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Mechanistic Investigation of the Stimulus Properties of 1-(3-Trifluoromethylphenyl)Piperazine

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HERNDON, J. L., M. E. PIERSON AND R. A. GLENNON. *Mechanistic investigation of the stimulus properties of 1-(3-trifluoromethylphenyl)piperazine.* PHARMACOL BIOCHEM BEHAV **43**(3) 739–748, 1992.—Using a standard two-lever operant procedure with rats trained to discriminate 1-(3-trifluoromethylphenyl)piperazine (TFMPP) (0.5 mg/kg) from saline, tests of stimulus antagonism and stimulus generalization were performed to better understand the stimulus properties of this agent. The agents examined for ability to antagonize the TFMPP stimulus were prazosin, quipazine, zacopride, buspirone, 8-hydroxy-2-(di-*N*-propylamino) tetralin (8-OH-DPAT), 1-(2-methoxyphenol)-4-[4-(2-phthalimido)butyl]-piperazine (NAN-190), haloperidol, and 1-(2-pyrimidinyl)piperazine (1-PP); only buspirone attenuated the response to TFMPP. In separate experiments, the lowest nondisrupting dose of buspirone (1.2 mg/kg) caused a rightward shift of the TFMPP dose–response curve (TFMPP alone, ED_{50} = 0.19 mg/kg; TFMPP + buspirone, ED_{50} = 0.43 mg/kg). In addition, 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one (CP 93, 129), 7-trifluoromethyl-4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxaline (CGS 12066B), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), 3-chlorophenylbiguanide (mCPBG), NAN-190, nisoxetine, zacopride, 1-PP, (+)-*N*-allylnormetazocine ((+)-NANM), and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) were analyzed in tests of stimulus generalization. The TFMPP stimulus generalized only to CGS 12066B (ED_{50} = 4.2 mg/kg) and (+)-NANM (ED_{50} = 8.8 mg/kg). Tests with DOI and MDMA resulted in partial generalization. Up to doses that disrupted behavior, all other agents had little effect on TFMPP-appropriate responding. The results of these and other published studies suggest roles for 5-hydroxytryptamine $_{1B}$ (5-HT_{1B}), 5-HT_{1C}, and, possibly, σ-receptors in the mediation of the TFMPP stimulus and indicate a lack of involvement of 5-HT_{1A}, 5-HT_2, dopaminergic, and adrenergic mechanisms in this behavior.

TFMPP Buspirone Drug discrimination Stimulus generalization 5-HT 5-HT receptor subtypes

IN the years since our initial report (11) that 1-(3-trifluoromethylphenyl)piperazine (TFMPP) serves as a discriminative stimulus in animals, several studies, including our own, have implicated a role for the 5-hydroxytryptamine $_{1B}$ (5-HT_{1B}) receptor subtype in the mediation of this behavior (4,30,35). These early studies, conducted prior to the discovery of some of the more recently described 5-HT receptors, based their conclusions primarily upon the lack of TFMPP stimulus generalization to agents "selective" for other subpopulations of serotonergic binding sites [e.g., 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT), quipazine, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)], as well as on the generalization that occurs to agents selective for 5-HT_{1B} receptors [e.g., 1-(3-chlorophenyl)piperazine (mCPP), RU 24969]. To date, no agent has been reported that completely blocks the TFMPP stimulus and this lack of selective antagonism has hampered attempts at characterizing the TFMPP stimulus. Furthermore, many of the above agents are now recognized as being much less selective than originally reported.

The selectivity of TFMPP as a 5-HT_{1B} serotonergic agent has been questioned. The binding profiles of TFMPP and related arylpiperazines at various central 5-HT receptors show an apparent lack of selectivity (9,38). For example, TFMPP binds at 5-HT_{1B} and [^{3}H]DOB-labeled 5-HT_2 sites with equal affinity (K_i = 27 and 30 nM, respectively). Furthermore, its binding affinity at certain other serotonergic sites is less than an order of magnitude lower than its affinity at 5-HT_{1B} and 5-HT_2 sites (9,38). In addition, many behavioral responses to TFMPP may be associated with receptors other than 5-HT_{1B} receptors. For example, TFMPP stimulus generalization oc-

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curs to the 5-HT_{1C} agent mesulergine, leading us to suggest that mesulergine may be a 5-HT_{1C} partial agonist and that the TFMPP stimulus may involve a 5-HT_{1C} component of action (14). The TFMPP stimulus also generalizes to the 5-HT_{1B}/5-HT_{1C} agonist mCPP (30), and the hypophagic (21,22), hypolocomotor (23,28), and anxiogenic (26) effects of TFMPP and structurally related mCPP have also been suggested to arise from 5-HT_{1C} receptor activation. In fact, like mCPP (24), TFMPP is now considered a nonselective 5-HT_{1C} agonist.

In addition to mCPP, several other "selective" agents that had been originally used to characterize the TFMPP stimulus have since been found to be nonselective. Quipazine, like the related arylpiperazines TFMPP and mCPP, displays an appreciable affinity for multiple 5-HT receptors (9). We have also shown that DOM, like many 5-HT_2 ligands, possesses high affinity for 5-HT_{1C} sites (40). Furthermore, RU 24969, in addition to its binding at 5-HT_{1B} sites, binds with high affinity at 5-HT_{1A} sites (42) and in pigeons (which lack 5-HT_{1B} receptors) trained to discriminate RU 24969 from saline stimulus generalization occurs to the 5-HT_{1A} agonist 8-OH-DPAT but not to TFMPP (19).

We previously raised the possibility of α_1-adrenergic, dopaminergic, and 5-HT_{1C} serotonergic components to the TFMPP stimulus (14). In an effort to better characterize the stimulus properties of TFMPP, we began a search for agents that could serve as a TFMPP antagonist. Preliminary evidence in our laboratory indicated that the antianxiety agent buspirone, a 5-HT_{1A} ligand, partially antagonizes the TFMPP stimulus. Buspirone has been variously reported to be a 5-HT_{1A} agonist, partial agonist, and antagonist (39). In earlier studies we have shown that neither the selective 5-HT_{1A} agonist 8-OH-DPAT nor buspirone produce TFMPP stimulus generalization (15). Others have found, at least at one relatively high dose (0.32 mg/kg), that 8-OH-DPAT fails to antagonize the TFMPP stimulus (4). Nevertheless, a detailed investigation of the possible antagonism of the TFMPP stimulus by a 5-HT_{1A} agonist (i.e., 8-OH-DPAT) or a putative 5-HT_{1A} antagonist [e.g., 1-(2-methoxyphenol)-4-[4-(2-phthalamido)butyl]piperazine (NAN-190)] has not been reported. In addition, buspirone also possesses dopaminergic activity (34), suggesting the possible involvement of a dopaminergic mechanism in the discriminative stimulus of TFMPP. A recent report (27) showed that buspirone has considerable affinity for [^{3}H]3-PPP-labeled σ-receptors (IC_{50} = 129 nM). Therefore, to better understand the underlying mechanisms of the TFMPP stimulus we further investigated the potential involvement of α_1-adrenergic, serotonergic, dopaminergic, and σ-receptors.

METHOD

Animals used in this study were 15 male Sprague-Dawley (225–350 g) rats. Animals were housed individually and had free access to water. They were maintained at 80% of their free-feeding body weight by partial food deprivation. The discrimination training procedure and stimulus generalization studies were conducted as previously described in greater detail (11) and will only be briefly outlined here. Using standard two-lever operant chambers (Coulbourn Instruments, model E10-10), animals were trained to discriminate TFMPP from saline employing a variable-interval 15-s schedule of reinforcement for food (sweetened powdered milk) reward, that is, after lever-responding was established each daily session was preceded by intraperitoneal administration of either TFMPP (0.5 mg/kg) or vehicle (0.9% saline, 1.0 ml/kg). A presession injection interval of 15 min was used and the training sessions were of 15 min duration. Responding on one of the levers was reinforced after administration of TFMPP and responses on the opposite lever were reinforced after administration of saline; the right lever was designated the drug-appropriate lever for approximately half the animals. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. Data collected during the extinction sessions included responses on the drug-appropriate lever (as a percent of total responses) and response rates (responses per minute). Once animals consistently made greater than 80% of their responses on the drug-appropriate lever after administration of TFMPP, and less than 20% of their responses on this same lever after administration of saline (for 3 consecutive weeks), the stimulus generalization studies were begun.

Stimulus Generalization Studies

Maintenance of the TFMPP/saline discrimination was ensured by continuation of the training sessions throughout this part of the study. On one of 2 days prior to a generalization test, approximately half the animals would receive training drug and half would receive saline; after an initial 2.5-min extinction period, training was continued for 12.5 min. Animals not meeting the original 80/20% criteria were excluded from the immediately following generalization test session. During investigations of stimulus generalization, test sessions were interposed among the training sessions; however, after the 2.5-min extinction period animals were returned to their home cages. Doses of challenge drugs were administered in random order, using a 15-min presession injection interval (except where otherwise noted), to groups of normally three to six rats. Percent TFMPP-appropriate responding and response rates were recorded. Stimulus generalization was said to have occurred when animals made $\geq$ 80% of their responses on the drug-appropriate lever; animals making fewer than five total responses during the 2.5-min extinction session were reported to be disrupted. ED_{50} doses (i.e., doses at which animals would be expected to make 50% of their responses on the drug-appropriate lever) were calculated by the method of Finney (6).

Stimulus Antagonism Studies

During the course of these studies, TFMPP/saline discrimination was maintained as described above. Tests of stimulus antagonism evaluated the effect of test drugs in combination with TFMPP on TFMPP-appropriate responding. Doses of test drugs were administered 15 min prior to administration of (0.5 mg/kg) TFMPP (unless otherwise noted); 15 min later, animals were tested. Percent TFMPP-appropriate responding and response rates were recorded, as above, during a 2.5-min extinction session.

Drugs

Buspirone HCl was obtained from Dr. J. Rosecrans (MCV/VCU). 7-Trifluoromethyl-4-(4-methyl-1-piperazinyl)-pyrolo[1,2-a]quinoxaline dimaleate (CGS 12066B) was obtained from CIBA-GEIGY Corp. (Summit, NJ). 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one dihydrate (CP 93, 129) was obtained from Pfizer, Inc. (Groton, CT). Nisoxetine HCl was obtained from the Eli Lilly Co. (Indianapolis, IN). Zacopride HCl was obtained from A. H. Robins (Richmond, VA). Haloperidol (HALDOL®) for injection was purchased from the MCV Hospital Pharmacy. 1-(2,5-Dimeth-

oxy-4-iodophenyl)-2-aminopropane HCl (DOI), *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA), NAN-190 HBr, 1-(2-pyrimidinyl)piperazine HCL (1-PP), and 3-chlorophenylbiguanide (mCPBG) were previously synthesized in our laboratory. (+)-N-Allylnormetazocine HCl (NANM) was obtained from NIDA (Bethesda, MD). The following compounds were obtained from commercial sources: TFMPP HCl and 8-OH-DPAT HBr (Research Biochemicals Inc., Natick, MA), prazosin HCl (Sigma Chemical Co., St. Louis, MO), and quipazine maleate (Miles Laboratories, Elkhart, IN). With the exception of the compounds noted below, solutions of all agents were prepared fresh daily in sterile 0.9% saline. Haloperidol for injection (5.0 mg/ml) was diluted to the appropriate dosage in saline. CP 93,129 (free base) was first dissolved in one equivalent of 0.01 N hydrochloric acid before dilution with saline. All injections were via the intraperitoneal route.

RESULTS

The TFMPP discrimination was maintained throughout the course of this study such that animals made greater than 80% of their responses on the TFMPP-appropriate lever after administration of 0.5 mg/kg TFMPP and less than 20% of their responses on the same lever after administration of 1.0 ml/kg saline. The results of the TFMPP stimulus antagonism studies are shown in Table 1; of the agents examined, only buspirone was effective in attenuating the TFMPP stimulus when administered in combination with TFMPP. Four doses of prazosin were tested; the highest dose (0.5 mg/kg) produced 85% TFMPP-appropriate responding but significantly reduced response rates to 50% of that for TFMPP administered alone. Two doses of zacopride were tested and the highest dose tested (1.0 mg/kg) resulted in 100% TFMPP-appropriate responding. Up to doses that disrupted behavior, quipazine, 8-OH-DPAT, NAN-190, haloperidol, and 1-PP all resulted in TFMPP-appropriate responding when administered in combination with TFMPP. All animals not disrupted at 0.05 and 0.1 mg/kg 8-OH-DPAT and 0.1 mg/kg haloperidol responded 100% on the TFMPP-appropriate level. Buspirone at the lowest nondisrupting dose (1.2 mg/kg) produced 53% TFMPP-appropriate responding when administered with the training dose of TFMPP. In separate experiments, buspirone (1.2 mg/kg) in combination with doses of TFMPP displaced the dose-response curve for TFMPP in a rightward fashion in animals trained to discriminate 0.5 mg/kg TFMPP from saline (Fig. 1); for TFMPP alone, the ED_{50} dose is 0.19 mg/kg (Table 2) while in animals pretreated with buspirone (1.2 mg/kg) the ED_{50} dose is 0.43 mg/kg. Response rates were not significantly effected except: a) for haloperidol and 1-PP, where all doses tested depressed response rates by 50–70% of that observed for saline (or TFMPP alone); b) at the highest nondisruption doses tested, where response rates were depressed by 50–70%; and c) where disruption of behavior occurred.

The results of the stimulus generalization studies are shown in Table 2. Of the challenge drugs administered, only CGS 12,066B and (+)-NANM produced TFMPP stimulus generalization; their ED_{50} values are 4.2 and 8.8 mg/kg, respectively. Administration of nisoxetine, up to doses that resulted in disruption of behavior, failed to produce stimulus generalization; the maximum response (17%) occurred with a 3.0-mg/kg dose. Five doses of CP 93,129 were tested; the maximum response (20%) was obtained at 3.0 mg/kg. The highest dose tested (12.0 mg/kg) produced 9% TFMPP-appropriate responding. Three doses of zacopride were evaluated; the maximum response (21%) occurred with 1.0 mg/kg. The highest dose tested (2.0 mg/kg) resulted in 3.5% TFMPP-appropriate responding and significantly reduced response rates. Four doses of mCPBG were evaluated; the highest nondisrupting dose (2.0 mg/kg) produced the maximum response (29%) but significantly reduced response rates. NAN-190 (0.5 mg/kg) and 1-PP (13.5 mg/kg) produced a maximum of 10 and 29% TFMPP-appropriate responding, respectively. At the highest doses tested, administration of NAN-190 (3.0 mg/kg) and 1-PP (15.0 mg/kg) resulted in disruption of behavior. Administration of DOI and MDMA (although not necessarily at their highest dose tested) both resulted in partial generalization; maximal TFMPP-appropriate responding for these agents was 35% (at 0.3 mg/kg) and 42% (1.0 mg/kg), respectively. Again, there was no significant effect on response rates except: a) at the highest nondisruption doses of MDMA and zacopride; b) for (+)-NANM, where a 50% depression was seen at 8.0 mg/kg and at the highest nondisruption dose (13.0 mg/kg) tested; c) for nisoxetine and mCPBG, where response rates were depressed >50% at most test doses; and d) where disruption of behavior occurred.

DISCUSSION

Adrenergic Involvement

In our earlier work, we raised the possibility that α_1-adrenergic receptors may be involved in the stimulus effects of TFMPP (14). This possibility arises partly from the fact that mesulergine, an agent that generalizes to the TFMPP stimulus (14), displays modest affinity for α_1-adrenergic receptors (3). Although we considered this involvement unlikely and at best minimal, it could not be discounted on the basis of the available evidence. Therefore, we tested the selective α_1-adrenergic antagonist prazosin (5) for its ability to attenuate the TFMPP stimulus (Table 1).Up to doses that significantly reduce animals' response rates, prazosin produces no antagonism of this effect. Additional support is provided by the lack of any activity for NAN-190 (Tables 1 and 2, vide infra), a 5-HT_{1A} agent (K_i = 0.6 nM) with known affinity for α_1-adrenergic receptors (K_i = 0.8 nM) (13). TFMPP possesses a modest affinity for α_2- as well as β-adrenergic receptors (K_i = 230 and 2,417 nM, respectively) (31), suggesting alternative adrenergic mechanisms for its discriminative stimulus properties. To test the general role, if any, for adrenergic receptors in the TFMPP stimulus, we evaluated the selective adrenergic uptake inhibitor nisoxetine in tests of TFMPP stimulus generalization. The TFMPP stimulus failed to generalize to nisoxetine, up to doses of the challenge drug that significantly disrupted behavior, arguing against a role for adrenergic receptors in the discriminative stimulus properties of TFMPP.

5-HT_{1B} Involvement

Considerable evidence has been developed to suggest involvement of a 5-HT_{1B} mechanism in the stimulus effects of TFMPP (30,35). Recent research has resulted in the development of two new 5-HT_{1B}-selective agonists: CP 93,129 and CGS 12066B. CP 93,129 is an analog of RU 24969 with significantly increased selectivity for 5-HT_{1B} receptors (200-fold greater affinity for 5-HT_{1B} than for 5-HT_{1A} receptors) (29). However, CP 93,129 does not substitute for TFMPP in TFMPP-trained animals (Table 2). This lack of effect was seen at doses nearly 300 times that needed to inhibit feeding when directly infused into the paraventricular medial hypothalamus

TABLE 1

RESULTS OF STIMULUS ANTAGONISM STUDIES

Pretreatment*	(mg/kg)	n†	% TFMPP-Appropriate Responding (±SEM)‡	Responses/Min (±SEM)‡
Prazosin	0.04	5/5	78 (20)	12.2 (4.1)
	0.1	4/6	90 (6)	8.3 (4.4)
	0.3	4/6	91 (5)	6.3 (0.4)
	0.5	6/6	85 (15)	3.9 (1.0)
Quipazine	0.2	3/4	97 (3)	20.7 (8.6)
	1.0	4/6	88 (7)	4.4 (1.8)
	1.2	3/4	75 (17)	9.2 (6.8)
	1.5	4/6	94 (6)	10.6 (3.1)
	2.0	2/6	—§	
Zacopride	0.1	3/3	95 (5)	7.2 (4.6)
	1.0	4/4	100	8.1 (3.4)
Buspirone	0.5	4/4	75 (5)	6.3 (2.1)
	1.0	3/4	59 (20)	10.0 (3.5)
	1.2	6/8	53 (11)	8.1 (2.6)
	1.8	0/6	—	
	2.2	2/5	—	
8-OH-DPAT	0.01	4/4	95 (5)	6.3 (2.1)
	0.05	1/3	—	
	0.1	1/3	—	
	0.2	0/3	—	
	0.5	0/3	—	
NAN-190	0.2	4/5	91 (6)	10.2 (3.4)
	0.5	3/5	90 (10)	3.7 (0.7)
	2.0	4/5	85 (8)	5.3 (0.8)
	2.2	1/4	—	
	3.0	2/5	—	
Haloperidol	0.01	2/3	100	2.8 (0.4)
	0.03	4/4	96 (4)	3.1 (0.6)
	0.06	0/3	—	
	0.1	2/7	—	
1-PP	0.2	4/4	95 (5)	3.2 (1.0)
	1.0	3/3	97 (3)	2.8 (0.6)
	1.4	3/4	94 (6)	2.8 (0.6)
	2.0	1/4	—	

*Animals were pretreated with test drugs 15 min prior to TFMPP (0.5 mg/kg) administration, except: prazosin (30 min), quipazine (10 min), and NAN-190 (5 min). There was a 15-min presession injection interval after administration of TFMPP.

†n = number of animals responding/number to receive drug.

‡Data obtained during a 2.5-min extinction period.

§Disruption of behavior (i.e., no responding).

(PVN) of rats (29), a purported 5-HT_{1B} receptor-mediated behavior (25). Whereas lack of stimulus generalization could be due to a lack of a common behavioral activity at 5-HT_{1B} receptors for TFMPP and CP 93,129, it could as well be due to an inability of CP 93,129 to penetrate the blood–brain barrier. Indeed, during the course of this study a similar lack of systemic activity was reported, leading the authors to suggest a structural limitation to free distribution of CP 93,129 in the brain (41). CGS 12066B has been reported to be a 5-HT_{1B}-selective agonist (31). This claim has been called into question with different authors asserting that it is, in fact, selective for 5-HT_{1A} over 5-HT_{1B} sites (29). Nevertheless, CGS 12066B administration results in stimulus generalization (Table 2; ED_{50} = 4.2 mg/kg). Given the fact that the affinity of CGS 12066B at 5-HT_{1A} sites is significant [IC_{50} = 876 nM (31) or 19 nM (29)], the question remains open as to whether TFMPP stimulus generalization to CGS 12066B is a 5-HT_{1A}- or 5-HT_{1B}-mediated effect. However, that the selective 5-HT_{1A} agonist 8-OH-DPAT is inactive in tests of TFMPP stimulus generalization, and that the putative 5-HT_{1A} antagonist NAN-190 blocks the 8-OH-DPAT stimulus (12) but not the TFMPP stimulus, would argue against the former possibility and for a role for 5-HT_{1B} mediation.

5-HT_{1C}/5-HT_2 Involvement

In the time since our original publication on the discriminative stimulus effects of TFMPP (11), much has been done on the characterization of central serotonin receptors, resulting in an increased number of known sites (7). For example, we

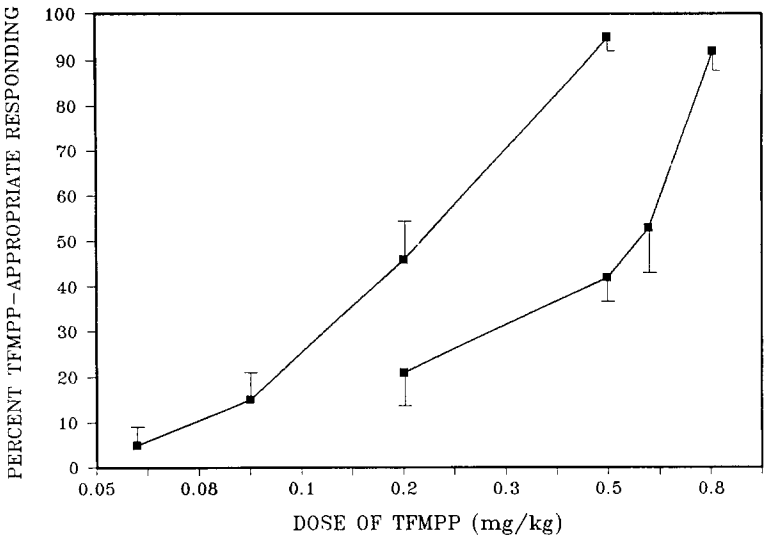

FIG. 1. Stimulus effects of TFMPP (left) and TFMPP + 1.2 mg/kg buspirone (right) in animals trained to discriminate 0.5 mg/kg TFMPP from saline. Buspirone doses were administered 15 min prior to TFMPP.

originally used DOM as a selective ligand to characterize 5-HT_2 involvement in the TFMPP stimulus (11). However, we have since shown that DOM and related phenylalkylamines have significant affinity for 5-HT_{1C} sites (40), a subpopulation of serotonergic sites with a significant genetic relationship to 5- HT_2 receptors (33) but that, at the time of our first TFMPP stimulus studies, was yet to be discovered. We have shown that DOM (1.0 mg/kg) also serves as a discriminative stimulus in rats and that its effects are potently attenuated by pretreatment of animals with the 5-HT_2 antagonists ketanserin (ED_{50} = 0.18 mg/kg) and pirenperone (ED_{50} = 0.01 mg/kg) (17). The DOM stimulus does not generalize to TFMPP (17); however, the TFMPP stimulus partially generalizes to DOM (11). We originally attributed the partial generalization of the TFMPP stimulus to DOM [up to 68% TFMPP-appropriate responding (11)] to a "5-HT_1 component" of DOM. Subsequently, given that the TFMPP stimulus generalizes to mesulergine, we raised the possibility of a 5-HT_{1C} component of the TFMPP stimulus (14); this may explain the partial generalization of the TFMPP stimulus to DOM and may also account for the 5-HT_1 component of DOM that we had earlier proposed. To test this possibility, we evaluated the structurally related phenylalkylamine DOI, which binds at 5-HT_{1C} sites with higher affinity than DOM (40), in rats trained to discriminate TFMPP from saline. Although not as significant as with DOM, DOI also produces only partial generalization (35% at 0.3 mg/kg; Table 2). Doses greater than 1.2 mg/kg DOI resulted in disruption of behavior. Because it is possible that TFMPP stimulus generalization might have occurred at higher doses had animals' behavior not been disrupted, a 5-HT_{1C} component of action cannot be ruled out. Indeed, Schechter (35) reported up to 50% TFMPP-appropriate responding after administration of DOI. However, because TFMPP appears to behave as a 5-HT_2 antagonist (9), and because the TFMPP stimulus is not attenuated by pretreatment with 5-HT_2 antagonists (4,11), it is unlikely that the TFMPP stimulus involves a 5-HT_2 agonist mechanism. Indeed, administration of TFMPP in combination with DOM, in rats trained to discriminate DOM from saline, results in attenuation of DOM-appropriate responding (10). In earlier studies, we (30) and others (4) demonstrated that the TFMPP stimulus partially generalizes to the structurally related arylpiperazine quipazine. Although quipazine is a nonselective agent that binds at several populations of 5-HT sites, it is equipotent at binding to 5-HT_{1B} and 5-HT_{1C} receptors (38). Evidence from functional assays suggest that quipazine is an agonist at 5-HT_{1C} receptors but an antagonist at 5-HT_{1B} receptors (38). To determine if quipazine may be an antagonist of the TFMPP stimulus, it was examined for its ability to attenuate the response to TFMPP in rats trained to discriminate TFMPP from saline. Administered in combination with the training dose of TFMPP, quipazine had essentially no effect on the TFMPP stimulus at doses up to 1.5 mg/kg (Table 1). A dose of 2 mg/kg resulted in disruption of behavior. This lack of antagonism by quipazine, together with a) partial (30–60%) generalization to quipazine (4,30), b) partial generalization to the 5-HT_{1C}/5-HT_2 agonists DOM and DOI, c) generalization to the 5-HT_{1C} partial agonist mesulergine (14), and d) lack of stimulus antagonism by 5-HT_2 antagonists (4,11), suggests that the TFMPP stimulus may possess a 5-HT_{1C} component of action.

5-HT_3 Involvement

Certain arylpiperazines bind with high affinity to 5-HT_3 receptors. For example, quipazine and mCPP, two agents that in the past were often used to characterize the TFMPP stimulus, have since been shown to bind to 5-HT_3 receptors (K_i = 1 and 30 nM, respectively) (9,20). TFMPP itself displays a modest affinity for 5-HT_3 receptors (K_i = 2,090 nM) (43). Therefore, we investigated the stimulus antagonism and generalization properties of zacopride (a selective 5-HT_3 antagonist) in animals trained to discriminate TFMPP from saline. At the doses tested, zacopride neither antagonized nor substituted for the TFMPP stimulus. In addition, we evaluated the selective 5-HT_3 receptor agonist mCPBG in tests of stimulus generalization. We have recently shown that the selective 5-HT_3 agonist 2-methyl-5-hydroxytryptamine (2-Me-5-HT) serves as a training drug in drug discrimination studies and that mC-

TABLE 2
RESULTS OF STIMULUS GENERALIZATION STUDIES

Agent*	(mg/kg)	n†	% TFMPP-Appropriate Responding (±SEM)‡	Responses/Min (±SEM)‡
TFMPP	0.06	6/6	5 (4)	12.6 (2.1)
	0.1	6/6	15 (7)	14.1 (3.6)
	0.2	6/6	46 (12)	11.3 (1.8)
	0.5	15/15	95 (3)	7.8 (2.6)
		ED_{50} = 0.19 (0.11–0.31) mg/kg§		
CP 93,129	1.0	3/3	17 (8)	6.5 (1.2)
	3.0	4/4	20 (6)	20.1 (10.0)
	5.0	2/3	10 (10)	5.6 (2.4)
	7.0	4/4	2 (2)	5.5 (1.4)
	12.0	5/5	9 (6)	7.8 (2.6)
CGS 12,066B	0.5	3/3	24 (13)	11.2 (4.3)
	1.2	3/4	0	11.2 (7.2)
	2.0	3/4	17 (8)	8.3 (3.1)
	4.0	3/4	38 (14)	7.1 (2.2)
	6.0	7/8	66 (23)	7.2 (3.3)
	7.0	3/4	83 (6)	5.1 (2.0)
	8.0	0/4	–¶	
		ED_{50} = 4.2 (2.5–7.2) mg/kg		
Nisoxetine	0.5	3/3	0	3.2 (0.6)
	3.0	3/3	17 (17)	2.7 (0.2)
	3.5	2/3	0	2.6 (0.6)
	4.0	0/3	–	
	5.0	2/5	–	
Zacropride	0.1	3/3	19 (10)	6.1 (1.9)
	1.0	4/4	21 (21)	5.6 (2.3)
	2.0	2/3	3.5 (3.5)	2.4 (0.4)
mCPBG	0.3	2/3	8.5 (8.5)	2.8 (0.4)
	1.5	2/3	0	2.4 (0.4)
	2.0	2/3	29 (29)	3.4 (0.6)
	5.0	1/3	–	
DOI	0.1	3/3	18 (3)	16.4 (4.2)
	0.3	3/4	35 (1)	17.8 (6.6)
	0.5	3/3	30 (6)	13.0 (6.1)
	0.8	3/3	30 (5)	14.6 (2.2)
	1.0	3/3	14 (10)	7.3 (2.8)
	1.2	2/4	15 (13)	6.8 (2.4)
	1.3	0/4	–	

continued

PBG substitutes for 2-Me-5-HT in rats trained to discriminate 2-Me-5-HT from saline (16). However, in tests of TFMPP stimulus generalization mCPBG did not substitute for the TFMPP stimulus. This result, taken together with the demonstrated inability of zacopride to antagonize or substitute for the TFMPP stimulus, argues against involvement of 5-HT_3 receptors in the stimulus properties of TFMPP.

5-HT_{1A} Involvement

In tests of stimulus antagonism, buspirone partially attenuates the TFMPP stimulus (Table 1). Attempts to administer buspirone in doses sufficient to result in complete blockade resulted in disruption of behavior. A comparison of the dose-response curve for TFMPP (ED_{50} = 0.19 mg/kg) to the dose-response curve of TFMPP in animals pretreated with the highest nondisrupting dose of buspirone (Table 1; 1.2 mg/kg) resulted in a rightward shift (ED_{50} = 0.43 mg/kg) of the curve (Fig. 1). Apparently, the disruptive effects of buspirone prevent a demonstration of complete stimulus antagonism (Table 1); nevertheless, buspirone does produce a surmountable antagonism of the TFMPP stimulus (Fig. 1). Buspirone has effects at more than one central binding site but key among them is its activity at 5-HT_{1A} sites. Buspirone has at various times been termed a 5-HT_{1A} agonist, antagonist, and partial agonist (39). To determine if the inhibition of the TFMPP stimulus is mediated by 5-HT_{1A} receptors, tests were conducted employing 8-OH-DPAT and NAN-190. We have previously shown that neither the selective 5-HT_{1A} agonist 8-OH-DPAT nor buspirone substitute for TFMPP (15). In this study, 8-OH-DPAT was further shown to be ineffective in attenuating the TFMPP stimulus (Table 1; note: animals not disrupted at 0.05 and 0.1 mg/kg responded 100% on the TFMPP-appropriate lever). This confirms the result of an earlier single-dose study with 8-OH-DPAT (4). In addition, NAN-190, a compound developed in our laboratory as a selective

TABLE 2 (continued)

Agent*	(mg/kg)	n†	% TFMPP-Appropriate Responding (±SEM)‡	Responses/Min (±SEM)‡
NAN-190	0.5	4/5	12 (3)	8.5 (1.4)
	2.0	2/4	6 (6)	5.0 (1.4)
	2.6	3/5	10 (3)	6.1 (1.0)
	3.0	1/5	–	
1-PP	0.5	5/5	17 (6)	14.2 (0.6)
	1.0	3/5	17 (10)	8.0 (3.4)
	4.0	5/6	14 (11)	8.3 (3.4)
	8.0	4/7	15 (9)	8.0 (2.1)
	12.0	5/5	23 (17)	7.1 (4.7)
	13.5	4/7	29 (11)	5.8 (1.4)
	15.0	1/5	–	
(+)–NANM	1.0	3/3	5 (3)	11.6 (3.4)
	3.0	3/4	8 (4)	18.4 (10.3)
	5.0	3/3	6 (6)	12.3 (4.3)
	8.0	2/3	52 (9)	3.8 (1.8)
	10.0	8/12	52 (11)	13.0 (2.9)
	12.0	4/9	58 (8)	17.0 (4.4)
	13.0	3/6	89 (11)#	3.5 (1.8)
	14.0	1/4	–	
			ED_{50} = 8.8 (4.8–16.4) mg/kg	
MDMA	0.5	3/3	4 (2)	19.5 (9.4)
	1.0	3/3	42 (16)	9.6 (1.9)
	1.5	1/3	–	
	2.0	0/4	–	
Saline (1 ml/kg)		15/15	9 (4)	9.5 (2.8)

*There was a 15-min presession injection interval after administration of test drugs.
†n = number of animals responding/number to receive drug.
‡Data obtained during a 2.5-min extinction period except #.
§ED_{50} value followed by 95% confidence limits.
¶Disruption of behavior (i.e., no responding).
#One animal inadvertently tested for 3.5-min extinction period.

5-HT_{1A} antagonist (12), neither substituted for (Table 2) nor antagonized (Table 1) the TFMPP stimulus. Taken together, including the antagonism exhibited by buspirone and the stimulus generalization that occurs to CGS 12066B, these data argue against 5-HT_{1A} involvement in the mediation of the TFMPP stimulus.

Dopaminergic Involvement

Buspirone also possesses affinity for central dopamine receptors (34). To evaluate the possible role of dopamine receptors in the antagonism of the TFMPP stimulus by buspirone, we examined the effects of the dopamine antagonist haloperidol. However, at relatively low doses haloperidol failed to antagonize the TFMPP stimulus (Table 1). At slightly higher doses (i.e., > 0.03 mg/kg), haloperidol in combination with TFMPP resulted in disruption of behavior (Table 1). Due to the disruptive effects produced by low doses of haloperidol, the present results are inconclusive; however, they are consistent with the lack of antagonism previously reported by Cunningham and Appel (4). Although spiperone partially antagonizes the TFMPP stimulus (4), the above results, coupled with a lack of stimulus generalization to the indirect acting dopamine agonist amphetamine and the dopamine agonist apomorphine (4), make a significant role for dopamine seem unlikely.

Buspirone is extensively metabolized in vivo to 1-PP (2). We examined 1-PP for effects in animals trained to discriminate TFMPP from saline. As 1-PP neither substituted for (Table 2) nor antagonized (Table 1) the TFMPP stimulus, the activity of buspirone in this assay is most likely not attributable to its conversion to this metabolite.

σ Involvement

As mentioned previously, buspirone has been recently shown to bind (IC_{50} = 129 nM) at σ-receptors (27). TFMPP also binds at σ-receptors with modest affinity (K_i = 1,340 nM) (18). This led us to investigate additional σ-ligands in tests of stimulus generalization. Substitution tests using the standard σ-agonist NANM resulted in stimulus generalization (ED_{50} = 8.8 mg/kg), pointing to a potential involvement for σ-receptors (or at least an NANM-related mechanism) in the mediation of the TFMPP stimulus. It might be noted that animals receiving 13 mg/kg NANM were severely disrupted; animals receiving doses of 10–14 mg/kg were also severely disoriented for at least 1 h after removal from the operant chambers.

We previously reported that certain designer drugs such as MDMA ("ecstasy") bind at σ-receptors (44). Consequently, this agent was evaluated in the present study. MDMA results in up to 42% TFMPP-appropriate responding (at a dose of 1

TABLE 3

SUMMARY OF DATA FOR MECHANISTIC INTERPRETATIONS

Receptor	Agent	Action	Comments
5-HT	Fenfluramine	5-HT release	Generalization*†
	Norfenfluramine	5-HT release	Generalization‡
	Metergoline	Antagonist	Attenuation†
5-HT_{1A}	8-OH-DPAT	Agonist	No generalization*†
			No antagonism§
	Buspirone	Partial agonist	No generalization§
			Attenuation§
	NAN-190	Antagonist	No generalization§
			No antagonism§
	Spiperone	Antagonist	Attenuation†
	Propranolol	Antagonist	No antagonism#
	Pindolol	Antagonist	No antagonism#
5-HT_{1B}	mCPP	Agonist	Generalization*†**
	CGS 12,066B	Agonist	Generalization§
	RU 24969	Agonist	Generalization† ††
5-HT_{1C}	Mesulergine	Partial agonist	Generalization#
	Mesulergine	Partial agonist	No antagonism#
	DOM	Agonist	Partial generalization††
	DOI	Agonist	Partial generalization‡§
	Quipazine	Agonist	Partial generalization*†
	mCPP	Agonist	Generalization*†
5-HT_{2}	DOM	Agonist	Partial generalization††
	DOI	Agonist	Partial generalization‡§
	Ketanserin	Antagonist	No antagonism††
	Pirenperone	Antagonist	No antagonism†
5-HT_{3}	mCPBG	Agonist	No generalization§
	Zacopride	Antagonist	No antagonism§
			No generalization§
Adrenergic	Prazosin	α-Antagonist	No antagonism§
	Nisoxetine	Uptake inhibitor	No generalization§
	Propranolol	β-Antagonist	No antagonism#
	Pindolol	β-Antagonist	No antagonism#
Dopaminergic	Haloperidol	Antagonist	No antagonism†§
	Spiperone	Antagonist	Attenuation†
	Amphetamine	Agonist	No generalization†
	Apomorphine	Agonist	No generalization†
σ	(+)NANM	Agonist	Generalization§

*Ref. 30.
†Ref. 4.
‡Ref. 35.
§Present study.
#Ref. 14.
**Ref. 15.
††Ref. 11.

mg/kg; Table 2) and disruption of behavior at slightly higher doses. Schechter (35) reported similar effects with MDMA in animals trained to discriminate TFMPP; interestingly, however, Schechter reported stimulus generalization to TFMPP in animals trained to discriminate MDMA from saline (36). It should be noted that TFMPP is a releaser of endogenous stores of 5-HT (1,32). Whereas the site of action of this release appears to be distinct from the 5-HT_{1B} autoreceptor (1), a consensus has emerged that the serotonergic effects of TFMPP are likely mediated by direct 5-HT receptor agonism (8,32). MDMA also possesses 5-HT-releasing capabilities (37) and the generalization that occurs to TFMPP has been attributed to this effect (36). The present study presents an alternative hypothesis that the σ-receptor (or a NANM-related mechanism) may be a common site of action of these two agents and may mediate a portion of the TFMPP stimulus. There is an absence of data regarding the serotonergic activities of the other σ-ligand utilized in this study (i.e., (+)-NANM) and it should be mentioned that other 5-HT-releasing agents (e.g., fenfluramine and norfenfluramine) generalize both in MDMA- and TFMPP-trained animals (4,30,35,36). Therefore, 5-HT release as a mechanism of action in the TFMPP stimulus generalization to MDMA remains a viable explanation.

SUMMARY

Buspirone (present study) and spiperone (4) partially attenuate the TFMPP stimulus. This combination of effects would normally conjure up visions of a dopaminergic, 5-HT_2, or 5-HT_{1A} mechanism. However, lack of complete stimulus antagonism by these agents, coupled with the results of tests of stimulus generalization and stimulus antagonism with other agents (see Table 3 for summary), fail to support these mechanisms. It is also unlikely that antagonism by buspirone is due to the buspirone metabolite 1-PP. On the basis that fenfluramine substitutes for, and metergoline partially antagonizes, the TFMPP stimulus, it is evident that a serotonergic mechanism is involved. Whereas radioligand binding studies indicate that TFMPP binds at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and 5-HT_3 receptors, the present (and previously published) drug discrimination studies all but eliminate a major role for 5-HT_{1A}, 5-HT_2, and 5-HT_3 receptors but implicate a role for 5-HT_{1B} and 5-HT_{1C} receptors (Table 3). The stimulus effects of TFMPP may possibly involve other, yet to be identified, 5-HT receptors.

A major role for dopaminergic and adrenergic receptors also seems unlikely on the basis of the results presented in Table 3. However, TFMPP and buspirone share modest binding affinities for σ-receptors, and the TFMPP stimulus generalizes to the σ-ligand (+)NANM. Thus, the possibility exists that TFMPP may produce some of its effects via a NANM-like (possibly a σ-receptor) mechanism.

Due to the complexity of the TFMPP stimulus, and because most of the standard ligands used to investigate this stimulus possess actions in addition to those that might be considered "TFMPP-like," TFMPP stimulus generalization and antagonism is invariably associated with severely depressed response rates. TFMPP does not seem to produce its stimulus effects solely via a 5-HT_{1B} mechanism as previously thought; TFMPP is, at best, a promiscuous ligand.

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