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Temporal Differences in Behavioral Effect of Fenfluramine and Norfenfluramine

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SCHECHTER, M. D. *Temporal differences in behavioral effect of fenfluramine and norfenfluramine.* PHARMACOL BIOCHEM BEHAV **35**(3) 527–531, 1990.—Ten male rats were trained to discriminate the anorectic drug d,l-fenfluramine (2.0 mg/kg intraperitoneally administered) from its vehicle using a food-reinforced (fixed-ratio 10 schedule) two-lever operant task. Once learned, the fenfluramine stimulus was dose-dependent ($ED_{50}=0.8$ mg/kg) and stereoselective with the d-isomer ($ED_{50}=0.6$ mg/kg) approximate twice as potent as the l-isomer ($ED_{50}=1.2$ mg/kg). Time-course data indicate that the fenfluramine metabolite norfenfluramine produces a significantly faster onset and longer duration of action than does the parent compound. The results suggest that both stereoisomers of fenfluramine have discriminative stimulus properties and that the fenfluramine metabolite, norfenfluramine, contributes to the discriminative stimulus properties of the parent drug.

Drug discrimination Fenfluramine Norfenfluramine Time-course Rats

FENFLURAMINE [(m-trifluoromethyl)-N-ethyl-amphetamine], commercially available as the racemic mixture in the United States, is a much-prescribed anorectic agent (20). Fenfluramine is metabolized by N-dealkylation to norfenfluramine, a compound with its own marked anorectic properties (5,6). The d- and l-isomers of both fenfluramine and norfenfluramine appear to have characteristically unique biochemical and pharmacological properties (2,9) and each may be metabolized at a different rate (11,14). These stereoisomers and the active metabolite of fenfluramine have each received attention as a result of fenfluramine's ability to produce neurotoxicity in rats (1).

The drug discrimination paradigm has proven to be a useful drug "detection" assay that has allowed for suggestive evidence as to the mechanism of action of psychoactive drugs. In this procedure, a drug serves as a discriminative stimulus, i.e., an interoceptive cue, that enables an animal to differentiate one response from another based solely upon the drug or nondrug condition under which it is placed. Once the animal is able to respond differently to the two states, other drugs can be tested for stimulus generalization and classification as to the similarity and dissimilarity between the trained drug condition and the novel drug can be made. The discriminative properties of fenfluramine have been well-established by several investigators (12, 19, 25), for example, fenfluramine was shown not to generalize to the structurally similar anorectic drug amphetamine (12). Previous work from this laboratory indicated that rats trained to discriminate amphetamine will not generalize to fenfluramine (22) and this observation has been extended to both gerbils (13) and humans (8). The symmetrical nongeneralization between amphetamine and fenfluramine has led to training rats to discriminate between these two agents (4). These results have suggested that fenfluramine acts as a drug capable of controlling discrimination by mediation of serotonergic mechanisms (19,25), whereas amphetamine acts as an indirect dopamine agonist (13,22). Lastly, drug discrimination has been used to investigate the stereoisomeric potency of both fenfluramine (19) and amphetamine (21).

Although the drug discrimination paradigm has been used extensively to indicate similarities and dissimilarities between drugs, and to determine potency differences between the isomers of the same drug, there are fewer studies involving the time-course of action of drugs. The purpose of the present research was to train rats to discriminate fenfluramine, to examine the potency ratios of its isomers and to compare the time-course of action between fenfluramine and its active metabolite norfenfluramine.

METHOD

Subjects

Ten male Sprague-Dawley rats, purchased from Zivic-Miller Laboratories, Allison Park, PA, weighing 280–320 g at the beginning of the experiments, were housed singly in cages. They were kept in a room maintained at a constant temperature (21–22°C) and humidity (50–65%) and illuminated 12 hr per day (lights on at 0600 hr). The rats had free access to water except during experimental sessions and were maintained at approximately 85% of their free-feeding body weights. All training and testing was done on Monday through Friday of each week at approximately 1000–1100 hr.

Apparatus

Ten standard rodent operant test chambers (Lafayette Instru-

ment Co., Lafayette, IN) were housed in light-proof, sound-attenuated and fan-ventilated outer shells. Each operant chamber was equipped with two levers mounted 7 cm apart and 2 cm above the grid floor. Equidistant between the levers was located a food-pellet receptacle that delivered 45 mg Noyes food pellets as reinforcement. Solid-state programming equipment (Med Assoc., E. Fairfield, VT), located in an adjacent room, was used to control and record each training and test session.

Shaping to Lever-Press Procedure

The food-deprived rats were administered vehicle (distilled water) intraperitoneally (IP) 20 min prior to the start of the experiments and were trained to press either the right (n = 5) or the left (n = 5) lever to receive food reinforcement under a fixed-ratio 1 (FR 1) schedule. Training continued as the FR schedule was gradually increased to an FR 10 schedule over a period of 7 days; this FR 10 schedule was maintained for 3 additional days. On the following training session, the rats received (IP) an equal volume (1 ml/kg) of the distilled water vehicle containing 2.0 mg/ml d,l-fenfluramine hydrochloride (as base) 20 min prior to the session. The rats were then placed on an FR 1 schedule on the opposite (the drug-correct) lever. The FR schedule was, likewise, gradually increased over a 5-day period until a stable FR 10 schedule was attained; this schedule was maintained for 3 additional days.

Discriminative Training

Once FR 10 responding was achieved on both levers, the discriminative training phase began in which the food-motivated rats were required to press the drug-appropriate lever after fenfluramine administration and the vehicle-appropriate lever after vehicle administration to receive reinforcement. A biweekly repeating schedule of administrations with either drug (D) or vehicle (V) injected IP at 20 min prior to beginning of the training session was in effect throughout this phase of training: V-D-D-V-V, D-V-V-D-D. The lever pressed 10 times first was designated as the "selected" lever and every 10th response on the fenfluramine-correct was reinforced on days when the rats were injected with fenfluramine, whereas every 10th response on the opposite lever was reinforced after vehicle administration. Discrimination sessions were continued, using the repeating biweekly schedule, until each rat reached the performance criterion of choosing the appropriate lever, according to the state imposed, on 16 daily sessions out of a total of 20 consecutive sessions.

Dose-Response Relationship of Fenfluramine and Its Isomers

After all the rats attained the training criterion and were, thus, judged able to discriminate between 2.0 mg/kg d,l-fenfluramine and its vehicle, the animals received various doses of fenfluramine (dose-response; DR) different from the training dose according to the following biweekly schedule: F-DR_1-V-DR_2-F, DR_2-V-DR_1-F-DR_3, etc., where F = fenfluramine training dose; V = vehicle; DR_1 = one other dose of F; DR_2 = second other dose of F. Doses were administered IP at 20 min prior to testing and, on these test days, the animals were allowed to lever press until 10 responses were made on either lever. At that time, the rats were immediately removed from the operant test cages without receiving reinforcement and placed into their home cages in order to preclude any continued training at a dose other than the 2.0 mg/kg d,l-fenfluramine dose used in training.

Following the dose-response experiments with d,l-fenfluramine generalization tests with both the d-isomer and l-isomer were conducted according to the above schedule for the dose-response experiments. Thus, each dose of each isomer was preceded both by a vehicle and a 2.0 mg/kg d,l-fenfluramine maintenance session. This counterbalanced design detects and corrects for any possible carry-over effect from the previous day's (drug) effects. The racemer and two isomers were each administered in doses of 0.5, 1.0, 2.0 and 2.5 mg/kg.

Time-Course of Fenfluramine and Norfenfluramine Action

To determine the time-course of the fenfluramine-produced discriminative cue, rats were injected IP with 2.0 mg/kg d,l-fenfluramine, returned to their home cage and allowed to remain there for varying intervals from 5 to 480 min before being placed into the test chambers. The order in which the various time-delays after fenfluramine administration were tested was randomized between subjects such that each rat received each postinjection time interval delay twice with each time preceded by one maintenance session with 2.0 mg/kg fenfluramine and one session with vehicle tested at 20 min postinjection. Animals failing to maintain criterion discrimination during these interspersed maintenance sessions were to be eliminated from the time-course study. This occurred with one animal and is reflected in an n = 9.

To determine the time-course for the generalization to norfenfluramine in the fenfluramine-trained rats, 2.0 mg/kg d,l-norfenfluramine was administered to rats and from 5 to 1440 min (24 hr) later the rats were placed into the operant chamber; each postinjection time was employed on two occasions. In all time-course sessions, the rat was immediately removed from the operant chamber, without receiving reinforcement, upon pressing either lever ten times.

Second Dose-Response Relationship of Fenfluramine

Although the present behavioral study employed a dose of fenfluramine far below that shown to produce neurotoxicity in the rat (16), it seemed prudent to investigate the possibility of functional neurotoxicity caused by long-term drug administration. To this end, a second dose-response relationship was determined by administering 0.5, 1.0 and 1.5 mg/kg fenfluramine during test sessions, interspersed with maintenance trials, using the methodology described (above) for the initial dose-response experiments.

Measurements and Statistics

The lever pressed 10 times first was designated as the "selected" lever. The percentage of rats selecting the lever appropriate for fenfluramine was the quantal measurement of discrimination and quantal data are presented as percent correct first choices on the fenfluramine lever. In addition, the number of lever-presses made upon the fenfluramine-appropriate lever divided by the total number of responses on both levers at the tenth response on either lever, times 100, constitutes the quantitative measurement. Both measurements were utilized as previously suggested (24). The quantal data were analyzed by application of the method of Litchfield and Wilcoxon (18) which employs probit vs. log-dose effects, allows for the generation of ED_{50}'s and can test for parallelism between dose-response curves. Quantitative data were analyzed with a two-tailed Student's *t*-test with $p<0.05$ set as the criterion for significance.

Drugs

The drugs used in this study were: d,l-fenfluramine HCl and d,l-norfenfluramine HCl from A. H. Robins, Richmond, VA and the d- and l-isomer of fenfluramine HCl from Servier Laborato-

TABLE 1

DOSE-RESPONSE RELATIONSHIP OF d,l-, d-, AND l-FENFLURAMINE IN RATS (n = 10) TRAINED TO DISCRIMINATE 2.0 mg/kg d,l-FENFLURAMINE

Drug	Dose	Quantal	Quantitative (SD)
d,l-Fenfluramine	2.5	95.0	85.5 (2.2)
	2.0	90.0	78.1 (7.5)
	1.0	65.0	53.8 (1.6)
	0.5	25.0	32.8 (6.9)
	0.0 (veh)	8.3	20.4 (6.6)
d-Fenfluramine	2.5	100.0	90.1 (1.1)
	2.0	70.0	65.1 (0.6)
	1.0	55.0	52.6 (8.5)
	0.5	50.0	45.4 (6.0)
l-Fenfluramine	2.5	85.0	73.1 (13.5)
	2.0	55.0	51.3 (14.7)
	1.0	45.0	41.3 (17.0)
	0.5	20.0	27.1 (1.4)

ries, Paris, France. All doses were calculated for the salt and the drugs were dissolved in deionized water and were injected IP at a constant volume of 1 ml/kg.

RESULTS

Discriminative Learning

The rats rapidly learned to discriminate 2.0 mg/kg d,l-fenfluramine from its vehicle and attained the first of 16 correct out of 20 consecutive sessions in a mean of 18.6 (±3.9) sessions with a range of 12 to 25 sessions. Thus, all rats were capable of correctly discriminating 2.0 mg/kg fenfluramine from its vehicle by the 26th session (13 sessions with each of vehicle and drug).

Dose-Response to d,l-Fenfluramine and Its Isomers

Maintenance sessions with 2.0 mg/kg d,l-fenfluramine produced 90% of first choice responses on the fenfluramine-appropriate lever, whereas vehicle administration resulted in 8.3% of first choices being made on the drug-appropriate lever (Table 1). Decreasing doses of the racemer produced decreased discriminative response performance both in terms of quantal and quantitative measurements and allowed a calculation of a quantal ED_{50} (with 95% confidence limits) value of 0.79 (0.58–1.07) mg/kg. Administration of 2.5 mg/kg d-fenfluramine produced complete generalization in the animals trained to 2.0 mg/kg d,l-fenfluramine. Likewise, decreasing doses of the d-isomer produced decreased discriminative performance and allowed for a calculation of a quantal ED_{50} value equal to 0.60 (0.39–1.02) mg/kg. Lastly, l-fenfluramine in doses of 0.5–2.5 mg/kg produced a dose-responsive generalization in the d,l-fenfluramine trained rats with an ED_{50} value of 1.20 (0.88–1.63) mg/kg. Analysis (18) of the slopes of the dose-response lines indicates that the calculated t for each is less than the critical t for significance (2.776) and this indicates that all lines are parallel to each other. The potency ratio of the d vs. l isomer was calculated (18) to be 0.53; significant at the level of $p<0.05$.

Time-Course of Action for Fenfluramine and Norfenfluramine

As shown in Table 2, fenfluramine discriminative performance reached maximal levels at 20 min postadministration and continued at this relative level for 4 hr (240 min) at which time the discriminative performance decreased, eventually falling to 5.6% at 480 min postadministration. The quantitative measurement at 480 min is not significantly different from that of vehicle and, therefore, longer injection-to-test intervals were not determined.

TABLE 2

TIME-COURSE OF 2.0 mg/kg FENFLURAMINE AND NORFENFLURAMINE IN RATS (n = 9) TRAINED TO DISCRIMINATE FENFLURAMINE FROM ITS VEHICLE AT 20 MIN POSTADMINISTRATION

	Fenfluramine		Norfenfluramine	
Post-administration Time (min)	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)
5	50.0	48.1 (14.7)	56.3	55.4 (14.8)
10	50.0	45.3 (3.8)	84.6	70.1 (11.4)*
20	92.6	78.7 (4.7)	94.4	78.6 (0.4)
30	83.3	71.7 (2.5)	ND	ND
60	83.3	74.4 (24.7)	94.4	80.3 (15.1)
90	83.3	78.6 (8.1)	94.4	72.9 (2.2)
120	88.9	79.9 (18.2)	100.0	89.6 (6.4)
240	100.0	84.2 (2.2)	94.4	75.1 (10.8)
360	66.7	55.3 (5.3)	72.2	61.0 (16.1)
480	5.6	15.9 (7.0)	61.1	64.1 (2.9)*
960	ND	ND	27.8	36.1 (18.6)
1200	ND	ND	16.7	23.3 (10.0)
1440	ND	ND	16.7	22.9 (0.5)

*Significant difference from quantitative measurement after fenfluramine ($p<0.01$, t-test).
ND: Not determined.

The onset of the norfenfluramine discriminative performance peak appears to occur earlier than after fenfluramine with the quantal discrimination reaching 84.6% at 10 min postinjection. The quantitative measurement at 10 min (70.1 ± 11.4) was significantly greater than seen 10 min after the administration of an equal dose of fenfluramine (45.3 ± 3.8). The norfenfluramine-produced discriminative stimulus cue remained at this high level for the same length of time as after fenfluramine, but continued longer, with the quantitative measurement (64.1 ± 2.9) being significantly greater at 480 min postadministration than after fenfluramine (15.9 ± 7.0). The quantitative measurement after norfenfluramine did not drop to vehicle levels until 20 hr postadministration.

The second dose-response experiments using 2.0 (training dose), 1.5, 1.0, 0.5 and 0.0 (vehicle) mg/kg fenfluramine produced 95.0, 90.0, 50.0, 40.0 and 12.5% quantal responding, respectively, upon the fenfluramine-appropriate lever. Analysis (18) indicates an ED_{50} value (with 95% confidence limits) of 0.70 (0.51–0.94) mg/kg.

DISCUSSION

The results of this stu ly demonstrate that the commercially available anorectic drug d,l-fenfluramine (Pondimin®) can control differential operant responding in rats on the basis of its discriminative stimulus properties as previously reported (12, 19, 25). The acquisition of the criterion level for discrimination with the training dose of 2.0 mg/kg fenfluramine required an average of 18.6 training sessions. A comparable number of training sessions was required in other laboratories where fenfluramine was used to produce a differential discriminative stimulus in rats (12, 19, 25).

Varying the dose of the racemer produced a stimulus generalization gradient which, when analyzed (18), yielded the dose of fenfluramine that would produce 50% fenfluramine-appropriate lever selections (ED_{50}) as 0.79 mg/kg. This is approximately 40% of the training dose, reflecting previous studies that indicated that the ED_{50} value in rats trained to either 1.0 mg/kg (25) or 3.0 mg/kg (19) fenfluramine was approximately 50% of the training dose.

Stimulus generalization tests with the isomers of fenfluramine indicated that both the d- and the l-isomer are behaviorally active. Furthermore, the d-isomer was observed to be approximately twice as potent as the l-isomer, a potency difference previously shown to occur in experiments determining the effects of each isomer upon food intake (11) and in work indicating isomeric differences in altering brain serotonin levels (16). In contrast, the l-isomer has been shown to be more potent than the d-isomer in affecting striatal dopamine metabolism in the brains of rats (11,15). Thus, it has been suggested that the d-isomer is more selective for serotonergic mechanisms which appear to mediate the anorectic activity of the drug, whereas the l-isomer contributes less to the anorexic effects and may act preferentially upon brain catecholamines (17,26).

Time-course experiments indicate that the onset of action of norfenfluramine is more rapid and longer-lasting than that of its parent compound. The greater speed of onset for norfenfluramine was previously reported to occur in time-course generalization experiments performed in rats trained to discriminate norfenfluramine (3). Norfenfluramine has also been reported to produce a more rapid depletion of brain serotonin than fenfluramine (10). In addition to the difference in onset of action, norfenfluramine has been reported to have a prolonged activity, i.e., a longer half-life, than fenfluramine in both animals and man (7).

Although the doses of drugs used in this investigation are lower than those needed to produce neurotoxicity (16), the possibility of functional deficits in the rats' discriminative performance may be of concern. To determine if the multiple administrations of fenfluramine, as well as the other agents used in this study, affected discriminative performance, a second dose-response relationship was conducted and the ED_{50} value determined. As indicated (see the Results section), the initial ED_{50} value of 0.79 mg/kg was similar to the ED_{50} value generated after the second dose-response relationship was determined (0.70 mg/kg) 50 weeks later. This observation, once again, illustrates the stability of the drug discriminative stimulus (23). Furthermore, it is suggestive evidence that the repeated administrations of fenfluramine, and its congeners, did not significantly alter the rats' "perception" of the fenfluramine-induced discriminative stimulus over time.

The results of this experiment would indicate that the prolonged activity of d,l-fenfluramine in rats may be caused by its metabolite norfenfluramine and that norfenfluramine constitutes a major part of the discriminative stimulus complex of fenfluramine. However, since d,l-fenfluramine is constituted of both d- and l-isomers, and it is rapidly metabolized to norfenfluramine, there may be a simultaneous presence of four compounds, each with a different specificity and half-life. This possibility makes it difficult to establish exactly which compound is responsible for the well-investigated fenfluramine-produced interoceptive discriminative stimulus.

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