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A Comparison of the Effects of Risperidone, Raclopride, and Ritanserin on Intravenous Self-Administration of *d*-Amphetamine

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FLETCHER, P. J. *A comparison of the effects of risperidone, raclopride, and ritanserin on intravenous self-administration of* d-*amphetamine*. PHARMACOL BIOCHEM BEHAV **60**(1) 55–60, 1998.—These experiments were conducted to examine the effects of simultaneous blockade of dopamine D_2 and 5-hydroxytryptamine$_2$ (5-HT) receptor function on responding for intravenous infusions of *d*-amphetamine. Rats were trained to self-administer *d*-amphetamine intravenously according to a progressive ratio schedule of reinforcement, in which response requirements increased for successive infusions until responding extinguished. In the first experiment it was shown that increases in the unit infusion dose of *d*-amphetamine resulted in an increase in the number of amphetamine infusions earned. Thus, the strength of responding for *d*-amphetamine was linked to the dose of drug received. The mixed D_2 and 5-HT_2 receptor antagonist risperidone (0.1, 0.2, and 0.4 mg/kg) reduced responding for *d*-amphetamine (60 μg/kg infusion). The selective D_2 antagonist raclopride (0.1, 0.2, and 0.4 mg/kg) also reduced responding for *d*-amphetamine. In contrast, the selective 5-HT_2 antagonist ritanserin (0.63, 1.25, and 2.5 mg/kg) failed to alter amphetamine self-administration. Combined injections of raclopride (0.05 or 0.1 mg/kg) and ritanserin (2.5 mg/kg) were no more effective than injections of raclopride alone in reducing responding for *d*-amphetamine. Overall, these results suggest that 5-HT_2 receptor blockade plays a negligible role in the rewarding effects of *d*-amphetamine measured by intravenous self-administration, and does not contribute to the suppressant effects of risperidone on this behavior. © 1998 Elsevier Science Inc.

Risperidone Raclopride Ritanserin *d*-Amphetamine Self-administration Reward D_2 5-HT_2

IT is well established that the rewarding effects of psychomotor stimulants such as amphetamine and cocaine are mediated, at least in part, by increased dopaminergic neurotransmission within the nucleus accumbens. Thus, depletion of dopamine levels in the nucleus accumbens following treatment with the neurotoxin 6-hydroxydopamine leads to a reduction in self-administration of amphetamine (21) and cocaine (34). This manipulation also prevents the development of place preferences for environments paired with amphetamine (38). Antagonists selective for either dopamine D_1 or D_2 receptors appear to attenuate the rewarding effects of self-administered cocaine (3,4,8,14). Similarly, D_1 or D_2 antagonists block the acquisition of amphetamine induced place preference, and following injection into the nucleus accumbens they block the expression of amphetamine-induced place preference (13). Such results indicate the involvement of both D_1 and D_2 receptors in mediating the rewarding effects of psychomotor stimulants.

A number of other neurotransmitter systems are known to modulate mesolimbic dopamine function, and to modify the expression of behaviors mediated by this system. One such neurotransmitter is serotonin (5-hydroxytryptamine; 5-HT). At the behavioral level manipulations of serotonin function have been shown to alter responding for intravenous infusions of amphetamine and cocaine. Increased 5-HT function has been shown to reduce responding for both amphetamine (16,35) and cocaine (5). Conversely, reduced 5-HT function following treatment with the neurotoxin 5,7-DHT (22) or the nonselective antagonist metergoline (20) increased responding for amphetamine. These increased response rates were interpreted in terms of a reduction in the reinforcing effectiveness of *d*-amphetamine, because the increased responding resembled that seen following a lowering of the unit infusion dose. Contradictory to this hypothesis, 5,7-DHT lesions apparently increased the motivation to respond for cocaine when responding was reinforced according to a progressive ratio schedule (19). However, because these lesions also increased food reinforced responding (33), it is possible that 5-HT depletion simply results in a generalized facilitation of responding [e.g. (37)].

Results obtained from other behavioral procedures suggest a role for 5-HT systems, and 5-HT_2 receptors in particular, in mediating psychomotor stimulant drug reward. Thus, the 5-HT_2 receptor antagonist ritanserin has been reported to preferentially reduce oral cocaine intake (25). Using the conditioned place preference procedure ritanserin was found to abolish the preference for an environment previously paired with amphetamine injections (27). These results suggest that 5-HT_2 receptors may be important for modulating the rewarding effects of psychomotor stimulants, and that ritanserin is apparently effective at attenuating such reward.

A number of atypical antipsychotic drugs, such as clozapine and risperidone, are antagonists of both 5-HT_2 and D_2 dopamine receptors, and evidence suggests that 5-HT_2 antagonism is an important component of the action of atypical antipsychotics [e.g. (18)]. Indeed, 5-HT_2 receptor blockade following treatment with ritanserin has been reported to exhibit some antipsychotic activity (10,42). In contrast to dopamine D_2 antagonists, such drugs have been suggested to exert a more selective influence on mesolimbic dopamine function, and this had been attributed to their ability to block 5-HT_2 receptors (1,39). Given that blockade of either D_2 or 5-HT_2 receptors may alter the rewarding effects of psychomotor stimulants, which are mediated via the mesolimbic dopamine system, it is of interest to determine the effects of risperidone on amphetamine self-administration. Accordingly, the present study investigated the effects of mixed D_2/5-HT_2 receptor blockade in rats responding for *d*-amphetamine delivered under a progressive ratio schedule of reinforcement (9,31). Following the demonstration that risperidone reduced responding for *d*-amphetamine, the relative contributions of 5-HT_2 and D_2 receptor blockade to this effect were examined. This was achieved by investigating the effects of the relatively specific D_2 antagonist raclopride (26), and the 5-HT_2 receptor antagonist ritanserin (2,6,17), administered either alone or in combination, on intravenous amphetamine self-administration.

METHOD

Subjects

Adult male Sprague–Dawley rats weighing 280–340 g at the time of surgery were housed individually in hanging wire-mesh cages. Unless otherwise stated, food and water were freely available. The housing room was maintained at a constant temperature of 22 ± 2°C.

Surgery

Rats were anaesthetised with 45–50 mg/kg sodium pentobarbital (Somnotol). A catheter constructed of PE tubing and Silastic tubing was implanted in the right jugular vein. This catheter was a slightly modified version of the one described by Corrigall (7). The terminal end of the catheter was a length of 23 g stainless steel tubing, which was cemented inside a nylon bolt. The catheter exited between the scapulae, and could be quickly attached and detached from the drug delivery line by means of a small plastic nut cemented to the end of a stainless steel spring protecting the line.

Apparatus

Testing was conducted in 12 operant chambers measuring 28 cm long, 21 cm wide, and 21 cm high (Med. Associates Inc., St. Albans, VT). Each chamber contained a food pellet dispenser, two response levers 4.5 cm wide and 7 cm above the floor of the chamber, and a stimulus light located 6 cm above each lever. A counterbalanced arm held a fluid swivel above the ceiling of the chamber. This swivel was attached at one end by tubing to a syringe mounted on a motor driven syringe pump (Razel) located outside the chamber. At the other end of the swivel a length of tubing, encased in a stainless steel spring, was used to connect the animal's catheter to the syringe. Each chamber was illuminated by a house light and housed in a sound-attenuating box equipped with a ventilating fan. The apparatus was controlled, and the data collected, by a 386-SX IBM-type computer.

Procedure

Prior to surgery rats were food restricted (approximately 15–20 g food per day) and trained to press a lever for 45 mg food pellets. Initially responses were reinforced according to a fixed ratio (FR) 1 schedule, and this was raised to FR10 over the course of 10 days with sessions running for either 30 min or until 100 pellets had been obtained. Once rats had acquired the lever pressing response they were given free access to food for the remainder of the study. Five days following surgery rats were reintroduced to the operant chambers with the catheter connected to the drug delivery line. Rats were allowed to respond for infusions (approximately 0.1 ml during 4 s) for *d*-amphetamine (60 μg/kg) on a FR1 schedule. Each infusion was signalled by a stimulus light that remained illuminated for a 20-s time-out period. After several days of stable responding, a progressive ratio (PR) schedule was implemented (31, 32). On this schedule the number of responses required to obtain an infusion increased for successive infusions. The progression was derived from the equation response ratio = $[5 \times e^{(0.2 \times \text{infusion no.})} - 5]$, and yielded response ratios of 1,2,4,6,9,12,15,20,25, 32,40,50,62,77,95,118, etc. Sessions lasted until a period of 1 h elapsed without an infusion, or were a maximum of 5 h in length. The number of infusions before this breaking point was recorded.

Experimental Details

Five experiments were conducted.

Nine rats were used to examine the effects of varying the dose of amphetamine on breaking points. These rats were trained to self-administer 60 μg/kg/infusion *d*-amphetamine in daily sessions according to the PR schedule. Once responding was stable, defined as ±3 infusions across 3 successive days, the dose of *d*-amphetamine was then varied (0, 15, 30, 60, 120 μg/kg/infusion) in a randomized order and breaking points determined. In between each test day rats were maintained on the 60 μg/kg dose.

For the remaining four experiments involving antagonist pretreatment a pool of 12 rats was used with each rat participating in a maximum of three experiments. The infusion dose of *d*-amphetamine was 60 μg/kg throughout. The effects of risperidone (0.1, 0.2, and 0.4 mg/kg SC, 30 min prior to testing) raclopride (0.1, 0.2, and 0.4 mg/kg SC, 30 min prior to testing) and ritanserin (0.63, 1.25, and 2.5 mg/kg SC, 1 h prior to testing) were examined. For each rat a dose–response curve to each drug was completed before the next drug was tested. At least 3 days intervened between each test dose, and a minimum of 5 days elapsed before a new drug was tested. The order of testing each drug, or drug combination, was randomized for each rat. Following completion of these experiments the effects of combining ritanserin (2.5 mg/kg SC) and raclopride (0.05 and 0.1 mg/kg SC) were examined. In this study rats were tested six times with 0, 0.05, and 0.1 mg/kg raclopride in combination with 0 or 2.5 mg/kg ritanserin. Ri-

tanserin was injected 1 h before raclopride which was given 30 min before the self-administration session. The order of testing was randomized for each animal.

Drugs

Risperidone (Janssen) and raclopride (Astra) were dissolved in saline; ritanserin (RBI) was dissolved in a few drops of glacial acetic acid and 20% propylene glycol, with sonication. The appropriate vehicle solutions were used for control injections. All drugs were administered in a volume of 1 ml/kg. *d*-Amphetamine sulfate (Bureau of Drug Surveillance, Ottawa, Ontario) was dissolved in sterile 0.9% saline.

Data Analysis

The number of infusions obtained in both the *d*-amphetamine and antagonist dose–response curves were analyzed using one-way analysis of variance with repeated measures. Post hoc comparisons against the control mean were made using Dunnett's test. For the *d*-amphetamine dose–response curve a number of other parameters were analyzed, including the number of responses emitted, the session length (incorporating the 1-h break-point criterion), and the mean interinfusion interval. This latter value was calculated after omitting the first and last interinfusion interval (9). The data were analyzed by one-way analysis of variance followed where appropriate by either Dunnett's test for comparisons against a control mean, or Tukey's test for pairwise comparisons. The number of infusions earned in the raclopride + ritanserin study was analyzed using two-way analysis of variance with repeated measures on both factors (raclopride dose and ritanserin dose).

RESULTS

Figure 1 shows the effects of varying the infusion dose of *d*-amphetamine on the number of infusions earned. A significant main effect of dose $F(4,32) = 26.96, p < 0.001$ confirmed that the number of infusions earned increased with increasing dose of *d*-amphetamine. The number of infusions earned appeared to reach a maximal level at a unit dose of 60 μg/kg/infusion because a doubling of this unit dose failed to induce a significant increase in responding. The number of infusions taken was significantly greater as the dose per infusion increased, except for the two highest doses. Table 1 shows several other parameters of *d*-amphetamine self-administration under the PR schedule. Increases in dose resulted in higher ratios completed, longer mean interinfusions intervals, and an increase in session length before a period of 1 h without an earned infusion. For the measures of mean interinfusion interval and session length post hoc analyses using Tukey's test showed that the values obtained when the infusion dose was 120 μg/kg were significantly higher than those obtained with an infusion dose of 60 μg/kg.

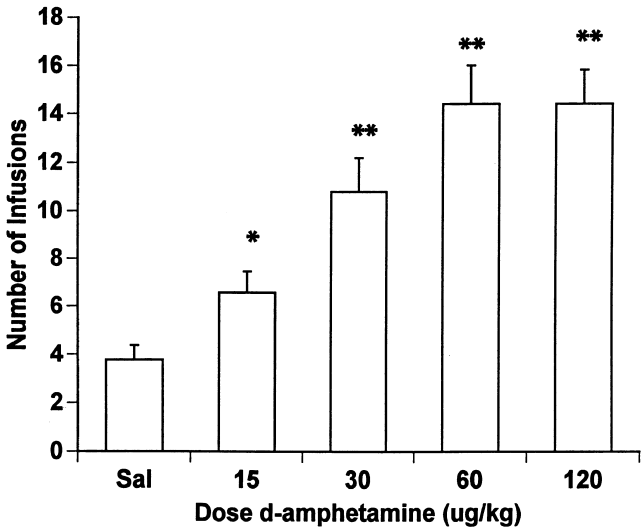

FIG. 1. The effects of varying the unit dose on the number of intravenous infusions of *d*-amphetamine ($n = 9$). Sal = saline. *$p < 0.05$, **$p < 0.01$ compared to saline treatment.

Figure 2 illustrates the effects of risperidone, raclopride, and ritanserin on the number of *d*-amphetamine infusions earned. A significant main effect of dose, $F(3, 21) = 3.99, p = 0.02$ was found, with all three doses of risperidone significantly reducing the number of infusions of *d*-amphetamine. Although there was a trend towards an increase in the latency to obtain the first *d*-amphetamine infusion this was not significantly altered by risperidone, $F(3, 21) = 1.91, p > 0.1$. Latency values in seconds were: saline 26.3 ± 3.4; 0.1 mg/kg: 57.0 ±

TABLE 1

PARAMETERS OF *d*-AMPHETAMINE SELF-ADMINISTRATION ON A PROGRESSIVE RATIO SCHEDULE

	Dose of *d*-Amphetamine (μg/kg/inf.)					
Parameter	Sal	15	30	60	120	F ratio (*df*)
Highest ratio completed*	6.2	16.4§	38.2¶	97.7¶	103.4¶	10.3
	(1.6)	(5.1)	(13.3)	(25.9)	(28.1)	(4,32)
Mean inter infusion interval(s)†	ND	387.2	523.1	680.7	1066.6	26.9
		(71.6)	(63)	(88.0)	(112.6)	(3,24)
Session length (min)‡	24.5	60.2§	126.0¶	180.7¶	220.8¶	20.7
	(13.4)	(12.8)	(18.7)	(16.5)	(18.3)	(4,32)

Values represent the mean values (±SEM) from nine rats.

*Highest ratio completed.

†Mean infusion interval is the mean of all interinfusion intervals after excluding the first and last intervals [see(9)]. See test for statistical details.

‡Session length is the time elapsed from the beginning of the session until the last infusion was obtained.

ND—not determined.

§$p < 0.05$, ¶$p < 0.01$—compared to saline.

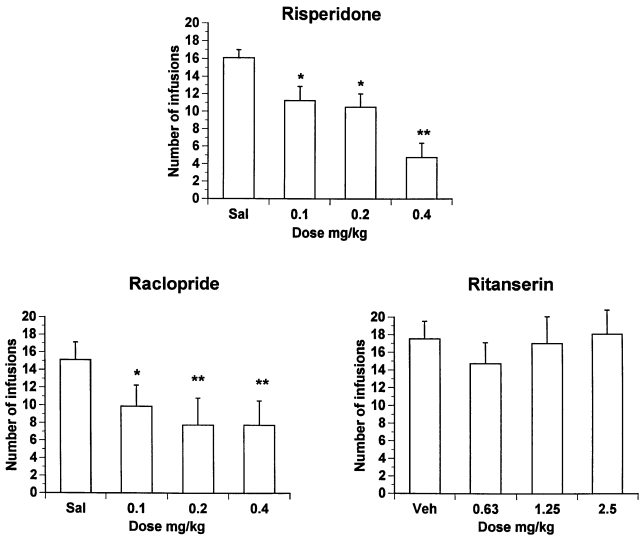

FIG. 2. The effects of various doses of risperidone ($n = 8$), raclopride ($n = 8$), or ritanserin ($n = 7$) on responding for intravenous infusions of *d*-amphetamine. Sal = saline, Veh = vehicle. $^{*}p < 0.05$ compared to Sal; $^{**}p < 0.01$ compared to Sal.

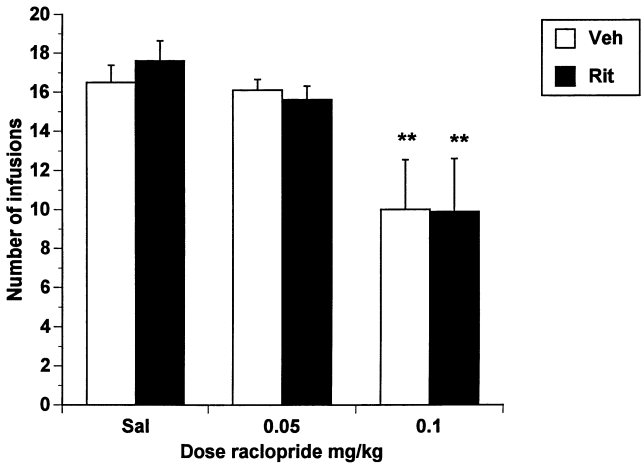

FIG. 3. The effects of combing 2.5 mg/kg ritanserin (Rit) or vehicle (Veh) with raclopride or saline (Sal) on responding for intravenous infusions of *d*-amphetamine ($n = 8$). $^{**}p < 0.01$ compared to appropriate saline-treated condition.

15.2; 0.2 mg/kg: 47.6 ± 19.6; 0.4 mg/kg: 98.9 ± 35.6. Raclopride also significantly reduced responding for *d*-amphetamine, $F(3, 21) = 11.86$, $p < 0.0001$, and, again, all doses were effective. Latencies to obtain the first *d*-amphetamine infusion were: saline: 35.1 ± 7.6; 0.1 mg/kg: 88.1 ± 42.4; 0.2 mg/kg: 67.4 ± 30.2; 0.4 mg/kg: 68.6 ± 13.7. These differences were not significant, $F(3, 21) = 0.67$, $p > 0.1$, nor was a significant effect observed when the data were analyzed following a square-root transformation. Ritanserin did not alter responding for *d*-amphetamine, $F(3, 18) < 1$, NS) at any of the doses tested. Again, latencies to respond for the first *d*-amphetamine infusion were not significantly changed by ritanserin, $F(3, 18) = 0.35$, $p > 0.1$: vehicle: 33.7 ± 5.8; 0.63 mg/kg: 24.3 ± 6.3; 1.25 mg/kg: 32.7 ± 6.5; 2.5 mg/kg: 31.7 ± 10.6.

The effects of combined raclopride plus ritanserin are shown in Fig. 3. Two-way analysis of variance showed that overall responding was reduced by raclopride, $F(2, 14) = 10.59$ $p < 0.002$. Neither the main effect of ritanserin, $F(1, 7) < 1$, NS, nor the ritanserin × raclopride interaction, $F(2, 14) < 1$, NS, were significant. Post hoc tests showed that the lower dose of raclopride did not affect the number of *d*-amphetamine infusions, and that the 0.1 mg/kg dose reduced responding to 62% of control levels. The effects of raclopride were not altered by ritanserin.

DISCUSSION

The results of the first experiment demonstrate that rats will respond for *d*-amphetamine according to a PR schedule of reinforcement. The break point (i.e., the number of infusions earned) varied as a function of dose, with increases in dose up to 60 μg/kg/infusion resulting in increased break points. A further doubling of the dose of *d*-amphetamine did not increase the number of infusions earned. However, at this dose the interinfusion interval was significantly increased, as was the session length before the breaking-point criterion was reached. This suggests that had a longer criterion length than 1 h been used, greater breaking points may have been reached at this higher dose. A similar dose–response relationship for *d*-amphetamine using the same progressive ratio schedule has been described previously (31), and the finding of an increase in interinfusion interval with increasing doses of *d*-amphetamine is consistent with the pattern observed using a fixed ratio schedule of drug delivery (30).

Treatment with risperidone resulted in a reduction in the number of *d*-amphetamine infusions. This effect was also observed with raclopride but not with ritanserin. Risperidone is an antagonist at D_2 and 5-HT_2 receptors (18), whereas raclopride and ritanserin show selectivity for the D_2 (18,28) and 5-HT_2 receptors (2,17), respectively. At the doses of risperidone used in these studies, behavioral tests have shown that this compound is an effective antagonist of both D_2 and 5-HT_2 receptors (24). Given the lack of effect of ritanserin on responding for amphetamine, it would appear that 5-HT_2 receptor blockage does not contribute to the ability of risperidone to reduce responding for *d*-amphetamine. Further evidence for this comes from the results of the study combining raclopride with ritanserin. These results showed that the ability of raclopride to alter responding for *d*-amphetamine was not changed by cotreatment with ritanserin. This lack of interaction was observed at a dose of raclopride (0.05 mg/kg), that by itself, failed to alter responding for *d*-amphetamine, as well as at a dose (0.1 mg/kg) that induced an approximate 40% reduction in responding for *d*-amphetamine.

Ritanserin has been found to alter the firing rate of midbrain dopamine cells (1,36,41) and to induce modest increases in dopamine release in the nucleus accumbens (1). More importantly, ritanserin has been found to potentiate the effects of raclopride on burst-firing rate of dopaminergic cells in the ventral tegmental area, but not the substantia nigra, and on extracellular concentrations of dopamine in the nucleus accumbens, but not the dorsal striatum (1). Thus, it has been proposed that a combination of 5-HT_2/D_2 receptor blockade selectively influences the mesolimbic dopaminergic system, and that this is an important mechanism for the mode of action of atypical antipsychotic drugs (1,39). Behaviorally, ritanserin has also been found to potentiate the effects of raclopride on the consumption of weak and strong sucrose solutions (26). These results were also interpreted as being indicative of a selective action on mesolimbic dopamine systems. However, because raclopride alters sucrose consump-

tion following injection into other dopaminergic terminal areas including the anterodorsal striatum and amygdala (29), it is possible that one or more of these sites is responsible for mediating the synergistic effects of raclopride and ritanserin on sucrose intake.

If 5-HT_2 receptor blockade selectively enhances the effects of D_2 receptor blockade on the functioning of mesolimbic dopamine system, then it would be predicted that behaviors mediated predominantly by the mesolimbic dopamine system should be especially sensitive to combined 5-HT_2 and D_2 receptor blockade. Amphetamine self-administration is mediated principally by enhanced dopaminergic neurotransmission in the nucleus accumbens [e.g., (21)]. The fact that ritanserin failed to alter *d*-amphetamine self-administration, or to enhance the suppressant effect of raclopride, argues strongly against an interaction of these two receptors at the level of the mesolimbic dopamine system. Responding for brain stimulation reward (BSR) derived from ventral tegmental area electrodes, as well as amphetamine-induced facilitation of responding for BSR also involve activation of mesolimbic dopamine neurons [reviewed in (43)]. In tests of BSR, risperidone and selective D_2 antagonists reduced the reinforcing efficacy of BSR and reversed amphetamine's facilitatory effect on this behavior (11,40). Antagonism of 5-HT_2 receptors did not alter baseline responding for BSR nor the facilitating effect of amphetamine. When given in combination with D_2 antagonists 5-HT_2 antagonists did not modify the effects of D_2 receptor blockade (40). This pattern of results is similar to that obtained for *d*-amphetamine self-administration in the present studies. Thus, using two positively reinforced operant procedures that involve activation of the mesolimbic dopamine system, it has been shown that 5-HT_2 receptor blockade has negligible effects on the rewarding effects of *d*-amphetamine, nor does it appear to alter the behavioral effects of D_2 receptor blockade.

The lack of effect of ritanserin on responding for amphetamine is consistent with the finding that another 5-HT_2 antagonist, ketanserin, failed to alter cocaine self-administration (15). However, these results contrast with the observation that ritanserin attenuated a conditioned place preference for environments paired with amphetamine (27). This effect was interpreted within the context of ritanserin attenuating the rewarding effects of amphetamine. An extension of this interpretation is that 5-HT_2 receptors "may mediate some of the rewarding effects of amphetamine" (27). The finding that ritanserin failed to alter operant responding for *d*-amphetamine, which presumably directly measures the primary reinforcing effects of amphetamine, contradicts this hypothesis. Instead, it is likely that the effects of ritanserin in the place preference procedure may involve some other mechanism. A major component of place preference learning involves the learned association between the rewarding properties of the drug and the environmental cues in which the drug is experienced. Ritanserin has been shown to interfere with associative learning. Specifically, this drug was found to retard acquisition of the conditioned nictitating membrane response in rabbits (12). Consequently, it may be possible to reconcile the differing effects of ritanserin on *d*-amphetamine self-administration and place preference learning (27) by postulating that the primary effect of ritanserin is to disrupt the formation of stimulus-reward associations, which play a prominent role in place preference conditioning, but only a minor, if any, role in maintaining established responding on a progressive ratio schedule of drug reinforcement. Further evidence to support this view is the finding that ritanserin also blocks or attenuates conditioned place preferences elicited by other unconditioned stimuli (morphine and diazepam), with differing pharmacological activities from amphetamine (27). A recent study (23) showing that rats treated with ritanserin fail to learn a conditioned odor preference is also consistent with the view that 5-HT_2 receptor antagonism disrupts associative learning.

When dopamine antagonists are given to animals responding for intravenous infusions of psychomotor stimulants under fixed ratio schedules, with small time-out periods, increased responding is frequently observed (3,4,8,14). This effect has been interpreted in terms of a compensatory response to overcome the effects of dopamine receptor blockade. A recent report, however, demonstrated that raclopride did not alter fixed-ratio responding for cocaine (4). This observation is potentially important in two respects. First, because response rates were unchanged, it shows that raclopride does not seriously affect motor performance. This is further corroborated by the fact that in the present experiments raclopride, as well as risperidone, did not significantly alter the mean latency to begin responding for *d*-amphetamine. Secondly, the lack of effect of raclopride on fixed-ratio responding implies that raclopride, in contrast to other D_2 receptor antagonists (3,4,8,14), may not alter the reinforcing efficacy of cocaine. However, in the present experiments raclopride reduced breaking points for amphetamine, indicating that this drug does apparently reduce the motivation to self-administer *d*-amphetamine.

In summary, these results show that risperidone and raclopride reduce responding for intravenous infusions of *d*-amphetamine under a progressive ratio schedule of reinforcement. In the case of risperidone, blockade of 5-HT_2 receptors does not appear to play a role in this behavioral response; furthermore, 5-HT_2 receptor blockade alone does not alter the reinforcing efficacy of *d*-amphetamine. Neurochemical and electrophysiological results indicate that low levels of D_2 dopamine receptor blockade may exert a preferential effect on the functioning of the mesolimbic dopamine system when 5-HT_2 receptors are simultaneously blocked (1,39). However, the results of the present study, together with those obtained using a BSR procedure (10,37), have not provided evidence that this additional influence of 5-HT_2 receptor blockade translates into significant behavioral effects when the mesolimbic dopamine system is activated.

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