Pharmacology Biochemistry & Behavior, Vol. 41, pp. 37–41. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/92 $5.00 + .00

Effect of Altering Dopamine or Serotonin Neurotransmitters Upon Cathinone Discrimination

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Received 14 June 1991

SCHECHTER, M. D. *Effect of altering dopamine or serotonin neurotransmitters upon cathinone discrimination.* PHARMACOL BIOCHEM BEHAV **41**(1) 37–41, 1992.—Rats were trained to discriminate between the stimulus properties of 0.8 mg/kg *l*-cathinone and its vehicle in a two-lever, food-motivated operant task. Once trained, rats showed a dose-related decrease in discriminative performance when tested with lower cathinone doses. An analysis of the dose-response curve indicated an ED_{50} value of 0.23 mg/kg. Pretreatment with CGS 10746B (5–20 mg/kg) resulted in a dose-related decrease in cathinone discrimination with the highest dose blocking cathinone discrimination. In contrast to the ability of this dopamine release inhibitor to decrease cathinone discrimination, pretreatment with three doses of the calcium channel blocker isradipine (2.5–10 mg/kg) or with the 5-HT_3 antagonist MDL 72222 (0.1–0.4 mg/kg) had no effect upon cathinone discrimination. The results suggest that cathinone controls differential responding in a discriminative stimulus task by a mechanism involving presynaptic release of dopamine, which may not be regulated by either neuronal calcium influx through L-type calcium channels or by serotonergic neurons.

Stimulus properties of drugs Cathinone MDL 72222 Dopamine CGS 10746B Isradipine ICS 205-903 Rats

THE fresh leaves of the shrub *Catha edulis* (Khat) contain the psychostimulant cathinone and chewing them produces euphoria, excessive talkativeness, increased ability to concentrate, excitement, decreased hunger and insomnia (15, 21, 37). These actions are reminiscent of those produced by amphetamine and not only are these two agents structurally similar but both behavioral and biochemical studies have indicated the similarity between them (18–20). This (10, 29, 33), as well as at least two other (11,16) laboratories, have been the site of studies that have shown that cathinone can function as a drug capable of controlling discriminative responding in rats. The discriminative stimulus properties of another psychostimulant *d*-amphetamine have been consistently reported to be antagonized by pretreatment with the postsynaptic dopamine blocking drug haloperidol (5, 27, 28, 32) and this has led to the suggestion that the stimulus properties of *d*-amphetamine reside in dopaminergic neuronal systems (32). In contrast, pretreatment with haloperidol, in a dose of 0.07 and 0.15 mg/kg, did not significantly attenuate discrimination of cathinone (12), whereas a higher pretreatment dose of 0.2 mg/kg haloperidol attenuated the discrimination of *l*-cathinone (29). The benzothiadiazepine CGS 10746B has been reported to decrease dopamine release without either changing dopamine metabolism or occupying dopaminergic receptors (1). Employing this novel agent allows for a different mechanism, i.e., one differing from postsynaptic dopaminergic blockade, to be tested in rats who can discriminate the psychostimulant cathinone. In fact, CGS 10746B has been shown to successfully antagonize discriminative behavior in rats trained with 0.8 mg/kg *d*-amphetamine in a similar behavioral paradigm (31).

Evidence has been reported that suggests that 5-HT_3 receptors may be involved in modulating dopamine release since 5-HT_3 agonists have been shown to release dopamine from rat striatal slices (2). In contrast, 5-HT_3 antagonists decrease morphine-induced dopamine release into the nucleus accumbens of rats (17). Two selective 5-HT_3 antagonists, MDL 72222 (7) and ICS 205-903 (26), will be administered to cathinone-trained animals in an effort to observe if selective antagonism of the 5-HT_3 receptor alters the dopamine-mediated interoceptive cue produced by cathinone.

Several compounds have been shown to inhibit the effects of psychostimulants and also been reported to function as calcium channel blockers (6,13). If calcium channel blockade attenuates the cathinone-induced relase of dopamine, then there is a probability that this drug will decrease cathinone discrimination. In other investigations, calcium channel blockers have been given to mice either before performing amphetamine-induced turning behavior (8) or locomotor stimulation (14) and, in each case, the behavior was antagonized. Using rats in a behavioral paradigm similar to the one used herein, Nencini and Woolverton (25) showed that the calcium channel blocker nimodipine attenuated the discriminative properties of amphetamine. It would, therefore, be of interest to investigate if the calcium channel blocker isradipine had a similar effect on cathinone discrimination.

METHOD

Subjects

Twenty experimentally naive male Sprague-Dawley rats were purchased from the Zivic-Miller Laboratories (Allison Park, PA) and weighed 150–174 g at arrival. The rats were individually housed in a room maintained on a 12-h (0600–1800) light/12-h

dark cycle and kept at a constant temperature and humidity. They were given water ad lib in their home cages as well as a daily rationing of commercial rat chow so as to maintain them at approximately 85–90% of their free-feeding weights as determined by a growth chart from the supplier.

Apparatus

Twelve standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN), each containing two levers situated 7 cm apart and 7 cm above a metal grid floor, were used as the environmental space. Equidistant between the levers was placed a food receptacle that received delivery of 45 mg Noyes food pellets. Each operant chamber was enclosed in a sound-attenuated cubicle with an exhaust fan and a 9-W houselight. Solid-state programming equipment (Med Associates, E. Fairfield, VT) was located in an adjacent room and was used to control and record discrimination sessions.

Shaping to Lever-Press

The food-deprived rats were trained (shaped) to press one lever under the drugged condition and a second lever in a non-drugged state. Training sessions were conducted once a day, five days a week, with one lever in each chamber designated as the "vehicle-lever" and the second lever designated as the "cathinone-lever." For 10 of the animals, the vehicle-lever was to the right of the food receptacle, whereas for the other 10 animals it was to the left. Initially all rats were trained to respond on the vehicle-lever 15 min after the intraperitoneal (IP) administration of 1 ml/kg of distilled water (vehicle) on a fixed ratio (FR) schedule of 1, i.e., one response resulted in one reinforcement. During eight consecutive training sessions, the FR schedule was gradually incremented to an FR10 in which 10 responses on the vehicle-lever yielded one reinforcement. The rats were removed from the operant chamber and returned to their home cages after receiving 40 reinforcements on the FR10 schedule.

Once an FR10 schedule was established on the vehicle-lever, training began on the opposite lever (15 min) following the injection (IP) of an equal volume (1 ml/kg) of vehicle containing 0.8 mg/ml of cathinone (hydrochloride calculated as the salt). Rats were only rewarded for responses upon the cathinone-lever and, as with previous vehicle training, the initial reinforcement schedule of FR1 was gradually increased to FR10; this was accomplished over a period of five daily sessions.

Discrimination Training

The rats were considered to be trained to lever-press once FR10 responding was established on both levers. Discrimination training subsequently began 15 min after the daily administration of either vehicle (V) or 0.8 mg/kg cathinone (C) and these were administered on a 2-week repeating injection schedule: C-V-V-C-C; V-C-C-V-V. The first lever upon which ten responses were accumulated at the beginning of each session was considered the "selected" lever for that daily session. At the time of the 10th response, presses on both the selected and unselected levers were recorded. The session was continued, regardless of the correctness of the selected lever, until 400 responses were made on the correct lever for the session and, therefore, until 40 reinforcements (on the FR10 schedule) were received. Presses upon the incorrect lever produced no programmed consequence. Animals were required to select the correct lever, appropriate for the substance injected, in eight of ten consecutive training sessions. This 8/10 performance criterion was required twice before dose-response testing commenced.

Dose-Response Tests

All rats reached the discriminative criteria and, subsequently, the discriminative training regimen was limited to every other day to maintain discrimination. On intervening days, rats were tested with three lower doses of cathinone. Each dose (0.1, 0.2 and 0.4 mg/kg) was tested twice; once following a drug (0.8 mg/kg cathinone) maintenance session and once following a vehicle maintenance session. This counterbalancing was used to control for any possible residual influence from the previous maintenance session. If at any time during testing a rat's maintenance discrimination fell below the 80% criterion, data on that animal would be dropped from the results. This occurred in one rat during dose-response testing, in one additional rat during the antagonist study and in one more rat during a second dose-response determination (below) as reflected in an $n = 19$, 18 and 17, respectively. This second, multiple dose-response experiment was conducted following the antagonist and cotreatment experiments to determine the stability of the animals' discrimination performance.

Antagonists Experiments

Each of the three putative antagonists, viz., CGS 10746B, isradipine and MDL 72222, was administered prior to cathinone injection by a route and at a time which, according to the scientific literature, allowed for maximal central efficacy. Thus CGS 10746B in doses previously shown to block discrimination of amphetamine (31) was administered IP 20 min prior to the injection of cathinone and the animals were tested, in extinction, 15 min after the second injection. Similarly, isradipine was administered IP and 60 min later cathinone was injected 15 min before testing. Lastly, MDL 72222 was administered 45 min prior to cathinone injection and, therefore, 60 min before testing. Each of the three antagonists was used in ascending doses until a dose was reached that produced behavioral disruption, i.e., one or more of the rats did not respond on either lever.

Measurements and Statistics

The data collected in the drug discrimination sessions are expressed as both quantal and quantitative measurements. Each of the individual measurements provides a different indicator of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats that choose the cathinone-appropriate lever as their selected lever, i.e., the lever to first accumulate 10 presses. The quantitative measurement is the number of responses on the cathinone-lever divided by the total number of responses on both the cathinone- and the vehicle-lever at the time that 10 responses are accumulated on either single lever; this fraction is expressed as a percentage. In all test days with either lower doses of cathinone or with antagonists, the rats were immediately removed upon pressing one of the two levers 10 times. This precluded any possible reinforcement/training at a cathinone dose, or with a drug, different from the 0.8 mg/kg of cathinone used in training and maintenance. Unlike the all-or-none quantal measurement, the quantitative measurements allow for responses on both the selected and unselected levers to be considered and, thus, provide a relative measure of the magnitude, as well as the direction of lever performance. Additionally, statistics can be performed on the quantitative data. The advantages in using both types of measurements are fully discussed by Stolerman and D'Mello (35). A computer-based (36) formulation of the Litchfield-Wilcoxon procedure (23), which

TABLE 1

Dose Cathinone (mg/kg)	Quantal	Quantitative (S.D.)
(A) STC (S.D.)		Range:
#1	3.5 (3.0)	1–11
#2	13.7 (3.3)	11–22
0.8	91.0	82.7 (11.7)
0.4	76.3	73.2 (8.9)
0.2	27.7	32.7 (22.8)
0.1	11.1	14.8 (0.5)
0.0 (veh)	7.9	16.2 (2.7)
ED_{50} (mg/kg) (95% CL)	0.23 (0.18–0.30)	
(B)		
0.8	92.2	86.0 (6.0)
0.4	73.5	68.8 (19.0)
0.2	23.5	33.4 (9.6)
0.1	3.4	8.6 (2.8)
0.0 (veh)	2.0	6.3 (5.9)
ED_{50} (mg/kg) (95% CL)	0.30 (0.23–0.34)	

(A) Learning rate and dose-response effect of discriminative performance in rats (n = 19) trained with 0.8 mg/kg cathinone and vehicle prior to novel drug testing.

(B) Dose-response in same rats (n = 17) after novel drug treatments.

employs probits vs. log-dose effects, was used to generate ED_{50} values and confidence limits from the cathinone dose-response data prior to and following novel drug testing.

RESULTS

The results indicate that rats readily learn to discriminate between 0.8 mg/kg cathinone and its distilled water vehicle. The first session of 10 consecutive sessions in which at least eight correct lever selections were made was reached in a mean of 3.5 sessions and attained a second time in 13.7 sessions (Table 1A). Thus all rats were capable of discriminating between cathinone and its vehicle by the 32nd training session (16 with cathinone and 16 with vehicle). The dose-response relationship in experiments conducted immediately after discriminative training indicates that 0.8 mg/kg cathinone, as it was used in maintenance sessions, produced 91% of all first lever selections upon the cathinone-lever. In maintenance sessions with vehicle (0.0 mg/kg in Table 1), the cathinone-lever was first pressed 10 times in 7.9% of all sessions (or, to look at it a different way, the vehicle-lever was first selected in 92.1% of all sessions). Decreasing doses of cathinone resulted in decreasing quantal and quantitative performance and the quantal ED_{50} value was calculated (36) to be 0.23 mg/kg. When a second dose-response was determined, after all antagonists were tested, in rats which maintained their discriminative performance during maintenance sessions, the ED_{50} value generated was 0.30 mg/kg, not significantly different (36) from that previously determined (Table 1B).

The results of pretreatment with three distinct classes of putative antagonists are represented on Table 2. When CGS 10746B was administered in increasing doses prior to cathinone, the highest dose (20.0 mg/kg) significantly attenuated cathinone discrimination without any significant effect when tested prior to vehicle discrimination (Table 2A). In contrast, doses of isradipine (2.5–10.0 mg/kg) and MDL 72222 (0.1–0.4 mg/kg) had no similar effect upon cathinone discrimination. In fact, there was indication that MDL 72222 may have actually increased cathinone discrimination (Table 2C). It was, therefore, thought prudent to test the highest dose of MDL 72222 (0.4 mg/kg) with various doses of cathinone to see if a significant increase in cathinone discrimination would occur. In addition, a behaviorally active dose of another 5-HT_3 antagonist ICS 205-930 was, likewise, administered with various doses of cathinone. The results of this testing appear in Table 3 and, although there is a trend to increased cathinone discrimination with the combination of drugs, the results are not significant at any dose and the ED_{50} values when compared (36) to cathinone doses administered alone do not differ significantly (data not shown).

TABLE 2

EFFECT OF PRETREATMENT WITH CGS 10746B, ISRADIPINE AND MDL 72222 UPON DISCRIMINATION OF 0.8 mg/kg CATHINONE OR ITS VEHICLE

Dose (mg/kg)		Quantal	Quantitative (S.D.)
(A) CGS 10746B (n = 19)			
5.0	+ cathinone	78.9	60.0 (20.4)
10.0		63.2	61.2 (2.8)
20.0		10.5	24.6 (12.3)
20.0	+ vehicle	5.3	12.8 (0.4)
(B) Isradipine (n = 18)			
2.5	+ cathinone	94.4	86.9 (2.8)
5.0		83.3	81.6 (11.9)
10.0		94.4	86.4 (12.5)
10.0	+ vehicle	5.6	10.1 (5.9)
(C) MDL 72222 (n = 18)			
0.1	+ cathinone	100.0	92.3 (1.2)
0.2		75.0	81.7 (10.6)
0.4		100.0	90.0 (7.4)
0.4	+ vehicle	0.0	10.1 (5.9)

TABLE 3

COTREATMENT OF 0.0–0.8 mg/kg CATHINONE WITH 0.5 mg/kg ICS 205-930 OR 0.4 mg/kg MDL 72222

Cathinone (Dose)	Quantal	Quantitative (S.D.)
(A) 0.5 mg/kg ICS 205–930 +		
0.8	100.0	92.8 (2.5)
0.4	94.4	91.0 (11.0)
0.2	44.4	52.3 (9.0)
0.1	22.2	26.5 (6.0)
0.0 (veh)	16.7	16.1 (5.0)
(B) 0.4 mg/kg MDL 72222 +		
0.8	100.0	90.0 (7.4)
0.4	88.9	87.6 (2.3)
0.2	33.3	42.3 (1.7)
0.1	16.7	20.7 (14.6)
0.0 (veh)	5.6	8.0 (2.9)

DISCUSSION

In a thoughtful review regarding the behavioral paradigm using drugs as discriminative stimulus cues, Glennon and Rosecrans (9) discussed the high degree of specificity and sensitivity inherent in the task. These factors, as well as the stability and reproducibility of the technique, have been evidenced in the present work in that the ED_{50} value presented in Table 1A (0.23 mg/kg) is almost exactly the same value calculated in other rats used in previous experiments from this laboratory in 1986 [0.27 mg/kg (29)] and in 1989 [0.34 mg/kg (30)]. In addition, the stability of the technique is emphasized by comparisons of the ED_{50} value generated in the second dose-response curve (0.30 mg/kg) as compared to that generated after the first dose-response immediately following training (Table 1). This stability has previously been shown in rats whose ED_{50} values were determined as much as a year apart (34).

An alternative approach to postsynaptic dopaminergic blockade with haloperidol, and other antipsychotic agents, resides in the possibility of modifying dopamine release presynaptically. This possibility has become a reality with the recently synthesized drug CGS 10746B which reduces the release of dopamine without any binding affinity to postsynaptic dopaminergic receptors (1). The ability of CGS 10746B to attenuate cathinone discriminative performance lends evidence to the dopaminergic mediation of this behavioral effect and expands upon previous work in which CGS 10746B was able to inhibit both amphetamine (31) and the cathinone congener cathine (30). The findings, furthermore, support the scientific evidence (9, 16, 20, 21) that the mechanism of cathinone's action resides in its ability to release presynaptic dopamine.

In contrast to the blockade of cathinone discriminative performance with CGS 10746B pretreatment, the calcium channel blocker isradipine had little or no effect upon cathinone discrimination. In a recent drug discrimination experiment using rats, another calcium-channel blocker nimodipine was shown to produce slightly less than a two-old shift in the amphetamine (training dose: 0.5 mg/kg, IP) dose-response ED_{50} value. This was contrasted with a four-fold displacement of the dose-response curve to the right by a low dose (0.125 mg/kg) of haloperidol. These results suggested to the authors (25) a partial antagonism of the discriminative properties of amphetamine and only a minimal role for calcium channel mechanisms in the drug discrimination properties of psychostimulants. Indeed, psychostimulant-induced release of dopamine may not be under the control of voltage-sensitive calcium channels since various types of calcium channel blockers have been shown to be unable to affect neurotransmitter release (24). Thus the necessity for influx of calcium through the L-type calcium channels as it may be affected by isradipine may not be required for the behavioral effects of cathinone. Any decrease in the discriminative stimulus properties of psychostimulants that would occur may, instead, be related to nonspecific factors (e.g., pharmacokinetic alternations) elicited by coadministration of these psychostimulants with calcium channel antagonists (3).

The $5\text{-}HT_3$ antagonists ICS 205-930 and MDL 72222 have been reported to prevent the conditioned place preference induced by morphine and nicotine, but not that produced by amphetamine (4). These investigators suggested that antagonism of $5\text{-}HT_3$ receptors blocks the ability of various drugs of abuse to stimulate dopamine release. This is especially true of drugs that release dopamine by stimulating the firing of dopaminergic neurons such as morphine, nicotine and ethanol. In contrast, the $5\text{-}HT_3$ antagonists do not seem to affect dopamine when it is released by a drug, such as cathinone. Thus the interaction between $5\text{-}HT_3$ receptor antagonists and drugs that raise dopamine levels depends on how the dopamine system is activated. In contrast to antagonism, there was a trend toward increased cathinone discrimination when it was coadministered with the $5\text{-}HT_3$ antagonists. The possibility exists that both MDL 72222 and ICS 205-930 share a common structure (an aromatic nucleus that is attached to a tropane heterocyclic group by way of a side chain containing a carboxyl group) and that this structure is similar to cocaine which, in fact, was used as a starting point for the synthesis of these two $5\text{-}HT_3$ antagonists (22).

The results of the present experimentation indicate that the ability of the psychostimulant cathinone to produce discriminative stimuli may be mediated by release of dopamine, which may not be regulated by neuronal calcium influx through L-type calcium channels. Furthermore, $5\text{-}HT_3$ antagonists have only minimal effect upon the cathinone-induced dopamine release needed for optimal discriminative performance.

ACKNOWLEDGEMENTS

The author would like to extend his thanks to Mrs. Denise McBurney for her consistent excellence in the conduct of these experiments, and to Marty Hilgert and Karen Kelley for their perseverance in typing this manuscript. CGS 10746B was generously donated by Dr. Richard Lovell of Ciba-Giegy Pharmaceutical Company and isradipine was generously donated by Sandoz Pharmaceuticals. This work was funded entirely by NIDA grant No. 3591.

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