Pharmacology Biochemistry & Behavior, Vol. 22, pp. 913–916, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Cathinone, Cocaine and Methamphetamine: Similarity of Behavioral Effects

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Received 19 March 1984

SCHECHTER, M. D. AND R. A. GLENNON. *Cathinone, cocaine and methamphetamine: Similarity of behavioral effects.* PHARMACOL BIOCHEM BEHAV 22(6) 913–916, 1985.—The discriminative stimulus properties of (±)-cathinone were tested by training eight rats to discriminate between the interoceptive cues produced by 0.6 mg/kg (±)-cathinone and saline in a food-reinforced, two lever operant task. Doses of cocaine and methamphetamine were observed to transfer to the cathinone cue and all three drugs exhibited decreased discriminative performance with decreasing doses. The ED_{50} for (±)-cathinone, (±)-methamphetamine and cocaine were 0.23, 0.17, and 1.97 mg/kg, respectively, and the three curves were shown to be parallel. These data indicate the possibility of a common mechanism/site of action for these three stimulants, presumably by their actions upon central dopaminergic neurons.

Drug discrimination Dopamine Cathinone Methamphetamine Cocaine Khat Stimulus properties

THE discriminative stimulus properties of psychoactive drugs in experimental animals have been the focus of four recent textbooks [5, 6, 14, 21] and procedures for assessing these properties have proven to be sensitive, specific, and stable in determining the mechanism of drug action in the central nervous system [10,25]. Within this behavioral paradigm, which is essentially a drug detection procedure, animals are trained to discriminate between drug and non-drug (vehicle or saline) using operant techniques. The usefulness of this procedure in determining mechanism of drug action is contingent upon the animal subjects' learning and retaining the acquired discriminative stimulus, i.e., the interoceptive cue produced as a consequence of drug administration. Once the discrimination is attained and maintained, studies can subsequently be conducted to ascertain the ability of the animals to discriminate other drugs.

The khat plant is indigenous to East Africa where, according to record, fresh khat leaves have been chewed for hundreds of years [1]. Khat-chewing constitutes a serious abuse problem in numerous countries, a problem which has been recognized by international organizations since the time of the League of Nations [8,31]. Cathinone has been established as an active psychostimulant component of the khat plant and it is similar in structure and pharmacological activity to amphetamine [3]. Thus, the central nervous system effects of this agent include euphoria, excessive talkativeness, increased ability to concentrate, excitement, elimination of hunger, and insomnia [13]. Furthermore, several behavioral and biochemical studies have indicated the similarity between cathinone and amphetamine [17–19].

The ability of (±)-cathinone to act as a discriminative stimulus in rats has recently been reported by this and other laboratories [11, 26, 27]. The purpose of the present study was to train rats to discriminate the interoceptive cue produced by (±)-cathinone and to determine the ability of other known drugs of abuse to substitute for cathinone in this behavioral paradigm. In addition, the experimentation sought to investigate the possible commonality of the mechanism of action between these agents and to determine the potency ratios between them.

METHOD

Subjects

The subjects were eight male ARS/Sprague-Dawley rats used in a previous series of experiments [11,27]. They were housed in individual cages and their weights were adjusted, by daily rationing of commercial rat chow, to approximately 80–85% 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 cage, kept in a room at a controlled temperature (20–22°C) with daily cycle of 12 hours (0600–1800) light and 12 hours (1800–0600) dark.

Apparatus

The experimental space consisted of four identical standard rodent operant test cages (Lafayette Instruments Corp., Lafayette, IN) each equipped with two levers located 7 cm apart and 7 cm above the grid floor. The 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 [27]. There were 2 training phases. In the first phase, food-deprived subjects were trained to lever press on both levers for food delivery (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 minute 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 minutes prior to being placed into the two-lever operant box. Immediately following attainment of the FR10 performance 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/ml (±)-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 injections, 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 day per week with alternation of correct lever assignment proceeding in a pseudo-random sequence. 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 pressed the appropriate lever 10 times first, according to the substance administered, on 8 of 10 consecutive sessions.

Generalization Studies

After the rats attained the discriminative training criterion, 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 was meant to insure and maintain discrimination to the training drug conditions. On Tuesdays and Thursdays, challenge compounds, i.e., drugs other than cathinone or doses of cathinone other than the 0.6 mg/kg training dose, were administered 15 min before placing animals into the operant chamber. During these sessions, animals were allowed to lever press in extinction until 10 responses were made on either lever and they were immediately returned to their home cages to preclude training with a drug/dose different from that of 0.6 mg/kg cathinone employed in training.

Measurements and Statistics

The lever pressed 10 times first during maintenance and challenge sessions was designated as the "selected" lever. The percentage of rats selecting the lever appropriate for the training drug constitutes 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

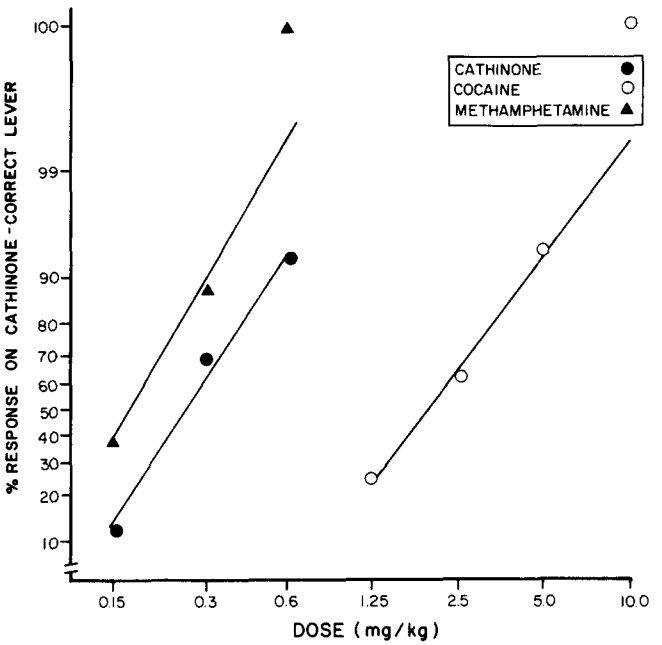

FIG. 1. Quantal dose-response relationships for cathinone, cocaine, and methamphetamine. Ordinate: Percentage of rats (n=8) making first lever selection upon the cathinone-correct lever on probit scale. Abscissa: log dose in mg/kg. All values, except 0.6 mg/kg cathinone training (maintenance) dose, represent two determinations each preceded by a saline and 0.6 mg/kg cathinone maintenance session.

number of responses on the cathinone-correct lever divided by total responses made prior to 10 responses, times 100. This measurement was calculated separately for each rat and, subsequently, means for all rats were taken. This latter measurement has distinct advantages over previously used methodologies as described by Stolerman and D'Mello [29] and allows for statistical manipulations that are not possible with the quantal measurement, which is, in fact, an all-or-none response [34]. The quantal data were analyzed by the method of Litchfield and Wilcoxon [24] which employs probit vs. log-dose effects and generates ED_{50} values and tests for parallelism between dose-response curves.

RESULTS

Maintenance sessions with 0.6 mg/kg (±)-cathinone produced 92.9% of (quantal) responses upon the cathinone-correct lever, whereas administration of an equal volume of saline, administered on alternate days, produced 4.2% responses on this lever (or 95.8% first responses upon the saline-correct lever). Decreasing doses of cathinone resulted in decreasing discriminative performance with the 0.3 mg/kg dose producing 68.8% cathinone responses and 0.15 mg/kg resulting in 12.5% of first responses on this lever. The ED_{50} for cathinone was determined by the probit method [24] to be 0.23 (95% confidence range: 0.15–0.35) mg/kg.

The cathinone-trained rats were observed to completely substitute 10.0 mg/kg cocaine and 0.6 mg/kg of racemic methamphetamine for cathinone. Decreasing doses of both cocaine and methamphetamine produced decreasing quantal responses upon the cathinone-correct lever. The ED_{50} of cocaine was found to be 1.97 mg/kg (95% confidence range:

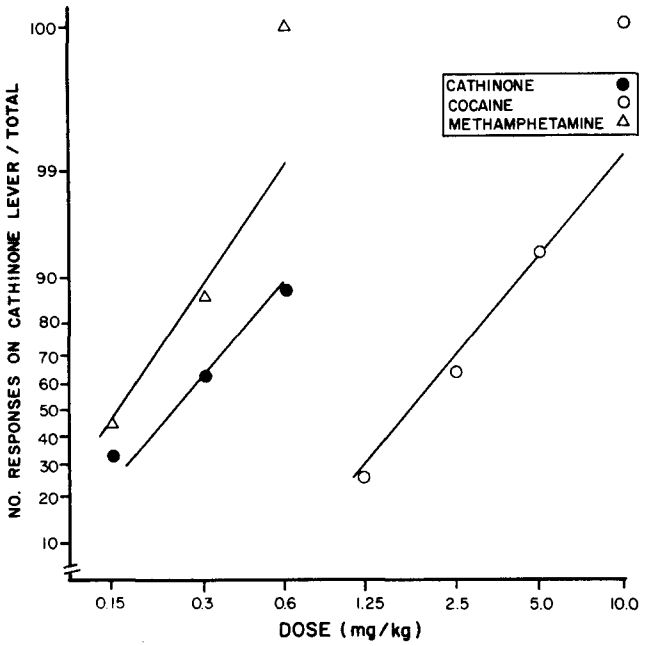

FIG. 2. Quantitative dose-response relationships for cathinone, cocaine, and methamphetamine. Ordinate: Mean number of responses on cathinone-correct lever divided by total responses made prior to 10 presses on either lever, times 100 on probit scale. Abscissa: log dose in mg/kg.

1.27–3.07 mg/kg) and for methamphetamine, 0.17 mg/kg (0.10–0.26 mg/kg). Graphical representation of the quantal dose-response data using best-fitted curves [24] appears in Fig. 1. Tests for parallelism of these lines [24] indicate that they are not significantly different (calculated t for cocaine = 2.73 and for methamphetamine = 0.18 vs. critical t = 4.30) and, therefore, parallel within 95% confidence limits. Lastly, methamphetamine was observed to be slightly more potent than cathinone in this behavioral paradigm, whereas cathinone was approximately 8 times more potent than cocaine.

Graphical representation of the quantitative measurements (see the Method section) appears in Fig. 2. As with the quantal data, decreasing doses of each drug produced decreasing quantitative responding and the dose-response lines are parallel.

DISCUSSION

The originally-reported [27] cathinone discrimination was maintained throughout the course of this study; the rats consistently responded upon the cathinone-appropriate lever when administered 0.6 mg/kg (±)-cathinone, whereas saline administration produced less than 5% of quantal discriminative responses on the same lever. Administration of the highest doses of both cocaine (10 mg/kg) and methamphetamine (0.6 mg/kg) produced 100% responding upon the cathinone-correct lever and decreasing doses of each resulted in decreased discrimination both in quantal and quantitative measurements. Previous investigation in rhesus monkeys trained to discriminate intramuscular administration of 0.25 mg/kg cocaine indicated that the discriminative stimulus properties of both (+)-amphetamine and (−)-cathinone are similar to cocaine in that at least one dose of these two drugs controlled more than 90% cocaine lever responding [7].

The present observation regarding the parallelism of the three dose-response curves for both quantal and quantitative discriminative measurements suggests the possibility of a common mechanism and/or site of action [23]. Indeed, numerous behavioral studies have indicated that cathinone is (+)-amphetamine-like in its ability to increase activity [9], decrease food intake [9], reduce food-reinforced responding [28] and maintain self-administration [28], and various neurochemical studies indicate a common effect [18, 19, 32]. Furthermore, in a drug discrimination study similar to the present report, (±)-cathinone produced responding on a lever previously reinforced following (+)-amphetamine administration [26].

The comparisons of cathinone with cocaine and methamphetamine confirm that, in sufficient doses, these drugs can substitute for one another as far as drug-produced stimulus control is concerned. This extends the findings of other reports indicating generalization between cocaine and amphetamine in rats, cats, pigeons, and rhesus monkeys [2, 4, 15, 20, 22]. Furthermore, D'Mello and Stolerman [30] found that (+)-amphetamine was 6–9 times more potent than cocaine in the rat and its discriminative properties varied as a function of training dose [29]. In the present study, methamphetamine was observed to be equipotent to cathinone and both were approximately 8 times more potent than cocaine. The comparison between quantal and quantitative measurements indicated that the two methods of expressing discriminative performance were in very close agreement for the dose-response functions of the three drugs tested. This confirms a previous report by Stolerman and D'Mello [29].

The most parsimonious explanation for the commonality of the discriminative stimulus cues between these three stimulants resides in a common effect upon dopaminergic neurons. Thus, amphetamine and cathinone have been reported to both release and block the reuptake of dopamine with racemic cathinone being less potent and efficacious [32,33] and cocaine has recently been reported to have a similar effect upon mesolimbic dopamine neurons [12]. A similar conclusion was reached by Huang and Wilson after analyzing generalization results between rats trained to discriminate either 1.0 mg/kg (±)-cathinone, 0.9 mg/kg (+)-amphetamine or 7.5 mg/kg cocaine from saline [16].

ACKNOWLEDGEMENTS

The authors would like to thank Dr. John A. Rosecrans for his creative input and Ms. Denise M. Lovano for her technical output. Funded by NIDA grant No. 03591-01.

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