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Comparison of Phencyclidine and Three Analogues on Fixed-Interval Performance in Rhesus Monkeys[1]

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BRADY, K. T., R. L. BALSTER, L. T. MELTZER AND D. SCHWERTZ. *Comparison of phencyclidine and three analogues on fixed-interval performance in rhesus monkeys*. PHARMAC. BIOCHEM. BEHAV. **12**(1) 67–71, 1980.—The effects of four arylcyclohexylamines on operant performance in rhesus monkeys were compared. Four rhesus monkeys were trained to lever press on a multiple fixed-interval 5 min time out 1 min schedule of food presentation during daily 1½ hour sessions. Dose-response curves and median effective doses were determined for phencyclidine, N-ethyl-1-phenylcyclohexylamine, 1-(1-(2-thienyl) cyclohexyl) piperidine and ketamine. Ketamine was found to be approximately 1/10 as potent as the other drugs which were approximately equipotent. The drugs had qualitatively similar effects. High doses of all four drugs decreased overall response rates and the slopes of the dose-response curves were comparable. A dose-related rate-dependent effect was found for all four drugs. Onset and duration of the drug effects were also presented.

Phencyclidine Ketamine Arylcyclohexylamines Fixed-interval performance
Schedule-controlled behavior Monkeys

THE illicit synthesis of phencyclidine (PCP) and many of its derivatives is a relatively simple process and several analogues, most notably 1-[1-(2-thienyl) cyclohexyl] piperidine (TCP) and N-ethyl-1-phenylcyclohexylamine (PCE), are known to have appeared in street use [18]. For this reason, there is a need to determine the pharmacological properties of different arylcyclohexylamines and how they compare to those of PCP [4].

McCarthy *et al.* [11] found that ketamine, 2-(0-chlorophenyl)-2-methyl aminocyclohexanone, had much the same spectrum of activity as PCP, but was less potent. They reported that the duration of anesthesia produced by ketamine in monkeys was shorter than that of PCP, and the onset of the anticonvulsant activity of ketamine in mice was more rapid than with PCP. Chen [5] found that PCP, TCP, PCE and ketamine all produced a similar, characteristic catalepsy in pigeons. TCP and PCE were found to be relatively equipotent to PCP, and ketamine was approximately 1/10 as potent as PCP.

Pinchasi *et al.* [16] compared PCP, PCE and TCP on forced rotarod performance in mice. They found PCE to be slightly more potent than PCP or TCP. Furthermore, PCE was found to have a rapid onset and offset. Peak effects of PCE were observed 5 to 10 min after subcutaneous injection, with performance returning to normal within 60 min, even at the highest dose (20 mg/kg). Kalir *et al.* [6,7] also found PCE to be slightly more potent than PCP in disrupting mouse rotarod activity. Several investigators [9, 10, 13, 14, 16, 19] have reported that PCP, PCE and TCP have both anticholinergic and anitcholinesterase activity using both receptor binding and bioassay procedures. The purpose of this study was to compare the effects of PCP, TCP, PCE, and ketamine (Fig. 1) on fixed-interval performance in rhesus monkeys.

METHOD

Animals

The subjects were four adult male rhesus monkeys which had previously been used in a study of the effects of cannabinoids on fixed-interval responding (Brady and Balster, submitted for publication). At least two months during which no drugs were administered intervened between these studies. The same behavioral performance was used in both studies. The animals were maintained at a constant weight (6–8 kg) by adjusted post-session feedings and had free access to water in their home cages.

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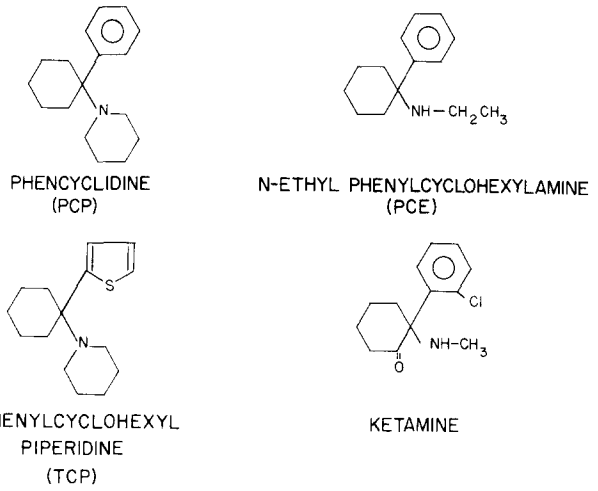

FIG. 1. Chemical structures of PCP and analogues.

Apparatus

The experimental sessions were conducted in an upright refrigerator shell equipped with an exhaust fan and a house light on the ceiling. The monkeys were seated in a primate chair, which restricted movement by a waist stock and shoulder rings, for the duration of the experimental session. Immediately before initiation of the session, the chair was placed in the chamber facing the front door upon which a response lever, three colored stimulus lights and a food trough were mounted. Lever pressing was maintained by the presentation of two 1 g banana flavored food pellets (Noyes, Formula L) by an automatic feeder (BRS/LVE PDC) located outside on the chamber door. The experimental contingencies were controlled by solid state programming equipment located in an adjacent room. Data were recorded automatically in the form of response totals and cumulative response recordings.

Procedure

The animals had been trained to respond on a multiple FI 5 min time out 1 min schedule of food presentation. At the beginning of the session, the house light and the lights over the lever were illuminated. The first response after 5 min resulted in food delivery. If the animal did not respond within 1 min (limited hold 1 min) after the 5 min interval had elapsed, the available food pellets were forfeited and the schedule advanced into a 1 min time out during which the lever lights were turned off and responding had no consequence. A reinforced response automatically advanced the schedule into the time out which occurred between each fixed-interval. The session was terminated after the fifteenth FI component, at which time the house light and lever lights were extinguished. Experimental sessions were conducted seven days a week.

When stable responding was achieved, drug injections were given IM on the day following 3 consecutive baseline days when response rates varied by less than 20%, usually every fourth day. The animals were injected while in the primate chair 5 min before the initiation of the session. The animals were then kept in a holding area until immediately before the initiation of the session, when the chair was placed in the operant chamber. The different drugs were given in a random sequence which differed for each animal. Each drug was given to two subjects in an ascending dose order, and to the remaining two subjects in a descending dose order.

Data Analysis

Non-injection response rates for the three days preceding each injection were used to calculate baseline response rates. For rate-dependency analysis [8], the FI was divided into 5 one min segments and drug effects on local response rates were graphed as a function of the average rates of responding in corresponding segments of the FI for the baseline days. The duration of the limited hold was not used in the calculation of response rates for the terminal bin. Only treatment days during which overall responding exceeded 0.1 response per sec were included in rate-dependency calculations.

Responses per sec for each of the fifteen intervals in the session were calculated by measuring the height of the peak for each interval on the cumulative records and calculating the number of responses.

Drugs

Phencyclidine HCl was supplied by Bio Ceutic Laboratories (Sernylan). Ketamine HCl was supplied by Parke-Davis Co. (Ketalar). They were diluted with 0.9% saline to a concentration that resulted in an injection volume of 0.2 ml/kg. PCE and TCP as the HCl salts were supplied by the National Institute on Drug Abuse. These drugs were dissolved in saline in a concentration that resulted in an injection volume of 0.2 ml/kg. Vehicle injections of 0.2 ml/kg saline were given once during the testing of each drug. All injections were given IM, 5 min pre-session. Doses refer to the salts.

RESULTS

The FI 5 min schedule of reinforcement generated positively accelerated patterns of responding characteristic of FI performance. The baseline rates ± SEM throughout the experiment for each of the four subjects were 1.36 ± 0.08, 1.1 ± 0.05, 0.23 ± 0.01, and 1.53 ± 0.05 responses per sec. Although response rates for each monkey were fairly stable, there were wide differences between monkeys. As a consequence the data is presented as percent change from baseline rates, averaged across animals.

Figure 2 shows the group dose-response curves for each of the four compounds tested. Dose-related decreases in responding were seen for all four compounds. The slope of the dose-effect curve was also similar for each of the drugs. Although only decreases in average response rates are seen in this figure, each of the four compounds produced modest response rate increases at lower doses. These increases are not evident in the group averages because they were small increases and they occurred at different doses in the different subjects. At the higher doses of each compound, similar observable effects could be seen prior to or after the sessions while the subjects were seated in the restraining chair. Sedation, incoordination, excessive salivation and nystagmus were often noted. Animal B7784 showed an unusual insensitivity to TCP. Doses up to six times those which completely suppressed responding in the other animals were needed to suppress responding in this animal. The large

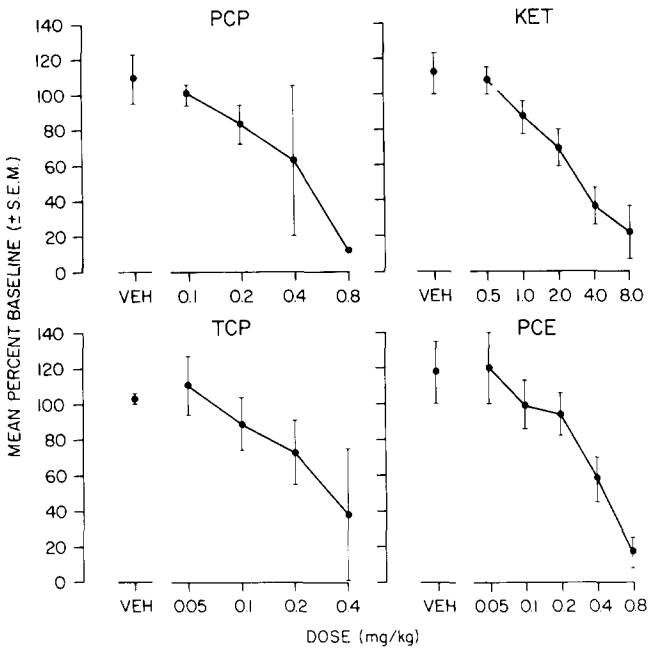

FIG. 2. Group dose-response curves for PCP and three analogues on suppression of operant responding. The effect as percent of baseline is plotted as a function of drug dose. Baseline rates were determined by averaging the non-injection response rates for the three days preceding each injection. The points above VEH represent the results of vehicle injections. Points represent means ± SEM for four subjects except TCP where data is from three subjects. Only one animal was tested at 0.8 mg/kg PCP.

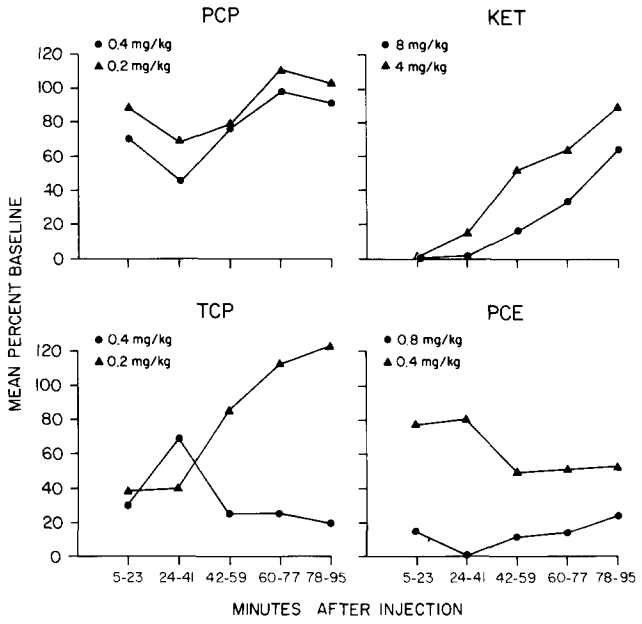

FIG. 3. Time course of the effects of PCP and three analogues on operant responding during a 1 1/2 hour operant session. On the ordinate is percent baseline responding. The baseline rates were determined by averaging the non-injection response rates for the three days preceding the injection. The abscissa represents the 15 six min intervals of the 1 1/2 hour session graphed in groups of three, such that each point represents 18 min of responding.

TABLE 1

POTENCY OF PCP AND THREE ANALOGUES ON FIXED-INTERVAL PERFORMANCE IN RHESUS MONKEYS

Drug	ED50* Dose (mg/kg)	Ratio to PCP (mg/kg)	Ratio to PCP (moles/kg)
PCP	0.28	—	—
TCP	0.25	1.12	1.14
PCE	0.33	0.84	0.725
KET	2.89	0.097	0.095

*Dose resulting in a 50% decrease in response rates as determined by linear regression.

standard error for the percent of baseline decrease with 0.4 mg/kg TCP is largely due to the lack of effect of this dose of TCP on animal B7784.

Table 1 shows the ED50 values for suppression of operant responding for each of the four compounds tested as calculated by linear regression. A comparison of the potency of the three analogues to PCP shows that TCP is slightly more potent than PCP, PCE is slightly less potent than PCP, and ketamine is approximately 1/10 as potent as PCP in suppressing operant responding. The differences between PCP, PCE and TCP are not reliable suggesting that these drugs are roughly equipotent.

Figure 3 shows the time course of the effects of two doses of each drug tested in all animals except TCP where the data is from only 3 animals. Each data point represents the mean percent of baseline responding for 3 consecutive 5 min intervals plus the time outs. PCP and 0.8 mg/kg PCE showed peak activity 24–41 min after drug injection. The lower dose of PCE (0.4 mg/kg) showed maximum activity 42–59 min after injection. The onset of activity for ketamine was apparent during the first 18 min of the session. Recovery from the low dose (4.0 mg/kg) of ketamine began within 30 min of drug administration. At both doses recovery from PCP began within one hour of drug administration. At both doses of PCE and the high dose of TCP the animals did not recover during the 1 1/2 hour session.

Figure 4 shows a rate-dependency plot for the two highest doses of all drugs tested in one subject, monkey B002. Because the effect was similar in all animals, only the graphs from one representative subject are shown. The rate-dependency plot for the high dose of TCP (0.4 mg/kg) is not shown since it resulted in overall response rates less than 0.1 response per sec in this subject. Each point is the ratio of the drug rate of responding to control rate of responding plotted against the control rate of responding during each of the five 1 min portions of the FI. The heavy dashed horizontal line represents the no-effect line, where the drug rate is equal to the control rate during each portion of the interval. A typical rate-dependent effect is evidenced by a shift from the no-effect line towards a line with a negative slope. All four drugs produced this effect in all animals at least at one dose and generally at both high doses. In a number of cases this was a dose-dependent effect (as seen for PCP with monkey B002) with a greater negative slope at the highest dose.

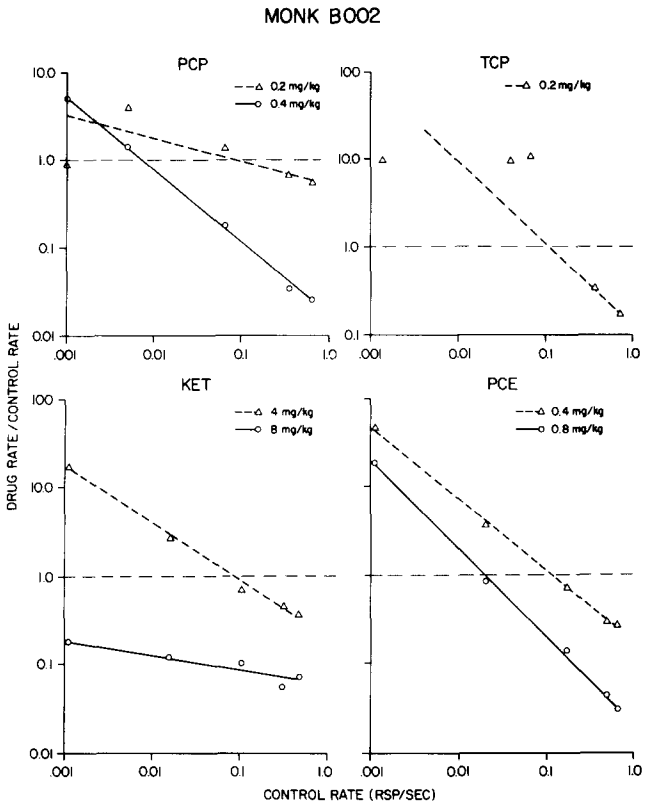

FIG. 4. Rate-dependency plots for PCP and anlogues in animal B002. Only the two highest doses not producing complete suppression were plotted, except in the case of TCP where the high dose (0.4 mg/kg) resulted in overall response rates less than 0.1 response per sec. On the ordinate is drug rate/control rate. On the abscissa is control rate in responses per second. Control rate was determined by averaging the non-injection response rates for the three days preceding the drug injection day.

DISCUSSION

Our findings show marked similarities between the actions of PCP, PCE, TCP and ketamine. Although not quantitated in this experiment, high doses of all four drugs produced a similar set of observable alterations in the animals which included incoordination, excessive salivation and nystagmus. These effects are similar to those reported by Balster and Chait [1] for moderate doses of PCP in nonhuman primates. Some evidence of response rate increases at low doses of each drug were seen, but these increases were not substantial enough to be evident in the group dose-effect curve. Response rate decreases were seen at the higher doses of all drugs. Chait and Balster [2,3] have reported a similar effect in squirrel monkeys using schedule-controlled performances. Low doses of PCP produced small increases in rates of responding, while higher doses produced a dose-dependent decrease in response rate.

In addition, all four drugs had a similar rate-dependent effect. The rate-dependency hypothesis states that the effect of a drug on a performance will depend on the baseline rate of that performance [8]. The FI schedule is particularly well suited to study rate-dependent effects because it generates a typical positively accelerating pattern of responding characterized by low rates of responding in the initial segments of the interval followed by high rates of responding near the end of the fixed interval. A typical rate-dependent effect of a drug is to increase the low rates of responding at the beginning of the fixed interval, and decrease the typically high rates of responding in the later part of the interval [8]. This would be represented graphically by a line with a negative slope, indicating an increase in responding in the initial bins, where the control rates were lower and a decrease in the later bins where the control rates were higher. In the case of the higher doses of the drugs which decreased responding in all bins, the negatively sloped line which falls below the no-effect line indicates a greater decrease in the later bins than in the initial bins. This type of rate-dependent effect is similar to that described for a variety of behaviorally active compounds [8]. Several other investigators have reported similar effects of PCP on local rates of responding in operant performance in squirrel monkeys [3], mice [21] and pigeons [20]. In the present study, this rate-dependent effect was dose-dependent. The negative slope of the regression line was generally more marked at higher doses than at the lower doses.

The potency differences between the four compounds were similar to those found by Chen [5] where PCP was roughly equipotent to TCP, slightly more potent than PCE, and more than 10 fold more potent than ketamine in producing catalepsy in pigeons. This comparison of PCP and PCE is in disagreement with the findings of Kalir *et al.* [7] and Pinchasi *et al.* [15] who found PCE to be slightly more potent than PCP in disrupting mouse rotarod performance. It is difficult to draw any conclusions concerning the cause of this discrepancy, because the species used as well as the performance measured differs in these studies.

The time course results indicate that the effects of ketamine on operant performance are evident 5–23 min after IM injection, and recovery begins within 1/2 hour of the injection. The onsets of PCE and PCP were similar, requiring at least 24–41 min to peak effect. Kalir *et al.* [7] measured brain and liver levels of PCE and PCP and correlated these with activity in disrupting rotarod performance in mice. They found a maximum accumulation at 20 min after subcutaneous administration and a slow time course of elimination. They found that while peak behavioral activity correlated with peak brain levels, the offset of behavioral activity was faster than the elimination of the compound from mouse brain.

The marked insensitivity of animal B7784 to TCP warrants further comment. After the experiment was over, this animal and subject B4115 were injected with 0.4 mg/kg PCP. This dose produced dramatic observable behavioral effects in animal B4115, but had no observable effects on animal B7784. It is difficult to attribute the insensitivity of animal B7784 to his history of PCP dosing, since this degree of tolerance was not seen in the other subjects who had a similar history of PCP injections. In addition, a study by Chait and Balster [3] using squirrel monkeys given chronic PCP progressing to four daily injections found only a 2 fold shift in the dose response curves. It is more likely that this is an idiosyncratic response. Further observations will be made with this animal in an attempt to characterize this phenomenon.

In conclusion, these four drugs have been found to have qualitatively similar effects on operant responding in the rhesus monkey. This is consistent with other studies showing these compounds to have similar pharmacological effects [5, 6, 7, 11, 13, 16, 19] and research demonstrating that the

stimulus properties of the three analogues generalize to PCP in a drug discrimination paradigm [12,17]. It is clear that PCP is only representative of a class of arylcyclohexylamines with similar behavioral effects and possibly similar potential for abuse.

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