Pharmacology Biochemistry & Behavior, Vol. 34, pp. 289–292. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Temporal Parameters of Cathinone, Amphetamine and Cocaine

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Received 24 March 1989

SCHECHTER, M. D. *Temporal parameters of cathinone, amphetamine and cocaine*. PHARMACOL BIOCHEM BEHAV 34(2) 289–292, 1989.—Rats were trained to discriminate intraperitoneally administered 0.8 mg/kg l-cathinone from its vehicle in a two-lever operant procedure. The normal injection-to-session interval was fifteen minutes. When tested in session at 2–180 min postadministration, cathinone discrimination was seen to have a rapid onset (5 minutes) and offset (60 minutes). When the same rats were tested with either 0.8 mg/kg *d*-amphetamine or 10.0 mg/kg cocaine at the same postinjection time periods, the peak discriminative generalization to each of these other psychostimulants was observed to be later, i.e., an onset of action at 15–30 minutes with a slightly longer duration of action. The results indicate that cathinone exerts discriminative response control within five minutes of intraperitoneal injection and that it has a shorter duration than amphetamine and cocaine.

Drug discrimination Cathinone Time-course Amphetamine Cocaine Dopamine

CATHINONE is the psychostimulatory component in the leaves of Khat *(Catha edulis)*, a shrub native to Arabia through eastern Africa to the Cape of South Africa, and it has been abused for centuries by Moslem peoples and by the Copts of Ethiopia. The use of cathinone has spread as others have learned of the exhilarating properties of this "flower of paradise" (3). The subjective effects of Khat chewing, which include euphoria, improved intellectual efficiency and alertness, are reminiscent of the effects of both amphetamine and cocaine, and cathinone has been shown, in numerous laboratory studies, to possess pharmacological properties that are analogous to those of amphetamine [see reviews (16,17)]. This relationship to amphetamine is not surprising because of the close similarity between the chemical structures of cathinone and amphetamine, i.e., the only difference between them is that the two hydrogens on the beta carbon of the amphetamine side chain are substituted by an oxygen in cathinone. In regards to cocaine, monkeys trained to press a lever for cocaine injections have been observed to continue to respond at a high rate when cocaine is replaced by cathinone (14).

The behavioral paradigm that employs drug-induced stimulus cues to allow for discriminative responding has been evidenced to be a specific, stable and highly reproducible technique (4) that has resulted in over a thousand publications from 1951 to 1987 (29). Indeed, almost every psychoactive drug tried has been shown to be able to produce discriminative stimuli that control differential responding in laboratory animals; the drugs of importance in the present study have each been reported capable of controlling discrimination. Thus, amphetamine, cocaine and cathinone have been utilized in this behavioral paradigm [see review (31)]. Once drug discrimination is acquired, drugs other than those used in training can be compared with the trained drug in order to assess the degree of generalization between compounds. When tested in this manner, cross-generalization has been shown between cocaine and amphetamine (1, 2, 11, 12, 18, 20, 30), between amphetamine and either cocaine or cathinone (31), and between cathinone and either cocaine or amphetamine (6, 8, 25, 26).

In addition to these generalization studies, there have been some (but fewer) studies concerning the time-course of the discriminative effect with each of these agents. Thus, several investigators have studied the duration of amphetamine's stimulus action in rats trained with amphetamine (13, 15, 18), for that of cocaine in animals trained with cocaine (20) and, more recently, the time-course of cathinone discrimination in rats trained with that psychostimulant (7,23). The purpose of the present series of experiments was to determine the discriminative performance with each of these structurally-similar central stimulants over time in the same animals. Thus, rats were trained to discriminate cathinone and were, subsequently, tested with amphetamine and cocaine with each of the three drugs being tested at numerous postadministration times. In this way, the time-course of generalization between these drugs could be determined.

METHOD

Subjects

Fifteen male Sprague-Dawley rats weighing approximately 270–290 g at the start of the experiments were purchased from Zivic-Miller Laboratories, Allison Park, PA. The animals were housed singly in hanging wire cages in a room maintained at a relatively constant temperature and humidity, and illuminated 12 hr per day (lights on at 0600 hr). Throughout the study, all rats received free access to water while in their home cages and were on a restricted diet of standard laboratory rodent chow to maintain their body weight at 80–85% of ad lib weight as determined by the growth chart supplied by the breeder. All training and testing were

TABLE 1

TEMPORAL EFFECTS OF CATHINONE (0.8 mg/kg) AMPHETAMINE (0.8 mg/kg) AND COCAINE (10.0 mg/kg) IN RATS (n = 15) TRAINED TO DISCRIMINATE CATHINONE FROM VEHICLE

Post Adm. Time (min)	Cathinone		Amphetamine		Cocaine	
	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)
2	11.5[a]	20.8(11.8)	0.0[b]	10.3 (4.5)	33.3	35.3 (1.8)
5	100.0	90.7 (1.2)	43.5[c]	43.6 (2.1)†	45.5[d]	46.3(28.8)
10	93.3	90.0 (9.7)	67.9[b]	64.8 (2.0)*	63.3	64.3(18.1)
15	93.9	89.3 (6.1)	80.0	78.6 (2.7)	80.0	69.2(24.5)
30	90.0	84.7 (2.2)	90.0	79.3(11.7)	66.7	61.9 (4.5)
45	73.3	67.1 (9.2)	80.0	76.3 (1.1)	56.6	54.2(10.3)
60	16.7	26.6 (8.4)	70.0	67.2 (6.0)†	33.3	42.8(21.0)
90	6.7	11.7 (8.5)	30.0	36.0(12.4)	33.3	37.3(15.5)
120	26.7	33.6(12.3)	13.3	25.7(10.8)	6.6	11.8 (2.5)
180	6.7	14.5(13.2)	0.0	10.1 (7.9)	6.6	9.2 (2.6)

[a–d]Number of rats responding (n) less than number of rats tested (N), n/N = (26[a]/30); (22[b]/30); (23[c]/30); (28[d]/30).

*Significant difference from quantitative measurement after cathinone at same postadministration time; $p<0.05$; †$p<0.01$.

done Monday through Friday of each week.

Behavioral Apparatus

Twelve standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN) were housed in sound-attenuated and fan-ventilated outer shells. Each operant chamber was equipped with two levers mounted 7 cm apart and 7 cm above a metal grid floor. Equidistant between levers and 2 cm above the floor was located a food receptacle. Solid-state programming equipment (Med Associates, E. Fairfield, VT) was located in an adjacent room and was used to record and control the discrimination sessions.

Discrimination Training

At the start of training, one lever in each chamber was designated as the "vehicle lever" and the rats were trained to respond on this lever on a fixed ratio (FR) schedule of 1, i.e., one response resulted in one reinforcement (45 mg Noyes food pellet). Prior to each daily training session, the animals were intraperitoneally (IP) administered 1 ml/kg distilled water and placed into the operant chamber 15 min after injection. Once lever pressing was well-established, the reinforcement contingency was increased incrementally to an FR10 schedule. Next, the rats were trained to press the second lever designated the "cathinone lever," starting with an FR1 schedule of reinforcement, 15 min after the IP injection of an equal volume of distilled water containing 0.8 mg/ml cathinone. The FR1 schedule after cathinone administration was gradually increased to an FR10 reinforcement requirement. Subsequently, every tenth response on the cathinone-correct lever was reinforced on days when the rat was pretreated with cathinone, whereas every tenth response on the opposite lever was reinforced after vehicle injection. In each two-week period, there were five drug (D) and five vehicle (V) days according to the schedule: D-D-V-V-D; V-V-D-D-V. Discrimination sessions were continued until each rat selected the appropriate lever, according to the drug or nondrug (vehicle) state imposed, in 8 of 10 consecutive sessions. To be considered capable of discriminating between cathinone and its vehicle, the rats were required to achieve this 80% performance criterion twice.

Time-Course Testing

Once drug discrimination was well-established, a series of experiments using different injection-to-testing intervals was conducted with the 0.8 mg/kg cathinone used in training. Test days were interspersed between maintenance cathinone and vehicle days so that each time interval postadministration was tested on two occasions; one following 0.8 mg/kg cathinone at 15 min and one following vehicle at 15 min postadministration. On test days, the rat was immediately removed from the operant chamber upon making 10 responses on either of the two levers. Thus, there was no food presentation after 10 responses so as to avoid reinforcement and possible training at times different then used in training, i.e., at 15 min postadministration.

Following postinjection intervals of 2 to 180 min with 0.8 mg/kg cathinone, both amphetamine (0.8 mg/kg) and cocaine (10.0 mg/kg) were administered to the animal on test days at similar postinjection times. The doses of cocaine and amphetamine were previously reported to produce generalization in cathinone-trained rats (8,25). During these tests, the animals were, once again, immediately removed upon pressing one lever 10 times. If, however, the rat did not press one of the levers 10 times within 2 min of being placed into the operant chamber, it was removed. This was necessary on some tests especially at the shorter injection-to-testing intervals of 2, 5 and 10 min. This is reflected in the Results section (superscript a–d in Table 1).

Measurements and Statistics

The data collected in the drug discrimination session are expressed as both quantal and quantitative measurements. Each of the individual measurements provides an indication of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats that selected the cathinone-appropriate lever as their selected lever, i.e., the lever was pressed 10 times first. The quantitative measurement is the number of responses on the cathinone lever divided by the total number of responses on both the cathinone- and vehicle-appropriate lever at the time that the tenth response is made on either lever. This fraction is expressed as a percentage. Unlike the all-or-none quantal measurement, the quantitative measurement accounts for responses on both the selected and unselected levers and, thus, provides a relative measure of the magnitude as well as the direction of lever performance. The advantages in using both types of measurements are more fully discussed by Stolerman and D'Mello (28). The quantitative measurements were compared by an unpaired *t*-test

with $p<0.05$ chosen as the level for significance.

RESULTS

All rats learned to discriminate 0.8 mg/kg cathinone from its vehicle after 36 sessions, i.e., 18 sessions with cathinone and a like number with vehicle. The results of varying the injection-to-testing times with either cathinone, amphetamine or cocaine in animals trained to 0.8 mg/kg cathinone at 15 min postadministration are presented in Table 1. Each of the drugs at each of the postinjection times were tested on two occasions with the exception of the 15 min postadministration time after cathinone which was both the training time and the time used in interspersed maintenance sessions. The left-most column would indicate that at 5 min after the administration of cathinone, the 15 rats pressed the cathinone-appropriate lever first in all (thirty) trials and that this high level of discriminative performance continued until 45 min postadministration when performance dropped to 73.3% of first choice responses. This continued to fall at 60 and 90 min with a slight increase at 120 and a continued decrease at 180 min. The quantal and quantitative ($\pm$SD) measures for the interspersed vehicle maintenance sessions were 1.2 and 5.0 (5.1), respectively. Thus, fifteen minutes after IP administration of vehicle, the rats chose the cathinone-correct lever on 1.2% of all trials or, to look at it differently, they (correctly) chose the vehicle-correct lever on 98.8% of the interspersed vehicle maintenance trials.

The results after 0.8 mg/kg of amphetamine and 10.0 mg/kg cocaine show a somewhat different time-course in that both amphetamine and cocaine are seen to peak later than cathinone, i.e., amphetamine reached its maximum discriminative effectiveness at 30 min postadministration, whereas cocaine peaked at 15 min. Likewise, the offset of amphetamine was longer than cathinone with 70% of first choice lever selections made upon the cathinone-correct lever at 60 min after amphetamine administration. Comparison of quantitative measurements indicates that cathinone produces greater discriminative performance than amphetamine at both 5 and 10 min but the situation is reversed at 60 min postadministration. There was no significant difference in the time-course of discrimination when amphetamine is compared to cocaine.

DISCUSSION

The present series of experiments sought to investigate the effective duration of l-cathinone action by varying the interval between intraperitoneal administration and discriminative testing and to, subsequently, determine the time-course of *d*-amphetamine and cocaine in the same rats. The results indicate that when cathinone is trained at 15 min postadministration, testing rats at 5 to 30 min produced peak discrimination. This is in agreement with previous temporal investigations concerning the discriminative performance of racemic cathinone in that the training dose of 0.6 mg/kg *d,l*-cathinone peaked at 15 min and dissipated to 40% correct responding at 90 min (23) and 2 mg/kg *d,l*-cathinone, trained at 15 min IP, which similarly peaked at the training time with 33.3% responding at 60 min and 0% at 2 hr postadministration (7). An area of surprise with the present time-course data was the errorless discrimination at 5 min postadministration of cathinone. This would indicate a very rapid onset of discrimination as has previously been shown to occur in rats, trained at a presessions injection interval of 15 min, with 1.0 mg/kg *d*-amphetamine (27). In that study, the onset of effect was reported to be quite rapid with approximately 20% amphetamine-appropriate responding occurring at 2 min and a peak effect of over 90% seen at 5 min. These authors reference a similar 5-min peak central effect of amphetamine after IP administration in a single unit recording study (10). Another area of interest is the apparent slight increase in discriminative performance seen at 120 min postadministration, i.e., at 90 and 180 min discriminative responding with cathinone was essentially saline-like, whereas at 120 min it rose to 26.7%. The possibility exists that *l*-cathinone is metabolized to an active product, namely *d*-cathine, which has been shown to have a delayed onset (16) and to be active in this discriminative task (5). Recent investigations in this laboratory using brain dialysis techniques to determine the degree of dopaminergic release after cathinone administration have shown a similar "burst" at approximately the same postcathinone administration time (Pehek *et al.*, in preparation).

Previous reports using the discriminative paradigm have indicated that amphetamine will produce cathinone-like effects in rats trained to discriminate either 2 mg/kg (7) or 0.6 mg/kg (26) of racemic cathinone. In the present study, amphetamine was shown to produce a cathinone-appropriate response of 80% at 15, 30 and 45 min postadministration with a peak effect at 30 min. When compared to the discriminative performance of cathinone at 5 and 10 min postadministration, amphetamine was shown to produce a significantly slower onset than cathinone (Table 1). In addition, at 60 min postadministration, amphetamine produced a significantly greater discriminative performance than did cathinone at the same postadministration time indicating a longer offset and duration of action. Other laboratories have trained animals to discriminate *d*-amphetamine and tested its duration of action. For example, Kuhn *et al.* (18), employing 1 mg/kg and a 30 min postadministration training time, showed that 30 min was maximal for the amphetamine effect with a saline-like response occurring at 150 min postadministration. Likewise, Huang and Ho (13), using 0.8 mg/kg *d*-amphetamine, reported 88–89% discriminative performance at both 15 and 30 min with a decrease to 45% at 120 min, and Jones *et al.* (15), training with 0.8 mg/kg amphetamine, reported the onset of stimulus properties within 10 min, a maximal effect obtained by 15–30 min and minimal or absent stimulus effects at 120–240 min postinjection. Biochemical studies had previously shown that tissue and plasma levels of *d*-amphetamine following doses between 0.25 and 8 mg/kg administered intraperitoneally reach maximum levels in less than 30 min for all doses (21). These levels declined to about 50% at one hour, 20% at 2 hr and 2% at 8 hr. Furthermore, analysis of radioactive amphetamine after IP administration produced rapidly increasing concentrations that reached a peak effect within 15 to 20 min and then declined with a half-life of approximately 1 hr (19).

Like amphetamine, cocaine has been shown to produce cathinone-appropriate responses in rats trained to cathinone (8,25). In the present study, the generalization was seen to be maximal at 15 min postadministration and the time-course of cocaine was not significantly different from that seen with amphetamine. When 10 mg/kg cocaine was trained at 15 min in rats, discrimination was seen to decrease to 67% at 60 min, 33% at 120 min and 11% at 240 min (20). Biochemical evidence indicates that the elimination half-life of cocaine in rats is approximately 20 min (22).

The cross-generalization of each of the three psychostimulants (see Introduction) may best be explained by the probability that they all act by similar mechanisms in the brain. Thus, amphetamine (31), cocaine (20) and cathinone (24) have individually been shown to rely upon dopaminergic mechanisms in the brain for the expression of their discriminative stimulus properties. The slight difference in the onset and offset of cathinone when compared to both amphetamine and cocaine would indicate the possibility that they may differ in subtle ways as has recently been evidenced by the ability of rats to be trained to discriminate between 1 mg/kg amphetamine and 5–12.5 mg/kg cocaine (9).

ACKNOWLEDGEMENTS

The author would like to express his sincere gratitude to Ms. Denise

McBurney for her continued expertise in all aspects of the present experimentation. Funded entirely by NIDA (Grant #03591) which also provided the cathinone.

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