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RAPID COMMUNICATION

Orally Delivered Cocaine as a Reinforcer for Rhesus Monkeys

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MEISCH, R. A., F. R. GEORGE AND G. A. LEMAIRE. *Orally delivered cocaine as a reinforcer for rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **35**(1) 245–249, 1990.—Orally delivered cocaine was established as a reinforcer for six rhesus monkeys. Cocaine and its vehicle, water, were available from separate spouts under independent concurrent fixed-ratio schedules. The positions of cocaine and water were reversed between spouts from session to session. Cocaine consistently maintained higher response rates than water. Cocaine concentration was systematically varied for three of the six monkeys tested, and cocaine intake (mg of drug/kg of body wt.) increased with increases in drug concentration.

Cocaine Cocaine self-administration Oral route Rhesus monkeys

THERE is an extensive research literature describing self-administration of cocaine by laboratory animals. The most commonly used procedure involves intravenous injection of the drug via a chronic indwelling catheter [e.g., see review in (23)]. The cocaine-reinforced behavior of primates has also been studied using the intramuscular (10,14) and intragastric (1,24) routes. In rats, intracerebral cocaine self-administration has been examined as well (8).

The present study of cocaine-reinforced behavior used the oral route of administration. In humans, chewing of coca leaves is a common route of cocaine administration in some locales (7,11). Further, when cocaine was placed in a gelatin capsule and taken by mouth, greater euphoria was reported by three of four human subjects than after intranasally administered cocaine (22). At present, however, there is a scarcity of information concerning oral cocaine self-administration by nonhuman primates. In the single such study of which we are aware, two rhesus monkeys' responding was maintained at low levels under a fixed-ratio 10 (FR 10) schedule of lever-pressing by cocaine-impregnated gum pieces, but both subjects preferred plain gum to cocaine gum when given a choice between them (20). However, findings from several other laboratories suggested that it might be feasible to establish orally delivered cocaine as a reinforcer for monkeys: First, in all five rhesus monkeys tested, intragastrically delivered cocaine served as a reinforcer (24). Second, in rats, schedule-induced polydipsia was effective in initiating and maintaining oral intake of cocaine (21). Third, Lewis rats preferred cocaine solutions over water in home-cage two-bottle choice preference tests (5). Finally, in C57 mice cocaine was added to an ethanol solution and subsequently the amount of ethanol in the solution was gradually decreased to zero (4); cocaine drinking persisted and was maintained under FR schedules at levels that significantly exceeded water-control values.

METHOD

Subjects

All six male rhesus monkeys that served (M-D, M-JY, M-KT, M-MK, M-SM, and M-TY) had histories of behavior reinforced by ethanol, and (except M-KT) by other drugs as well. Subjects

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were maintained at reduced body weights during the experiment: The mean body weight of the six subjects was 74% of the subjects' weights under 24-hr-per-day free-feeding conditions. As discussed in previous reports [e.g., (18)], laboratory free-feeding conditions result in various degrees of obesity; maintaining subjects at 74% of their free-feeding weights is thus very different from reducing subjects to 74% of their nonobese weights. Food deprivation results in an increase in the magnitude of drugs' reinforcing effects [cf. (15)], and self-administration of many reinforcing drugs is increased, including IV self-administration of cocaine by rhesus monkeys (3).

Apparatus

Experiments were controlled, and data recorded, with equipment (Coulbourn Instruments, Inc.) located in a room adjacent to the room containing the experimental chambers, and the time-course of responding was tracked by cumulative recorders (Gerbrands Corp.). Subjects were singly housed in stainless-steel cages (Hoeltge No. HB-108) 24 hr per day, and cages for all six subjects were located in the same room. Cage dimensions ($76 \times 102 \times 81$ cm) provided adequate housing space for rhesus monkeys (2). The fronts of the cages were barred. A liquid-delivery apparatus panel attached to the outside of one side wall, and elements fastened to the panel protruded into the cage through holes cut in that wall. These elements included two brass drinking spouts and an associated discriminative-stimulus light located above each spout. The operant responses were mouth contacts with either spout. At each liquid delivery, a solenoid-operated valve at the rear of a spout was activated for a maximum of 150 msec, allowing approximately 0.65 ml of liquid to pass through the spout and into the monkey's mouth. The liquid-delivery apparatus has been described extensively elsewhere (6, 12, 15).

Procedure

Experimental sessions were 3 hr in length, and were begun at the same time each day, seven days per week. A one-hour time-out (TO) period was in effect immediately before sessions, during which intersession water-drinking values were recorded. During this period liquids appropriate for the session were also placed in the reservoirs that fed each spout. Some of each side's solution was flushed through the respective tubing leading from the reservoir to the spout, to displace water remaining in the tubing from the intersession period or to displace solution remaining from the previous day's session. This ensured that the appropriate solution was present on the very first liquid delivery of the session. Time-out periods were also in effect for the hour after the session and for the third hour after the session. During the first of these, data from the session were collected, and water placed in one of each monkey's reservoirs and flushed through the tubing to the spout. The spout from which water was available between sessions alternated from day to day. During the second postsession TO period, subjects were fed their daily food rations of Purina High Protein Monkey Chow. Feeding was delayed until 2 hr after sessions to allow any drug effects to dissipate.

Between sessions, when TO periods were not in effect water was available under an FR 1 reinforcement schedule from one spout, and the stimulus light above that spout was continuously illuminated. Responses on the other spout were recorded, but had no programmed consequences; the stimulus light over this spout was not illuminated.

During experimental sessions, the jewelled stimulus light above the spout at which drug was available flickered at a rate of 10 Hz, and a mouth-contact response on that spout resulted in its green-lensed pair of spout lights being illuminated for the duration of each mouth contact. The jewelled stimulus light above the spout at which water was available was steadily illuminated, and a mouth-contact response on that spout resulted in its white-lensed pair of spout lights being illuminated for the duration of each mouth contact.

The procedure used to establish orally delivered cocaine as a reinforcer involved adding gradually increasing amounts of cocaine to an ethanol solution and then gradually removing the ethanol. {A similar procedure has been employed with monkeys to achieve a transition from oral ethanol self-administration to oral pentobarbital self-administration [see (17)].} All six monkeys had a history of ethanol-reinforced behavior. A baseline of stable responding was first established at 8% (W/V) ethanol under a

TABLE 1

SEQUENCE OF COCAINE AND ETHANOL CONCENTRATIONS THAT WERE USED IN ESTABLISHING COCAINE AS A REINFORCER*

Cocaine Concentrations Faded-In Upon an 8% Ethanol Baseline	Ethanol Concentrations as Ethanol was Faded-Out From a Solution Containing 0.8 mg/ml Cocaine
0.00625 mg/ml	7.4%
0.0087 mg/ml	6.8%
0.0125 mg/ml	6.3%
0.0175 mg/ml	5.7%
0.025 mg/ml	5.2%
0.035 mg/ml	4.8%
0.05 mg/ml	4.4%
0.0707 mg/ml	4%
0.1 mg/ml	3.66%
0.0109 mg/ml	3.35%
0.119 mg/ml	3.08%
0.129 mg/ml	2.82%
0.141 mg/ml	2.59%
0.154 mg/ml	2.38%
0.183 mg/ml	2.18%
0.2 mg/ml	2%
0.218 mg/ml	1.83%
0.238 mg/ml	1.68%
0.259 mg/ml	1.54%
0.282 mg/ml	1.41%
0.308 mg/ml	1.29%
0.335 mg/ml	1.19%
0.366 mg/ml	1.09%
0.4 mg/ml	1%
0.44 mg/ml	0.84%
0.48 mg/ml	0.707%
0.52 mg/ml	0.59%
0.57 mg/ml	0.5%
0.63 mg/ml	0.35%
0.68 mg/ml	0.25%
0.74 mg/ml	0.125%
0.8 mg/ml	0.0625%

*Six sessions of stable behavior were obtained at 0.1, 0.2, 0.4, 0.57 (for M-JY and M-TY only), and 0.8 mg/ml cocaine as that drug was faded-in, and at 4, 2, and 1% ethanol as that drug was faded-out. All other ethanol/cocaine combinations were present for a single session, unless there was an unusual decrement in the level of responding at a particular condition (in which case the condition remained in effect for additional sessions, until responding returned to normal levels).

TABLE 2

MEAN (n = 6) DELIVERIES OF 8% ETHANOL OR 0.2 mg/ml COCAINE AND CONCURRENTLY AVAILABLE WATER UNDER VR 8 SCHEDULES DURING 3-HR SESSIONS*

	8% Ethanol Baseline		Cocaine Probe (0.2 mg/ml)		8% Ethanol Retest	
Monkey	Ethanol	Water	Cocaine	Water	Ethanol	Water
M-D	204 (8.5)	1 (0.2)	27 (5.8)	2 (1.0)	195 (3.6)	1 (0.2)
M-JY	219 (17.3)	0 (0.2)	15 (12.8)	23 (12.7)	279 (18.8)	0 (0.1)
M-KT	355 (17.7)	1 (0.4)	65 (3.3)	10 (2.6)	267 (7.5)	3 (1.8)
M-MK	162 (8.7)	14 (4.2)	30 (10.6)	30 (14.6)	151 (9.4)	1 (0.2)
M-SM	174 (8.9)	0 (0.2)	5 (0.4)	1 (0.7)	149 (5.1)	2 (1.4)
M-TY	325 (15.5)	1 (0.7)	23 (5.6)	5 (5.3)	257 (10.0)	0 (0.2)

*Standard errors are given in parentheses.

variable-ratio 8 (VR 8) schedule (in random order, ratio size shifted between 2, 4, 6, 8, 10, 12, and 14 responses from one reinforcer delivery to the next). Stability was defined as no increasing or decreasing trends in the number of liquid deliveries across six consecutive sessions. Water was concurrently available under an identical VR 8 schedule, and the side positions of the water and ethanol were reversed each session. An initial probe was carried out by abruptly substituting a 0.2-mg/ml cocaine concentration for ethanol. As when ethanol was present, above the spout from which cocaine was available, the jewelled stimulus light blinked at a rate of 10 Hz, and above the spout from which water was available the stimulus light was constantly lit. {The 0.2-mg/ml cocaine concentration appeared to be an intermediate concentration, based on George *et al.*'s (4) successful establishment of cocaine as a reinforcer for mice using an ethanol-fading technique [also see (21)].} Following this probe, 8% ethanol returned as the available drug solution, and six sessions of stable ethanol-reinforced responding were again obtained. The purpose of this A-B-A probe procedure was to determine rates of cocaine self-administration (0.2 mg/ml) in the absence of a systematic establishment procedure.

In the next phase, increasing amounts of cocaine were added to the ethanol solution until a combination of 8% ethanol and 0.8-mg/ml cocaine was reached. Subsequently, across sessions the concentration of ethanol was gradually decreased to zero. The progression of cocaine and ethanol concentrations used with three monkeys (M-JY, M-KT, and M-TY) is shown in Table 1 (the sequence of events for the remaining three subjects is described below).

The schedule was shifted from VR 8 to FR 8, and with three monkeys (M-JY, M-KT, and M-TY) concentration-response functions were then obtained: Following six sessions of stable responding at 0.8-mg/ml cocaine, the concentration was cut in half (to 0.4 mg/ml), and each subject was tested under these conditions until another six sessions of stable responding were obtained; the concentration was then cut in half again (to 0.2 mg/ml) for a further six sessions of stable responding; and so on. The lowest cocaine concentration tested with each monkey was that at which the subject's responding was markedly less well maintained than it had been at the immediately preceding, higher concentration. After completion of testing at the lowest concentration, the identical series of cocaine concentrations was retested for two monkeys (M-JY and M-KT), but in reverse (ascending) order. Due to the length of M-TY's original test series, an impending relocation of our laboratory forced a curtailment of his retest series; M-TY was retested only at 0.8 mg/ml.

Drug

A concentrated stock solution of cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was prepared with tap water weekly and stored at 3°C. Monkeys' daily drug solutions were mixed by adding appropriate amounts of tap water to a measured amount of stock solution approximately 2 hr prior to each session, and solutions were at room temperature at the start of sessions. Drug concentrations are expressed in terms of the salt.

RESULTS AND DISCUSSION

Within each condition in Table 2, the left- and right-side columns show, respectively, the mean numbers (n = 6) of obtained drug and water deliveries during the initial probe substitution of cocaine for ethanol. Standard errors are in parentheses. During the baseline condition, the six monkeys obtained a mean of 240

TABLE 3

MEAN DELIVERIES (n = 6) OF 0.2 mg/ml COCAINE AND CONCURRENTLY AVAILABLE WATER*

	Monkey M-D		Monkey M-MK		Monkey M-SM	
Reinf. Schedule	Cocaine	Water	Cocaine	Water	Cocaine	Water
VR 8	39 (13.5)	4 (4.3)	Not Tested	Not Tested	61 (26.6)	0 (0.0)
FR 8	44 (12.8)	0 (0.0)	57 (13.7)	14 (2.9)	46 (18.1)	0 (0.0)
FR 4	206 (14.9)	0 (0.2)	102 (16.0)	43 (8.7)	93 (27.5)	0 (0.2)

*Values in parentheses are standard errors.

deliveries of ethanol and 3 deliveries of water. When cocaine replaced ethanol for six sessions, the mean number of drug deliveries dropped to 28 and the mean number of water deliveries increased to 12. Values at retest with 8% ethanol were close to original values.

The results of this early probe showed that cocaine did not maintain high rates of behavior. What responding did occur may have resulted from the presence of the blinking discriminative stimulus light which indicated the spout that delivered cocaine, and which in the past had been paired with ethanol.

For the three monkeys with whom a systematic concentration-response function was obtained, the quantity of cocaine consumed (mg/kg/session) was directly related to drug concentration. At the highest concentration (0.8 mg/ml), mean cocaine intakes were 5.3, 5.0, and 3.6 mg/kg/session for Monkeys M-JY, M-KT, and M-TY, respectively. These amounts are similar to those taken intravenously (0.05 mg/kg/injection) by rhesus monkeys during 3-hr sessions (9). Figure 1 shows that, for two of the monkeys, the number of drug deliveries first increased and then decreased as cocaine concentration was decreased (note that the scales on the ordinates differ across subjects). With the third monkey (M-TY), the number of drug deliveries increased and then remained high. At the very low concentrations M-TY's total cocaine intake was so low that it appeared unlikely that the behavior was being maintained by cocaine. Consequently, we replaced the cocaine with water. Thus, for this monkey water was present on both sides; however, on one side the light blinked and on the other side the light was steady. As before, the side positions of the steady and blinking lights were reversed each session. From the spout with the blinking light above it, the monkey obtained a mean of 844 deliveries over six sessions, and on the opposite spout a mean of 3 deliveries. These findings demonstrate that the blinking light was an extraordinarily effective discriminative stimulus in controlling this subject's responding, due to past correlation with cocaine reinforcement. The persistent responding demonstrated by this monkey has occasionally been seen in monkeys very experienced in pentobarbital self-administration (unpublished results) and in monkeys receiving intravenous delivery of cocaine as a reinforcer (13). Use of larger fixed-ratio sizes would probably make the animal's behavior more sensitive to concentration changes at the low end of the range (16). Further experimentation will be necessary to assess the significance of individual differences that were present in the numbers of drug deliveries obtained at some cocaine concentrations.

The time course of cocaine-maintained responding was negatively accelerated for all three subjects at the 0.8-mg/ml concentration, and for M-KT and M-TY at 0.4 mg/ml, with the largest drinking bout occurring at the very beginning of the session; at lower cocaine concentrations, responding often was more evenly distributed throughout sessions. Further research will be necessary to fully characterize the time course of oral cocaine self-administration.

During the ascending series of cocaine concentrations that constituted the retest phase, two monkeys (M-KT and M-TY) had retest values at 0.8 mg/ml similar to test values. One (M-JY) had a lower retest value at 0.8 mg/ml; nevertheless, his retest mean was far in excess of water values (48 drug deliveries versus 1 water delivery). As with his retest value at 0.8 mg/ml, M-JY's retest values at 0.1, 0.2, and 0.4 mg/ml were lower than original values. In contrast, M-KTs retest values were very similar to the original values. All three monkeys obtained very low numbers of concurrent water deliveries across all cocaine concentrations, during both the test (descending) and retest (ascending) drug-concentration series. It should be noted that during both the test and retest series, the 0.2-mg/ml cocaine solution maintained behavior at higher levels than it had during the initial probe condition (except for the retest condition with M-JY, the levels were substantially higher; cf. Table 2).

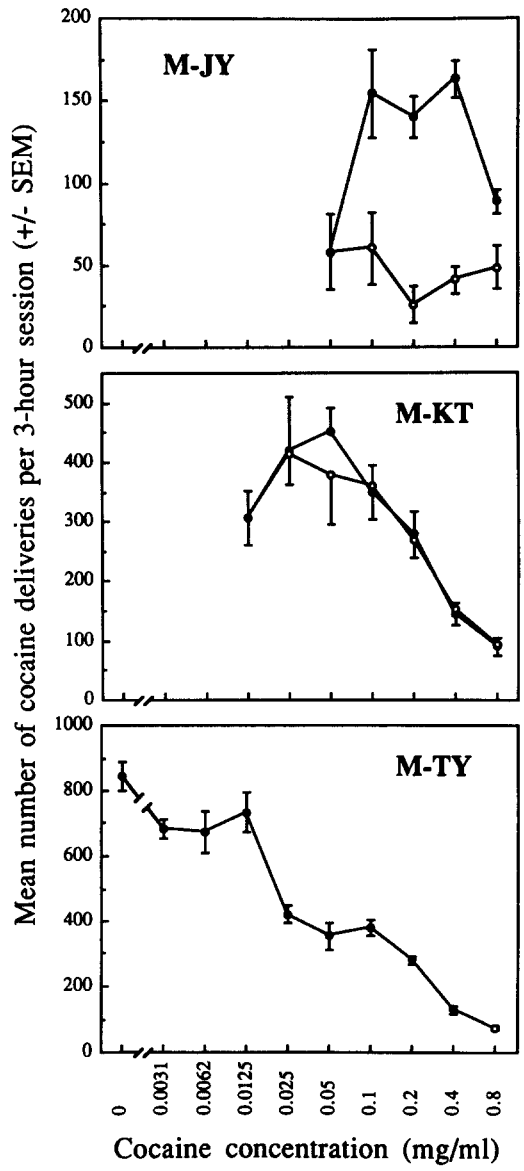

FIG. 1. Mean numbers (n = 6) of cocaine deliveries during daily 3-hr sessions. Filled and open symbols represent test and retest values, respectively. Brackets indicate the standard error of the mean (SEM); absence of brackets indicates that the SEM fell within the area occupied by a data point. For each subject, testing began at a cocaine concentration of 0.8 mg/ml, and progressively lower concentrations were then tested. After testing at the lowest concentration, the same concentrations were then tested in an ascending order for M-JY and M-KT; due to time constraints, the only concentration retested with M-TY was 0.8 mg/ml. Water was concurrently available at all conditions. Water deliveries are not shown because they were exceedingly low in number across all conditions [the mean values across conditions were 5.7, 4.4, and 3.2 for M-JY, M-KT, and M-TY, respectively; these were calculated on the basis of 54 sessions for M-JY (6 sessions × 9 conditions), 78 sessions for M-KT (6 sessions × 13 conditions), and 60 sessions for M-TY (6 sessions × 10 conditions)]. Note that different scales appear on the ordinates of different subjects' graphs.

The three remaining monkeys (M-D, M-MK, and M-SM) were not tested at multiple cocaine concentrations in the absence of ethanol. With these monkeys, it was necessary to modify the

acquisition procedure: While the cocaine concentration was held constant at 0.8 mg/ml and the ethanol concentration was being gradually decreased, points were reached where responding dropped to low levels. Consequently, the cocaine concentration was decreased first to 0.4 mg/ml and then to 0.2 mg/ml. At the end of this acquisition phase, cocaine did maintain responding in the absence of ethanol. Subsequently, the schedule was shifted from a VR to an FR schedule. Results listed in Table 3 show that at FR 8 a 0.2-mg/ml cocaine solution clearly maintained higher response rates than did concurrently available water; however, because of rather high variability in the numbers of drug deliveries obtained by each subject across sessions (note the relatively large standard errors of the mean in Table 3), only Monkey M-SM's behavior can confidently be said to have been maintained at higher levels by the 0.2-mg/ml cocaine solution under these conditions than during the initial probe condition under a VR 8 schedule (see Table 2). Furthermore, the 0.2-mg/ml concentration maintained much lower levels of behavior in these subjects than in the three subjects whose data appear in Fig. 1. Schedule size was then decreased to FR 4, which resulted in a substantial increase in drug-maintained responding (Table 3); under these conditions the 0.2-mg/ml cocaine solution clearly functioned as a reinforcer for M-D, M-MK, and M-SM. The large increase in behavior that resulted upon the shift from an FR schedule requiring 8 responses (a relatively low FR size) to one requiring 4 responses may indicate that the cocaine solution was a relatively poor reinforcer for these subjects. Further experimental manipulations to clarify this matter were not possible due to the relocation of the laboratory.

Although the monkeys displayed differences in cocaine-reinforced behavior, we were able to establish orally delivered cocaine as a reinforcer for all six monkeys that were studied. It was possible to engender and maintain high rates of responding, and toxicity was not observed; the latter finding is consistent with the observation that severe toxicity is not seen when humans chew coca leaves (19). The present data systematically replicate the findings obtained in mice by George *et al.* (4). The current findings also complement those already obtained in other laboratories where cocaine-reinforced behavior of rhesus monkeys has been studied using the intravenous route; for example, when cocaine is taken intravenously, there is an inverted U-shaped relation between drug dose and responding [for a review see (23)]. The oral preparation is an unusually stable one, which will permit long-term, systematic studies of variables affecting cocaine-reinforced behavior.

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