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The Effects of *dl*-Cathinone, *d*-Amphetamine and Cocaine on Avoidance Responding in Rats and Their Interactions with Haloperidol and Methysergide

D. HUANG AND M. C. WILSON

Department of Pharmacology, School of Pharmacy, University of Mississippi, University, MS 38677

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HUANG, D. AND M. C. WILSON. *The effects of* dl-*cathinone,* d-*amphetamine and cocaine on avoidance responding in rats and their interactions with haloperidol and methysergide.* PHARMACOL BIOCHEM BEHAV **20**(5) 721–729, 1984.—The effects of *dl*-cathinone (*dl*-CAT), *d*-amphetamine (*d*-A), and cocaine (COC) on conditioned shock avoidance responding and their interactions with haloperidol and methysergide on this behavior were studied in male Wistar rats. All three stimulants produced significant increases in intertrial interval (ITI) responding and in the number of avoidance responses and a decrease in avoidance latencies. These actions were antagonized by pretreatment with haloperidol (0.07 and 0.15 mg/kg, IP). Pretreatment with methysergide (1.0 and 2.0 mg/kg, IP) increased the effects of all three stimulants on ITI responding, but not on the other two parameters. These results suggest that the effects of these stimulants on avoidance responding may be mediated by dopaminergic systems. In addition, these stimulant-induced changes on ITI responding probably also involve actions on serotonergic systems.

Catha edulis Khat Conditioned avoidance responding *dl*-Cathinone *d*-Amphetamine Cocaine Haloperidol Methysergide

CATHA edulis (khat) is a shrub or small tree whose leaves and twigs are widely used in parts of East Africa and Southern Arabia for their stimulating and anorectic effects in a way highly reminiscent of coca chewing in the Andes. Khat chewing has caused concern among the international community because the socioeconomic consequences of khat use were deemed detrimental both to the individual and to the community [7]. In view of this concern, a series of studies have been conducted by the United Nations Narcotics Laboratory [15, 21, 23], with collaboration of others [3,16], in order to determine the active constituent(s) of khat. As a result of these studies, a new phenylalkylamine-type alkaloid was isolated from fresh khat material for which the name *l*-cathinone has been proposed [22]. The chemical structure of *l*-cathinone bears close resemblance to that of *d*-amphetamine, the only difference being that the two hydrogen atoms on the β-carbon of the amphetamine side chain are substituted with an oxygen atom in *l*-cathinone. The behavioral effects of *l*-cathinone have also been shown to be very similar to that of *d*-amphetamine. For example, both substances are equally effective in producing an increase in locomotor activity in mice [6, 11, 27] and suppressing food intake in rats [25]. Furthermore, cathinone, like amphetamine, produces stereotypy [2, 11, 27] and circling behavior [26] in rats. Rats trained to discriminate *d*-amphetamine from saline in a two lever drug discrimination paradigm, respond on the *d*-amphetamine-appropriate lever when treated with *dl*-cathinone [13]. In addition, both cathinone and amphetamine can induce a gustatory avoidance response in rats [5]. Finally, both substances function as positive reinforcers and disrupt food-maintained behavior in rhesus monkeys [10].

However, reports on the effect of *l*-cathinone on behaviors maintained by negative reinforcement schedules are as yet unavailable in the literature. It was therefore of interest in the present study to compare the effects of *dl*-cathinone, *d*-amphetamine, and cocaine in a conditioned avoidance paradigm, and to further clarify the role of dopaminergic and serotonergic systems in these actions.

METHOD

Animals

Twenty-four male Wistar rats (Harlan Industries, Inc.) weighing 200–250 g at the beginning of the experiment were used. Rats were individually housed and were provided Rodent Laboratory Chow (Ralston Purina Co.) and water ad lib. Room lights were illuminated from 0600 to 1800 and ambient temperature was maintained at 22–23°C. Prior to testing, animals were given at least one week to acclimate to the animal room environment and to confirm their physical well-being.

Drugs

dl-Cathinone HCl was synthesized (using a previously reported method [23]) and analyzed by Dr. R. F. Borne in the

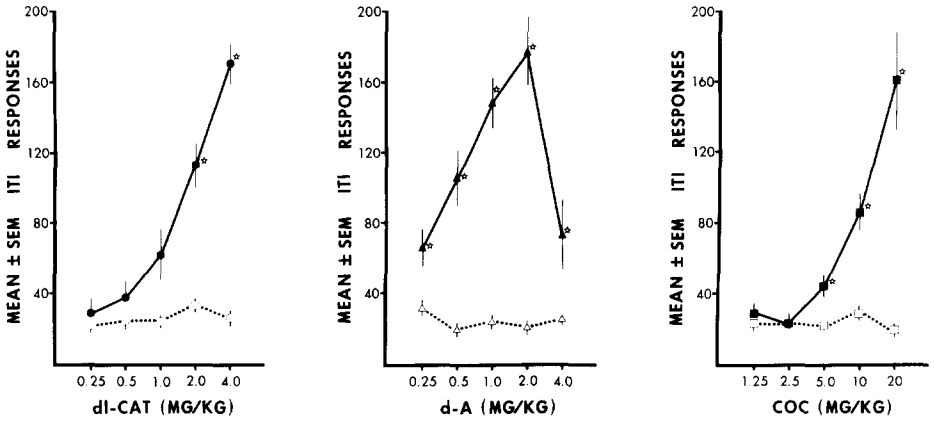

FIG. 1. Effects of *dl*-cathinone (*dl*-CAT), *d*-amphetamine (*d*-A), and cocaine (COC) on intertrial interval (ITI) responses in the conditioned avoidance test in rats. The open symbols represent data obtained on control sessions. The closed symbols represent data obtained on drug sessions. Pretreatment-treatment combinations were saline-saline on control sessions and saline-drug on drug sessions. Data points represent mean ITI responses and the vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between drug and control values.

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), haloperidol (McNeil Laboratories), and methysergide maleate (Sandoz Pharmaceuticals). 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 (0.001 ml per mg of haloperidol) and then diluting with distilled water. All drugs were injected intraperitoneally in a volume of 1.0 ml per kg of body weight. With the exception of haloperidol, all dosages were calculated on the basis of the corresponding salts.

Apparatus

Experiments were conducted in three toggle-floor shuttle boxes which measure 46 cm (L) × 20 cm (W) × 19 cm (H) each. The grid floor of each box rested upon a central pivot which was connected to a microswitch. The pivoting motion of the floor caused by the animal crossing from one end of the box to the other, operated the microswitch which in turn determined which half of the floor was electrified. The unconditioned stimulus (UCS) was a 100 msec, 1.0 mA AC constant current scrambled shock delivered through the grid floor. A 2.5 KHz auditory stimulus delivered by a buzzer (Sonalert) positioned in the center of the ceiling directly above the central pivot of the toggled floor served as the warning stimulus (CS). Experimental contingencies were programmed in SKED (a computer language trademark of State Systems, Inc., Kalamazoo, MI) using a PDP-12 computer (Digital Equipment Corporation) located in a separate room.

Procedure

Training period. On the first day of training, each rat was given a 5-min adaptation period in the shuttle box. Following this period, 60-trial training sessions were initiated. Each trial consisted of a 5-sec auditory stimulus (CS) presentation followed by shock (UCS) presentation. The subject could avoid shock by crossing the central pivot in the shuttle box during the presence of the CS. This response immediately turned off the CS and prevented the impending UCS. Failure to make this crossing response within 5 sec resulted in the termination of the CS and the presentation of the shock, which was repeated ten times at 1-sec intervals. This repeated shock presentation was designed to facilitate the acquisition of the avoidance response. A crossing response during this period terminated the UCS. The intertrial interval (ITI) was 30 sec, and all sessions (60 trials each) started with an ITI. Responses made during an ITI were recorded but had no programmed consequences. The houselight was turned on at the beginning of the session and remained on until the end of the session.

The parameters recorded during each session were as follows: the number of intertrial interval responses (i.e., the number of crossings made during the 30 sec ITI), the number of avoidance responses, the latency of each avoidance response (i.e., the time from onset of CS to making the avoidance response) and the number of shocks received. Training sessions were conducted daily, five days per week. The training criterion was reached when the total session avoidance efficiency (i.e., the number of avoidances per session/the number of trials per session) was 80% or greater on three consecutive sessions.

Testing period. Drug testing was implemented once performance had reached the stated criterion. Sixty-trial experimental sessions were conducted daily, five days per week. During each week, maintenance training sessions were conducted Monday through Wednesday; on Thursday and Friday, test sessions were conducted. The experimental contingencies used in test sessions differed from those of the training sessions in that the shock (UCS) was delivered only once per trial, as compared to the repeated shock presentation programmed for each trial during the training session.

Two injections were given prior to placing the subjects in the shuttle box. Sessions on Thursday served as a control for the sessions on Friday. On Thursday, 45 min prior to testing, subjects were removed from the home cage, injected IP with

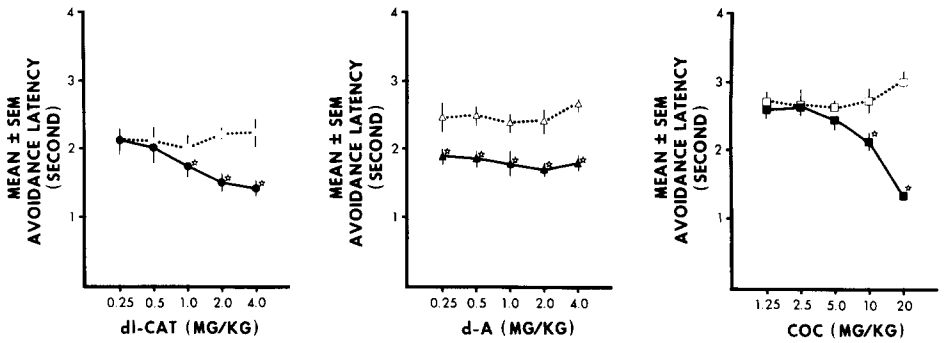

FIG. 2. Effects of *dl*-cathinone (*dl*-CAT), *d*-amphetamine (*d*-A), and cocaine (COC) on avoidance latencies in the conditioned avoidance test in rats. The open symbols represent data obtained on control sessions. The closed symbols represent data obtained on drug sessions. Pretreatment-treatment combinations were saline-saline on control sessions and saline-drug on drug sessions. Data points represent mean avoidance latencies and the vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between drug and control values.

either saline, haloperidol vehicle, one of the doses of haloperidol (0.07, or 0.15 mg/kg) or methysergide (1.0 or 2.0 mg/kg) and returned to the home cage. Fifteen min prior to testing, the subject was again removed from the home cage, injected IP with normal saline and returned to the home cage.

On Friday, 45 min prior to testing, subjects were removed from the home cage, injected IP with either saline, one of the doses of haloperidol (0.07 or 0.15 mg/kg), or methysergide (1.0 or 2.0 mg/kg) and returned to the home cage. Fifteen min prior to testing, the subject was again removed from the home cage, injected IP with either saline, one of the doses of *dl*-cathinone (0.25, 0.5, 1.0, 2.0, or 4.0 mg/kg), *d*-amphetamine (0.25, 0.5, 1.0, 2.0, or 4.0 mg/kg), or cocaine (1.25, 2.5, 5.0, 10, or 20 mg/kg) and then returned to the home cage. Each stimulant (i.e., *dl*-cathinone, *d*-amphetamine or cocaine) was tested in a group of 8 animals. Haloperidol and methysergide pretreatments were tested in all three groups. The dosages of the drugs in each pretreatment-treatment combination were tested in random order.

Statistical analyses of the parameters recorded in test sessions were accomplished by using the Wilcoxon Matched-pairs Signed Ranks Test [18]. The results obtained in the drug session on Friday were compared to the preceding control session on Thursday. Comparisons were also made between drug sessions after vehicle pretreatment and drug sessions after pretreatment with haloperidol or methysergide.

RESULTS

The effects of *dl*-cathinone, *d*-amphetamine and cocaine on conditioned avoidance responding are presented in Figs. 1 and 2 and Table 1. All three stimulants produced a dose-related increase in intertrial interval (ITI) responding (Fig. 1) and a decrease in avoidance latencies (Fig. 2). A significant increase in the number of avoidance responses was also observed with one or two of the test doses of *dl*-cathinone, *d*-amphetamine, and cocaine (Table 1). The fact that much higher doses of cocaine were needed to generate a dose-response curve similar to that of *d*-amphetamine and *dl*-cathinone suggests that the former is several times less potent that the latter agents in its effects on avoidance responding. Furthermore, even though the same dose range was

TABLE 1

EFFECTS OF *dl*-CATHINONE (*dl*-CAT), *d*-AMPHETAMINE (*d*-A), AND COCAINE (COC) ON CONDITIONED AVOIDANCE RESPONSES IN RATS

Treatment	(mg/kg, IP)	N	Total avoidances per session† Mean ± SEM: Saline control‡ (Thursday)	Drug session‡ (Friday)
dl-CAT	0.25	7	59.29 ± 0.18	60.00 ± 0.00*
	0.5	7	59.43 ± 0.30	59.43 ± 0.20
	1.0	7	58.14 ± 0.63	59.86 ± 0.14*
	2.0	7	58.86 ± 0.55	59.43 ± 0.30
	4.0	7	58.86 ± 0.51	59.57 ± 0.20
d-A	0.25	8	59.25 ± 0.25	60.00 ± 0.00*
	0.5	8	59.50 ± 0.38	59.88 ± 0.13
	1.0	8	58.88 ± 0.35	59.63 ± 0.26
	2.0	8	59.13 ± 0.40	59.63 ± 0.18
	4.0	8	58.88 ± 0.35	59.00 ± 0.00
COC	1.25	8	58.63 ± 0.46	58.63 ± 0.57
	2.5	8	58.50 ± 0.89	59.00 ± 0.33
	5.0	8	59.25 ± 0.25	58.88 ± 0.23
	10.0	8	58.00 ± 0.71	59.38 ± 0.18*
	20.0	7	58.29 ± 0.68	59.71 ± 0.18

*Significantly different ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) from control.

†A session consisted of 60 trials each.

‡Saline or drug treatments were given 15 min prior to each session and were always preceeded (30 min) by a saline injection.

TABLE 2

EFFECT OF HALOPERIDOL (H) OR HALOPERIDOL VEHICLE (L) PRETREATMENT ON INTERTRIAL INTERVAL RESPONSES (ITIR), AVOIDANCE RESPONSES (AVDR) AND THE AVOIDANCE LATENCY (AVDL) IN THE CONDITIONED AVOIDANCE TEST IN RATS

Subject Group	Treatments† (mg/kg, IP)	ITIR Mean ± SEM	AVDR Mean ± SEM	AVDL (sec) Mean ± SEM
dl-CAT‡	L+S (T)§	31.57 ± 6.61	60.00 ± 0.00	2.02 ± 0.15
	H0.07 +S (F)§	23.71 ± 4.50	57.57 ± 0.78*	2.74 ± 0.16*
	L+S (T)	16.71 ± 4.66	58.14 ± 0.46	2.62 ± 0.19
	H0.15 +S (F)	15.57 ± 3.59	34.00 ± 7.83*	3.90 ± 0.27*
d-A‡	L+S (T)	15.38 ± 3.05	59.25 ± 0.49	2.39 ± 0.08
	H0.07 +S (F)	14.88 ± 2.24	57.75 ± 1.00*	2.88 ± 0.09*
	L+S (T)	38.88 ± 17.99	57.75 ± 1.16	2.82 ± 0.17
	H0.15 +S (F)	24.50 ± 4.61	38.50 ± 6.26*	3.82 ± 0.20*
COC‡	L+S (T)	12.00 ± 2.08	59.00 ± 0.46	2.76 ± 0.15
	H0.07 +S (F)	15.38 ± 3.22	56.88 ± 1.04*	3.22 ± 0.10*
	L+S (T)	21.75 ± 3.62	58.13 ± 0.85	2.81 ± 0.15
	H0.15 +S (F)	58.13 ± 0.85	15.88 ± 3.98*	4.54 ± 0.13*

*Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between drug and control values for that week.

†Pretreatments and treatments were given at 45 min and 15 min, respectively, prior to each session.

‡Abbreviations: *dl*-CAT=*dl*-Cathionone, *d*-A=*d*-Amphetamine, COC=Cocaine, S=Saline.

§(T) indicates the treatment received on Thursday, whereas (F) indicates the treatment received on the succeeding Friday.

employed, a close examination of the dose-response curves generated by *d*-amphetamine and *dl*-cathinone indicates that the *d*-amphetamine curve lies to the left of that of *dl*-cathinone (Figs. 1 and 2), which suggests that *d*-amphetamine is more potent in producing these effects than *dl*-cathinone.

Table 2 presents the effect of haloperidol on conditioned avoidance responding. Haloperidol (0.07 and 0.15 mg/kg, IP) pretreatments produced a dose-related decrease in avoidance responses and an increase in avoidance latencies without altering ITI responding.

Figures 3 through 5 present the effects of *dl*-cathinone, *d*-amphetamine and cocaine on conditioned avoidance responding in rats following haloperidol (0.07 mg/kg, IP) pretreatment. Two doses of each stimulant were tested with this dose of haloperidol. In general, the increases in ITI (Fig. 3) and avoidance responses (Fig. 4) and the decrease in avoidance latencies (Fig. 5) produced by the lower, but not the higher, dose of *dl*-cathinone, *d*-amphetamine, and cocaine were significantly less following haloperidol, as compared to the saline pretreatment values. A similar reduction in stimulant-induced effects on avoidance responding was observed when a higher dose (0.15 mg/kg, IP) of haloperidol was used (Fig. 6). It should be noted here that, with both doses of haloperidol, results seem to be less consistent with regard to the stimulant-induced changes in ITI responding, as compared to the other two parameters monitored. With 0.07 mg/kg (IP) of haloperidol, only the effects of *dl*-cathinone and cocaine, but not that of *d*-amphetamine, on ITI responses were antagonized. In addition, the effect of cocaine, but not those of *dl*-cathinone or *d*-amphetamine, on ITI responses was significantly antagonized by the higher pretreatment dose (0.15 mg/kg, IP) of haloperidol.

Even though neither test dose of haloperidol itself produced a significant change in ITI responses (Table 2), a significant increase in ITI responses was obtained when haloperidol pretreatment was followed by treatment with either dose of the three stimulants (Figs. 3 and 6). In addition, the decrease in avoidance responses and the increase in avoidance latency produced by haloperidol (0.07 and 0.15 mg/kg) pretreatment were significantly antagonized by treatment with both doses of *dl*-cathinone, *d*-amphetamine and cocaine (Figs. 4 through 6).

The effects of methysergide pretreatment (1.0 and 2.0 mg/kg, IP) on conditioned avoidance responding are presented in Table 3. The higher dose (2.0 mg/kg, IP) of methysergide produced a decrease in avoidance responses and an increase in avoidance latencies without altering ITI responses, when compared to the saline control values. No significant change in these parameters was observed when the lower dose (1.0 mg/kg, IP) of methysergide was given.

Figures 7 and 8 and Table 4 present the effects of *dl*-cathinone, *d*-amphetamine, and cocaine on conditioned avoidance responding in rats following methysergide (1.0 or 2.0 mg/kg, IP) pretreatment. The effects of all three stimulants on ITI responses were consistently augmented by both doses of methysergide. A significant increase in ITI responses was observed when *dl*-cathinone, *d*-amphetemine, or cocaine was given following pretreatment with methysergide, as compared to methysergide pretreated saline control (Figs. 7 and 8). No changes in the effects of all three stimulants on avoidance responses or avoidance latencies were observed following methysergide pretreatment. On the other hand, the increase in avoidance latency produced by both pretreatment doses of methysergide was significantly reduced by treatment with all three stimulants (Figs. 7 and 8).

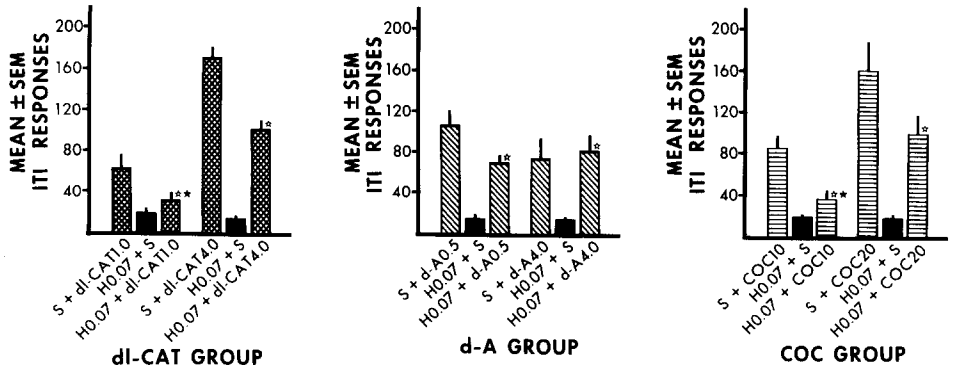

FIG. 3. Effects of IP *dl*-cathinone (*dl*-CAT, mg/kg), *d*-amphetamine (*d*-A, mg/kg), and cocaine (COC, mg/kg) on intertrial interval (ITI) responses in the conditioned avoidance test in rats following haloperidol (H, 0.07 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with haloperidol pretreatment and the drug value with saline pretreatment.

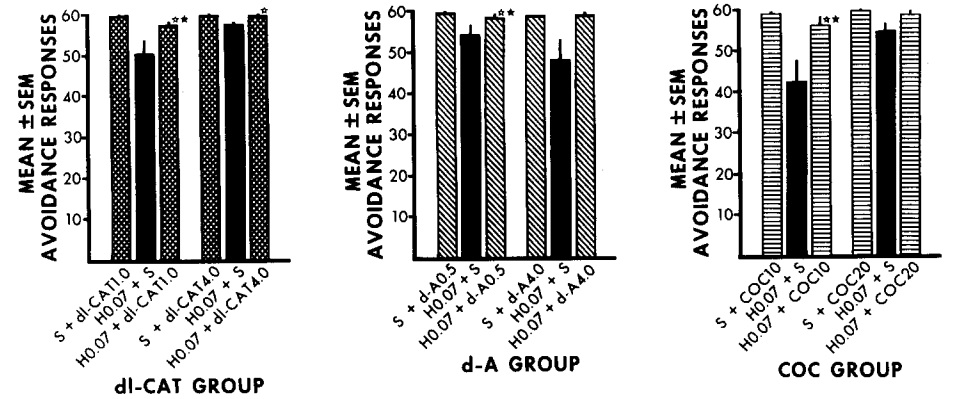

FIG. 4. Effects of IP *dl*-cathinone (*dl*-CAT, mg/kg), *d*-amphetamine (*d*-A, mg/kg), and cocaine (COC, mg/kg) on avoidance responses in the conditioned avoidance test in rats following haloperidol (H, 0.07 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with haloperidol pretreatment and the drug value with saline pretreatment.

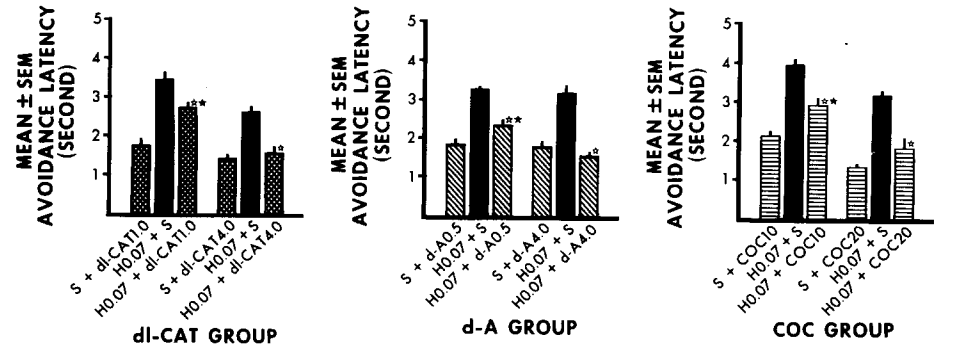

FIG. 5. Effects of IP *dl*-cathinone (*dl*-CAT, mg/kg), *d*-amphetamine (*d*-A, mg/kg), and cocaine (COC, mg/kg) on avoidance latencies in the conditioned avoidance test in rats following haloperidol (H, 0.07 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with haloperidol pretreatment and the drug value with saline pretreatment.

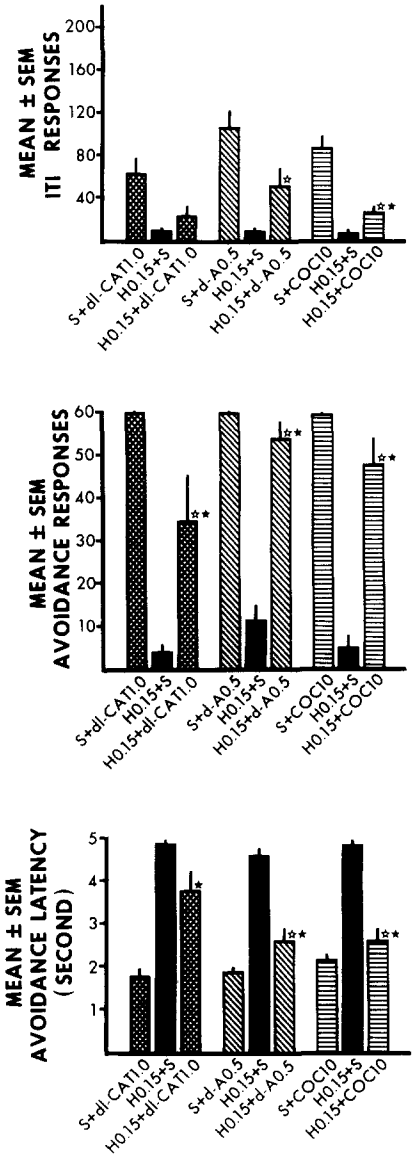

FIG. 6. Effects of IP *dl*-cathinone (*dl*-CAT, 1.0 mg/kg), *d*-amphetamine (*d*-A, 0.5 mg/kg), and cocaine (COC, 10 mg/kg) on all three parameters of avoidance responding in the conditioned avoidance test in rats following haloperidol (H, 0.15 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with haloperidol pretreatment and the drug value with saline pretreatment.

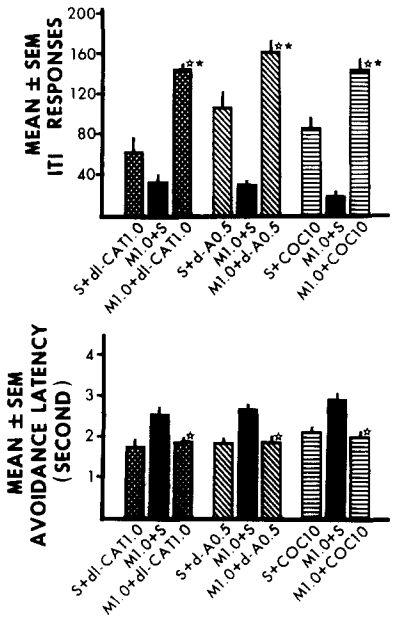

FIG. 7. Effects of IP *dl*-cathinone (*dl*-CAT, 1.0 mg/kg), *d*-amphetamine (*d*-A, 0.5 mg/kg), and cocaine (COC, 10 mg/kg) on intertrial interval (ITI) responses and avoidance latencies in the conditioned avoidance test in rats following methysergide (M, 1.0 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$ Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with methysergide pretreatment and the drug value with saline pretreatment.

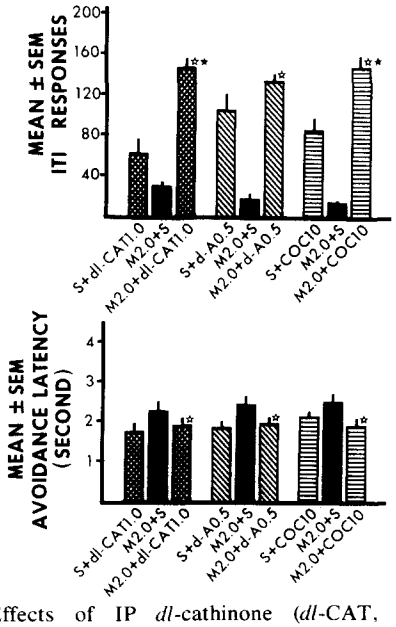

FIG. 8. Effects of IP *dl*-cathinone (*dl*-CAT, 1.0 mg/kg), *d*-amphetamine (*d*-A, 0.5 mg/kg), and cocaine (COC, 10 mg/kg) on intertrial interval (ITI) responses and avoidance latencies in the conditioned avoidance test in rats following methysergide (M, 2.0 mg/kg, IP) pretreatment. The vertical lines represent the standard error of the mean. N=7–8/dose. ☆Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between drug plus pretreatment and pretreatment control values. ★Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between the drug value with methysergide pretreatment and the drug value with saline pretreatment.

TABLE 3

EFFECT OF METHYSERGIDE (M) PRETREATMENT ON INTERTRIAL INTERVAL RESPONSES (ITIR), AVOIDANCE RESPONSES (AVDR) AND THE AVOIDANCE LATENCY (AVDL) IN THE CONDITIONED AVOIDANCE TEST IN RATS

Subject Group	Treatments† (mg/kg, IP)	ITIR Mean ± SEM	AVDR Mean ± SEM	AVDL (sec) Mean ± SEM
dl-CAT‡	S+S (T)§	20.71 ± 3.08	59.00 ± 0.38	2.42 ± 0.17
	M1.0+S (F)§	23.00 ± 4.14	58.57 ± 0.48	2.43 ± 0.13
	S+S (T)	31.57 ± 6.61	60.00 ± 0.00	2.02 ± 0.15
	M2.0+S (F)	23.71 ± 11.91	57.57 ± 2.07*	2.74 ± 0.16*
d-A‡	S+S (T)	18.63 ± 3.28	59.50 ± 0.19	2.46 ± 0.12
	M1.0+S (F)	22.13 ± 3.02	59.25 ± 0.41	2.46 ± 0.11
	S+S (T)	15.38 ± 3.05	59.25 ± 0.49	2.39 ± 0.08
	M2.0+S (F)	14.88 ± 2.24	57.75 ± 1.00*	2.88 ± 0.09*
COC‡	S+S (T)	17.13 ± 2.60	57.38 ± 1.41	3.04 ± 0.14
	M1.0+S (F)	17.00 ± 4.22	58.00 ± 1.05	2.93 ± 0.16
	S+S (T)	12.00 ± 2.08	59.00 ± 0.46	2.76 ± 0.15
	M2.0+S (F)	15.38 ± 3.22	56.88 ± 1.04*	3.22 ± 0.10*

*Denotes a significant difference ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) between drug and control values for that week.

†Pretreatments and treatments were given at 45 min and 15 min, respectively, prior to each session.

‡Abbreviations: *dl*-CAT=*dl*-Cathionone, *d*-A=*d*-Amphetamine, COC=Cocaine, S=Saline.

§(T) indicates the treatment received on Thursday, whereas (F) indicates the treatment received on the succeeding Friday.

TABLE 4

EFFECTS OF *dl*-CATHINONE (*dl*-CAT), *d*-AMPHETAMINE (*d*-A), AND COCAINE (COC) ON CONDITIONED AVOIDANCE RESPONSES FOLLOWING METHYSERGIDE (M) PRETREATMENT IN RATS

N	Treatments on Thursday† (mg/kg, IP)	Total avoidances per session‡ Mean ± SEM	Treatments on Friday (mg/kg, IP)	Total avoidances per session Mean ± SEM
7	S+S	58.14 ± 0.63	S+*dl*-CAT1.0	59.86 ± 0.14*
7	M1.0+S	58.86 ± 0.51	M1.0+*dl*-CAT1.0	59.57 ± 0.20
7	M2.0+S	58.86 ± 0.70	M2.0+*dl*-CAT1.0	58.71 ± 0.47
8	S+S	59.50 ± 0.38	S+*d*-A0.5	59.88 ± 0.13
8	M1.0+S	58.25 ± 0.65	M1.0+*d*-A0.5	59.25 ± 0.41
8	M2.0+S	59.63 ± 0.26	M2.0+*d*-A0.5	59.38 ± 0.38
8	S+S	58.00 ± 0.71	S+COC10.0	59.38 ± 0.18*
8	M1.0+S	57.63 ± 0.89	M1.0+COC10.0	58.88 ± 0.48
8	M2.0+S	58.25 ± 1.33	M2.0+COC10.0	59.00 ± 0.33

*Significantly different ($p \leq 0.05$, Wilcoxon Matched-pairs Signed Ranks Test) from pretreatment controls.

†Pretreatments and treatments were given at 45 min and 15 min, respectively, prior to each session.

‡A session consisted of 60 trials each.

DISCUSSION

The present study shows that *dl*-cathinone, *d*-amphetamine, and cocaine produced similar effects on conditioned avoidance responding in rats. All three stimulants produced an increase in ITI responding and in the number of avoidance responses and a decrease in avoidance latencies. The effect of *d*-amphetamine on conditioned avoidance responding is consistent with previous reports [20]. It is noted that *d*-amphetamine produced an inverted U-shaped dose response curve on ITI responding. This is most probably due to the increased stereotypic behavior in rats induced by the highest test dose of *d*-amphetamine [1,4]. A similar *d*-amphetamine dose-response curve for ITI responding has also been reported by Satinder [14] in rats.

Pretreatment with haloperidol produced a dose-related decrease in avoidance responses and an increase in avoidance latencies without altering ITI responding. These effects resulting from haloperidol treatment have also been reported by other investigators in rats [8,19] and mice [12]. When haloperidol was given prior to the lower test dose of *dl*-cathinone, *d*-amphetamine, or cocaine, a fairly consistent antagonism of the stimulant-induced effects on avoidance responding was observed across all three stimulants. When haloperidol was given prior to the higher test doses of the three stimulants, the effects of the stimulants appeared to outweigh those of haloperidol since no significant change in stimulant-induced effects on avoidance responding was observed. It could be noted that, with both doses of haloperidol, results seem to be less consistent with regard to the stimulant-induced changes in ITI responding, as compared to the other two parameters monitored.

Wagner *et al.* [24] observed that, like *d*-amphetamine, *dl*-cathinone released and blocked the uptake of tritiated dopamine in rat neostriatal synaptosomal preparations. In addition, these authors reported that repeated high doses of *dl*-cathinone produced long-lasting dopamine depletions in various rat brain regions and decreased the number of synaptosomal dopamine uptake sites in a manner similar to that seen after repeated *d*-amphetamine administration. Similar results produced by *dl*-cathinone and *d*-amphetamine on the release and uptake of dopamine have also been reported by Zelger and Carlini [26]. Based on these observations and the present results, it seems reasonable to suggest that the effects of *dl*-cathinone, *d*-amphetamine, and cocaine on conditioned avoidance responding in rats may be similarly mediated by a dopaminergic system.

Pretreatment with the higher test dose of methysergide produced a decrease in avoidance responses and an increase in avoidance latencies without altering ITI responding. When methysergide was given prior to *dl*-cathinone, *d*-amphetamine, or cocaine treatment, the changes in ITI responding (but not on the other two parameters) induced by the stimulants were significantly greater than the changes produced by saline pretreated stimulant controls. These data seem to suggest that the effects of *dl*-cathinone, *d*-amphetamine, and cocaine on different parameters of conditioned avoidance responding in rats are mediated by different neurochemical mechanisms. These data indicate that serotonergic systems may play an inhibitory role in the effects of all three stimulants on ITI responding. In addition, stimulant-induced effects on ITI responding may reflect the effects of these compounds on the general activity of the animal [14]. Therefore, augmentation of stimulant-induced effects on ITI responding following methysergide pretreatment may also indicate an inhibitory role of serotonergic systems in drug-induced increases in general activity. This conclusion agrees with the well documented finding that brain serotonergic systems play an inhibitory role in the locomotor effects of *d*-amphetamine [9,17].

In conclusion, the present data indicate that all three stimulants produced similar effects on conditioned avoidance responding in rats. These effects of *dl*-cathinone, *d*-amphetamine, and cocaine may be mediated by dopaminergic systems. In addition, these stimulant-induced changes on ITI responding probably also involve actions on serotonergic systems.

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