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BRIEF COMMUNICATION

Aminorex Produces Stimulus Effects Similar to Amphetamine and Unlike Those of Fenfluramine

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YOUNG, R. *Aminorex produces stimulus effects similar to amphetamine and unlike those of fenfluramine.* PHARMACOL BIOCHEM BEHAV **42**(1) 175–178, 1992.—A 4-methyl derivative of aminorex has recently appeared on the clandestine market as a designer drug. In the present study, the stimulus effects of aminorex itself were evaluated in rats trained to discriminate either 0.75 mg/kg S(+)-amphetamine or 1.5 mg/kg fenfluramine from saline. The amphetamine stimulus (ED_{50} = 0.14 mg/kg) generalized to aminorex (ED_{50} = 0.23 mg/kg), which was found to be slightly less potent than (+)-amphetamine. Fenfluramine stimulus generalization did not occur to aminorex. Thus, the stimulus effects of aminorex are qualitatively similar to those of amphetamine and unlike those of fenfluramine.

Aminorex Amphetamine Fenfluramine Drug discrimination Drug abuse

IN a recent report (7), the discriminative stimulus effects of a new designer drug, 4-methylaminorex ["U4Euh", "ICE", see (2)], were assessed in rats trained to discriminate (+)-amphetamine from saline. The amphetamine stimulus generalized (i.e., substituted) to this drug and was found to be slightly more than four times less potent than (+)-amphetamine. 4-Methylaminorex is a derivative of aminorex, a cyclic phenylisopropylamine that was prescribed in the 1960s under the trade names Apiquel® and Menocil®. Aminorex was reported to possess the anorectic properties of amphetamine, but with lessened cardiovascular and CNS stimulant effects (11,14). However, it was withdrawn from the marketplace approximately 20 years ago amid reports that it induced chronic pulmonary hypertension and consequent death (5,9,10).

Psychoactive phenylisopropylamines are capable of producing a wide spectrum of pharmacological effects in animals, including humans [e.g., (1,6,16)]. Two of the best-known examples are amphetamine and fenfluramine, anorectics whose neurochemical and behavioral effects are quite different. Amphetamine reduces food intake by interacting with brain catecholamine systems, increases locomotor activity, and is readily self-administered by animals and abused by humans. In contrast, fenfluramine decreases food intake by affecting serotonergic mechanisms, decreases locomotor activity, is not self-administered by animals, and has negligible abuse potential by humans [for reviews, see (1,8,16)].

Drug discrimination studies have been particularly useful in establishing similarities and differences among phenylisoproplamines (6,16). For example, animals have been trained to discriminate either amphetamine or fenfluramine from saline. In tests of stimulus generalization, amphetamine is not recognized by animals trained to discriminate fenfluramine from saline and fenfluramine is not recognized by animals trained to discriminate amphetamine from saline [e.g., (12, 13,15)]. To date, the stimulus properties of aminorex have not been evaluated. The appearance on the clandestine market of a derivative of aminorex has prompted the present evaluation of the stimulus effects of aminorex, employing rats trained to discriminate either S(+)-amphetamine or fenfluramine from saline.

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METHOD

Animals

Twenty-one male Sprague-Dawley rats, weighing 260–310 g at the start of training, were used; body weights were reduced to approximately 80% of expected free-feeding weights by partial food deprivation. Animals were individually housed and had free access to water.

Apparatus

Commercially available two-lever operant chambers (BRS/LVE, Model RTC-025) housed within sound- and light-attenuated outer chambers were used. A dipper situated between the two levers delivered 0.01 ml of sweetened condensed milk (diluted 2 : 1 with tapwater). Standard electromechanical and solid-state programming and recording equipment were used.

Procedure

Rats were trained to lever respond to a fixed-ratio 10 (FR10) schedule of reinforcement on each lever. After schedule responding was established, animals were divided into two groups and drug administration was begun. The first group of 12 rats was injected IP with either 0.75 mg/kg S(+)-amphetamine sulfate or saline 15 min prior to each session. The second group of nine rats was injected IP with either 1.5 mg/kg fenfluramine HCl or saline 30 min before each session. Those presession intervals were chosen on the basis of previous drug discrimination studies with (+)-amphetamine and fenfluramine (15). For approximately half the animals in each of the two groups, responses on the right lever were reinforced after drug administration while responses on the left lever were reinforced after saline administration; these conditions were reversed for the remaining animals in each group. Drug or saline was administered on a random schedule with the constraint that no more than two consecutive sessions with the drug or vehicle could occur. During training sessions (and generalization tests; see below), discrimination learning was assessed for each subject by dividing the number of responses occurring on the drug-designated lever by the total number of responses occurring on both levels prior to obtaining the first reinforcer. This value was then multiplied by 100 to obtain the percent of responding on the drug-appropriate lever. In addition, for each 15-min session the overall response rate (responses/min) for both levers was calculated for each rat. For each treatment, the mean (±SEM) was calculated for each group for both of those measures.

Maintenance of the amphetamine/saline or fenfluramine/saline discrimination was ensured by continuation of training sessions throughout generalization test periods. At least one drug training session and one vehicle training session intervened between each test session. Generalization test sessions were identical to training sessions except a challenge drug was administered before a test session. Thus, rats were given a test treatment and then allowed to select one of the two levers in a 15-min session. The lever on which the rat first totaled 10 responses was regarded as the selected lever. Subsequent reinforcement was delivered for responses on this lever according to the FR10 schedule of reinforcement. With amphetamine-trained rats, generalization tests evaluated animals' responses to lower doses of (+)-amphetamine and to various doses of aminorex. Doses of these drugs were administered in a random sequence using a 15-min presession injection interval. With fenfluramine-trained rats, generalization tests evaluated rats' responses to lower doses of fenfluramine and to various doses of aminorex. A 30-min presession injection interval was used with these animals. Stimulus generalization was said to occur when animals, after being administered a given dose of challenge drug, made 80% or greater of their responses on the drug-appropriate lever. Rats making fewer than 10 responses on one of the levers during the entire 15-min test session were reported as being disrupted. For those compounds that generalized, ED_{50} values were determined from the dose–response data by the method of Finney (4). These ED_{50} values are doses at which animals would be expected to make 50% of their responses on the drug-appropriate lever.

TABLE 1

EFFECTS OF AMINOREX IN RATS TRAINED TO DISCRIMINATE FENFLURAMINE FROM SALINE

Agent	mg/kg	*n/N**	% Fenfluramine-Appropriate Responding (±SEM)	Mean Responses/min (±SEM)	ED_{50}† (mg/kg)
Fenfluramine	0.10	4/4	20 (5.9)	42.7 (9.7)	
	0.50	5/5	58 (11.7)	39.8 (8.3)	
	1.00	6/6	83 (7.3)	38.1 (11.4)	
	1.50	9/9	95 (2.1)	38.4 (9.4)	0.36 (0.24–0.48)
Saline (1 ml/kg)		9/9	8 (2.7)	43.7 (6.9)	
Aminorex	0.10	4/4	6 (3.1)	47.6 (8.2)	
	0.50	5/5	11 (5.2)	44.8 (6.7)	
	1.00	4/4	10 (6.8)	46.9 (16.0)	
	2.00	6/6	26 (10.7)	49.4 (14.1)	
	3.00	4/7	17 (9.5)	30.3 (12.1)	
	3.50	3/5	11 (11.0)	20.1 (13.6)	
	4.00	1/5	Disruption‡		

*Number of animals responding/number that received particular dose of drug.

†With 95% confidence limits.

‡Rats making fewer than 10 responses on one of the two levers during the entire 15-min test session are reported as disrupted.

TABLE 2

EFFECTS OF AMINOREX IN RATS TRAINED TO DISCRIMINATE AMPHETAMINE FROM SALINE

Agent	mg/kg	n/N*	% Amphetamine-Appropriate Responding (±SEM)	Mean Responses/min (±SEM)	ED_{50}† (mg/kg)
(+)Amphetamine	0.01	4/4	12 (4.9)	46.5 (8.6)	
	0.10	5/5	44 (10.7)	46.9 (7.5)	
	0.25	6/6	70 (15.2)	43.7 (9.1)	
	0.50	6/6	89 (4.3)	51.7 (7.3)	
					0.14 (0.10–0.18)
	0.75	12/12	97 (1.2)	49.2 (8.1)	
Saline (1 ml/kg)		12/12	8 (3.1)	45.2 (7.9)	
Aminorex	0.10	5/5	13 (6.5)	48.7 (6.7)	
	0.25	6/6	41 (10.0)	47.8 (8.7)	
	0.50	5/5	98 (1.8)	52.2 (9.6)	
	1.00	6/6	94 (3.4)	48.7 (5.9)	
	2.00	6/6	100	56.9 (8.3)	
					0.23 (0.21–0.25)
	3.00	5/5	100	46.2 (9.3)	

*Number of animals responding/number that received particular dose of drug.
†With 95% confidence limits.

Drugs

S(+)-Amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), fenfluramine HCl (A. H. Robins Co., Richmond, VA), and aminorex fumarate (McNeil Labs Inc., Fort Washington, PA) were dissolved in 0.9% sterile saline. Doses of each compound were based on the weight of the salt. All drugs were administered IP in a 1.0 ml/kg injection volume.

RESULTS AND DISCUSSION

Animals were trained to discriminate either 1.5 mg/kg fenfluramine or 0.75 mg/kg (+)-amphetamine from saline (Tables 1 and 2). After 50 training sessions, rats in each group responded >90% on the drug-appropriate lever when administered their particular dose of training drug, while responding on the same lever was <10% following their injection of saline. The administration of lower doses of the training drugs resulted in decreased percentages of drug-appropriate lever responding. Response rates were not substantially different under drug and saline treatments.

Amphetamine and fenfluramine are structurally related phenylisopropylamines that produce dissimilar stimulus effects regardless of which is used as the training drug (12, 13,15). To determine if the stimulus effects of aminorex could be characterized as being felfluramine- or amphetamine-like, stimulus generalization tests were conducted between the fenfluramine and amphetamine training stimuli and aminorex. In the fenfluramine-trained group of rats, aminorex produced saline-like responding at doses of 3.5 mg/kg or less and disruption of behavior (i.e., no responding) at 4.0 mg/kg (Table 1). This suggests that those two drugs apparently produce qualitatively dissimilar stimulus effects. Administration of aminorex to amphetamine-trained rats resulted in stimulus generalization and, based on their ED_{50} values, (+)-amphetamine (ED_{50} = 0.14 mg/kg, 0.38 μM/kg) is approximately twice as potent as aminorex (ED_{50} = 0.23 mg/kg 0.69 μM/kg). Animals' response rats were not appreciably altered following injections of saline, amphetamine, or aminorex (Table 2). These data indicate that aminorex is recognized as amphetamine-like by rats trained to distinguish (+)-amphetamine from saline.

Structure-activity relationship (SAR) studies of amphetamine have suggested that cyclization of the alkyl side chain reduces CSN stimulant effects (1). A previous drug discrimination study (3), using pigeons trained to recognize (+)-amphetamine from saline, evaluated the stimulus effects of methylphenidate, phenmetrazine, and phendimetrazine, compounds in which the terminal amine has been incorporated into a cyclic structure. All three drugs were found to be less potent than (+)-amphetamine. Aminorex is another example of a cyclized agent; the side chain is incorporated into an oxazoline ring. Thus, the reduced potency of aminorex noted here is consistent with a reported SAR generality of amphetamine.

Taken together, the present results indicate that aminorex does not possess fenfluramine-like stimulus effects but does appear to be a slightly less potent amphetamine-like agent. Moreover, it can be speculated that aminorex's stimulus effects could be mediated by catecholamine systems and it would readily serve as a reinforcer in self-administration paradigms. Future studies should address those issues.

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