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BRIEF COMMUNICATION

Cocaine as a Discriminative Stimulus for Responding Maintained by Food in Squirrel Monkeys

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WOOLVERTON, W. L. AND R. C. TROST. *Cocaine as a discriminative stimulus for responding maintained by food in squirrel monkeys.* PHARMAC. BIOCHEM. BEHAV. 8(5) 627–630, 1978. – Squirrel monkeys were trained in a choice procedure to discriminate a dose of 100 μg/kg cocaine from saline. Following an injection of cocaine, responding on the right lever was reinforced with food, whereas following an injection of saline, responding on the left lever was reinforced with food. A high degree of stimulus control (100% correct) was established within 20 experimental sessions. The dose-response function of cocaine on lever choice was then determined. When intermediate doses (10, 25 and 50 μg/kg) were administered prior to test sessions, a dose-dependent generalization decrement was seen. One monkey was found to discriminate as low as 25 μg/kg cocaine from saline.

Cocaine Squirrel monkey Discriminative stimulus

MANY experiments have shown that drugs can serve as discriminative stimuli for differential responding using a variety of procedures [11]. Major research strategies have included: (1) choice between the two arms of a T-maze as a function of drug state, and (2) a lever choice situation with the drug acting as the discriminative stimulus. In the T-maze, animals are trained to turn into one or the other maze arm to escape an electric shock; the drug state serves as the discriminative stimulus for choice between the arms [8, 9, 10]. In the other type of procedure, animals are given a choice between two or more levers, with the drug state serving as the discriminative stimulus for the choice. Responding on the correct lever is usually followed by food reinforcement. Schuster and Balster [11] have written an excellent review of the voluminous literature using these methods for studying the discriminative stimulus properties of drugs. In general, experimentation in this area has been restricted to the use of rats as experimental subjects. In addition, although the discriminative stimulus properties of cocaine have been reported [3,6], the only psychomotor stimulant drug that has been studied extensively is *d*-amphetamine.

The present experiment was therefore designed to test the ability of squirrel monkeys to discriminate low doses of cocaine from saline; this species and this drug have rarely been used to study the discriminative stimulus properties of drugs [3, 4, 6]. The monkeys were trained to respond on one lever following an injection of 100 μg/kg cocaine, and on the other lever following an injection of saline. Subsequently, intermediate doses of cocaine were administered to study stimulus control following drug doses other than the training doses.

METHOD

Animals and Apparatus

Three squirrel monkeys (*Saimiri sciureus*) M1, M2, and M3, served as experimental animals. They were reduced to 85% of their free-feeding body weights (700–800 g) and adapted to restraining chairs with a wasit lock similar to those available commercially. The experimental chamber was a ventilated, sound-attenuated cubicle (29.2 cm x 43.2 cm high x 45.8 cm deep) equipped with a houselight and a white noise generator to mask any room noise that might affect responding. A food cup was positioned between the two levers, and there was a stimulus light above each lever. Electromechanical programming and recording apparatus was located in an adjacent room.

Procedure

The animals were placed in the chair and cubicle only for the 30 min experimental session each day. During the initial training sessions, a stimulus light was illuminated above one of the two levers (red-left, green-right lever); a single depression (fixed ratio 1 schedule: FR 1) of the signalled lever resulted in the delivery of food (97 mg Noyes banana pellets). To eliminate possible lever preferences, the illuminated lever was switched randomly

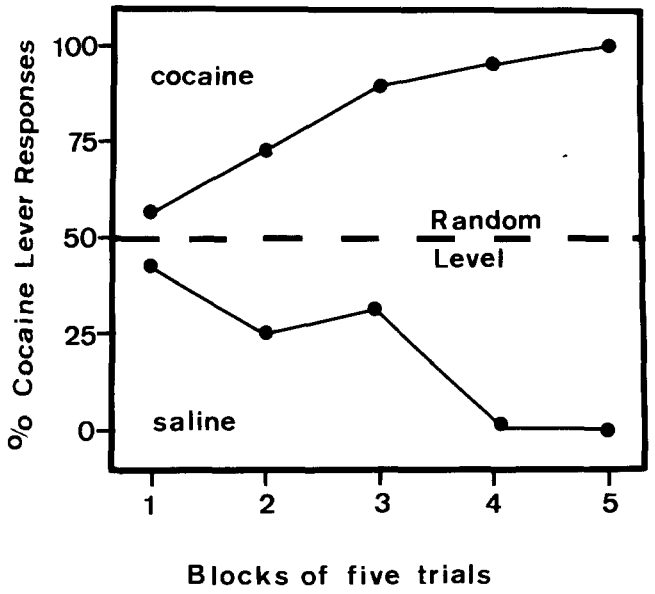

FIG. 1. The percent of the total responses that occurred on the cocaine lever as training progressed following pretreatment with cocaine (100 μg/kg) or saline. On the ordinate is percent cocaine lever responses following either pretreatment, averaged over three monkeys. On the abscissa are blocks of five training trials. Only the first 20 responses in a training session were used in data analysis.

until responding was stable on both levers. The response requirement for food was then gradually increased to 20 (FR 20). Characteristic high rates of fixed ratio responding were evident within seven days, and similar patterns of responding were observed on both levers.

After stable responding had been established, the lever lights were eliminated as discriminative stimuli and animals were pretreated with either 100 μg/kg cocaine hydrochloride or 0.9% saline 15 min before the session. All injections were given intramuscularly in a volume of 0.5 cc and drug doses refer to the salt. Following an injection of cocaine, 20 responses on the right lever were required for food delivery, whereas following an injection of saline, 20 responses on the left lever were required for food delivery. Incorrect lever presses were counted but had no other programmed consequences.

After stable choice behavior following 100 μg/kg cocaine and saline had been established (100% correct, i.e. the first 20 responses in a session were all made on the drug appropriate lever – see below), doses of cocaine between 10 and 100 μg/kg were administered to examine the dose-response curve of cocaine on lever choice and to construct a generalization gradient of responding following novel doses of cocaine. To examine this generalization gradient, 10 min test sessions were conducted during which no food was delivered (extinction testing). All conditions (pretreatment time, injection volume, etc.) remained the same as in training sessions (at least three of which intervened between test days) except that 10, 25, or 50 μg/kg cocaine was given instead of the training dose of cocaine or saline. All doses were randomly administered to control for order effects on generalization. Further, each dose was tested once with each training condition in effect on the preceding day to correct for any tendency to respond on the lever that had been reinforced on the preceding day.

Data Analysis

In all data analysis, only the first 20 responses of each session were used as a measure of stimulus control since reinforcement served as a potent stimulus for correct responding. That is, if the correct lever had been chosen, food delivery would follow the twentieth response and responding would be likely to continue on this lever. Conversely, if the incorrect lever had been chosen, the lack of food delivery following the twentieth response would tend to make responding on the other lever more probable. This was also the case in extinction testing.

RESULTS

Figure 1 shows the mean data from all animals as training progressed. As can be seen, initial responding was random, indicating a lack of position preference and stimulus control. Correct choices reached a point of statistical significance by trial block two (χ^2 cocaine = 27.5, $p<0.001$; χ^2 saline = 37.5, $p<0.001$). After the fifth trial block (25 sessions) responding reached 100% correct levels following both saline and 100 μg/kg cocaine. Visual inspection of cumulative response records revealed no difference in response patterning whether the animals had been pretreated with cocaine or saline.

Figure 2 (left panel) shows the generalization gradient obtained over the range of doses indicated, with each monkey receiving two tests at each dose. As can be seen, responding in sessions following pretreatment with the training doses (saline and 100 μg/kg cocaine) was 100% correct, with intermediate values at intermediate doses.

The right panel of Fig. 2 shows the choice behavior of the three individual monkeys. The data show that the lowest dose of cocaine which served as a discriminative stimulus for responding on the cocaine lever was different for the different monkeys. It is emphasized that the histogram values here are the means of two determinations per dose per monkey. M1 and M3 were consistent in their choice behavior, despite the fact that as much as one month sometimes elapsed between any two tests at the same dose. M3 was able to discriminate 25 μg/kg cocaine from saline while M1 always chose the saline lever following doses less than 50 μg/kg cocaine. M2 during an early test of 25 μg/kg chose the cocaine lever but in a subsequent test at this dose, he chose the saline lever. At 50 μg/kg, however, this animal chose the saline lever on both tests.

DISCUSSION

The data presented here demonstrate that cocaine can serve as a discriminative stimulus for squirrel monkeys responding in a lever choice situation. Similar discriminative stimulus properties have been demonstrated for many other psychomotor stimulant drugs [5]. In addition, the lack of disruptive effects of the training dose of cocaine (100 μg/kg) on fixed ratio responding is consistent with other data in the literature. It has been reported [2] that this dose of cocaine had no effect on fixed ratio responding for food delivery in squirrel monkeys when given IM 5 min before the session. It may be that slow absorption from an IM injection site exposes the drug to rapid breakdown by serum esterases, presumably a major route of cocaine

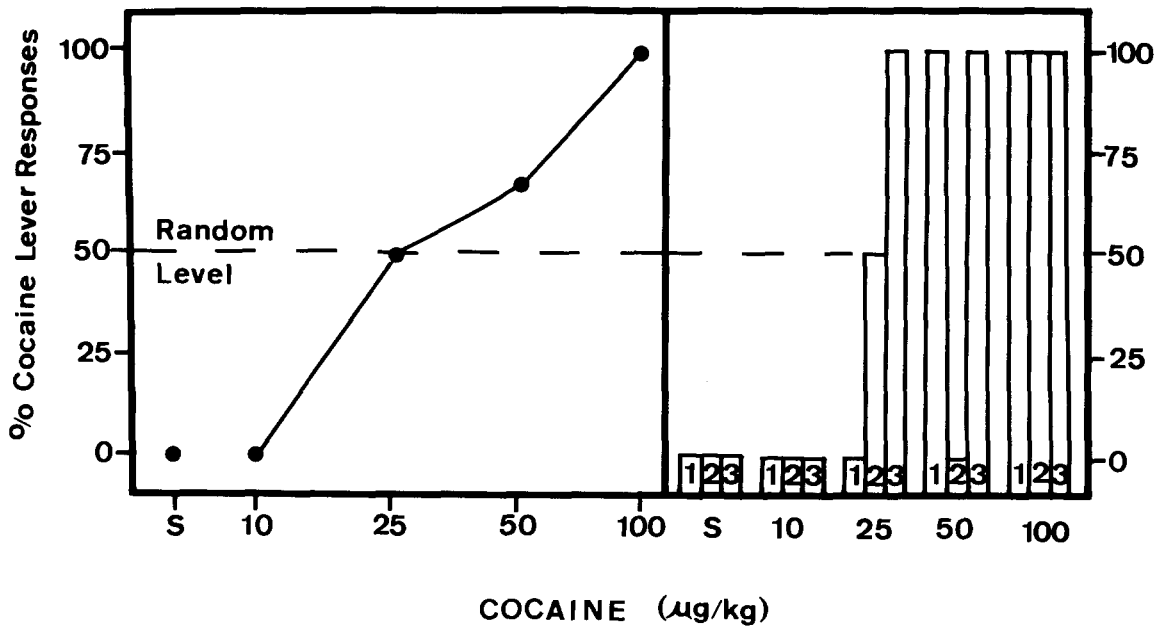

FIG. 2. Stimulus control in test sessions as a function of dose of cocaine. On the ordinate is the percent of the total responses that occurred on the lever associated with food reinforcement following 100 µg/kg cocaine. On the abscissa is dose of cocaine. The data above S represent choice behavior following saline injections. Left Panel: The effect of varying dose of cocaine on choice behavior. Each point is averaged over two test sessions at each dose for all three monkeys. Right Panel: The choice behavior of individual monkeys, averaged over two tests at each dose.

metabolism [1]. On the other hand, when this dose of cocaine was delivered intravenously to rhesus monkeys responding on a DRL 20 second schedule for food delivery, considerable disruption of ongoing responding was observed [7]. Clearly, species, route of administration and schedule of reinforcement are important determinants of the effects of cocaine on schedule-controlled behavior. In both of these experiments, however, the duration of action of cocaine was brief. In view of these facts, it is somewhat surprising that such strong stimulus control was observed 15 min after an IM injection. It may be that a brief exposure served as a discriminative stimulus for responding although little or no disruptive effect was present throughout the session.

In other experiments describing the discriminative stimulus properties of cocaine [3,6] doses used for discrimination training in rats were 100 times as large as those used here. It is possible that the squirrel monkey is more sensitive to the stimulus properties of cocaine than is the rat. Indeed, one monkey was found to reliably discriminate 25 µg/kg cocaine from saline. Although the squirrel monkey has rarely been used to study the discriminative stimulus properties of drugs [4], this sensitivitiy would seem to recommend it as a subject for such experiments.

Finally, it should be noted that the discriminability of a dose of cocaine seems to be more a function of individual differences than of repeated trials and testing at the doses used. Despite the fact that sometimes a month of training and testing trials elapsed between two tests of the same dose of cocaine, except for one monkey at one dose there was no indication of any change in sensitivity to its discriminative stimulus properties as a function of repeated administration. This is in contrast to other data reporting the development of tolerance to the discriminative stimulus properties of cocaine [6]. It is likely that the differences between the present results and those of McKenna and Ho [6] can be accounted for by the fact that in the latter experiment rats received 20 mg/kg cocaine three times/day in contrast to the dose of 100 µg/kg cocaine once/day with saline days interspersed that was used in our experiment. Certainly a regimen of more frequent injection with higher doses of cocaine would be expected to induce a greater amount of tolerance.

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