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Use of TFMPP Stimulus Properties as a Model of 5-HT_{1B} Receptor Activation

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SCHECHTER, M. D. *Use of TFMPP stimulus properties as a model of 5-HT_{1B} receptor activation.* PHARMACOL BIOCHEM BEHAV 31(1) 53–57, 1988.—Recent evidence indicates that when 1-(3-trifluoromethylphenyl)piperazine (TFMPP) is used as a training drug in the drug discrimination paradigm it produces a stimulus effect that is site-selective at the 5-HT_{1B} receptor. The present study sought to employ this procedure in order to assess the similarity of novel agents to TFMPP. First, rats were trained to reliably discriminate between the stimulus properties of intraperitoneally administered 1.0 mg/kg TFMPP and its vehicle. Following the acquisition of this discrimination, administration of various doses of TFMPP produced a typical dose-response relationship with an ED_{50} of 0.27 mg/kg. Rats were subsequently tested with another 5-HT_{1B} specific agonist 1-(3-chlorophenyl)piperazine (mCPP) and a 5-HT releasing agent norfenfluramine and both produced TFMPP-like discriminative responding in a dose-dependent manner. In contrast, the 5-HT_2 agonist 4-iodo-1-(2,5-dimethoxyphenyl)-2-aminopropane (DOI) did not generalize from TFMPP. Other drugs, previously trained in other rats and shown to generalize to TFMPP, viz., ethanol, tetrahydro-beta-carboline (THBC) and 3,4-methylenedioxymethamphetamine (MDMA) did not produce TFMPP-like responding. These results provide further evidence for the 5-HT_{1B} receptor acting as the site for the discriminative effects of TFMPP. In addition, the transfer of discrimination between TFMPP and either ethanol, THBC or MDMA appears to be asymmetrical. Reasons for this one-way generalization are suggested.

Drug discrimination TFMPP 5-HT_{1B} Serotonin Behavior Norfenfluramine MDMA Ethanol Rats

THERE is strong, and ever increasing, neurochemical and anatomical evidence that suggests the existence of numerous types of serotonin (5-HT) receptors in the central nervous sytem. These scientific advances have resulted from the recognition of molecules with high affinities and selectivities for individual receptor sites (3). Receptor classifications, as they resulted from the use of ligand-binding techniques, have also generated identification of site-selective agonists that may specifically affect each of these receptor types. The discovery of these site-selective agents may allow for the opportunity to study the specific actions and/or functions of 5-HT in the brain.

In an effort to determine the functional significance of each of these 5-HT binding sites, Glennon and his associates have reported an ingenious series of studies in which they employ the ability of drugs to function as discriminative stimuli. In each of these studies, they trained rats to discriminate the interoceptive cue produced by a site-specific 5-HT agonist. Thus, groups of rats were trained to discriminate the selective 5-HT_2 agonist DOM (8), the 5-HT_{1A}-selective agonist 8-OH DPAT (6) and a third group was trained to discriminate the 5-HT_{1B}-selective agonist TFMPP from its vehicle (9). These investigators reported that any one group of animals trained to a specific 5-HT receptor agonist would not discriminate (generalize to) either of the other two agents as the drug used in training. Thus, for example, the 8-OH DPAT trained rats generalize when treated with other 5-HT_{1A} agonists, but not to 5-HT_{1B} or 5-HT_2 agonists (6). This lack of cross-substitution among 5-HT receptor subtype agonists indicates the specificity of each of the agonists, as well as that of the drug discrimination procedure. Additional work in Glennon's laboratory (11), and an independent investigation in another laboratory (2), has well-characterized the discriminative stimulus properties of TFMPP as occurring via 5-HT_{1B} receptors; thus confirming previous in vitro studies (12). Previous work in this laboratory has shown that rats trained to discriminate various drugs generalize to TFMPP. Thus, rats trained with either 600 mg/kg ethanol (17), 1.5 mg/kg MDMA (16) or 20 mg/kg THBC (15) select the trained drug-appropriate lever after TFMPP administration. The purpose of the present investigation was to provide another independent verification of the ability of TFMPP to function as a drug capable of controlling discriminative responding and to employ this paradigm to investigate if drugs previously shown to generalize to TFMPP will produce a TFMPP-like response when administered to rats trained to discriminate TFMPP.

METHOD

Ten male rats (Sprague-Dawley/Zivic-Miller), with weights

TABLE 1

LEARNING RATE IN RATS (n=10) TRAINED TO DISCRIMINATE 1.0 mg/kg TFMPP FROM ITS VEHICLE

	Responses on TFMPP-Correct Lever After			
	TFMPP		Vehicle	
Weeks*	Quantal†	Quantitative‡ (SD)	Quantal	Quantitative (SD)
1 and 2	92.0	88.0 (6.0)	52.0	53.7 (27.5)
3 and 4	92.0	81.4 (5.1)	10.0	22.4 (5.6)

*Each two-week period consisted of 5 trials with 1.0 mg/kg TFMPP and 5 trials with its vehicle, injected intraperitoneally 20 min prior to training.

†Quantal measurement refers to percentage of rats selecting the TFMPP-correct lever.

‡Quantitative measurement refers to the number of responses upon the TFMPP-lever divided by the number of responses on both levers at the fulfillment of the selection criterion (10 presses) as a percentage.

ranging from 250–295 g at the beginning of experimentation, were housed individually in a temperature (21–23°C) controlled room; lights on from 0600–1800 hr. Individual weights were adjusted to approximately 85±5% of their freely feeding weights by daily rationing of commercial rat chow. Water was continuously available in the home cages throughout the experiment.

Ten standard rodent test chambers (Lafayette Instrument Co., Lafayette, IN) were each equipped with two operant levers placed 7 cm apart and 7 cm above the floor. A food receptacle for pellet (45 mg Noyes) delivery was mounted equidistant between the two levers and 2 cm above the grid floor. A sound-attenuating cubicle housed this test cage and was equipped with an exhaust fan and 9 W houselight. Experimental events and data collection were performed by solid-state programming equipment (Med Associates, E. Fairfield, VT) located in an adjacent room.

The training procedure is based upon previous reports from this laboratory (14–17). Briefly, rats were equally and randomly divided into two groups and trained to press either the left (n=5) or right (n=5) lever 20 min after intraperitoneal (IP) saline administration. Initially, rats responded on a fixed ratio 1 (FR1) schedule. This schedule was progressively increased in ratio during daily 15 min sessions, over 8–10 days, until an FR10 schedule was attained. Upon reaching the FR10 schedule after saline administration, the rats were trained, on an FR1 schedule, to press the other lever following an IP injection of an equal volume (1 ml/kg) containing 1.0 mg/ml TFMPP. The schedule for the second lever was also gradually increased in work requirements to attain the FR10 schedule; training to the FR10 on the second lever required 5–6 days. After attainment of this second FR10 schedule, the rats were put on a pseudorandom sequence for discrimination training. Thus, they were trained 5 days a week and, in each two-week period, there were 5 days with the drug lever (D) correct and 5 days with the saline lever (S) correct. The repeating pattern was D,S,S,D,D; S,D,D,S,S and all training sessions took place between 1000 and 1200 hr.

Each animal was considered to have accurately discriminated the drug, on any one day, if it responded ten times first on the correct (drug) lever before responding ten times on the incorrect (saline) lever. Likewise, when administered saline, on another day, rats were required to respond ten times on the saline-correct lever. The training criterion was met when the animals selected the correct lever, according to the state that they were in, i.e., TFMPP or saline, on 8 out of 10 consecutive trials. The number of trials required to meet this (8/10 correct) criterion has been called (13) the session-to-criterion (STC).

Dose-Response Testing

Once all ten rats met the criterion for training, dose-response testing began. In this series of experiments, the animals were tested for their discriminative performance to doses that differed from the 1.0 mg/kg TFMPP training dose. Thus, doses of 0.25 and 0.5 mg/kg were administered (IP) to the animals and, as with the training dose, 20 min later the rats were placed into the operant chamber and required to press one of the two levers ten times. Upon pressing one lever ten times the rat was immediately removed (without receiving reinforcement). This immediate removal was done during dose-response testing and for all subsequent tests to prevent any unintentional training. The TFMPP dose-response testing was performed on alternate days with maintenance testing. Maintenance testing refers to sessions in which animals received the training dose of TFMPP or saline interspersed between test days. This protocol served to counterbalance for any residual effects of the preceding day and also was intended to ensure the maintenance of the 80% level of performance; thus, animals were required to maintain an 80% correct lever selection on maintenance sessions to be included in the results.

Substitution Tests

Subsequent to the dose-effect studies, the well-maintained rats were administered 3–4 doses of various agents in an effort to determine if the TFMPP-induced interoceptive cue would transfer (generalize) to other drugs. The rationale (see the Discussion section) and the dose used for each of these agents was obtained from the recent scientific literature. The substitution sessions were, like the dose-response test, preceded by both TFMPP and saline maintenance sessions and were run in random order. Rats were removed upon making 10 responses on either lever.

TABLE 2

RESULTS OF TESTING VARIOUS DOSES OF TFMPP IN RATS (n=10) TRAINED TO DISCRIMINATE 1.0 mg/kg TFMPP FROM ITS VEHICLE

Dose of TFMPP (mg/kg)	Quantal	Quantitative (SD)
1.0	90.0	78.2 (7.2)
0.5	85.0	77.9 (10.3)
0.25	40.0	48.6 (6.3)
0.0 (vehicle)	5.0	17.1 (2.5)
ED_{50} (mg/kg)	0.27	0.21
(95% confid. limits)	(0.15–0.47)	(0.09–0.50)

TABLE 3

RESULTS OF SUBSTITUTION TESTS WITH DRUGS IN RATS (n=10) TRAINED TO DISCRIMINATE 1.0 mg/kg TFMPP FROM ITS VEHICLE

Drug	Dose (mg/kg)	Quantal	Quantitative (SD)
Norfenfluramine	2.0	80.0	72.1 (7.4)
	1.5	75.0	61.9 (2.8)
	1.0	60.0	53.3 (19.2)
	0.5	5.0	13.0 (5.4)
mCPP	1.2	95.0	87.6 (17.6)
	0.8	75.0	74.0 (7.9)
	0.6	65.0	59.5 (27.5)
	0.4	25.0	26.6 (1.9)
DOI	1.0	50.0	49.0 (1.5)
	0.8	20.0	30.0 (11.2)
	0.5	20.0	33.7 (0.1)
THBC	20.0	55.0	50.8 (12.9)
	15.0	45.0	46.4 (3.7)
	10.0	45.0	46.6 (7.7)
Ethanol	900.0	35.0	45.8 (1.8)
	600.0	20.0	30.0 (6.4)
MDMA	2.0	35.0	39.8 (3.9)
	1.5	40.0	41.3 (9.1)
	1.0	30.0	29.4 (8.9)

Measurements and Statistical Analysis

The percentage of rats selecting the lever appropriate for the drug (TFMPP) used in training was the quantal measurement of discrimination. Quantal data are presented as percentage of rats making the correct first-choice selection on the TFMPP-correct lever (all-or-none). The dose-response quantal data were subjected to analysis by the procedure of Litchfield and Wilcoxon (10) that employs log-dose vs. probit measurements. A computer-generated formulation of the Litchfield-Wilcoxon analysis (19) yielded an ED_{50} for the dose-response curve of TFMPP and for each of the agonist test drugs. This analysis also allowed for tests of parallelism between dose-response curves.

TFMPP-trained animals were required to maintain a minimum of 80% TFMPP-appropriate lever selection (quantal) during TFMPP maintenance sessions and were permitted a maximum of 20% TFMPP-appropriate lever selection after saline injection over any 10 consecutive maintenance sessions. This established that an animal needed only to recognize the TFMPP or saline cues correctly on 80% of all trials as previously required to attain performance criterion (above). Therefore, it was determined that, in a substitution test, the test drug needed only to produce equal to or greater than 80% TFMPP-appropriate quantal responding as the criterion for generalization or transfer of TFMPP-trained rats to the test drug.

A second measurement used was the quantitative measurement which represents the number of TFMPP lever responses divided by the total number of responses made on both levers before ten were made on either lever, as a percentage. The advantage in using this second measure has been previously discussed (18).

RESULTS

The learning rates for 10 rats in discrimination between 1.0 mg/kg TFMPP and its saline vehicle appear in Table 1. In weeks 1 and 2, consisting of five trials with drug and five trials with saline (see the Method section), 92% of first-choice lever selections (quantal) were on the TFMPP-appropriate lever after TFMPP and this lever was selected on 52% of all trials after saline administration. The high rates of TFMPP-lever selection after saline may be most easily explained by the fact that the rats had just been trained on the TFMPP-correct lever over 5–6 days prior to this training week. On weeks 3 and 4, 92% of responses were made on the TFMPP-correct lever after TFMPP but during this period the number of responses on that lever decreased to 10% after saline. To look at it a different way, 90% of responses were made on the saline-correct lever after saline during this time period. The sessions-to-criterion, i.e., the number of sessions to attain the first of 8 correct out of 10 consecutive sessions, averaged 14 sessions with a range of 12 to 16 sessions. Thus, all rats were trained by the twentieth session, i.e., 10 sessions with drug and 10 sessions with saline.

The dose-response relationship with various doses of TFMPP appears in Table 2. Maintenance trials with TFMPP produced 90% of first choice responding on the TFMPP-lever and saline produced 5% responses on this lever. Lower doses of TFMPP resulted in progressively decreasing frequency of drug lever choices both in terms of quantal and quantitative measurements and the ED_{50} for the former was 0.27 mg/kg and for the latter, a similar, 0.21 mg/kg.

The results of substitution tests with various drugs are presented in Table 3. Throughout this testing, maintenance days with both TFMPP and saline resulted in sustained criterion performance. The highest dose of norfenfluramine produced 80% quantal responding and, thus, would qualify this drug/dose as transferring from the TFMPP discriminative cue. Decreasing doses of norfenfluramine resulted in decreased TFMPP-like discrimination and the ED_{50} for norfenfluramine was 1.09 mg/kg. Higher doses of norfenfluramine were precluded by the appearance of behavioral disruption, i.e., delays in the onset of lever-pressing, at the highest dose used. Similarly, mCPP at 1.2 mg/kg produced 95% of first-choice responses on the TFMPP-appropriate lever and decreasing doses produced a typical dose-response curve. The ED_{50} for mCPP in TFMPP-trained animals was calculated to be 0.54 mg/kg. Analysis (10) of these two dose-response curves compared with the dose-response curve generated from data in Table 2 indicated that both norfenfluramine and mCPP were parallel to that of the

TFMPP dose-response curve (calculated $t=0.26$ and $0.50 <$ critical $t=3.18$).

In contrast to these transfers, the four other drugs tested for generalization in TFMPP-trained animals did not produce this effect. THBC produced a maximum of 55% responding on the TFMPP-appropriate lever but this dose (20 mg/kg) produced long delays prior to the onset of lever selection. Likewise, ethanol at 900 mg/kg produced 35% of responses on the drug lever and a single experiment with a higher dose (1200 mg/kg) was shown to produce excessive disruption and sedation in all animals. Administration of DOI and MDMA, at 3 doses each, produced responses that may be considered intermediate, i.e., they were neither TFMPP-like nor saline-like at the most effective dose.

DISCUSSION

The results indicate that TFMPP (1-(3-trifluoromethylphenyl)piperazine) can serve as a discriminative stimulus in rats as reported by others (2,9). In contrast to the extended period of time previously found to be necessary for training with this drug, the animals in the present study were more rapidly trained, i.e., by the 20th training session. A statistical comparison (unpaired t-test of means; quantitative data) indicates a significant ($p<0.02$) improvement in discrimination in the saline "state" between weeks 1–2 and weeks 3–4. An explanation for the discrepant amount of time to learn might be inherent in the fact that in one previous study (2), in which rats required an average of 27 sessions to learn to discriminate TFMPP, a lower dose of the drug and a stricter criterion (0.8 mg/kg; 85% correct responses for 10 consecutive sessions) were employed. In contrast, another study (9) required 70 training sessions to reach a criterion described as "stable (i.e., TFMPP, approximately 98%; saline, approximately 15%)." The explanation for this extended period of time may reside in other procedural differences (Glennon, personal communication). In any case, it took 14 sessions to meet the criterion (8/10 correct) and, as with most drugs, the STC is lower as the dosage increases (13).

In comparing previously published dose-response curves in rats trained to discriminate approximately the same dose of TFMPP, the present ED_{50} of 0.27 mg/kg is virtually identical to those previously reported [0.23 mg/kg, (2); 0.25 mg/kg, (9)]. Similarly, the present study employed mCPP as a drug to test the transferability of the TFMPP stimulus cue and, as reported previously (2,11), it was capable of this generalization. The ED_{50} for the transfer of mCPP was shown here to be 0.54 mg/kg; similar to the previously reported values of 0.38 mg/kg (2) and 0.47 mg/kg (11). mCPP is structurally similar to TFMPP and has been shown to possess a like function in its pharmacological action (4,12).

Like mCPP, norfenfluramine, the first and active metabolite of fenfluramine, was shown to generalize in TFMPP-trained animals. The ED_{50} for this effective transfer was calculated to be 1.09 mg/kg. In a previous study, Cunningham and Appel (2) tested the transferability of fenfluramine in doses of 0.8–1.6 mg/kg and found that this drug was transferable with an ED_{50} of 1.28 mg/kg. Likewise, McKenney and Glennon (11) found an ED_{50} of 1.23 mg/kg for this drug. The present finding that norfenfluramine is slightly more potent, but similarly effective, as fenfluramine is reminiscent of recent research in this laboratory that indicates that norfenfluramine is more potent in its discriminability than is its parent compound (1). The mechanism of action by which norfenfluramine may act on 5-HT_{1B} receptors may reside in its ability to act as a 5-HT releaser and reuptake inhibitor (5). Thus, the 5-HT released by norfenfluramine has the ability to interact with all 5-HT receptors, including those designated as 5-HT_{1B}.

Unlike the ability of TFMPP-trained rats to discriminate both mCPP and norfenfluramine as their trained drug state, the administration of the 5-HT_2-specific agent DOI did not produce TFMPP-like responding. Previously, TFMPP was observed to not generalize to another 5-HT_2 specific agonist DOM (1-[2,5-dimethoxy-4 methylphenyl]-2-aminopropane) (9). In addition, when rats trained to discriminate 0.5 mg/kg DOI were tested with 0.3–0.8 mg/kg TFMPP their discriminative performance indicated that they perceived TFMPP as dissimilar to DOI (7). The present study indicates that this lack of cross-generalization between two 5-HT site-selective agonists, TFMPP and DOI, is symmetrical.

Administration of other agents, at best, produced intermediate responses on the TFMPP-appropriate lever. Thus, THBC produced a maximum of 55%, ethanol produced 35% and MDMA produced 40% of selected lever responses on the TFMPP-correct lever (Table 3). Incomplete substitution of a novel drug tested in well-trained discriminating rats may occur because the effect of the test drug is weaker in its discriminative stimulus properties than is the training drug. The simplest way to increase the transferability of the novel drug would be to increase the dose tested. However, increasing doses generally resulted in longer delays due to disruption of behavioral performance. Thus, the mediation of the interoceptive cue of the novel test agent may reach a maximum at a certain dose and other central mechanisms may be brought into play when higher doses are administered. A second possibility for "intermediate" discriminative transferability resides in the notion that the test drug is qualitatively different from the training drug. This possibility is supported by the observation reported in previous publications from this laboratory that THBC (15), ethanol (17) and MDMA (16) each generalize to TFMPP in rats trained to discriminate each of these agents from vehicle. These one-way generalizations have been shown to occur in other studies and the suggestion has been made (20) that subjects trained to a drug state may attend to only the major component of the compound discriminative stimuli produced by the training drug. Animals trained to another, more selective component of this complex cue may generalize only partially to the minor component inherent in the multi-component pathway mediating the larger cue. Thus, THBC, ethanol and MDMA produce a complex discriminative cue with a component due to 5-HT_{1B} receptor stimulation; it is to this component that the rats trained to discriminate these drugs generalize when tested with TFMPP. In contrast, rats trained with the selective drug TFMPP discriminate solely upon its actions at 5-HT_{1B} receptors and when they are tested with a drug (like THBC or ethanol or MDMA) with multiple effects, only a partial interoceptive cue is available to allow for differential responding, i.e., discrimination.

In conclusion, TFMPP has been, once again, shown capable of serving as a drug to control discriminative responding and previous studies (2, 9, 11) have been expanded to include other agents as tested. In a continued attempt to elucidate the functional significance of specific 5-HT binding sites, the 5-HT_{1B} receptor agonist activity of TFMPP was, thus, generalized to both mCPP and norfenfluramine; drugs which, by different mechanisms of action, may result in stimulation of this receptor locus.

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