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Tetrahydro-β-Carboline May Produce its Stimulus Effects via $5HT_{1B}$ Receptors

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SCHECHTER, M. D. *Tetrahydro-β-carboline may produce its stimulus effects via $5HT_{1B}$ receptors.* PHARMACOL BIOCHEM BEHAV **28**(1) 1–6, 1987.—To further clarify the role of 5-hydroxytryptamine (5HT) in the behavioral effects of tetrahydro-β-carboline, male rats were trained to discriminate either 20 mg/kg THBC from its vehicle (n=10) or 2.0 mg/kg fenfluramine from saline (n=5). THBC was observed to produce fenfluramine-like effects in the fenfluramine-trained rats while fenfluramine produced THBC-like effects in the THBC-discriminating rats. To investigate which of the serotonergic receptors may mediate the THBC-induced discriminative stimulus, various putatively specific 5HT agonists were administered to THBC-trained rats. Results indicate that the $5HT_{1B}$ receptor agonists TFMPP and m-CPP substitute for THBC in a dose-response manner whereas $5HT_{1A}$ agonists do not generalize to the THBC-induced discriminative stimulus. These observations support a role for the $5HT_{1B}$ receptor site in the discriminative stimulus properties of THBC.

Drug discrimination Tetrahydro-β-carboline 5-Hydroxytryptamine-(5HT) $5HT_{1B}$ receptor $5HT_{1A}$ receptor

RECENT work in this laboratory [30] has shown that tetrahydro-β-carboline (THBC) can serve as a drug that can control discriminative responding in the rat and, by virtue of complete generalization of this discrimination to the serotonergically-active drug fenfluramine, it was suggested that this action of THBC may be mediated by brain serotonin (5HT). Biochemical evidence has led to the distinction of at least two 5HT receptor types in the central nervous system [25]. These receptor subtypes have been designated as $5HT_1$ and $5HT_2$ and each site is characterized by a unique pattern of pharmacological interactions with serotonergic agents [12, 15, 24, 26]. Furthermore, the $5HT_1$ receptors appear to represent a heterogeneous population of serotonin sites and this has led to a further subclassification, viz., $5HT_{1A}$ and $5HT_{1B}$ [32].

THBC is a condensation product of tryptamine and formaldehyde and, as such, has been observed to interact relatively specifically with brain 5HT neurons via numerous mechanisms. These include: (a) release of 5HT [28,34]; (b) inhibition of 5HT reuptake [1, 13, 27]; (c) inhibition of monoamine-oxide A, for which 5HT is a preferred substrate [2] and (d) direct stimulation of postsynaptic 5HT receptors [22,23]. Any, or all, of these mechanisms may lead to a THBC-induced increase in brain concentrations of 5HT and, in turn, may be responsible for the cited ability of THBC to act as a drug to control differential responding in the drug discrimination paradigm.

The purpose of the present study was to further characterize the serotonergic mediation of the discriminative properties of THBC by elucidating its relationship to fenfluramine discrimination. In addition, this study sought to employ currently available specific $5HT_{1A}$ and $5HT_{1B}$ agonists and 5HT antagonists to investigate if a specific 5HT receptor mediates this behavioral effect of THBC.

METHOD

Subjects

Ten male Sprague-Dawley rats had previously been trained to discriminate between 20 mg/kg THBC and its vehicle [30]. Likewise, five female lean (Fa/−) Zucker rats had previously been trained to discriminate 2.0 mg/kg fenfluramine from saline [31]. All rats were housed in individual cages and their weights were adjusted, by daily rationing of commercial rat chow, to approximately 80–85% of their free-feeding weights. Water was continuously available in the home cages which were kept at a constant temperature (20–22°C) and maintained on a 12-hour (0600–1800) light/12-hour dark daily cycle.

Apparatus

The apparatus used consisted of ten identical standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN) each equipped with two operant levers placed 7 cm apart and 7 cm above the grid floor. A food receptacle for pellet delivery was mounted 2 cm above the grid floor at an equal distance between the two levers. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and a 9 W house-light. Solid-state programming equipment (Med Associates, E. Fairfield, VT) was used to control and record the sessions and was located in an adjacent room.

Discrimination Training

Drug discrimination training was based upon procedures described in detail elsewhere [30,31]. There were two training phases. In the first phase, the food-deprived rats learned to press the lever indicating vehicle/saline administration and

received a food reward (45 mg Noyes pellet) for each correct response, fixed ratio 1 (FR1) schedule. This FR schedule was made progressively more difficult, in daily 15 min sessions, until an FR10 schedule was achieved. This was accomplished during 10 days. Throughout this phase of lever-press training, the fenfluramine-trained rats received daily intraperitoneal (IP) injections of saline (0.9% sodium chloride) 30 min prior to being placed into the two-lever operant box. The THBC-trained rats received an equal volume (1 ml/kg) of THBC vehicle and were also trained 30 min after injection. Immediately following the attainment of the FR10 schedule after saline or vehicle administration, the opposite lever was activated and rats received a food reward for each correct response, fixed ratio 1 (FR1) schedule, after the IP administration of an equal volume (1 mg/kg body weight) of vehicle containing either 2.0 mg/ml fenfluramine hydrochloride or 20 mg/ml THBC. Daily sessions, of 15 min duration, were continued with drug administration over 5 days when an FR10 schedule was attained. In order to minimize effects due to any possible position preference, the rats in each group were divided into two equal (in the 10 THBC-trained rats) and unequal (for the 5 fenfluramine-trained rats) subgroups. For one subgroup responding on the left lever was reinforced by delivery of food pellets in every session following drug injection, whereas the other group was reinforced with food after responding on the right lever following drug injection. Responses on the opposite lever were reinforced with food pellets after vehicle injection.

Phase II discrimination training then began. Subjects were trained 5 days per week with reinforcement in a pseudo-random sequence. Thus, in each two week period, there were five days with drug lever (D) and five days with vehicle lever (V) correct. The pattern was D,V,V,D,D; V,D,D,V,V. Rats were required to respond on the stimulus-appropriate (either drug or vehicle) lever to receive reinforcement and accuracy was judged by the first lever pressed ten times (FR10). Criterion performance was set so that an animal had to perform two sets of ten consecutive sessions with an accuracy rate of 80%, according to the drug state imposed, before it was allowed to be used for further test runs or data collection. These rats were run once a day, 5 days per week, between 1000 and 1400 hours. The assignment of rat to operant chamber was done at random to avoid possible position cues based upon olfactory cues [6].

Test Sessions

After both groups of rats attained the discriminative training criterion, test sessions were initiated. These test sessions were conducted on alternate days with the other days used for maintenance sessions in which either the drug used for training or vehicle was tested and rats were allowed to continue training for 10 min. The lever first pressed ten times was designated as correct or incorrect according to the state imposed (i.e., drug or vehicle administered). If a rat was observed to fall below the 80% criterion on maintenance days, that rat was not considered capable of discriminating between drug- and vehicle-states and its results were not included in the data obtained from that time onward. This did not occur in any of the fenfluramine-trained rats; however, two of the ten THBC-trained rats fell below the 80% criterion and were eliminated from the subsequent data. This is reflected in the results.

There were three types of experiments conducted during these test sessions: (1) In dose-effect experiments, rats were tested with doses of the drug to which the were trained that differed from the training dose. Thus, the 20.0 mg/kg THBC-trained rats received doses of 1.25–10 mg/kg THBC and the 2.0 mg/kg fenfluramine-trained rats received 0.5 and 1.0 mg/kg fenfluramine; (2) In generalization (transfer or substitution) experiments, rats of each group were administered various doses of novel compounds in place of the drug used in their training. Thus, the fenfluramine-trained rats received various doses of THBC whereas the THBC-trained rats were tested with fenfluramine. This constitutes the cross-generalization experiments. In addition, the THBC-trained rats were tested with various serotonergic receptor agonists to investigate the generalization of THBC to these drugs; (3) In antagonism tests, the rats from each group were pretreated with purported serotonergic receptor antagonists (in addition to their trained drug or vehicle) to investigate the effect of specific receptor antagonism upon the drug-induced discriminated cue.

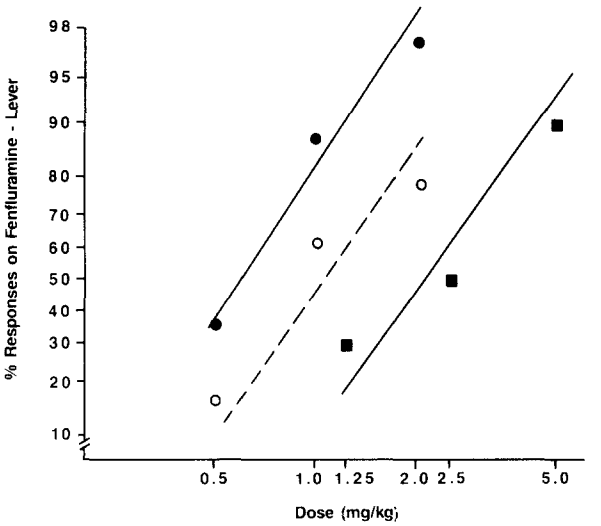

FIG. 1. Dose-effect curves with fenfluramine, with and without pretreatment with 0.16 mg/kg pirenpirone, and THBC in fenfluramine-trained rats (n=5). Ordinate: Percent of rats selecting the fenfluramine-correct lever, on probit scale; Abscissa: Dose (in mg/kg) on log scale. Each point represents two tests in each rat. ● Fenfluramine, ■ THBC, ○ pirenpirone + fenfluramine.

All of these tests were preceded by both a (maintenance) drug and vehicle session to ensure and maintain discriminative performance and to counterbalance for any possible lingering drug effect. On test days, the rat was immediately removed after it had pressed one lever ten times, without receiving reinforcement, to preclude any possible training to a condition/dose other than to which it had been trained.

Measurements and Statistical Treatment

The lever pressed 10 times first was designated as the "selected" lever. The percentage of rats selecting the drug-appropriate lever in their first 10 cumulative responses on one lever was the quantal measurement of discrimination. In addition, the total number of lever presses on both levers made before completion of ten presses on either lever constitutes the quantitative measurement, i.e., the number of responses on the drug-correct lever divided by total responses

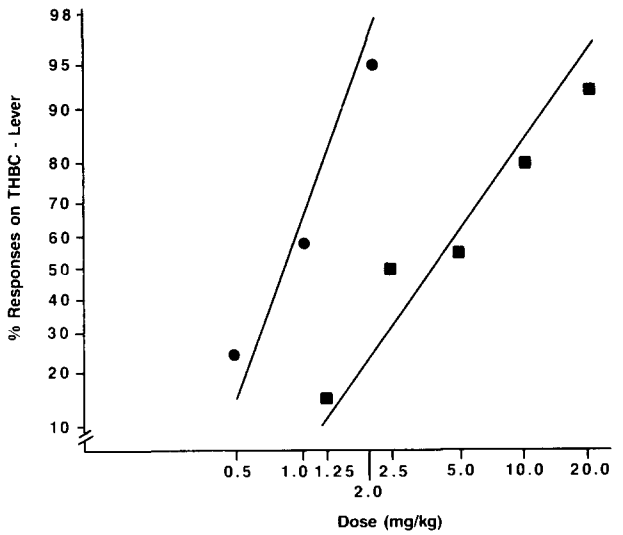

FIG. 2. Dose-effect curves with THBC and fenfluramine in THBC-trained rats (n=10). Ordinate: Percent of rats selecting the THBC-correct lever, on probit scale; Abscissa: Dose (in mg/kg) on log scale. Each point represents two tests in each rat. ● Fenfluramine, ■ THBC.

made (including the ten on the drug lever), times 100. This measurement was used to analyze data on both levers and to incorporate counts on the "unselected" lever in the statistical analysis. The advantages in using both measurements have been discussed by Stolerman and D'Mello [33]. The quantal data for the dose-response experiments were analyzed by the method of Litchfield and Wilcoxon [17] which employs probit vs. log-dose effects and generates ED50s and tests for parallelism. The quantitative data were analyzed by a Student's t-test of means with $p<0.05$ selected as the criterion for significant differences.

Drugs

Unless otherwise noted, dose-response and generalization tests were conducted 30 min after administration of either THBC, fenfluramine or test compounds; antagonists were administered 60 min, and the training drug or vehicle 30 min, prior to testing. The following drugs were dissolved in deionized water; doses refer to the weights of the base (abbreviation, supplier): fenfluramine hydrochloride (A. H. Robins); pirenperone (Janssen); metergoline (Farmitalia); 8-hydroxy-2(di-n-propylamino)-tetralin hydrobromide (8-OHDPAT, Research Biochemical Inc.; RBI); m-chlorophenylpiperazine hydrochloride (m-CPP, RBI); 1-(m-trifluoromethylphenyl) piperazine hydrochloride (TFMPP, RBI); 5-methoxy-N-N-dimethyltryptamine hydrogen oxalate (5-MeODMT, Sigma); buspirone hydrochloride (Bristol-Myers); fluoxetine (Lilly); norleagnine (THBC, Sigma) as the hydrochloride. Doses of agonists and antagonists to be used were selected from the available literature.

RESULTS

The results of the dose-response experiments with both fenfluramine and THBC in fenfluramine-trained rats are illustrated in Fig. 1. The 2.0 mg/kg training dose of fenfluramine maintained discriminative performance at 97.5% quantal responding whereas doses of 1.0 and 0.5 mg/kg produced 87.5 and 37.5% first responses upon the fenfluramine-correct lever, respectively. Analysis of this dose-response curve [17] yields an ED50 (with 95% confidence limits) of 0.56 (0.34–0.94) mg/kg. Administration of 5.0 mg/kg THBC produced 90% first choice responses in these fenfluramine-trained rats. Decreasing doses of THBC produced decreased discriminative performance, yielding an ED50=2.06 (1.06–4.02) mg/kg. Analysis [17] of the slopes of these two dose-response lines indicates that they are parallel within 95% confidence limits (critical $t=4.303$ > calculated $t=1.162$). Pretreatment of the fenfluramine-trained rats with 0.16 mg/kg pirenperone produced a shift of the fenfluramine dose-response curve to the right and an ED50 of 0.95 (0.66–1.37) mg/kg. The pirenperone + fenfluramine dose-response curve was, likewise, parallel to the fenfluramine dose-response curve (critical $t=4.303$ > calculated $t=0.39$).

The results of dose-response experiments in THBC-trained rats are presented, from a previously published table [30], in Fig. 2. In addition, the generalization of discrimination after the administration of three doses of fenfluramine is illustrated and these dose-response curves are not parallel (calculated $t=6.34$ > critical $t=3.18$).

TABLE 1

GENERALIZATION TESTS WITH SEROTONERGIC AGONISTS IN THBC-TRAINED RATS (n=10)

Treatment	Dose (mg/kg)	Quantal*	Quantitative† (SD)
THBC	20.0	94.3	88.6 (8.6)
Vehicle	—	2.8	14.4 (5.5)
8-OHDPAT	0.50	45.5	49.7 (1.9)
	0.375	54.6	50.8 (6.3)
	0.25	41.7	42.9 (0.5)
5 MeODMT	5.0	15.0	20.7 (16.3)
	3.0	45.0	47.9 (11.1)
	2.0	40.0	43.0 (7.6)
Buspirone	3.0	25.0	32.0 (2.4)
	1.5	18.8	32.6 (8.8)
	0.75	12.5	16.9 (15.5)
Fluoxetine	15.0	43.8	45.7 (11.1)
(30 min)	10.0	62.5	55.5 (10.5)
	5.0	6.3	19.3 (7.4)
(240 min)	10.0	25.0	26.4 (15.3)
	5.0	25.0	25.9 (17.1)
TFMPP	2.0	87.5	70.5 (0.4)
	1.5	62.5	52.3 (3.3)
	1.0	50.0	52.6 (13.4)
m-CPP	1.4	91.0	75.0 (7.1)
	1.0	66.6	61.4 (8.6)
	0.6	33.3	34.4 (14.9)

*Percentage of rats selecting the THBC-appropriate lever.
†Number of presses on THBC-appropriate lever divided by total responses made prior to 10 presses on either lever, times 100.

TABLE 2

PRETREATMENT WITH SEROTONIN ANTAGONISTS PRIOR TO VEHICLE AND THBC DISCRIMINATION

Pretreatment	Dose (mg/kg)	Treatment	Dose (mg/kg)	Quantal	Quantitative (SD)
Pirenpirone	0.16	vehicle	—	12.5	19.4 (2.3)
		THBC	20.0	87.5	75.3 (4.7)
	0.32	vehicle	—	14.3	26.9 (2.6)
		THBC	20.0	100.0	90.3 (0.9)
Metergoline*	0.5	vehicle	—	10.0	18.9 (4.6)
		THBC	20.0	95.0	81.6 (11.0)
	1.0	vehicle	—	0.0	4.8 (1.3)
		THBC	20.0	95.0	82.3 (0.5)

*Pretreatment for metergoline was 180 min prior to testing.

The results of testing various putatively specific 5HT receptor agonists in THBC-trained rats are presented in Table 1. Administration of three doses each of 8-OHDPAT, 5 MeODMT, buspirone and fluoxetine at 30 min prior to testing produced results that may be viewed as "intermediate," i.e., neither THBC- nor vehicle-like. Higher doses of each were precluded by the appearance of behavioral disruption, i.e., extended periods of non-activity, at the highest dose tested. Fluoxetine, tested at 240 min post-injection, produced saline-like responding.

In contrast, both 2.0 mg/kg TFMPP and 1.4 mg/kg m-CPP produced THBC-like responding. Decreasing doses of each produced decreased discriminative performance and analysis of each dose-effect curve indicates that each is parallel to that generated by various doses of THBC (critical $t=2.78$ > calculated $t=1.68$ and 2.73, respectively).

Table 2 presents the results of pretreatment tests with two putative serotonergic antagonists prior to THBC or vehicle. Two doses each of pirenperone and metergoline did not significantly effect either vehicle or THBC discrimination. Higher doses were precluded because of the appearance of delayed onset of discrimination performance (behavioral disruption) seen at the highest antagonist dose used.

DISCUSSION

The previously reported ability of two groups of rats to discriminate between fenfluramine and saline [31] and between THBC and its vehicle [30] was generally maintained throughout this study. Fenfluramine, previously shown to be capable of maintaining discriminative behavior [11, 18, 36] was dose-responsive and its discriminative cue was generalized (transferred) to THBC (Fig. 1). The mechanism of action of fenfluramine has recently been reviewed [29] and it is generally thought to involve release of 5HT. The mechanism(s) of action proposed for THBC may involve release of 5HT [28,34], direct stimulation of serotonergic receptors [22,23], inhibition of 5HT reuptake [1, 13, 27] and/or inhibition of monoamine oxidase [2].

In the THBC-trained rats, fenfluramine produced THBC-like effects and the generalization to THBC was dose-responsive (Fig. 2). In contrast to the effect of THBC in fenfluramine-trained rats, the dose-response curve of fenfluramine in THBC-trained rats was not parallel to that produced by various doses of THBC. Generally when two drugs produce the same maximal effect and possess parallel dose-response curves they are thought to act by a similar mechanism of action and/or upon a common receptor population [14]. Under this assumption, therefore, it would appear that in fenfluramine-trained rats, THBC possesses the same receptor agonistic properties. Since fenfluramine may release 5HT and this 5HT would be available to interact with all 5HT receptors, then the generalization of the discrimination cue of fenfluramine to THBC would occur if THBC acted upon any of those receptors. The ability of pirenperone, a specific $5HT_2$ receptor blocker [16], to antagonize the fenfluramine-induced cue (Fig. 1) would suggest that at least a part of the discriminative properties of fenfluramine are mediated by $5HT_2$ receptors. Indeed, other less specific serotonin receptors antagonists (i.e., they may block both $5HT_1$ and $5HT_2$ receptors) [9], such as methysergide or cinanserin, have been shown to attenuate the discrimination of fenfluramine [18].

In contrast, the dose-response curve for the generalization of fenfluramine in THBC-trained rats is not parallel (within statistical limitations) to that generated by various doses of THBC. An explanation for this observation, in light of the symmetrical generalization to one dose each of THBC and fenfluramine, resides in the possibility that the discriminative properties of THBC involve direct stimulation of a specific receptor of serotonin whereas fenfluramine, a more "general" and indirect serotonergic agonist, produces its discriminative effect by a different (non-selective) mechanism. Thus, fenfluramine would lack selectivity with respect to binding sites and produce a discriminative stimulus that also lacks selectivity. In contrast, THBC may be selective both with respect to binding (site-selective) and stimulus properties. Thus, animals trained to discriminate a selective agonist can still recognize a non-selective agent such as fenfluramine but the ultimate mechanism/site of that recognition (produced by the stimulus cue) may be different. An alternative explanation is that THBC is, like fenfluramine, essentially non-selective, being both a direct and indirect-acting 5HT agonist. It may, thus, produce a "general cue" but, unlike fenfluramine, that cue may have a slightly greater site-selective ($5HT_{1B}$) mechanistic component.

Evidence for the site-selective nature of THBC is suggested by the results presented in Table 1 in which no

dose of any of the $5HT_{1A}$ specific agonists, i.e., 8-OHDPAT [21], 5 MeODMT [32] or buspirone [35] produced THBC-like discrimination whereas both of the reputedly specific $5HT_{1B}$ ligands TFMPP [20] and m-CPP [8] generalized to the THBC cue. Two other laboratories [5, 10, 19] have been the sites of experiments that well-characterized the discriminative properties of the serotonergic agonist TFMPP. The conclusion of these three studies is that TFMPP most probably produces its stimulus effects by agonist activity at $5HT_{1B}$ receptors, thus confirming similar conclusions from *in vitro* studies [20,32]. Furthermore, the structurally related [7] drug m-chlorophenylpiperazine or m-CPP was shown to substitute for TFMPP [5]. In the present study, not only did each of these specific $5HT_{1B}$ receptor agonists generalize when given to the THBC-trained rats, but the dose-response curves for each were shown to be parallel to that of THBC, suggesting a common site/action. It must, however, be noted that the receptor specificity of these 5HT ligands is derived from radioligand binding studies *in vitro* and, in some cases, the differential affinities to one or the other receptors are relative and slight. In addition, while extensive efforts are being made to determine the functional significance of serotonin binding sites, very few conclusions can be drawn at this date [9].

The results of the antagonism studies indicate that neither of the 5HT antagonists used antagonized the THBC-produced discriminative stimulus. Thus, pirenperone, which is selective for $5HT_2$ over $5HT_1$ sites [9], did not attenuate the THBC-induced cue. Metergoline, less selective for $5HT_2$ vs. $5HT_1$ sites and, thus, having antagonist activity at both receptors [9], similarly did not affect the THBC cue.

In conclusion, the fenfluramine cross-generalization and the specific receptor agonist and antagonist results would suggest that the discriminative stimulus cue produced by THBC may be mediated by $5HT_{1B}$ receptors. However, the role of other neurotransmitters, especially tryptamine [3,4], should be investigated.

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