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A Neuropharmacological Analysis of the Discriminative Stimulus Properties of Fenfluramine

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Abstract. Rats were trained to discriminate fenfluramine (1.0 mg/kg) from saline in a two-lever drug discrimination task. The dose-response curve for this discrimination was orderly with an ED_{50} of about one-half of the training dose (0.52 mg/kg). In substitution tests, indirect (*p*-chloroamphetamine) and direct (quipazine, MK-212, lisuride) serotonin (5-HT) agonists substituted for fenfluramine. Since none of these compounds have been reported to be hallucinogenic and the potent hallucinogen LSD did not substitute completely, it was suggested that the discriminative stimulus properties of fenfluramine are not related to its ability to produce hallucinations in humans. The fenfluramine cue, like the quipazine cue, was antagonized by the 5-HT antagonists cyproheptadine and methiothepin. Unlike quipazine, fenfluramine was also partially antagonized by the 5-HT uptake inhibitor, fluoxetine, and the 5-HT synthesis inhibitor, *p*-chlorophenylalanine. Thus, the fenfluramine cue differs from that of quipazine in that it is mediated via indirect actions on 5-HT receptors. Since the indirect dopamine (DA) agonist *d*-amphetamine failed to substitute and the DA antagonist haloperidol failed to block the fenfluramine cue, a mediating role for DA was not indicated. Another indirect DA agonist, cocaine, substituted partially for fenfluramine, a result which paralleled that seen with fluoxetine. Both of these partial substututions were reduced by cyproheptadine; therefore, it was concluded that these effects may be due to the common ability of cocaine, fluoxetine, and fenfluramine to inhibit 5-HT uptake.

Key words: Fenfluramine – Hallucinogens – LSD – Lisuride – Quipazine – MK-212 – *p*-Chloroamphetamine – *p*-Chlorophenylalanine – *d*-Amphetamine – Cocaine – Fluoxetine – Serotonin – Serotonin agonists – Serotonin antagonists – Drug discrimination

Fenfluramine (*N*-ethyl-α-methyl-3-trifluromethyl-β-phenylethylamine), like its structural analogue *d*-amphetamine, has been used as an anorexigen in humans (Silverstone et al. 1975). Nevertheless, these compounds are pharmacologically distinct: *d*-amphetamine promotes release of the catecholamines, particularly dopamine (DA), and inhibits their reuptake (Glowinski 1970; Weissman et al. 1966) while fenfluramine has comparable effects on serotonergic (5-HT) neurons (Fuxe et al. 1975; Garattini et al. 1975). These neuropharmacological actions appear to mediate different behavioral and subjective effects. For example, in animals, fenfluramine is devoid of reinforcing properties (Woods and Tessel 1974) whereas *d*-amphetamine is readily self-administered (Pickens and Harris 1968); in humans, fenfluramine produces an unpleasant lethargy rather than the energized, euphoric "high" that is usually experienced following *d*-amphetamine (Gotesman and Gunne 1972). Thus, it is not surprising that the two drugs have different discriminative stimulus properties (Goudie 1977; Schechter and Rosecrans 1973).

We became interested in fenfluramine for two reasons. First, it has been reported that this agent can induce an LSD-like hallucinogenic syndrome in humans (Griffith et al. 1975) and might, therefore, be expected to have discriminable effects similar to LSD in rats. In this regard, we found that animals trained to discriminate the 5-HT agonist quapazine from saline respond to either fenfluramine or LSD as if they had received quipazine (White et al. 1979); that is, both fenfluramine and LSD substitute for quipazine. More direct evidence that the fenfluramine and LSD cues are similar has been reported by Winter (1980), who found that, when rats are trained to discriminate LSD from saline, fenfluramine substitutes for LSD, although this substitution is not complete.

The second reason for our interest in fenfluramine concerns the extent to which the analysis of the discriminative stimulus properties of drugs can elucidate neuronal mechanisms of action. For example, it is well known that substitution between the direct DA agonist apomorphine and the indirect DA agonist *d*-amphetamine is not symmetrical. That is, in rats trained to discriminate *d*-amphetamine from saline, substitution of apomorphine for *d*-amphetamine has been reported by some investigators (Bueno et al. 1976; Schechter 1977; Schechter and Cook 1975) but not others (D'Mello and Stolerman 1978; Hernandez et al. 1978; Ho and Huang 1975). When rats are trained to discriminate apomorphine from saline, substitution of *d*-amphetamine for apomorphine does not occur (D'Mello and Stolerman 1978; Hernandez et al. 1978). It is important to know the extent to which drug discrimination experiments can differentiate similar relationships with regard to 5-HT mechanisms.

Fenfluramine is reportedly an indirect 5-HT agonist, i.e. it releases 5-HT from pre-synaptic terminals and inhibits its reuptake (Fuxe et al. 1975; Garattini et al. 1975), whereas quipazine is primarily a direct 5-HT agonist (White et al. 1979). It is known that fenfluramine substitutes for quipazine (White et al. 1979), but whether or not the substitution

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between indirect and direct 5-HT agonists is symmetrical cannot be determined until animals trained to discriminate fenfluramine are tested with quipazine. To investigate these and related issues, rats were trained to discriminate fenfluramine (1.0 mg/kg) from saline in a two-lever, water reinforced discrimination task. After accurate performance was obtained animals were injected with various agents and given substitution, antagonism, and pretreatment tests.

Materials and Methods

Subjects. Sixteen male albino rats (Sprague-Dawley), weighing between 280 and 350 g at the inception of the experiment, were maintained at 80–85% of expected free-feeding weight by restricting water intake. They were housed individually with free access to laboratory chow in a room with controlled temperature (21°–23°C), humidity (40–50%), and lighting (12 h light-dark cycle).

Apparatus. Eight sound-attenuated and light-attenuated chambers (LVE 143–24) located in two testing rooms (four per room) were used. Each was equipped with two response levers on one wall separated by a dipper which delivered 0.1 ml of tap water. Illumination was provided by a 28 V white house light; an exhaust fan supplied both ventilation and masking noise. Electromechanical and solid-state programming and recording circuits were located in an adjoining room.

Discrimination Training. Twenty minutes before being placed in experimental chambers, the rats were injected with either fenfluramine (1.0 mg/kg) or isotonic saline (0.9% NaCl). Training began with only the stimulus-appropriate lever present and with the apparatus programmed for a continuous schedule of water reinforcement (FR 1). For half of the rats, the left lever was designated as correct for fenfluramine and the right lever for saline while, for the other half, the right lever was correct for fenfluramine and the left lever for saline. The number of bar-presses necessary for reinforcement was gradually increased to 32 (FR 32). The order of fenfluramine-saline administration was irregular across sessions with the restriction that neither condition was present for more than three consecutive sessions. When responding stabilized at FR 32, both levers were presented simultaneously and discrimination testing began. The animals were reinforced only for responding on the stimulus-appropriate lever; there was no programmed consequence for incorrect responding. During discrimination training, accuracy was defined as the number of correct responses (32) divided by the total number of responses before the first reinforcer was delivered. Discrimination training continued until the discriminative performance of all rats was above 85% for five consecutive sessions and the group mean was above 85% for at least ten consecutive sessions. The sessions were 20 min long and were conducted 6 days per week.

Substitution Testing. After criterion performance was achieved, substitution testing began. In these tests, the rats were injected with various doses of fenfluramine or some novel compound and tested for lever selection at an appropriate time thereafter (see below). Five doses of fenfluramine (0.125, 0.25, 0.50, 1.0, and 2.0) were given to obtain a dose-response curve. The novel compounds included quipazine, MK-212 (6-chloro-2-(1-piperazinyl)-pyrazine), *d*-lysergic acid diethylamide (LSD), lisuride hydrogen maleate (LHM), *p*-chloramphetamine (PCA), *d*-amphetamine, cocaine and fluoxetine. All drugs were administered 20 min before testing except fluoxetine, which was given 90 min before testing. At least four doses of each compound were tested. Fluoxetine was also tested in conjunction with a low dose of fenfluramine by injecting fenfluramine (0.125 mg/kg) 20 min prior to fluoxetine and testing 90 min after the fluoxetine injection. All tests were administered randomly throughout the course of the experiment. Each test was preceded by at least one fenfluramine and one saline session and was conducted under extinction conditions, i.e., no responses were reinforced.The session ended when the rat had made a total of 32 responses on one of the two levers or when 20 min had elapsed, whichever occurred first. Only the data from rats making at least ten total responses were included. Data from test sessions are expressed as the number of responses on the fenfluramine lever (0–32) divided by the total number of responses on both levers (10–63).

Antagonism Testing. The 5-HT antagonists methiothepin and cyproheptadine and the DA antagonist haloperidol were injected 60 min prior to fenfluramine (1.0 mg/kg) injection and rats were tested for lever selection 20 min after fenfluramine. Three doses of each antagonist were given. Fluoxetine was administered 90 min prior to fenfluramine (1.0 mg/kg) and rats were tested 20 min later. These tests were also administered randomly throughout the experiment and were conducted, as always, under extinction conditions. Time intervals for test compounds were usually determined on the basis of previous drug-discrimination studies (Kuhn et al. 1978; White et al. 1979).

PCPA pretreatment. After all other testing had been completed, rats were given 100 mg/kg *p*-chlorophenylalanine (PCPA) for 3 consecutive days. Four days after the last injection, rats were tested with saline. Twenty min before the next session, half the rats received fenfluramine (1.0 mg/kg) and half received quipazine (1.0 mg/kg). On the following day, the treatment for each rat was reversed. The percentage of fenfluramine responses was recorded for each session and the data were pooled for each treatment.

Pharmacological Procedures. Doses of the following drugs are expressed as the weight of the salt: fenfluramine HCl, lisuride hydrogen maleate, *d*-lysergic acid diethylamide tartrate, MK-212 HCl, quipazine maleate, *p*-chloroamphetamine HCl, *d*-amphetamine sulfate, cocaine HCl, fluoxetine HCl, cyproheptadine HCl, and methiothepin maleate. Doses of PCPA methyl ester refer to the free base. Haloperidol (Haldol) was diluted with saline from ampoule solutions prepared by McNeil Laboratories, Cyproheptadine was dissolved in 15% aqueous propylene glycol. PCA was dissolved in de-ionized water. All other drugs were dissolved in isotonic saline solution. All solutions were injected (IP) in a constant volume of 1 ml/kg.

Data Analysis. Data from both substitution and antagonism tests were analyzed using a treatment by subjects (repeated measures) analysis of variance (ANOVA) which included the data from all doses of each treatment in addition to typical saline and fenfluramine performance. Individual means were then compared with the Newman-Keul's multiple range test (Winer 1971). The effect of PCPA treatment on fenfluramine responding was analyzed using Student's *t*-statistic for correlated measures. All comparisons were made with the probability of a Type I error set at $P < 0.05$.

Results

Acquisition of the Fenfluramine-Saline Discrimination. The rats acquired the discrimination rapidly. The average number of sessions for meeting the individual criterion (five consecutive sessions above 85% correct) was 13 (range: 7–37). The group met the criterion of ten consecutive sessions above 85% correct on the 25th session. Testing began on session 40.

Dose-Response Effect. The results obtained during fenfluramine test sessions are shown in Fig. 1. As can be seen, the percentage of responses on the fenfluramine-appropriate lever increased as a function of dose. The ED_{50} was 0.52 mg/kg, approximately one-half of the training dose. One rat died during dose-response testing; therefore, the data corresponding to doses of 0.5 and 2.0 mg/kg are the means of 15 rats and all other points are the means of 16 rats.

Substitution Tests with Novel Compounds. Figure 2 shows the results of substitution tests with various novel compounds. Treatment with LHM, quipazine, MK-212, and PCA produced dose-related increases in percent fenfluramine-lever responding such that each drug eventually substituted for fenfluramine; i.e. percent fenfluramine responding at some dose of each test compound was not significantly different

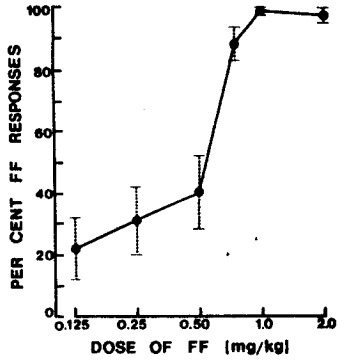

Fig. 1. Dose-response relationship for rats trained to discriminate 1.0 mg/kg fenfluramine (*FF*) from saline. Each point represents the mean of either 15 or 16 rats. Vertical lines represent SE. Ordinate: Mean percentage of FF-lever responses. Abscissa: Dose of FF plotted on a log scale

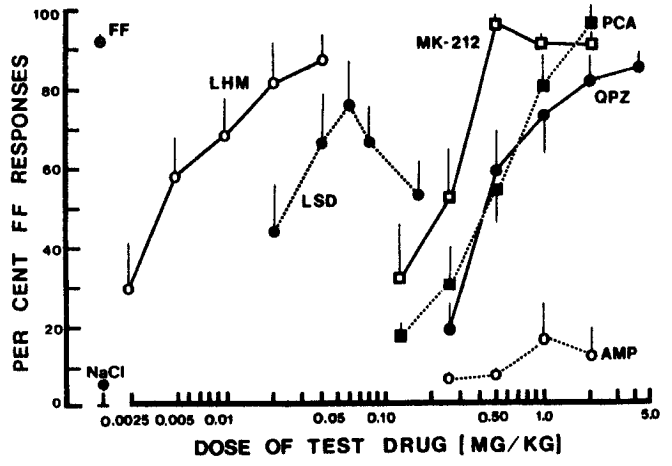

Fig. 2. Results of substitution tests with lisuride hydrogen maleate (*LHM*), *d*-lysergic acid diethylamide (*LSD*), MK-212, *p*-chloroamphetamine (*PCA*), quipazine (*QPZ*), and *d*-amphetamine (*AMP*) in rats trained with fenfluramine (*FF*) as a discriminative stimulus. Sample size for all points except AMP (12) and PCA (10) was 14. Typical FF and saline (*NaCl*) performance are shown on far left of the graph. Vertical lines represent SE. Ordinate: Mean percentage of FF-lever responses. Abscissa: Dose of test drugs plotted on a log scale

from responding following fenfluramine itself. Peak effects were as follows; lisuride, 89% at 0.04 mg/kg; quipazine, 87% at 4.0 mg/kg; MK-212, 97% at 0.5 mg/kg; and PCA, 97% at 2.0 mg/kg.

Doses from 0.02 – 0.06 mg/kg of LSD caused a dose-related increase in fenfluramine responding but at 0.06 mg/kg the curve reached a peak (73%) which was significantly different from both saline and fenfluramine. At 0.08 and 0.16 mg/kg of LSD, percent fenfluramine responding declined. *d*-Amphetamine produced responding (6 – 17%) that was not significantly different from saline at any dose tested.

Antagonism of the Fenfluramine Cue. Figure 3 shows that the 5-HT antagonists cyproheptadine (CYP) and methiothepin (MTP), when administered in conjunction with fenfluramine, produced dose-related decreases in responding on the fenfluramine lever. Each compound resulted in approximately 30% fenfluramine responses at the highest dose, a 65% reduction from responding following fenfluramine alone. When administered prior to fenfluramine, fluoxetine (FLU)

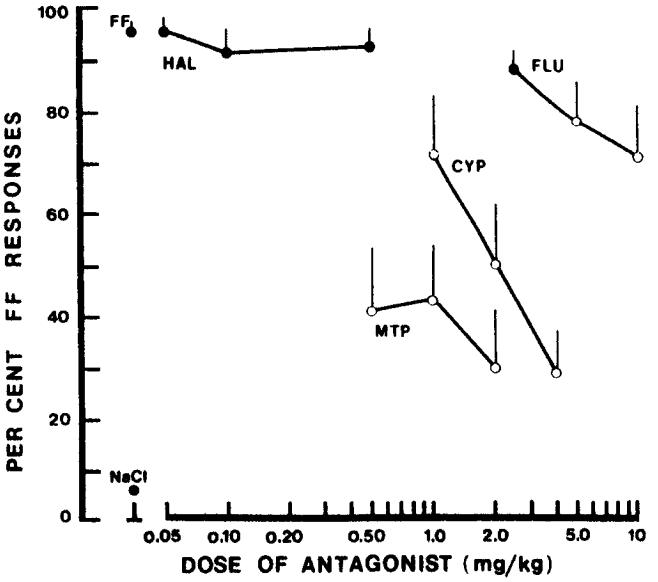

Fig. 3. Effects of haloperidol (*HAL*), methiothepin (*MTP*), cyproheptadine (*CYP*), and fluoxetine (*FLU*) on the fenfluramine (*FF*) cue when given in combination with FF (1.0 mg/kg). Sample size was 12 for all points except FLU (14). Typical FF and saline (*NaCl*) performance are indicated on the far left of the graph. Open circles represent performance which is significantly different from FF alone ($P < 0.05$). Vertical lines represent SE. Ordinate: Mean percentage of FF-lever responses. Abscissa: Dose of antagonists plotted on a log scale

had a slight antagonistic effect, i.e., fenfluramine-lever responding was reduced to 78% following 5 mg/kg fluoxetine and to 71% following 10 mg/kg fluoxetine. The DA antagonist haloperidol (HAL) had no effect on the fenfluramine cue.

Tests with Cocaine and Fluoxetine. The results of substitution tests with cocaine and fluoxetine are shown in Fig. 4. These drugs produced similar, dose-dependent increases in fenfluramine responding. However, the maximal effect of both compounds (64%) was intermediate, i.e., significantly different from both saline and fenfluramine. Each of these partial substitutions was significantly reduced by cyproheptadine. Haloperidol completely blocked the substitution of cocaine but had no effect on that of fluoxetine.

When administered subsequent to a low, sub-threshold dose of fenfluramine (0.125 mg/kg), fluoxetine (5 mg/kg) caused a significant increase in fenfluramine responding as compared to either 0.125 mg/kg of fenfluramine alone or 5 mg/kg of fluoxetine alone, i.e., there was a significant additive effect. The combination of 10 mg/kg of fluoxetine and 0.125 mg/kg of fenfluramine produced responding that was significantly greater than 0.125 mg/kg fenfluramine alone but not 10 mg/kg of fluoxetine alone.

Effects of PCPA Treatment. Table 1 shows that PCPA caused a significant decrease in the discriminability of fenfluramine ($t = 2.83$, $df = 10$, $P < 0.05$) but had no effect on the ability of quipazine to mimic the fenfluramine cue. PCPA also had no effect on saline accuracy.

Discussion

The results indicate that a dose of 1.0 mg/kg fenfluramine is readily discriminable from saline and, therefore, extend

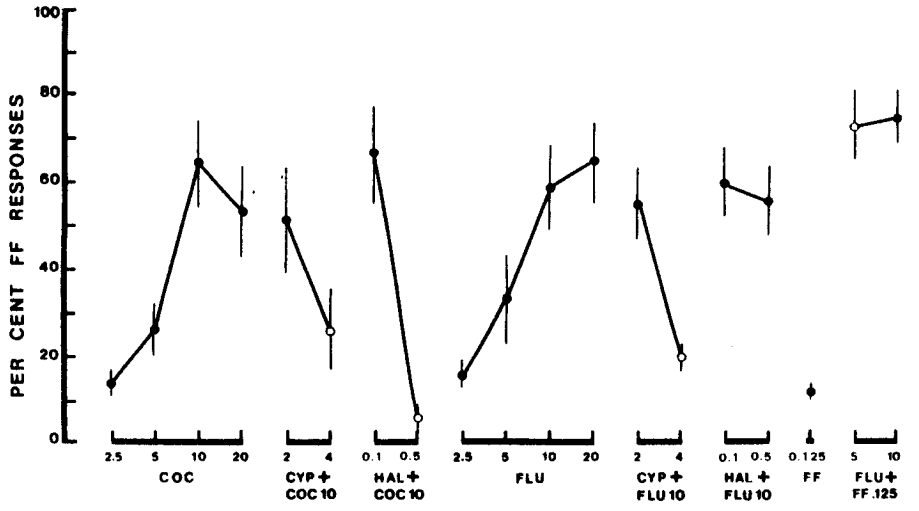

Fig. 4
Effects of cocaine (*COC*) and fluxetine (*FLU*) in rats trained to discriminate fenfluramine (*FF*) from saline. Four doses of each drug were administered in substitution tests. One dose of each drug (10 mg/kg) was also administered 60 min after pretreatment with either haloperidol (*HAL*) or cyproheptadine (*CYP*). Displayed on the far right are the effects of FLU given in combination with a low dose of FF which was administered 20 min prior to FLU; tests were conducted 90 min after FLU. Open circles represent significant decreases ($P < 0.05$) from either COC or FLU alone or, in the last segment, a significant increase over both FF alone and FLU alone. Vertical lines represent SE. All points are means of 14 rats. Ordinate: Mean percentage of FF-lever responses. Abscissa: Dose of test drug plotted on a log scale

Table 1. Effect of PCPA treatment on the fenfluramine cue and the substitution of quipazine for fenfluramine. Data represent mean ($N = 11$) percent responding on the fenfluramine-lever ± SE

	Saline	Fenfluramine (1.0 mg/kg)	Quipazine (1.0 mg/kg)
Before PCPA	2 ± 1	97 ± 3	80 ± 10
After PCPA	2 ± 2[a]	45 ± 12[b]	87 ± 5[a]

[a] Not significantly different from before PCPA
[b] Significantly less than before PCPA ($P < 0.05$)

previous findings (Goudie 1977) that a higher dose of fenfluramine (3.0 mg/kg) can exert stimulus control. Acquisition of this discrimination was rapid and the dose-response curve was orderly and relatively steep with an ED_{50} of 0.52 mg/kg, which was approximately one-half of the training dose.

Of the drugs tested for similarity to fenfluramine, only those that act as 5-HT agonists produced complete substitution. PCA which, like fenfluramine, promotes release of neuronal 5-HT (Sanders-Bush et al. 1974) and MK-212, which is a direct acting 5-HT agonist (Clineschmidt and McGuffin 1978), produced the strongest substitutions (97%). Another direct 5-HT agonist, quipazine, also mimicked fenfluramine (89%). Since fenfluramine substituted for quipazine in rats trained to discriminate quipazine from saline (White et al. 1979), the transfer between direct and indirect 5-HT agonists is symmetrical, a situation that does not occur with DA agonists (D'Mello and Stolerman 1978; Hernandez et al. 1978). The fact that the 5-HT antagonists methiothepin and cyproheptadine block both the fenfluramine (Fig. 3.) and quipazine (White et al. 1977, 1979) cues also indicates considerable similarity between the states produced by these compounds.

Despite the similarities of the fenfluramine and quipazine cues, the actions of these agonists can be differentiated by several pharmacological manipulations. (1) The selective 5-HT uptake inhibitor fluoxetine (Fuller et al. 1974) substituted for fenfluramine (Fig. 4) more so than for quipazine (White et al. 1979). Thus, inhibition of the 5-HT uptake mechanism plays a greater role in the fenfluramine cue than in the quipazine cue. (2) When fluoxetine is administered subsequent to a low dose of fenfluramine or quipazine, it potentiates the effects of fenfluramine (Fig. 4) but not those of quipazine (unpublished results). Thus, inhibiting the uptake system, consequently prolonging the action of 5-HT at its receptors, increases the efficacy of a low dose of fenfluramine. (3) Pretreatment with fluoxetine results in a partial decrease in the discriminability of the training dose of fenfluramine (Fig. 3), but not quipazine (unpublished results), probably because inactivating the uptake system decreases the ability of fenfluramine to enter the neuron, which is a prerequisite for its releasing action (Clineschmidt and McGuffin 1978). This antagonism was incomplete because fluoxetine itself produces a partial fenfluramine-like cue. (4) PCPA, in doses known to deplete 5-HT (Koe and Weissman 1966), reduced the discriminability of fenfluramine (Table 1) and the substitution of fenfluramine for quipazine (White et al. 1979) but did not diminish the substitution of quipazine for fenfluramine (Table 1) and actually potentiated the discriminability of low quipazine doses (White et al. 1979) Taken together, these data indicate clearly that the fenfluramine cue differs from the quipazine cue in that it is mediated via indirect actions on 5-HT receptors, i.e., via the release of 5-HT and the inhibition of its re-uptake.

The lack of complete substitution of LSD for fenfluramine is consistent with the finding that fenfluramine does not substitute completely for LSD (Winter 1980). However, it is surprising in that another structurally related ergot derivative, lisuride, substituted completely for fenfluramine. Although lisuride is similar to LSD in terms of many behavioral (Pieri et al. 1978b; Silbergeld and Hruska 1979), biochemical (Pieri et al. 1978a) and electrophysiological (Rogawski and Aghjanian 1979; Walters et al. 1979) properties, it is reportedly not hallucinogenic in humans (Sommerville and Herrmann 1978); indeed, none of the compound that substitute for fenfluramine have been reported to be hallucinogenic. Thus, the discriminative stimulus properties of fenfluramine in rats may not be related to its ability to induce hallucinations in humans (Griffith et al. 1975).

The incomplete substitution of LSD for fenfluramine may also reflect some neuropharmacological difference in the

actions of LSD and of other 5-HT agonists. One such difference, which has been proposed previously (Kuhn et al. 1978), concerns in vitro evidence that [^{3}H]LSD and [^{3}H]5-HT receptors are related but not identical, i.e., [^{3}H]LSD binds to sites in addition to those that recognize [^{3}H]5-HT (Fillion et al. 1978; Lovell and Freedman 1976). More recent studies have proposed the existence of at least two distinct 5-HT receptors, designated 5-HT$_1$ and 5-HT$_2$, which preferentially recognize [^{3}H]5-HT and [^{3}H]spiroperidol respectively (Hamon et al. 1980; Peroutka and Snyder 1979). While 5-HT agonists have higher affinity for the [^{3}H]5-HT receptor (5-HT$_1$) (Fillion et al. 1978; Hamon et al. 1980), [^{3}H]LSD has an equally high affinity for both of these sites (Hamon et al. 1980; Peroutka and Snyder 1979) and could, therefore, produce effects that are similar, but not identical, to those of other 5-HT agonists.

A role for DA in the fenfluramine cue is not indicated since *d*-amphetamine and fenfluramine do not substitute for one another (Goudie 1977; Schechter and Rosecrans 1973; present results). Furthermore, haloperidol antagonizes the *d*-amphetamine cue (Schechter and Cook 1975) but not the fenfluramine cue. Since cocaine, like *d*-amphetamine (Ho and Huang 1975), exerts its cueing effect by releasing DA (McKenna and Ho 1980), it is surprising that this agent produced a dose-related partial substitution for fenfluramine (64%). The similarity of this result to that produced by fluoxetine and the fact that cocaine inhibits 5-HT uptake to a greater extent than does *d*-amphetamine (Taylor and Ho 1978) suggest that these partial substitutions may be due to the common ability of cocaine, fluoxetine and fenfluramine to inhibit 5-HT uptake. This hypothesis is supported by the fact that cyproheptadine significantly reduced the effect of both cocaine and fluoxetine. Since haloperidol completely blocked the substitution of cocaine but had no effect on fluoxetine, the action of cocaine on 5-HT neurons may be secondary to DA stimulation.

An important aspect of the actions of fenfluramine, which has not been addressed by the present study, is the reported ability of this compound, like that of PCA, to cause a long-lasting reduction in 5-HT levels (Harvey 1978). However, it should be noted that during this research (over 18 months), there was no evidence of a decreased ability to discriminate fenfluramine. Furthermore, replication of the partial substitution of LSD (0.08 mg/kg) at three different times revealed no significant differences in percent fenfluramine responding. Thus, the rats were probably capable of making adaptive compensatory adjustments to any changes in biochemistry that may have been caused by fenfluramine.

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