Psychopharmacology (1987) 93:158–166

Psychopharmacology

Serotonin receptor subtype mediation of the interoceptive discriminative stimuli induced by 5-methoxy-N,N-dimethyltryptamine

D.G. Spencer, Jr*, T. Glaser, and J. Traber
Neurobiology Department, Troponwerke, Neurather Ring 1, D-5000 Köln 80, Federal Republic of Germany

Abstract. Male Wistar rats were trained to discriminate the interoceptive effects of 5-methoxy-N,N-dimethyltryptamine (5-OMe-DMT; 1.25 mg/kg, IP) from saline in a two-lever operant chamber. Following discrimination learning, the following drugs (with ED_{50} dose in mg/kg IP) dose-dependently generalized: lysergic acid diethylamide (LSD, 0.04), 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT, 0.11), 6-methoxy-4-(dipropyl-amino)-1,3,4,5-tetrahydrobenz(c,d)indole hydrochloride (BAY R 1531, 0.15), 5-OMe-DMT itself (0.63), ipsapirone (TVX Q 7821, 2.7), and buspirone (3.8). The potencies of these drugs in generalization tests were best correlated with their binding affinities for the 5-HT_{1A} serotonin receptor subtype (as measured by displacement of ^{3}H-ipsapirone in the hippocampus). Drugs not, or only partially generalizing included quipazine, bufotenin, *m*-trifluoromethylphenylpiperazine (TFMPP), 5-methoxy-3(1,2,3,6-tetrahydropyridine-4-yl)-1H-indole succinate (RU 24969), citalopram, clomipramine, 1,4-dihydro-2,6-dimethyl-3-nitro-4(2-trifluoromethylphenyl)-pyridine-5-carboxylate (BAY K 8644), the buspirone metabolite 1-pyrimidinyl-piperazine (1-PP), methysergide, metergoline, and metitepine. Of the last three compounds with antagonistic activity at 5-HT receptors, as well as ketanserin, pizotifen, and ritanserin, only metitepine and pindolol could fully block the 5-OMe-DMT stimulus. Pizotifen blocked the generalization of quipazine fully, that of 5-OMe-DMT only partially, and that of ipsapirone not at all. These data indicate that the 5-HT_{1A} receptor subtype is strongly involved in the transduction of the interoceptive discriminative stimuli induced by 5-OMe-DMT, with 5-HT_2 agonism also playing a possible role.

Key words: Behavior – Drug discrimination – 5-HT_{1A} receptor – Rats – 5-Methoxy-N,N-dimethyltryptamine – Serotonin receptors

Analyses of the serotonin (5-HT) receptor subtype affinities of 5-OMe-DMT reveals an apparent relative preference of this compound for the 5-HT_{1A} receptor over the 5-HT_{1B} or 5-HT_2 receptors sites (Glennon et al. 1980; Glennon et al. 1984; Sills et al. 1984; Peroutka 1985; Hamon et al. 1986). Evidence for some degree of 5-HT_{1B} agonistic specificity can also be found in vivo: 5-OMe-DMT produces a behavioral syndrome in rats that is primarily made up of elements produced via 5-HT_{1A} receptor activation (Lucki et al. 1984; Spencer et al. 1984; Sills et al. 1985; Tricklebank et al. 1985; Smith and Peroutka 1986).

The results from experiments in which various 5-HT agonists and antagonists have been trained as discriminative stimuli in a drug discrimination framework are not so clear, however. While it is true that animals trained to detect the interoceptive stimuli induced by the 5-HT_{1B} agonist TFMPP do not give TFMPP-like responses after administration of 5-OMe-DMT (McKenney and Glennon 1986), conflicting data have been collected with regard to the role of the 5-HT_2 receptor. First, rats can be trained to discriminate the effects of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and the potencies of various drugs in mimicking or antagonizing this stimulus correlate well with their affinities for the 5-HT_2 receptor (Glennon et al. 1984). 5-OMe-DMT also substituted for the DOM stimulus (Glennon et al. 1983a, b; Glennon et al. 1984). Furthermore, the 5-OMe-DMT substitution for DOM could be blocked by the 5-HT_2 antagonist pirenperone (Glennon et al. 1983b). Second, rats trained to detect the 5-HT_{1A} agonist 8-OH-DPAT did not fully generalize their drug responses to challenges with 5-OMe-DMT (Cunningham et al. 1985; Fozard et al. 1986; Glennon 1986). On the other hand, rats discriminating the 5-HT_{1A}-selective drug ipsapirone did exhibit full generalization to the effects of 5-OMe-DMT (Spencer and Traber 1987).

The situation becomes almost contradictory when one examines the results from experiments in which 5-OMe-DMT itself was the training substance. Glennon et al. (1979, 1980) found that in rats so trained, DOM substituted fully. In addition, the 5-HT_2 antagonist pizotifen antagonized the 5-OMe-DMT cue. Alternatively, Spencer et al. (1984, 1985, 1986) showed that 5-OMe-DMT-trained rats generalized fully to 8-OH-DPAT, the novel putative anxiolytic drug ipsapirone (Traber et al. 1984, 1985), and other substances, the potencies correlating best with affinities for the 5-HT_{1A} receptor.

Some clues to the solution of this controversy do exist, and indicate that 5-OMe-DMT may have agonistic actions at both 5-HT_{1A} and 5-HT_2 receptors. Accordingly, Fozard et al. (1986) found that in rats trained to discriminate 8-OH-DPAT, although 5-OMe-DMT when given alone did not substitute for the training drug, pretreatment with the 5-HT_2 antagonist ketanserin converted the 5-OMe-DMT effect to full substitution. Their conclusion was that the

* *Present address:* Bayer AG, Aprather Weg 18a, D-5600 Wuppertal 1, Federal Republic of Germany

Offprint requests to: D.G. Spencer

concurrent presence of 5-HT_2 agonism interfered with the detection of the 5-HT_{1A} properties of this drug. There is also evidence that the 5-HT_{1A}/5-HT_2 balance of effects of 5-OMe-DMT may be dose dependent. Like 8-OH-DPAT, low doses of 5-OMe-DMT produce hypothermia in rats, whereas larger doses have the opposite effects (Gudelsky et al. 1986). The goal of the present series of experiments was to examine the pharmacological properties of the 5-OMe-DMT-induced interoceptive stimulus in enough detail to evaluate the roles of the 5-HT receptor subtypes.

Materials and methods

Behavioral studies. Male albino rats of the Wistar strain (Winkelmann, Borchen-Kirchenborchen, FRG) served as subjects. Weight upon receipt was 140–160 g, which stabilized during the course of behavioral testing to 320–350 g, due to continual 22 h/day food deprivation. Rats were individually housed and given water as required. Temperature was maintained at $21 \pm 2°$ C and room lights were on from 7:00 A.M. to 6:00 P.M. Discrimination training took place in standard two-lever operant chambers (Coulbourn Instruments) and were controlled by TRS-80 Model III microcomputers (Tandy) using the OPN software package (Spencer and Emmett-Oglesby 1985). After an initial 1-week adaptation period, rats were daily food-deprived and trained to discriminate the effects of IP injections of 5-methoxy-dimethyltryptamine (5-OMe-DMT, 1.25 mg/kg) from those of an equal volume of saline; overall methodology was similar to that described by Glennon et al. (1980). On any specific day, either 5-OMe-DMT or saline would be injected 15 min before the behavioral session; responses on one lever being reinforced with 45 mg food pellets on a fixed-ratio of 10 (FR 10) schedule after drug treatment and responses on the other lever being reinforced on the same schedule after saline treatment. Sessions lasted a maximum of 10 min, but were also terminated upon the delivery of 50 reinforcements. Subjects were counterbalanced on assigned drug lever (left or right) and treatment over sessions (drug or saline) varied semi-randomly following correct session performance (less than six responses on the incorrect lever prior to the first reward). Incorrect session performance resulted in repetition of treatment condition on the following day. The discrimination learning criterion was ten correct consecutive sessions. Training sessions were carried out 5 days a week.

Following discrimination acquisition, generalization tests were conducted: injections of various doses of test drugs were substituted for the injection of 5-OMe-DMT at the training dose or saline. Test sessions were separated from each other by at least three practice sessions in which saline and 5-OMe-DMT were correctly discriminated. On these test sessions, the lever on which ten responses first accumulated was rewarded and only responses on that lever were subsequently rewarded. For generalization testing, all test compounds were injected 15 min before the behavioral session except metitepine and metergoline, which were injected 60 min before the session. Drug effects were assessed not only on lever selection, but also on lever pressing rate. Rate effects were calculated as per cent control lever pressing rate: rate on test day for each animal was divided by that on the most recent saline session and multiplied by 100. These percentages were then averaged for the tested group. ED_{50} values for those substances fully substituting for the 5-OMe-DMT stimulus were calculated by linear regression analysis of the probit dose-response functions.

Various drugs acting as antagonists at 5-HT receptors were also tested for their ability to block the stimulus properties of the training drug, 5-OMe-DMT. The first series of such tests included ketanserin, metergoline, methysergide, metitepine, and ritanserin. Antagonism was tested by pretreating the trained rats with one of several doses of the antagonist (IP) 45 min before administration of the normal training dose of 5-OMe-DMT. Pizotifen (BC-105) was also tested for antagonism of the 5-OMe-DMT stimulus, but was given only 15 min before the training drug. Drug effects on lever pressing rate were assessed in the same manner as that described above for generalization tests, but the session taken as control was the most recent 5-OMe-DMT session.

Thereafter, two further series of antagonism tests were conducted and all injections were again via the IP route. The purpose of both test series was to examine the ability of a specific antagonist to block the generalizations of a number of agonistic compounds. Pizotifen (10 mg/kg) was selected for the first such test series, and was administered 15 min before either quipazine (2.0 mg/kg) or ipsapirone (10 mg/kg). The next such test series employed racemic pindolol (20 mg/kg); pindolol was given 15 min before either quipazine (2.0 mg/kg), 5-OMe-DMT (1.25 mg/kg), ipsapirone (10 mg/kg), or 8-OH-DPAT (0.32 mg/kg). The doses of these three agonists were selected to provide the same degrees of nearly complete generalization. The effects of these drug combinations on lever-pressing rate within subjects was calculated as described for generalization tests.

Receptor binding. Binding experiments were performed as described by Dompert et al. (1985), Glaser et al. (1985), Peroutka and Snyder (1981), and Leysen et al. (1982), using either calf or rat hippocampal membranes with ^{3}H-5-HT (1 nM, 15 min incubation, specific activity 25 Cu/mmol (New England Nuclear): the 5-HT_1 site, which represents a mixture of 5-HT_{1A} and 5-HT_{1B} sites) or ^{3}H-ipsapirone (2 nM, 30 min incubation, specific activity 30 Cu/mmol (Amersham): the 5-HT_{1A} site), or rat frontal cortical membranes with ^{3}H-ketanserin (1 nM, 20 min incubation, specific activity 90 Cu/mmol (New England Nuclear): the 5-HT_2 site). For the three ligands, a 50 mM Tris-HCl buffer was used (pH 7.7, 25° C) which, for the first two ligands, contained an additional 4 nM $CaCl_2$. Scatchard analyses of ^{3}H-5-HT, ^{3}H-ipsapirone, and ^{3}H-ketanserin binding were characterized by dissociation constants of 1.5, 1.0, and 1.7 nM and binding capacities of 0.65, 0.2, and 0.89 pmol/mg, respectively. Analysis of substance interactions with the 5-HT_{1B} site was performed in rat cortex membranes with ^{3}H-5-HT (as described above for calf hippocampus membranes), but in the additional presence of 600 nM 8-OH-DPAT to block the 5-HT_{1A} sites. All determinations of inhibition constants (K_is) were carried out in triplicate and then replicated three times in order to allow calculation of a mean value plus standard deviations.

The following drugs were obtained as gifts from the following companies, and their assistance is gratefully acknowledged: clomipramine HCl (CIBA-GEIGY), metergoline (Farmitalia), metitepine maleate (Hoffmann-La Roche), ketanserin tartrate and ritanserin (Jannsen), citalopram HCl (Lundbeck), buspirone HCl (Mead-Johnson),

quipazine maleate (Miles), and LSD, methysergide hydrogen maleate, and pizotifen hydrogen maleate (Sandoz). BAY K 8644, BAY R 1531, ipsapirone (synthesized as hydrochloride salt), 8-OH-DPAT, 1-PP, and RU 24969 were synthesized by the Chemistry Department of Bayer AG, Sector Pharma, Wuppertal, Federal Republic of Germany. The remaining substances were obtained from commercial sources. All drug doses were calculated on the basis of the weight of the base or salt received.

Results

A total of 51 rats were trained to discriminate the discriminative stimulus effects of 1.25 mg/kg 5-OMe-DMT from saline. In a representative group of ten rats, discrimination acquisition required 60 sessions until asymptotic accuracy was reached (85% correct session performance, sessions 60–75).

The following drugs (ED_{50} in mg/kg) fully and dose-

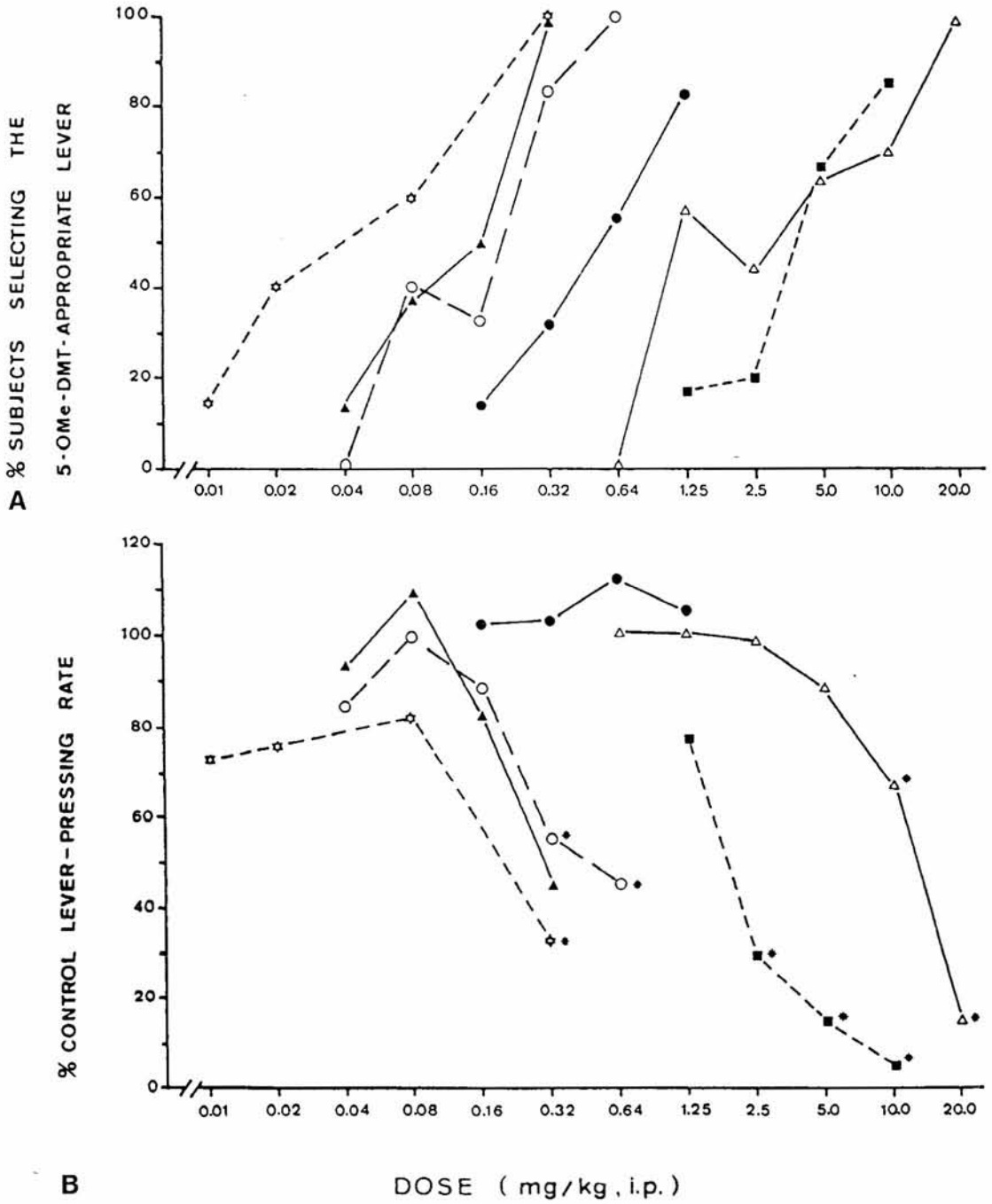

Fig. 1A, B. Dose-response functions of those drugs substituting for 5-OMe-DMT: effects on lever selection (*panel* **A**) and lever-pressing rate (*panel* **B**). *Asterisks* in panel **B** indicate drug doses that resulted in statistically significant reduction of response rate (paired *t*-test, see Results). The following numbers of subjects selected a lever at each drug and dose, with numbers listed for doses in ascending order: LSD – 7, 5, 5, 5; 8-OH-DPAT – 8, 8, 8, 5; BAY R 1531 – 7, 10, 9, 6, 7; 5-OMe-DMT – 7, 41, 47, 49; ipsapirone – 7, 9, 8, 13, 5; buspirone – 6, 5, 6, 7. *----* LSD, ▲—▲ 8-OH-DPAT, ○—○ BAY R 1531, ●—● 5-OMe-DMT, △—△ ipsapirone, ■----■ buspirone

dependently substituted for the 5-OMe-DMT stimulus: LSD (0.04), 8-OH-DPAT (0.11), BAY R 1531 (0.15), 5-OMe-DMT itself (0.63), ipsapirone (2.7), and buspirone (3.8; see Fig. 1, panel A). While 5-OMe-DMT did not suppress response rate at doses up to and including the training dose of 1.25 mg/kg under the present response-reinforcement contingencies, the other drugs tested did to greater or lesser extents (Fig. 1, panel B). Significant response suppression was observed with the following drugs and doses: LSD at 0.32 mg/kg [$t(4)=2.78$, $P<0.05$], BAY R 1531 at 0.32 [$t(5)=4.21$, $P<0.01$] and 0.64 mg/kg [$t(6)=3.41$, $P<0.02$], ipsapirone at 10 [$t(13)=3.79$, $P<0.001$] and 20 mg/kg [$t(4)=10.2$, $P<0.001$], and buspirone at 2.5 [$t(4)=3.90$, $P<0.02$], 5.0 [$t(5)=7.36$, $P<0.001$] and 10 mg/kg [$t(6)=7.43$, $P<0.001$]. The response rate data reported in Fig. 1 were calculated only for those animals selecting a lever. At least one animal failed to select a lever after treatment with the following drugs and doses: LSD (0.08 and 0.32 mg/kg), 8-OH-DPAT (1.25 mg/kg, all animals tested), BAY R 1531 (0.32 and 0.64 mg/kg), ipsapirone (20 mg/kg), and buspirone (2.5, 5.0, and 10 mg/kg). Both sources of response suppression data indicate that buspirone had the most disruptive effects on lever-pressing performance in the dose ranges studied.

Several other substances studied in generalization tests did not substitute fully for 5-OMe-DMT, and their effect on lever selection and lever-pressing rate are shown in Table 1. Also indicated in this table are those test drug doses in which at least one test animal failed to select a response alternative. Neither drugs acting directly at 5-HT_{1B} receptors (RU 24969 and TFMPP) nor those acting directly but relatively non-selectively at 5-HT receptor subtypes (bufotenin, quipazine, metergoline, methysergide, and metitepine) induced dose-dependent and complete selection of the 5-OMe-DMT-appropriate lever. Quipazine induced appreciable drug lever selection, however, and was selected for further tests with antagonists as described below. A lack of generalization was also observed with drugs acting indirectly to increase synaptic levels of 5-HT (citalopram, clomipramine, fenfluramine, and BAY K 8644). Finally, 1-pyrimidinyl-piperazine also failed to induce drug lever selection across a relatively wide dose range. All compounds tested reduced responding markedly at the highest dose tested.

In antagonism tests with the training drug at the training dose, metitepine was found to dose-dependently and completely block the 5-OMe-DMT stimulus with ED_{50} of 0.5 mg/kg (Fig. 2). This effect was accompanied by significant response suppression at all doses examined, however [0.32 mg/kg, $t(7)=2.81$, $P<0.05$; 0.45 mg/kg, $t(7)=6.12$, $P<0.001$; 0.64 mg/kg, $t(8)=7.22$, $P<0.001$]. Other 5-HT receptor antagonists that did not completely block the 5-OMe-DMT stimulus included ketanserin, metergoline, methysergide, pizotifen, and ritanserin (Table 2). A tendency towards blockade was seen with pizotifen at 10 mg/kg and further antagonism tests with this compound were next carried out.

In order to provide additional information concerning the receptor mediation of some of the data described above, further antagonism tests were conducted with pizotifen (10 mg/kg) against the generalizations induced by quipazine (2.0 mg/kg) and ipsapirone (10 mg/kg), and with pindolol (20 mg/kg) against these same drugs in addition to 5-OMe-DMT (1.25 mg/kg) and 8-OH-DPAT (0.32 mg/kg). While, as described above, the pizotifen antagonism of 5-OMe-DMT was only partial, pizotifen pretreatment eliminated the generalization of quipazine. Conversely, pizotifen had no effect on the ipsapirone generalization (see Table 3, compare with Fig. 1A in the case of ipsapirone). Pindolol pretreatment resulted in complete behavioral suppression after quipazine injection (also occurring after 10 mg/kg pindolol, data not shown). However, pindolol pretreatment did markedly antagonize the stimulus effects of 5-OMe-DMT, ipsapirone, and 8-OH-DPAT (Table 3).

The results of the 5-HT receptor sub-type binding analysis with agonists are presented in Table 4, along with ago-

Table 1. Test substances not fully substituting for the 5-OMe-DMT stimulus

Test substance	Dose (mg/kg, IP)	N^a	% DL^b	% $Rate^c$
Drugs with high affinity for 5-HT_{1B} sites				
RU 24969	0.64	8	0	25*
TFMPP	0.64	5	20	50*
Direct, non-selective 5-HT agonists and antagonists				
Bufotenin	1.25	5	20	88
	2.5	5	20	70
	5.0	7	43	17*
Quipazine	1.25	5	20	88
	2.0	14	57	60*
	2.5	8	63	21
Metergoline	5.0	5	20	97
	20	7	43	20*
Methysergide	0.64	5	20	112
	2.5	2	0	98
	10	3	0	102
	20	6	50	67
	40	5	40	55
Metitepine	0.64	4	0	71
	1.25	–	–	–*
Drugs indirectly increasing extraneuronal 5-HT levels				
Citalopram	2.5	5	0	141
	5.0	7	29	81
	10	6	0	86
	20	1	0	1*
Clomipramine	5.0	9	22	90
	10	5	0	53*
Fenfluramine	1.25	3	0	119
	2.5	2	0	52
	5.0	–	–	–*
BAY K 8644	0.32	3	0	56*
	0.64	3	33	36*
	1.25	4	0	66*
	2.5	4	0	21*
Other drugs				
1-PP	2.5	3	0	87
	10	3	0	67
	20	4	25	81
	40	5	20	17*

[a] Number of subjects tested that selected a lever

[b] Per cent subjects selecting the drug (5-OMe-DMT)-appropriate lever

[c] Per cent control lever pressing rate

* At this dose, at least one additional subject failed to select a lever

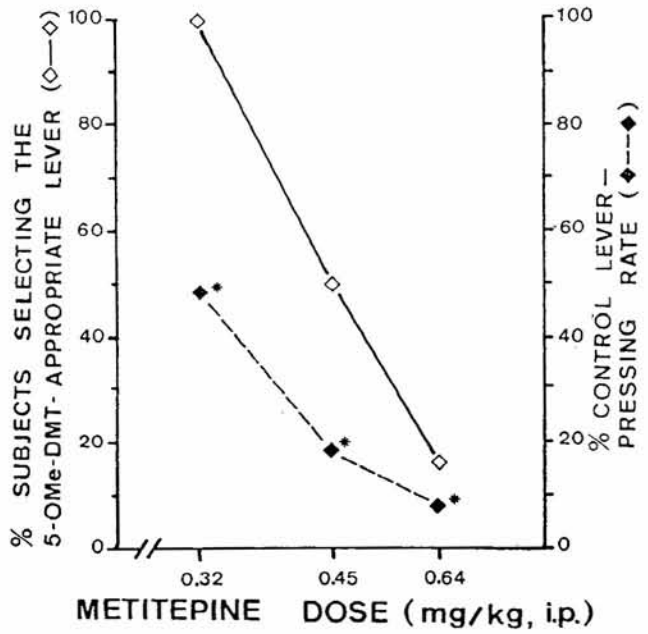

Fig. 2. Effects of metitepine pretreatment on lever selection and response rate induced by 5-OMe-DMT, 1.25 mg/kg. *Asterisks* indicate drug doses that resulted in statistically significant reduction of response rate (paired *t*-test, see Results)

Table 2. Test substances not fully antagonizing the 5-OMe-DMT stimulus

Test substance	Dose (mg/kg, IP)	N^a	% DL[b]	% Rate[c]
Ketanserin	2.5	5	80	104
	10	5	80	126
	20	8	50	103
	40	6	67	77
Metergoline	5.0	6	100	47
	10	7	86	18*
Methysergide	0.64	6	67	93
	1.25	6	100	118
	5.0	5	100	122
	10	5	80	103
Pizotifen	5.0	6	100	89
	10	6	50	41*
	20	2	100	17*
Ritanserin	2.5	5	100	91
	5.0	4	100	56
	10	5	100	42*

[a] Number of subjects tested that selected a lever
[b] Per cent subjects selecting the drug (5-OMe-DMT)-appropriate lever
[c] Per cent control lever pressing rate

* At this dose, at least one additional subject failed to select a lever

nist ED_{50} values from the behavioral experiments. 5-HT itself showed similar high affinities for the 5-HT_1, 5-HT_{1A}, and 5-HT_{1B} binding sites, but an approximately 1000 times lower affinity for the 5-HT_2 receptor. BAY R 1531, 8-OH-DPAT, ipsapirone, and buspirone were all similar in that their affinities for the 5-HT_1 and 5-HT_{1A} receptors were on the same close order of that of 5-HT itself, while affinities for the 5-HT_{1B} and 5-HT_2 receptors were 50–5000 times lower. 5-OMe-DMT revealed a similar pattern of receptor affinities, with the exception that the affinity for the 5-HT_{1B} receptor was only 10 times less than that for the 5-HT_1 and 5-HT_{1A} receptors. Quipazine showed rather poor affinity for all receptor studies; highest affinity was seen for the 5-HT_{1B} receptor. TFMPP likewise showed highest affinity for this site.

Table 3. Effects of pizotifen or pindolol pretreatment on responses to drugs mimicking the 5-OMe-DMT stimulus

Generalizing substance, dose[a]	Pretreatment, dose[b]	N^c	% DL[d]	% Rate[e]
Pizotifen antagonism				
Quipazine, 2.0	Saline	7	86	77*
	Pizotifen, 10	10	18	58*
Ipsapirone, 10	Pizotifen, 10	8	87	58*
Pindolol antagonism				
Quipazine, 2.0	Pindolol, 20	–	–	–*
5-OMe-DMT, 1.25	Pindolol, 20	12	33	61*
Ipsapirone, 10	Pindolol, 20	12	50	47*
8-OH-DPAT, 0.32	Pindolol, 20	16	38	57*

[a] Substance producing 5-OMe-DMT-similar discriminative effects, and its dose in mg/kg, when given 30 min before the behavioral test
[b] Substance and dose (mg/kg) given 15 min before the generalizing drug
[c] Number of subjects tested that selected a lever
[d] Per cent subjects selecting the drug (5-OMe-DMT)-appropriate lever
[e] Per cent control lever pressing rate

* At this dose, at least one additional subject failed to select a lever

Discussion

Following an initial separation of 5-HT receptors into 5-HT_1 and 5-HT_2 binding sites on the basis of their selective affinities for tritiated 5-HT (^{3}H-5-HT) and spiperone, respectively (Peroutka and Snyder 1981), the 5-HT_1 site was then further subdivided into 5-HT_{1A} and 5-HT_{1B} sites on the basis of the higher affinity of spiperone in displacing ^{3}H-5-HT from 5-HT_{1A} sites (Pedigo et al. 1981). 5-HT_{1C} sites have also been recently proposed, and are found mainly in rat choroid plexus (e.g. Hoyer et al. 1985; Hoyer et al. 1986b). The postulation of such 5-HT receptor subtypes has also been accompanied by the accumulation of an impressive amount of evidence for the functionality of at least of 5-HT_{1A} site, and probably also the 5-HT_{1B} site. Concerning 5-HT_{1A} receptors (usually as activated or bound by the prototype agonist 8-OH-DPAT), GTP-sensitivity of binding and coupling to adenylate cyclase has been demonstrated (Hamon et al. 1984; De Vivo and Maayani 1985, 1986; Markstein et al. 1986). Electrophysiologically, raphe cell bodies apparently possess 5-HT_{1A} autoreceptors, activation of which results in the inhibition of raphe cell activity (Verge et al. 1985; Basse-Tomusk and Rebec 1986; Sprouse and Aghajanian 1986; Trulson and Trulson 1986; Van der Maelen et al. 1986). Physiological and behavioral effects now linked with 5-HT_{1A} receptor activation include

Table 4. Serotonin receptor subtype affinities in membranes compared to behavioral activity in the 5-OMe-DMT drug discrimination

Substance	Receptor affinities (K_i, nmol/l) ± SEM				5-OMe-DMT discrimination ED_{50} (mg/kg, IP)
	5-HT_1 [a]	5-HT_{1A} [b]	5-HT_{1B} [c]	5-HT_2 [d]	
5-HT	1.6±0.05	2.2±0.3	2±0.3	1800±350	–
BAY R 1531	0.6±0.2	0.4±0.1	2730±220	770±225	0.25
8-OH-DPAT	2 ±0.5	0.7±0.1	6350±1850	6230±1050	0.11
Ipsapirone	15 ±2	2.6±0.5	>10000	2940±240	2.7
Buspirone	24 ±6	8 ±1	>10000	1220±490	3.8
5-OMe-DMT	4 ±1	5 ±1	70±13	1530±70	0.63
Quipazine	1660 ±60	2120 ±650	130±10	810±80	–
TFMPP	190 ±40	160 ±7	10±4	445±125	–

[a] Calf hippocampus, 1 nM ^{3}H-5-HT
[b] Rat hippocampus, 1 nM ^{3}H-ipsapirone
[c] Rat cortex, 1 nM ^{3}H-5-HT + 600 nM 8-OH-DPAT
[d] Rat cortex, 1 nM ^{3}H-ketanserin

hypothermia (Goodwin and Green 1985; Goodwin et al. 1986; Gudelsky et al. 1986), the flat body posture and forepaw treading elements of the serotonin syndrome (Lucki et al. 1984; Tricklebank et al. 1985; Smith and Peroutka 1986), facilitation of male rat sexual behaviour (Ahlenius et al. 1981; Morali and Larson 1984; Glaser et al. 1987), elicitation of feeding (Dourish et al. 1985; Bendotti and Samanin 1986; Hutson et al. 1986) and induction of the interoceptive stimuli associated with 8-OH-DPAT (Cunningham et al. 1985; Glennon 1986) and ipsapirone (Spencer and Traber 1987). On the other hand, 5-HT_{1B} receptor activation has been associated with axonal terminal 5-HT autoreceptors and the inhibition of serotonin release (Middlemiss 1985; Bonanno et al. 1986; Engel et al. 1986; Hibert and Middlemiss 1986; Raiteri et al. 1986), decreased locomotor activity (Sills et al. 1985), and induction of the interoceptive stimuli associated with TFMPP (Cunningham and Appel 1986).

8-OH-DPAT, 5-OMe-DMT, ipsapirone, and buspirone were found in the present study to have higher relative affinity for the 5-HT_{1A} receptor, in agreement with earlier studies (Glaser and Traber 1983, 1985; Gozlan et al. 1983; Sills et al. 1984; Glaser et al. 1984, 1985; Peroutka 1985). In addition, BAY R 1531, a novel tetraline derivative with structural similarities to 8-OH-DPAT, was also found to possess high relative affinity for the 5-HT_{1A} receptor (see also Glaser et al. 1987). The results of the present behavioral experiments showed furthermore that these five compounds not only substituted for the 5-OMe-DMT stimulus, but that their potencies in doing so correlated well with their affinities for the 5-HT_{1A} receptor (Table 4). Quipazine and TFMPP, lacking relative affinity for this receptor, did not fully generalize.

One puzzle in the present data, though, is that while no signs of generalization were seen in the case of TFMPP, generalization was noted for quipazine. This generalization is viewed as partial, however, because the first 2.0 mg/kg dose that resulted in 86% generalization with seven animals in Table 4 only yielded 57% when tested with 14 animals on another occasion. In addition, the more suppressive dose of 2.5 mg/kg did not improve the generalization. This occurred in spite of a relatively similar 5-HT receptor binding profile of the two compounds. The ten times higher affinity of TFMPP for the 5-HT_{1B} receptor may account for this, since competing activity at this site may overshadow any 5-HT_{1A}- or 5-HT_2-mediated events (Asarch et al. 1985, also note the greater specificity of TFMPP for the 5-HT_{1B} receptor). A remaining uncertainty is the cause of quipazine's partial generalization. The ligands used in the present study to label the 5-HT_1, 5-HT_{1A}, and 5-HT_{1B} sites are agonists; that used for the 5-HT_2 site is an antagonist. Titeler et al. (1985) have recently described a new agonist ligand for the characterization of 5-HT_2 receptors: ^{3}H-DOB (1-(2.5-dimethoxyphenyl-4-bromo)-2-aminopropane). Interestingly, drugs with agonistic activity at the 5-HT_2 receptor have higher affinities in displacing this ligand than they do in displacing antagonists such as ketanserin (Lyon et al. 1986); antagonist affinities remain unaltered. Indeed, Lyon and coworkers determined affinity constants of quipazine and TFMPP for this new high affinity 5-HT_2 site of 25 and 32 nM, respectively.

These data may indicate that while TFMPP has high affinities for both 5-HT_{1B} and 5-HT_2 receptors, quipazine has relative specificity for the 5-HT_2 receptor. This hypothesis agrees well with the findings of Lucki et al. (1984), that quipazine produces a serotonin syndrome that seems to be selectively mediated by the 5-HT_2 receptor. TFMPP, on the other hand, has no such behavioral effects (Ortmann 1984), resulting instead in locomotion disturbances and backward movements. Hyperlocomotion has been reported to result from treatment with RU 24969 (Green et al. 1984; Tricklebank et al. 1986), another ligand with high affinity for 5-HT_{1B} receptors (Sills et al. 1984; Peroutka 1985), although an appreciable affinity for 5-HT_{1A} receptors also seems to be present (Hoyer et al. 1985). Nevertheless, the 5-HT_{1B} receptor-mediated effects of this drug may again have been responsible for a lack of substitution for the 5-OMe-DMT interoceptive stimulus.

1-PP is a metabolite of buspirone in rats and man and can reach plasma concentrations in man even in excess of the parent drug (Caccia et al. 1986). It is therefore possible that this compound is responsible for at least a portion of the pharmacological effects of buspirone. However, 1-PP across a wide dose range was inactive in the 5-OMe-DMT discrimination procedure. Furthermore, 1-PP only weakly displaces ^{3}H-5-HT from 5-HT_1 receptors in the bovine hippocampus (K_i = 1700, data not shown in Table 4).

Four substances were studied in generalization tests that may increase synaptic levels of 5-HT indirectly. These consisted of the 5-HT reuptake blockers citalopram and clomi-

pramine (e.g., Smith 1986) and drugs leading to increased release of 5-HT, fenfluramine and BAY K 8644 (Fuxe et al. 1975; Garattini et al. 1975; Middlemiss and Spedding 1985). None of the drugs in question substituted for 5-OMe-DMT. These data, along with those from the non-selective agonist bufotenin (Peroutka 1986), indicate that non-selective activation of 5-HT receptors cannot mimic the 5-OMe-DMT stimulus.

Non-selective antagonism of 5-HT receptors also appears to be ineffective in blocking the 5-OMe-DMT cue. Methysergide and metergoline have high affinity for all known 5-HT receptor subtypes (Hoyer et al. 1985; Peroutka 1986) and were unable to antagonize the effects of 5-OMe-DMT. Likewise, antagonists such as ketanserin and ritanserin having highest affinity for the 5-HT_2 receptor (Hoyer et al. 1985; Leysen et al. 1985) also could not fully block the training drug. Among the antagonists listed in Table 2, only pizotifen has a slight selectivity for the 5-HT_{1A} receptor over the 5-HT_{1B} and 5-HT_{1C} sites (Peroutka 1986), although 5-HT_2 affinity is equally high (Hoyer et al. 1986a) and 5-HT_2 antagonistic effects in a drug discrimination framework have been found (Friedman et al. 1984). Again, at most only partial antagonism resulted in the present study. In light of the previous reports of 5-OMe-DMT antagonism by pizotifen in a drug discrimination setting (e.g. Glennon et al. 1979; Young et al. 1983), further antagonism tests were conducted in the present study. As was shown in Table 3, pizotifen fully antagonized the generalization induced by the 5-HT_2 agonist quipazine but did not affect that induced by the selective 5-HT_{1A} agonist ipsapirone. These data indicate that despite a marked affinity of pizotifen for the 5-HT_{1A} receptor, antagonism could not be demonstrated at a behavioral level.

Metitepine distinguished itself from the antagonists described above by dose-dependently antagonizing the 5-OMe-DMT stimuli. Strangely enough, however, metitepine also binds to 5-HT receptors with a relatively non-specific pattern, having the highest affinity for the 5-HT_2 receptor (Hoyer et al. 1985). Metitepine is somewhat differentiated from the other antagonists by being very efficacious in blocking the inhibitory effects of 5-HT_{1B} agonists like RU 24969 or of 5-HT itself on 5-HT release (Middlemiss 1985; Brazell et al. 1985; Bonanno et al. 1986; Engel et al. 1986; Hibert and Middlemiss 1986; Martin and Marsden 1986). However, the above cited lack of generalization of the 5-HT_{1B} agonists RU 24969 and TFMPP reduce the likelihood that the crucial effect of metitepine in antagonizing 5-OMe-DMT is mediated by this receptor. Rather, these data point out a general problem in trying to interpret the effects of "5-HT antagonists". Namely, although the receptor binding profiles of such antagonists are relatively easily derived, it is much more difficult to generate the corresponding functional information as to agonism or antagonism at each receptor. Thus, although metitepine quite apparently is a 5-HT_{1B} antagonist, the extent to which it is also a 5-HT_{1A} antagonist is largely unknown. The present data would suggest such an activity, and this hypothesis is supported by observations that metitepine can block the increased acoustic startle and hypothermic responses to 8-OH-DPAT (Svensson 1985; Gudelsky et al. 1986).

In order to obtain a somewhat clearer answer to the question as to whether a 5-HT_{1A} antagonist can block the discriminative stimuli induced by 5-OMe-DMT and other more selective agonists, we employed the beta noradrenergic antagonist pindolol. Pindolol has recently been shown to possess high affinity for the 5-HT_{1A} receptor [especially the (−) form, Hoyer et al. 1985] and also to possess 5-HT_{1A} antagonistic activity at the behavioral level (Tricklebank et al. 1985; Gudelsky et al. 1986). In agreement with these data, pindolol effectively antagonized the stimulus effects of 8-OH-DPAT, 5-OMe-DMT and ipsapirone in 5-OMe-DMT-trained animals.

In conclusion, the results of the present series of experiments indicate that rats trained to discriminate the stimuli induced by 1.25 mg/kg 5-OMe-DMT detect an interoceptive event that is primarily mediated by the 5-HT_{1A} receptor. However, the partial generalization of quipazine and its selective antagonism by pizotifen indicate that animals so trained may also be sensitive to 5-HT_2-mediated effects.

Acknowledgements. The technical assistance of Ms. G. Alscher, Ms. M. Fassbender and Mr. W. Lüdtke is gratefully acknowledged.

References

Ahlenius S, Larsson K, Svensson L, Hjorth S, Carlsson A, Lindberg P, Wikström H, Sanchez D, Arvidsson L-E, Hacksell U, Nilsson JLG (1981) Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacol Biochem Behav 15:785–792

Asarch KB, Ransom RW, Shih JC (1985) 5-HT-1a and 5-HT-1b selectively of two phenylpiperazine derivatives: evidence for 5-HT-1b heterogeneity. Life Sci 36:1265–1273

Basse-Tomusk A, Rebec GV (1986) Ipsapirone depresses neuronal activity in the dorsal raphe nucleus and the hippocampal formation. Eur J Pharmacol 130:141–143

Bendotti C, Samanin R (1986) 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) elicits eating in free-feeding rats by acting on central serotonin neurons. Eur J Pharmacol 121:147–150

Bonanno G, Maura G, Raiteri M (1986) Pharmacological characterization of release-regulating serotonin autoreceptors in rat cerebellum. Eur J Pharmacol 126:317–321

Brazell MP, Marsden CA, Nisbet AP, Routledge C (1985) The 5-HT_1 receptor agonist RU-24969 decreases 5-hydroxytryptamine (5-HT) release and metabolism in the rat frontal cortex in vitro and in vivo. Br J Pharmacol 86:209–216

Caccia S, Conti I, Vigano C, Garattini S (1986) 1-(2-pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat. Pharmacology 33:46–51

Cunningham KA, Appel JB (1986) Possible 5-hydroxytryptamine$_1$ (5-HT_1) receptor involvement in the stimulus properties of 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP). J Pharmacol Exp Ther 237:369–377

Cunningham KA, Callahan PM, Appel JB (1985) Similarities in the stimulus effects of 8-hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT), buspirone and TVX Q 7821: implications for understanding the actions of novel anxiolytics? Soc Neurosci Abstr 11:45

DeVivo M, Maayani S (1985) Inhibition of forskolin-stimulated adenylate cyclase activity by 5-HT receptor agonists. Eur J Pharmacol 119:231–234

DeVivo M, Maayani S (1986) Characterization of the 5-hydroxytryptamine$_{1A}$ receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes. J Pharmacol Exp Ther 238:248–253

Dompert WU, Glaser T, Traber J (1985) ^{3}H-TVX Q 7821: identification of 5-HT_1 binding sites as target for a novel putative anxiolytic. Naunyn-Schmiedeberg's Arch Pharmacol 328:467–470

Dourish CT, Hutson PH, Curzon G (1985) Low doses of the putative serotonin agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) elicit feeding in the rat. Psychopharmacology 86:197–204

Engel G, Göthert M, Hoyer D, Schlicker E, Hillenbrand K (1986) Identity of inhibitory preynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT_{1B} binding sites. Naunyn-Schmiedeberg's Arch Pharmacol 332:1–7

Fozard JR, Kidd EJ, Neill J, Tricklebank M (1986) Further characterization of the discriminative stimulus induced by 8-hydroxy-2-(di-*n*-propylamino) tetralin in rats. Br J Pharmacol [Suppl] 88:371p

Friedman RL, Barrett RJ, Sanders-Bush E (1984) Discriminative stimulus properties of quipazine: mediation by serotonin$_2$ binding sites. J Pharmacol Exp Ther 228:628–635

Fuxe K, Friedholm LO, Hamburger B, Ogren SO (1975) On the "in vivo" and "in vitro" actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons and their relation to the anorectic activity of fenfluramine. Postgrad Med J [Suppl] 51:35–45

Garattini S, Buczko W, Jori A, Samanin R (1975) On the mechanism of action of fenfluramine. Postgrad Med J [Suppl] 51:27–34

Glaser T, Traber J (1983) Buspirone: action on serotonin receptors in calf hippocampus. Eur J Pharmacol 88:137–138

Glaser T, Traber J (1985) Binding of the putative anxiolytic TVX Q 7821 to hippocampal 5-hydroxytryptamine (5-HT) recognition sites. Naunyn-Schmiedeberg's Arch Pharmacol 329:211–215

Glaser T, Dompert WU, Schuurman T, Traber J (1984) 5-HT_1 receptors as target for the putative anxiolytic TVX Q 7821. Soc Neurosci Abstr 10:259

Glaser T, Rath M, Traber J, Zilles K, Schleicher A (1985) Autoradiographic identification and topographical analyses of high affinity serotonin receptor subtypes as a target for the novel putative anxiolytic TVX Q 7821. Brain Res 358:129–136

Glaser T, Dompert WU, Schuurman T, Spencer DG, Traber J (1987) Differential pharmacology of the novel 5-HT_{1A} receptor ligands 8-OH-DPAT, BAY R 1531 and ipsapirone. In: Dourish CT, Ahlenius S, Hudson P (eds) Brain serotonergic mechanisms: the pharmacological, biochemical and potential therapeutic actions of 8-OH-DPAT and other 5-HT_{1A} agonists. Ellis Horwood, London

Glennon RA (1986) Discriminative stimulus properties of the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Pharmacol Biochem Behav 25:135–139

Glennon RA, Rosecrans JA, Young R, Gaines J (1979) Hallucinogens as discriminative stimuli: generalization of DOM to a 5-methoxy-N,N-dimethyltryptamine stimulus. Life Sci 24:993–998

Glennon RA, Young R, Rosecrans JA, Kallman MJ (1980) Hallucinogenic agents as discriminative stimuli: a correlation with serotonin receptor affinities. Pyschopharmacology 68:155–158

Glennon RA, Young R, Jacyno JM, Slusher M, Rosecrans JA (1983a) DOM-stimulus generalization to LSD and other hallucinogenic indole alkylamines. Eur J Pharmacol 86:453–459

Glennon RA, Young R, Rosecrans JA (1983b) Antagonism of the effects of the hallucinogen DOM and the purported 5-HT agonist quipazine by 5-HT_2 antagonists. Eur J Pharmacol 91:189–196

Glennon RA, Titeler M, McKenney JD (1984) Evidence for 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 35:2505–2511

Goodwin GM, Green AR (1985) A behavioral and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT_1 and 5-HT_2 receptors. Br J Pharmacol 84:743–753

Goodwin GM, De Souza RJ, Green AR (1986) The effects of a 5-HT_1 receptor ligand ipsapirone (TVX Q 7821) on 5-HT synthesis and the behavioral effects of 5-HT agonists in mice and rats. Psychopharmacology 89:382–387

Gozlan H, El Mestikawy S, Pichat L, Glowinsky J, Hamon M (1983) Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. Nature 305:140–142

Green AR, Guy AP, Gardner CR (1984) The behavioural effects of RU 24969, a suggested 5-HT_1 receptor agonist in rodents and the effect on the behaviour of treatment with antidepressants. Neuropharmacology 23:655–661

Gudelsky GA, Koenig JI, Meltzer HY (1986) Thermoregulatory responses to serotonin (5-HT) receptor stimulation in the rat: evidence for opposing roles of 5-HT_2 and 5-HT_{1A} receptors. Neuropharmacology 25:1307–1313

Hamon M, Bourgoin S, Gozlan H, Hall MD, Goetz C, Artaud F, Horn AS (1984) Biochemical evidence for the 5-HT agonist properties of PAT [8-hydroxy-2-(di-*n*-propylamino)tetralin] in the rat brain. Eur J Pharmacol 100:263–276

Hamon M, Cossery J-M, Spampinato U, Gozlan H (1986) Are there selective ligands for 5-HT_{1A} and 5-HT_{1B} receptor binding sites in brain? TIPS 7:336–338

Hibert M, Middlemiss DN (1986) Stereoselective blockade at the 5-HT autoreceptor and inhibition of radioligand binding to central 5-HT recognition sites by the optical isomers of methiothepin. Neuropharmacology 25:1–4

Hoyer D, Engel G, Kalkman HO (1985) Molecular pharmacology of 5-HT_1 and 5-HT_2 recognition sites in rat and pig brain membranes: radioligand binding studies with (^{3}H)-5-HT, (^{3}H)8-OH-DPAT, (−)(^{125}I)iodocyanopindolol, (^{3}H)mesulergine and (^{3}H)ketanserin. Eur J Pharmacol 118:13–23

Hoyer D, Pazos A, Probst A, Palacios JM (1986a) Serotonin receptors in the human brain. II. Characterization and autoradiographic localization of 5-HT_{1C} and 5-HT_2 recognition sites. Brain Res 376:97–107

Hoyer D, Srivatsa S, Pazos A, Engel G, Palacios JM (1986b) (^{125}I) LSD labels 5-HT_{1C} recognition sites in pig choroid plexus membranes. Comparison with (^{3}H)mesulergine and (^{3}H)5-HT binding. Neurosci Lett 69:269–274

Hutson PH, Dourish CT, Curzon G (1986) Neurochemical and behavioral evidence for mediation of the hyperphagic action of 8-OH-DPAT by 5-HT cell body autoreceptors. Eur J Pharmacol 129:347–352

Leysen JE, Niemegeers CJE, Van Nueten JM, Laduron PM (1982) (^{3}H)Ketanserin (R 41 468), a selective ^{3}H-ligand for serotonin$_2$ receptor binding sites. Mol Pharmacol 21:301–314

Leysen JE, Gommeren W, Van Gompel P, Wynants J, Janssen PFM, Laduron PM (1985) Receptor binding properties in vitro and in vivo of ritanserin: a very potent and long acting serotonin-S_2 antagonist. Mol Pharmacol 27:600–611

Lucki I, Nobler MS, Frazer A (1984) Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J Pharmacol Exp Ther 228:133–139

Lyon RA, Titeler M, Glennon RA (1986) Serotonin receptor selectivity of serotonergic drugs: the role of a 5-HT_2 agonist (^{3}H-DOB) radioligand. Soc Neurosci Abstr 12:311

Markstein R, Hoyer D, Engel G (1986) 5-HT_{1A}-receptors mediate stimulation of adenylate cyclase in rat hippocampus. Naunyn-Schmiedeberg's Arch Pharmacol 333:335–341

Martin KF, Marsden CA (1986) In vivo voltammetry in the suprachiasmatic nucleus of the rat: effects of RU24969, methiothepin and ketanserin. Eur J Pharmacol 121:135–139

McKenney JD, Glennon RA (1986) TFMPP may produce its stimulus effects via a 5-HT_{1B} mechanism. Pharmacol Biochem Behav 24:43–47

Middlemiss DN (1985) The putative 5-HT_1 receptor agonist, RU24969, inhibits the efflux of 5-hydroxytryptamine from rat frontal cortex slices by stimulation of the 5-HT autoreceptor. J Pharm Pharmacol 37:434–437

Middlemiss DN, Spedding M (1985) A functional correlate for the dihydropyridine binding site in rat brain. Nature 314:94–96

Morali G, Larsson K (1984) Differential effects of a new serotonin-omimetic drug, 8-OH-DPAT, on copulatory behaviour and pelvic thrusting pattern in the male rat. Pharmacol Biochem Behav 20:185–187

Ortmann R (1984) Then 5-HT syndrome in rats as tool for the screening of psychoactive drugs. Drug Dev Res 4:593–606

Pedigo NW, Yamamura HI, Nelson DL (1981) Discrimination

of multiple ^{3}H-5-hydroxytryptamine binding sites in rat brain by neuroleptics. J Neurochem 36:220–226

Peroutka SJ (1985) Selective labelling of 5-HT_{1a} and 5-HT_{1b} binding sites in bovine brain. Brain Res 344:167–171

Peroutka SJ (1986) Pharmacological differentiation and characterization of 5-HT_{1a}, 5-HT_{1b}, and 5-HT_{1c} binding sites in rat frontal cortex. J Neurochem 47:529–540

Peroutka SJ, Snyder SH (1981) Two distinct serotonin receptors: regional variations in receptor binding in mammalian brain. Brain Res 208:339–347

Raiteri M, Maura G, Bonanno G, Pittaluga A (1986) Differential pharmacology and function of two 5-HT_1 receptors modulating transmitter release in rat cerebellum. J Pharmacol Exp Ther 237:644–648

Sills MA, Wolfe BB, Frazer A (1984) Determination of selective and nonselective compounds for the 5-HT_{1A} and 5-HT_{1B} receptor subtypes in rat frontal cortex. J Pharmacol Exp Ther 231:480–487

Sills MA, Lucki I, Frazer A (1985) Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. Life Sci 36:2463–2469

Smith DF (1986) The stereoselectivity of serotonin uptake in brain tissue and blood platelets: the topography of the serotonin uptake area. Neurosci Biobehav Rev 10:37–46

Smith LM, Peroutka SJ (1986) Differential effects of 5-hydroxytryptamine$_{1A}$ selective drugs on the 5-HT behavioral syndrome. Pharmacol Biochem Behav 24:1513–1519

Spencer DG Jr, Emmett-Oglesby (1985) Parallel processing strategies in the application of microcomputers to the behavioral laboratory. Behav Res Methods Instrum Comput 17:294–300

Spencer DG Jr, Traber J (1987) The interoceptive discriminative stimuli induced by the novel putative anxiolytic TVX Q 7821: behavioral evidence for the specific involvement of serotonin 5-HT_{1A} receptors. Psychopharmacology 91:25–29

Spencer DG Jr, Glaser T, Schuurman T, Traber J (1984) Behavioral and neurochemical correlates of the 5-HT1 receptor. Soc Neurosci Abstr 10:1072

Spencer DG Jr, Glaser T, Traber J (1985) The relationship between the interoceptive stimuli produced by 5-methoxy-N,N-dimethyltryptamine and the serotonin 5-HT1 receptor. Naunyn-Schmiedeberg's Arch Pharmacol 330:R66

Spencer DG Jr, Glaser T, Traber J (1986) The role of the 5-HT_{1A} receptor in the interoceptive discriminative stimuli generated by 5-methoxy-dimethyltryptamine. Soc Neurosci Abstr 12:574

Sprouse JS, Aghajanian GK (1986) (−)-Propranolol blocks the inhibition of serotonergic dorsal raphe cell firing by 5-HT_{1A} selective agonists. Eur J Pharmacol 128:295–298

Svensson L (1985) Effects of 8-OH-DPAT, lisuride and some ergot-related compounds on the acoustic startle response in the rat. Psychopharmacology 85:469–475

Titeler M, Herrick K, Lyon RA, McKenney JD, Glennon RA (1985) (^{3}H)DOB: a specific agonist radioligand for 5-HT_2 serotonin receptors. Eur J Pharmacol 117:145–146

Traber J, Davies MA, Dompert WU, Glaser T, Schuurman T, Seidel P-R (1984) Brain serotonin receptors as a target for the putative anxiolytic TVX Q 7821. Brain Res Bull 12:741–744

Traber J, Glaser T, Spencer DG, Schuurman T, Zilles K, Schleicher A (1985) Behavioral pharmacology and autoradiographic brain distribution of a novel anxiolytic: TVX Q 7821. Proceedings of the IVth World Congress of Biological Psychiatry:80

Tricklebank MD, Forler C, Middlemiss DN, Fozard JR (1985) Subtypes of the 5-HT receptor mediating the behavioural responses to 5-methoxy-N,N-dimethyltryptamine in the rat. Eur J Pharmacol 117:15–24

Tricklebank MD, Middlemiss DN, Neill J (1986) Pharmacological analysis of the behavioral and thermoregulatory effects of the putative 5-HT_1 receptor agonist, RU 24969, in the rat. Neuropharmacology 25:877–886

Trulson ME, Trulson TJ (1986) Buspirone decreases the activity of serotonin-containing neurons in the dorsal raphe in freely-moving cats. Neuropharmacology 25:1263–1266

Van der Maelen CP, Matheson GK, Wilderman RC, Patterson LA (1986) Inhibition of serotonergic dorsal raphe neurons by systemic and iontophoretic administration of buspirone, a non-benzodiazepine anxiolytic drug. Eur J Pharmacol 129:123–130

Verge D, Daval G, Patey A, Gozlan H, El Mestikawy S, Hamon M (1985) Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the 5-HT_{1A} subtype. Eur J Pharmacol 113:463–464

Young R, Rosecrans JA, Glennon RA (1983) Behavioral effects of 5-methoxy-N,N-dimethyltryptamine and dose-dependent antagonism by BC-105. Psychopharmacology 80:156–160

Received January 1, 1987 / Final version May 6, 1987