Pharmacology Biochemistry & Behavior, Vol. 19, pp. 145–148, 1983.

BRIEF COMMUNICATION

The Discriminative Stimulus Properties of Cocaine in the Rhesus Monkey

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Received 8 November 1982

GARZA, R. DE LA AND C. E. JOHANSON. *The discriminative stimulus properties of cocaine in the rhesus monkey.* PHARMACOL BIOCHEM BEHAV **19**(1) 145–148, 1983.—Three rhesus monkeys were trained to discriminate IM injections of cocaine (0.25 mg/kg) from saline under conditions where responding was maintained on one of two levers under a fixed-ratio 30 schedule of food delivery. The ability of other doses of cocaine and other compounds to substitute for the training dose of cocaine in controlling cocaine-appropriate responding was assessed. Cocaine (0.008–0.5 mg/kg), *d*-amphetamine (0.03–0.25 mg/kg) and *l*-cathinone (0.03–0.5 mg/kg) produced dose dependent increases in the percent of cocaine-appropriate responding in test sessions. At the highest doses tested, these three compounds produced more than 90% cocaine-appropriate responding suggesting that they share discriminative stimulus properties. When nicotine (0.125–16 mg/kg) and procaine (0.06–8.0 mg/kg) were tested, some of the monkeys responded 90% or more on the cocaine-appropriate lever; in other cases there was a trend towards generalization at lower doses but when higher doses were administered, responding was suppressed. These data suggest that these two compounds have discriminative stimulus properties which differ to some extent from cocaine. Finally, when pentobarbital (2–16 mg/kg) was administered, responding occurred on the saline-appropriate lever indicating that this drug does not share the discriminative stimulus properties of cocaine.

Cocaine Rhesus monkey Drug discrimination

A DRUG can function as both a reinforcing and a discriminative stimulus. Although the reinforcing properties of cocaine have been studied extensively particularly in rhesus monkeys [11], relatively few experiments have evaluated the discriminative stimulus properties of cocaine in primates. In rats and pigeons, the discriminative stimulus effects of cocaine have been shown to be pharmacologically specific since the administration of other psychomotor stimulants such as *d*-amphetamine as well as norcocaine, a metabolite of cocaine, results in cocaine-appropriate responding [3, 6, 9]. Conversely, many compounds such as chlordiazepoxide and LSD that are not pharmacologically related to cocaine do not produce cocaine-appropriate responding in these species [3, 6, 7, 8].

Although experiments with primates have yielded somewhat comparable results, only limited data are available. For instance, an experiment using squirrel monkeys found that cocaine can function as a discriminative stimulus in controlling food-maintained responding but no other drugs were evaluated [14]. In the only experiment which has been conducted using rhesus monkeys, intravenous cocaine was an effective discriminative stimulus in the two monkeys tested [1]. When other drugs were tested, however, there were inconsistencies between monkeys and the results were not always pharmacologically specific. The present study was designed to extend these findings on the discriminative stimulus properties of cocaine in the rhesus monkey and to continue to evaluate the similarity of other central nervous system drugs.

METHOD

Animals

Three experimentally naive female rhesus monkeys (8084, 8085, 8086) weighing between 4 and 6 kg were used in this study. The monkeys were maintained at 85% of their free

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feeding weights during the course of the experiment. Vitamins and fruit were provided as dietary supplements. Water was available ad lib.

Apparatus

Each monkey was housed in a sound attenuating wooden cubicle (inside dimensions: 70×80×70 cm) that served as the experimental space. Each cubicle was equipped with a fan for ventilation and masking extraneous sounds. Mounted on the inside front door of the cubicle were two metal boxes (12.5×15×10 cm) located 23 cm apart. Each box contained a response lever (PRL-001, BRS/LVE, Beltsville, MD, and four white lights located above the lever. The cubicle could be illuminated by a white overhead light.

Each monkey wore a stainless steel harness connected to a spring arm 42 to 47 cm long (E & H Engineering, Chicago, IL). The spring arm was attached to the back of the cubicle allowing the monkey relatively unrestrained movement within the cubicle. Cables connected the experimental cubicle to solid state programming and recording equipment located in an adjacent room.

Procedure

A two lever discrimination procedure was employed with injections given 10 min presession. Following an intramuscular injection of 0.25 mg/kg cocaine, responding on one lever resulted in the delivery of a 1 g food pellet (P. G. Noyes, Lancaster, NH). Following an intramuscular injection of saline, responding on the alternative lever resulted in the delivery of a food pellet. For monkey 8085 and 8086, the left lever was associated with cocaine and for monkey 8084 the right lever was associated with cocaine. For each monkey, saline was associated with the alternative lever. Following either injection, responding was maintained under a fixed ratio 30 schedule on the appropriate lever and each session terminated either after 50 reinforcers were obtained or 30 min had elapsed, whichever came first. Incorrect responses reset the FR 30 requirement on the correct lever. Cocaine and saline sessions alternated daily in a semirandom sequence with the restriction of no more than two consecutive sessions with cocaine or saline injections. Training was continued until six consecutive sessions occurred with more than 90% of total session responding on the correct lever and less than 30 responses were emitted on the incorrect lever before the delivery of the first reinforcer.

When these criteria were met, testing sessions were begun to determine whether other doses of cocaine and other drugs would substitute for the training dose of cocaine in controlling responding. Cocaine and saline training sessions were intermixed with testing sessions in a six day sequence. Each test session was preceded by two training sessions, one with saline and one with cocaine. Each test dose was generally tested twice and was preceded once by cocaine and once by saline. Therefore, each 6-day sequence consisted of two cocaine, two saline and two test sessions. If the criteria established were not met during the training sessions, additional training sessions were added. During testing, both levers were made operational i.e., food was delivered following responding on either lever. Each dose response function for a given compound was completed before another compound was tested.

All three monkeys were tested initially with cocaine (0.008–0.5 mg/kg), and then *d*-amphetamine (0.03–0.25 mg/kg), *l*-cathinone (0.03–0.5 mg/kg) and procaine (0.06–8.0 mg/kg) were tested in mixed order. In two monkeys (8085, 8086), the cocaine dose-response function was repeated followed by tests with nicotine (0.125–16 mg/kg) and pentobarbital (2–16 mg/kg). The third monkey (8084) died before these last two drugs could be tested from causes unrelated to the experiment.

Drugs

Cocaine HCl, and *d*-amphetamine sulfate were obtained from the National Institute on Drug Abuse. The United Nations Narcotics Laboratory furnished cathinone HCl. Nicotine tartrate was kindly provided by Dr. Everett May of the Medical College of Virginia. Sodium pentobarbital and procaine HCl were obtained commercially. All drugs were dissolved in physiological saline and doses are expressed as the salt. Injection volumes were less than 1 ml.

RESULTS

All monkeys responded throughout the experiment on the appropriate lever during training sessions above the 90% level following both cocaine and saline injections. When the dose of cocaine was decreased during test sessions, there was a dose-related decrease in cocaine-appropriate responding during the session (Fig. 1). These initial dose-effect functions were similar for monkeys 8084 and 8086 but monkey 8085 was less sensitive to the stimulus effects of cocaine. While the second determination of the cocaine dose-effect function was similar to the first one for 8085, it was shifted to the right for 8086 (Fig. 1). The dose effect functions for *d*-amphetamine and *l*-cathinone were almost identical and the highest dose of each compound produced 100% cocaine-appropriate responding.

Rates of responding following the administration of cocaine, *d*-amphetamine and *l*-cathinone are shown in Fig. 2. For monkeys 8084 and 8085, there were decreases in rates as the doses were increased but even at the highest doses, these decreases were small. For monkey 8086, there was a tendency for rates of responding to increase as the dose of cocaine and cathinone increased. With amphetamine and during the second determination with cocaine, rates for all doses were similar to those following saline. Comparing Figs. 1 and 2 it can be seen that in many instances, monkeys 8084 and 8085 responded on the cocaine lever at criterion levels at doses that had little if any effect on rates of responding. For monkey 8086, rates at these doses were either increased or unaffected.

Both procaine and nicotine produced inconsistent patterns of cocaine lever responding across monkeys (Fig. 1). Monkeys 8085 and 8086 responded above 90% on the cocaine lever at the highest dose of procaine. For monkey 8084, the maximum level of cocaine-appropriate responding was 40% following a dose of 1.0 mg/kg. However, this monkey was particularly sensitive to the rate-decreasing effects of procaine and the next higher dose, 2 mg/kg, totally suppressed responding. Since the other two monkeys also did not respond on the cocaine-appropriate lever at a dose of 1.0 mg/kg, this sensitivity may have prevented an adequate evaluation of procaine's discriminative stimulus effects in monkey 8084.

Monkey 8085 responded above 90% on the cocaine lever at the highest dose of nicotine but for monkey 8086, the maximum level of cocaine-appropriate responding following doses of nicotine which did not suppress responding was

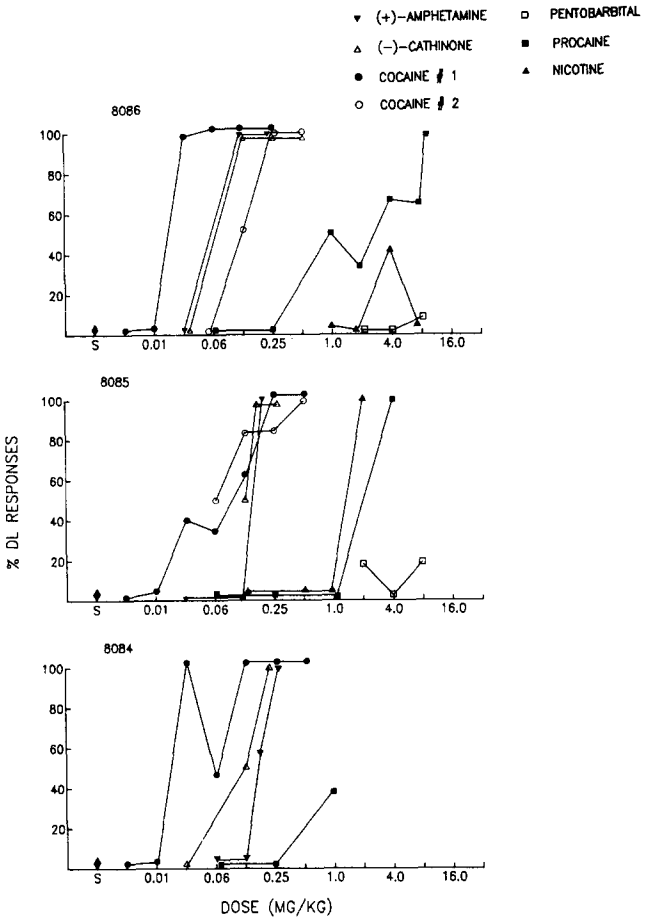

FIG. 1. The percentage of cocaine-appropriate responses are plotted as a function of dose for each compound. The point above saline (S) is the mean of all the saline test days obtained during the determination of each dose response function.

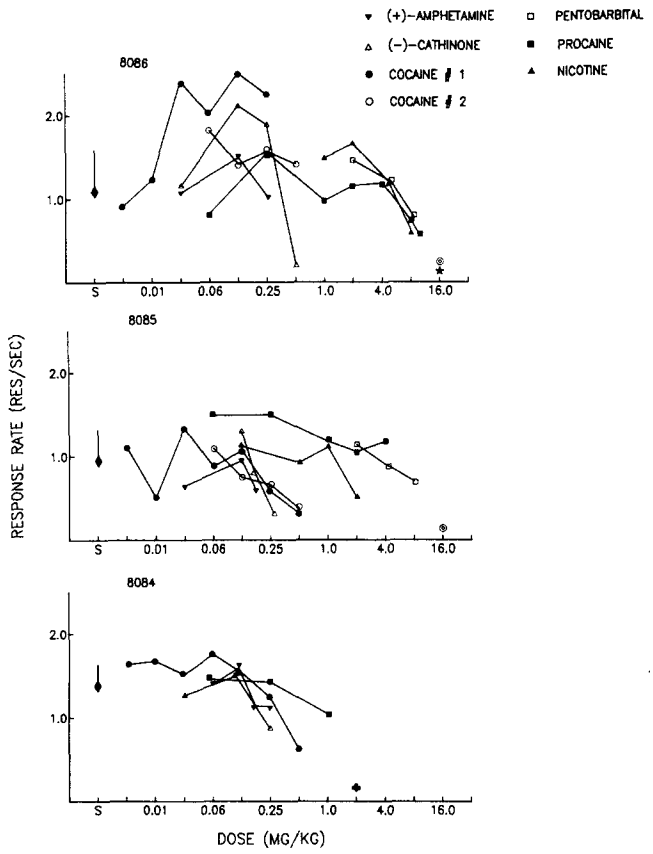

FIG. 2. Response rate represents the total number of responses emitted on both levers divided over the session time in seconds. The point above saline (S) is the mean of the response rates of all the saline test days obtained during the determination of each dose response function. The line above the mean is the standard deviation of the mean. The symbol above a particular dose indicates: (*) that nicotine suppressed the behavior of the monkey during the test session; (◉) that pentobarbital suppressed the behavior of the monkey during the test session; (+) that procaine suppressed the behavior of the monkey during the test session.

40%. For both monkeys, pentobarbital controlled less than 20% cocaine-appropriate responding (Fig. 1) and rates of responding were markedly reduced at 16 mg/kg (Fig. 2).

DISCUSSION

The results of this experiment show that cocaine administered intramuscularly can function as a discriminative stimulus controlling lever responding in the rhesus monkey. Similar results have been reported by Ando and Yanagita [1] with rhesus monkeys using a different procedure. In that experiment, the IV administration of cocaine at a dose as low as 0.05 mg/kg controlled 80% cocaine-appropriate responding. In the present experiment, only doses of 0.25 mg/kg or more consistently controlled criterion levels of cocaine-appropriate responding. Nevertheless, there were two monkeys who at least initially responded at criterion levels at a dose of 0.03 mg/kg. However, when one of the two monkeys was retested (8086), the second determination of the cocaine dose-response function was shifted to the right.

The discriminative stimulus properties of both *d*-amphetamine and *l*-cathinone were similar to those of cocaine in that at least one dose of the two compounds controlled more than 90% cocaine lever responding. The doses of all three of these psychomotor stimulant compounds that were effective in producing cocaine lever responding were similar. In contrast, many investigators have found *d*-amphetamine to be more potent than cocaine in producing cocaine-appropriate responding in rats and pigeons [2, 4, 7, 12]. On the other hand, Ando and Yanagita [1] showed amphetamine and cocaine to be similar in potency in one monkey. In the second monkey amphetamine appeared less potent but only produced 60% cocaine-appropriate responding at the highest dose tested.

The local anesthetic procaine was not found to substitute for cocaine in a consistent manner; two monkeys responded on the cocaine-appropriate lever above the 90% criterion level whereas one monkey responded a maximum of 40%. However, it was not possible in this monkey to test doses of procaine (4–10 mg/kg) which resulted in cocaine-appropriate responding in the other two monkeys because a dose as low as 2 mg/kg suppressed responding. Inconsistent patterns of

procaine substitution have also been reported by Jarbe [6] in pigeons and McKenna and Ho [8] in rats but in other studies there was no generalization [3,5] suggesting that the discriminative stimulus effects of cocaine and procaine may not be equivalent. On the other hand, Woolverton and Balster [19] found that cocaine substituted for procaine in rats trained to discriminate procaine from saline which may indicate that the discriminative stimulus effects of cocaine and procaine can be asymmetrical.

Nicotine was found to produce an inconsistent pattern of cocaine-appropriate responding. Similar results were found by Ando and Yanagita and other drug discrimination experiments in rats also have suggested that nicotine and *d*-amphetamine are only partially related [10]. These findings suggest that nicotine may share some, but not all, the properties of the psychomotor stimulants. Pentobarbital failed to substitute for cocaine during test sessions i.e., neither monkey responded on the cocaine-appropriate lever above the 20% level. This finding suggests that the method used in this study has pharmacological specificity since a drug in the sedative class did not produce any cocaine stimulus effects.

In summary, cocaine was shown to be an effective discriminative stimulus controlling responding in the rhesus monkey. The drug class specificity shown in the substitution tests indicates that this method can be useful in classifying compounds in terms of their discriminative stimulus properties related to cocaine.

ACKNOWLEDGEMENTS

This research was supported by a research grant from the National Institute on Drug Abuse (DA 00250) awarded to Charles R. Schuster, Principal Investigator. The authors would like to thank Dr. Schuster for his support and continued guidance. Rene de la Garza was partially supported with a scholarship from CONACYT, Mexico. The authors would like to thank Dr. Olav J. Braenden of the United Nations Narcotics Laboratory for furnishing cathinone and Dr. Inayat Khan, Senior Medical Officer of the Division of Mental Health of the World Health Organization for his assistance in this matter.

REFERENCES

1. Ando, K. and T. Yanagita. The discriminative stimulus properties of intravenously administered cocaine in rhesus monkeys. In: *Stimulus Properties of Drugs: Ten Years of Progress*, edited by F. C. Colpaert and J. A. Rosecrans. Amsterdam: Elsevier/North, 1978, pp. 125–136.
2. Colpaert, F. C., C. J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of cocaine and *d*-amphetamine, and antagonism by haloperidol: A comparative study. *Neuropharmacology* **17:** 937–942, 1978.
3. Colpaert, F. C., C. J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of cocaine: Neuropharmacological characteristics as derived from stimulus generalization experiments. *Pharmacol Biochem Behav* **10:** 535–546, 1979.
4. D'Mello, G. D. and I. P. Stolerman. Comparison of the discriminative stimulus properties of cocaine and amphetamine in rats. *Br J Pharmac* **61:** 415–422, 1977.
5. Huang, D. and M. C. Wilson. Comparative stimulus properties of cocaine and other local anesthetics in rats. *Res Commun Sub Abuse* **3:** 129–140, 1982.
6. Jarbe, T. U. C. Cocaine cue in pigeons: Time course studies and generalization to structurally-related compounds (Norcocaine, WIN 35,428 and 35,065-2) and (+)-amphetamine. *Br J Pharmacol* **73:** 843–852, 1981.
7. Jarbe, T. U. C. Discriminative stimulus properties of *d*-amphetamine in pigeons. *Pharmacol Biochem Behav* **17:** 671–675, 1982.
8. McKenna, M. L. and B. T. Ho. The role of dopamine in the discriminative stimulus properties of cocaine. *Neuropharmacology* **19:** 297–303, 1980.
9. McKenna, M. L., B. T. Ho and L. F. Englert. Generalization of norcocaine to the discriminative stimulus properties of cocaine. *Pharmacol Biochem Behav* **10:** 273–276, 1979.
10. Rosecrans, J. and N. Chance. Cholinergic and non-cholinergic aspects of the discriminative properties of nicotine. In: *Symposium on the Discriminative Stimulus Properties of Drugs*, edited by H. Lal. New York: Plenum Press, 1977, pp. 119–129.
11. Schuster, C. R. and C. E. Johanson. An analysis of drug-seeking behavior in animals. *Neurosci Biobehav Rev* **5:** 315–323, 1981.
12. Stolerman, I. P. and G. D. D'Mello. Role of training conditions in discrimination of central nervous system stimulants by rats. *Psychopharmacology (Berlin)* **73:** 295–303, 1981.
13. Woolverton, W. L. and R. L. Balster. Behavioral pharmacology of local anesthetics: reinforcing and discriminative stimulus effects. *Pharmacol Biochem Behav* **16:** 491–500, 1982.
14. Woolverton, W. L. and R. C. Trost. Cocaine as a discriminative stimulus for responding maintained by food in squirrel monkeys. *Pharmacol Biochem Behav* **8:** 627–630, 1978.