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Failure of Ritanserin to Block the Discriminative or Reinforcing Stimulus Effects of Cocaine

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PELTIER, R. L., M. W. EMMETT-OGLESBY, W. H. THOMAS AND S. SCHENK. *Failure of ritanserin to block the discriminative or reinforcing stimulus effects of cocaine.* PHARMACOL BIOCHEM BEHAV 48(2) 473–478, 1994.—Ritanserin, a 5-$HT_{2/1C}$ antagonist, has been suggested to reduce the preference for cocaine in rats. In the present experiment, the action of ritanserin was investigated in locomotor activity, cocaine drug discrimination, and cocaine self-administration paradigms in rats. A low dose of ritanserin (1.0 mg/kg) was without effect on locomotor activity, while a higher dose (10.0 mg/kg) reduced both horizontal and vertical locomotor activity counts during the first 30 min of the test session. Ritanserin (0.32–32 mg/kg) did not significantly affect the discrimination of 10 mg/kg of cocaine, nor did a dose of 10.0 mg/kg significantly modify the dose-effect curve for cocaine discrimination. Ritanserin (1.0 and 10.0 mg/kg) had no significant effect on the dose-response curve for cocaine self-administration. Thus, ritanserin was without effect against either the discriminative or reinforcing stimulus effects of cocaine, suggesting that ritanserin has limited efficacy as a potential treatment for cocaine abuse.

Cocaine Ritanserin Self-administration Drug discrimination Locomotor activity

ALTHOUGH a large body of evidence supports the conclusion that central dopaminergic systems are critical for the expression of cocaine's reinforcing (13,31), discriminative stimulus (2,3,12,32), and locomotor activating (11) effects, recent data suggest that central serotonergic systems may also play a role in some of these behavioral effects. For example, increasing synaptic serotonin levels via L-tryptophan loading (5,16), or administration of the serotonergic uptake inhibitor, fluoxetine (4,26), suppressed self-administration of some doses of cocaine and decreased the breaking point under a progressive ratio schedule of intravenous cocaine self-administration. Neurotoxic lesions of forebrain serotonin increased breaking points on a progressive ratio schedule of cocaine self-administration (15), suggesting an increase in the incentive motivational properties of cocaine following serotonin depletion. In drug discrimination studies, serotonin reuptake inhibitors enhanced the effects of low doses of cocaine but failed by themselves to mimic the stimulus properties of cocaine (6).

Interactions between the behavioral effects of cocaine and drugs active at specific serotonergic receptor subtypes have produced less impressive results than those described above. For example, the 5-HT_3 antagonist, ondansetron, failed to alter either the reinforcing (7,22) or discriminative stimulus (7,21) properties of cocaine, and the 5-HT_{1A} agonist, 8-OH-DPAT, decreased self-administration of only low doses of cocaine (24).

Although the 5-HT_2 receptor antagonist, cinanserin, failed to alter responding for intravenous cocaine (25), ritanserin, a 5-$HT_{2/1C}$ antagonist (1), has been reported to reduce the preference for cocaine in an oral drinking model in rats (18). In that experiment, rats were first water deprived and then given access to a cocaine solution (0.1 mg/ml). After this period of forced drug exposure, subjects were given a choice between the cocaine solution and water, at which time they preferred the cocaine solution. Treatment with ritanserin (0.04 mg/kg to 10.0 mg/kg) decreased the intake of cocaine while simultaneously increasing water intake, resulting in a consistent total daily intake of fluid. Using the same oral consumption paradigm, ritanserin has also been shown to decrease the preference for alcohol and fentanyl, but not for sucrose,

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suggesting a specific action of ritanserin on drugs of abuse (17,19). This hypothesis is consistent with observations that ritanserin reduces the place-preference induced by either *d*-amphetamine, morphine or benzodiazepines (20).

The aim of the present experiment was to determine whether ritanserin would antagonize the locomotor, discriminative (S^D), and/or reinforcing (S^R) effects of cocaine in rats. The doses of ritanserin tested (0.32, 1.0, 3.2, 10.0, and 32.0 mg/kg) were chosen based on the findings of Meert and Janssen, described above. Ritanserin was first examined in a locomotor activity paradigm to determine whether the upper range of doses tested (10 mg/kg and higher) had effects on the normal activity level of rats. Ritanserin (0.32, 1.0, 3.2, 10.0, and 32.0 mg/kg) was next tested in a cocaine discrimination paradigm to determine whether it blocked the discriminative effects of the training dose of cocaine (10 mg/kg) in rats. In addition, a single dose of ritanserin (10.0 mg/kg) was also examined for its effects against the entire dose–effect curve for cocaine discrimination. Ritanserin (1.0 and 10.0 mg/kg) was then tested for its ability to modify the dose–response curve for cocaine self-administration. Based on the results of the locomotor activity tests which showed that pretreatment with ritanserin (10 mg/kg) resulted in a decrease in locomotor activity with a peak effect at 30-min postadministration, ritanserin (10.0 mg/kg) was again tested in the self-administration paradigm using a shorter period of cocaine access.

METHOD

Locomotor Activity

Subjects. Ten male Sprague-Dawley rats were used as subjects. All rats were housed singly and kept on a 12 L : 12 D cycle. Food and water was available ad lib.

Apparatus. Locomotor activity testing took place in an automated, commercially designed, activity monitoring apparatus (Digiscan-16 E61-32; Coulbourn Instruments Inc., Lehigh Valley, PA). The Digiscan apparatus was used to measure horizontal (distance traveled) as well as vertical (time spent rearing) activity. For testing, the rats were placed in a 40 × 40 × 30.5 cm clear acrylic chamber. The components of locomotor activity were recorded by a multiplex/analyzer (E61-58, Coulbourn Instruments Inc., Lehigh Valley, PA) that combines input from two arrays of 16 photocell beams arranged to detect movement in the horizontal plane, and one array of 16 photocell beams arranged to detect movement in the vertical plane. Room lights were off during testing and a contiguous white noise (45–55 dB) was present throughout testing.

Testing. Subjects were randomly assigned to three groups. One group ($n = 6$) received vehicle; a second group ($n = 4$) received ritanserin (1.0 mg/kg); and the third group ($n = 6$) received ritanserin (10 mg/kg). Immediately after being injected, subjects were placed in the Digiscan boxes for 120 min and locomotor activity was recorded.

Cocaine Discrimination

Subjects. Twelve male Long-Evans rats were housed singly and maintained at 330 ± 10 g by restricting their access to food to once daily feeding of measured quantities.

Apparatus. Discrimination training and testing were conducted in standard operant chambers (Coulbourn Instruments Inc., Lehigh Valley, PA). Each chamber was equipped with two levers, one on either side of a central food cup. A stimulus light was mounted directly above the food cup. Each operant chamber was enclosed in a light- and sound-attenuating box. A solenoid-operated feeder delivered food pellets (45 mg pellets, Bio-Serv Inc., Frenchtown, NJ). IBM-PC compatible microcomputers programmed with OPN software (27) were used to record lever responses and to schedule reinforcement conditions.

Discrimination training. Rats were trained to press a lever (left or right) until 10 lever-press responses (FR10) resulted in the delivery of a food reinforcer, with a maximum of 50 reinforcers available during a session. They were then trained to press one of the two levers (here after called the cocaine lever) after an injection of cocaine, 10 mg/kg (given in a volume of 1.0 ml/kg of 0.9% saline), and the other lever (here after called the saline lever) after an injection of 0.9% saline. For this training, they were injected 15 min before the beginning of the training sessions. During the training sessions, only condition-appropriate responding was reinforced under the FR10 schedule (responses on the cocaine lever after a cocaine injection, and responses on the saline lever after a saline injection); however, responses on both levers were recorded. Sessions lasted either until 50 reinforcers were obtained or until 10 min elapsed. Discriminative control was defined as 10 successive sessions of correct lever responding at the start of the session; i.e., when cocaine was injected, 10 responses were emitted on the cocaine lever with fewer than 10 on the saline lever; and when saline was injected, 10 responses were made on the saline lever with fewer than 10 on the cocaine lever. Once a criterion of 9 out of 10 consecutive correct lever selections was met, tests were conducted. Cocaine discrimination was acquired in 40 training sessions (20 cocaine sessions and 20 saline sessions), during which no condition occurred in more than three successive training sessions.

Testing. Discrimination testing was conducted by two methods. In one, rats were pretreated 30 min prior to the test session with ritanserin (0.32 through 32.0 mg/kg), and were then given the training dose of cocaine (10 mg/kg) 15 min prior to the test session. The test then lasted until either one reinforcer was obtained or until 10 min elapsed. The lever that accumulated 10 responses first was designated as the selected lever. As soon as reinforcement was given, the chamber lights were extinguished and the test was terminated. In the other method, test sessions were conducted using a cumulative dose–effect method (28,14), which permits determination of an entire dose–effect curve in a single session. For these tests, rats were pretreated 20 min prior to the test session with either ritanserin (10 mg/kg) or vehicle. In the cumulative testing method, the dose of cocaine to be injected is achieved by subtracting any dose of cocaine that has previously been injected from the current dose that is required, and the remainder is then injected. Thus, if doses of 0.32, 1.0, 3.2, and 10.0 mg/kg were required, the first injection would be 0.32 mg/kg, the second injection would be 0.68 mg/kg (1.0–0.32 mg/kg, totaling 1.0 mg/kg), the third injection would be 2.2 mg/kg (3.2–1.0 mg/kg, totaling 3.2 mg/kg), and the final injection would be 6.8 mg/kg (10.0–3.2 mg/kg, totaling 10.0 mg/kg). Immediately following the completion of the test on the previous dose, the group would be injected with the next appropriate dose, so that an approximate 20 min time span occurred between successive doses. The entire procedure required 1 h. Lever selection for each test was defined by the first lever to accumulate 10 responses (resulting in one reinforcer).

Self-Administration

Subjects. Ten male Fisher F-344 rats were housed singly and maintained at 270 ± 10 g by restricting their access to food through once daily feeding of measured quantities.

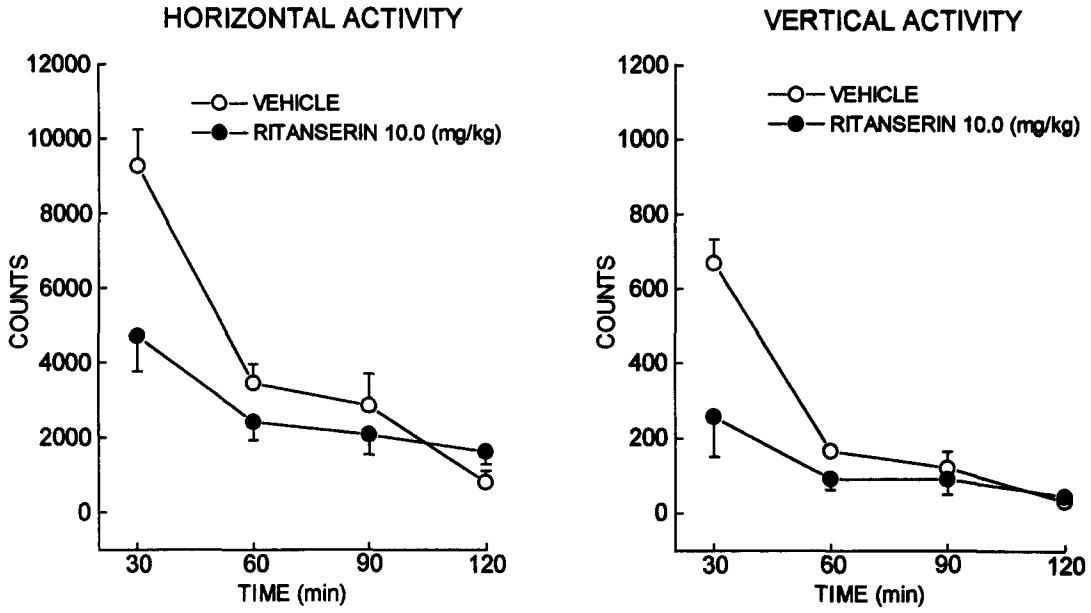

FIG. 1. Effect of ritanserin (10.0 mg/kg, IP) on horizontal activity (left panel) and vertical activity (right panel) in rats. Abscissa: time in 30-min intervals. Ordinate: number of activity counts. Data are shown as mean ± SEM. Open circles indicate activity counts with a pretreatment of CMC (n = 6) alone; closed circles indicate activity counts after pretreatment with ritanserin (10.0 mg/kg; n = 6).

Apparatus. Self-administration experiments took place in custom-designed and locally built operant chambers. The chambers contained a single lever and were equipped with two stimulus lights (3 W), one located on the ceiling and the other above the lever. The chambers were placed in sound- and light-attenuating enclosures. Syringe pumps located outside of the enclosures (Razel, Model A; driver at 3.33 rpm) were used to drive 10 ml syringes. Four pump/syringe sets were used for each self-administration operant chamber: Three of these syringes contained a cocaine solution (0.125, 0.25, or 0.5 mg/kg), and the fourth syringe contained 0.9% saline solution with 2 U heparin/ml. The four syringes were connected through a series of tygon tubing (0.06 in. o.d. Tygon Microbore Tubing, Norton Performance Plastics, Akron, OH) and T-connectors to a single-channel fluid swivel (Model 375/22, Instech Laboratories, Inc., Plymouth Meeting, PA).

Catheter implantation and training. Rats were anesthetized and a catheter was inserted into the right external jugular vein. The free end of the catheter was connected to a modified C313G cannula assembly (Plastic One, Roanoke, VA). The catheter/cannula unit was fixed to the skull. Subjects were treated (IV) with a mixture of ticarcillin and clavulanate (Timentin: Beecham Laboratories, Bristol, TN), 3.3 mg, every 12 h for 5 days following surgery. After recovery, subjects were given the opportunity to self-administer cocaine on an FR1 schedule with a maximum of 25 cocaine infusions. Once rats self-administered all 25 infusions within 3 h for two consecutive training sessions, they were then switched to an FR2 schedule that had a maximum of 15 reinforcers and was limited to 3 h. Rats were tested once a stability criterion was met. This criterion was defined as the average time occurring between reinforcers (the interreinforcer time; IS^RT, in min) not varying by more than 20% across three consecutive training sessions. Before each self-administration session, patency of the catheter was assessed by drawing blood into the catheter and then by flushing 0.1 ml of heparinized saline (10 U/ml) back into the catheter. For a detailed description of the apparatus, surgery, and training methods, see Emmett-Oglesby et al., 1993 (9).

Cocaine self-administration testing. In the first experiment, rats (n = 5) were tested using a multidose procedure. With this procedure, three doses of cocaine (0.125, 0.25, and 0.5 mg/infusion) were available for self-administration during a single test session. This test session consisted of a standard priming infusion (0.3 mg) followed by 24 infusions. These 24 infusions were divided into three blocks of eight infusions each, with the first block of eight reinforcers containing 0.5 mg/infusion of cocaine, the second containing 0.25 mg/infusion, and the third containing 0.125 mg/infusion. Cocaine self-administration tests were conducted in a descending order of cocaine doses (0.5, 0.25, 0.125 mg/kg/infusion) to increase the probability that the rats begin self-administration. When testing a compound that has the potential to block the reinforcing effects of cocaine, it is possible that rats will not begin self-administration if the lower doses of cocaine (0.125 and 0.25) are available for self-administration at the beginning of the test session. Thus, to optimize the probability of obtaining a positive effect with a potential cocaine antagonist, all tests are done in a descending dose order. In the absence of an antagonist, we have previously shown that the order of doses tested does not significantly alter the dose-effect curve for cocaine (9). Thirty minutes prior to a multidose test session, rats were injected with either ritanserin (1.0 or 10.0 mg/kg) or vehicle. Each subject was tested under each pretreatment condition in a random order.

In a second experiment, rats (n = 5) were pretreated with ritanserin (10.0 mg/kg) or vehicle 10 min prior to a self-administration session. During this test session, 0.25 mg/kg/infusion of cocaine was available as the reinforcer. Only the reinforcers obtained during the first 20 min of the test session were included in the data analysis.

Drugs. Cocaine HCl (National Institute of Drug Abuse,

TABLE 1

RATS TRAINED TO DISCRIMINATE COCAINE (10 mg/kg) FROM SALINE WERE INJECTED IP WITH RITANSERIN 30 MIN PRETEST

	Ritanserin (mg/kg)				
	0.32	1.0	3.2	10.0	32.0
Rats selecting cocaine lever	11	11	11	10	10
N	11	11	11	11	10
% Cocaine lever selection	100	100	100	91	100

Research Triangle Park, NC) was dissolved in 0.9% saline for drug discrimination experiments and injected IP. For self-administration experiments, cocaine HCl was dissolved in heparinized saline (0.5 U/ml) and filtered through 0.22 μm filters (Millipore, Bedford, MA) into sterile 10 ml syringes immediately before use. Ritanserin (Research Biomedical, Natick, MA) was homogenized in 3% carboxy methylcellulose (CMC) and was injected IP.

Data analysis. In the locomotor activity experiment, data were collected in 30-min samples over a 2-h period. Horizontal and vertical activity data were analyzed using a two-way analysis of variance (ANOVA) for between factors. In the cocaine discrimination experiment, data were scored and analyzed in terms of the percent of subjects selecting the cocaine lever. Full cocaine lever selection was defined as 80% or more of the animals choosing the cocaine lever. Antagonism of cocaine was defined as 80% or more of the animals choosing the saline lever. In self-administration experiments, data were scored as the average time between administration of consecutive reinforcers (interreinforcer interval, IS^RT) and analyzed using a two-way repeated measures ANOVA with treatment condition as the between factor and dose of cocaine as the repeated factor. SYSTAT software (30) was used for data analysis.

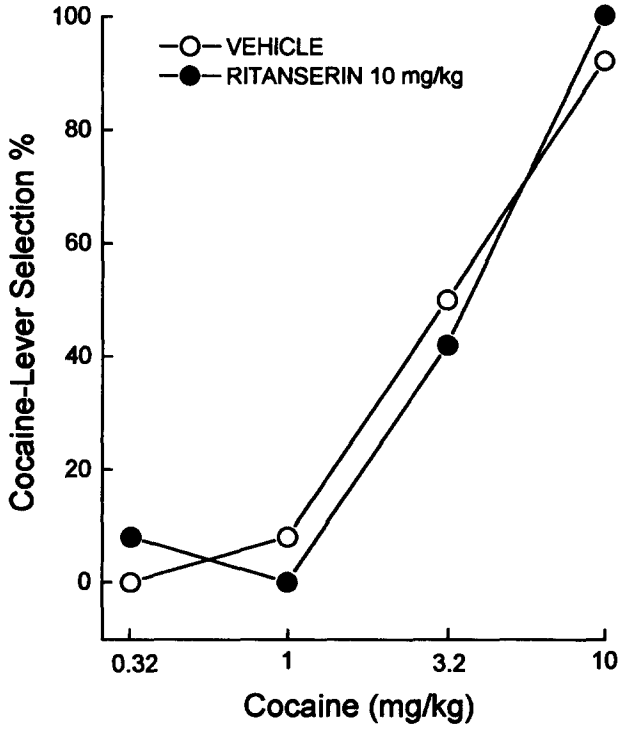

FIG. 2. Effect of ritanserin (10.0 mg/kg, IP) on the discriminative stimulus produced by cocaine. Abscissa: dose of cocaine obtained in a cumulative dosing procedure. Subjects were tested repeatedly with increasing doses of cocaine as shown on the abscissa. Twenty minutes prior to the first dose of cocaine tested (0.32 mg/kg), they were treated with either CMC or ritanserin. Ordinate: percent of subjects selecting the cocaine lever. Open circles indicate pretreatment with CMC (n = 12) alone; closed circles indicate pretreatment with 10.0 mg/kg of ritanserin (n = 12).

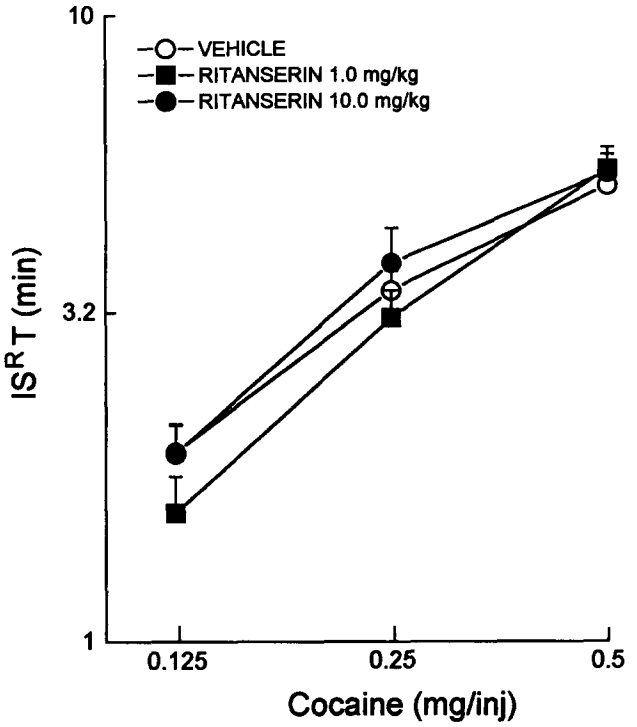

FIG. 3. Effect of ritanserin on self-administration of cocaine by rats. Abscissa: dose of cocaine made available for self-administration. Ordinate: interreinforcer time (min). Data are shown as mean ± SEM. Open circles indicate self-administration with a pretreatment of CMC alone; closed squares indicate self-administration of cocaine after 30-min pretreatment with 1.0 mg/kg of ritanserin; closed circles indicate self-administration of cocaine after 30-min pretreatment with 10.0 mg/kg of ritanserin. The same subjects (n = 5) received all treatments in a randomized order.

RESULTS

Locomotor Activity

Effect of ritanserin on locomotor activity. Rats that were pretreated with vehicle had horizontal locomotor activity that initially averaged approximately 10,000 counts per 30 min, whereas vertical locomotor activity averaged only 650 counts during the first 30 min. Horizontal activity decreased about 60% during the remainder of the test period, while vertical activity decreased about 30%. Pretreatment with ritanserin (1.0 mg/kg) was without effect (data not presented) on either of these measures. Pretreatment with the larger dose of ritan-

TABLE 2

RATS WERE PRETREATED (10 min; IP) WITH RITANSERIN (10 mg/kg) OR CMC

Rat No.	CMC	Ritanserin (10.0 mg/kg)
17	5.39	5.77
19	2.78	3.90
20	5.77	4.83
21	1.94	1.66
23	2.86	2.39
mean	3.75	3.71
SEM	0.77	0.76

serin (10.0 mg/kg) resulted in a significant decrease in both components of locomotor activity tested (horizontal activity, $F(1, 40) = 8.75$, $p < 0.01$, and vertical activity, $F(1, 40) = 11.947$, $p < 0.01$. This decrease in activity was restricted to the first 30-min sample (Fig. 1).

Cocaine Discrimination

Effect of ritanserin on the discrimination of cocaine. In subjects trained to detect cocaine and tested with the training dose (10.0 mg/kg), pretreatment with ritanserin (0.32 to 32.0 mg/kg) did not significantly affect the percent of rats selecting the cocaine lever (Table 1). The only dose of ritanserin combined with cocaine that did not result in full cocaine lever selection was the 10 mg/kg pretreatment. Consequently, this dose of ritanserin was examined against a broad range of cocaine doses to determine whether it would shift the dose-effect curve for cocaine to the right, which it failed to do (Fig. 2).

Self-Administration

Effect of ritanserin on the rate of cocaine self-administration. Increasing the dose of cocaine resulted in an orderly increase in the time between injections, $F(2, 8) = 64.16$, $p < 0.001$ (Fig. 3), such that independent of the concentration of cocaine available, rats maintained approximately a constant intake of the drug. Ritanserin (1.0 or 10.0 mg/kg, IP) given 30 min prior to the test session had no significant effect on the rate of cocaine self-administration.

In a second experiment, ritanserin (10.0 mg/kg) was given 10 min prior to access to cocaine, 0.25 mg/infusion, for 15 injections. Again, ritanserin had no significant effect on the rate of cocaine self-administration (data not shown). The data were further analyzed to determine if ritanserin had an effect during the first 20 min of the session (a time comparable to the peak locomotor reducing effects seen in Fig. 1) and, again, there was no significant difference in the $IS^{R}Ts$ for rats pretreated with ritanserin vs. vehicle (Table 2).

DISCUSSION

Rats showed a decrease in locomotor activity during the first 30 min after they were injected with ritanserin, 10.0 mg/kg. This effect was observed in both horizontal and vertical activity. Nomikos and Spyraki (20) did not observe any effects of small doses of ritanserin (1.0 and 2.5 mg/kg) on either spontaneous locomotor activity, or the locomotor activity produced by *d*-amphetamine, morphine, or diazepam; the present results also failed to find a significant effect of ritanserin, 1.0 mg/kg, on locomotor activity. Thus, doses of ritanserin of approximately 10.0 mg/kg may represent the upper end of the dose-effect curve that can be tested without significant motor effects of this compound.

Using this 10 mg/kg dose, there was no effect of ritanserin pretreatment on the cumulative dose-effect curve for rats trained to detect cocaine (10 mg/kg) from saline in a two-lever discrimination paradigm. Similarly, a broad range of ritanserin doses (0.32, 1.0, 3.2, 10.0, and 32.0 mg/kg) were without effect on the detection of the training dose of cocaine. It is not likely that the failure of ritanserin to affect the discriminative properties of cociane is due to either the pretreatment time that was used or the vehicle in which the drug was homogenized because, in the Locomotor Activity Experiment, an identical pretreatment regimen with ritanserin resulted in a decrease in locomotor activity. Meert and Janssen (18) also reported that ritanserin (0.63, 2.5, 10.0, and 40.0 mg/kg) did not antagonize the discriminative stimulus effects of cocaine, and they found that these doses did not substitute for cocaine. Because drug discrimination procedures provide high concordance with human reports of subjective drug effects (10), these data suggest that ritanserin is unlikely to influence the subjective effects of cocaine.

Based on the results obtained in an oral paradigm of cocaine consumption, Meert and Janssen (18) suggested that ritanserin may reduce the preference for cocaine in rats. Although they did not describe what might lead to a cocaine preference in this paradigm, presumably it could occur either because withdrawal from cocaine serves as a motivator to continue cocaine taking or because of the direct reinforcing effects of cocaine. Although chronic cocaine consumption may lead to tolerance (8,9) and withdrawal (29), it is unlikely that these factors contributed significantly to the drinking phenomenon described by Meert and colleagues. Among other considerations, the oral cocaine consumption of their subjects averaged no more than 1 mg/h at the largest dose of cocaine tested, which particularly considering the route of administration, is far lower than the doses necessary to show withdrawal in other experimental paradigms (29). In addition, although there may be a role for withdrawal in mediating preference for cocaine, there is general consensus that the direct reinforcing effects of cocaine are significantly more important in maintaining use of this drug than is withdrawal (31).

Positive results have been reported for the effects of nonspecific serotonin agents on cocaine self-administration. Pretreatment with either dietary *l*-tryptophan (5,16) or fluoxetine (4,26) resulted in the suppression of some doses of cocaine in a low-value FR schedule of cocaine self-administration and decreased the breaking point under a progressive-ratio schedule of cocaine self-administration. However, the only specific serotonergic agent that mimicked those effects was 8-OH-DPAT, a 5-HT_{1A} agonist, and this occurred over a limited range of cocaine doses (24). Tests with the 5-HT_3 antagonist, ondansetron, have also been consistently negative with regard to the effect of this compound on cocaine self-administration in animals (14,22).

The lack of positive results with 5-HT_{1A} and 5-HT_3 receptor agents were extended in the present experiments to include a 5-$HT_{2/1C}$ compound. In the first cocaine self-administration experiment, rats pretreated with ritanserin (1.0 and 10.0 mg/kg) and tested using the multidose procedure did not have significantly different cocaine dose-response curves from when they were pretreated with vehicle. However, ritanserin was given 30 min before the test began, and the test session

lasted approximately 2 h. In accordance with the data obtained in the locomotor activity experiments, it is possible that by using the multidose test procedure with a 30-min pretreatment time, we were not examining the rate of cocaine self-administration during the maximally effective time period of ritanserin. To investigate this possibility, another group of rats were injected with either ritanserin (10 mg/kg; IP) or its vehicle 10 min prior to self-administration of cocaine, 0.25 mg/infusion, and only the data obtained during the first 20 min of this test session were analyzed. Again, ritanserin failed to effect the rate of cocaine self-administration of these subjects. The failure of ritanserin to modify the reinforcing effects of cocaine in the present experiments are consistent with data previously reported in preliminary form (23) showing that ritanserin (0.1, 1.0, and 10.0 mg/kg, IP) did not affect the rate of IV cocaine self-administration in rats. The results also extend those of Porrino and colleagues (25), who found that the selective 5-HT_2 antagonist cinanserin failed to alter cocaine self-administration in rats. The failure of ritanserin to modify cocaine taking further supports the conclusion that antagonists for the 5-HT_2 receptor are unlikely to be efficacious in modifying the reinforcing effects of cocaine.

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