects on behavior maintained by fixed-interval (FI) schedules of shock termination (7,18). In addition, studies in which 6-hydroxydopamine was used to selectively destroy mesolimbic DA neurons have shown that such treatment disrupts cocaine self-administration (15). However, DA antagonists do not seem to be the drug of choice in therapeutic situations since they only antagonize cocaine's effects at doses that increase anhedonia in general (6).

As suggested above, cocaine administration not only affects DA neurotransmission but also involves NA and 5-HT receptors. Even though it has been shown that destruction of NA and 5-HT neurons in the mesolimbic system does not affect cocaine self-administration as similar destruction of DA neurons (15), evidence is available to show that manipulations of these systems may interfere with cocaine's behavioral effects and reinforcing efficacy. For instance, it has previously been shown that the administration of prazosin (a selective α_1-adrenergic antagonist) antagonizes cocaine's behavioral effects on schedule of reinforcement and measures of general activity (17,19,20). Other studies have shown that interference with the serotonergic system does not necessarily affect cocaine self-administration (11,12) or the discriminative stimulus properties of cocaine (10), but depletion of forebrain serotonin increases the breakpoint for cocaine self-administration on progressive-ratio schedules (9). In a similar vein, pretreatment with fluoxetine (a 5-HT reuptake inhibitor) reduces the breaking point on a progressive-ratio schedule in which behavior is maintained by intravenous cocaine administration (14).

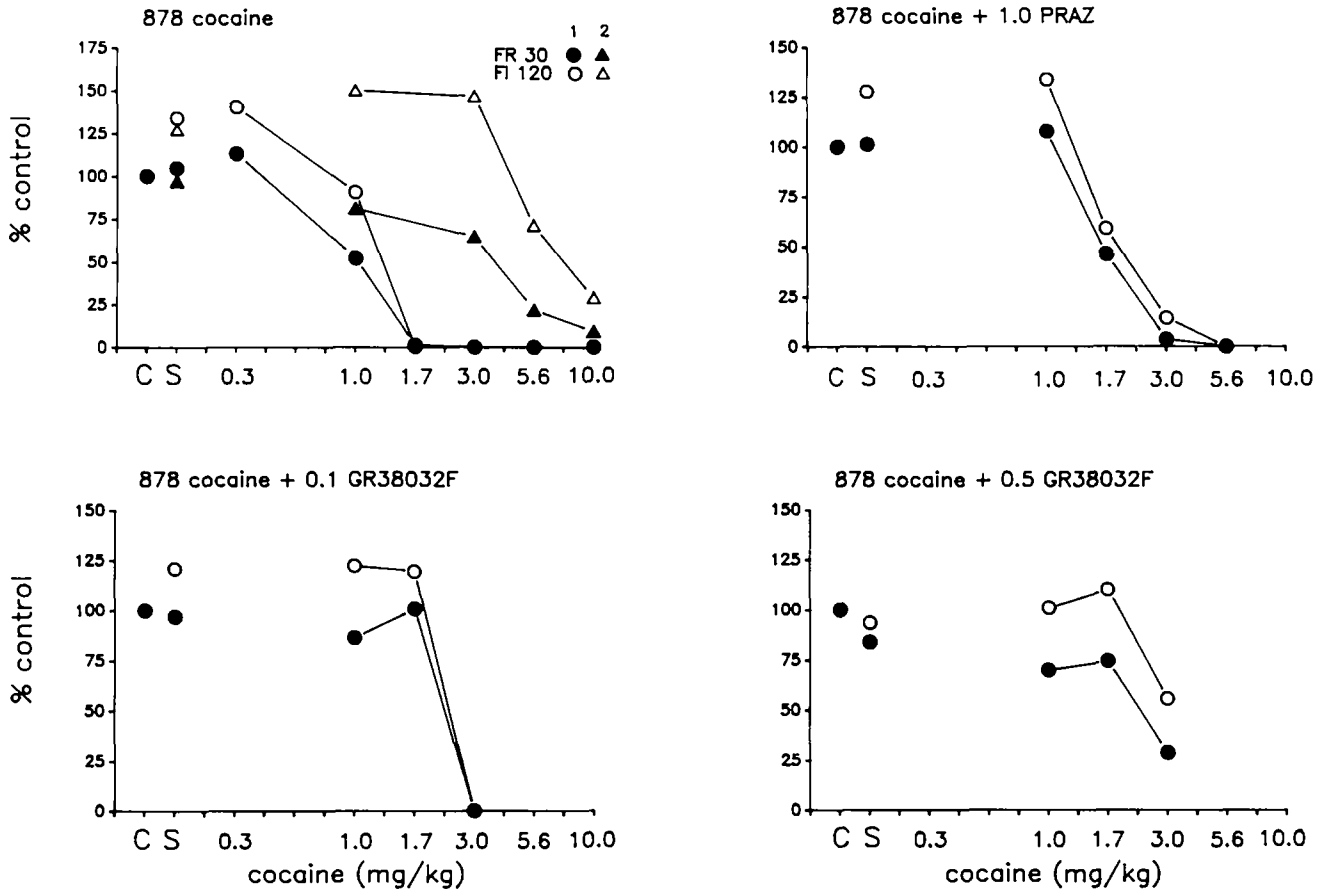

FIG. 1. Effects of cocaine alone (upper left panel; circles, first determination; triangles, second determination), effects of cocaine in the presence of 1.0 mg/kg prazosin (upper right panel), and behavioral effects of cocaine in the presence of 0.10 or 0.50 mg/kg ondansetron (bottom left and bottom right panels, respectively) for subject 878, expressed as a percentage of baseline control rates. The data presented above S represent saline administration (upper left panel) and the administration of prazosin and ondansetron alone in the other panels.

Other studies have suggested a role for a specific 5-HT_3 antagonist (ondansetron) in alleviating drug withdrawal symptoms (3-5).

The present experiment was designed to study the behavioral effects of cocaine alone and in combination with prazosin and ondansetron on the schedule controlled behavior of pigeons maintained on a multiple FI 120 s, fixed-ratio (FR) 30 schedule of food reinforcement. This schedule arrangement allowed for the study of the effects of these drugs on low (FI) and high (FR) rates of responding, which have frequently been shown to be differentially affected by administration of psychomotor stimulant drugs (1).

METHOD

Subjects

Three White Carneau pigeons of undetermined sex, originally obtained from the Palmetto Pigeon Plant (Sumter, SC) served as subjects. They were approximately 8 years old at the start of experimentation and had previously been used in an undergraduate laboratory course at the University of Florida. Pigeons were maintained at 85% of free-feeding body weight by limiting access to food in their home cages, in which water was available at all times.

Apparatus

Experimental sessions were conducted in one Lehigh Valley Electronics (Lehigh Valley, PA) standard three-key operant conditioning chamber (35 × 33 × 35 cm, internal dimensions). A houselight was mounted above the center key approximately 2.5 cm from the ceiling of the chamber. Only the center key, which could be illuminated by a red or white keylight, was used in the present experiment. The key required a force in excess of 0.20 N to be operated. Access to mixed grain could be provided through a 5.2 × 5.8 cm rectangular opening located approximately 10.2 cm below the center key. The chamber was enclosed in a sound-attenuating cabinet, while white noise was constantly present in the experimental room itself. The chamber was connected to a PDP 11-23 microcomputer (Digital Equipment Corporation, Maynard, MA) located in an adjoining room. Experimental contingencies and data acquisition procedures were programmed in SKED-11 (16).

Procedure

Before the start of the actual experiment, pigeons were exposed to a sequence of differently valued random-interval (15, 30, and 45 s) schedules in the presence of both the red

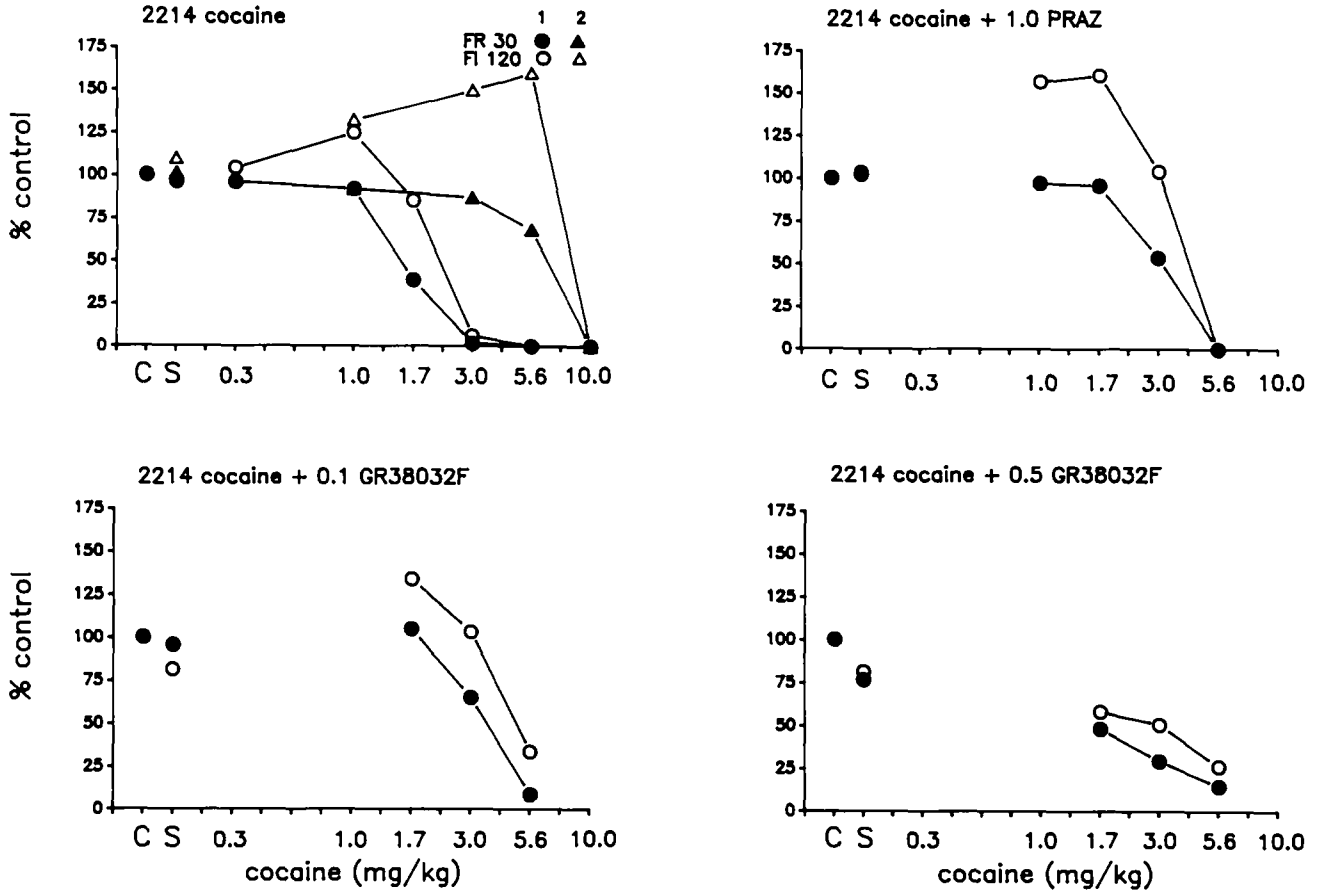

FIG. 2. Effects of cocaine alone (upper left panel; circles, first determination; triangles, second determination), effects of cocaine in the presence of 1.0 mg/kg prazosin (upper right panel), and behavioral effects of cocaine in the presence of 0.10 or 0.50 mg/kg ondansetron (bottom left and bottom right panels, respectively) for subject 2214, expressed as a percentage of baseline control rates. The data presented above S represent saline administration (upper left panel) and the administration of prazosin and ondansetron alone in the other panels.

and white keylights to reinstate stable responding. They were then trained on a multiple fixed-interval 120 s, fixed ratio 30 (mult FI 120 s-FR 30) schedule of reinforcement. When the FR 30 component was in effect, the red keylight was illuminated; when the FI 120 s component was active, the white keylight was illuminated. Subjects were allowed 30 s to complete the FR 30 component of the schedule and 150 s to complete the FI 120 s component of the schedule. Food was presented only when subjects completed the schedule requirements within the limited hold established for each component. The houselight and keylight were extinguished during the 4-s presentation of mixed grain, while the feederlight was illuminated. One of the components was randomly selected at the start of the session and the houselight and the appropriate keylight were illuminated. Thereafter, the multiple schedule components alternated regularly. The session was terminated after 15 presentations of each schedule component. Sessions were run 5 days a week (Monday-Friday).

Drug administration. Once responding had stabilized, subjects were challenged with different doses of cocaine in irregular order (saline, 0.3, 1.0, 3.0, 5.6, 7.4, and 10.0 mg/kg/ml, IM, 5 min before the start of the session). After the dose-effect curve was established, prazosin or ondansetron were injected in combination with behaviorally active doses of cocaine or saline. All injections were given IM 5 min before the start of the session. Prazosin (1.0 mg/kg) was tested first, followed by ondansetron (0.10 and 0.50 mg/kg). Following completion of these experimental conditions, the dose-effect curve for cocaine administration alone was redetermined. Each individual dose of cocaine and all drug combinations were given at least twice (range 2–6).

RESULTS

The two schedules of reinforcement maintained distinctively different response rates in the absence of cocaine administration. During the initial determination of the behavioral effects of cocaine and cocaine in combination with prazosin and ondansetron, FR response rates averaged 250, 175, and 175 responses per minute, while FI response rates averaged 90, 85, and 35 responses per minute for subjects 878, 1447, and 2214, respectively. Because of the fact that FR and FI control rates differed considerably between schedule components, drug effects are expressed as percentage of baseline control rates in Figs. 1–3.

The behavioral effects of cocaine alone are presented in the upper left panel of each figure (circles: first determination; triangles: redetermination), the effects of cocaine in the presence of 1.0 mg/kg prazosin in the upper right panel of each

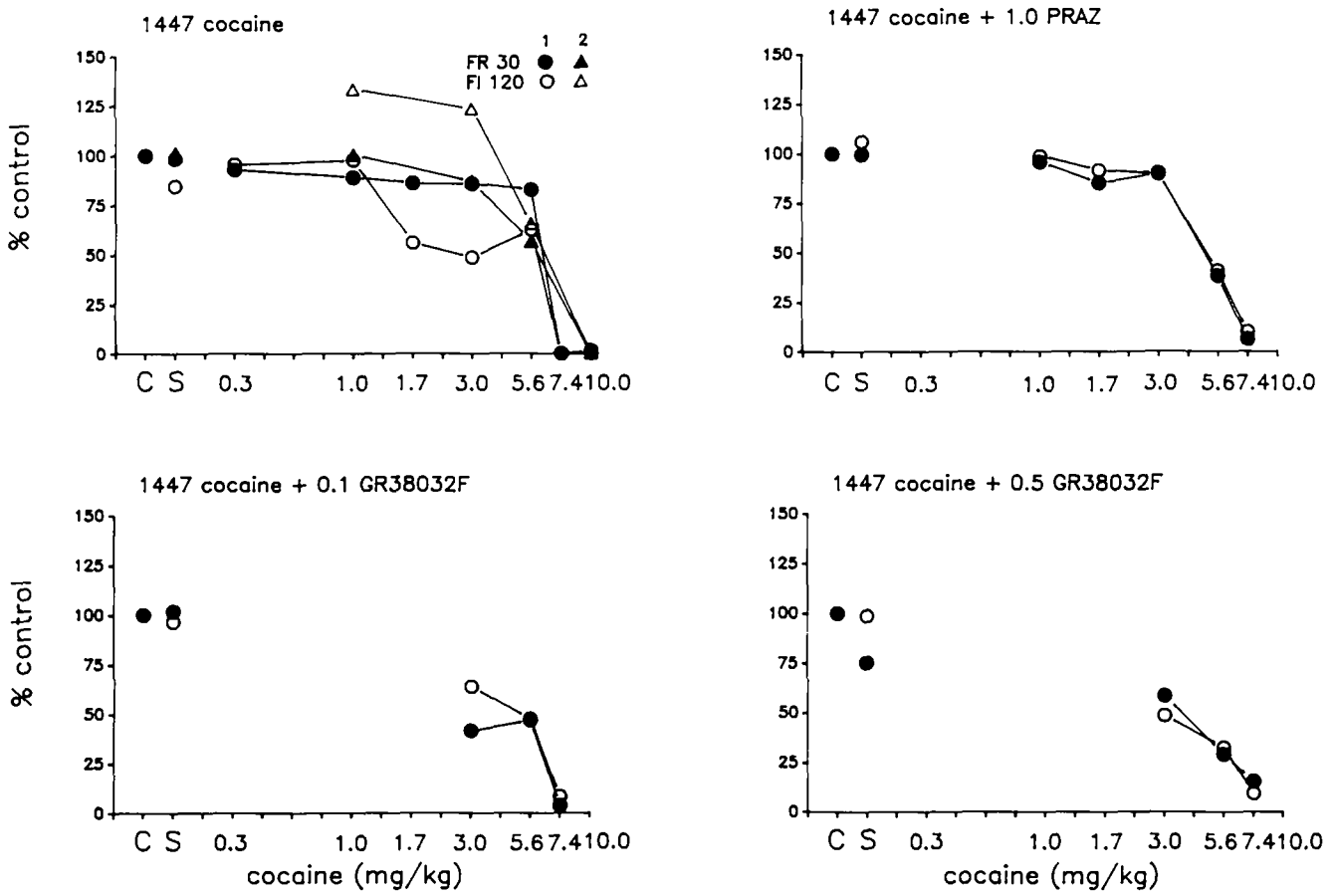

FIG. 3. Effects of cocaine alone (upper left panel; circles, first determination; triangles, second determination), effects of cocaine in the presence of 1.0 mg/kg prazosin (upper right panel), and behavioral effects of cocaine in the presence of 0.10 or 0.50 mg/kg ondansetron (bottom left and bottom right panels, respectively) for subject 1447 expressed as a percentage of baseline control rates. The data presented above S represent saline administration (upper left panel) and the administration of prazosin and ondansetron alone in the other panels.

figure, and the behavioral effects of cocaine in the presence of 0.10 or 0.50 mg/kg ondansetron in the bottom left and bottom right panels of each figure, respectively. Low doses of cocaine (0.3 and 1.0 mg/kg) increased the low response rates maintained by the FI schedule for subjects 878 and 2214 while not affecting or decreasing the high response rates maintained by the FR schedule. Intermediate doses (1.7 and 3.0 mg/kg cocaine) decreased responding or eliminated responding altogether, while the highest doses (5.6 and 10.0 mg/kg) completely eliminated responding in these two subjects. Different results were obtained for subject 1447 as FR rates were not affected while FI rates decreased at doses up to 5.6 mg/kg. Higher doses (7.4 and 10.0 mg/kg) eliminated responding in this subject as well.

Administration of 1.0 mg/kg prazosin in combination with different doses of cocaine increased FR and FI response rates at 1.0, 1.7, and 3.0 mg/kg for subjects 878 and 2214 while increasing FI response rates and not affecting FR responding for 1447. Prazosin administration by itself (the data presented above S in each figure) increased FI rates in subject 878 compared to baseline rates but did not otherwise significantly affect response rates. Prazosin administration in combination with 1.7 and 3.0 mg/kg cocaine reinstated FR and FI responding, which previously had been totally suppressed in subjects 878 and 2214, respectively. The data for 0.10 and 0.50 mg/kg ondansetron alone are presented above S in the lower left and right panels of each figure. The higher dose of ondansetron by itself (0.50 mg/kg) consistently decreased response rates, an effect not observed for the lower dose (0.10 mg/kg). These doses of ondansetron in combination with doses of cocaine that were previously behaviorally inactive decreased FR and FI response rates for subject 1447. Both doses of ondansetron increased FR and FI responding for subjects 878 and 2214. The lower dose of ondansetron in combination with 1.0 and 1.7 mg/kg cocaine for subject 878 and in combination with 1.7 and 3.0 mg/kg cocaine for subject 2214 maintained response rates at levels comparable to those in the absence of cocaine. The higher dose of ondansetron, although still antagonizing the behavioral effects of cocaine observed in baseline conditions, was less effective than the lower dose.

When the original dose-effect curve was reestablished to complete the experiment, all individual curves had shifted to the right (triangles in the upper left panel of each figure).

DISCUSSION

The results of the present experiment are interesting for a number of reasons. First, they confirm that the behavioral effects of cocaine, like those of *d*-amphetamine, are very much dependent upon response rates maintained in the ab-

sence of drug administration (1). Whether or not such rate dependency is a result of differences in response rates per se, or of the way in which schedule variables allow for response rates to vary without affecting other variables such as the rate of reinforcement, has recently been called into question (van Haaren, submitted). In addition, the results of the present experiment seem to show that the administration of prazosin in combination with behaviorally active doses of cocaine not only reinstates previously suppressed FR response rates, as had already been shown (20), but also previously suppressed FI response rates. Similarly, the lower dose of ondansetron (0.10 mg/kg) coadministered with cocaine returned responding to levels observed in the absence of any drug, while a higher dose of ondansetron was somewhat less effective. These results seem to support the notion that the behavioral effects of cocaine administration may be antagonized by the administration of a selective 5-HT_3 antagonist. However, all these results have to be interpreted with some caution as the redetermination of the dose-effect curve for cocaine alone at the end of the experiment revealed a significant shift to the right. This observation could imply that the behavioral antagonism observed after prazosin and ondansetron may only have been a function of the development of tolerance due to continued exposure to cocaine administration or that administration of any of the three antagonists may have rendered subjects less sensitive to the effects of subsequent cocaine administration. These results emphasize the necessity of redetermining the original dose-effect curve in all experiments in which subjects are exposed to neurochemically active substances that are thought to either enhance or diminish the behavioral effects of other neurochemical agents. If the original dose-effect curve is replicated, the results of the antagonist or agonist tests are easier to interpret than when, as was the case in the present experiment, the dose-effect curve has shifted (irrespective of the direction of the shift). Unfortunately, to redetermine the original dose-effect curve is not yet accepted and standard practice in behavioral pharmacology.

Even if the administration of 5-HT_3 antagonist drugs [MDL 7222, ICS-205,930, (10)] does not significantly affect the discriminative stimulus properties of cocaine or decrease cocaine self-administration [ondansetron (11)], experiments have shown that these drugs can antagonize the increase in locomotor activity after cocaine administration in rodents (13). The administration of a variety of abused drugs, including cocaine, alcohol, and nicotine, enhances extracellular dopamine concentrations in a variety of limbic areas, most notably in the nucleus accumbens. Recently, it has been shown through microdialysis that activation of the 5-HT_3 receptor in the nucleus accumbens by application of the 5-HT receptor agonist *1*-phenylbiguanide causes a dose-dependent increase in extracellular dopamine content that could be antagonized by coperfusion of the 5-HT_3 antagonist ondansetron (2). These recent observations suggest that, although cocaine administration produces persistent activation of mesolimbic DA systems, such activation may be mediated and modulated by activation of other neurotransmitter systems. Such interactions, especially with agents that interact with the serotonergic system, are worthwhile to pursue in future research efforts.

ACKNOWLEDGEMENTS

The research reported in this article was supported by grants USPHS DA-04074 and DA-04940 from the National Institute of Drug Abuse. The preparation of the manuscript was facilitated by Grant USPHS DA-06463 from the same institute and a Research Career Development Award from the University of Florida. Dr. Arthur G. Snapper of State Systems, Inc. provided some of the equipment used in this experiment. The author is grateful for his generosity. Ondansetron was generously supplied by GLAXO (United Kingdom).

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