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BRIEF COMMUNICATION

Lack of Neuroleptic-Like Activity of *l*-Fenfluramine

MARTIN D. SCHECHTER

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272

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SCHECHTER, M. D. *Lack of neuroleptic-like activity of* l-*fenfluramine*. PHARMACOL BIOCHEM BEHAV **39**(2) 549–551, 1991.—Rats were trained to differentiate between the dopaminergically mediated discriminative stimuli produced by intraperitoneal administration of 4.8 mg/kg cathine and its vehicle. Once trained, three doses of *l*-fenfluramine (1.0, 2.0 and 2.5 mg/kg) were administered to determine if this agent would produce cathine-appropriate discriminative performance. All doses of *l*-fenfluramine were observed to produce vehicle-like responding. The 2.0 mg/kg dose of *l*-fenfluramine as well as 3.0 mg/kg chlorpromazine were administered in separate experiments prior to either cathine or vehicle. Chlorpromazine attenuated cathine-lever responding after cathine administration but did not affect vehicle responding. In contrast, *l*-fenfluramine had no effect upon cathine discrimination. The results indicate that *l*-fenfluramine shares neither agonist nor antagonist activity in the dopamine-mediated discriminative performance produced by cathine.

Drug discrimination Cathine Fenfluramine Dopamine Neuroleptic Khat

RACEMIC fenfluramine is similar in structure to amphetamine, and both drugs are clinically useful anorectics. The scientific consensus is that these drugs produce this same common effect by different neurochemical pathways, as amphetamine is mediated predominantly by release of dopamine, whereas fenfluramine actions are mediated by the release of serotonin. However, racemic fenfluramine, by definition, can be resolved to afford *d*- and *l*-fenfluramine, and each of these isomers has been shown to have differential activity upon central neurons with the *d*-isomer more potent that the *l*-isomer in affecting serotonin (4) and the *l*-isomer capable of increasing the metabolism of striatal dopamine at doses that do not cause any changes in serotonin levels or metabolism (1). Thus a neuroleptic-like activity of *l*-fenfluramine has been biochemically evidenced. When coupled with *l*-fenfluramine's ability to inhibit amphetamine- and apomorphine-induced stereotypic behaviors (3), these factors lend support to the notion that *l*-fenfluramine has effects on central dopaminergic mechanisms similar to those produced by neuroleptics.

The psychoactive ingredients contained in the leaves of the Khat plant, which is used for its central nervous system stimulant activity, have been found to be cathinone and cathine. The psychopharmacological activity of these "khatamines" have, like amphetamine, been shown to be dopaminergically mediated (5). The ability of cathine to serve as a drug capable of controlling differential responding in a drug discrimination procedure was first observed in this laboratory (7). Furthermore, the mediation of this discriminative action was evidenced to be dopaminergically mediated by the ability of both a dopaminergic-blocking neuroleptic drug haloperidol (7), as well as a dopamine release inhibiting agent CGS 10746B (8), to block cathine discrimination. It was, therefore, the purpose of the present experiment to test the dopamine agonist and antagonist activity of *l*-fenfluramine in rats trained to discriminate the dopaminergically mediated interoceptive cues produced by cathine.

METHOD

Subjects

Twelve singly housed male Sprague-Dawley rats, weighing 200–235 g at the beginning of experimentation, were purchased from the Zivic-Miller Laboratories (Allison Park, PA). These rats were maintained at body weight levels approximately 90% of their free-feeding weights by rationing of commercial rat chow after experiments, so as to provide incentive for performance. Water was available ad lib in their home cages, kept in a room of constant temperature and humidity, exposed to a 12-hour light (0600–1800 h)/dark cycle.

Apparatus and Discriminative Training

The equipment and discriminative training procedure have been detailed in a previous publication (7). Briefly, the rats were trained to discriminate between the effects of 4.8 mg/kg cathine and its distilled water vehicle in a two-lever food-motivated operant task. Once each of the animals had reached criterion performance set at 80% correct lever selections (first lever pressed 10 times according to the substance administered), their discrim-

inative performance was ensured and maintained by every second experimental day comprised of a maintenance session in which either 4.8 mg/kg cathine or vehicle was injected and tested. Training continued until the rats received 40 reinforcements (45 mg Noyes food pellets) by pressing the correct lever 400 times on an FR10 schedule of reinforcement. Interspersed between these maintenance sessions were test days in which the rats were tested with one of three doses (1.0–2.5 mg/kg) of *l*-fenfluramine and immediately removed from the test chamber upon making 10 responses on either of the two levers. These experiments were performed to determine if the cathine-appropriate discrimination would generalize after *l*-fenfluramine administration (agonism study).

In addition to these substitution studies, test days were employed to investigate antagonism. In these experiments, the cathine-trained rats were administered (IP) either 2.0 mg/kg *l*-fenfluramine or 3.0 mg/kg chlorpromazine and, 15 min later, a second injection of either 4.8 mg/kg cathine or its vehicle. At 15 min after the second injection, the rats were placed into the two-lever chamber and allowed to press one of the two levers 10 times. Each of the three doses of *l*-fenfluramine, as well as the pretreatments with 2.0 mg/kg *l*-fenfluramine or chlorpromazine, were conducted in two sessions, with one following a cathine maintenance session and the other following a vehicle session; this was done to counterbalance any possible previous day's effects on discrimination of a novel circumstance.

Measurements and Statistics

Within each experiment, all rats received all treatments, and the treatment order was randomized. Two types of data were generated: a) quantitative measurements—the number of lever presses on the drug lever divided by the total number of presses accumulated on both levers when either lever accumulated 10 presses, and b) quantal—the number of rats responding with 10 presses first upon the cathine-correct lever divided by the total number of rats ($n=12$) multiplied by 100. Student's *t*-tests were applied to compare the quantitative measurement produced by a dose of *l*-fenfluramine that produced the greatest amount of cathine-like quantal discriminative activity with the quantitative measurement following the training dose of cathine. In the antagonism study, the effects of pretreatment of both *l*-fenfluramine and chlorpromazine upon vehicle were compared to the effects of these pretreatments on cathine discrimination. Significance was said to occur when $p<0.05$ was calculated.

RESULTS

The effects of testing *l*-fenfluramine at doses of 1.0, 2.0, and 2.5 mg/kg in rats trained to discriminate between 4.8 mg/kg cathine and its vehicle appear in Table 1A. The cathine and vehicle quantal and quantitative measurements were derived by measuring the responses of the rats on maintenance sessions. These measurements indicate that, on those days in which cathine was administered, the animals chose the cathine-appropriate lever on 95% of all trials, whereas, when vehicle was injected, the animals chose the cathine-appropriate lever on 15% of all trials (or, to look at it a different way, selected the vehicle-appropriate lever on 85% of all trials). The highest dose of *l*-fenfluramine tested (2.5 mg/kg) produced 29.2% of first lever selections upon the cathine-appropriate lever. A higher dose of *l*-fenfluramine (3.0 mg/kg) was administered but produced behavioral disruption, in that 8 of the 12 rats did not press either lever for at least 15 min. The quantitative measurement after 2.5 mg/kg *l*-fenfluramine (38.0 ± 14.1) was not significantly different ($t=2.367$) from that of vehicle.

TABLE 1

EFFECT OF L-FENFLURAMINE (L-FEN) OR CHLORPROMAZINE (CPZ) IN RATS ($N=12$) TRAINED TO DISCRIMINATE 4.8 mg/kg CATHINE FROM ITS VEHICLE

A.

Drug	Dose (mg/kg)	Quantal	Mean Quantitative Score (S.D.)
Cathine	4.8	95.0	83.4 (6.0)
Vehicle	—	15.0	21.4 (6.1)
l-fen	1.0	8.3	9.5 (11.1)
	2.0	12.5	14.5 (13.6)
	2.5	29.2	38.0 (14.1)

B.

Pretreatment	Dose (mg/kg)	Treatment	Dose (mg/kg)	Quantal	Mean Quantitative Score (S.D.)
l-fen	2.0	vehicle	—	8.3	23.7 (2.3)
		cathine	4.8	87.5	69.6 (4.0)
CPZ	3.0	vehicle	—	8.3	22.2 (8.6)
		cathine	4.8	16.7	29.6 (21.6)

The effects of pretreatment with 2.0 mg/kg *l*-fenfluramine upon cathine or vehicle discriminative performance are presented in Table 1B. The combination of *l*-fenfluramine and vehicle allowed for 8.3% of first-choice responses to be made on the cathine-appropriate lever, whereas the combination of *l*-fenfluramine with cathine produced 87.5% of all selections on this lever. There is no significant difference between pretreatment of *l*-fenfluramine with vehicle and *l*-fenfluramine with cathine when compared to vehicle and cathine maintenance session measurements, respectively. In contrast, the 3.0-mg/kg dose of chlorpromazine was shown to significantly disrupt the animals' ability to discriminate 4.8 mg/kg cathine in that the quantal measurement was reduced to 16.7%, and the quantitative measurement (29.6 ± 21.6) was not significantly different ($t=0.447$) from that of the combination of chlorpromazine and vehicle.

DISCUSSION

The results of the present experiments indicate that *l*-fenfluramine shares neither agonist nor antagonist activity in the dopamine-mediated discriminative performance produced by cathine. The first of these observations is not surprising in light of the fact that fenfluramine has generally been found to be dissimilar from amphetamine in the drug discrimination paradigm (2) and, more pertinent to the present investigation, the *l*-isomer of fenfluramine does not produce amphetamine-like activity (9).

The results of the antagonism study indicate that chlorpromazine, at a dose shown to significantly decrease the effects of amphetamine-induced discriminative performance (6), decreased cathine discrimination to discriminative values seen after vehicle. Previous work from this laboratory indicated that another neuroleptic, haloperidol, significantly decreased cathine discrimination, whereas a structurally similar drug that does not enter the central nervous system via the blood-brain barrier, viz., domperidone, does not affect cathine discrimination (7). In addition, a second mechanism that disrupts dopaminergic activity, i.e., the ability of CGS 10796B to inhibit dopamine release, was shown to attenuate cathine-produced discriminative performance (8). In contrast to the ability of chlorpromazine to affect the dopamine-mediated discriminative performance of cathine, 2.0 mg/kg *l*-fenfluramine had no significant effect upon cathine dis-

crimination. This is suggestive evidence that *l*-fenfluramine, which has recently been shown to produce increases in the release of dopamine and its metabolites with a pattern of effects similar to other neuroleptics such as haloperidol (1), does not produce a functional antagonism of dopaminergically mediated behavior.

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