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Comparative Behavioral Profile of Cocaine and Norcocaine in Rats and Monkeys[1]

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BEDFORD, J. A., R. F. BORNE, AND M. C. WILSON. *Comparative behavioral profile of cocaine and norcocaine in rats and monkeys.* PHARMAC. BIOCHEM. BEHAV. 13(1) 69–75, 1980.—The effects of cocaine and norcocaine were compared using locomotor activity, fixed-ratio 100 (FR 100) and fixed-interval 4 min (FI 4 min) food reinforcement and free feeding paradigms in rats and intravenous self-administration tests in rhesus monkeys. Cocaine was shown to significantly increase locomotor activity at doses of 20 and 40 mg/kg, while norcocaine had no effect at these doses and produced convulsions and death at 60 and 80 mg/kg. Both compounds significantly reduced food consumption at one or more of the doses tested. Cocaine and norcocaine at doses of 20 and 40 mg/kg, produced decreases in FR responding. Cocaine at doses of 10, 20, and 40 mg/kg, produced increases in FI responding; norcocaine had no effect following 10 mg/kg and decreased responding at 20 and 40 mg/kg. Cocaine (0.2 mg/kg/inj) and norcocaine (0.5, 0.2, 0.8 mg/kg/inj) maintained intravenous self-administration in all three monkeys tested. The data indicate that norcocaine is a pharmacologically active metabolite of cocaine which could account for some of the activity heretofore attributed to cocaine. However, the lack of any stimulatory effect of norcocaine on locomotor activity and the lack of increased responding produced by norcocaine on fixed-interval behavior suggest that norcocaine differs qualitatively from cocaine.

Cocaine Norcocaine Fixed-interval Fixed-ratio Locomotor activity Self-administration Rat Rhesus monkey

IT has been shown that the majority of a dose of cocaine administered to man and several laboratory species is hydrolyzed by blood and liver enzymes to form the two major metabolites, benzoylecgonine and ecgonine. These compounds have been isolated in human blood and liver [12] and in rat urine [10], blood and liver [3, 9, 13]. It has further been shown in rodents, dogs, and nonhuman primates that part of the administered dose of cocaine is demethylated to form norcocaine [5, 9, 11]. Although the primary metabolites of cocaine, benzoylecgonine and ecognine have been shown to be relatively inactive, norcocaine is reported to be biologically active in a number of situations. It has been shown that norcocaine inhibits the uptake of norepinephrine in rat synaptosomal preparations [5] and produces many cocaine-like effects on several physiological parameters such as heart rate, respiration and colonic temperature in monkeys [1] and rats [10,11]. Furthermore, norcocaine has been reported to be a substantially more potent local anesthetic than cocaine [6].

Although considerable work has been done with norcocaine, there has not been an evaluation of the comparative behavioral profile of cocaine and norcocaine. The purpose of the present study was to compare the behavioral responses to cocaine and norcocaine in two species, rats and monkeys. Equal doses of cocaine and norcocaine [1] were studied using a food consumption paradigm, a locomotor activity paradigm, fixed-ratio (FR), and fixed-interval (FI) food reinforcement paradigms in rats and an intravenous self-administration procedure in rhesus monkeys.

EXPERIMENT 1: THE EFFECTS OF COCAINE AND NORCOCAINE ON FOOD CONSUMPTION IN RATS

METHOD

Subjects

Subjects for this study were 60 male Wistar rats (Harlan Industries, Cumberland, IN) weighing 250–300 g. Prior to testing the subjects were individually housed for seven days in a temperature (21±1°C) and humidity (40–60%) controlled environment with free access to food (Purina rat chow) and water. A 12 hr light/dark cycle was maintained.

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Procedure

Experimental sessions consisted of one hr/day access to ground rat chow (Purina) which was placed in specially constructed metabolic feeders. The amount of food consumed was measured following each session. Once consumption had stabilized (8–10 sessions), the subjects were randomly assigned to one of six experimental groups (N=10). Following stabilization each subject was injected IP with 1 ml/kg of sterile normal saline 10 min prior to a session. On the following day individual groups of subjects were injected IP with a dose of cocaine or norcocaine (10, 20, or 40 mg/kg) in 1 ml of saline 10 min prior to the session. Following testing the subjects were sacrificed and injection sites verified by visual inspection of the peritoneal cavity. Both cocaine and norcocaine are potent local vasoconstrictors. It has been our experience that subcutaneous injections and those given into the gut produce a black necrotic spot usually quite visible. Statistical comparisons between saline and drug sessions were accomplished via the Wilcoxon Matched-Pairs Signed-Ranks nonparametric test [15]. Statistical comparisons between groups receiving different doses and/or drugs was accomplished via the Mann-Whitney U Test [15].

Drugs and Solutions

Drug solutions for this and subsequent experiments were prepared on the morning of use. All dosages were calculated on the basis of the hydrochloride salt. Cocaine hydrochloride flakes U.S.P. were obtained from Mallinkrodt Chemical Corp. (St. Louis, MO). Norcocaine hydrochloride was prepared and analyzed by a previously reported method [1].

RESULTS

Figure 1 presents the effects of cocaine and norcocaine on food consumption. Both drugs reduced food consumption in a dose-related manner. Statistical comparisons conducted between the data obtained from the session in which drugs were administered prior to food access and the preceding day when the vehicle injection (saline) preceded food access, demonstrated several points. First, both drugs significantly reduced food consumption at all doses tested. Second, when the highest doses of each drug was compared to the lowest dose, significant differences were obtained with both drugs, indicating that the observed dose-effect curve was significant. Comparison of the two drugs demonstrated that norcocaine, at 10 and 20 mg/kg produced a significantly greater reduction in consumption than did cocaine.

EXPERIMENT 2: THE EFFECTS OF COCAINE AND NORCOCAINE ON LOCOMOTOR ACTIVITY IN RATS

METHOD

Subjects

Subjects were 80 male Wistar rats (Harland Industries, Cumberland, IN) weighing 300–350 g. Prior to testing, subjects were individually housed for seven days in a temperature (21±1°C) and humidity (40–60%) controlled environment with free access to food (Purina) and water. A 12 hr light/dark cycle was maintained. Following this acclimation period subjects were randomly divided into 8 groups of 10 subjects each.

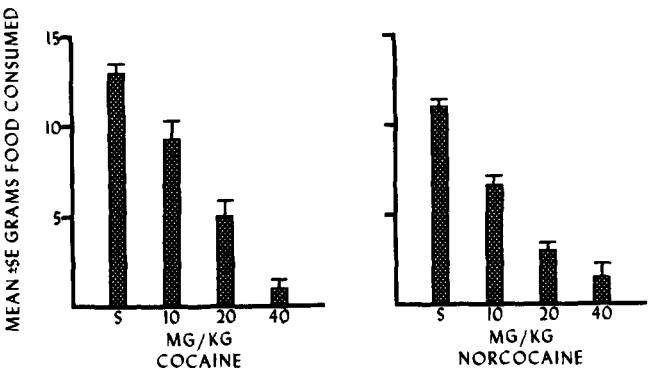

FIG. 1. Mean (±SEM) grams of food consumed during a one hour period as a function of the intraperitoneal dose of either saline, cocaine or norcocaine.

Apparatus

Testing utilized ten circular photocell actometers, homebuilt and previously described [14]. A unique feature of these units is that two adjacent beams must be suquentially interrupted for a count to be recorded. Therefore grooming or stereotypic rearing or movement would not result in a false recording of *locomotor* activity. The actometers were located in a dark, temperature controlled experimental room. A white noise generator provided a continuous auditory environment and masked subject vocalizations and extraneous auditory stimuli.

Procedure

Experimental sessions began at approximately 9:00 a.m., were 3 hr in length and were divided into three parts. Subjects were initially acclimated to the apparatus for 30 min. Following this period subjects were removed and injected IP with 0.5 ml of sterile normal saline and immediately returned to the actometers for 30 min. After this initial hour of the session, subjects were again removed from the actometers and injected IP with either 0.5 ml of sterile normal saline or a comparable volume of a saline solution of cocaine (10, 20, 40 mg/kg) or norcocaine (10, 20, 40, 80 mg/kg). Subjects were then returned to the actometers and locomotor activity recorded for an additional 2 hr. Following testing subjects were returned to their home cages and housed as previously described for two days. At that time subjects were sacrificed and necropsied to insure that all injections were given IP.

The mean locomotor activity scores for the last 2 hrs of the session were calculated for each group. An ANOVA (2-way) and Duncan's New Multiple Range Test [2] were used to make statistical comparisons between groups.

RESULTS

Figure 2 illustrates that treatment with cocaine (20, 40 mg/kg) significantly enhanced locomotor activity, as compared to saline. However, no such effect occurred following treatment with equivalent dosages of norcocaine. Furthermore, increasing the norcocaine dosage to 80 mg/kg resulted in convulsions and death in all subjects during the 2 hr following dosing. No apparent elevation in activity occurred prior to death.

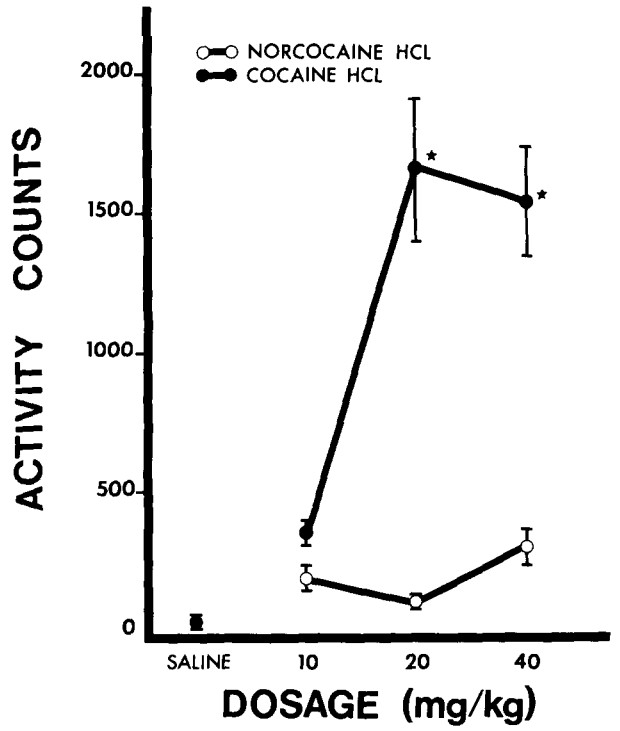

FIG. 2. Mean (±SEM) activity counts as a function of the intraperitoneal dose of either cocaine or norcocaine. A star ★ indicates those values significantly greater than saline control ($p<0.05$).

EXPERIMENT 3: THE EFFECTS OF COCAINE AND NORCOCAINE ON FIXED RATIO AND FIXED INTERVAL FOOD MAINTAINED RESPONDING

METHOD

Subjects

The subjects were male Wistar rats (Harlan Industries, Cumberland, IN) weighing between 200–250 g at the start of the experiment. Subject weights were reduced to and maintained at 85% of their free feeding weight for the duration of the experiment. Water was freely available except during experimental sessions. When not in the experimental chambers, subjects were maintained in individual self-cleaning, self-watering stainless steel cages (Hoeltge, Cincinnati, OH). Ambient temperature was maintained at 21±1°C and the light/dark cycle was 12 hr on, 12 hr off.

Apparatus

Standard operant conditioning chambers (BSR-LVE, Beltsville, MD) measuring 20 cm long and 20 cm high by 30 cm wide were enclosed in sound attenuating enclosures (BRS-LVE). Two rodent response levers (BRS-LVE) were located 5 cm up from the grid floor and 2.5 cm from the front and rear walls respectively. A food cup was located equidistant between the two levers and 2 cm up from the floor. Three jeweled panel lights were located 5 cm above each lever. Ambient illumination was provided by two 28 VDC panel lights located behind a transparent panel near the top of the chamber. Forced air ventilation provided a continuous air exchange, and also served as a source of masking noise. The two chambers used in studies of fixed-interval behavior also had white noise presented through a speaker to provide further masking noise in order to prevent the subject from hearing microswitch clicks on the tape programmer used to program the FI schedule.

Procedure

Experimental sessions were conducted daily Monday through Friday. Eight subjects were trained under a fixed-ratio 100 (FR-100) schedule of food delivery with 45 mg food pellets (P. J. Noyes, Lancaster, NH) serving as the reinforcer. The FR-100 schedule requires the subject to emit 100 responses for each reward. Fixed-ratio sessions lasted 45 min. Nine subjects were trained under a fixed-interval 4 minute (FI-4 min) schedule of food delivery, also for 45 mg food pellets. Under the FI-4 min schedule the first response occurring 4 minutes after the beginning of the interval was reinforced. Fixed interval sessions were terminated when the subject had received 12 food pellets or when 50 min had elapsed, whichever occurred first.

All injections (see Experiment 1, drug preparation) were administered IP 5 min prior to the start of a session. On Thursday of each week all subjects were injected with saline and on Friday the appropriate dose of either cocaine or norcocaine was administered. Three doses of cocaine HCl (10, 20, 40 mg/kg) were tested first in a randomized sequence followed by three doses of norcocaine (10, 20, 40 mg/kg) also administered in a separately randomized sequence. Each subject received all cocaine and norcocaine treatments. Statistical analysis were accomplished via the Mann-Whitney U and the Wilcoxon Matched-Pairs Signed Ranks-tests [15].

RESULTS

The Effects of cocaine and norcocaine on overall responding under the fixed-ratio and fixed-interval schedules. These data are presented in Fig. 3. Both drugs produced a dose-related decrease in the overall rate of responding for those subjects trained under the fixed-ratio contingency. Statistical comparisons between high and low doses within drugs were significant. In addition, statistical comparison of responding during drug sessions with responding during preceding saline control sessions demonstrated that all observed differences were significant. Although it would appear from Fig. 3 that norcocaine was somewhat more potent than cocaine, statistical comparison of the absolute change between the two drugs at identical doses revealed no significant differences.

As can also be seen from Fig. 3 the two drugs produced quite different effects on responding maintained by the fixed-interval contingency. Cocaine produced an inverted U shaped gradient while norcocaine produced a dose-related decrease in responding. Statistical comparison between the 10 and 40 mg/kg norcocaine doses substantiated this dose-related decrease. Statistical comparison between drug sessions and saline control sessions demonstrated significant differences at the low and middle doses of cocaine and at the middle and highest doses of norcocaine. The lack of significance at the highest dose of cocaine appears to be a function of excessive intersubject variability engendered by this dose. As the dose of cocaine was increased there was a dramatic increase in intersubject variability, while as the dose of norcocaine was increased the variability remained either approximately the same (FI) or decreased (FR).

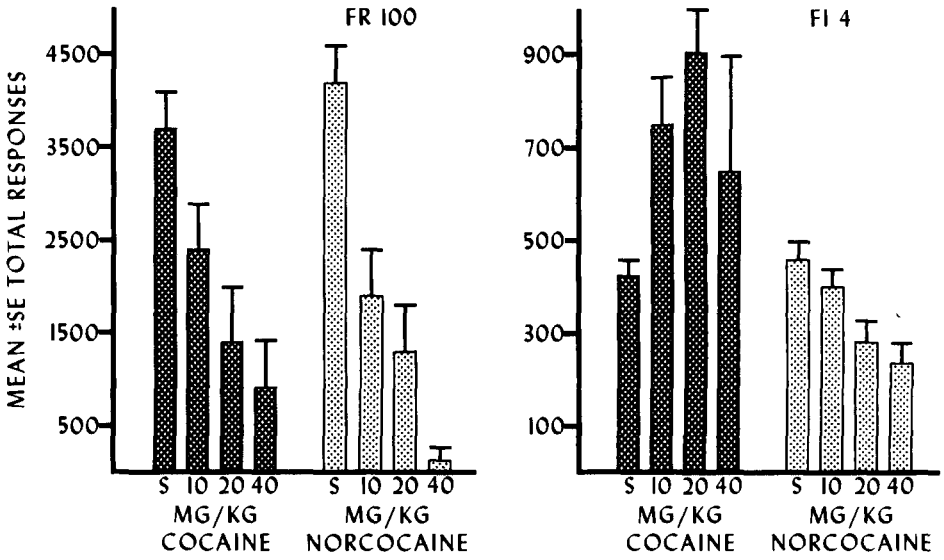

FIG. 3. Mean (±SEM) total responses as a function of the intraperitoneal administration of saline, cocaine or norcocaine. The left panel demonstrates the effects on FR behavior and the right panel, FI behavior.

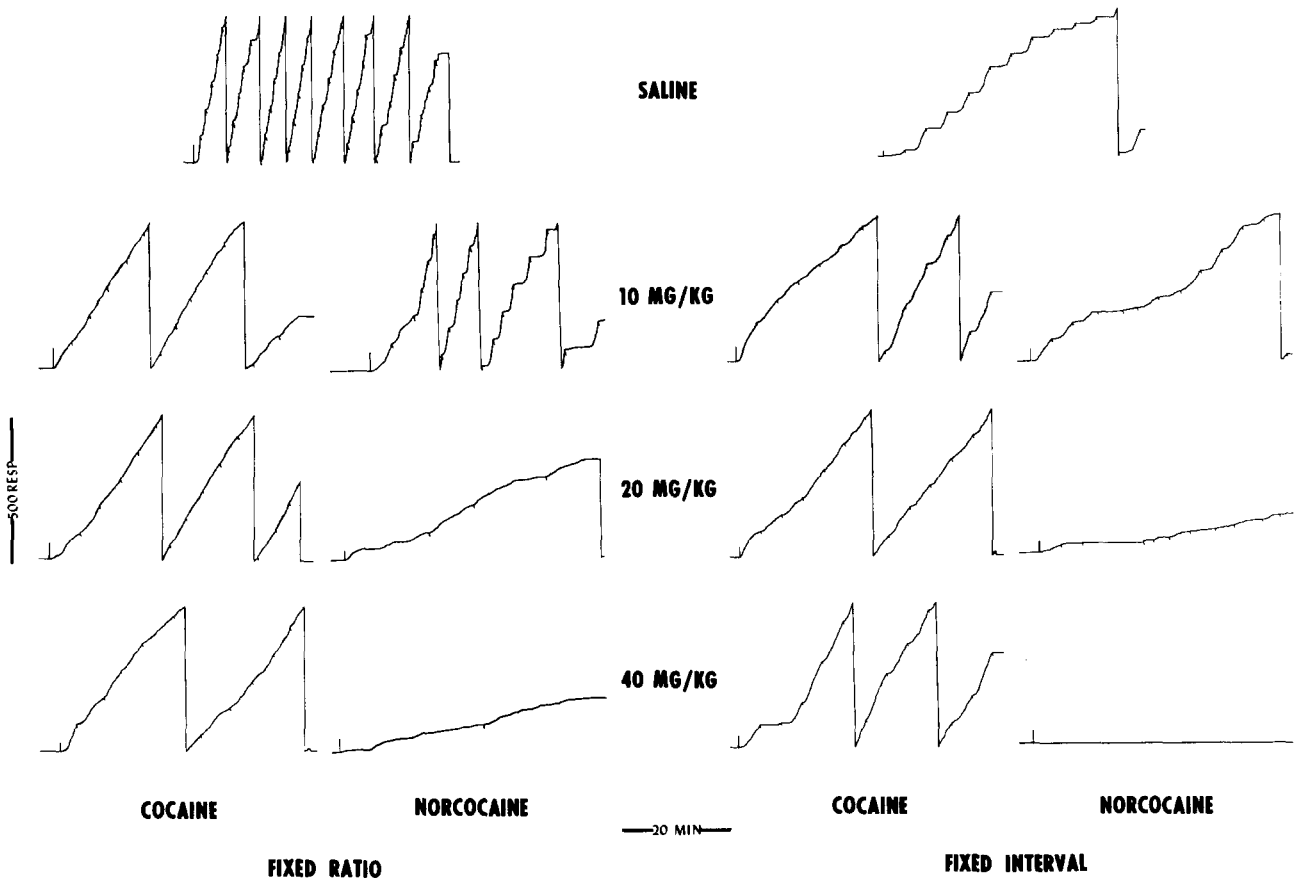

FIG. 4. Representative cumulative records of responding under the FI and FR schedules as a function of the intraperitoneal dose of either cocaine, norcocaine or saline. All ratio records were obtained from the same subject and all interval records from the same subject.

The effect of cocaine and norcocaine on local response rates. Although equipment limitations precluded a detailed analysis of the effects of cocaine and norcocaine on the two schedules, examination of the cumulative records did reveal some effects of the drugs on local rates. Figure 4 presents representative cummulative records for both schedules at all doses tested plus the vehicle control. Control responding was quite similar to that reported for these schedules. The FR showed the typical run and pause while the FI showed the usual pause following reinforcement followed by a gradually accelerating rate until reinforcement occurred. As was pointed out earlier, both drugs produced dose-related decreases in ratio responding on the FR schedule. This is illustrated in the left hand portion of the figure. It is clear with this animal that norcocaine produced a greater reduction in overall responding than cocaine. Other subjects showed this same effect, but to a lesser degree. Cocaine had two effects on local response rates. Cocaine increased low rates of responding which occurred at the beginning of each ratio, whereas high rates of responding which occurred during the remainder of each ratio run were decreased. The overall effect was a decrease in rate indicating a greater effect on high rates than on low rates.

The FI schedule, presented in the right hand portion of Fig. 4, produced a somewhat different picture. Cocaine produced an increase in overall response rate. This increase generally reflects the elimination of the typical postreinforcement pause (PRP) with apparently little to no effect on the higher rates of responding at the end of each interval. Norcocaine, on the other hand, produced no systematic effect on PRP's. Responding was decreased by 10 and 20 mg/kg and completely eliminated by the 40 mg/kg dose.

EXPERIMENT 4: INTRAVENOUS SELF-ADMINISTRATION OF COCAINE AND NORCOCAINE IN RHESUS MONKEYS

METHOD

Subjects

The subjects utilized in this experiment were three experimentally naive male rhesus monkeys (*Macacca* malatta) weighing approximately 4–5 kg at the start of the experiment. The subjects had free access to water and were fed appropriate amounts of monkey chow (Purina) twice daily. The monkeys were surgically prepared under anesthesia (thiamylal NA SURITAL®, and Ketamine HCl KETALAR®, Park Davis, Detroit, MI) with chronic silicone rubber catheters (Silitube, Rodhelm-Reiss, Inc., Bell Mead, NJ), which were threaded through either the internal jugular, external jugular, or the femoral vein to the level of the right atrium.

Apparatus

Each subject was fitted with a stainless steel metal harness which was connected to a hollow spring (E & H Engineering, Chicago, IL), which was in turn connected to the back wall (25 cm above the floor) of the experimental enclosure which measured 91 cm × 124 cm. The subjects were individually housed in these enclosures 24 hr per day until completion of the experiment. Two primate response levers were mounted on one wall 43 cm above the grid floor. Three panel lights (red, green, blue) were located 10 cm above each lever. Ambient illumination was provided during the experimental session by a 7-W incandescent houselight. A ventilating fan provided continuous air exchange and masking noise at approximately 70 dba. One-half sec 0.5 ml infusions of either saline or drug solutions were administered by means of a peristaltic type infusion pump (Masterflex®, Cole-Parmer, Chicago, IL) through vinyl tubing, which was passed through the hollow restraint arm. Within the back of the harness the tubing was connected to the catheter which exited the subject's back under the harness. Experimental contingencies were programmed automatically by electromechanical programming equipment located in a separate room. Data were recorded on cumulative recorders and from impulse counters.

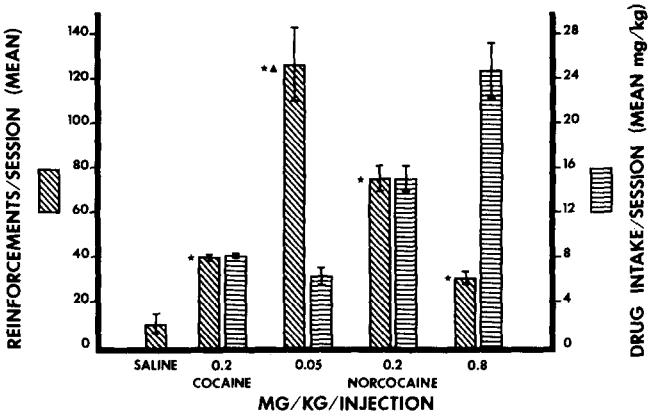

FIG. 5. Mean (±SEM) injections per four hour session (left ordinate) or mean (±SEM) drug intake per session (right ordinate) as a function of the dose per injection of either cocaine or norcocaine. A star ★ indicates values significantly greater than seen with cocaine, 0.2 mg/kg/injection ($p<0.05$). A ▲ indicates that the 0.05 mg/kg/injection dose of norcocaine was self-administered at a significantly greater rate than either the 0.2 or 0.8 dose ($p<0.05$).

Procedure

Four-hour experimental sessions were conducted daily, seven days per week. The onset of each session was indicated by the illumination of the house light. Response on the right-hand lever had no programmed consequences. Each subject was initially trained to press the left-hand lever by making a 0.2 mg/kg infusion (0.5 sec duration) of cocaine hydrochloride contingent upon each lever-press. Following acquisition of the lever-press response the subject's control rate of responding was measured for 5 days, under a fixed ratio 1 (FR 1) schedule of reinforcement. The subjects were then tested with three unit doses (dose per injection) of norcocaine (0.05, 0.2, 0.8 mg/kg/inj) 5 days per dose, in separately randomized sequences. Each 5 day test with a dose of norcocaine was separated by three successive sessions in which cocaine (0.2 mg/kg/inj) was contingent on each lever-press. At the conclusion of the foregoing series, the administration of saline (0.5 ml/inj) was contingent on the lever-press response for 5 consecutive days. Data analysis was accomplished by the Wilcoxon Matched-Pairs Signed-Ranks test [15].

RESULTS

Figure 5 presents the results of the self-administration

studies with cocaine and norcocaine. Both drugs maintained self-administration behavior significantly above saline control levels. In addition it can be seen that norcocaine was self-administered at approximately twice the rate of cocaine at an equivalent unit dose (0.2 mg/kg/inj). Figure 5 also shows that as the unit dose of norcocaine was increased from 0.5 to 0.8 mg/kg/inj the mean number of responses (and consequently the number of injections per 4 hr session) decreased. Mean total drug intake per session also varied systematically with the unit dose. As the unit dose was increased, mean drug intake per session was increased in a dose-related fashion. Statistical comparison revealed that drug intake at the 0.8 mg/kg/ unit dose was significantly greater than intake at the two lower doses.

GENERAL DISCUSSION

Both drugs were observed to produce significant dose-related decreases in food consumption. Norcocaine, however, was shown to be considerably more potent in this effect, since the 20 and 40 mg/kg doses of norcocaine produced significantly greater reductions in intake than did equal doses of cocaine. This apparent difference in potency is interesting since the two drugs appeared to be equipotent in their ability to disrupt an ongoing food-reinforced operant, a more detailed discussion of which appears below.

The finding that norcocaine did not increase locomotor activity is interesting since tests reported here and data reported by others [1, 10, 11], clearly indicate a number of similarities between the behavioral effects of norcocaine and its parent compound, cocaine. One could argue that this lack of effect on locomotor acitivity was a result of the dose range, however, further increases in the norcocaine dose produced convulsions and death with no apparent elevation in activity prior to death.

Both drugs produced quantatively similar effects on responding maintained by the fixed-ratio contingency. Decreases in overall responding were observed with both drugs with norcocaine having a more pronounced effect at the 40 mg/kg dose. Decreases in responding by rats maintained on a fixed-ratio schedule have been reported by others [4, 8, 19]. Two of these papers [8,19] reported decreases in overall response rate but demonstrated that these decreases were a result of a dose-related increase in the initial pause as opposed to a change in rate once the animals began to respond. Referring to Fig. 4, the present data demonstrates no systematic change in initial pause, on the contrary our data clearly indicate that the reduction in overall rate observed in the present paper is due to a change in rate throughout the entire session. In the two reports discussed above [8,19] the subjects were maintained on an FR 40 schedule whereas in the present paper an FR 100 was utilized. Whether this schedule difference can explain this discrepancy in effect is not known, however, we are currently training animals on an FR 40 in order to determine if this schedule difference might explain the difference in the observed effects of cocaine on fixed-ratio performance.

Dose-related decreases in FR responding following cocaine administration have also been reported for squirrel monkeys [17], rhesus monkeys [18], and pigeons [16] further substantiating the effects reported in the present paper. In a recent paper [17] both cocaine and norcocaine were shown to decrease fixed-ratio responding for food in squirrel monkeys. In a related paper [7] norcocaine was shown to generalize completely to cocaine when IP injections of the drugs were used as discriminative stimuli.

While the two drugs produced similar effects on responding maintained by the fixed-ratio contingency, the effects obtained on the FI schedule were strikingly different. Cocaine was shown to produce an increase in responding while norcocaine produced a decrease in responding. A recent report [4] indicated that a 10 mg/kg dose of cocaine produced a 40% reduction in responding in rats maintained under a fixed-interval food reinforcement contingency. In an earlier paper [16] cocaine was shown to produce an increase in responding by pigeons under a fixed-interval food reinforcement contingency. The present data clearly demonstrated that cocaine produces an increase in fixed-interval responding, while norcocaine was clearly demonstrated to produce a decrease in responding. In a report discussed earlier [17] cocaine and norcocaine were shown to decrease FR responding in squirrel monkeys. Under an FI contingency cocaine (0.3–1.0 mg/kg im) and norcocaine (1.0–3.0 mg/kg im) were reported to increase responding while these authors report that higher doses usually decreased responding. The differences between the drug effects in that report [17] and the present report are perhaps a result of methodological differences (i.e. route of administration, dose, species, schedule of reinforcement).

Although the compounds appear to be approximately equipotent in their ability to modify food reinforced leverpressing, this was not the case in either the food consumption or self-administration studies reported above. Both drugs produced a significant dose-related reduction in food consumption. Norcocaine at 20 and 40 mg/kg produced a significantly greater reduction in food intake than equal doses of cocaine. In the self-administration studies, although only one dose (0.2 mg/kg/inj) of cocaine was studied, the same dose of norcocaine was self-administered at approximately twice the rate of cocaine, suggesting either a difference in potency or duration of action.

In conclusion the foregoing data clearly demonstrated that norcocaine, a metabolite of cocaine, has considerable behavioral activity of its own, activity which may very well contribute to the overall effects observed after cocaine administration. The above data also indicate that norcocaine and cocaine do not possess an identical pharmacological spectrum.

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