Psychopharmacology (1989) 97:179–182

Psychopharmacology

Effects of fixed ratio size and dose on phencyclidine self-administration by rats

Karen L. Marquis, Michael G. Webb, and J. Edward Moreton
Department of Pharmacology and Toxicology, School of Pharmacy, University of Maryland, 20 N. Pine Street, Baltimore, MD 21201, USA

Abstract. Female Sprague-Dawley rats were trained to self-administer phencyclidine (PCP; 0.125, 0.25, or 0.5 mg/kg/injection) on a fixed ratio (FR) schedule of reinforcement under limited access conditions (3 h). Initial training began with cocaine, which was later replaced with ketamine and then one of the three unit doses of PCP. Baseline rates of injection were determined at FR 10. The size of the ratio was then incremented geometrically every fifth daily session. Increasing the ratio resulted in a decrease in the number of injections per session. Furthermore, this decrease was greater for the 0.25 mg/kg dose than for the 0.5 mg/kg unit dose. The self-administration of the 0.125 mg/kg dose was variable and rapidly extinguished upon the increase in fixed ratio. The results indicate that PCP is self-administered by rats under the conditions imposed in this study. Furthermore, the relative reinforcing efficacy of the different unit doses of PCP could be discriminated using this type of response cost procedure.

Key words: Rats – Self-administration – Phencyclidine – Reinforcement – Fixed ratio

Phencyclidine (PCP) remains a popular drug of abuse in humans today. However, there are few reports of its self-administration in animal models of drug abuse. Initial studies (Balster et al. 1973; Pickens et al. 1973) indicated that both drug-naive and drug-experienced rhesus monkeys would self-administer PCP on an intermittent schedule of reinforcement during daily limited access sessions. Self-administration of PCP has also been observed in baboons (Lukas et al. 1984) and dogs (Risner 1982), but detailed studies using rats are lacking.

Of the two published studies using rats, one (Carroll et al. 1981) examined the effects of food deprivation on PCP self-administration. Using drug-naive subjects, three of the six rats tested reliably self-administered PCP at a unit dose of 0.125 mg/kg/injection under food-satiation conditions. Food deprivation increased rates of PCP self-administration in all the subjects. The other study (Collins et al. 1984) tested one or two unit doses of PCP and ketamine and observed injection rates which were greater than vehicle injection rates when drug was available on a 24 h/day basis. Neither study examined full dose-effect curves. Furthermore, continuous reinforcement schedules were used.

A preliminary investigation of the injection rates and drug intake of three unit doses of PCP in drug-experienced rats was conducted by Moreton and Goodman (1985). These authors observed dose-dependent changes in rates of self-administration under PCP; however, relatively high unit doses (0.5–2.0 mg/kg/injection) were used, resulting in low rates of self-administration. In addition, Marquis et al. (1986) reported that low unit doses of PCP (0.125–0.5 mg/kg/injection) were self-administered by rats under a rapid substitution paradigm. The results suggested that lower unit doses of PCP would possibly maintain stable self-administration behavior.

Moreton et al. (1977) examined the effects of varying the unit dose and the fixed ratio (FR) size on the self-administration of ketamine in rhesus monkeys. The results indicated that higher unit doses of drug were required to produce maximal rates of responding as the FR size was increased. More recently, Lemaire and Meisch (1984) reported a similar study using pentobarbital self-administration in monkeys. These authors found that as FR size was increased a decrease in the number of reinforcements occurred, and that this measure of self-administration behavior was affected less at a high unit dose than at lower unit doses. These authors interpreted their results as a measure of the reinforcing efficacy of the different unit doses.

The present study further extends our characterization of self-administration of PCP in drug-experienced rats. We hypothesize that if the reinforcing efficacy of a unit dose makes the behavior more resistant to the effects of a change in FR size, then high unit doses should show less of a decrease in the number of injections as the FR size is increased than lower unit doses. Thus, this study examined PCP self-administration by rats using an intermittent schedule of reinforcement at three unit doses and four FR sizes.

Methods

Subjects and apparatus. Female Sprague-Dawley rats (275–400 g) were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally) supplemented with Metofane (methoxyflurane, Pitman-Moore, Washington Crossing, NJ). They were prepared with a chronic jugular cannula as previously described (Weeks and Davis 1964), and a female miniature Dale connector was attached to the skull

Offprint requests to: J.E. Moreton

with 1/8 inch machine screws and dental acrylic. All subjects were housed individually on contact bedding. Food and water were continuously available throughout the experiment except during experimental sessions. A light/dark cycle of illumination from 0600 to 2200 hours was in effect.

The experimental chamber consisted of a custom-made Plexiglas^R enclosure (66 cm × 29 cm × 29 cm) equipped with a single rodent operant lever (BRS-LVE) mounted in the center of one wall 4 cm above the cage floor. Two jeweled lights were mounted side by side directly above the lever. One light (white) was illuminated during a lever press. The other light (red) was illuminated during injection of a drug. Two plexiglas shields (12.5 cm high × 5 cm wide) were mounted perpendicularly to the wall containing the lever, and 3.25 cm on either side. This "guard" served to protect the lever from inadvertent lever presses by the rat. A liquid swivel (Instech Laboratories, Horsham, PA) mounted in the center of the roof of the chamber connected the subject's cannula via polyethylene tubing to a pneumatically driven syringe (Ledger Technical Services, Kalamazoo, MI) which delivered a 0.1 ml injection in less than 1 s. Unit dose was varied by changing the concentration of the drug. A male Dale connector and metal spring leash joined the rat to the injection system and protected the tubing. Lever presses were detected and reinforcement was controlled by solid state modules (Ledger Technical Services, Kalamazoo, MI). Occurrences of lever-pressing and self-injection were recorded on an event record (Esterline Angus, Indianapolis, IN).

Procedure. The 15 rats used in this study were randomly divided into three groups. Each group was initially trained to self-administer cocaine HCl (1.0 mg/kg/injection) on an FR10 schedule of reinforcement in four to six daily sessions 3 h in duration. Cocaine was replaced with ketamine (3.0 mg/kg/injection) for the next four to five sessions. Preliminary investigations had indicated that this unit dose of ketamine allowed the most rapid transition from cocaine to stable ketamine self-administration. For each group ketamine was replaced with one of three unit doses of PCP (0.125, 0.25, or 0.5 mg/kg/injection) for five sessions on an FR10 schedule of reinforcement. During each subsequent 5-day block the FR size was increased by doubling the previous FR size. The number of injections earned during each session was recorded. Only the last three sessions at each FR size were used in the data analysis unless this was prevented by mechanical problems. Sessions were conducted at both 9 a.m. and 1 p.m. Monday through Friday. Sessions were suspended on Saturday and Sunday. A "free" injection was given after the first 10 min of each session if no self-injection had occurred. Also, a "free" injection was given at the end of the 1st and 2nd hour of each session if no self-injection had occurred. It was found during the course of this study that, regardless of unit dose, most subjects required only the initial free injection to initiate self-administration under the initial FR10 and under the retest FR10 if self-administration behavior occurred at all.

In addition, three rats were trained to self-administer cocaine and then ketamine as described above. Ketamine was replaced with saline for five consecutive sessions. The data from these subjects indicated the number of injections expected during extinction following our method of PCP self-administration training.

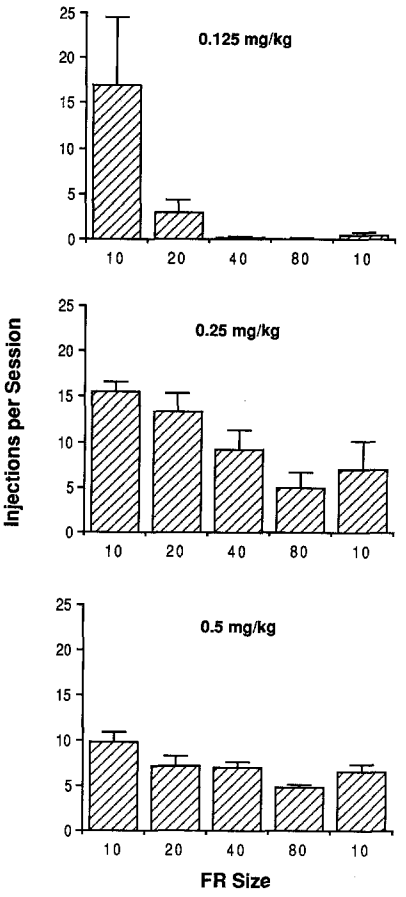

Fig. 1. Rats self-administered PCP at a unit dose of 0.125, 0.25, or 0.5 mg/kg/injection under increasing fixed ratio (FR) sizes. Each *bar* represents the mean (±SEM) number of injections per session for five subjects averaged across three sessions at each FR size. The *right bar* at FR10 for each panel represents a retest of that FR size at the end of the experiment. The *right bar* at FR10 for the 0.5 mg/kg dose represents the mean of only three subjects

Results

Figure 1 displays the average number of injections delivered under each FR size for the three unit doses of PCP and the number of injections earned at a retest of the baseline FR size (FR10). When saline was substituted for ketamine an average of 3±1.4 injections per session was observed (data not shown). While each of the subjects tested at the 0.125 and 0.25 mg/kg unit doses was retested at FR10, only three of the five subjects tested at the 0.5 mg/kg unit dose were retested. These data were analyzed using a three-way analysis of variance with two repeated measures (sessions and FR size). The data from the 0.125 mg/kg unit dose were eliminated from the statistical analysis because only two of the five subjects tested obtained a number of injections that was consistently greater than observed for saline under the initial FR10. Incrementing the FR size for the 0.125 mg/kg unit dose resulted in the loss of self-administration behavior that was not reinstated by reducing the FR size at the completion of the experiment. For the 0.25 and 0.5 mg/kg unit doses the main effect of incrementing the FR size was to reduce the number of injections [$F(3, 24) = 23.28$, $P < 0.05$]. Furthermore, the interaction of the unit dose with the FR size was found to be significant [$F(3, 24) = 4.48$, $P < 0.05$]. That is, the decrease in the absolute

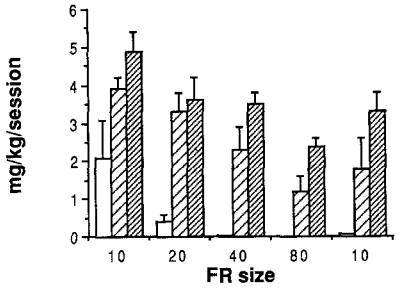

Fig. 2. Rats self-administering PCP at a unit dose of either 0.125, 0.25, or 0.5 mg/kg/injection decreased their level of drug intake (mg/kg/3 h session) as the fixed ratio (FR) size increased. Each *bar* represents the mean (±SEM) drug intake for five subjects averaged across three sessions at each FR size. The *right set of bars* represents a retest of FR10 at the end of the experiment. In this right set of bars, the bar for the 0.5 mg/kg dose represents the mean of only three subjects. □ 0.125 mg/kg; ▨ 0.25 mg/kg; ▨ 0.5 mg/kg

number of injections as the FR size was increased was greater for the 0.25 unit dose than for the 0.5 unit dose. Also, the number of injections tended to decrease over the three sessions analyzed [$F(2, 16)=4.62$, $P<0.05$]. There were no significant interactions of sessions with any other factor in the analysis. There was a tendency for the average number of injections to be less for the 0.5 mg/kg unit dose than for the 0.25 mg/kg unit dose [$F(1, 8)=5.01$]; however, this difference failed to reach the a priori level of significance.

The number of injections per session observed under retest was compared to baseline conditions for the 0.5 and 0.25 mg/kg unit doses using Student's t test. This measure was not significantly different for the 0.5 mg/kg unit dose [$t(2)=1.17$]. Injections per session were significantly decreased upon retest for the 0.25 mg/kg unit dose [$t(4)=3.49$, $P<0.05$].

Drug intake (mg/kg/session), shown in Fig. 2, was calculated by multiplying the number of injections earned in each session by the unit dose being self-administered. These data were then analyzed, as in the case for the number of injections per session, by a three-way analysis of variance with two repeated measures (sessions and FR size). Also, drug intake was assessed only at the 0.25 and 0.5 mg/kg unit doses. The results of this analysis indicated that increasing the FR decreased the drug intake [$F(3, 24)=17.95$, $P<0.05$]. Also, drug intake during initial sessions was greater than in later sessions [$F(2, 16)=3.83$, $P<0.05$]. Finally, there was a tendency for the drug intake during the self-administration of the 0.5 mg/kg unit dose to be greater than the 0.25 mg/kg unit dose [$F(1, 8)=4.47$]; however, this difference failed to meet the a priori level of significance. There were no significant interactions in this analysis.

Discussion

The results of the current study extend previous findings (Carroll et al. 1981; Collins et al. 1984; Moreton and Goodman 1985) by examining the self-administration of PCP in the rat under an intermittent schedule at lower unit doses than previously used. It has been shown that dose-effect curves for PCP and ketamine self-administration have the typical inverted U shape seen in self-administration studies (Balster et al. 1973; Moreton et al. 1977; Risner 1982). It should be noted that in many instances the ascending limbs of these dose-response curves are steep and injection rates on this portion of the curve are usually quite variable. In the present study a comparison of the dose-dependent changes in PCP self-administration under the baseline FR10 indicates that the doses used are near the peak and on the descending limb of the dose-effect curve.

The number of reinforcements earned for each of the last three sessions of the 5-day block was included in the analysis. The results indicated that there was a decline in the number of reinforcements earned as the number of sessions was increased. However, there was no significant interaction of this effect with dose or FR size. Thus, while the number of reinforcements was changing across the sessions, the relationship between dose, FR size and injections per session was unaffected.

The number of injections per session observed during the self-administration of the unit doses of PCP used in this study and in previous studies is relatively low (see also Marquis and Moreton 1987). However, the results of the current study indicate that the behavior is resistant to an increase in FR size. Moreover, this effect was dependent on the unit dose. The number of injections per session at the 0.5 mg/kg unit dose decreased to a lesser degree as the FR size was increased when compared with the 0.25 mg/kg unit dose. The self-administration behavior of the lowest unit dose was variable, even under the baseline FR conditions, and rapidly extinguished as the FR was increased. While nonspecific effects of PCP may have influenced the number of injections earned by the subjects of this study, the observation that self-administration behavior will continue even under a high FR indicates a significant rewarding value for some of the unit doses studied.

The relationship between unit dose and FR size appears to be a general phenomenon since it has been reported previously by other investigators studying ketamine (Moreton et al. 1977), pentobarbital (Lemaire and Meisch 1984), methohexital (Pickens et al. 1981) and cocaine (Goldberg et al. 1971) in either rats or rhesus monkeys. Direct comparison of the data from these studies requires some transformation of the data because different dependent measures were analyzed. An inverted U-shaped dose-effect curve was observed using a response rate measure in monkeys self-administering ketamine (Moreton et al. 1977). Increasing the FR size increased response rates and shifted the dose effect curve to the right, indicating that higher unit doses were required to maintain maximal responding at a higher FR. Pickens et al. (1981) studied rats self-administering methohexital. While dose-effect curves for response rates were not directly reported, these authors described the effect of increasing FR size on response rates at four different unit doses. Lemaire and Meisch (1984) transformed some of the data reported by Pickens et al. (1981) and expressed the data in terms of a percentage of the number of injections per session earned at an initial FR size. The general findings of each of these studies are the same. That is, an increase in FR size resulted in a decrease in the number of injections per session. Furthermore, the magnitude of this decrease was dose dependent. Specifically, the number of injections per session of a high unit dose changed to a lesser degree than low unit doses as FR size was increased. Lemaire and Meisch (1984) interpreted this relationship as an indication of the difference in relative reinforcing efficacy of the differ-

ent unit doses. Our results similarly indicate a discrimination between the reinforcing efficacy of the three unit doses of PCP self-administered by rats at four different FR sizes.

In summary, our findings indicate the dose range and expected number of injections of PCP which will occur under conditions of limited access in rats experienced with psychomotor stimulant self-administration. The injection rate for reinforcing doses of PCP was relatively low, and increasing the unit dose of PCP decreased the injection rate under the same FR size, although a large change was not observed. Thus, simple self-administration studies (e.g., utilizing a single FR size) do not provide a direct measure of reinforcing efficacy. In order to assess this characteristic of drugs of abuse a response cost analysis, such as the one used in this study, is a necessary procedure.

Acknowledgements. The authors wish to acknowledge the technical assistance of Mr. Michael Gentry. Our thanks also for the helpful comments of Mr. Rick Gussio, Dr. Gerald A. Young and Dr. Naim Khazan during the preparation of this manuscript. This study was supported by PHS Grant DA03173.

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Received March 14, 1988/Final version June 28, 1988