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Comparison of Behavioral Effects of Cathinone, Amphetamine and Apomorphine

MARTIN D. SCHECHTER,* JOHN A. ROSECRANS† AND RICHARD A. GLENNON‡

**Department of Pharmacology, Northeastern Ohio, Universities College of Medicine Rootstown, OH 44272*
and the †Departments of Pharmacology and ‡Pharmaceutical Chemistry Medical College of Virginia, Richmond, VA 23298

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SCHECHTER, M. D., J. A. ROSECRANS AND R. A. GLENNON. *Comparison of behavioral effects of cathinone, amphetamine and apomorphine.* PHARMACOL BIOCHEM BEHAV 20(2) 181–184, 1984.—Rats were trained to discriminate between the stimulus properties of 0.6 mg/kg ±-cathinone and its vehicle in a two-lever, food-motivated operant task. Once trained, rats showed a dose-related decrease in discriminative performance with lower cathinone doses and analysis of the dose-response curve indicated an ED50 of 0.24 mg/kg. Administration of 0.2–0.8 mg/kg *d*-amphetamine produced a pattern of responding similar to that observed with cathinone. The dose-response curve after *d*-amphetamine was shown to be parallel to that of cathinone and the ED50 generated was 0.21 mg/kg. Thus, cathinone was equi-potent to *d*-amphetamine in this behavioral paradigm. In contrast, administration of 0.16–0.32 mg/kg apomorphine produced intermediate results. The results suggest a common site and/or mechanism for action of ±-cathinone and *d*-amphetamine.

Drug discrimination Cathinone Amphetamine Dopamine Apomorphine Stimulus properties of drugs

CATHINONE has been established as the active psychostimulant component of the khat plant (*Catha edulis* Forsk.) [21] and it is similar in structure and pharmacological activity to amphetamine [1]. Indeed, the central effects of khat-chewing, seen in inhabitants of East Africa and the Arabian peninsula, include euphoria, excessive talkativeness, increased ability to concentrate, excitement, alleviation of hunger and insomnia [3–5, 15]. To date, however, little research has been conducted on the central effects of cathinone although it has been found that, in rats, cathinone (like amphetamine) increases oxygen consumption, inhibits food intake, prolongs reaction time on a hot plate, stimulates the hind limb reflex, and elicits stereotyped behavior [8, 12, 23]. In behavioral experiments, it has been shown that cathinone increases spontaneous motor activity in rats and mice similar to the increases produced by amphetamine [9, 12, 22]. The effect of cathinone on operant responding in rats again parallels effects produced by amphetamine with increases in response rates and corresponding decreases in reinforcement rates, as well as shortening of the inter-response time intervals [22]. It has also been demonstrated, in monkeys trained to respond on a multiple FI-5 minute, FR-30 schedule of food reinforcement, that cathinone produces amphetamine-like effects characterized by dose-related decreases in responding. In this study the potency of (+)-amphetamine was found to be twice that of (±)- and (−)-cathinone [19].

Thus, previous results of behavioral experimentation with cathinone clearly suggests that it is a potent psychoactive agent. It is the purpose of the present research to directly examine discriminative stimulus effects of cathinone by training rats to discriminate (±)-cathinone from its vehicle (saline). The drug discrimination procedure consists of training animals to discriminate a drug state from a non-drug (or vehicle) state and typically involves training rats to press one of two available levers in an operant chamber in the presence of the drug state for positive food reinforcement. In the non-drug state, presses on the other lever produce reinforcement. Thus, each of the two stimuli is associated with responding on a particular lever. When discrimination is attained, tests with other drugs can be conducted and this testing can provide information concerning the similarity of stimulus properties of other drugs to that of the training drug or the mechanisms which might be involved in the action of the training drug. In the present study, substitution of cathinone for the two dopaminergic agonists apomorphine and *d*-amphetamine was tested to investigate the similarity between these three drug states.

METHOD

Subjects

The subjects were 8 experimentally-naive male ARS/Sprague-Dawley rats weighing 330–450 g at the beginning of experimentation. They were housed in individual cages and their weights were adjusted, by daily rationing of commercial rat chow, to approximately 80 to 85% of their expected free-feeding weights as determined by daily weighing of 2 control free-feeding rats purchased from the supplier (Zivic-Miller, Allison Park, PA) at the same time. Water was continuously available in the home cages kept in a room at a

controlled temperature (20–22°C) with daily cycle of 12 hr (0600–1800) light and 12 hr (1800–0600) dark.

Apparatus

The experimental space consisted of 4 identical standard rodent operant test cages (Lafayette Instruments Corp., Lafayette, IN) each equipped with 2 levers located 7 cm apart and 7 cm above the grid floor. A food pellet receptacle was mounted 2 cm above the grid floor at an equal distance between the 2 levers. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and a 9 W house-light. Solid-state programming equipment (LVB Corp., Lehigh Valley, PA) was used to control and record the sessions and was located in an adjacent room.

Discrimination Training

Training was based upon procedures described elsewhere [2,18]. There were 2 training phases. In the first phase, food-deprived subjects were trained to lever press on both levers for food reinforcement (45 mg Noyes pellets) on a fixed ratio 10 (FR10) schedule. The saline-appropriate lever was activated first for all subjects. The rats were trained, by successive approximations, to press this lever on an FR1 schedule. The fixed ratio requirement was progressively increased, in daily 15 min sessions, over 10 days until an FR10 schedule was achieved. Throughout lever press training, rats received daily intraperitoneal (IP) injections of saline (0.9% sodium chloride) 15 min prior to being placed into the two-lever operant box. Immediately following attainment of the FR10 schedule after saline administration, the opposite lever was activated and rats were trained on a FR1 schedule after the IP administration of an equal volume of saline (1 ml/kg body weight) containing 0.6 mg/kg (±)-cathinone. Daily sessions of 15 min were continued over 8 days with cathinone administration until an FR10 schedule was attained. In order to minimize effects due to any possible position preference, the 8 rats were divided into 2 groups. For one group, responding on the left lever was reinforced by delivery of food pellets in every session following drug injection, whereas the other group was reinforced for responding on the right lever following drug injections. Responses on the opposite lever were reinforced with food pellets after saline injections and the running order was randomized amongst the 4 chambers.

Phase II discrimination training then began. Subjects were trained 5 days per week with alternation of reinforcement proceeding in a pseudo-random sequence. Thus, in each 2 week period, there were 5 days with drug lever (D) correct and 5 days with saline lever (S) correct. The pattern was D,S,S,D,D; S,D,D,S,S. The training criterion was reached when the animal selected the appropriate lever, according to the drug state imposed, on 8 of 10 consecutive sessions.

Dose-Response Relationships

After the rats attained the discriminative training criterion, testing and training sessions of 15 min duration with alternating administrations of 0.6 mg/kg cathinone and saline were continued on Mondays, Wednesdays and Fridays. This procedure endeavored to insure and maintain behavioral discrimination of the training drug conditions. It was intended that if a rat was observed to make more than 2 incorrect lever selections before making 10 correct selections in any of 10 consecutive maintenance sessions, the data on that rat's performance would be deleted from the results. This, however, did not occur. On Tuesdays and Thursdays, the rats were injected IP with different doses of cathinone than used for initial training, i.e., 0.3 and 0.15 mg/kg and, 15 min later, they were placed into the experimental chamber and were allowed to lever press, in extinction, until 10 responses were made on either lever. To preclude training at a cathinone dose different than the 0.6 mg/kg dose employed to train the animals, the rats were immediately removed from the experimental chamber upon making 10 responses on either lever. Each of the two lower doses of cathinone were tested in each animal on two occasions with each test preceded both by a 0.6 mg/kg cathinone and a saline maintenance session. The lever first pressed 10 times was designated as the "selected" lever.

Generalization to Other Dopamine Agonists

Once the dose-response relationship for cathinone was established various doses of the dopaminergic agonists apomorphine (0.16–0.32 mg/kg) and *d*-amphetamine (0.2–0.8 mg/kg) were administered IP and, 15 min later, the ability of the animals to press the lever previously associated with cathinone was tested. Each of the three doses of these drugs were tested on two occasions preceded by both a cathinone and saline maintenance session and the animals were immediately removed upon making 10 responses on either lever.

Drugs

(±)-Cathinone hydrochloride, freshly-prepared apomorphine hydrobromide and *d*-amphetamine sulfate were all dissolved in saline and doses were calculated as base except for cathinine. All drugs were administered IP in an equal volume of 1 ml/kg, 15 min prior to testing, with the identity of the test drugs unknown to the experimenter.

Measurements

The lever pressed 10 times first was designated as the "selected" lever. The percentage of rats selecting the lever appropriate for the training drug was the quantal measurement of discrimination. In addition, the total number of lever presses on both levers made before 10 presses on either lever were counted constitutes the quantitative measurement, i.e., the number of responses on the cathinone-correct lever divided by total responses made prior to 10 responses times 100. The advantages in using both measurements have been discussed by Stolerman and D'Mello [20]. The quantal data for the dose-response experiments were analyzed by the method of Litchfield and Wilcoxon [14] which employs probit vs. log-dose effects and generates ED50's and tests for parallelism.

RESULTS

Acquisition of Discrimination

The 8 rats required a mean (±S.E.M.) of 7.8 (1.4) sessions to criterion performance, i.e., to the first of 8 of 10 consecutive sessions in which the correct lever was selected. All subjects learned the discrimination between cathinone and saline within 30 sessions (15 sessions in each state).

Dose-Response Relationships

Administration of 0.3 and 0.15 mg/kg cathinone to rats

TABLE 1

DOSE-RESPONSE EFFECTS OF (±)-CATHINONE (A) AND TRANSFER TO *d*-AMPHETAMINE AND APOMORPHINE (B)

Treatment	(No. Trials)	Dose (mg/kg)	Quantal	Quantitative (±S.E.M.)
A. Saline	(16)	—	7.1	17.5 ± 3.8
Cathinone	(16)	0.6	92.9	87.4 ± 3.7
	(2)	0.3	68.8	63.7 ± 0.6
	(2)	0.15	25.0	33.8 ± 1.9
B. *d*-Amphetamine	(2)	0.8	100.0	97.6 ± 1.2
	(2)	0.4	93.8	87.0 ± 1.6
	(2)	0.2	50.0	57.6 ± 0.9
Apomorphine	(2)	0.32	43.8	55.4 ± 8.9
	(2)	0.24	50.0	52.5 ± 3.4
	(2)	0.16	62.5	58.9 ± 0.9

trained to discriminate between 0.6 mg/kg cathinone and saline (vehicle) indicated that decreasing doses produced decreased discriminative responding (Table 1A), both in terms of quantal and quantitative measurements.

Transfer of Discrimination to d-Amphetamine

Administration of 0.8 and 0.4 mg/kg *d*-amphetamine produced 100 and 93.8% of quantal discriminative responses on the cathinone-appropriate lever, respectively (Table 1B), whereas 0.2 mg/kg *d*-amphetamine elicited 50% of total first 10 responses on this lever. Application of the method of Litchfield and Wilcoxon [14] to the cathinone and *d*-amphetamine dose-response quantal data indicates an ED50 of 0.24 (95% confidence range: 0.16–0.35) mg/kg for cathinone and an ED50 of 0.21 (0.12–0.34) mg/kg for *d*-amphetamine. Therefore ±-cathinone is equi-potent to *d*-amphetamine in this behavioral paradigm. In addition, the slopes of the two dose-response lines were parallel (log probit analysis; [14]) within statistical limits, i.e., fSR (2.14) > SR (1.93).

Substitution Tests with Apomorphine

Administration of three doses of the dopamine agonist apomorphine produced only intermediate discriminative responding upon the cathinone-correct level with the lowest (0.16 mg/kg) dose producing the largest percentage (62.5%) of cathinone lever responses. Higher doses of apomorphine were precluded from use because of behavioral disruption.

DISCUSSION

The results of the present experiment indicate that a dose of 0.6 mg/kg ±-cathinone can function as a discriminative stimulus in rats and that decreasing doses of cathinone produce dose-related decreases in discrimination performance. Although a previous report [17] indicated that rats trained to discriminate 0.9 mg/kg *d*-amphetamine from saline will respond to ±-cathinone as if they were given *d*-amphetamine, this is the first report of discriminative control with ±-cathinone.

Substitution tests with various doses of *d*-amphetamine indicated that cathinone-trained rats discriminate *d*-amphetamine as cathinone. In light of the fact that cathinone closely resembles the amphetamine molecule, the only difference being that the two hydrogens on the β-carbon of the amphetamine side chain are substituted by an oxygen in cathinone [21], this is not surprising. However, the observation that cathinone is equi-potent to *d*-amphetamine in this behavioral paradigm is at variance with various studies that indicate that *d*-amphetamine is two [7, 17, 19] to five [16] times more potent. In addition, the parallelism of the slopes of the cathinone and *d*-amphetamine dose-response curves suggests that they may be acting via a common site and/or mechanism of action [13]. Biochemical findings further extend this observation showing that cathinone increases dopamine release and turnover like amphetamine [10], and may, thus, be considered an indirect sympathomimetic [11].

The results of substitution tests with apomorphine indicate that cathinone-trained rats do not readily transfer to this drug at the doses tested. Similarly, in rats trained with *d*-amphetamine, tests of generalization to apomorphine have yielded both positive and negative results [2, 6, 18] and these discrepancies were shown to be correlated to the training dose employed [20]. Administration of 1, 2 and 4 mg/kg ±-cathinone to five rats trained to discriminate 0.16 mg/kg apomorphine from saline produced 0, 7.1 and 16.7% apomorphine appropriate responding, respectively (Schechter, unpublished results).

Thus, the qualitative similarity between cathinone and amphetamine has been established in this discriminative behavioral paradigm. Continued research into possible quantitative differences between cathinone and other abused stimulants, such as cocaine and amphetamine, is warranted in light of the abuse potential of excessive consumption of khat [5].

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