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Effects of Ritanserin on the Rewarding Properties of d-Amphetamine, Morphine and Diazepam Revealed by Conditioned Place Preference in Rats

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NOMIKOS, G. G. AND C. SPYRAKI. *Effects of ritanserin on the rewarding properties of d-amphetamine, morphine and diazepam revealed by conditioned place preference in rats.* PHARMACOL BIOCHEM BEHAV **30**(4) 853–858, 1988.—The possibility that 5-HT_2 receptors mediate the reinforcing properties of d-amphetamine, morphine and diazepam was investigated in rats, using ritanserin, a 5-HT_2 antagonist, and the conditioned place preference paradigm. Ritanserin 1 or 2.5 mg/kg did not cause place conditioning. Place preference induced by 1.5 mg/kg d-amphetamine and 2 mg/kg morphine was inhibited and attenuated respectively by pretreatment with 2.5 mg/kg ritanserin. Diazepam- (1 mg/kg) induced place preference was completely blocked by both doses of ritanserin. Ritanserin pretreatment failed to influence amphetamine-induced hyperlocomotion, morphine-induced analgesia and diazepam-induced increased open arm exploration of rats on the elevated plus maze. These data are discussed in terms of (a) the possibility that serotoninergic mechanisms have a role in mediating reinforcement and (b) the relationship between appetitive properties and specific behavioral effects of psychostimulants, opiates and anxiolytics.

Ritanserin d-Amphetamine Morphine Diazepam Conditioned place preference

A role of serotonin (5-HT) in drug reward processes has been suggested in studies in which pretreatment with drugs affecting serotoninergic transmission was used to influence drug self-administration or drug-induced conditioned place preference. Relevant studies most frequently deal with d-amphetamine, a few concern morphine and none refer to diazepam; the rewarding properties of the latter drug in the rat were recently revealed by self administration [23] and by conditioned place preference [33] studies.

Specifically, reduced self-administration of d-amphetamine was observed following inhibition of serotoninergic transmission with the 5-HT receptor antagonists methysergide, cyproheptadine [14] and metergoline [17]. Paradoxically, increased serotoninergic transmission following treatment with l-tryptophan, fluoxetine or quipazine was also associated with decreased d-amphetamine self-administration [14]. d-Amphetamine-induced conditioned place preference was blocked by zimelidine, a serotonin uptake blocker [13]. Zimelidine failed to influence morphine-induced place preference [13]. However, in a choice situation, morphine intake was reduced by zimelidine administered to opiate addicted [27] or nonaddicted rats [26].

From the available data it is impossible to formulate conclusions as to whether serotonin facilitates or inhibits drug reward processes. This weakness may be attributed to the fact that the pharmacological approaches used were lacking in specificity. For instance, with l-tryptophan, fluoxetin or zimelidine the resulting increased amount of intrasynaptic serotonin affects both 5-HT_1 and 5-HT_2 receptors which are heterogenous. On the other hand, methysergide or cyproheptadine, usually classified as 5-HT antagonists [8], have other prominent pharmacological activities as well [2, 4, 8, 24].

Receptors of the 5-HT_2 variety, whose affinity for 5-HT is only about one thousandth that of the 5-HT_1 receptors, have been most frequently associated with functional responses [15].

The aim of this study was to examine the role of 5-HT_2 receptors for mediating drug-rewarding properties. To this end, we studied the effect of 5-HT_2 antagonist ritanserin [11] on the conditioned place preference induced by amphetamine, morphine and diazepam. We also sought to in-

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vestigate if ritanserin influences specific behavioral effects elicited by each studied drug. Thus, following the conditioned place preference experiments, locomotion, morphine analgesia and diazepam anxiolysis were examined in the relevant groups of animals.

METHOD

Animals

Male Wistar rats, reared in this laboratory, weighing 200–220 g at the beginning of the experiment, were used. They were housed six per cage with free access to food and water, under a 12 hr light/12 hr dark regime. Behavioral experiments were performed between 10.00 and 16.00 hr in a dimly lit, isolated experimental chamber.

Treatment and Groups

d-Amphetamine sulphate (Sigma), morphine HCl (Drug Administration, Ministry of Health, Greece) and diazepam (Roche) were administered IP in doses of 1.5, 2.0 and 1.0 mg/kg respectively. The doses used have been previously shown to be effective in inducing conditioned place preference [21, 31, 33]. Ritanserin, dissolved in two equivalents tartaric acid, was administered in two doses: 1 (R_1) and 2.5 (R_2) mg/kg, both being behaviorally active in the rat [6]. Ritanserin or vehicle were administered subcutaneously one hr prior to any drug treatment. According to the treatment, twelve separate groups of animals were formed: V-S (Vehicle-Saline); R_1-S; R_2-S; V-AMP (amphetamine); R_1-AMP; R_2-AMP; V-MOR (morphine); R_1-MOR; R_2-MOR; V-DIA (diazepam); R_1-DIA; R_2-DIA.

Conditioned Place Preference (CPP)

The apparatus for behavioral training and testing was a rectangular Plexiglas box divided into two compartments of equal size (40×45×30 cm) by a center area (15×45×30 cm) The white compartment had white walls and a grid floor; the other had a white wall with black stripes and a mesh floor; the center area had gray walls with grid floor. The compartments were separable by guillotine doors from the center area.

On three consecutive days the animals were placed in the center area and after three seconds both guillotine doors were raised and each rat was allowed to explore the apparatus for 15 min per day. The time spent by the rat on each compartment during the third day session was recorded (preconditioning test). The compartment in which the rat spent less time was called nonpreferred and the other preferred. Then the rats were assigned to the different treatment groups. Efforts were made to include in each group an equal number of rats preferring the white or the black + white compartment, to have groups which were not significantly different in their preconditioning scores and to have animals not exceeding 4/5 of the test time (~ >720 sec) on the preferred side.

Conditioning training lasted 8 days. On days 1, 3, 5 and 7, animals received drug treatment and were placed on the nonpreferred compartment. Animals received injections of morphine, amphetamine and diazepam, immediately, 10 and 30 min before being placed on the to-be-conditioned compartment for 60, 30 and 45 min respectively. The control group was injected with saline and immediately after placed on the training box for 30 min. All groups were injected with ritanserin or vehicle before any drug or saline treatment. On alternate days animals were injected with saline twice, one hr and immediately before being placed in the preferred compartment for the appropriate time which corresponded to that spent by the animal on the nonpreferred side the previous training day.

Twenty-four hours after the last conditioning training, each rat was allowed to explore the apparatus with the guillotine doors opened for 15 min (postcondition test). Behavior was registered as during the preconditioning test.

The difference in time spent on the drug associated side between post- and preconditioning tests indicated the change in preference induced by the drug. A positive difference reflected reward, a negative difference aversion.

The data from each drug treatment groups were separately compared to control groups. Two-way analysis of variance (ANOVA) was performed with pretreatment (saline-ritanserin) and treatment (vehicle-drug) as independent factors and the change in preference as the dependent variable.

Locomotor Activity

It was assessed with the use of an activity recording system (Ugo Basile) one week after the CPP experiments, in the same groups of animals.

Ritanserin or vehicle was administered 45 min before each animal was placed in the activity cage (35×23×20 cm) for a 15 min habituation time. Then the animal was injected with saline, amphetamine, morphine, diazepam and immediately returned to the activity box for another 60 min period.

The data were subjected to two-way ANOVA with the number of counts recorded in 60 min as the dependent and pretreatment and treatment as the independent variables. The data of the 15 min habituation test were pooled together as significant differences were not detected between groups.

Morphine Analgesia

It was assessed 4 days after the locomotion experiment, in controls and morphine groups. Saline or morphine (30 mg/kg, IP) was administered to rats injected one hour before with vehicle or ritanserin (R_1 and R_2). Pilot studies have shown that the dose of 30 mg/kg of morphine produces a reliable analgesic effect on the rats of the colony we are using tested by the hot-plate procedure. The hot surface, an electrically controlled metal plate, was maintained at 56°C. A Plexiglas cylinder, 30 cm high and open at the top, confined the rat to a defined area of the hot plate. The time before the animal licked one paw or jumped off the plate was recorded. Recordings were made before and at 30 min intervals over a 2 hr period after the injection of morphine or saline.

Diazepam Antianxiety Effect

It was determined by using the elevated plus maze (EPM) test [25], in control and diazepam treated groups, one week after the activity experiment.

The EPM consisted of two open arms (50×1×40 cm, each) and two enclosed arms, of the same dimensions and with open roof, arranged such that the two arms of each type were opposite to each other. The maze was elevated to a height of 50 cm. Before exposure to the EPM the rats were placed in a wooden arena (60×60×35 cm) for 5 min. Then each rat was placed on the center of the maze facing an enclosed arm. An arm entry was defined as the entry of the front half part of the body into one arm. During a 5 min test

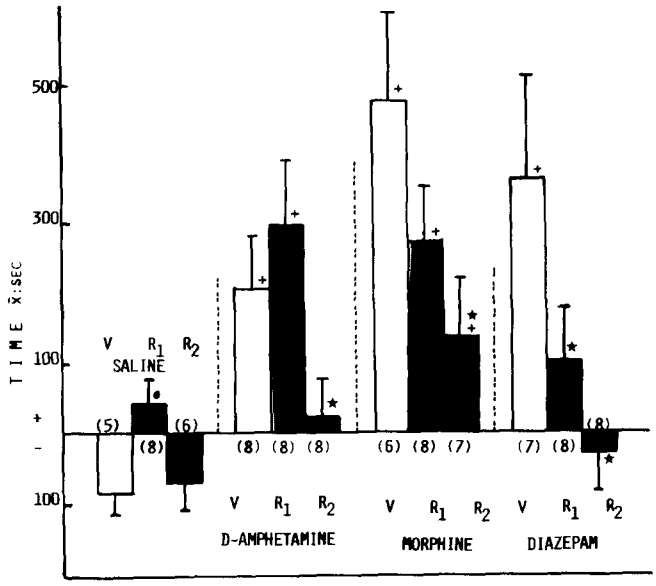

FIG. 1. Change in time spent on drug associated side as expressed in post- minus preconditioning responses (means±SEM). Number of animals in brackets. V: vehicle; R_1: Ritanserin 1 mg/kg; R_2: Ritanserin 2.5 mg/kg. See text for details. ★$p<0.05$–0.01 from respective V; +$p<0.05$–0.01 from respective saline; ●$p<0.05$ from respective V and R_2.

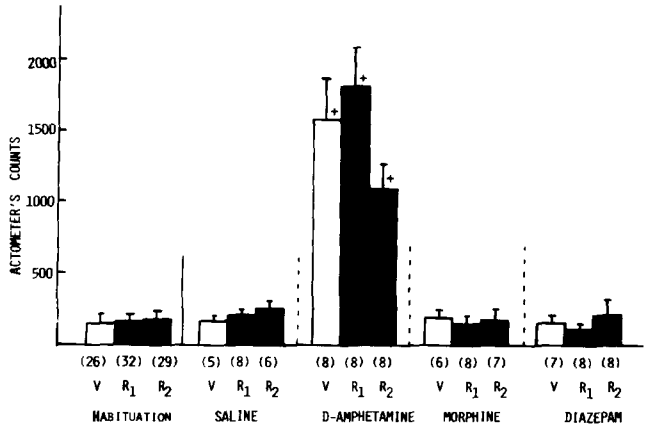

FIG. 2. Locomotor activity of animals pretreated with vehicle (V) or ritanserin (R_1: 1 mg/kg; R_2: 2.5 mg/kg) during a 15 min habituation period and during a 60 min period after the injection of d-amphetamine (1.5 mg/kg), morphine (2 mg/kg) or diazepam (1 mg/kg). Ritanserin was administered SC 1 hr before the animal being placed in the actometer. Each drug was injected after the 15 min habituation time. See text for details. +$p<0.01$ from respective saline. Number of animals in brackets.

period, an observer who was not aware of the treatment administered to the rat was recording the number of entries into and the time spent in the open and in the enclosed arms. Both the wooden arena and the maze were thoroughly wiped clean after each trial.

Recorded data were transformed to the percentage of entries into or time spent on the open arms (open/total × 100) and they were subjected to two-way ANOVA. When an increase in open arm entries parallelled the increase in total arm entries an analysis of covariance was performed to determine to what extent the increase in open arm entries was independent of any effect on closed arm entries.

RESULTS

Conditioned Place Preference (CPP)

The data are presented in Fig. 1. It can be seen that the preference of the animals for the drug associated side (Table 1) is increased following conditioning with amphetamine, morphine or diazepam. This effect appears to be influenced by ritanserin pretreatment. On its own ritanserin does not appear to have an effect on CPP. Both doses of ritanserin tested failed to change significantly the preference of the animals for the drug associated side. However, the group of 1 mg/kg ritanserin-vehicle differs significantly from the vehicle-vehicle and the 2 mg/kg ritanserin-vehicle groups ($p<0.05$).

Specifically, ANOVA on the amphetamine data revealed a significant effect of amphetamine as compared to controls, $F(1,37)=13.59$, $p<0.01$, and an effect of ritanserin pretreatment, $F(2,37)=3.67$, $p<0.05$.

ANOVA on the morphine data revealed an effect of morphine, $F(1,34)=28.46$, $p<0.01$, and a morphine × ritanserin interaction, $F(2,34)=3.3$, $p<0.05$. Post hoc comparisons revealed a difference between vehicle-morphine and ritanserin (2 mg/kg) -morphine groups, $t(13)=2.26$, $p<0.05$. The ritanserin (2 mg/kg) -morphine group differs significantly from the respective ritanserin-vehicle group, $t(11)=2.32$, $p<0.05$, i.e., it exhibits CPP to morphine. This shows that ritanserin (2 mg/kg) attenuates rather than blocks the effect of morphine on CPP.

ANOVA on the diazepam data yielded a diazepam effect, $F(1,36)=6.29$, $p<0.05$, and a diazepam × ritanserin interaction effect, $F(2,36)=3.49$, $p<0.05$. This is due to the fact that the vehicle-diazepam group differs from its respective control, i.e., vehicle-vehicle, $t(10)=2.63$, $p<0.05$, while both ritanserin-diazepam groups are not significantly different from the respective ritanserin-vehicle-treated groups. Moreover, the 2 mg/kg ritanserin-diazepam group differs

TABLE 1

TIME SPENT ON THE DRUG ASSOCIATED SIDE BEFORE CONDITIONING

	Saline	d-Amphetamine	Morphine	Diazepam
Vehicle	225.5 ± 63.3	264.5 ± 29.5	147.85 ± 13.0	189.25 ± 36.8
Ritanserin 1 mg/kg	153.3 ± 17.8	193.7 ± 33.3	258.60 ± 44.2	335.77 ± 40.4
Ritanserin 2 mg/kg	241.5 ± 28.9	224.2 ± 39.6	311.50 ± 49.2	279.44 ± 33.4

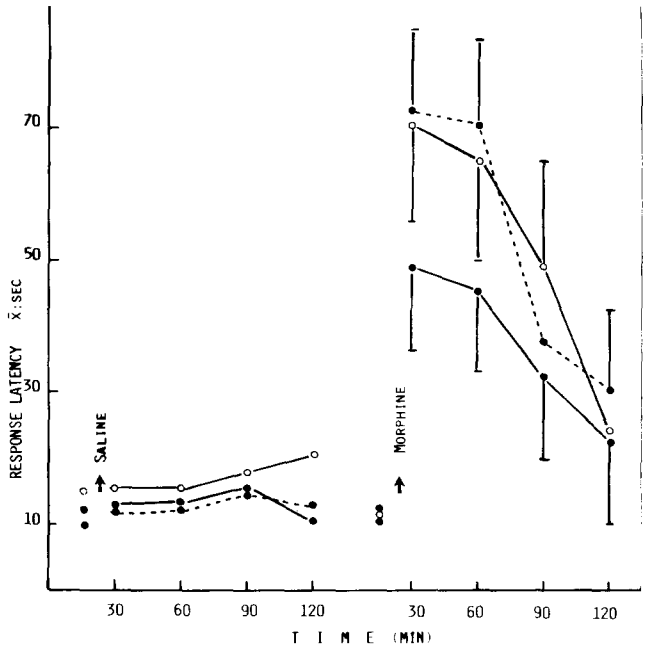

FIG. 3. Response latency (means±SEM) to painful thermal stimulus of rats pretreated with vehicle (○—○) or ritanserin (R_1: 1 mg/kg, ●---●; R_2: 2.5 mg/kg, ●—●) one hr before the injection of saline (1 ml/kg) or morphine (30 mg/kg). N=6–8/group.

from the vehicle-diazepam group, $t(13)=2.32$, $p<0.05$.

The results indicate that the amphetamine (1.5 mg/kg) and morphine (2.0 mg/kg) CPP is blocked and attenuated respectively by a high dose of ritanserin and that the diazepam (1.0 mg/kg) CPP is totally blocked by both doses of ritanserin.

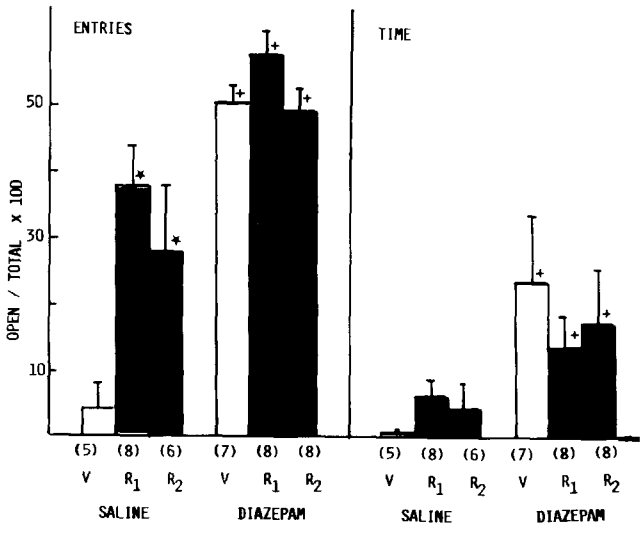

FIG. 4. Percentage of entries into and of time spent on the open arms of the elevated plus-maze (EPM) by rats pretreated with vehicle (V) or ritanserin (R_1: 1 mg/kg; R_2: 2.5 mg/kg) 1 hr before the injection of saline or diazepam (1 mg/kg). Number of animals in brackets. ★$p<0.05$–0.01 from respective V; +$p<0.05$–0.01 from respective saline.

TABLE 2
TOTAL NUMBER OF ARM ENTRIES

	Saline	Diazepam
Vehicle	3.2 ± 0.8 (5)	9.7 ± 1.7* (7)
Ritanserin 1 mg/kg	5.1 ± 1.2 (8)	7.7 ± 1.9 (8)
Ritanserin 2 mg/kg	4.3 ± 1.8 (6)	11.2 ± 2.37* (8)

Data are means (±SEM). Number of animals in brackets.
*$p<0.05$–0.01 from respective saline-injected.

Locomotor Activity

The effect of ritanserin on spontaneous and drug-induced locomotion is shown in Fig. 2. It is obvious that ritanserin failed to influence the locomotor activity of the animals or the locomotor response to an injection of amphetamine, morphine, or diazepam. There was only the effect of amphetamine that appeared significant, $F(1,93)=51.88$, $p<0.01$, following ANOVA performed on the data.

Morphine Analgesia

Figure 3 depicts the response latency to a thermal stimulus of vehicle or ritanserin pretreated animals, challenged with saline or morphine (30 mg/kg, IP).

Rats injected with morphine showed a time-dependent, $F(3,117)=10.36$, $p<0.01$, increase, $F(1,117)=20.47$, $p<0.01$, in response latency. Ritanserin failed to influence the sensitivity of animals to painful stimulus and the analgesic action of morphine after 2.5 mg/kg ritanserin did not reach significance.

Diazepam Exploration of the Elevated + Maze (EPM)

The data in Fig. 4 show that the percentage of time spent on the open arms is increased by diazepam, diazepam + ritanserin, but not by ritanserin-treated animals. ANOVA of the data revealed a significant effect of diazepam, $F(1,37)=6.45$, $p<0.05$.

Figure 4 also shows that the percentage of open arm entries (open/total × 100) is increased following ritanserin, diazepam and the combination thereof. ANOVA of the data revealed an effect of diazepam, $F(1,37)=42.9$, $p<0.01$, a ritanserin effect, $F(2,37)=7.07$, $p<0.01$, and a ritanserin × diazepam interaction, $F(2,37)=3.69$, $p<0.05$. This is due to a difference between the saline, $F(2,18)=15.25$, $p<0.01$, but not between the diazepam groups.

The increase in open arm entries parallelled the increase in total number of entries in the diazepam treated groups (Table 2). Analysis of covariance (open arm entries: dependent variable; closed arm entries: covariate) revealed a significant effect of diazepam-vehicle, $F(1,10)=22.15$, $p<0.01$, and for the ritanserin 1 mg/kg + diazepam groups indicating that for those two groups the increase in open arm entries (antianxiety effect) was independent of any effect on locomotion.

In general, the results show the ritanserin has by itself an antianxiety effect which is not additive to that of diazepam.

DISCUSSION

Our results clearly show that ritanserin antagonizes the effect of amphetamine, morphine and diazepam on place conditioning. As only one dose of each "rewarding" drug was used, it could be argued that the antagonism refers only to the doses selected. However, on the basis of previous dose response experiments [21, 31, 33], the chosen doses were suitably effective on CPP. The antagonistic action appeared to be dose-dependent as the lowest dose used was ineffective in amphetamine and morphine studies and it was less effective in diazepam experiments. Also it was limited to place conditioning as the antagonism was not apparent on amphetamine hyperlocomotion, morphine analgesia or diazepam anxiolysis, characteristic behavioral effects ascribed to psychostimulants, opiates and minor tranquilizers respectively.

As it is claimed that ritanserin is a selective 5-HT_2 receptor blocker [11], and assuming that CPP reflects the rewarding properties of the inducing drug [29], the attenuation of drug-induced CPP by ritanserin suggests that 5-HT_2 receptors are involved in drug reinforcement processes. This is consistent with the hypothesis that 5-HT subserves some function of drug seeking behavior, formulated on the basis of amphetamine studies [14, 17, 18]. However, the results of this and previous studies taken together do not offer a conclusion as to whether 5-HT plays a facilitatory or inhibitory role on the drugs' rewarding properties. For instance, blockade of amphetamine CPP was observed following treatments which increase [13] or decrease (this study) 5-HT transmission. Similarly, attenuation of amphetamine self administration was observed after treatment with drugs bearing 5-HT agonistic or antagonistic properties [14]. Furthermore, decreased morphine intake [26] or decreased morphine CPP (this study) was seen following increased or decreased availablility of 5-HT at receptor sites respectively.

The observed reduction of drug-induced CPP by ritanserin may be attributed either to blunted appetitive or to unmasked aversive properties of the studied drugs brought about following 5-HT_2 receptors blockade. The latter possibility seems unlikely as the animals following conditioning did not avoid the ritanserin + drug associated compartment; they simply did not change their preference for it. The attenuation of drug CPP could also be ascribed to unpleasant effects of ritanserin which would have masked the positive effects of amphetamine, morphine and diazepam. This also appears very unlikely, as in our hands ritanserin did not produce place aversion. The slight, nonsignificant aversion to the conditioned side, shown by two control groups, may be due to a certain discomfort felt by the animals associated with skin ulcers produced by the tartaric acid injections (vehicle).

In fact, ritanserin showed an anxiolytic effect on the elevated plus maze test, reported also in previous studies using other procedural approaches [6]. Such an effect could have influenced CPP by reducing the aversive value of some environmental stimuli. In this case, increased, rather than decreased drug-induced CPP following ritanserin would have been expected.

Another interpretation of our results would suggest that ritanserin may have not blocked the appetitive properties, but other behavioral effects of the drugs under investigation which can be conditioned and then elicited by the relevant environmental stimuli [1, 22, 36]. There are two points arguing against this interpretation. In the first place, recent findings questioned the early postulation that the motor activating properties of a drug contributes to the CPP [35]. Secondly, in this study, ritanserin failed to influence significantly specific behavioral effects of each studied drug, i.e., locomotion, analgesia, anxiolysis. However, as the mentioned behaviors were studied outside the CPP setting, the possibility remains that ritanserin may have influenced the conditioning of those effects.

From the above discussion it is inferred that 5-HT_2 receptors may mediate some of the rewarding properties of amphetamine, morphine and diazepam. To what extent those receptors are directly related to drug-induced reward it is not clear from our study. It is well known that injections of amphetamine, morphine or diazepam are associated with alterations of 5-HT transmission [9, 16, 28].

However, the attenuation of drug-induced CPP following 5-HT_2 receptor blockade may not be the result of the primary affected 5-HT transmission. It may rather be due to other secondarily influenced neurotransmitter systems. This speculation is not unreasonable in view of the ineffectiveness of the low dose of ritanserin to block amphetamine- and morphine-induced CPP. Previous studies have reported inhibition of clearly serotonin-mediated behaviors (LSD discrimination) by doses of ritanserin lower than 1 mg/kg [6] used in this study. In favor of this hypothesis is also the finding that 5-HT_2 binding sites are localized on GABAergic neurons [15]. This would have an implication specifically in diazepam-ritanserin interactions inasmuch as the minor tranquilizers, especially benzodiazepines, act by altering the GABAergic neurotransmission [7]. Furthermore, 5-HT-DA interactions have been repeatedly reported on behavioral level [5, 10, 12]. This has also to be taken into consideration as dopamine has been shown to play a critical role for psychostimulant- [20, 31, 34], opiate- [3,32] and diazepam- [30] induced CPP.

Whatever the mechanism by which 5-HT_2 receptor blockade disrupts the drug-induced CPP is, our results suggest the 5-HT does indeed participate in the perception of appetitive properties of the drugs of abuse. The understanding of the mechanism involved warrants further investigation which would probably lead to clinically exploitable findings.

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