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SEROTONERGIC MEDIATION OF FENFLURAMINE DISCRIMINATIVE STIMULI IN FAWN-HOODED RATS

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Abstract: Fenfluramine, a drug that induces increased synaptic serotonin, was used to train Fawn-Hooded rats in a drug discrimination paradigm. This strain of rats is thought to possess a genetic serotonin storage abnormality. The intent of the study was to see if the Fawn-Hooded rat was similar or dissimilar to the more frequently used strain of Sprague-Dawley rat in its ability to learn to discriminate 2.0 mg/kg fenfluramine administered intraperitoneally. In addition, drugs presumed to work upon central serotonergic neurons were given to the fenfluramine-trained Fawn-Hooded rats to investigate if the cueing properties of the training drug generalized to other agents. Results indicate that the Fawn-Hooded rats learn to discriminate fenfluramine from its vehicle at the same rate, and with a similar sensitivity to lower doses, as do the Sprague-Dawley rats. Furthermore, fenfluramine was shown to completely generalize to MDMA (over 90%); TFMPP, m-CPP, quipazine and fluoxetine produced intermediate results (over 70%) and 5-MeODMT and ibogaine were vehicle-like (less than 70%). As these results coincide with those previously found in Sprague-Dawley rats, the conclusion is that the functional capacity to discriminate fenfluramine appears to be like that of other rat lines, and serotonergically-mediated, in the Fawn-Hooded rat. Suggestions to explain these results are offered and discussed.

Key Words: **Fawn-Hooded rats, fenfluramine, serotonin, stimulus properties**

Introduction

Fawn-Hooded (FH) rats were initially derived from Wistar rats and possess either a greatly diminished (1) or total absence (2) of ^{3}H-imipramine binding sites in both their platelets and brain. As the serotonin (5-HT) function of platelets in the periphery has been thought to be a model of central serotonergic nerve function (3), it is generally believed that the FH rat has a genetic serotonin storage abnormality (4). This genetic impairment in normal 5-HT function may suggest why behavioral research employing this rat strain has shown that their responses to serotonergically-mediated drugs differ from those seen in Sprague-Dawley rats. For example, the body temperature (hyperthermia) and behavioral responses ("wet dog" shakes) to 5-HT agonists, such as 5-MeODMT and quipazine, are greater in the FH rat (5). In a test of food intake suppression with serotonergic agents, the FH rat was compared to the Sprague-Dawley strain and was shown to have a decreased anorectic response to these drugs (6). The FH rat has also been shown to be less sensitive to the prolactin-releasing effect produced by 5-HT agonism when compared to the Sprague-Dawley rat. Since prolactin release is

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mediated by post-synaptic 5-HT receptors, this observation suggests that there is a diminished serotonergic function in these rats (7). The effects of clonidine-induced increases in growth hormone in response to selective 5-HT antagonists have also been shown to be significantly reduced in FH rats (7). Neurochemical experiments examining selective serotonin receptors in Fawn-Hoods relative to other strains have also indicated differences in serotonergic receptor subtypes (8,9). Taken together, this evidence indicates that the FH strain of rat may prove to be a useful model for brain disorders with possible abnormalities in serotonergic function.

Fenfluramine is an anorectic agent whose actions are believed to be due to its ability to release 5-HT (10,11) or upon its ability to inhibit 5-HT reuptake (12,13), two mechanisms which would result in increased concentrations of 5-HT in the synapse and, thereby, hyperstimulation of all post-synaptic 5-HT receptors. The discriminative properties of fenfluramine have been well-established in the rat by several investigators(14-18). Rats used in all of these studies were either Sprague-Dawley (16,18) or an unspecified (14,15,18) strain. It is the purpose of the present investigation to employ fenfluramine as a discriminative stimulus that will enable FH rats to differentiate one response from another based solely upon the drug or the non-drug condition. In this way, evidence as to the 5-HT function of the FH rat brain can be compared to that of Sprague-Dawley rats trained on the same dose/regimen.

Materials and Methods

Subjects Twelve male Fawn-Hooded (FH) rats were received from the New York State Department of Health and were isolated for 1 week after being placed into individual wire hanging cages. They were housed in a Vivarium facility with an ambient temperature of 20-22°C and maintained on a 12:12 light:dark cycle with lights on at 0600 h. Tap water was available in the home cage ad lib and their weights were adjusted by daily rationing of commercial rat chow so as to maintain them at 85-90% of their free-feeding weights. This procedure facilitated motivation of operant performance for food reward. The 12 Sprague-Dawley rats used for comparison of learning rates were approximately the same age at the beginning of training and were trained with the same equipment, procedure and personnel.

Apparatus Twelve standard operant test chambers (Lafayette Instrument Co., Lafayette, IN) were housed in light-proof, sound-attenuated and fan-ventilated outer shells. Each chamber was equipped with two levers mounted 7 cm apart and 2 cm above a grid floor. A food pellet receptacle was equidistant between the levers and programmed to deliver a 45 mg Noyes (Lancaster, NH) food pellet as reinforcement. Located in an adjacent room, to control and record each training and test session, was solid-state programming equipment (Med Assoc., St. Albans, VT).

Discrimination Training The food-deprived rats were administered distilled water vehicle intraperitoneally (i.p.) 20 min prior to the start of the experiments and were trained to press either the right (half the animals) or the left (the other half) lever to receive reinforcement under a fixed ratio 1 (FR 1) schedule. Training continued, as the FR schedule was made increasingly more demanding, until an FR 10 schedule was achieved over a period of 7 days; this FR 10 schedule was maintained for 3 additional days. On the following training session, the rats received (i.p.) an equal volume (1 ml/kg) of the vehicle containing 2.0 mg/ml d,l-fenfluramine hydrochloride (calculated as base) 20 min prior to the training session. At that time, the rats were placed into a randomly assigned operant chamber and an FR 1 schedule on the opposite (the designated "fenfluramine-correct") lever was in effect. The FR schedule was gradually increased over a 5 day period, until a stable FR 10 schedule was attained on the second lever and this schedule was maintained for 3 additional days.

Once FR 10 schedule responding was achieved on both levers, the discrimination training phase began

in which the food-motivated rats were required to press the fenfluramine-appropriate lever after fenfluramine administration and the vehicle-appropriate lever after vehicle administration in order to receive reinforcement. A biweekly repeating schedule of administration for either fenfluramine (F; 2.0 mg/kg) or vehicle (V), each injected (i.p.) at 20 min prior to the beginning of the training sessions, was in effect: V-F-F-V-V, F-V-V-F-F. The lever pressed 10 times first was designated as the "selected" lever and every 10th press on the fenfluramine-correct lever was reinforced on days when the animal was administered fenfluramine, whereas every 10th response on the opposite lever was reinforced after vehicle administration. On any daily session, the animals received 40 food pellets after making 400 correct responses (on the FR 10 schedule) on the state-appropriate lever. Discrimination sessions were continued until each rat reached criterion performance, i.e., selecting (pressing 10 times first) the appropriate lever according to the state imposed on 8 of 10 consecutive daily sessions. When this criterion was attained, the number of the first session of the 10 consecutive sessions was the measure referred to as "sessions-to-criterion" (STC_1). The animals were required to choose the state-appropriate lever on one additional set of 8 of 10 consecutive sessions; this measure constituted the second sessions-to-criterion (STC_2); the first of 10 consecutive sessions in which 8 correct lever selections were made on the lever corresponding to the condition imposed on that day.

Dose-Response Relationship to Various Doses of Fenfluramine After all the rats attained the training criterion and were, thus, judged able to discriminate between 2.0 mg/kg fenfluramine and its vehicle, they 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, etc. All doses, i.e., 0.5, 1.0, 1.5 and 2.0 mg/kg, were administered i.p. at 20 min prior to testing and on test days the rats were allowed to lever press until 10 responses accumulated on either lever. At that time, the rat was immediately removed from the operant test cage without receiving reinforcement and placed into their home cage in order to preclude any reinforcement (training) at a dose different than the 2.0 mg/kg fenfluramine dose used to train them. This procedure allowed calculation of the dose of fenfluramine that produced 50% discriminative performance, i.e., the ED_{50} value for both the Sprague-Dawley and Fawn-Hooded rats.

Measurements and Statistics The lever accumulating 10 presses first was designated the "selected" lever and the percentage of rats selecting this lever was the quantal measurement of discrimination. In addition, the number of lever-presses made upon the fenfluramine lever divided by the total number of responses on the fenfluramine and vehicle levers at the time that the 10th response was made on either lever, times 100, constitutes the quantitative measurement. The quantal data were analyzed by a computer generated program (19) of the Litchfield and Wilcoxon procedure (20) which employs probits vs. log-dose effects and allows for generation of ED_{50} values. The quantitative data were calculated for each animal for each session, e.g., for an animal who pressed the fenfluramine lever 10 times and the vehicle lever twice after the administration of fenfluramine, the quantal (all-or-none) score would be fenfluramine as the selected lever and the quantitative measurement would be fenfluramine lever responses divided by fenfluramine plus vehicle lever responses or 10 over 10 + 2 = 0.833 X 100; thus, the quantitative measurement on this animal's test session would be 83.3%. The STC and quantitative data between rats lines were analyzed by application of the Student's t-test with $p<0.05$ set as the criterion for significance.

Agonists Studies Tests of stimulus generalization commenced with various doses of other agents in order to determine if those agents produced stimulus effects that would be recognized as similar or dissimilar to the stimuli produced by fenfluramine in the FH rats. These agents have each been reported to have actions upon serotonergic neurons in the central nervous system, as detailed in the Discussion. Testing was carried out according to the following repeating schedule: F-SG_{d1}-V-SG_{d2}-F,

SG_{d2}-V-SG_{d1}-F-SG_{d3}, etc., where F = 2.0 mg/kg fenfluramine, V = vehicle, SG_{d1} = stimulus generalization dose 1, SG_{d2}= stimulus generalization dose 2, etc. Generalization from fenfluramine to the novel drug was said to occur if responding on the F-appropriate lever was 80% or above. This seemed appropriate as the original training criterion was the same 80%, as described above.

Drugs The drugs (chemical name; supplier; post-administration time) administered to the fenfluramine discriminating rats were: TFMPP; 1-[(3-Trifluoromethyl)phenyl]piperazine hydrochloride (Research Biochemicals Inc, RBI; Natick, MA; 20 min), m-CPP; 1-(3-chlorophenyl)piperazine hydrochloride (RBI; 20 min), 5-MeODMT; 5-Methoxy-N,N-dimethyltryptamine hydrogen oxalate (RBI; 20 min), quipazine; 2-(1- piperazinyl) quinoline dimaleate (RBI; 20 min), fluoxetine; (±) N-methyl-γ-[4-(tri-fluromethyl)phenoxy] benzene propamine (Eli Lilly & Co., Indianapolis, IN; 90 min), MDMA; 3,4-methylenedioxymethamphetamine (National Institutes on Drug Abuse; 20 min), ibogaine; 12-methoxyibogamine hydrochloride (Sigma Chemical Co., St. Louis, MO; 30 min), fenfluramine; S (+)-ethyl-α-methyl-3-(tri-fluoromethyl)-benzeneethanamide hydrochloride (A.H. Robins; 20 min). All drugs were dissolved in deionized water and were injected i.p. in a constant volume of 1 ml/kg. Doses were calculated as the salts.

Results

The learning rates of Sprague-Dawley and Fawn-Hooded rats over the 30 sessions (6, 5-day weeks) required to reach criterion performance appear in Table I. As training continued, the percent of animals choosing the fenfluramine-appropriate lever after vehicle administration decreased, whereas this number generally increased when testing occurred after fenfluramine administration. At no time during training were there significant differences (paired t-tests of quantitative measurements) between the Sprague-Dawley and Fawn-Hooded rats. In addition, the first and second sessions-to-criterion ($STC_{1,2}$) are not significantly different between these strains. Table I also represents the ED_{50} values for each group of rats, after testing with either 0.5, 1.0 or 1.5 mg/kg fenfluramine on test days interspersed with maintenance trials. The ED_{50} values were not significantly different (i.e., they were within 95% confidence limits (20)).

TABLE I

Discriminative Performance Learning after 2.0 mg/kg Fenfluramine or its Vehicle, and ED_{50} Values, in Sprague-Dawley (n=12) and Fawn Hooded (n=9) rats.

	SPRAGUE-DAWLEY				FAWN HOODED			
	Fenfluramine-lever presses after:				Fenfluramine-lever presses after:			
	Vehicle		Fenfluramine		Vehicle		Fenfluramine	
Week	Quantal	Quant. (SD)	Quantal	Quant. (SD)	Quantal	Quant. (SD)	Quantal	Quant. (SD)
1, 2	76.7	70.9 (20.7)	85.0	75.4 (11.9)	57.8	51.9 (16.9)	91.1	67.5 (11.8)
3, 4	35.0	44.9 (12.1)	85.0	77.4 (15.7)	42.2	40.3 (16.5)	91.1	71.0 (12.7)
5, 6	18.3	27.0 (10.0)	86.7	81.6 (9.6)	17.8	27.2 (18.1)	84.4	76.9 (7.5)
STC_1 (SD) (Range)	3.4 (1.7) (1-7 Sessions)				5.0 (2.4) (2-8 Sessions)			
STC_2 (SD) (Range)	13.5 (1.8) (11-17 Sessions)				17.9 (6.5) (12-29 Sessions)			
	ED_{50} (95% CL)		0.71 mg/kg (0.52-0.95)				1.09 mg/kg (0.02-1.29)	

Generalization test results with serotonergically-active drugs in FH rats trained to discriminate fenfluramine from vehicle are represented in Table II in which the doses of each drug were tested in random order but the drugs were tested going from top to bottom. During these tests, two rats died and one other was found to not maintain discrimination criterion during interspersed maintenance trials. Thus, the "n" went from 9 rats tested with TFMPP and m-CPP to 6 rats tested with ibogaine. TFMPP, administered at a dose of 2.0 mg/kg, resulted in 72.2% of first lever selections being made upon the fenfluramine-appropriate lever. The higher dose of 2.5 mg/kg was shown not to increase this generalization. Likewise, administration of 1.5 mg/kg m-CPP to the rats resulted in 77.8% responding on the fenfluramine-appropriate lever but at the higher dose of 2.0 mg/kg this effect was seen to decrease. 5-MeODMT, administered in doses of 2-4 mg/kg, generated, at best, 43.8% fenfluramine responding, whereas quipazine injections showed a dose-responsive increase in fenfluramine-like responding from 2 to 4 mg/kg with the highest dose producing 75% responding. A higher dose of quipazine was precluded by behavioral disruption in which the animals did not press either lever. Likewise, fluoxetine, in a dose of 10 mg/kg, administered 90 min prior to generalization testing, resulted in 78.6% of choice selection upon the fenfluramine lever and a higher dose was precluded by behavioral disruption. MDMA administered to 7 viable rats was seen to produce fenfluramine-lever (92.9%) selection at a dose of 1.5 mg/kg, whereas ibogaine in doses of 10-30 mg/kg never produced greater than 66.6% lever selection on the fenfluramine lever. The quantitative measurement after 1.5 mg/kg MDMA (84.6 ± 1.5) was not significantly different from the quantitative measurement after interspersed maintenance fenfluramine sessions (86.6 ± 8.8).

TABLE II

Generalization Tests with Serotonergically-active Drugs in Fawn Hooded Rats Trained to Discriminate 2.0 mg/kg Fenfluramine from its Vehicle.

Drug	No. Rats	Dose (mg/kg)	Quantal	Quantitative (SD)
TFMPP	9	2.5	44.4	51.9 (7.9
		2.0	72.2	65.3 (3.0)
		1.0	66.7	58.9 (7.7)
		0.5	33.3	36.5 (0.2)
m-CPP	9	2.0	61.1	55.3 (0.4)
		1.5	77.8	60.9 (4.1)
		1.0	66.7	61.2 (2.4)
		0.5	33.3	38.8 (4.0)
5-MeODMT	8	4.0	18.8	29.2 (5.4)
		3.0	43.8	41.0 (18.5)
		2.0	25.0	36.3 (0.2)
Quipazine	8	4.0	75.0	60.1 (4.7)
		3.0	56.3	50.8 (1.8)
		2.0	37.5	47.1 (16.6)
Fluoxetine	7	10.0	78.6	53.8 (4.2)
		5.0	35.7	39.7 (15.5)
MDMA	7	1.5	92.9	84.6 (1.5)
		1.0	57.1	56.0 (2.0)
		0.5	14.3	26.1 (1.7)
Ibogaine	6	30.0	58.3	53.4 (7.1)
		20.0	66.6	59.1 (2.5)
		10.0	33.3	28.8 (27.1)

Discussion

The discriminability of a drug can be measured by the duration of training required to establish the drug vs. non-drug discrimination (21). The present experimentation indicates that the Fawn-Hooded rats learn to discriminate 2.0 mg/kg fenfluramine from its vehicle at the same rate and, furthermore, with similar sensitivity to lower doses, as the Sprague-Dawley rats (Table I). Thus, it appears that the FH rats, which may have a genetic 5-HT storage abnormality (1,2) and have been shown to react to serotonergically-mediated drugs differently than Sprague-Dawley rats (5,6,7,22), are similarly affected when drug discrimination to fenfluramine is the behavioral task. This observation is especially interesting in light of a recent finding in this laboratory indicating that Fawn-Hooded rats learn to discriminate the interoceptive discriminative stimuli produced by (600 mg/kg) ethanol at a significantly slower rate then do either Sprague-Dawley or N/Nih strains (23). In addition, heightened ethanol consumption by the Fawn-Hooded rat line over the Sprague-Dawley line (24) has been shown to be associated with heightened serotonin neuronal uptake (25,26).

The apparently intact nature of central serotonergic functioning in the FH rats is further demonstrated by the ability of other serotonergically-mediated drugs to produce partial or complete generalization. The reason that fenfluramine was chosen as the training drug to be used in FH rats is based upon the observation that fenfluramine is a 5-HT releasing agent (10-12) and, thus, would be indicative of central serotonergic functioning. It is, therefore, unexpected that 5-MeODMT, a drug considered to be a 5-HT_{1A} agonist (27), produced the least amount of fenfluramine-like responding (43.8% at 3.0 mg/kg). In addition, a study mentioned in a published abstract (17) suggests that 5-MeODMT is generalized from fenfluramine with an ED_{50} of 7.19 mg/kg. In the present study, doses greater than 4.0 mg/kg 5-MeODMT were seen to produce behavioral disruption in which the rats did not press either lever.

In contrast to these negative results, the 5-$HT_{1B/1C}$ selective agonists TFMPP and m-CPP (27), as well as the 5-$HT_{1B/2}$ selective drug quipazine, each produced intermediate results. This last finding had previously been shown to occur in male rats of the Sprague-Dawley strain (18). Likewise, the drug fluoxetine which inhibits 5-HT uptake (28) was shown to produce fenfluramine-like discriminative effects (78.6% lever selection) in these FH animals as previously shown to occur in Sprague-Dawley rats (18). The indole alkaloid ibogaine has been shown to stimulate serotonin release in striatal tissue in both mice and rats (29) and, at a dose of 20 mg/kg, it produced 66.6% of selected lever responses on the fenfluramine-appropriate lever. Complete (i.e., greater than 80% lever selection) generalization from fenfluramine occurred only with MDMA (3,4-methylenedioxymethamphetamine) a serotonergically-mediated drug which had previously been shown to generalize from fenfluramine in Sprague-Dawley rats (16,30).

Taken together, the comparison of learning rates, sessions-to-criteria, and ED_{50} values between FH and Sprague-Dawley rats would indicate that both strains of rats learn to discriminate 2.0 mg/kg fenfluramine at the same pace and with the same sensitivity. Furthermore, testing of various serotonergically-mediated drugs in the FH animals indicates that their ability to discriminate/generalize these drugs is not different from that seen with Sprague-Dawley rats used in previous studies from this and other laboratories. This is in contrast to the reports that the FH rat exhibits an apparent subsensitivity to serotonergic stimulation in other behavioral tasks (31,32). In neurochemical investigations, this line also shows differences in serotonin uptake sites in five brain regions when compared to Sprague-Dawley rats (33). Thus, the functional capacity to discriminate fenfluramine appears to be like that of other rat lines and serotonergically-mediated. One explanation for the inability to observe a difference in fenfluramine discrimination between the serotonin-dysfunctional

Fawn-Hooded rat and another strain may, in fact, be inherent in the discriminative task itself. Fenfluramine must be administered on repeated occasions during training and this dosing regimen may preclude or "readjust" subtle, inherited serotonergic differences. Given that this behavioral paradigm requires repeated administrations of fenfluramine for acquisition of discrimination at a dose within the range that causes short-term depletion of 5-HT even after a single administration (34), it is possible that fenfluramine treatment may alter 5-HT levels in the SD rats before criterion performance is reached. This would, therefore, allow for equivalent 5-HT brain concentrations to exist in both rat lines. Lastly, the training dose of fenfluramine may have been supra-maximal precluding detection of subtle differences between strains. Discrimination of a lower dose of fenfluramine (1 mg/kg) has been reported in the literature (18) and its use may have revealed differences between strains. Nevertheless, the continued use of the Fawn-Hooded animals as a potential animal model for serotonin deficits that may model other human diseases, such as depression and alcoholism (35), is substantiated by the large, yet still growing, volume of data on this inbred line of rats.

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