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Comparative Discriminative Stimulus Properties of *dl*-Cathinone, *d*-Amphetamine, and Cocaine in Rats

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HUANG, D AND M C WILSON *Comparative discriminative stimulus properties of* dl-*cathinone,* d-*amphetamine, and cocaine in rats* PHARMACOL BIOCHEM BEHAV **24**(2) 205–210, 1986 —The discriminative stimulus properties of *dl*-cathinone (*dl*-CAT), *d*-amphetamine (*d*-A), and cocaine (COC) were compared and effects of haloperidol pretreatment on these properties were studied in rats The ED50's of each drug were also determined Stimulus generalization (i e , greater than 75% of responses occurring on the drug lever) occurred with each of the three training drugs to all three test drugs The degree of generalization was less between *d*-amphetamine and *dl*-cathinone than between *d*-amphetamine and cocaine or between cocaine and *dl*-cathinone No significant differences were observed among the ED50's of each test drug obtained in all three training groups Pretreatment with haloperidol failed to alter the stimulus properties of *dl*-cathinone Haloperidol administration did partially antagonize the stimulus complex induced by *d*-amphetamine and cocaine It is concluded that all three agents share somewhat similar but not identical, stimulus properties The stimulus properties of the training dose of *d*-amphetamine may be somewhat different from those of *dl*-cathinone and may be more dependent on functional dopaminergic pathways

dl-Cathinone *d*-Amphetamine Cocaine Haloperidol Dopamine Drug discrimination

l-CATHINONE (1-α-aminopropiophenone) is an alkaloid that has been isolated from the plant, Catha edulis Forsk , Celastraceae [29] The leaves and twigs of this plant, which is better known as khat, are extensively used as a stimulant in a way highly reminiscent of coca chewing in the Andes [8] Structurally, *l*-cathinone is very similar to *d*-amphetamine [27] In addition, pharmacological studies have demonstrated close similarities between the peripheral actions of cathinone and *d*-amphetamine [11, 17, 21, 34] Furthermore, both substances increase locomotor activity in mice [7, 10, 31, 36], induce antinociceptive activity in mice and rats [22], suppress food intake in rats [35], produce stereotypy [1, 10, 36] and circling behavior [35] in rats, induce a gustatory avoidance response in rats [4], and have been shown to function as positive reinforcers and to disrupt food-maintained behavior in rhesus monkeys [9] Tolerance to the suppressant effects of these compounds on feeding has been demonstrated and cross-tolerance reported between *dl*-cathinone and *d*-amphetamine [5]

dl-Cathinone, like *d*-amphetamine, releases tritiated norepinephrine [15] and dopamine [12, 13, 14, 32], blocks the uptake of tritiated dopamine [32], decreases DOPAC levels and inhibits the firing rate of dopamine neurons in various regions of the rat brain [20]

Rats trained to discriminate amphetamine or *dl*-cathinone from saline, respond on the amphetamine-appropriate lever when treated with *dl*-cathinone [23] and vice versa [26] However, in spite of all the above-mentioned similarities, Rosecrans, *et al* [23] reported that pretreatment with haloperidol inhibited the discriminative stimulus properties of *d*-amphetamine, while having no effect on those of *dl*-cathinone These results suggest that the stimulus properties of *dl*-cathinone and *d*-amphetamine may not be mediated by identical neurochemical mechanisms In view of this finding, and the close resemblance among various effects of *d*-amphetamine and cocaine, the present study was undertaken to compare the discriminative stimulus properties of *dl*-cathinone, *d*-amphetamine, and cocaine and to clarify the importance of dopamine in mediating these stimulus properties

METHOD

Subjects

Male Wistar rats weighing 200–250 g at the beginning of the experiment were used Rats were individually housed in galvanized cages with free access to tap water except during the experimental sessions Room lights were illuminated from 0600 to 1800 and ambient temperature was controlled at 22–23°C After the initial 7 days of acclimation to this environment, subjects weights were reduced to 85% of their free feeding weight Animals were maintained at this weight

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TABLE 1

GENERALIZATION OF THE STIMULUS PROPERTIES AMONG dl-CATHINONE, COCAINE, AND D-AMPHETAMINE

Test Drug		Mean ± SEM % Responding on Drug Lever Training Drug			% Subjects Selecting Drug Lever Training Drug (N)			
		CATH (1 0 mg/kg)	DA (0 8 mg/kg)	COC (7 5 mg/kg)	CATH (1 0 mg/kg)	DA (0 9 mg/kg)	COC (7 5 mg/kg)	Total
Saline		18 ± 5	31 ± 12	21 ± 14	0 (18)	0 (21)	0 (23)	
dl-CATH	0 25 mg/kg	62 ± 13*	52 ± 7*	62 ± 3*	50 (6)	28 6 (7)	14 3 (7)	30 (6/20)
	0 5 mg/kg	39 ± 16	61 ± 6*	64 ± 9*	16 7 (6)	28 6 (7)	57 1 (7)	35 (7/20)
	1 0 mg/kg	65 ± 16*	83 ± 3*	85 ± 5*	50 (6)	71 4 (7)	85 7 (7)	70 (14/20)
	2 0 mg/kg	90 ± 2*	59 ± 15*	73 ± 17*	83 3 (6)	42 9 (7)	71 4 (7)	65 (13/20)
COC	1 25 mg/kg	58 ± 12*	50 ± 4	37 ± 9	20 (5)	28 6 (7)	11 1 (9)	19 (4/21)
	2 5 mg/kg	46 ± 18	57 ± 12	30 ± 6	20 (5)	28 6 (7)	11 1 (9)	19 (4/21)
	5 0 mg/kg	58 ± 13*	54 ± 11	90 ± 2*	20 (5)	57 1 (7)	88 8 (9)	61 9 (13/21)
	10 mg/kg	88 ± 4*	81 ± 3*	72 ± 11*	80 (5)	85 7 (7)	77 7 (9)	80 9 (17/21)
DA	0 25 mg/kg	37 ± 10	42 ± 11	43 ± 11	28 6 (7)	14 3 (7)	14 3 (7)	19 (4/21)
	0 5 mg/kg	73 ± 11*	78 ± 6*	73 ± 9*	57 1 (7)	71 4 (7)	57 1 (7)	61 9 (13/21)
	1 0 mg/kg	45 ± 14	82 ± 4*	90 ± 2*	28 6 (7)	57 1 (7)	85 7 (7)	61 9 (13/21)
	2 0 mg/kg	76 ± 10*	93 ± 1*	91 ± 2*	71 4 (7)	100 (7)	85 7 (7)	85 7 (18/21)

*Denotes a significant difference from the corresponding saline control value, $p \leq 0.05$ via two-tailed Student's t-test

throughout the experiment by daily feeding of appropriate amounts of laboratory chow following each experimental session

Drugs

dl-Cathinone HCl was synthesized using a previously reported method [30] and analyzed by Dr R F Borne in the Department of Medicinal Chemistry, University of Mississippi School of Pharmacy Other drugs used included *d*-amphetamine sulfate (Smith Kline and French Laboratories), cocaine HCl (Merck, Sharp and Dohme), and haloperidol (McNeil Laboratories) All drug solutions except for haloperidol were prepared by dissolving each compound in physiological saline Haloperidol solutions were prepared by dissolving the compound in warm lactic acid solution (0 01 ml per mg of haloperidol) and then diluting with distilled water All drugs were injected IP in a volume of 1 0 ml/kg of body weight With the exception of haloperidol, all dosages were calculated on the basis of the corresponding salts

Apparatus

The experiments were conducted in commercial operant chambers equipped with 2 levers, and a reinforcement cup mounted midway between the levers Reinforcement consisted of delivery of a single 45 mg food pellet (Bioserv, Inc , Frenchtown, NJ) Experimental contingencies were programmed with electromechanical control equipment

Discrimination Training

Subjects were randomly assigned to three experimental groups of 12 animals each Bar press training initially consisted of daily 20-min sessions following an IP injection of normal saline, 10 min prior to session onset Half of the animals in each group were randomly assigned to press the left lever and the other half, the right lever for food reinforcement The schedule requirements were gradually increased in specific increments from FR1 to FR30 The training criterion for each ratio step was met when 80% of all responses prior to completion of the first reinforced ratio occurred on the correct lever for three consecutive sessions

The second phase of bar press training was started immediately after the training criterion for FR30 responding had been reached in phase 1 Subjects were then trained to press the lever on which responding was not reinforced in phase 1 The three subject groups were injected IP with either *dl*-cathinone (0 5 mg/kg), *d*-amphetamine sulfate (0 9 mg/kg), or cocaine HCl (7 5 mg/kg) 10 min prior to each session The dose of *dl*-cathinone was later increased to 1 0 mg/kg due to unsatisfactory results obtained in training with the initial dose The same training criterion and sequence of schedule requirements were used as in phase 1

Drug discrimination training was initiated after the training criterion had been reached on the second lever Discrimination training consisted of daily 20 min sessions during which the two sets of pretreatments (drug or saline) employed in the previous training sessions were administered in a double alternation sequence Reinforcement resulting from responding on a given lever was always associated with either the drug or saline state in a particular subject The double alternation sequence was used to insure that the number of reinforcements associated with either the right or left lever would be similar This procedure also tended to minimize any lever preference Furthermore, the probability that the reinforced lever for a given session was the same or opposite lever on which responding was reinforced during the preceding session, were equal The sequence was repeated until the aforementioned training criterion, i e , 80% or more of all responses prior to initial reinforcement, occurred on the correct lever for three consecutive sessions, had been achieved

Substitution Tests Without Pretreatment

Substitution sessions differed from the training sessions

TABLE 2

MEDIAN EFFECTIVE DOSE (ED50s)* DETERMINED FROM DRUG GENERALIZATION TESTS CONDUCTED WITH IP SALINE, *dl*-CATHINONE, *d*-AMPHETAMINE, AND COCAINE IN RATS TRAINED TO DISCRIMINATE 1 0 mg/kg *dl*-CATHINONE, 0 9 mg/kg *d*-AMPHETAMINE, OR 7 5 mg/kg COCAINE FROM SALINE

Test Drug	Training Drug	ED50* mg/kg (95% Ci)
dl-Cathinone	*dl*-Cathinone	0 77 (0 35– 1 68)
	d-Amphetamine	0 55 (0 22– 1 39)
	Cocaine	1 27 (0 25– 6 46)
d-Amphetamine	*dl*-Cathonine	0 91 (0 22– 3 69)
	d-Amphetamine	0 51 (0 27– 0 97)
	Cocaine	0 45 (0 16– 1 25)
Cocaine	*dl*-Cathinone	6 34 (2 78–14 45)
	d-Amphetamine	7 95 (3 93–16 06)
	Cocaine	4 71 (2 45– 9 06)

*The lowest dose calculated by the method of Litchfield and Wilcoxon [18] which resulted in 80% responding on the drug lever during generalization testing, in 50% of the subjects

in that responding on neither lever was reinforced The session was terminated either after 90 responses had occurred on either lever or after 8 min of the session had elapsed, whichever occurred first The total number of responses in each substitution session may therefore range from 90 to 179 (i e , with 90 responses on one lever and 89 responses on the other) Substitution tests were conducted weekly on Fridays with training sessions conducted Monday through Thursday Efforts were made to insure that for a given substitution test, half of the subjects received the treatment following a S (saline) training day and the other half following a D (drug) training day Ten min prior to testing, subjects in each group were removed from the home cage, injected IP with saline or one of the doses of *dl*-cathinone (0 25, 0 5, 1 0, or 2 0 mg/kg), *d*-amphetamine (0 25, 0 5, 1 0, or 2 0 mg/kg), or cocaine (1 25, 2 5, 5 0, or 10 mg/kg) and returned to the home cage All three subject groups were tested with all three drugs Doses of test drugs were administered in a random order Testing with one drug was completed prior to testing with another agent Generalization from a training drug to a test drug was defined as having occurred when 80% or more of the total responses during a substitution test occurred on the drug lever Using this criterion, the ED50 values and 95% confidence intervals were determined using the method of Litchfield and Wilcoxon [18], for each test drug in each of the 3 experimental groups

Substitution Tests with Pretreatment

Forty min prior to testing, subjects were injected IP with saline or haloperidol (0 07 or 0 15 mg/kg) and returned to the home cage Ten min prior to testing, subjects were injected IP with *dl*-cathinone, *d*-amphetamine, or cocaine and returned to their home cages The doses of *dl*-cathinone, *d*-amphetamine, and cocaine were 1 35, 0 6, and 8 4 mg/kg, respectively These values correspond to the ED75 of each compound determined from the previously determined generalization gradients Each compound was tested only in the group of animals trained to discriminate that same compound from saline

RESULTS

Table 1 presents the generalization data of *dl*-cathinone, *d*-amphetamine, and cocaine in rats trained to discriminate 1 0 mg/kg of *dl*-cathinone, 0 9 mg/kg of *d*-amphetamine, or 7 5 mg/kg of cocaine, respectively, from saline Complete stimulus generalization (at least 80% of responses occurred on the drug lever during the substitution tests) resulted between the training dose of *dl*-cathinone and cocaine Complete generalization did not occur between the training dose of *dl*-cathinone and *d*-amphetamine, although rats trained with *dl*-cathinone produced an average of 76±10% of responding on the drug lever when treated with the high dose of *d*-amphetamine Complete stimulus generalization occurred between the training dose of *d*-amphetamine and *dl*-cathinone and cocaine and between the training dose of cocaine and *dl*-cathinone and *d*-amphetamine Furthermore, greater than 75% of those animals trained to discriminate cocaine and saline responded on the drug lever following amphetamine or cocaine treatment Likewise, over 75% of the animals trained to discriminate *d*-amphetamine from saline tended to respond on the drug lever following cocaine administration However, this was not true following *dl*-cathinone treatment Only 42 9% of the subjects chose the *d*-amphetamine lever after treatment with the highest dose of *dl*-cathinone Subjects trained to discriminate *dl*-cathinone from saline selected the drug lever following pretreatment with the highest dose of cocaine However, only 71 4% of the subjects chose the drug lever following treatment with the largest dose of *d*-amphetamine Therefore, generalization between cocaine and cathinone and cocaine and *d*-amphetamine appeared greater than between *dl*-cathinone and *d*-amphetamine

Table 2 presents the ED50's of *dl*-cathinone, *d*-amphetamine, and cocaine calculated from the generalization gradients of all three compounds obtained in each of the three groups of rats The effect chosen to generate these values was defined as 80% responding on the drug lever in generalization testing No significant differences were found among the ED50's of each test compound determined in all three training groups However, the ED50 for *d*-amphetamine in cathinone trained subjects was almost twice that of *d*-amphetamine in either cocaine or *dl*-cathinone-treated subjects Therefore, it appears that the stimulus properties of *d*-amphetamine more closely resemble those of cocaine than those of *dl*-cathinone

Table 3 presents the results of haloperidol pretreatment on the stimulus properties of *dl*-cathinone, *d*-amphetamine, and cocaine Cathinone's stimulus properties did not appear to be as sensitive to disruption by haloperidol as did those of cocaine or especially *d*-amphetamine Both doses of haloperidol reduced the mean±SEM percent responding on the drug lever following *d*-amphetamine administration below the 80% criterion, even for the calculated ED75 dose Furthermore, only 4 of 12 *d*-amphetamine-treated subjects selected the drug lever following pretreatment with the two doses of haloperidol Likewise, only 10 of 14 cocaine-treated subjects chose the drug lever after haloperidol pretreatment as compared to all subjects choosing the drug lever when saline preceded the cocaine injection, indicating that haloperidol partly blocked cocaine's stimulus complex Examination of the percent of responding on the drug lever data also indicates that the values for saline versus haloperidol pretreatment do not overlap for cocaine treatment suggesting some antagonism, even though the percent of response occurring

TABLE 3

EFFECTS OF HALOPERIDOL (H) PRETREATMENT ON THE STIMULUS PROPERTIES OF IP *dl*-CATHINONE (*dl*-CAT, 1 35 mg/kg), *d*-AMPHETAMINE (*d*-A, 0 6 mg/kg), OR COCAINE HCl (COC, 8 4 mg/kg) IN RATS TRAINED TO DISCRIMINATE 1 0 mg/kg *dl*-CAT, 0 9 mg/kg *d*-A, OR 7 5 mg/kg COC, RESPECTIVELY, FROM SALINE

Pretreatment (mg/kg, IP)	Treatment	N	Percent responding on drug lever: Mean ± SEM	*p* value**	Ratio of lever selection
S	*dl*-CAT	6	90 25 ± 4 58	—	5/6 (83 3%)
H 0 07	*dl*-CAT	6	94 87 ± 2 86	0 55	6/6 (100 0%)
H 0 15	*dl*-CAT	6	84 23 ± 4 77	0 178	4/6 (66 7%)
S	*d*-A	6	81 33 ± 3 76	—	5/6 (83 3%)
H 0 07	*d*-A	6	65 73 ± 8 29*	0 134	1/6 (16 7%)
H 0 15	*d*-A	6	62 93 ± 11 11*	0 315	3/6 (50 0%)
S	COC	7	96 21 ± 2 56	—	7/7 (100 0%)
H 0 07	COC	7	81 13 ± 7 05	0 059	5/7 (71 4%)
H 0 15	COC	7	80 54 ± 7 84	0 146	5/7 (71 4%)

*Denotes those instances where the mean ± SEM percentage of responding on drug lever failed to reach the generalization criterion (equal to or above 80% rounded to the nearest percent, drug-lever responding) used in defining the training criterion The stimulant doses used in this drug interaction phase of the study were the ED75 values calculated for achieving the training criterion

**Two-tailed Student's *t*-test

on the drug lever is still above criterion levels There was no indication using either the percent of animals responding or the drug lever, or percent of responses on the drug lever measures that haloperidol pretreatment interfered with cathinone's stimulus complex

DISCUSSION

In general, the results of the present study demonstrate a cross-generalization among *dl*-cathinone, *d*-amphetamine, and cocaine in rats trained to discriminate these drugs from saline Although a complete generalization did not occur from *dl*-cathinone to any of the doses of *d*-amphetamine tested, it was observed that rats trained to discriminate *dl*-cathinone from saline made an average of 75 8% responses on the *dl*-cathinone lever when treated with 2 0 mg/kg of *d*-amphetamine These data seem to indicate a trend that a complete generalization from *dl*-cathinone to *d*-amphetamine may be obtained with higher doses of *d*-amphetamine However, higher doses of *d*-amphetamine nonselectively suppressed responding below criterion levels The finding that similar ED50's were obtained when either *dl*-cathinone or *d*-amphetamine was tested in rats trained to discriminate either *dl*-cathinone or *d*-amphetamine from saline is in agreement with data reported by Rosecrans *et al* [23] and Schechter *et al* [26]

D'Mello and Stolerman [3] reported that higher ED50's for *d*-amphetamine and cocaine were obtained in cross-generalization tests, as compared to those values obtained when each drug was tested in rats trained to discriminate that same drug from saline These authors suggested that their data may indicate some difference in the discriminative stimulus properties of the two drugs In the present study, however, statistically similar ED50's were obtained when *d*-amphetamine and cocaine were tested in rats trained to discriminate either drug from saline However, the ED50 for cocaine in cocaine trained rats was only approximately half that of the ED50 obtained in *d*-amphetamine trained subjects Similar ED50's for *d*-amphetamine were obtained in both cocaine and *d*-amphetamine treated subjects

Pretreatment with haloperidol failed to alter *dl*-cathinone discriminability, therefore, these data suggest that the stimulus properties of *dl*-cathinone are not mediated by dopaminergic systems The results are consistent with data reported by Rosecrans *et al* [23] in which haloperidol pretreatment (0 1 mg/kg) failed to antagonize the stimulus properties of *dl*-cathinone, but did indeed antagonize those of *d*-amphetamine Cathinone has been reported to both possess affinity for peripheral serotonin receptors [6] and to cause the release of serotonin from striatal tissue [16], suggesting that perhaps the discriminative complex induced by this agent is dependent on both serotonergic and dopaminergic processes Therefore, treatment with a dopamine antagonist may not be capable by itself of significantly disrupting these stimuli

Although the stimulus properties of *d*-amphetamine and cocaine were reduced by pretreatment with haloperidol, it was surprising that a greater antagonism was not observed Several previous reports have shown that pretreatment with haloperidol antagonizes the stimulus properties of *d*-amphetamine [2, 23, 24, 25] and cocaine [2,19] in rats Although the mean percent of responding on the *d*-amphetamine lever was not significantly reduced by haloperidol as compared to saline pretreatment, only four out of twelve animals treated with 0 6 mg/kg *d*-amphetamine chose to respond on the *d*-amphetamine lever In addition, the mean percentage of responding on the *d*-amphetamine lever following haloperidol pretreatment failed to reach the generalization criterion These data seem to suggest that pretreatment with haloperidol did indeed influence the stimulus properties of *d*-amphetamine, although complete antagonism did not result Haloperidol also reduced the number of subjects choosing the drug levels following cocaine dosing, when compared to the saline controls which supports previ-

ous reports of antagonism of cocaine's stimulus properties with dopaminergic antagonists

Since more complete antagonism had not been observed, it was hypothesized that perhaps the haloperidol used in this study had decomposed Chemical analysis of this compound showed that its m p [148°C, as compared to literature m p (Merck Index, ninth ed) 148 0–149 4°C], and infrared and ^{1}H-NMR spectral data were all consistent with the structure of haloperidol

In conclusion, the results of the present study suggest that *dl*-cathinone, *d*-amphetamine, and cocaine share a similar but not identical stimulus complex The involvement of dopaminergic systems in these stimulus properties is equivocal The possibility that the stimulus properties of cathinone may be partially medicated by serotonergic systems should be considered These data strongly suggest that the stimulus complex associated with *d*-amphetamine or cocaine is more dependent on dopaminergic transmission than is that of *dl*-cathinone However, it also appears that the stimulus properties of cocaine and *d*-amphetamine are not totally dependent on dopaminergic function

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