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Phencyclidine Self-administration in the Rhesus Monkey[1]

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BALSTER, R. L., C. E. JOHANSON, R. T. HARRIS AND C. R. SCHUSTER. *Phencyclidine self-administration in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 1(2) 167–172, 1973.–Two experiments were performed in which rhesus monkeys self-administered phencyclidine through indwelling venous catheters. In the first experiment, monkeys trained to lever press for cocaine injections, maintained higher response rates as compared to saline control rates when phencyclidine at unit doses from 1.5–25.0 μg/kg were substituted for the cocaine baseline. In the second experiment, experimentally naive monkeys spontaneously initiated lever-pressing for injections of 50 μg/kg/inj phencyclidine. In both studies the animals self-administered enough drug to produce behavioral effects resembling general anesthesia.

Phencyclidine Self-administration Substitution procedure Drug abuse Cocaine Psychotomimetics Piperidines Rhesus monkey

THE laboratory study of problems of drug abuse has frequently used the self-administration of drugs by animals as an important research tool. A number of significant advances have been made in this field in recent years since the introduction of techniques for allowing animals to self-administer drugs intravenously, using a remotely operated infusion pump connected to a chronically implanted venous catheter [14]. Most studies to date have been concerned primarily with the opiates [16], psychomotor stimulants [11,15], and barbiturates [2,5]. There has been only one reported attempt to study the intravenous self-administration of a psychotomimetic drug. Deneau, Yanagita, and Seevers [3] found that monkeys would not self-administer mescaline either spontaneously or after one month of programmed administration.

The present paper reports two studies demonstrating that rhesus monkeys will self-administer phencyclidine, a drug with marked psychotomimetic effects in man. In the first study, monkeys with a long history of drug self-administration were tested to see if they would continue self-administration when phencyclidine was substitued for a known drug reinforcer, cocaine. In the second study, experimentally naive animals were tested to see if they would spontaneously initiate lever pressing for phencyclidine reinforcement.

EXPERIMENT 1

SUBSTITUTION OF PHENCYCLIDINE IN MONKEYS MAINTAINED ON COCAINE SELF-ADMINISTRATION

Method

Animals. One female (A019) and two male (A041, A055) rhesus monkeys weighing 4.0–6.1 kg, with histories of self-administration of psychomotor stimulant and opiate drugs using the basic procedure of this study, were used.

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They were fitted with a stainless steel harness [3] and a connecting arm constructed from a steel spring. Under pentobarbital anesthesia, the animals were surgically prepared with indwelling venous catheters of siliconized rubber. The catheter exited through the skin on the monkey's back and ran through the harness and arm to the outside of the experimental cubicle where it connected to a peristaltic infusion pump.

Apparatus. The experimental cubicles were commercially available, top loading, large animal cages modified for the present experiment by mounting an intelligence panel on the front of the cage. This panel consisted of a response lever and two stimulus lights. One light was mounted above the lever, and the other in the center of the panel. All programming and recording was accomplished automatically with electromechanical equipment located in an adjacent room.

Procedure. Prior to this experiment the monkeys had been trained to press the response lever for an injection of 200 μg/kg cocaine hydrochloride during a daily three-hour session. The session was signalled by the illumination of the light over the response lever. Ten responses were required to produce an injection [fixed-ratio (FR) 10]. The infusion duration was approximately 10 sec depending upon the animal's body weight. During infusions the light over the response lever was turned off and the center light was illiminated. Responses during injections had no consequences. Both drugs used in this study were dissolved in physiological saline to allow the unit dose to be delivered in 0.2 ml/kg. All doses refer to the salt.

The substitution tests consisted of replacing the cocaine solution with the test solution for six consecutive daily sessions. Between tests the animals were returned to cocaine self-administration for a minimum of three days to reestablish baseline. Phencyclidine hydrochloride (Sernylan®) at unit doses of 3.1, 6.2, 12.5, and 25.0 μg/kg and physiological saline were tested in all three animals. In addition, animal A041 was tested with 1.5 μg/kg/inj. phencyclidine. The order of testing was randomized for each animal.

Results and Discussion

The total number of injections of phencyclidine or saline self-administered each session was recorded. Only the last three days at each test dose are included in the data analyses. Figure 1 presents the mean number of injections and the range over the last three days for each test dose for each monkey. When saline was substituted for cocaine, responding was considerably reduced, not exceeding 40 injections per session. Although the data for the first three days of saline substitution are not graphed, all the animals self-administered a large number of injections on the first day of saline, with the rate decreasing to an asymptote by the last three days of substitution. It is for this reason that only the last three days of responding are used for comparison. Responding on these days presumably represents extinction levels for an ineffective reinforcer, saline.

Each of the monkeys self-administered at least three unit doses of phencyclidine above their saline control range. The relationship between unit dose and response rate is an inverted U-shaped function; the unit dose maintaining the highest rate was different for each animal.

The mean total phencyclidine intake per session for each of the three animals is presented in Fig. 2. Drug intake is

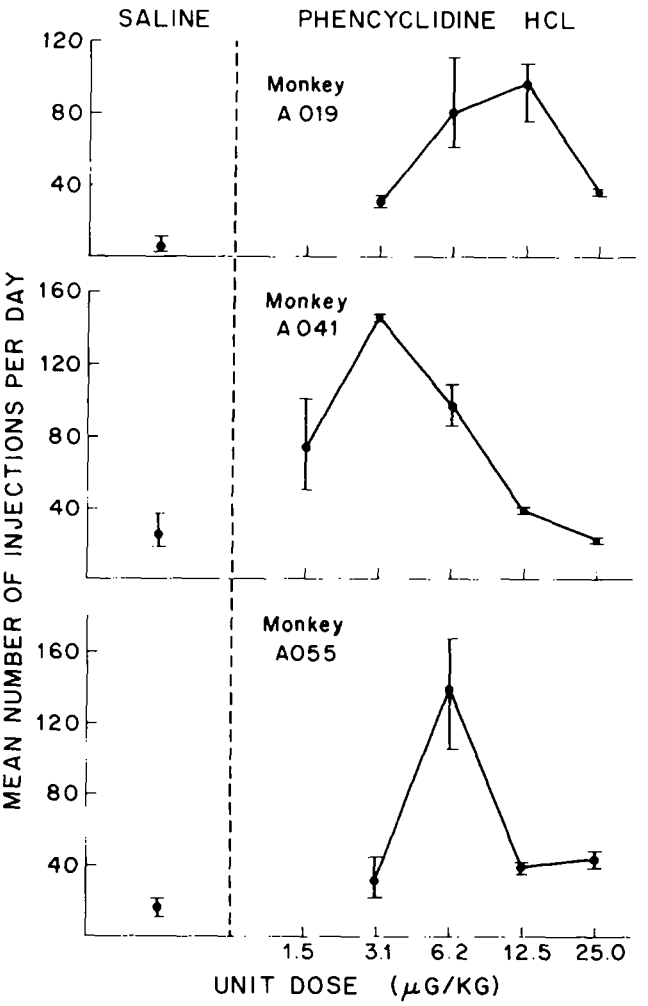

FIG. 1. The number of saline and phencyclidine injections self-administered as a function of unit dose. Values represent the mean and range for the last three days of substitution on a cocaine baseline for each of the three animals.

generally positively related to unit dose, reaching levels of 0.5 to 1.2 mg/kg/session. Monkeys A019 and A055 self-administered up to twice as much phencyclidine as did Monkey A041. In general, Monkey A041 was more sensitive to this drug in that response rate reached a maximum at a dose lower than that needed for the other two animals..

It is clear from these results that phencyclidine can serve to reinforce self-administration behavior in rhesus monkeys maintained on cocaine. Although no systematic attempt was made to assess the behavioral effects of the doses of phencyclidine self-administered by these animals, observation of the monkeys showed them to be highly intoxicated. They often were unable to remain in the sitting position without supporting themselves with their arms. Phencyclidine is used extensively as a general anesthetic in subhuman primates [9] with a dose of 1.0 mg/kg injected intramuscularly being sufficient for complete immobilization of the animal. This dose is comparable to the doses self-administered intravenously in the present study over the

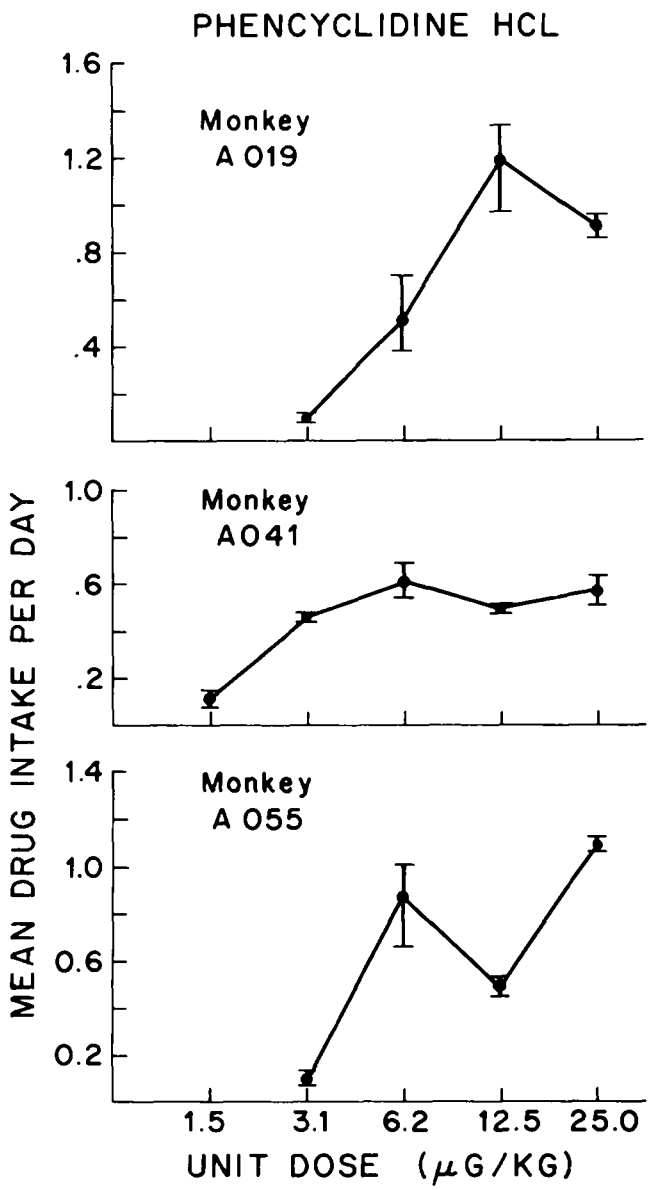

FIG. 2. Drug intake of phencyclidine self-administered as a function of unit dose. Values represent the mean and range for the last three days of substitution on a cocaine baseline for each of the three animals.

three hour test session. It was the nonspecific disruption of behavior produced by these high doses that undoubtedly prevented the animals from self-administering as many injections at high unit doses as at lower ones.

EXPERIMENT 2

SPONTANEOUS INITIATION OF PHENCYCLIDINE SELF-ADMINISTRATION BY NAIVE MONKEYS

Experiment 1 demonstrated that monkeys experienced at drug self-administration will self-administer phencyclidine to high total doses. It is important to know if naive monkeys will spontaneously initiate self-administration of this drug when given unlimited access. In addition, 24 hr a day access provides data on the pattern of drug self-administration and on the behavioral toxicity associated with doses chosen by the experimental animal [13].

Method

Animals and Apparatus. Two male rhesus monkeys weighing 3.0 and 4.0 kg, with no experimental history, were used. They were catheterized as described in Experiment 1. The only significant differences in the apparatus from Experiment 1 was that in this experiment the restraining arm was constructed of jointed steel tubing [3], the infusion pump was of the syringe type, and the intelligence panel was mounted on the side of a front-loading cubicle.

Procedure. After adaptation to restraint and catheterization, operant rate of saline self-administration was determined for 10 days for both animals. The light over the lever was illuminated 24 hr per day, and responses on the lever resulted in the infusion of 0.5 ml/kg physiological saline. During infusions the light over the lever was turned off and the center light was illuminated. Infusion duration was 10 sec for both animals.

On Day 11 the saline solution was replaced with phencyclidine hydrocloride. Each response produced an injection (FR1) of 50 μg/kg dissolved in 0.5 ml/kg saline. The animals were allowed unlimited access to this dose for 8 consecutive days, following which the response requirement was raised to FR2 on Day 19 and FR5 on Day 21.

After 7 days of fixed-ratio responding the access period was shortened to 4 hr per day beginning at 12:00 noon and the response requirement was returned to FR1. After 8 days of 4-hr access to 50 μg/kg/inj phencyclidine, the drug solution was replaced with saline for 7 days.

Results and Discussion

During the 24-hr access periods, data was recorded at 12:00 noon and the mean number of infusions per hour was calculated for the preceeding 24-hr period. Figure 3 presents these results for each animal. The operant rate for saline injections was uniformly low averaging between 12 and 24 injections per day. The range for the 10 days is shown for each animal.

On the first day of phencyclidine access both monkeys increased their response rate, one animal to 46 injections and the other to 118 for a total daily drug intake of 2.3 mg/kg and 5.9 mg/kg respectively. Although there was some variability from day to day, the response rate for phencyclidine continued above saline control levels. Observation of the animals during this period showed them to be even more highly intoxicated than in Experiment 1. Frequently the animals could be found lying in awkward positions on the floor of the cubicle, briefly raising themselves up to press the lever only to fall back down to the floor after the injection. Periods of almost complete anesthetization were followed by periods in which the animals were only mildly uncoordinated. During these latter periods the animals would eat and drink close to their normal amount of food and water.

The pattern of self-administration of phencyclidine over a 24-hr period was assessed by counting the number of injections self-administered each hour. A typical day for each monkey is presented in Fig. 4. The animals almost always showed periods of nonresponding lasting 3–8 hr each day. This period always occurred at night. When the

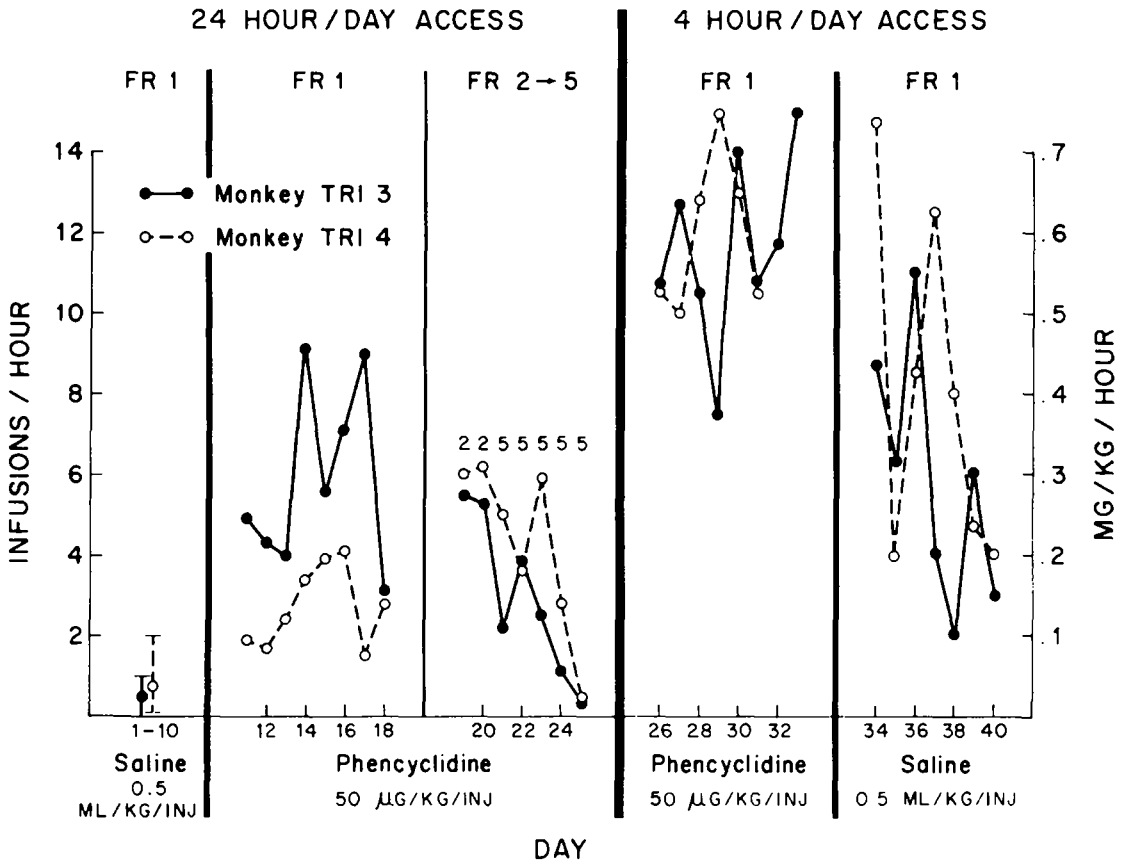

FIG. 3. Number of infusions and drug intake per hr of saline and phencyclidine self-administered by two naive animals with 24 hr per day access. Values for saline represent the mean and range over ten preceeding control days. Right panel: Number of infusions and drug intake per hr of phencyclidine and saline with 4 hr per day limited access.

animals were observed during these periods they would appear to be asleep, for if aroused they would frequently resume bar pressing.

The animals maintained their levels of drug intake when the response requirement was raised from FR1 to FR2 (Fig. 2); in fact, Monkey TR1 4 increased the number of injections self-administered. However, when the response requirement was further increased to FR5 the number of injections decreased for both animals. This result parallels the effect of changing the fixed-ratio parameter from 1–10 on pentobarbital self-administration [5], where the number of injections earned also decreased with increasing FR. This is in contrast to the effect of changing fixed-ratio values from 1 10 [5] or 1–20 [10] responses for cocaine where the number of injections remained constant.

Responding for phencyclidine reinforcement was rapidly reestablished by returning the response requirment to FR1 (Fig. 3). This, in combination with a restricted access of 4 hr per day, increased the hourly intake to about 12 infusions. At these rates the animals self-administered about 2.5 mg/kg/4-hr session. This dose is well above the minimum intramuscular dose necessary for anesthesia in naive animals. These high levels of intake are evidence for the development of tolerance. This tolerance and the lower response requirement undoubtedly accounts for the high levels of self-administration seen in these animals compared with those in Experiment 1.

When phencyclidine access was terminated and saline made available 4 hr per day, response rate decreased to well below the levels seen for drug reinforcement (Fig. 3). That these levels were higher than on Days 1–10 of the experiment can be accounted for at least in part by the difference in access time resulting in a change in stimuli for the limited access condition. The animals on limited access, after 20 hr of timeout, would usually self-administer 8 10 injections of saline when the stimulus light indicating an experimental session was first illuminated, and then rapidly quit responding each session.

GENERAL DISCUSSION

Phencyclidine is a compound which is appearing with increasing frequency in street samples of drugs sold as hallucinogens [6,12]. The drug is ostensibly abused because of its marked psychotomimetic properites in man [1,7]. The present experiments, therefore, describe a successful attempt to obtain an animal self-administration model for psychotomimetic drug abuse. However, a significant question which remains is whether phencyclidine is representative of psychotomimetic drugs since it has other pharmaco-

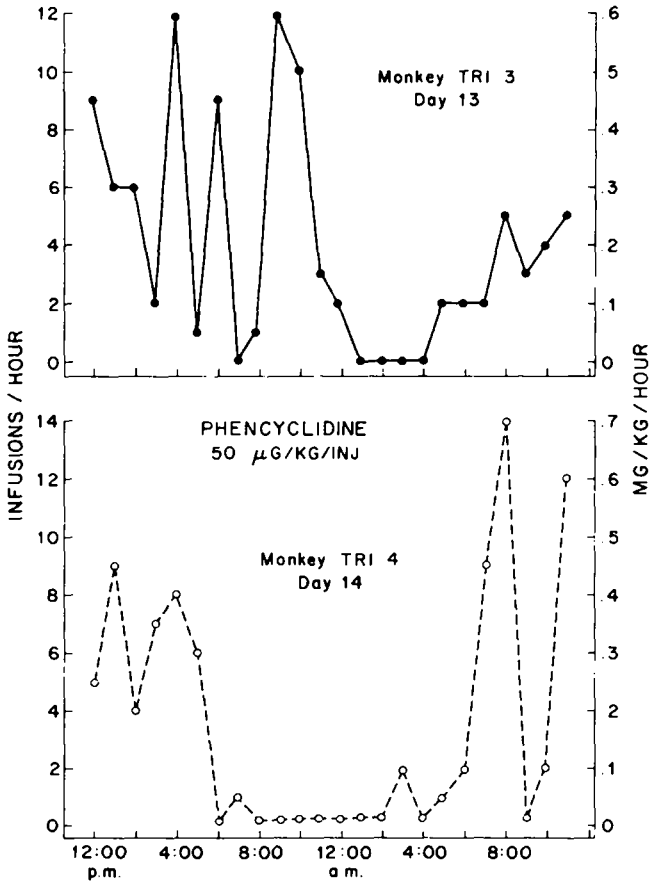

FIG. 4. Representative hourly distributions of phencyclidine injections self-administered by two monkeys with 24 hr per day access.

logical properties not possessed by most hallucinogens which might account for its reinforcing properties in monkeys.

The primary pharmacological effect of phencyclidine not characteristic of other psychotomimetics is its anesthetic properties [4]. In this regard, phencyclidine self-adminstration may be expected to parallel barbiturate self-administration. A study of pentobarbital self-administration in rhesus monkeys [5] evidenced the following parallels to the present experiments. First, the animals would self-administer pentobarbital to levels which would produce general anesthesia, particularly at higher unit doses. Secondly, the number of injections of pentobarbital decreased with increases in the fixed-ratio requirement. And thirdly, there was a greater tendency for animals to show an increase in total drug intake with increases in unit dose for pentobarbital than observed for cocaine.

The question of whether or not phencyclidine is self-administered for its psychotomimetic properties or for its CNS depressant effects cannot be resolved here. An assessment of the relative reinforcement efficacy of phencyclidine and a related compound, ketamine (Ketelar®), would provide some evidence relating to this question since signs of CNS depression are more predominant with ketamine than with phencyclidine [8].

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