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5HT-2 mediation of acute behavioral effects of hallucinogens in rats

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Abstract. In rats tested during their first exposure to a Behavioral Pattern Monitor chamber, acute injections of the 5HT-2 agonists mescaline, quipazine, 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-methylamphetamine (DOM), or 2,5-dimethoxy-4-ethylamphetamine (DOET) produced an inhibition of locomotor and investigatory behavior during the first 30 min of the test session. This suppression of exploratory behavior was attenuated when rats were familiarized with the testing chamber prior to the administration of DOI. Hence, as previously observed with both LSD and DOM, 5HT-2 agonists appear to potentiate the normal neophobic reaction to a novel environment. The mixed 5HT-1 and 5HT-2 agonist 5-methoxy-N,N-dimethyltryptamine (5MeODMT) also produced a decrease in activity when animals were tested in the novel environment. However, as previously found with 5HT-1A agonists, this effect was unchanged when animals were tested in the familiar environment and may therefore reflect a generalized sedation. The receptor specificity of these differential effects of 5HT-1 and 5HT-2 agonists in this paradigm was tested by assessing the ability of selective 5HT-2 antagonists to block the effects of the agonists. A dose of the 5HT-2 antagonist ketanserin which had no effect by itself significantly reduced the behavioral effects of mescaline, DOM, and quipazine. Similarly, the selective 5HT-2 antagonist ritanserin blocked the effect of quipazine. In contrast, ketanserin had no significant effect on the suppression of activity produced by the 5HT-1A agonist 8-hydroxy-2(di-n-propylamino)tetralin (8OHDPAT). These results demonstrate that the behavioral effects of 5HT-1 and 5HT-2 agonists can be differentiated both phenomenologically and pharmacologically within a single paradigm. The findings provide further support for the hypothesis that the potentiation of neophobia produced by hallucinogens in rats is attributable to their agonist actions at 5HT-2 receptors.

Key words: Serotonin – Mescaline – Quipazine – DOI – LSD – Locomotor activity

Previous studies using a Behavioral Pattern Monitor (BPM) have defined a behavioral profile in rats that has been suggested to provide a model for the behavioral effects of acute administrations of hallucinogens in humans (Adams and Geyer 1985a). Specifically, LSD and all other hallucinogens tested produce a suppression of locomotor and investigatory responses that is limited to the initial exploratory phase of activity exhibited by rats tested in a novel environment. With either LSD or DOM, this initial suppression of exploratory behavior was absent when animals were tested in a familiar environment (Adams and Geyer 1985a, b). This behavioral profile was interpreted as reflecting a potentiation of neophobia, due to an increased responsiveness to stimuli associated with handling (Geyer and Light 1979) and the introduction of the animal to the novel environment (Adams and Geyer 1982). While both phenylethylamine and indoleamine hallucinogens consistently produce these effects, a variety of other psychoactive drugs have been shown to produce different effects in this paradigm (Geyer et al. 1986; Gold et al. 1988; Mittman and Geyer 1989), including inactive congeners of DOM (Geyer et al. 1979) or LSD (Adams and Geyer 1985c). In keeping with the psychological effects of hallucinogens in humans, tolerance occurs rapidly to the effects of LSD in this paradigm (Adams and Geyer 1985a).

The identification of multiple subtypes of serotonin binding sites in brain has revitalized interest in the traditional hallucinogens in part because many of them appear to be among the most selective of the compounds having agonistic activity at 5HT-2 sites (Titeler et al. 1988). This selectivity and the ability of putative 5HT-2 antagonists to block some behavioral effects of hallucinogens in animals have led to the hypothesis that the hallucinogenic actions of these drugs derive from their actions as agonists at 5HT-2 receptors. Also, it is known that 5HT-1 agonists do not mimic the effects of LSD on a discriminative stimulus task, while 5HT-2 antagonists were able to block the effects of LSD (Cunningham and Appel 1987). However, most of the behavioral paradigms used previously to assess the relative involvement of serotonin receptor subtypes in hallucinogen actions require the repeated administration of the hallucinogen. Given the rapid tolerance to these drugs in humans, such paradigms may not reflect the acute effects of the hallucinogens that are presumably most relevant to the subjective effects of these drugs in humans.

Accordingly, the present series of experiments was designed to assess the hypothesized involvement of 5HT-2 receptors in the behavioral effects of hallucinogens using a paradigm that is specifically sensitive to the acute effects of these drugs. A number of 5HT-2 agonists were studied

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to test the hypothesis that 5HT-2 activation underlies the potentiation of neophobic responses in a novel, but not familiar, environment as previously observed with hallucinogens such as LSD and DOM. First, the dose-response curve for each compound was determined in the novel environment paradigm. It was predicted that naive animals would show a dose-dependent decrease in behavioral measures in response to 5HT-2 agonists in this novel environment. Specifically, behavioral effects similar to those produced by LSD were expected, including a decrease in the number of crossovers and center entries, as well as a decrease in holepokes and a suppression of rearings. Subsequently, other animals were familiarized with the BPM chamber on two occasions before receiving the drug upon their third exposure to the test environment. It was predicted that animals which had been exposed to the test chamber twice prior to receiving a particular agonist would exhibit attenuated neophobic effects in this familiar environment paradigm.

Finally, to address the issue of specificity of the action of these 5HT-2 agonists, antagonists specific to the 5HT-2 binding site were used as pretreatments prior to behavioral testing with a 5HT-2 agonist. The 5HT-2 antagonists employed were ketanserin and ritanserin (Van Neuten et al. 1981; Janssen and Laduron 1985). It was expected that pretreatment with a 5HT-2 antagonist would attenuate the suppressive behavioral effects of quipazine, DOI, DOM, and mescaline, but would not attenuate the effects of 5HT-1A agonists such as 8-hydroxy-2(di-n-propylamino) tetralin HBr (8OHDPAT; Arvidsson et al. 1981).

Materials and methods

Drugs

The behavioral effects of the following compounds were examined in this study: mescaline sulfate (Sigma Biochemicals, St. Louis, MO); 2-(1-piperazino)quinoline maleate (quipazine; Miles Laboratories, West Haven, CT); 2,5-dimethoxy-4-iodoamphetamine HCl (DOI; Research Biochemicals Inc., Natick, MA); 2,5-dimethoxy-4-ethylamphetamine HCl (DOET; NIDA, Rockville, MD); 2,5-dimethoxy-4-methylamphetamine HCl (DOM; NIDA, Rockville, MD); 5-methoxy-N,N-dimethyltryptamine (5MeODMT; Sigma Biochemicals, St. Louis, MO); 8-hydroxy-2(di-n-propylamino) tetralin hydrobromide (8OHDPAT; Research Biochemicals Inc., Natick, MA); ketanserin tartrate and ritanserin (Janssen Pharmaceuticals, Piscataway, NJ). All compounds were dissolved in isotonic saline and injected subcutaneously in a 1 ml/kg volume. Agonists were administered 10 min prior to the testing session; for the interaction studies, pretreatment with the antagonist occurred 30 min prior to the administration of the agonist.

Animals

Male Sprague Dawley-derived rats were obtained from Simonsen Laboratories, Gilroy, CA, and from Bantin and Kingman Laboratories, Fremont, CA, at a weight of 300–350 g. Animals were housed in pairs, maintained on a reverse light/dark cycle (lights on from 7 p.m. to 7 a.m.), and tested during their dark cycle. Each group was allowed a minimum of 5 days for acclimation to the colony room before beginning behavioral testing. Food and water were available ad libitum except during behavioral testing. Independent treatment groups contained 9–12 rats, each used only once. All groups were counterbalanced for testing order, the time of day during which animals were tested, and chamber assignment.

Behavioral pattern monitor (BPM)

A more detailed description of the apparatus is available elsewhere (Geyer et al. 1986). Briefly, each of the eight BPM chambers is a 30.5×61 cm box which contains three floor holes and seven wall holes, each equipped with an infrared beam. Each chamber is also criss-crossed with infrared beams 2 cm above the floor. The area of the chamber is divided into eight 15 cm squares, and movements between these squares are defined as crossovers. Regions of the BPM have been displayed graphically elsewhere (Geyer et al. 1986), and are used primarily to define entries into the corners and center of the chamber. Rearings against the wall of the chamber were detected by a touch-plate 15 cm above the floor. The animal's successive holepokes and rearings were monitored and stored on disk, as were its positions in an X-Y coordinate system with a resolution of 0.1 s in time and 3.8 cm in space.

Testing procedure

For each behavioral testing session, animals were brought to the laboratory under black cloth in groups of eight, 1 h prior to the start of the session. Following the appropriate pharmacological manipulation, each animal was placed into a chamber. Data were collected for 1 h, after which each animal was removed and the testing chambers thoroughly cleaned before the testing of the next group of animals.

Behavioral effects in a novel environment. Naive rats were given a subcutaneous injection of either saline or a single dose of an agonist, for example, mescaline (3.1, 6.2, 12.4 or 24.8 mg/kg), 10 min prior to being placed in the BPM for the 1 h test session. Animals also were tested in this novel environment paradigm following administration of each of the following compounds: quipazine (0.4, 1.0 and 2.5 mg/kg); DOI (0.03, 0.09, 0.27, 0.81 and 2.40 mg/kg); and DOET (0.5 mg/kg). Each drug series included its own saline-injected control group. In the case of 5MeODMT, two dose-response studies were conducted, one with the lower doses (0, 0.125, 0.25 and 0.50 mg/kg) and the other with the higher doses (0, 0.5, 1.0 or 2.0 mg/kg). There were no significant inter-group differences between the two saline control groups or the two groups tested with 0.5 mg/kg 5MeODMT. Thus, the two studies were combined for the statistical analysis.

Behavior in a familiar environment. In the familiar environment paradigm, animals were tested in the BPM on three occasions at 48-h intervals, but only injected with the drug prior to their third exposure to the BPM chamber. This sequence was followed in testing animals for their behavioral response to DOI (0.27 or 0.81 mg/kg) and 5MeODMT (0.25 mg/kg).

Behavioral effects of ketanserin pretreatment on 5HT-2 activation. To confirm the role of 5HT-2 receptors in the mediation of the behavioral effects observed, the 5HT-2 antagonist ketanserin (Leysen et al. 1981) was used as a pretreat-

ment prior to an injection of one of the 5HT agonists studied. A dose-effect curve was determined for the 5HT-2 antagonist ketanserin using the following doses: 0, 0.016, 0.40, 1.0 and 2.5 mg/kg. None of these doses of ketanserin had significant effects on the behaviors monitored (data not shown). Based on these results, and evidence of behavioral effects of ketanserin in other paradigms (Geyer and Tapson 1988), a dose of 1.0 mg/kg ketanserin was chosen as the pretreatment to be combined with the following agonists: mescaline (10 mg/kg); DOM (0.5 mg/kg); quipazine (0.4 mg/kg); and 8OHDPAT (0.3 mg/kg). These doses were selected to be near the midpoint of the ascending limb of the dose-effect function for each of the agonists in this paradigm (Table 1; Adams and Geyer 1985b; Mittman and Geyer 1989). Ritanserin (2.0 mg/kg), a more specific 5HT-2 antagonist (Goodwin and Green 1985), was used as a pretreatment in combination with a higher dose of quipazine (1.0 mg/kg).

Statistical analyses

Raw data were translated into frequencies and durations of events cumulated over 10-min epochs. The data were then transmitted to the University's VAX computer for statistical analyses, using the Biomedical Computer Programs (BMDP; Dixon 1988). Mixed-design analyses of variance (ANOVAs) were performed for selected variables using BMDP2V, with drug treatment as the between-subjects factor and 10 min or half-hour blocks as the within-subjects factor. To determine the influence of familiarity in the test environment, an experience-by-drug two-factor ANOVA on the initial 30 min of the test session was used. Examination of interactions between an antagonist and an agonist used a repeated measures (10 min or half-hour blocks) three-factor mixed ANOVA, with the pretreatment and treatment as between-subjects factors. Post-hoc comparisons were performed for main effects and interactions using pair-wise ANOVAs, Dunnett's *t*-test, or Tukey's test, as appropriate. The criterion for significance was set at $P < 0.05$.

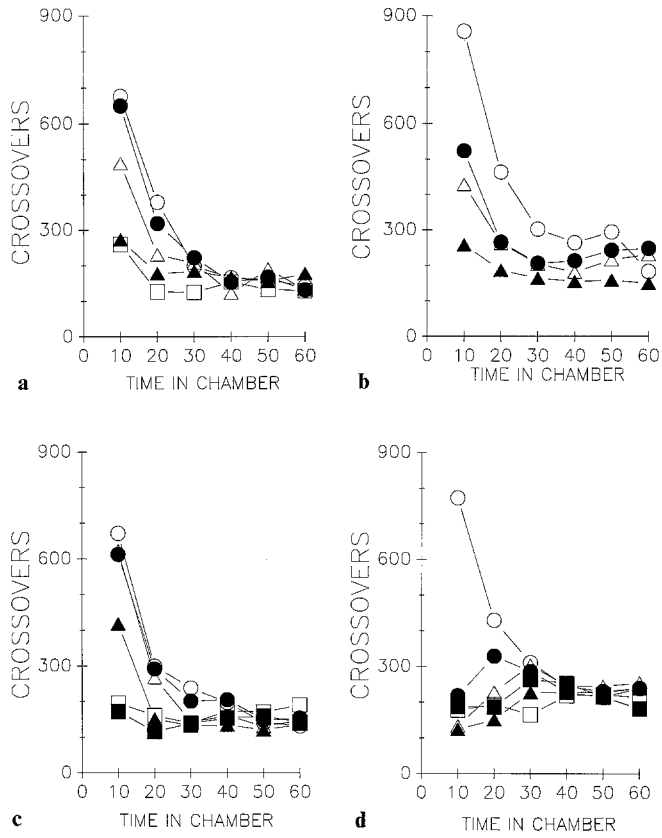

Fig. 1a–d. Dose-dependent effects of the 5HT agonists **a** mescaline (MESC), **b** quipazine (QUIP), **c** DOI, and **d** 5MeODMT, on crossovers are shown as group means for successive 10 min intervals for the 1-h test session. **a** ○—○ Saline; ●—● Mesc 3.1; △—△ Mesc 6.2; ▲—▲ Mesc 12.4; □—□ Mesc 24.8. **b** ○—○ Saline; ●—● Quip 0.4; △—△ Quip 1.0; ▲—▲ Quip 2.5. **c** ○—○ Saline; ●—● DOI 0.03; △—△ DOI 0.09; ▲—▲ DOI 0.27; □—□ DOI 0.81; ■—■ DOI 2.40. **d** ○—○ Saline; ●—● 5MeODMT 0.125; △—△ 5MeODMT 0.25; ▲—▲ 5MeODMT 0.50; □—□ 5MeODMT 1.0; ■—■ 5MeODMT 2.0

Results

The novel environment paradigm

Crossovers. The dose-dependent decreases in crossovers in response to mescaline, quipazine, DOI and 5MeODMT are shown in 10-min intervals for the hour-long session (Fig. 1). As expected (Geyer et al. 1986), similar patterns of habituation across time were evident for other behavioral measures such as holepokes and rearings (data not shown). Significant dose-dependent behavioral effects in the novel environment paradigm were most notable in the first 30 min of the test session for all variables. Thus, group means for crossovers, center duration, holepokes and rearings are presented in Table 1 for this first half hour. The highest of each of the multiple doses studied for each agonist resulted in at least a 51% decrease in crossovers during the first half of the session (Table 1).

The possibility that the failure to obtain a dose-dependent effect with 5MeODMT due to a ceiling effect was considered and a lower series of doses than that reported in Table 1 was studied. Animals were tested after subcutaneous injection of 0, 0.1, 0.03, 0.06 or 0.125 mg/kg 5MeODMT (data not shown). While the 0.01 and 0.03 doses did not affect crossovers, an intermediate decrease in crossovers was obtained at the 0.06 dose that was limited to the first 10 min.

Center duration. Time spent in the center of the test chamber was greatly decreased during the first half of the test session by all agonists (Table 1). In fact, in the first 30 min of testing, drug-treated animals spent as few as 15 s in the center of the chamber, while controls typically spent more than 2 min in the center (Table 1). Drug-treated animals spent significantly more time in the corners of the holeboard test chamber than did their saline counterparts during the first 30 min (data not shown). This effect was observed with quipazine, DOI, mescaline, DOET, and 5MeODMT.

Holepokes and rearings. Investigatory behaviors such as holepokes and rearings were greatly attenuated during the first half of the test session in response to mescaline, quipazine, DOI and DOET, even at the mid-range doses (Table 1) and virtually abolished in the 5MeODMT-treated animals. At the higher doses studied, rearings were near zero after

Table 1. Effects of serotonin agonists in a novel environment. Shown are means ± SEM for the initial 30 min

Drug	*N*	Crossovers	Center duration	Holepokes	Rearings
Mescaline					
0	9	1265 ± 55	102.1 ± 13.2	108 ± 11	130 ± 11
3.1	10	1190 ± 85	122.0 ± 18.5	102 ± 11	110 ± 8*
6.2	9	926 ± 64	73.8 ± 14.0	79 ± 12*	79 ± 12*
12.4	9	530 ± 136*	26.2 ± 7.1*	41 ± 4*	25 ± 5*
24.8	10	510 ± 54*	17.6 ± 5.6*	27 ± 3*	30 ± 8*
$F(4, 32) =$		13.22	12.53	14.22	39.90
$P <$		0.0001	0.0001	0.0001	0.0001
Quipazine					
0	9	1587 ± 41	157.4 ± 20.0	117 ± 8	79 ± 8
0.4	10	994 ± 150*	48.6 ± 9.9	56 ± 10*	41 ± 9*
1.0	10	892 ± 159*	37.2 ± 12.5*	44 ± 8*	27 ± 4*
2.5	10	606 ± 74*	29.2 ± 8.0*	27 ± 4*	3 ± 1*
$F(3, 35) =$		11.30	20.20	23.29	33.47
$P <$		0.0001	0.0001	0.0001	0.0001
DOI					
0	10	1207 ± 46	113.5 ± 15.2	135 ± 16	128 ± 7
0.03	10	1104 ± 83	108.4 ± 10.7	114 ± 16	101 ± 10
0.09	10	1031 ± 44	103.7 ± 21.2	99 ± 11	84 ± 6
0.27	10	699 ± 79*	54.5 ± 30.2	42 ± 4	55 ± 23
0.81	10	494 ± 29*	10.5 ± 2.1*	21 ± 2*	4 ± 2*
2.4	10	426 ± 53*	58.1 ± 28.5	15 ± 3*	15 ± 3*
$F(5, 54) =$		31.88	3.94	24.17	23.25
$P <$		0.0001	0.005	0.0001	0.0001
DOET					
0	9	1385 ± 62	128.1 ± 28.1	125 ± 17	125 ± 7
0.5	9	701 ± 73*	22.4 ± 6.8*	32 ± 6*	13 ± 4*
$F(1, 16) =$		57.22	14.61	28.41	199.9
$P <$		0.0001	0.001	0.0001	0.0001
5MeODMT					
0	20	1512 ± 60	138.9 ± 14.0	114 ± 12	80 ± 9
0.125	10	832 ± 100*	65.0 ± 10.6*	83 ± 11	18 ± 7*
0.25	10	664 ± 85*	39.7 ± 8.5*	49 ± 8*	14 ± 5*
0.50	17	587 ± 57*	45.3 ± 11.7*	23 ± 4*	2 ± 2*
1.00	9	474 ± 49*	34.1 ± 19.5*	13 ± 2*	2 ± 1*
2.00	9	535 ± 103*	36.3 ± 19.9*	8 ± 2*	1 ± 0*
$F(5, 69) =$		36.31	9.99	22.34	27.89
$P <$		0.0001	0.0001	0.0001	0.0001

* $P < 0.05$. Center duration expressed in seconds

quipazine, DOI and 5MeODMT, and greatly reduced in frequency after mescaline (Table 1).

The familiar environment paradigm

As previously noted, dose-dependent behavioral effects in the novel environment paradigm were observed primarily in the first half of the test session. Hence, group means for crossovers are presented in Table 2 for this first half hour. Familiarization with the environmental stimuli of the test chamber altered the response of drug-treated animals to DOI, but not 5MeODMT.

DOI in the novel versus familiar environment paradigm. The 5HT-2 agonist DOI (0.27 and 0.81 mg/kg) significantly decreased the number of crossovers made by rats in the familiar environment as was previously observed under novel test conditions (Table 2). However, the fact that animals had previous experience with the test chamber also exerted a significant effect on their behavior, as described in more detail elsewhere (Adams and Geyer 1985a; Geyer et al. 1986). As predicted from the effects of LSD and DOM (Adams and Geyer 1985a, b), experience attenuated the decrease observed in the familiar environment in comparison to the decrease in crossovers observed in the novel environment in the first 30 min. This attenuation was reflected in a significant experience-by-drug interaction on crossovers (Table 2).

5MeODMT in the novel versus familiar environment paradigm. In the novel environment, 0.25 mg/kg 5MeODMT significantly decreased the number of crossovers made during the first 30 min of the session [$F(1, 22) = 63.53$, $P < 0.0001$]. The mixed 5HT-1/5HT-2 agonist 5MeODMT con-

Table 2. Crossovers made in novel or familiar environments: DOI vs 5MeODMT. Shown are means ± SEM for the initial 30 min

Novel environment			Familiar environment		
Treatment	*N*	Crossovers	Treatment	*N*	Crossovers
DOI					
Saline	10	1207 ± 45	Saline	10	826 ± 67
DOI 0.27	10	699 ± 79	DOI 0.27	11	545 ± 49
DOI 0.81	10	493 ± 29	DOI 0.81	11	557 ± 34
Experience		$F(1,56) = 13.10$, $P < 0.001$			
Drug		$F(2,56) = 47.09$, $P < 0.0001$			
Interaction		$F(2,56) = 8.62$, $P < 0.0005$			
5MeODMT					
Saline	10	1527 ± 81	Saline	12	1081 ± 73
5MeODMT 0.25	10	664 ± 85	5MeODMT	12	400 ± 44
Experience		$F(1,40) = 25.03$, $P < 0.0001$			
Drug		$F(1,40) = 118.23$, $P < 0.0001$			
Interaction		$F(1,40) = 1.64$, ns			

tinued to exert this inhibition on the number of crossovers made in the familiar environment (Table 2), an effect unattenuated by experience. Hence, the experience-by-drug interaction was not significant. This same decrease was also observed in other behavioral measures such as holepokes and rearings in both novel and familiar test conditions (data not shown).

Pharmacological specificity of 5HT-2 agonist effects

The specificity of 5HT-2 involvement in the production of the behavioral effects observed was tested by pretreating animals with the 5HT-2 antagonist ketanserin (1.0 mg/kg) prior to behavioral testing with either mescaline, DOM, quipazine, or 8OHDPAT. The group means and statistical values are given in Table 3 for crossovers, time spent in the center of the test chamber, and investigatory holepokes and rearings made in the first 30 min. In the DOM/quipazine experiment, the ketanserin pretreatment had no significant effect by itself on the amount of locomotor activity, as indexed by crossovers, but did decrease center duration and holepokes (Table 3). However, these effects were not observed consistently, as indicated by the results from the mescaline/8OHDPAT experiment, and were not corroborated by the results of the ritanserin study insofar as ritanserin had no significant effects by itself (Table 3). Pretreatment with the 5HT-2 antagonist effectively attenuated the inhibitory effects of DOM, mescaline, and quipazine at the doses studied. In contrast, ketanserin had no effect on the behavioral effects of 8OHDPAT.

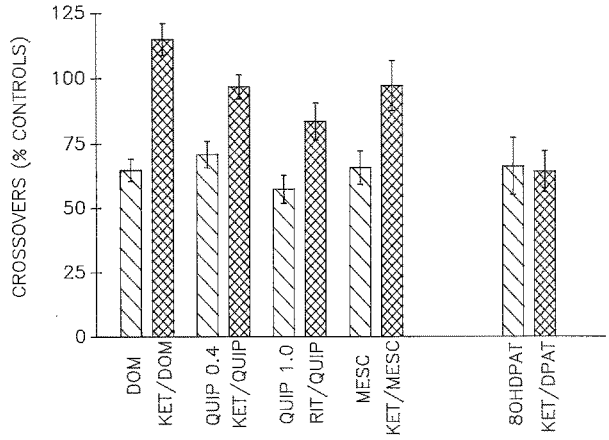

Fig. 2. Group mean crossovers ± SEM for the first 30 min are shown as per cent of corresponding pretreatment controls

Ketanserin/DOM. Studies of the effects of ketanserin-pretreatment on the behavioral effects of 0.5 mg/kg DOM and of 0.4 mg/kg quipazine were conducted concurrently, and therefore share the same saline-saline and ketanserin-saline control groups. With regard to the combination of ketanserin and DOM, significant pretreatment-by-drug interactions on crossovers were found (Table 3). Significant interactions were also evident in the amount of time spent in the center of the test chamber as well as for measures of investigatory responses such as holepokes and rearings in the first part of the session. Ketanserin pretreatment restored DOM-injected animals to the level of activity of controls (Fig. 2). In fact, post-hoc analyses revealed no differences between saline-saline animals and ketanserin-pretreated, DOM-injected animals on any of the measures studied.

Ketanserin/quipazine 0.4 mg/kg. As with DOM, 1.0 mg/kg ketanserin blocked the behavioral effects of 0.4 mg/kg quipazine. Significant pretreatment-by-drug interactions were observed in the first half-hour for crossovers, center duration, and investigatory responses such as holepokes and rearings (Table 3). These interactions all reflected the significant reduction by ketanserin of the behavioral effects of quipazine.

Ritanserin/quipazine 1.0 mg/kg. Very similar effects were observed in this ritanserin-quipazine study as with the ketanserin-quipazine experiment (Table 3). There were significant pretreatment-by-drug interactions for crossovers, center duration, holepokes and rearings during the first 30 min, indicative of the ability of 2.0 mg/kg ritanserin to block the effects of 1.0 mg/kg quipazine.

Ketanserin/mescaline. Studies of the effects of ketanserin pretreatment on the behavioral effects of 8OHDPAT and mescaline were conducted concurrently, and therefore shared the same saline-saline and ketanserin-saline groups. With the combination of 1.0 mg/kg ketanserin and 10 mg/kg mescaline, there were also significant pretreatment-by-drug interactions on crossovers made during the first half of the session as well as on rearings, but not center duration or holepokes (Table 3). No interaction was found for these latter two measures because this dose of mescaline failed

Table 3. Effects of pretreatment with 5HT-2 antagonists on 5HT agonist action. Shown are means ± SEM for the initial 30 min

Treatment	*N*	Crossovers	Center dur.	Holepokes	Rearings
Saline/Saline	10	1451 ± 46	180.5 ± 13.9	125 ± 9	117 ± 11
Ketanserin/Saline	10	1245 ± 55	94.9 ± 18.4[a]	90 ± 9[a]	111 ± 6
Saline/DOM	10	940 ± 62[a, b]	92.3 ± 24.5[a]	45 ± 5[a, b]	34 ± 7[a, b]
Ketanserin/DOM	10	1429 ± 76[c]	160.6 ± 31.5[c]	119 ± 14[c]	99 ± 13[c]
Interaction	$F(1, 36) =$	5.36	11.12	31.60	13.91
	P	< 0.05	< 0.005	< 0.0001	< 0.001
Saline/QUIP 0.4	10	1027 ± 76[a]	58.6 ± 12.1[a]	58 ± 5[a]	40 ± 7[a]
Ketanserin/QUIP	10	1205 ± 57[a, c]	121.8 ± 15.0[a, c]	96 ± 12[c]	109 ± 7[c]
Interaction	$F(1, 36) =$	10.42	24.45	16.35	21.60
	P	< 0.005	< 0.0001	< 0.0005	< 0.0001
Saline/Saline	12	1468 ± 62	136.9 ± 19.6	120 ± 14	118 ± 9
Ritanserin/Saline	12	1367 ± 70	101.6 ± 16.1	95 ± 8	98 ± 9
Saline/QUIP 1.0	12	842 ± 80[a]	55.8 ± 18.5[a]	35 ± 8[a, b]	9 ± 3[a]
Ritanserin/QUIP	12	1142 ± 96[a, b, c]	113.3 ± 26.5[c]	71 ± 7[a, c]	57 ± 10[a, b, c]
Interaction	$F(1, 44) =$	6.63	5.10	9.64	17.61
	P	< 0.05	< 0.05	< 0.005	< 0.0001
Saline/Saline	10	1043 ± 77	138.7 ± 32.6	98 ± 13	127 ± 9
Ketanserin/Saline	10	889 ± 78	86.1 ± 19.4	94 ± 15	99 ± 9
Saline/MESC	10	686 ± 71[a]	68.5 ± 16.3	75 ± 10	78 ± 11[a]
Ketanserin/MESC	10	864 ± 84[c]	86.5 ± 15.4	80 ± 13	88 ± 6[a]
Interaction	$F(1, 36) =$	4.62	2.55	0.11	4.42
	P	< 0.05	ns	ns	< 0.05
Saline/8OHDPAT	10	691 ± 115[a]	12.2 ± 5.6[a]	13 ± 2[a]	3 ± 2[a, b]
Ketan/8OHDPAT	10	571 ± 96[a]	6.0 ± 2.3[a, b]	11 ± 2[a, b]	3 ± 1[a, b]
Drug	$F(1, 36) =$	14.78	28.83	72.06	310.51
	P	< 0.0005	< 0.0001	< 0.0001	< 0.0001
Interaction	$F(1, 36) =$	0.04	1.45	0.02	4.82
	P	ns	ns	ns	< 0.05

[a] Significantly different from Saline/Saline controls
[b] Significantly different from Pretreatment/Saline controls
[c] Significantly different from Saline/Drug animals

ns = non-significant interaction

Doses (mg/kg): ketanserin 1.0; ritanserin 2.0; DOM 0.5; QUIP 0.4 and 1.0; mescaline 10.0; 8OHDPAT 0.3. Center duration expressed in seconds

to have significant effects on these measures in this experiment.

Ketanserin/8OHDPAT. 8OHDPAT produced behavioral effects similar to those previously described for 5MeODMT (Table 1) and primarily in the first half of the session. The effects observed with 0.3 mg/kg 8OHDPAT by itself were significant, replicating the observations of Mittman and Geyer (1989). However, unlike the effects of the 1.0 mg/kg ketanserin pretreatment on the response to 5HT-2 agonists, no pretreatment-by-drug interactions were observed except for rearings (Table 3). Even with rearings there was no indication that 1.0 mg/kg ketanserin reduced the effectiveness of 8OHDPAT.

Discussion

The present findings confirm that a variety of putative 5HT-2 agonists produce comparable effects on the behavioral profiles exhibited by rats in a novel environment and that these effects appear to be mediated by actions at 5HT-2 binding sites. Specifically, when rats were placed directly into the BPM chambers with no previous experience with this environment, the 5HT-2 agonists such as mescaline, quipazine, or DOI all produced dose-dependent reductions of exploratory activity in the first half of the hour-long test session. These reductions were reflected in significant decreases in crossovers, holepokes, rearings, and the amount of time spent in the center of the BPM chamber (see Table 1). As reported previously, hallucinogenic drugs including LSD, DMT, and DOM produce a characteristic profile of behavioral changes in this paradigm (Adams and Geyer 1985a, b). Other studies have demonstrated that a variety of non-hallucinogenic but psychoactive drugs produce different behavioral profiles in this model (Adams and Geyer 1985c; Geyer et al. 1986; Gold et al. 1988). The studies reported here demonstrate that the hallucinogen-like profile is reproduced by several drugs which differ in chemical structure but share an action as agonists at 5HT-2 receptors. Of the drugs studied here, mescaline, DOM, and DOET have all been identified as being hallucinogenic in humans (Shulgin and Dyer 1975; Mandell and Geyer 1976). By virtue of its close structural similarity to DOM and DOET, it may be reasonably assumed that DOI has hallu-

cinogenic actions, though we are not aware of explicit evidence to this effect. In any event, acute administrations of appropriate doses of mescaline, DOM, DOET, and DOI all resulted in a similar profile of effects when animals were tested during their initial exposure to the BPM chambers. Hence, these findings confirm that this behavioral profile is characteristic of the acute effects of hallucinogenic drugs derived from both the indoleamine and phenylethylamine families. The relative specificity of the drugs studied here for the 5HT-2 receptor further supports the hypothesis that the actions of LSD, mescaline, and related hallucinogens in this paradigm are attributable to their common agonist actions at 5HT-2 sites (Glennon et al. 1983; Titeler et al. 1988).

The results observed with quipazine indicate that this 5HT-2 agonist produces a similar behavioral profile in the novel environment paradigm. In preliminary studies, this effect, like that of LSD, was found to be attenuated in a familiar environment paradigm (Tapson et al. unpublished observations). Although clear evidence from human studies is lacking, quipazine has been used as a model hallucinogen in some animal studies (Glennon et al. 1983; Contreras et al. 1984; Mokler et al. 1984), and appears to have agonist activity at 5HT-2 binding sites (Heym and Jacobs 1988; Rech et al. 1988; Titeler et al. 1988). This use of quipazine as a hallucinogen is in agreement with the present evidence indicating that it shares a common behavioral profile with traditional hallucinogens. It is noteworthy, however, that quipazine has been reported to have effects on central dopaminergic systems (Schecter and Concannon 1982), has been used as a 5HT-1 agonist (Murphy and Zemlan 1988), and labels 5HT-3 binding sites (Peroutka 1988; Peroutka and Hamik 1988). Nevertheless, in the present paradigm, quipazine appeared to produce effects which were virtually identical to those found with more selective 5HT-2 agonists. Furthermore, both ketanserin and ritanserin were able to significantly reduce these effects of quipazine. Since ketanserin has some affinity for dopamine receptors (Leysen et al. 1988) as well as 5HT-2 receptors, the finding that it blocked the effects of quipazine could have been suggested to be related to the dopaminergic actions of both ketanserin and quipazine. However, the fact that ritanserin has little affinity for dopamine receptors (Janssen and Laduron 1985) and was also able to antagonize the effects of quipazine strongly suggests that these behavioral effects of quipazine were mediated by actions at 5HT-2 receptor sites.

With all the 5HT-2 agonists tested, the decrease in exploration observed during the first half of the hour test session was maintained throughout the second half of the session (Fig. 1). This continued suppression following quipazine, DOI, or mescaline is similar to that seen with DOM (Adams and Geyer 1985b), but contrasts with the previously observed effects of LSD during the second half of the test session (Geyer and Light 1979; Adams and Geyer 1982, 1985a). In the second half-hour, animals injected with LSD typically exhibit a "rebound" increase in exploratory behavior and are actually more active than are control animals. This phenomenon is independent of the time between injection and placement in the test chamber, and may be related to an impairment of behavioral habituation, as discussed elsewhere (Geyer and Light 1979; Geyer and Adams 1982). Manipulation of central serotonergic functioning such as with LSD has been suggested to impair the habituation of exploratory behavior (Gately et al. 1985). Serotonergic influences on habituation have also been observed in other behavioral paradigms such as tactile startle responding in rats in response to LSD (Geyer et al. 1978) and other serotonergic drugs (Geyer and Tapson 1988). Thus, it appears that the dose-dependent decrease in exploration in the first 30 min as well as the continued reduction in the second half hour observed here with DOI, quipazine, and mescaline and previously with DOM is likely to be a 5HT-2 agonist effect. The slight increase in the second 30 min observed with LSD appears to be a unique effect of LSD that may be related to its complex profile of combined 5HT-1, 5HT-2, dopaminergic, and noradrenergic influences.

The behaviorally suppressive effects of LSD (Adams and Geyer 1985a) and DOM (Adams and Geyer 1985b) are significantly attenuated in an environment with which the animal has had previous experience. Similarly, the initial suppressive effect of the 5HT-2 agonist DOI found in the present studies appears to reflect a potentiation of neophobia because it was also diminished in a familiar environment. This diminution of the effectiveness of DOI in the familiar environment could represent an increased willingness on the part of the drug-treated animal to explore the test chamber because the environmental stimuli associated with the chamber presumably have become less threatening by virtue of familiarity and habituation. Thus, we have interpreted the effects of hallucinogens on behavior in the novel environment paradigm as reflecting a potentiation of neophobia. In other words, the hallucinogen-treated animals exhibit an increased responsiveness to stimuli associated with handling and the introduction of the animal to the novel BPM chamber. Hence, this group of serotonergic agonists appears to increase the behavioral responsiveness of animals to tonic stimuli associated with the novelty of the situation.

The effects of the mixed 5HT-1 and 5HT-2 agonist 5MeODMT were very comparable to those described previously for several selective 5HT-1A agonists (Mittman and Geyer 1989). The decreases in locomotor and investigatory behaviors produced by 0.3 mg/kg 8OHDPAT, as summarized in Table 3, are illustrative of the dose-dependent suppressions of activity produced by all the 5HT-1A agonists tested in this paradigm to date. Specifically, the 5HT-1A agonists 8OHDPAT, gepirone, buspirone, and ipsapirone produced significant dose-dependent reductions in crossovers, holepokes, and rearings when animals were tested in the same novel environment paradigm used in the present studies. While both 5HT-1 and 5HT-2 agonists displayed similar behaviorally suppressive effects when tested in a novel environment, the differences between compounds specific to the two binding sites is clearly seen in the behavioral effects in the familiar environment. That is, in contrast to the effects found with 5HT-2 agonists, the effects of the 5HT-1A compounds were not diminished in animals previously familiarized with the test chambers (Mittman and Geyer 1989). In that study, rats injected with 8OHDPAT or ipsapirone on their third exposure to the chamber exhibited a reduction in exploratory behavior that was similar to that observed with animals having no prior experience with the test environment. Similarly, in the present study, virtually identical inhibitory effects were found when 5MeODMT was tested in either the novel or the familiar environment paradigms. Specifically, 0.25 mg/kg

5MeODMT decreased locomotor activity by 57% in the novel and 63% in the familiar environments (cf. Table 2). In contrast, 0.81 mg/kg DOI produced a 59% decrease in the novel environment and only a 33% decrease in the familiar environment. Hence, a significant interaction between the drug effect and the animals' experience was found for the 5HT-2 agonist DOI, but not for 5MeODMT. This lack of an experience-by-drug interaction implies that the reduction in locomotion induced by 5MeODMT is a sedative-like effect that is relatively independent of the animals' sensitivity to environmental stimuli, as observed previously with 5HT-1A agonists (Mittman and Geyer 1989). Thus, while the effects of 5HT-1A and 5HT-2 agonists exhibit some similarities in the novel environment paradigm, these drug classes produce differential behavioral effects in the familiar environment paradigm.

With regard to 5MeODMT itself, the above considerations lead to the conclusion that the drug is acting primarily as a 5HT-1A agonist in this particular behavioral paradigm. Much other evidence also suggests that 5MeODMT is primarily a 5HT-1A agonist (Blackburn et al. 1984; Tricklebank et al. 1985; Smith and Peroutka 1986). However, it may be that 5MeODMT has multiple actions not limited to the 5HT-1 binding site and that these actions have important influences in some behavioral paradigms (Critchley et al. 1988; Eide et al. 1988). Nevertheless, 5MeODMT has been used frequently as a model hallucinogen in animal studies (Grahame-Smith 1971; Fuxe et al. 1972; Sloviter et al. 1978). Hence, it is important to emphasize that the current findings using a well-validated model of the acute behavioral effects of hallucinogens (Adams and Geyer 1985a; Segal and Geyer 1985) indicate that 5MeODMT is quite different from the traditional hallucinogens and that its use as an exemplar of this drug class is questionable.

The relevance of 5HT-2 binding sites to the behavioral effects of the putative 5HT-2 agonists was examined by testing for interactions between the 5HT-2 antagonists ketanserin or ritanserin and selected agonists. Preliminary dose-response studies of ketanserin demonstrated that the antagonist had little effect by itself in this paradigm, despite the effectiveness of similar doses in modifying tactile startle responses (Geyer and Tapson 1988). Although some significant effects were found in one of the present studies with ketanserin (Table 3), most of the experiments with ketanserin and ritanserin in this paradigm have indicated that these 5HT-2 antagonists have minimal effects by themselves. In a tactile startle habituation paradigm, 5HT-2 agonists and antagonists appear to have opposite effects on behavior (Geyer and Tapson 1988). Interestingly, when effects are observed with the 5HT-2 antagonists in this paradigm, they are similar rather than opposite to the effects produced by 5HT-2 agonists. Such effects of the antagonists should make it more difficult to demonstrate their ability to prevent effects of the agonists. Nevertheless, significant interactions indicated that pretreatment with ketanserin effectively blocked the behavioral effects of the putative 5HT-2 agonists. Specifically, ketanserin significantly antagonized the effects of the 5HT-2 agonists DOM, quipazine, and mescaline on crossovers, time in the center, holepokes, and rearings, without reducing the qualitatively similar effects of the 5HT-1A agonist 8OHDPAT. With the more selective 5HT-2 antagonist ritanserin, virtually all the observed effects of quipazine at the higher dose studied (1.0 mg/kg) were blocked as well. This abolition of quipazine's behavioral effects by the 5HT-2 antagonists ritanserin and ketanserin is in contrast to the lack of interaction effects of ketanserin with 8OHDPAT. Ketanserin did not attenuate the inhibitory effects of 8OHDPAT (Table 3). Conversely, the effects of 5HT-1A agonists in this novel environment paradigm have been shown to be sensitive to blockade by drugs having 5HT-1A antagonist properties (Mittman and Geyer 1989).

In summary, hallucinogenic serotonin agonists consistently potentiate neophobia in rats, as evidenced by decreases in the locomotor and investigatory responses elicited by an animal's first exposure to a novel environment. Thus, taken together with previous studies, these results strongly suggest that the effects of hallucinogenic 5HT-2 agonists in the BPM are mediated by actions at 5HT-2 binding sites and that they are distinguishable from the generalized sedating effects exerted by the 5HT-1A agonists both phenomenologically and pharmacologically. These findings corroborate suggestions that modulatory influences of serotonergic systems on behavior are specifically related to responsiveness to environmental stimuli rather than to a more global influence on the arousal state of the animal.

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