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Comparison of the Reinforcing Properties of Cocaine and Procaine in Rhesus Monkeys[1]

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JOHANSON, C. E. AND T. AIGNER. *Comparison of the reinforcing properties of cocaine and procaine in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 15(1) 49–53, 1981.—Previous studies have shown that a variety of local anesthetics including procaine are self-administered at high rates by rhesus monkeys. In the present study two rhesus monkeys were given a mutually exclusive choice between various doses of intravenous cocaine and procaine. In almost all comparisons cocaine was preferred even when the procaine dose was 16 times that of cocaine. Other measures of performance such as rate of responding did not vary systematically with preference. These data provide further support for the idea that rate of responding under simple schedules of drug delivery is an unreliable measure of relative reinforcing efficacy. In addition, the consistent preference for cocaine over procaine in monkeys suggests that the infrequent abuse of procaine by humans may be related to its low reinforcing efficacy relative to drugs such as cocaine.

Cocaine Procaine Local anesthetics Reinforcing efficacy Abuse liability Choice procedure Rhesus monkeys

COCAINE has both local anesthetic and psychomotor stimulant properties. Nevertheless, it has always been assumed that its ability to serve as a reinforcer was a function of its psychomotor stimulant properties. However, several investigations have shown that other local anesthetics such as procaine can maintain responding leading to their delivery in rhesus monkeys [3, 6, 11, 20]. Furthermore, many local anesthetics including cocaine produce discriminative properties similar to the stimulus properties of procaine in rats [22]. Although most drugs which are self-administered by animals are abused by humans, the positive findings with local anesthetics are puzzling since these drugs, with the exception of cocaine, are not considered drugs of abuse. Furthermore in some self-administration studies conducted with local anesthetics, rates of responding have been extremely high relative to those maintained by cocaine [11]. These high rates should not be interpreted as demonstrating that other local anesthetics are more efficacious reinforcers than cocaine since rate of responding is a function of both a drug's reinforcing properties and other rate modifying effects [9]. In the present study, the relative reinforcing efficacy of cocaine and procaine was compared using a choice procedure in rhesus monkeys. This procedure utilizes a preference measure which is independent of rate of responding to indicate reinforcing efficacy. The results demonstrated that cocaine had greater reinforcing properties than procaine since in most comparisons it was preferred to procaine. These data would lead to the prediction that the abuse liability of procaine in humans is low relative to that of cocaine.

METHOD

Animals

Two adult male rhesus monkeys, weighing 7.4 (6019) and 6.2 (8004) kg were used. Both of these monkeys had prior experience in an experiment that was similar to the present one involving choices between various doses of cocaine. Each animal was surgically prepared with an intravenous polyvinyl chloride double-lumen catheter (U.S. Catheter and Instrument Company, Billerica, MA) under sodium pentobarbital anesthesia. The use of the double-lumen catheter allowed the sequential delivery of two drug solutions without intermixing. The proximal end of the catheter was inserted into a major vein and terminated near the superior vena cava; the distal end was threaded subcutaneously and exited through an incision in the back of the animal.

All animals had continuous access to water and were given 20–30 Purina Monkey chow biscuits daily along with a

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TABLE 1
OUTLINE OF PROCEDURE

Trial Sequence (N=50)	Lever 1: Switching Lever	Lever 2: Drug Delivery Lever
Switching	FR5→lever 2 stimulus change At least 3 switches required	Red or green stimulus lights Response→resets switching lever requirement
Choice	Can continue switching	FR 1→"locks in" stimulus color (red or green) and switching lever lights turned off
Self-administration	No consequences	FR 29→infusion→2 min TO (flashing stimulus light) or 2 min (LH)→2 min blackout

sugar cube saturated with liquid vitamins. Antibiotics were occasionally administered intramuscularly into the leg to combat infections.

Apparatus

Each animal was housed throughout the entire experiment in a wooden, front-opening, sound attenuating chamber that was 68.6 cm wide, 76.2 cm high, and 83.8 cm deep. A fan was located on the front door for ventilation. The monkeys were visually isolated but the door had a one-way mirror or peep-hole for observation. On the inside of the front door were two metal boxes (15.2×12.7×10.2 cm), 20 cm from the floor and 10 cm from the center, each containing a response lever (BRS/LVE, PRL-001, Beltsville, MD) and 4 stimulus lights. On the left lever (lever 1) the lights were covered with white Dialco lens caps and on the right lever (lever 2) two lights were covered with red Dialco lens caps and two with green Dialco lens caps. The lights were 6.4 cm above the lever and evenly spaced 3.8 cm apart. The entire ceiling of each chamber was made of Plexiglas and could be transilluminated by either white or red lights.

Each monkey wore a stainless steel harness that was attached to a spring arm that was 46 cm in length and 1.3 cm in diameter (E and H Engineering, Chicago, IL), which in turn was attached to the back wall of the cubicle (see [17] for details). This arrangement allowed the monkey relatively unrestricted movement and provided protection for the catheter, which was threaded through the spring arm. Outside of the cubicle each lumen of the catheter was connected to a peristaltic infusion pump (7540X, Cole-Parmer Instrument Co., Chicago, IL), which delivered solutions at the rate of 6 ml/min.

Procedure

Table 1 presents a brief outline of the procedure. Each session consisted of 50 trials. At the beginning of each trial the white houselight and lever 1 lights were illuminated and lever 2 was illuminated with either red or green lights. Five consecutive responses (FR 5) on lever 1 (switching lever) produced a stimulus change above lever 2, i.e., if the lights above lever 2 were red they changed to green after each FR 5 and vice versa. At least three such stimulus changes, i.e., a sequence of 3 completed ratios on the switching lever, were required before drug became available contingent upon responding on lever 2 (drug delivery lever). Lever 2 responses occurring prior to the completion of three stimulus changes reset the requirement so that 3 additional stimulus changes had to be completed by responding on the switching lever. Although a minimum of 3 switches were necessary, there were no restrictions on the number of stimulus changes allowed, i.e., the monkey could continue responding on the switching lever and each completed FR 5 resulted in a stimulus change above the drug delivery lever.

The first response on the drug delivery lever after the 3-switch minimum had been completed resulted in the lights above the switching lever and the white houselight being extinguished and responses on the switching lever had no further consequences during the trial, i.e., no additional stimulus changes could occur. An additional 29 responses (FR 30) on the drug delivery lever within 2 min (limited hold; LH 2 min) resulted in an infusion of drug over a 10-sec period (a completed trial). During this time, the lights which had been on above the drug delivery lever began flashing (on-off cycle of approximately 1 sec). These lights continued flashing during a 2 min timeout period (TO). If the monkey failed to complete the ratio requirements for drug delivery within the LH 2 min, all lights were extinguished for 2 min (2 min blackout) during which neither lever was operative (an incomplete trial). After either the timeout or blackout period, a new trial began. When this new trial began, the color of the lights above the drug delivery lever were the same as they had been when the last trial terminated. Therefore, in order for a monkey to continue choosing the same drug on successive trials, a minimum of 4 switches was required. Sessions continued until 50 trials were completed or 6 hours had elapsed, whichever occurred first and were conducted seven days a week at the same time each day.

During each trial, one of two drug solutions (drug 1 and drug 2) was available following the completion of the FR 30 on the drug delivery lever. The drug delivered depended upon which stimulus light (red or green) was selected by the monkey; one color light was associated with drug 1 and the other color was associated with drug 2. Therefore the monkey chose one drug over the other by its choice of which

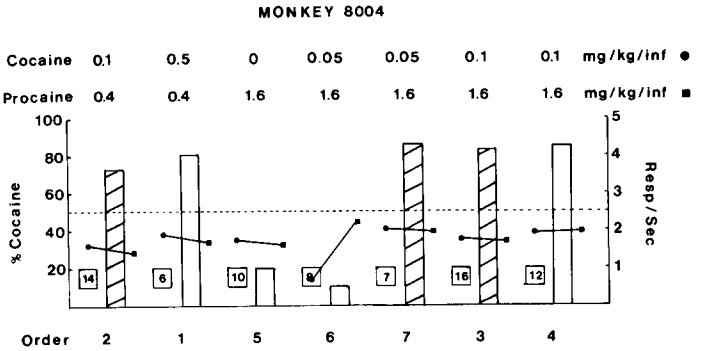

FIG. 1. The bar graph indicates mean percent of cocaine choices during the last 3 sessions of each comparison for monkey 8004. The doses of cocaine and procaine for each comparison was indicated across the top and order is indicated at the bottom. The numbered squares indicate number of sessions for each comparison. The open bars indicate that cocaine infusions were associated with the red stimulus and procaine infusions were associated with the green stimulus. The hatched bars indicate a reversed drug-color association. The data points indicate rate of responding (from 1st to 30th response) under the FR 30 schedule on lever 2 for cocaine (closed circles) and procaine (closed squares).

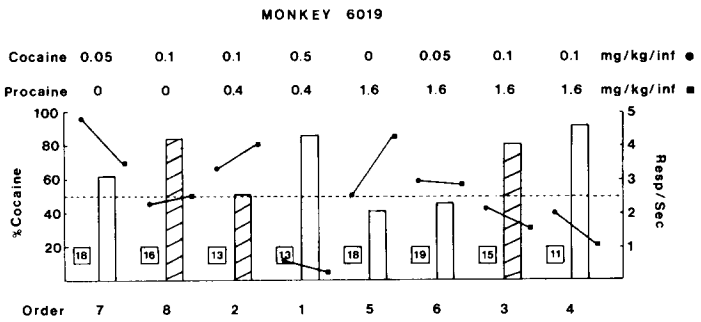

FIG. 2. The bar graph indicates mean percent of cocaine choices during the last 3 sessions of each comparison for monkey 6019. The doses of cocaine and procaine in each comparison are indicated across the top and order is indicated at the bottom. The numbered squares indicate number of sessions for each comparison. The open bars indicate that cocaine infusions were associated with the red stimulus and procaine infusions were associated with the green stimulus. The hatched bars indicate a reversed drug-color association. The data points indicate rate of responding (from 1st to 30th response) under the FR 30 schedule on lever 2 for cocaine (closed circles) and procaine (closed squares).

stimulus light was illuminated when the first correct lever 2 response was made.

Choices were given between doses of cocaine (drug 1) ranging from 0 (saline) to 0.5 mg/kg/infusion and doses of procaine (drug 2) ranging from 0 to 1.6 mg/kg/infusion. Figures 1 (monkey 8004) and 2 (monkey 6019) show the dose combinations and order of testing of each comparison. A particular combination of doses was tested until one of the alternatives was chosen on at least 75% of the completed trials for 3 consecutive sessions or until there was no trend in the choice results for 1–2 weeks. The color of the stimulus light associated with each drug was reversed following the comparison between 1.6 mg/kg procaine and 0.1 mg/kg cocaine in both monkeys and 1.6 mg/kg procaine and 0.05 mg/kg cocaine in monkey 8004.

Data Analysis

During each session, the following data were recorded: trials completed with drug 1 and drug 2, completed switches, incorrect lever 2 responses, incomplete trials (LH timed out) in the presence of each lever 2 stimulus, and the elapsed time between the first and 30th response of each ratio completed on the drug delivery lever in the presence of each stimulus. All data analyses are based upon performance during the last three sessions of each comparison. Choice results are ex-

pressed in terms of the mean percentage of completed trials in which cocaine was selected. Rates of responding on the drug delivery lever (running rate between the first and last response) are expressed as responses/sec.

Drug Solutions

Cocaine hydrochloride and procaine hydrochloride were dissolved in physiological saline so that all doses, expressed in terms of the salt, were delivered in a 1 ml volume. New solutions were prepared at least once every 2 weeks.

RESULTS

Figures 1 (8004) and 2 (6019) show the results of each comparison. In previous comparisons (not shown), both monkeys had preferred (over 75%) 0.1 mg/kg/infusion cocaine to saline. Monkey 8004 (Fig. 1) preferred 0.1 and 0.5 mg/kg cocaine over 0.4 and 1.6 mg/kg procaine. The higher dose of procaine was also preferred over saline. During the initial comparison between 0.05 mg/kg cocaine and 1.6 mg/kg procaine (comparison No. 6), procaine was preferred but the monkey was selecting the drug (procaine) associated with the green stimulus that had been paired with the preferred drug (also procaine) during the previous comparison (comparison No. 5). Therefore, a stimulus reversal was done but the monkey continued to select green which was now paired with cocaine indicating a color preference rather than a drug preference.

For monkey 6019, 0.5 mg/kg cocaine was preferred over 0.4 mg/kg procaine, 0.1 mg/kg cocaine was preferred to 1.6 mg/kg procaine and there was no preference between 0.1 mg/kg cocaine and 0.4 mg/kg procaine. In the comparison between 0.05 mg/kg cocaine and 1.6 mg/kg procaine as well as between each of these drugs and saline, both options were selected equally.

For monkey 8004 (Fig. 1) there did not appear to be any relationship between drug or dose and rate of responding maintained under the FR 30. In fact, with one exception, rates were similar across all comparisons for both drugs. For monkey 6019, rates were inversely related to dose (Fig. 2). There were also substantial differences between monkeys in pattern of responding. Monkey 6019 responded during the timeout and initiated and completed each trial soon after the 2 min TO was terminated. For monkey 8004, on the other hand, infusions were more widely spaced in time. Other measures of performance, such as completed trials, switches and incorrect lever 2 responses were insensitive to drug or dose changes.

DISCUSSION

Self-administration procedures have been used to assess the reinforcing properties of psychotropic drugs in animals and humans [4]. In these studies, the ability of a drug to maintain responding leading to its delivery indicates that the drug is a positive reinforcer [18]. Using a wide variety of paradigms and infrahuman species, it has been found that most psychomotor stimulants, sedative-hypnotics, and opiates can function as positive reinforcers [16]. In general, the same drugs which maintain responding in animals are abused by humans [4,12]. In addition, drugs which are not reinforcers in animals are not abused by humans. This remarkable concordance has led to the use of animals for the preclinical testing of the dependence potential of new compounds [19]. However, there are exceptions, a notable one being the local anesthetics which, with the exception of cocaine, are not considered drugs of abuse. Investigators have found that procaine [3, 6, 11, 20], chloroprocaine [11,22], tetracaine [20], dimethocaine [22] and dimethylprocaine [22] all maintain responding in rhesus monkeys. These local anesthetics have also been shown to have discriminative stimulus properties that are similar to those of procaine in rats [22]. In many of the self-administration studies in monkeys rates of responding maintained by the local anesthetics have been high in comparison to abused drugs such as cocaine [11]. On the basis of these results, it might be tempting to conclude that the reinforcing efficacy of local anesthetics in infrahuman species is greater than, or at least comparable to, that of many other drugs of abuse. The use of response rate as a measure of reinforcing efficacy is problematic since it is controlled not only by the reinforcing properties of the drug injection which follows it but as well by the rate-modifying effect of previous drug injections. This is particularly true with short fixed-ratio schedules of drug delivery where the effects of previous drug injections may cumulate to produce more marked rate-modifying effects [9]. Even in the present study, the relationship between rate of responding, drug and dose was inconsistent.

In the past few years several other strategies have been designed to assess the reinforcing properties of drugs in isolation from their other rate-modifying properties by using dependent variables other than rate of responding for the drug. One approach has been the use of preference procedures where the measure of reinforcing efficacy is the number of times an organism chooses to self-administer one drug solution rather than another [2,13]. The results from these studies have shown that a variety of psychomotor stimulants are preferred to saline as well as food, high doses are preferred to low doses of the same drug and that cocaine is preferred to diethylpropion [1, 13, 14]. Furthermore, preference for higher doses has been shown to decline following several manipulations designed to decrease reinforcing efficacy including increased response cost [7] and electric shock delivery [8]. These data taken as a whole indicate that the use of choice procedures is an excellent strategy for assessing relative reinforcing efficacy.

In the present investigation, a switching choice procedure was used to compare the reinforcing properties of cocaine and procaine. The switching procedure utilized was similar to those in previous studies comparing drugs and food [1, 5, 21, 23] modified in order to make a direct comparison between two drugs. It was found that in most cases cocaine was preferred to procaine regardless of dose.

For monkey 6019, 0.05 mg/kg cocaine and 1.6 mg/kg procaine had similar reinforcing properties. However, the strength of these reinforcing properties was low, resulting in a 50% choice when saline was the alternative. However, it is unlikely that these doses of cocaine and procaine had no reinforcing properties since responding continued to be well-maintained. In situations where catheters become dislodged, responding only continues for 1–2 sessions. For monkey 8004, 0.05 mg/kg cocaine and 1.6 mg/kg procaine also appeared to have similar reinforcing properties in that one drug was preferred during one comparison and the alternative was preferred after a stimulus reversal. In both comparisons, the monkey terminated each trial in the presence of the green stimulus. Under situations where 2 drugs are similar, it is not surprising that other variables such as the discriminative stimulus are capable of controlling responding. Unlike monkey 6019, however, 1.6 mg/kg procaine was preferred over saline. While it was unfortunate that 0.05 mg/kg

cocaine was not compared to saline in this monkey, its preference over 1.6 mg/kg procaine makes it likely that it would have been preferred over saline.

Several investigators have shown that local anesthetics such as procaine maintain high rates of responding under FR schedules in rhesus monkeys and that cocaine has discriminative stimulus properties similar to procaine in rats [11, 20, 22]. However, the abuse of procaine by humans has not been reported. This discrepancy has been attributed to a variety of factors including procaine's short duration of action or a failure to detect procaine abuse in humans because it has been assumed to be an adulterant of cocaine [3,11]. However animal studies with procaine have been limited to procedures where responding is maintained under low fixed ratios using response rate as the only dependent variable. In the present study, using a more complex schedule, the results indicate that although both procaine and cocaine maintain responding, cocaine is a more robust reinforcer. It is possible that potency differences could be a factor, although this is unlikely since the highest dose of procaine tested was 16 times as high as the lowest dose of cocaine which maintained preference over saline. Furthermore, 1.6 mg/kg is a relatively high dose of procaine for self-administration studies [11]. However since systematic comparisons of procaine and cocaine using complete dose-response functions on other behavioral effects in monkeys have not been done, further studies are needed to determine the importance of potency differences. However, the results of the present study are consistent with the failure to observe procaine abuse in humans and indicate the necessity of using a wide range of procedures in evaluating the reinforcing properties of drugs.

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