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BRIEF COMMUNICATION

Water Deprivation-Induced Oral Self-Administration of Cocaine in the Lewis Rat: Evidence for Locomotor Effects But Not Reinforcement

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BELL, S. M., M. J. MACENSKI, P. B. SILVERMAN AND R. A. MEISCH. *Water deprivation-induced oral self-administration of cocaine in the Lewis rat: Evidence for locomotor effects but not reinforcement.* PHARMACOL BIOCHEM BEHAV 45(3) 749–754, 1993.—Oral cocaine self-administration was studied in water-deprived Lewis rats. Liquid was available to rats only during daily 90-min sessions, in chambers equipped with spouts that delivered precise volumes of liquid following completion of lever-press responses. Blocks of training and testing sessions were alternately carried out during which increasing cocaine concentrations were presented: 0.0, 0.0125, 0.025, 0.05, 0.1, 0.2, 0.282, and 0.4 mg/ml. Although high cocaine intakes (23.3–33.0 mg/kg) were obtained, neither avoidance nor preference for cocaine developed. Subsequently, fixed-ratio size was increased, and then distinctive stimulus lights were correlated with each liquid. One rat showed a preference for water following these changes, but two rats continued to show no preference. To determine if the amounts of cocaine self-administered had behavioral effects, locomotor activity tests were run immediately following self-administration sessions. Locomotor activity was substantially higher following cocaine self-administration than following water self-administration. These results demonstrate that the cocaine intakes reached under the present conditions did produce locomotor, but not reinforcing, effects.

Self-administration Lewis rat Water deprivation Oral route Cocaine Locomotor activity Acquisition Reinforcement

USE of the oral route has important advantages for the experimental analysis of drug-seeking behavior. For example, the complications accompanying invasive surgical procedures (e.g., catheter implantation and the loss of catheter patency) are not encountered when the oral route is used, and experimental subjects live longer. With a longer life span, more elaborate sequential studies can be carried out over a period of years. However, one major problem encountered with the oral route, not encountered with other routes, is the aversive taste of many drugs. Acquisition procedures are used to adapt the subjects to these aversive tastes while simultaneously inducing intake of drug amounts that have behavioral effects due to CNS action.

It has been difficult to establish orally delivered cocaine as a reinforcer using some acquisition methods that have been successful in establishing other drugs as reinforcers. Specifically, in our laboratory the use of fading procedures (gradually adding a drug to a solution of another drug that is already serving as a reinforcer, and then gradually diminishing the concentration of the latter drug) and food-induced drinking procedures have not established cocaine as an orally delivered reinforcer for rats (2). Conversely, these procedures have been used, in a variety of species, to establish opioids (8,10), psychomotor stimulants (14,19), ethanol (12,20,24), barbiturates (16), and dissociative anesthetics (4) as orally delivered reinforcers.

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Two studies have demonstrated that orally delivered cocaine functioned as a reinforcer for rats. Falk et al. (13) used schedule-induced polydipsia to engender high rates of cocaine consumption. When vehicle was concurrently available with cocaine, one rat out of four consumed greater amounts of cocaine solution than vehicle. Suzuki et al. (26) allowed rats to consume only food that had cocaine mixed in it. Subsequently, when cocaine-admixed food and nondrug-admixed food were concurrently available, rats consumed more drug-admixed food than nondrug-admixed food.

A similar "forced consumption" procedure has also been successfully used with morphine solutions. Despite an initial aversion to a morphine solution, rats consumed significantly more drug than water after repeated exposure to the morphine solution (25). Forced drinking procedures may be especially effective in establishing orally delivered drugs as reinforcers because of two factors. First, water deprivation produces high rates of drinking and thus contact with the drug effects. Second, Carroll and Boe (5) reported that, like food deprivation (6,7,9), responding maintained by drug delivery increased when animals were water deprived, suggesting that water deprivation also increases the reinforcing effects of a drug. If incorporated into an acquisition procedure, both of these factors would increase the probability that the rats would experience cocaine effects. The current study examined the efficacy of water deprivation to engender oral cocaine self-administration and thereby establish cocaine as a reinforcer. To identify whether the amounts of cocaine consumed were having pharmacological effects, locomotor activity measures were also used.

METHOD

Animals

Three naive, male, Lewis rats (Charles River Laboratories, Wilmington, MA) served as subjects and were individually housed in stainless steel wire mesh cages within a colony room. Rats had free access to food and water until approximately 21 weeks of age, at which time their food intakes were limited to 8 g daily until they were reduced to 80% of their free-feeding weights. Rats were weighed daily, and food allotments were adjusted to maintain the 80% weights. Weights for SB1, SB2, and SBR were 308, 316, and 316 g, respectively, after weight reduction. The colony room was illuminated on a 12L : 12D cycle with lights on at 7:00 a.m., and the temperature was maintained at approximately 22°C.

Apparatus

Operant conditioning. The experimental chambers were octagonal in shape, with alternating Plexiglas and stainless steel walls, a wire mesh floor, and a stainless steel ceiling. Each chamber was equipped with a pair of levers, each located below a metal spout. Below each lever was a row of stimulus lights, and above each spout was a second row of lights. The lights, the lever, and the metal spout were situated in a columnar fashion and were duplicated on the stainless steel walls on the left and right sides of the foremost Plexiglas wall. The drinking device has been described in greater detail elsewhere (1). The operant chambers were contained within a darkened room with masking noise provided from a single speaker.

At the beginning of a session, the lights below the active lever were illuminated. When a rat operated a lever, the light below that lever was turned off and the lights above the solenoid were illuminated. While the upper lights were on, the rat was able to obtain liquid from the drinking system with licks of its tongue. Each tongue lick on the metal spout completed a drinkometer circuit and resulted in a brief activation (5 ms) of a solenoid-operated valve. Each opening of the valve delivered an average of 0.01 ml of liquid through the metal spout into the rat's mouth. The delivery component was programmed so that each lever press (fixed-ratio 1) resulted in access to 10 consecutive reinforced licks, which cumulatively yielded an average of 0.1 ml of liquid. When a series of 10 licks had been completed, the lights above the drinking spout were extinguished and the lights below the lever were again illuminated. Licks, when the spout lights were not illuminated, had no programmed consequences. Lever presses, when the spout lights were illuminated, also had no programmed consequences.

Experiments were controlled and data recorded by a DEC PDP-11 computer and SKED® software, located in a room apart from the one containing the experimental chambers. The time course of responding was recorded by the PDP-11.

Locomotor apparatus. Locomotor activity was measured in 42 × 42 cm Digiscan animal activity monitors (Omnitech Electronics, Inc.), each of which contained a Plexiglas cubical and a 12 × 12 array of infrared photocells. Photocell interruptions (horizontal activity counts) were counted via the monitoring system. The locomotor apparatus was placed within a darkened room with masking noise provided from a single speaker.

Procedure

Prior to the beginning of the experiment, rats were water deprived for 24 h and trained to press a lever to obtain deliveries of water. Initial training sessions were 3 h in length. Water was available only in the experimental chambers under a fixed-ratio 1 (FR 1) reinforcement schedule. Daily food allotments were provided in the experimental chambers during training sessions. These conditions remained in effect until behavior stabilized; stability was defined as six sessions with no increasing or decreasing trends in behavior evident, as judged by visual inspection of the data.

Following initial training, rats continued to be water-deprived and were allowed access to liquid only during daily 90-min sessions. An FR 1 schedule remained in effect. The rats were provided access to a cocaine solution from a single spout ("training sessions") in the initial set of sessions. Immediately following this set of sessions, cocaine solution was offered concurrently with water ("testing sessions"). Training and testing sessions were alternately carried out at each cocaine concentration in an increasing series: 0.0, 0.0125, 0.025, 0.05, 0.1, 0.2, 0.282, and 0.4 mg/ml cocaine. At each concentration, conditions were held constant until behavior was stable. From session to session cocaine was available alternately from the right and left spouts. Stimulus lights associated with each spout were identical during initial testing and training sessions. Daily food allotments were provided postsession in the rats' home cages.

Following the completion of six sessions of stable behavior with concurrent access to 0.4 mg/ml cocaine and water, the fixed-ratio size was increased in the following sequence: FR 1, FR 2, and FR 4. Rats were then water satiated and tested until their behavior had stabilized, and then retested water deprived. Under both conditions, 0.4 mg/ml cocaine and water were concurrently available. Distinctive stimuli were then introduced. A blinking stimulus light (10 Hz) was first paired with the lever associated with 0.4 mg/ml cocaine, and in a

subsequent set of training sessions, a nonblinking stimulus light was paired with the lever associated with water. A set of testing sessions was run in which the distinctive stimuli were paired, respectively, with concurrently available 0.4 mg/ml cocaine and water. Under these conditions, the FR was then increased from 4 to 8 for SB1 and SBR, and from 4 to 8 to 16, for SB2. Water-satiation conditions were introduced a second time under these differential stimulus conditions, for SB1. Under all conditions, sessions were continued until six stable sessions of behavior were obtained.

In a final experiment, locomotor activity was evaluated. Initially, the rats were given five daily 45-min sessions to acclimate to the locomotor apparatus. During this series of sessions, no drug administration or operant chamber activity preceded the introduction to the locomotor apparatus. Following this block of five sessions, the rats were water deprived for 23.5 h and were provided access to water in the operant chambers. An evaluation of the time course of responding during earlier sessions revealed that the majority of responding occurred during the initial 30 min of each session. Because of this 30-min time course, and to minimize time during which administered cocaine could be metabolized or rendered inactive, session length was thus reduced to 30 min. Immediately following the 30-min self-administration sessions, rats were placed in the locomotor apparatus for 45 min and locomotor activity was monitored. After five sessions, water was replaced with 0.4 mg/ml cocaine. Again, the rats were water-deprived for 23.5 h and were provided 30-min access to the liquid. Immediately following each 30-min period in the operant chambers, the rats were transferred to the locomotor apparatus for 45 min. These conditions were held constant for five daily sessions. Conditions in which water was available in the operant chamber were then repeated for five daily sessions. Finally, after being water deprived for 23.5 h, rats were given access for 30 min to water, injected intraperitoneally with 10 mg/kg cocaine, and placed in the locomotor apparatus for a single 45-min session.

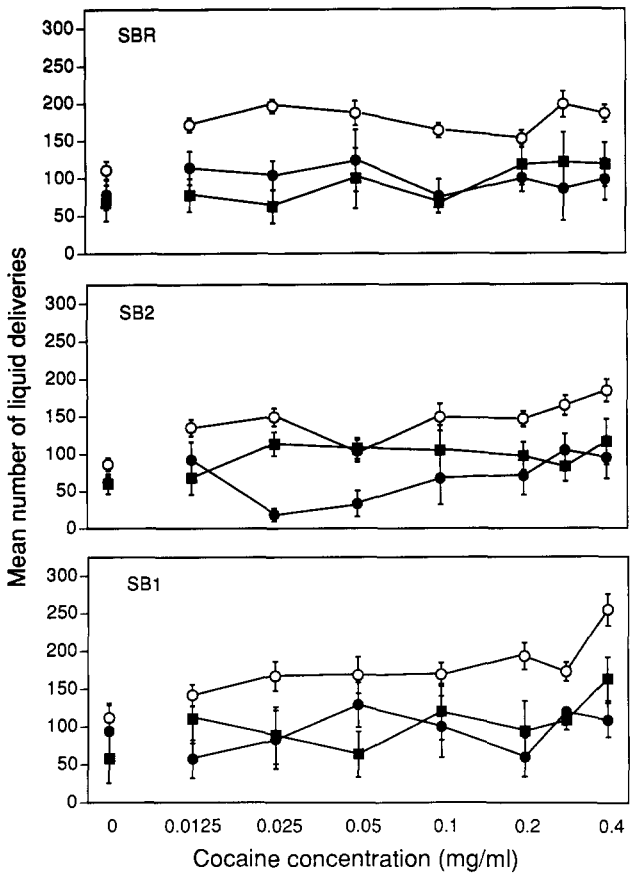

FIG. 1. Mean (n = 6) deliveries of cocaine when available alone (○), and of cocaine (●) and water (■) when available concurrently, as a function of cocaine concentration (mg/ml). Brackets indicate SEM.

RESULTS

Figure 1 shows that when cocaine alone was available, there was a slight increase in the mean number of deliveries of cocaine as its concentration was increased. There were no differences between numbers of deliveries of concurrently available cocaine and water. The range of deliveries of concurrently available cocaine and water overlapped for all three animals at all tested concentrations (also for SB2 at 0.025 and 0.05 mg/ml). There was no noticeable preference for cocaine or water during the first 20 min of each session. As cocaine concentration increased, cocaine intake increased in a positively accelerating manner. Peak cocaine intake levels ranged from 23.3 to 33.0 mg/kg when cocaine was the only liquid available, and from 12.0 to 14.1 mg/kg when both cocaine and water were simultaneously available.

As FR size was increased, water became slightly but consistently preferred to concurrently available 0.4 mg/ml cocaine (Fig. 2A). However, the rats continued to consume from 2.1 to 11.0 mg/kg cocaine. This water preference diminished somewhat following the introduction of distinctive stimuli, and as the FR size was increased further (Fig. 2B). When the rats were initially water satiated, only SBR showed a preference for water. However, in a retest following the introduction of discriminative stimuli, a preference for water was seen by SB1 as well.

Figure 3 shows there was no difference between the locomotor activity of the rats during the initial 5 days of acclimation in the locomotor apparatus, and the 5 days when the rats drank water before being placed in the apparatus. When 0.4 mg/ml cocaine was substituted for water in the operant chambers, cocaine intakes ranged from 11.0 to 23.0 mg/kg, and locomotor activity increased noticeably. Motor activity of SB1 continued to increase across the five consecutive cocaine sessions. When cocaine was replaced with water, locomotor activity decreased, but remained slightly higher than activity levels recorded following initial water drinking. As a final comparison, the rats were allowed to self-administer water for 30 min, and then were injected intraperitoneally with 10 mg/kg cocaine. This resulted in locomotor activity levels that exceeded those for orally administered cocaine for all three rats.

DISCUSSION

Cocaine was orally self-administered by rats both when the drug was presented alone (training sessions) and when presented concurrently with water (testing sessions). Peak mean total intakes ranged from 23.3 to 33.0 mg/kg during the training sessions, and from 12.0 to 14.1 mg/kg during the testing sessions. These high cocaine intakes were expected to increase the likelihood of cocaine serving as an orally delivered reinforcer. Although a similar method has successfully established morphine as an oral reinforcer for the rat (25), no evi-

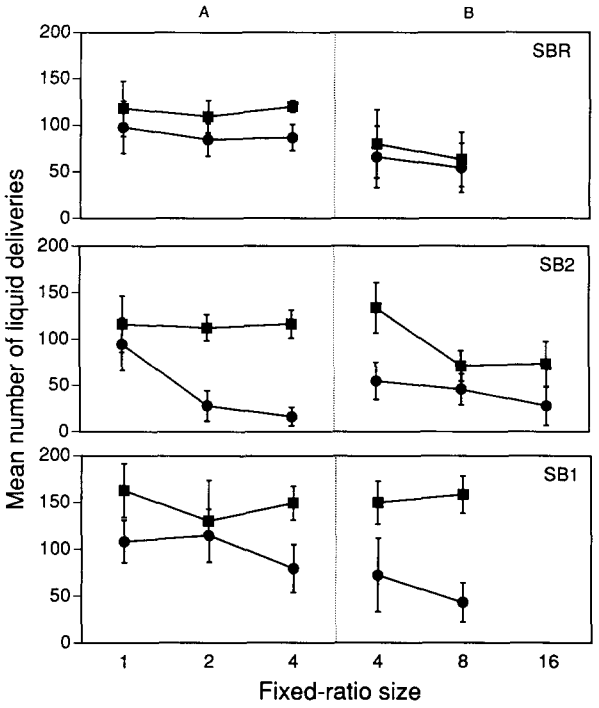

FIG. 2. Mean (n = 6) deliveries of cocaine (●) or concurrently available water (■) as a function of fixed-ratio size. Brackets indicate SEM. (A) Test sessions with no difference in stimuli between cocaine and water spouts. (B) Test sessions with a blinking stimulus light paired with the cocaine spout, and a nonblinking light paired with the water spout.

dence of cocaine's reinforcing effects was obtained in this study. It was expected that as drug concentration was systematically increased, cocaine would come to serve as a reinforcer as evidenced by greater responding maintained by cocaine than by water. However, no preference for cocaine or water, when they were concurrently available, was seen in the test sessions.

When no preference between two stimuli is initially observed, the stimulus with greater reinforcing effects will better maintain behavior following an increase in schedule size (17,21-23). In the present study, when the fixed-ratio was increased from 1 to 4, water became slightly but consistently preferred to concurrently available 0.4 mg/ml cocaine. However, the rats continued to self-administer cocaine with intakes ranging from 2.1 to 11.0 mg/kg. The water preference diminished somewhat when distinctive stimuli were paired with the water and drug solutions, and when the FR size was increased further. In previous studies in our laboratory, the introduction of distinctive stimuli paired separately with drug and water often intensified the differences in responding maintained by drug and water [e.g., (18)]. Results of the present study suggest that, although there was a preference for water over cocaine, this preference was minimal.

Cocaine serves as an orally delivered reinforcer for rhesus monkeys (19) and for C57BL/6J mice (14). Both of these studies used a drug-fading procedure to establish cocaine as an orally delivered reinforcer. That is, ethanol was initially established as a reinforcer, cocaine was added to the ethanol solution and systematically increased in concentration, and finally ethanol was faded from the combination. Following these procedures, for both monkeys and mice, orally delivered cocaine maintained higher response rates at FR 4 than did water. During the acquisition procedures, peak mean intakes of 6.4 mg/kg per 30-min sessions for mice, and 5.3 mg/kg per 3-h sessions for monkeys were reported. These intakes are markedly less than the peak intakes reported in the present study, yet cocaine was not established as an oral reinforcer for the rat. In our laboratory, the ethanol-fade acquisition procedure also did not successfully established cocaine as a reinforcer for the rat (2).

Despite the failure to establish cocaine as an orally delivered reinforcer for rats with the methods described in the present study, it is possible to establish cocaine as a reinforcer via the oral route using other methods. Suzuki et al. (26) demonstrated that cocaine, when admixed in food, was selected by rats more than concurrently available food with no admixed cocaine. During their study, total cocaine intakes reached nearly 80 mg/kg per 6-h session when the only food

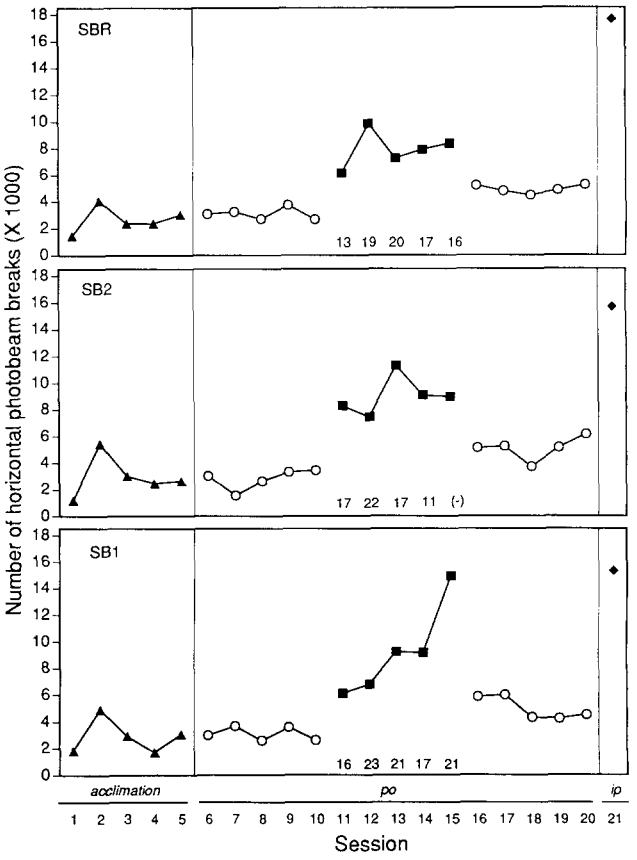

FIG. 3. Locomotor activity. Rats were given five consecutive sessions of acclimation to the locomotor apparatus (▲). Rats were water deprived for 23.5 h and provided 30-min access within an operant chamber to water (○) for 5 consecutive days, or to 0.4 mg/ml cocaine (■) for 5 consecutive days. After periods in the operant chambers, the rats were immediately placed in the locomotor apparatus for 45 min. The cocaine amount (mg/kg) that the animals orally self-administered is indicated above the ordinate for comparison; (-) indicates intake could not be determined due to spillage. After final 30-min water access session, 10 mg/kg cocaine was immediately administered IP (♦), and locomotor activity was recorded for 45 min.

available contained 1.0 mg cocaine per g food, and approximately 50 mg/kg per 6-h session when there was a choice between food containing cocaine and food without cocaine. These cocaine intakes are three to five times higher than those reported by Bell et al. (2), when fading and food-induced drinking acquisition procedures were used, and two to three times higher than the intakes reached in the present study. Falk et al. (13) showed in one rat significantly more cocaine than water drinking, under schedule-induced drinking conditions. Prior to tests with concurrently available cocaine and water, this particular rat reached intakes well over 100 mg/kg in a 3-h session. Such intakes are greater than those reported under fading, food-induced drinking, or water-deprivation acquisition conditions. It is necessary to note that comparisons of peak intakes across studies are difficult to make, and in this case, relevant only to the extent that in the previous studies (13,26) cocaine was established as an orally delivered reinforcer, but in the present study was not. However, these data suggest that methods that produce higher oral intakes than those reached in the present study may be necessary to establish cocaine as an orally delivered reinforcer.

The failure to establish orally delivered cocaine as a reinforcer may be due to pharmacokinetic factors. Rat liver microsomes have a seventyfold higher affinity for cocaine than do mouse liver microsomes (11), and in rat hepatocytes cocaine is converted to a reactive metabolite that irreversibly binds to protein (3). With a high affinity for cocaine in the liver and a high degree of irreversible protein binding, less cocaine may be available to enter the brain. This may explain, in part, why cocaine intakes for rats, which are similar to those obtained for mice, do not result in establishment of cocaine as a reinforcer for the rat. However, the cocaine intakes observed in the current study were sufficient to substantially increase activity levels. Activity increases following rats' oral ingestion of cocaine have also occurred when schedule-induced polydipsia was used to engender intake (15). Because of methodological differences, direct comparisons are difficult to make. Nonetheless, increases in locomotor activity were seen at a dose range similar to that seen in the present study. In a separate study, mice self-administered cocaine at intake levels below those reported to increase locomotor activity (F. R. George, personal communication, 1992). If a similar locomotor activity-reinforcement relationship exists in rats, cocaine should have been established as a reinforcer, since intakes necessary to increase locomotor activity were reached. The results here show that quantities of cocaine that increase activity do not necessarily constitute amounts that will lead to the establishment of the drug as a reinforcer.

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