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Discriminative Stimulus Properties of (+)Cathine, an Alkaloid of the Khat Plant

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PEHEK, E. A. AND M. D. SCHECHTER. *Discriminative stimulus properties of (+)cathine, an alkaloid of the khat plant.* PHARMACOL BIOCHEM BEHAV **36**(2) 267–271, 1990.—The effects of the psychostimulant (+)cathine (norpseudoephedrine) were examined in a two-choice, food-motivated, drug-discrimination paradigm. Rats were able to discriminate cathine from vehicle and this effect was dose- and time-dependent. Prior administration of cathine resulted in a diminished response (tolerance) to subsequent cathine and this effect developed and dissipated rapidly. Thus, different dose-response curves were generated depending upon whether cathine or vehicle was administered the day before testing. The development of tolerance also shortened cathine's time course of action and enhanced the ability of haloperidol to antagonize the cathine cue. These results suggest caution in interpreting effects produced by intermittent drug injection schedules.

Cathine Khat Drug discrimination Dopamine Haloperidol Cathinone

THE fresh leaves of the khat shrub (*Catha edulis*), found in Eastern Africa and the Arab Peninsula, are chewed by some inhabitants of this region, resulting in an amphetamine-like euphoric state (11,12). Research has shown that the primary psychoactive alkaloid of this plant is (−)cathinone [see (11) and (12) for review]. This agent has received considerable attention and, like (+)amphetamine, causes the release of dopamine (DA), blocks its reuptake (8, 9, 26, 28), induces hyperactivity and stereotypy in rodents (5, 7, 29) and is able to serve as a discriminative cue in rats (4, 20–22).

Less is known about (+)cathine (norpseudoephedrine), another constituent of the khat shrub. Relative to cathinone, small amounts of cathine are found in fresh khat leaves (11). Over time in the live plant, and during drying of the leaves, (−)cathinone appears to be converted into (+)cathine and, to a lesser extent, (−)cathine, the inactive isomer (11,23). Thus, considerable amounts of (+)cathine are found in older and dried leaves.

Few studies have examined the effects of (+)cathine in laboratory animals. Although the effects of cathine are qualitatively similar to those of cathinone [e.g., cathine induces DA release (10,28)], cathine is considerably less potent but has a longer duration of action in the central nervous system (3, 4, 18, 27–29). In order to further investigate the effects of (+)cathine administration, the present experiments examined the ability of this agent to control behavior in a food-motivated drug discrimination paradigm. The first experiment investigated the dose-response relationship for cathine while the second study examined its time-course of action. The third experiment examined whether cathine discrimination is mediated by central DA. The effects of the centrally acting DA antagonist haloperidol on cathine discrimination were compared to those of domperidone, a DA antagonist that does not cross the blood-brain barrier.

METHOD

Subjects

Twelve singly housed male Sprague-Dawley rats, obtained from Zivic-Miller (Allison Park, PA) and weighing 200–235 g at the start of the experiment, were used. In order to maintain body weights at levels lower than free-feeding weights and thus provide an incentive for performance in the discrimination task, commercial lab chow was rationed. Water was available ad lib in the home cage.

Apparatus

Twelve standard rodent operant cages (Lafayette Instruments Corp., Lafayette, IN) were used as test cages. Each cage had 2 levers that were 7 cm apart and 7 cm above the grid floor. A food magazine was positioned between and below these 2 levers (2 cm

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from the floor). A single 45 mg Noyes pellet was delivered into this magazine upon completion of a correct response. Each test cage was housed within a sound-attenuated chamber equipped with a 9-W light and an exhaust fan. Solid state programming equipment (LVB Corp., Lehigh Valley, PA), located in an adjacent room, was used to control reinforcement schedules, food delivery and data recording.

Drugs

(+)Cathine hydrochloride was obtained from the National Institute on Drug Abuse and was dissolved in distilled water. Doses of cathine were expressed as doses of the salt. Haloperidol (McNeil) and domperidone (Janssen Pharmaceutica) were obtained as the free bases. Each DA antagonist was dissolved in 25 μl glacial acetic acid and then diluted to the appropriate concentration with a phosphate buffer (final pH = 3.6–4.3). All drugs were injected IP in a volume of 1 ml/kg.

Discrimination Training

Discrimination training consisted of two parts. In the first part, animals were trained to press one lever (the left lever for six animals and the right for the remaining six) following vehicle administration. Initially a FR 1 reinforcement schedule was used but this ratio was gradually increased, over the course of five days, until a FR 10 was obtained. This procedure was then repreated, but the opposite lever was reinforced, following injections of the cathine training dose (4.8 mg/kg) 15 min before the rats were placed in the experimental chambers. This dose of cathine was chosen based on earlier work indicating that a training dose of 0.6 mg/kg (−)cathinone produced good discrimination and that (−) cathinone was approximately eight times more potent than (+)cathine (4). In the second part of training, a FR 10 schedule was always used. A pseudo-random injection order was employed (VDDVV DVVDD; V = vehicle, D = drug) so that animals received five cathine injections and five vehicle injections over a two-week period. For each rat, responses on any given day were considered correct if the first lever to receive 10 presses was the appropriate lever (i.e., the cathine lever after cathine administration and the vehicle lever after vehicle administration).

An animal was considered trained when a criterion of 8 correct out of 10 consecutive sessions was achieved twice. Subjects required an average (± SEM) of 19.92 (± 1.59) sessions before the onset of criterion performance (i.e., to the beginning of the first of 8 correct out of 10 consecutive sessions) and 31.91 (± 1.83) sessions to the second set of criterion performance.

Testing Procedure

Animals were tested in extinction on test days. A test session was terminated immediately after one lever had been pressed 10 times. These test sessions were interspersed among maintenance-training days so that, for a given experimental treatment (e.g., a dose of cathine lower than the training dose), one test occurred the day following training with cathine and one after training with vehicle. There were at least two cathine-free days preceding those tests that followed training with vehicle. This served to reduce the possibility that appreciable drug activity would be present during these tests.

Experimental Design and Statistics

Within each experiment, all rats received all treatments and the treatment order was randomized. Two types of data were generated: 1) quantitative (the number of lever presses on the drug lever divided by the total number of presses × 100, obtained for each rat) and 2) quantal (the number of rats responding with 10 presses on the drug lever divided by the total number of rats × 100). One-way ANOVAs with repeated measures, followed by post hoc Scheffe probes ($p<0.05$), were used to analyze quantitative data. Quantal data were analyzed by Cochran Q-tests for normative data, followed by McNemar probes (2). In addition, ED_{50}s were generated from quantal dose-response data by the method of Litchfield and Wilcoxon (15).

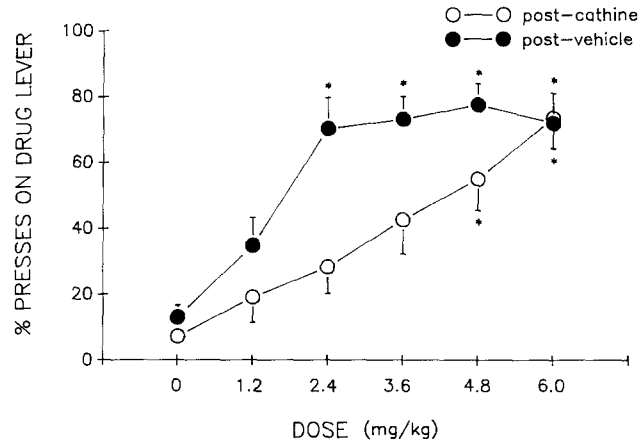

FIG. 1. The dose-response relationship for (+)cathine in rats trained with a dose of 4.8 mg/kg. Abscissa: dose (mg/kg); ordinate: % presses on drug lever (quantitative data). Post-cathine refers to tests conducted the day after training with cathine, whereas post-vehicle refers to tests following training with vehicle. *$p<0.05$ relative to vehicle (0). Values are the means ± SEM.

EXPERIMENT 1

Seven different doses of cathine, ranging from 0.8 to 6.0 mg/kg, were administered 15 min before testing in this experiment.

Results

The ability to discriminate cathine was observed to be dose-dependent but different dose-response curves were generated depending upon the prior day's treatment. Thus, discriminability was reduced on the day following a training session with cathine (ED_{50} = 3.94 mg/kg; 95% confidence limits = 2.96–5.25) relative to performance on the day after training with vehicle (ED_{50} = 1.30 mg/kg; 95% confidence limits = 0.81–2.08). Whereas the percentages of presses on the drug lever (quantitative data) were significantly different from vehicle following 4.8 and 6.0 mg/kg cathine administered on the day after training with cathine, $F(5,55) = 9.26$, $p<0.00001$ (see Fig. 1), doses ranging from 2.4–6.0 mg/kg differed significantly on test sessions that followed vehicle maintenance days, $F(5,55) = 12.24$, $p<0.00001$ (see Fig. 1). Analyses of the quantal data revealed a similar pattern of results (see Table 1). On tests following cathine training, significantly more animals chose the drug lever following administration of cathine doses ranging from 3.6–6.0 mg/kg, $Q(5) = 33.62$, $p<0.0001$. However, on tests following vehicle maintenance days, performance was significantly affected by administration of 2.4–6.0 mg/kg cathine $Q(5) = 26.43$, $p<0.0001$.

The attenuation of cathine's effects by prior drug administration was not dependent upon the performance of a behavioral discrimination in the operant chambers on the day before testing. This was demonstrated by the finding that the decreased efficacy

TABLE 1

THE PERCENTAGES OF RATS CHOOSING THE DRUG LEVER (QUANTAL DATA) FOLLOWING DIFFERENT DOSES OF (+)CATHINE

Dose (mg/kg)	Post-Cathine	Post-Vehicle
0	0	0
1.2	8.33	33.33
2.4	16.67	83.33*
3.6	33.33*	91.67*
4.8	58.33*	91.67*
6.0	83.33*	83.33*

Post-cathine refers to tests conducted the day following training with cathine whereas post-vehicle refers to tests after a vehicle training day. Tests were conducted 15 min after injection. *$p<0.05$ relative to vehicle (0).

of cathine was also observed when the rats were injected noncontingently with cathine (4.8 mg/kg) the day before testing with 2.4 mg/kg cathine (post-noncontingent cathine: mean quantitative = 49.75%, quantal = 33.33%; post-noncontingent vehicle: mean quantitative = 69.34%, quantal = 91.67%). Performance after 2.4 mg/kg cathine administered on the day after noncontingent cathine did not differ significantly from performance on the day after contingent cathine [quantitative data: $F(1,11)=0.73$, $p>0.05$]. Likewise, performance after 2.4 mg/kg cathine administered the day after noncontingent vehicle injections did not differ from performance after contingent vehicle injections [quantitative data: $F(1,11)=0.12$, $p>0.05$].

EXPERIMENT II

The training dose of 4.8 mg/kg cathine, administered at 7 different time intervals before testing and compared to vehicle administered 15 min before testing, was used to investigate the duration of action of cathine.

Results

Rats were able to discriminate cathine at longer time intervals following injection when they were trained with vehicle, rather than cathine, the day before testing. For quantitative data, whereas animals could discriminate cathine from vehicle for as long as two hours following administration when they received vehicle the day before, $F(7,77)=15.83$, $p<0.00001$ (see Fig. 2), they could only discriminate cathine up to one hour after injection when they were treated with cathine the day before, $F(7,77)=16.41$, $p<0.0001$ (see Fig. 2). Analyses of quantal data yielded results that were generally similar (see Table 2). More rats chose the drug lever at time points ranging from 15–240 min after cathine when the test was given the day following a vehicle maintenance session, $Q(7)=51.22$, $p<0.0001$. However, for tests given the day after training with cathine, performance was significantly different only at 15–120 min, $Q(7)=47.49$, $p<0.0001$.

EXPERIMENT III

The third experiment examined the relative abilities of the D2 antagonists haloperidol and domperidone to antagonize cathine administration. Each antagonist was administered 15 min prior to cathine administration (i.e., 30 min before testing began). Others have shown that the time courses of action for both drugs in the periphery is similar and that both have significant effects on

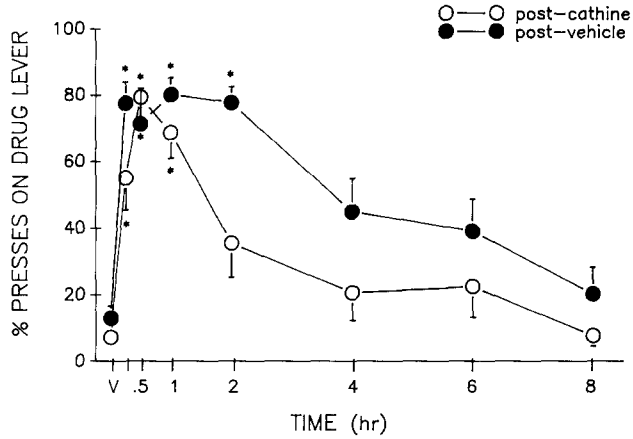

FIG. 2. The time-course of action for (+)cathine in rats trained with a dose of 4.8 mg/kg. Abscissa: time (hr); ordinate: % presses on drug lever (quantitative data). Post-cathine refers to tests conducted the day after training with cathine, whereas post-vehicle refers to tests following training with vehicle. *$p<0.05$ relative to vehicle administered 15 min before testing (V). Values are the means ± SEM.

peripheral DA function 10–70 min following administration (25). Following subcutaneous administration, haloperidol significantly affected brain DA release at the earliest time point measured (20 min) and this effect was still evident 2.5 hr following injection (2).

Results

The diminished effectiveness of cathine observed on the day following training with cathine was also seen when rats received haloperidol prior to cathine (4.8 mg/kg) on test days. Both 0.2 and 0.3 mg/kg haloperidol were able to partially antagonize the cathine cue when tests were conducted the day after cathine training [quantitative data: $F(4,28)=4.78$, $p<0.005$ (see Fig. 3); quantal: $Q(4)=11.56$, $p<0.025$ (see Table 3)]. This antagonism was evident by the finding that, on these tests, haloperidol plus cathine data did not differ significantly from vehicle data whereas cathine alone data did. However, the antagonism was only partial since haloperidol plus cathine data did not differ significantly from cathine alone data. Haloperidol was an even weaker antagonist of the cathine cue on tests following vehicle maintenance days since only the 0.3 mg/kg dose partially blocked cathine discrimination

TABLE 2

THE PERCENTAGES OF RATS CHOOSING THE DRUG LEVER (QUANTAL DATA) AT DIFFERENT TIMES FOLLOWING ADMINISTRATION OF (+)CATHINE

Time (min)	Post-Cathine	Post-Vehicle
15 vehicle	0	0
15 cathine	58.33*	91.67*
30	83.33*	75.00*
60	83.33*	91.67*
120	33.33*	100.00*
240	8.33	50.00*
360	16.67	33.33
480	0	8.33

Post-cathine refers to tests conducted the day following training with cathine, whereas post-vehicle refers to tests after a vehicle training day. A dose of 4.8 mg/kg cathine was employed. *$p<0.05$ relative to data gathered 15 min following vehicle administration (15 vehicle).

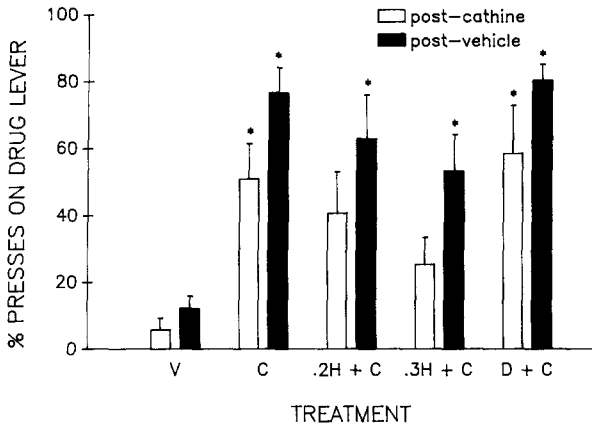

FIG. 3. The effects of haloperidol (H) and domperidone (D) on (+)cathine discrimination in rats trained with a dose of 4.8 mg/kg. Abscissa: treatment [vehicle (V), 4.8 mg/kg (+)cathine (C), 0.2 mg/kg haloperidol plus cathine (0.2H + C), 0.3 mg/kg haloperidol plus cathine (0.3H + C) and 1.0 mg/kg domperidone plus cathine (D + C)]; ordinate: percentage of presses on the drug lever (quantitative data). Post-cathine refers to tests conducted the day after training with cathine whereas post-vehicle refers to tests following training with vehicle. *$p<0.05$ relative to vehicle. Values are the means ± SEM.

during these tests [quantal: $Q(4)=23.57$, $p<0.0001$ (see Table 3); this blockade was not revealed by analyses of the quantitative data: $F(4,36)=9.58$, $p<0.00001$ (see Fig. 3)]. Administration of domperidone (1.0 mg/kg) did not block cathine's effects on any day.

DISCUSSION

The present results represent the first demonstration that rats can be trained to discriminate (+)cathine, an alkaloid of the khat plant, from its vehicle, and that this effect is both dose- and time-dependent. Furthermore, cathine's discriminability varies as a function of prior treatment so that prior administration of cathine results in a diminished response (tolerance) to subsequent cathine.

Cathine's tolerance effect developed rapidly (one day) and dissipated quickly (three days or less) and thus appears analogous to the acute tolerance observed with other agents [e.g., ephedrine (14)]. In particular, the present results are very similar to those observed after caffeine administration in a drug discrimination paradigm (17). Acute tolerance to cathine was also observed on the day following l-cathinone or d-amphetamine administration in animals trained to discriminate l-cathinone or d-amphetamine, respectively (19). The mechanism for the induction of acute tolerance by cathine is not known. It is still observed following noncontingent injections of cathine the day before testing, demonstrating that it is not dependent upon the performance of a behavioral response in the operant chambers the day before testing.

Previous research has shown that (−)cathinone, another alkaloid of the khat plant, can serve as a discriminative cue (4, 20–22). The ED_{50} for cathinone was 0.24 mg/kg (22), considerably lower than the average ED_{50} of 2.62 mg/kg in the present study (average of day after cathine and day after vehicle quantal data). Rats also acquired the cathinone discrimination in less time relative to the present results with cathine [as reflected by differences between the two studies in the average number of trials to the first 8 correct out of 10 consecutive sessions criterion; mean number of sessions: cathinone = 7.8 (22), cathine = 19.92]. Whereas rats were unable to discriminate cathinone from vehicle three hours postinjection (20), partial discrimination was still evident six hours following cathine administration in the present case. These results agree with other studies demonstrating that, in the central nervous system, cathine is less potent, but has a longer duration of action, than cathinone (3, 4, 18, 27–29).

Others have shown that (+)cathine is converted to (−)cathinone by dopamine-beta-hydroxylase in vitro (16). It is possible that this conversion occurs in vivo and that cathine may act as a prodrug for (−)cathinone (11). If this reaction does occur, it may explain why cathine's time course is prolonged relative to that of cathinone.

Few studies have examined cathine's mechanism of action, whereas it is now widely accepted that cathinone, like amphetamine, causes the release and blocks the reuptake of DA (11,12). Two reports demonstrated that cathine also caused DA release, but that it was substantially less potent than cathinone (10,28). In another study, both alpha-methyltyrosine (an inhibitor of tyrosine hydroxylase activity) and reserpine (which depletes catecholamine storage vesicles) blocked cathine-induced stereotypy, suggesting that cathine affected either DA and/or norepinephrine systems (29). The centrally acting DA antagonist haloperidol attenuated biting and gnawing induced by either cathine or cathinone administration, but was less effective in the case of cathine (29).

In the present report, haloperidol attenuated cathine discrimination whereas domperidone, a DA antagonist that does not cross the blood-brain barrier, did not. Others have shown that equivalent doses of haloperidol and domperidone produce similar effects on peripheral DA function (6,25), that these two drugs are approximately equipotent inhibitors of tritiated DA antagonist binding (1,13), but that only haloperidol binds to central DA receptors following systemic administration (13). Thus, in the present experiment, 1.0 mg/kg domperidone should have had a greater effect than 0.3 or 0.2 mg/kg haloperidol on peripheral DA receptors but no effect on central DA receptors. It is therefore likely that haloperidol's ability to attentuate cathine discrimination was due to its actions on central DA receptors. Thus, these results suggest that, similar to cathinone (21), cathine's behavioral effects may be partially due to actions on central nervous system (CNS) DA activity. Since haloperidol appears to only partially antagonize the cathine cue, future studies should examine the effects of cathine on other neurotransmitter systems, especially those that employ norepinephrine.

In the past, cathine has received relatively little experimental attention, presumably due to its diminished potency relative to cathinone. In the present study, behavior was affected by doses of cathine that were appreciably lower than those employed previously by others (18, 27–29). Thus, it is possible that cathine has

TABLE 3

THE PERCENTAGES OF RATS CHOOSING THE DRUG LEVER (QUANTAL DATA) FOLLOWING ADMINISTRATION OF VEHICLE (V), 4.8 mg/kg (+)CATHINE (C), 0.2 mg/kg HALOPERIDOL PLUS CATHINE (0.2H + C), 0.3 mg/kg HALOPERIDOL PLUS CATHINE (0.3H + C) OR 1.0 mg/kg DOMPERIDONE PLUS CATHINE (D + C)

Treatment	Post-Cathine	Post-Vehicle
V	0	0
C	58.33	91.67*
0.2H + C	50.00	66.67*
0.3H + C	12.50	40.00
D + C	75.00	100.00*

Post-cathine refers to tests conducted the day following training with cathine whereas post-vehicle refers to tests after a vehicle training day. A dose of 4.8 mg/kg cathine was employed. *$p<0.05$ relative to vehicle.

appreciable CNS activity and contributes to the euphoria induced by khat chewing in humans.

The present report increases our knowledge regarding the psychopharmacological properties of one alkaloid of the khat plant. Since khat abuse is a world health problem (11,12), such knowledge may prove beneficial in the efforts to curtail khat abuse and in the understanding of psychostimulant drug addiction in general. In addition, this report demonstrates that tolerance can develop and dissipate rapidly following cathine treatment, suggesting that caution should be used when employing intermittent drug injection schedules.

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