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Induced Tolerance to the Discriminative Stimulus Properties of Cocaine

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MCKENNA, MARY AND BENG T. HO. *Induced tolerance to the discriminative stimulus properties of cocaine.* PHARMAC. BIOCHEM. BEHAV. 7(3) 273–276, 1977. – Twenty-five male Sprague-Dawley rats were trained in five two-lever operant chambers on a DRL–15 sec schedule of positive food reinforcement to discriminate 10 mg/kg cocaine from 1 ml/kg saline. Following acquisition of discrimination a counterbalanced design of extinction tests was performed before and after repeated administration of 20 mg/kg cocaine or saline (three times a day at five hr intervals for seven days). The extinction tests consisted of testing responses of animals following 1 ml/kg saline, 2.5 mg/kg cocaine, or 5 mg/kg cocaine. The results showed no significant difference in animals' lever choice before and after repeated injection with saline. However, the percent cocaine lever choice with the two doses of cocaine was lower after repeated administration of cocaine than before the repeated injections. This indicates tolerance developed to the discriminative stimulus properties of cocaine.

Cocaine Drug discrimination Tolerance

COCAINE is a local anesthetic [1, 3, 8, 18] and CNS stimulant [2, 3, 19, 24]. Administered intravenously or nasally in man, cocaine produces euphoria, increased physical activity, anorexia and increased heart rate and blood pressure [2,16]. Tolerance to cocaine develops rapidly in man; consequently, increasing amounts of the drug up to 10 g/day are necessary to induce the euphoric effect [3,22]. Administration of cocaine to animals produces effects similar to those observed in man. Anorexia has been recorded in rats and dogs [5, 6, 20], antifatigue in dogs [9], stereotypy in rats [9,19], and increased motor activity in rats, guinea pigs, mice, rabbits, cats, dogs and monkeys [9, 10, 15, 19, 20, 23]. Unlike man, animals develop tolerance to some of these effects and show increased response (supersensitivity) to other cocaine effects. For example, anorexic tolerance has been demonstrated in some species. Dogs given daily subcutaneous injections of 15 mg/kg cocaine showed no alteration in weight gain [4]. Rats exhibited a depression of weight gain over a 6 week period following repeated intraperitoneal injections of 75 mg/kg cocaine [6]. However, less toxic doses of cocaine (20 and 40 mg/kg) did not affect weight gain in rats. Contrary to the anorexic effects of cocaine [4,6], supersensitivity is observed in the locomotor [12, 14, 21] and stereotyped activity [14,21] of animals injected repeatedly with cocaine. These examples illustrate cocaine tolerance and supersensitivity develop in animals, depending on various pharmacological measurements.

Recent studies in our laboratory have demonstrated the ability of rats to discriminte 10 mg/kg of cocaine from 1 ml/kg saline in a 2-lever operant chamber [13]. Furthermore, the discriminative stimulus properties of cocaine appear to be centrally mediated by the release of dopamine. The purpose of this study is to evaluate the effects of repeated administration of cocaine for the development of tolerance or supersensitivity in rats using drug discrimination as the performance measured. Although sensitivity to LSD [7] and tolerance to nicotine [17] have been explored utilizing the same behavioral paradigm, suitable animal models have not been developed. Such a model, if developed, would provide a useful tool for the study of cellular or functional alterations induced by repeated cocaine administration.

METHOD

Animals and Apparatus

Twenty-five male Sprague-Dawley rats initially weighing 250–275 g were food deprived to maintain a stabilized 85% of their normal body weight. Animals were then trained to discriminate 10 mg/kg cocaine from 1 ml/kg saline. Discrimination training was carried out in five two-lever sound attenuated operant chambers (Scientific Prototype Model PLS–1000). Solid state equipment (Grason-Stadler 1200 series) controlled reinforcement and recording of lever responses.

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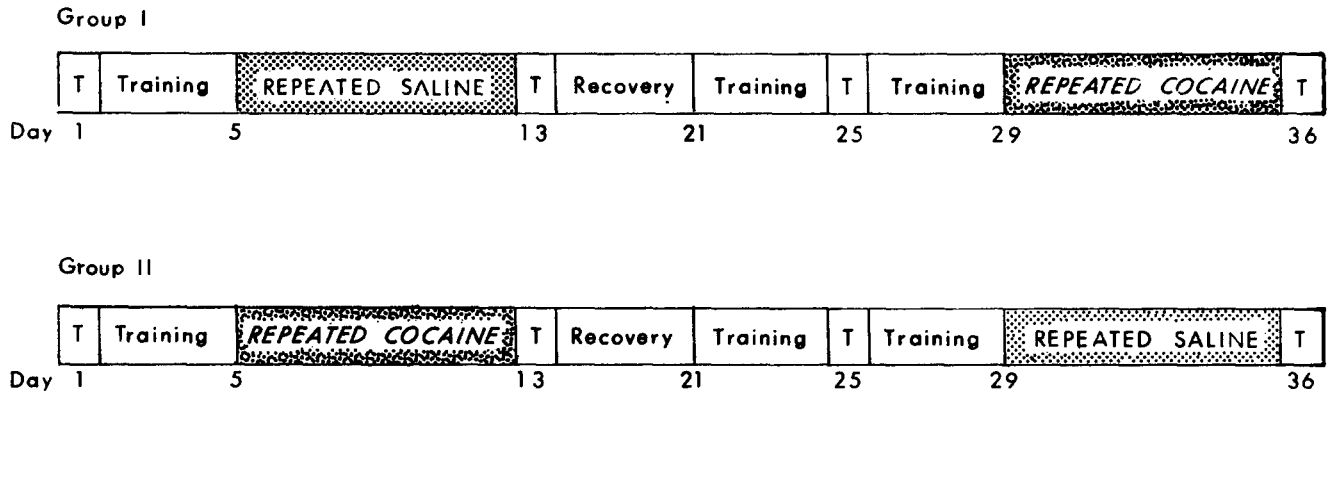

FIG. 1. Schedule used for studying tolerance to cocaine discrimination.

Preliminary Training

Animals were trained 30 min a day for three days on a continuous reinforcement schedule (CRF), followed by two days on a differential reinforcement of low response rate (DRL) 5-sec schedule, two days on a DRL-10 sec schedule, and finally four days on a DRL-15 sec schedule. Responses were reinforced continuously on the CRF schedule and on alternate levers following the appropriate time interval on DRL schedules by the delivery of a 45 mg Noyes standard flavor food pellet.

Acquisition of Discrimination

After completion of preliminary training, 10 mg/kg cocaine or 1 ml/kg saline was administered intraperitoneally 15 min before each daily training session. The left lever was designated the cocaine correct lever and the right lever the saline correct lever. Animals were reinforced during training sessions only when they responded on the designated correct lever according to administration of cocaine or saline. Ten-minute extinction tests, during which no reinforcement was available, were given every four days in such a manner that prior to each test day animals received 2 days' training on the cocaine lever and 2 days' training on the saline lever. An equal number of tests were performed following cocaine and saline administration. Animals were considered sufficiently trained when responses were more than 80% lever correct for four consecutive extinction tests: 2 tests following administration of cocaine and two tests following administration of saline. Twelve test sessions were required to achieve the criteria for discrimination.

Tolerance Tests

Following acquistion of discrimination, animals were divided into two groups. Before and after repeated administration of cocaine or saline four extinction tests were performed in each group with intraperitoneal injection of 1 ml/kg saline, 2.5 mg/kg cocaine, or 5.0 mg/kg cocaine (Fig. 1). A counterbalanced design allowed animals to serve as their own control. During the four daily 20 min training sessions, reinforcement was available two days on the cocaine lever and two days on the saline lever. On Day 5, Group 1 received 20 mg/kg cocaine and Group 2 1 ml/kg saline, intraperitoneally, three times a day at five hr intervals for 7 days. During this period no training was performed. Extinction tests were resumed 24 hr after the last repeated injection. A reversed sequence of injections was carried out on Day 29, following a 7-day recovery period, during which no training or injections were given. Animals previously administered saline for seven days were given 20 mg/kg cocaine for 7 days, and those previously receiving cocaine were administered 1 ml/kg saline for 7 days.

Drugs

All test drugs were administered intraperitoneally 15 min prior to testing. Saline (0.9% sodium chloride) with benzyl alcohol for preservative was obtained from Baxter. Cocaine hydrochloride (Merck and Co.) in saline was administered in a volume of 1 ml/kg.

Selection of cocaine test dosages was based on results of preliminary investigation in our laboratory. Animals administered 5 mg/kg cocaine responded more than 80% on the cocaine correct lever, while responding approximately 50% on the cocaine lever with 2.5 mg/kg cocaine. It was felt that the dose of 5 mg/kg, rather than 10 mg/kg, would be more sensitive for tolerance study. Any decrement in discriminability between 10 mg/kg and 5 mg/kg cocaine would not be detectable. Supersensitivity would be reflected best at 2.5 mg/kg in animals following repeated injection of 20 mg/kg cocaine. The choice of repeated administration of 20 mg/kg cocaine at 5 hr intervals was based on a preliminary study which showed that animals tolerated this dose without lethality and were relatively drug free 6 hr postinjection.

RESULTS

The results of extinction tests with 1 ml/kg saline, 2.5 mg/kg cocaine and 5 mg/kg cocaine before and after seven days' repeated administration of saline are presented in Fig. 2A. Prior to repeated saline administration animals responded on the cocaine correct lever 10.4% following a single dose of 1 ml/kg saline, 55.6% following 2.5 mg/kg cocaine, and 94% following 5 mg/kg cocaine. After repeat-

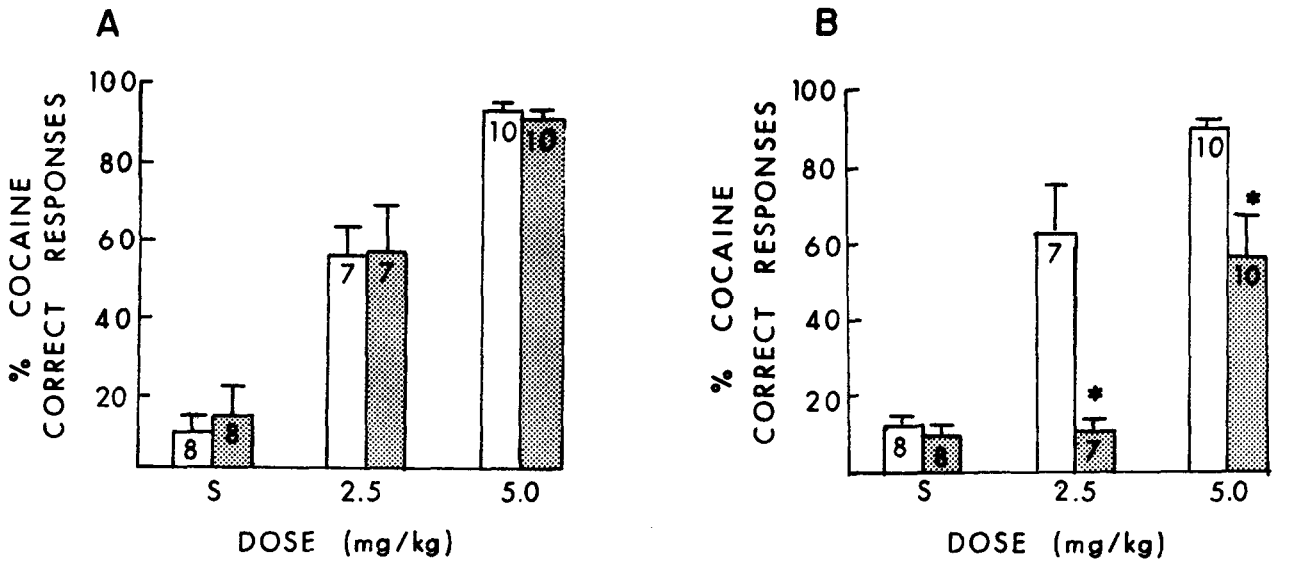

FIG. 2. Effects of the two doses of cocaine and saline (S) on the cocaine lever responses in rats before (open bars) and after (shaded bars) repeated administration of 1 ml/kg saline (A), or 20 mg/kg cocaine (B). The vertical bars represent ± SEM. Numbers of animals are shown inside the bars. Data were obtained by combining test scores for Group 1 and Group 2 (see Fig. 1). *Probability of difference from animals before repeated administration of cocaine, $p<0.01$ (analysis of variance two-factor mixed design with repeated measures on one-factor followed by Newman-Keuls test).

ed saline administration the responses on the cocaine correct lever were 14% following 1 ml/kg saline, 57% following 2.5 mg/kg cocaine, and 91% following 5 mg/kg cocaine. Repeated measures ANOV revealed no significant differences before and after repeated saline administration.

Before and after repeated 20 mg/kg cocaine, the discriminative behavior of animals to 1 ml/kg saline, 2.5 mg/kg cocaine, and 5 mg/kg cocaine are shown in Fig. 2B. Before repeated cocaine administation animals responded on the cocaine lever 12% following 1 ml/kg saline, 62% following 2.5 mg/kg cocaine, and 89% following 5 mg/kg cocaine. After repeated cocaine administration animals responded on the cocaine correct lever 10% following 1 ml/kg saline, 11% following 2.5 mg/kg cocaine, and 56% following 5 mg/kg cocaine. Repeated measures ANOV revealed significant differences with 2.5 mg/kg cocaine and 5 mg/kg cocaine before and after repeated cocaine administration. Furthermore, all three test dosages were significantly different from each other. No change in response rate was observed throughout the entire course of study.

During repeated cocaine administration behavioral observations were noted. A general increase in motor activity and stereotypic head bobbing and gnawing were observed in all animals. Three animals, one of which subsequently died, convulsed. The stimulant effects of cocaine made it necessary to provide more food to animals during repeated cocaine administration in order to maintain a stabilized body weight. Maintenance of a stabilized body weight, regardless of the amount of food consumed, assures stability of response rate and lever choice in drug discrimination studies.

DISCUSSION

This study demonstrated rats are capable of discriminating appropriate doses of cocaine from saline, and tolerance, as measured by discriminative behavior, develops following repeated cocaine administration. These results agree with tolerance to cocaine reported in man. The observed increase in animals' motor and stereotyped activities during our study agrees with reports in the literature on cocaine supersensitivity [5, 6, 12, 14, 21].

The experimental procedure used in this study allowed for detection of supersensitivity or tolerance following repeated cocaine administration. If supersensitivity had occurred a low dose of cocaine would have been perceived by animals as a higher dose. For example, animals which had developed supersensitivity to the repeated cocaine administration would have responded to 2.5 mg/kg cocaine in the range of 80–90% on the cocaine correct lever, while the responses to 5 mg/kg cocaine would not have changed. On the contrary, our results demonstrated tolerance, not supersensitivity, after repeated cocaine administration, as the responses to 2.5 mg/kg cocaine and 5 mg/kg cocaine lessened when compared to responses before repeated administration. Tolerance to the drug effect is evidenced; no alteration of discrimination was seen in animals receiving repeated saline administration. Previous attempts to demonstrate tolerance to discriminative stimulus properties of drugs have proven unsuccessful [4, 7, 11, 17]. For instance, morphine discriminative stimulus properties did not develop tolerance in experimental designs reported in the literature [4,11].

The cause of cocaine tolerance was not explored in this investigation. The possibility of metabolic tolerance is not ruled out. In this instance, induction of metabolic enzymes due to repeated drug administration could decrease the concentration of drug to the brain. We have previously shown cocaine discriminative properties are mediated by the release of brain dopamine [13] and, therefore, speculate cocaine tolerance may result through an alteration of dopamine function.

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