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# Effects of Terminating Chronic Phencyclidine on Schedule-Controlled Behavior in Rats

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MASSEY, B. W. AND W. D. WESSINGER. *Effects of terminating chronic phencyclidine on schedule-controlled behavior in rats.* PHARMACOL BIOCHEM BEHAV **36**(1) 117–121, 1990.—Six rats were trained to respond under a multiple fixed-ratio 30, fixed-interval 3-min schedule for food presentation. Acute administration of phencyclidine (0.1–3.2 mg/kg, IP) produced decreases in fixed-ratio response rates at doses above 0.3 mg/kg, but fixed-interval response rates were only decreased at the highest dose. However, the pattern of fixed-interval responding (as evidenced by quarter-life values) was affected at doses above 0.3 mg/kg. Osmotic minipumps were implanted, SC, which infused saline (2 rats) or phencyclidine (4 rats, 10.0 mg/kg/day) for 10 days, and then removed. Daily behavioral sessions were conducted during infusions and for 10 days afterwards. The effects of phencyclidine infusions on fixed-ratio responding were variable. Fixed-interval response rate and quarter-life values were only modestly affected during drug infusion. All three parameters were markedly affected upon cessation of chronic phencyclidine dosing, but there did not appear to be differential effects between the schedule components. No effects on responding were observed during or after saline infusions.

Operant behavior Phencyclidine PCP Multiple schedule Fixed-interval Fixed-ratio Chronic administration Drug dependence Rats

PHENCYCLIDINE [1-(1-phenylcyclohexyl)piperidine; PCP] is an arylcyclohexylamine which has a unique spectrum of central nervous system effects including depressant, stimulant, hallucinogenic, and analgesic actions. PCP was originally developed as a general anesthetic agent for human use, however, its use in humans was abandoned when it was determined to produce a form of emergence delirium. Following this discovery, PCP was developed as a veterinary anesthetic and used primarily in nonhuman primates. During the early 1970's, PCP gained popularity as a drug of abuse which led to the scheduling of PCP and its analogues and prompted researchers to investigate the behavioral pharmacology of these drugs (8).

The acute effects of PCP on operant behavior have been explored by a number of investigators. In mice performing under a multiple fixed-ratio, fixed-interval schedule of reinforcement, PCP produced dose-dependent decreases in response rate during the fixed-ratio component. During the fixed-interval component, PCP produced biphasic effects on response rate with low doses producing increases and higher doses producing decreases in response rate. The fixed-ratio component was more sensitive than the fixed-interval component to the rate decreasing effects of PCP(14). Similar results have been observed in the pigeon (13), however, in squirrel monkeys both components of a chained fixed-interval, fixed-ratio schedule were shown to be equally sensitive to PCP(6).

PCP has been shown to have both reinforcing and dependence producing properties in laboratory animals. Rhesus monkeys will self-administer PCP orally (4) or intravenously (1,2) and in sufficient quantities to produce significant behavioral toxicity (1,2). Upon removal of PCP, after a period of high dose self-administration, a moderate to severe withdrawal syndrome was observed (2). Rats, which are much less sensitive to the effects of PCP than primates, have exhibited similar signs of physical dependence after high doses of PCP (45 mg/kg/day, IV) administered for 7 days were discontinued (10). It seems unlikely that such high dose self-administration would occur in the human abuse situation and, in fact, only a few reports have appeared in which human physical dependence to PCP has been described (11). The symptoms reported in humans consisted of craving, anergia, depression, and physical discomfort. In animal studies which used lower, more clinically relevant doses, disruption of operant behavioral baselines upon discontinuation of drug administration has been shown to occur in the rhesus monkey (9),and in rats (3, 15, 16). The disruptions observed upon withdrawal of PCP were reversed by readministration of PCP (3,9). These studies examined the effects of PCP administration and withdrawal on behavior maintained by food presentation using doses of PCP that had little effect on schedule-maintained responding or on overt behavior. Previous work by this laboratory has shown that fixed-ratio performance in rats is disrupted after stopping 10-day intravenous infusions of PCP at doses from 5.6 to 17.8 mg/kg/day, but not after 3.2 mg/kg/day. The magnitude of behavioral disruption seen upon withdrawal was a function of infusion dose (16).

The purpose of this experiment was to determine if the particular schedule of reinforcement maintaining behavior was a determinant of the magnitude and/or duration of the behavioral

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disruption following the discontinuation of PCP administration. The present study investigated the effects of chronic PCP infusion and PCP withdrawal on multiple fixed-ratio, fixed-interval responding in rats. The dose of PCP used for chronic administration was 10.0 mg/kg/day over 10 days; a dose regimen which reliably produced behavioral disruption upon cessation of chronic dosing in other studies (16).

## METHOD

### *Subjects*

Six, male, Sprague-Dawley rats (Charles River Breeding Laboratories, Portage, MI) were used as subjects. They were experimentally and drug naive at the start of the study. Free-feeding weights ranged from 348 to 377 g. Their weights were reduced to, and maintained at, 300 g on a diet consisting of Purina Rat Chow (Formulab No. 5008; Purina Mills, Inc., St. Louis, MO). The rats were housed in individual cages in a rodent facility adjacent to the behavioral laboratory under a normal phase, 12-hour light/dark cycle. Water was continuously available in the home cages.

### *Apparatus*

The experimental chamber was a standard operant rat test cage (Model G7322; Gerbrands Corporation, Arlington, MA) equipped with two rat levers. Only responses made on the left lever were recorded and had programmed consequences. Located over the lever were two stimulus lights. A pellet dispenser (Model D1; Gerbrands) delivered 97 mg food pellets (Formula A; P. J. Noyes Co., Lancaster, NH) to a food tray located between the response levers when schedule contingencies were met. The test cage was placed inside a sound- and light-attenuating enclosure (Model G7210; Gerbrands) which had a fan for air circulation and masking noise. The behavioral schedule was controlled and responses recorded by a microcomputer (TRS80 Model 4; Tandy Corp., Fort Worth, TX) through an interface (Microcomputer Interface II, MED Associates, Inc., East Fairfield, VT). Responses and reinforcement delivery were also recorded on a cumulative recorder (Model C3; Gerbrands).

### *Procedure*

The rats were trained to respond under a multiple fixed-ratio, fixed-interval schedule of food presentation. Initially, the subjects were trained to lever press (by successive approximation) under a continuous reinforcement schedule (i.e., a single response resulted in delivery of a food pellet). This response requirement was raised gradually until responding was achieved under an fixed-ratio 10 schedule. The fixed-interval component of the multiple schedule was then introduced with an initial fixed-interval length of 10 sec. Under the fixed-interval component, the first response after the interval elapsed resulted in reinforcement. Over the following two weeks the fixed-ratio and fixed-interval requirements were gradually increased until the terminal parameter values were reached; fixed-ratio 30, fixed-interval 180 sec.

At the beginning of a session the subject was placed into a darkened test cage. Ten minutes later, the houselight was illuminated and the session began with the first fixed-ratio component. During the fixed-ratio component, two reinforcement opportunities were presented consecutively under a fixed-ratio 30 schedule. After the delivery of two food pellets, or if the rat did not complete a fixed-ratio 30 within 60 sec (60-sec limited hold), the schedule advanced to the fixed-interval component. A 5-sec period, during which all cage lights were extinguished, separated the fixed-ratio from the fixed-interval components. During the fixed-interval components, the houselight, as well as two white stimulus lights over the response lever, were illuminated. Under the fixed-interval component, the first response after 180 sec had elapsed resulted in the delivery of a food pellet. After delivery of a food pellet, or if the rat did not respond within 60 sec after the end of the interval (60-sec limited hold), the schedule cycled back to the fixed-ratio component. This cycle was repeated until 12 food presentation opportunities had occurred. Training sessions were usually conducted 5 days/week (Monday–Friday). After stable baselines of response rate and pattern were established (18 weeks), acute drug testing was initiated. For acute dose-effect determinations, doses of PCP were administered by IP injection immediately preceding the sessions which were conducted on Tuesdays and Fridays. Saline injections were administered on Mondays and Thursdays, with Thursday sessions serving as control sessions.

After the acute dose-effect relationships were determined, chronic phencyclidine dosing was initiated. Under ether anesthesia, Alzet osmotic minipumps (Model 2ML2; Alza Corp, Palo Alto, CA) containing either saline (2 rats) or PCP (4 rats, infusion rate: 10.0 mg/kg/day) were implanted subcutaneously, 10 hours prior to the next daily session. During the chronic infusion phase, daily test sessions were conducted for 10 consecutive days. The pumps were then removed, 10 hours prior to the session on the eleventh day, and daily test sessions were continued for another 10 consecutive days.

### *Drugs*

Phencyclidine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was dissolved in 0.9% physiological saline. For acute dose-effect determinations, dilutions were made to give an IP injection volume of 1.0 ml/kg. For chronic administration via osmotic pumps, dilutions were made to give a delivery of 10.0 mg of PCP per kg per day at a rate of 120 μl/day. All doses refer to the salt.

### *Data Analysis*

Response rates under the fixed-ratio and fixed-interval components of the behavioral schedule were determined and are expressed as the number of responses per second. Quarter-life values were also determined and are used to describe the temporal patterning of responding under the fixed-interval component. Quarter-life is the fraction of the interval that elapsed before 25% of the total number of fixed-interval responses were emitted. Data from the acute dose-effect determinations were averaged for the six subjects and are presented along with the mean control data (after saline injections on Thursdays) ± S.E. Data obtained during and after chronic administration are presented for individual subjects.

## RESULTS

The effects of acute PCP administration (0.1–3.2 mg/kg) on fixed-ratio responding, fixed-interval responding, and quarter-life values are shown in Fig. 1. The average fixed-ratio response rate was approximately equal to control values following administration of 0.3 mg/kg PCP and dose-dependent decreases in fixed-ratio response rate were observed at higher doses. Fixed-interval response rate was increased over control levels following acute administration of 1.0 mg/kg PCP, but were markedly decreased following administration of 3.2 mg/kg PCP (only one subject responded). The patterning of responding within the fixed-interval component, as evidenced by quarter-life values, changed as a function of dose following acute administration of PCP. Quarter-

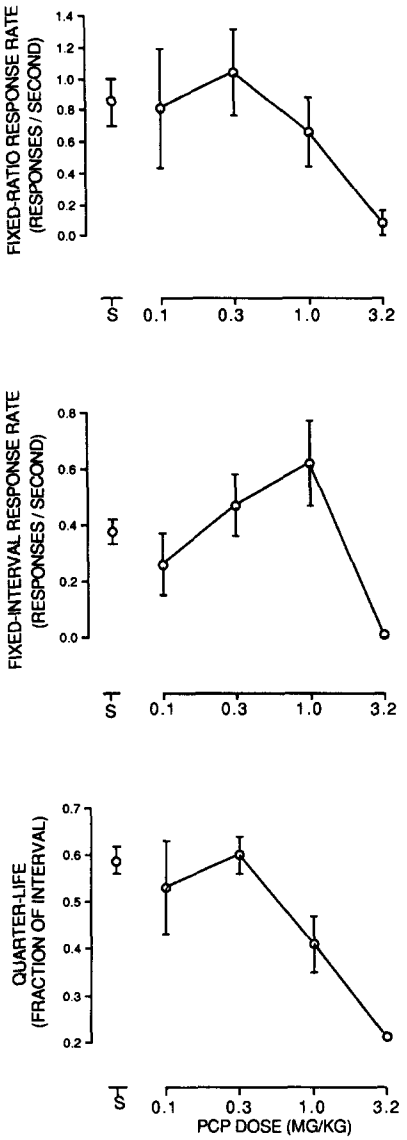


FIG. 1. Effects of acute PCP administration in rats responding under a multiple fixed-ratio, fixed-interval schedule of food presentation. The upper and middle panels show the effects of acute phencyclidine administration on fixed-ratio responding and fixed-interval responding, respectively. Group mean (n = 6) response rate (responses/sec) is plotted along the ordinates. The effects of acute phencyclidine administration on fixed-interval quarter-life values (ordinate) are shown in the lower panel. Phencyclidine doses (log scale) are shown on the abscissae. Averaged saline control values (S) are shown on the left-hand sides of the panels. The error bars represent ±1 S.E.

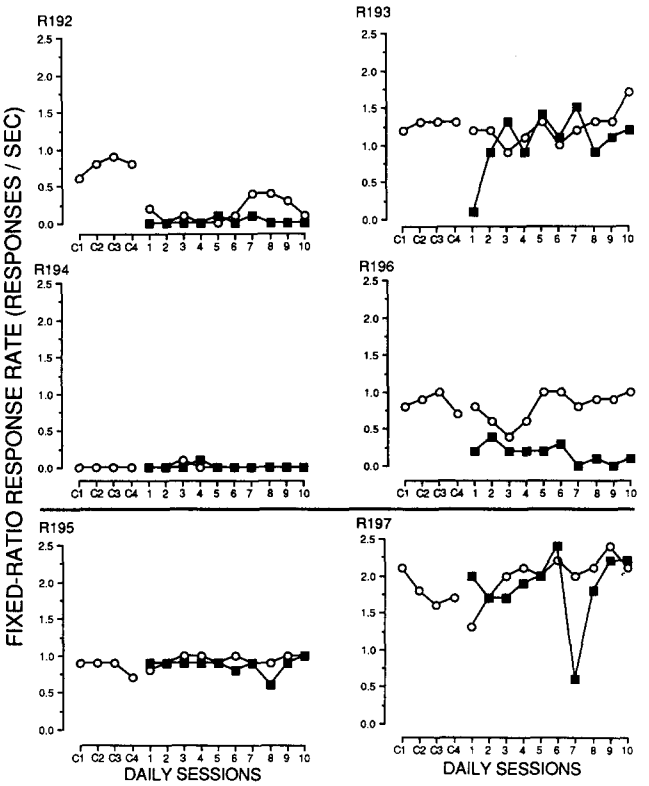


FIG. 2. Effects of chronic PCP administration (10.0 mg/kg/day) or saline administration, and the cessation of chronic administration on fixed-ratio responding. Response rate under the fixed-ratio component is plotted along the ordinates as responses/sec with consecutive daily sessions shown on the abscissae. In the four upper panels are data from the subjects that received chronic PCP administration; the two lower panels are data from the subjects that received chronic saline infusions. The open circles represent responding on the 10 days when PCP or saline was administered, while the filled squares represent responding on the 10 days following cessation of PCP or saline administration. The fixed-ratio response rates from 4 sessions prior to osmotic minipump implantation serve as controls and are plotted along the far left of the abscissae (C1–C4). Consecutive days of PCP or saline administration and withdrawal are also shown on the abscissae (daily sessions 1–10).

life values decreased in a dose-dependent fashion reflecting an increasingly equal distribution of responses within the interval as the dose was increased from 0.3 to 3.2 mg/kg PCP.

The effects of chronic PCP or saline administration via osmotic minipumps on response rate (responses/sec) during the fixed-ratio component are shown in Fig. 2 (open circles). Also shown in this figure are the results obtained for 10 sessions following removal of the pumps (filled squares). Two of the four subjects that received chronic PCP (R193 and R196) did not exhibit disruption in fixed-ratio response rate upon initiation of chronic drug administration and these subjects continued to maintain relatively constant response rates throughout the 10-day chronic administration period. Following implantation of the osmotic minipump, another subject receiving chronic PCP, R192, exhibited a severe disruption in fixed-ratio response rate that continued throughout the chronic administration period. R194 had ceased responding under the fixed-ratio component before the PCP pump was implanted, and did not respond appreciably under this component during the chronic treatment phase. The two subjects that received chronic saline administration (R195 and R197) did not show any disruption in fixed-ratio responding upon implantation of the pumps or over the 10-day infusion period.

Upon removal of the osmotic pumps, the fixed-ratio response rate of the two subjects which had continued to respond under the fixed-ratio component during chronic PCP administration (R193 and R196) dropped to very low levels. In R193, fixed-ratio responding returned to control levels by the third day following removal of PCP, but response rates remained low and did not return to control levels throughout the remainder of the experiment in subject R196. For R192, the subject that ceased responding

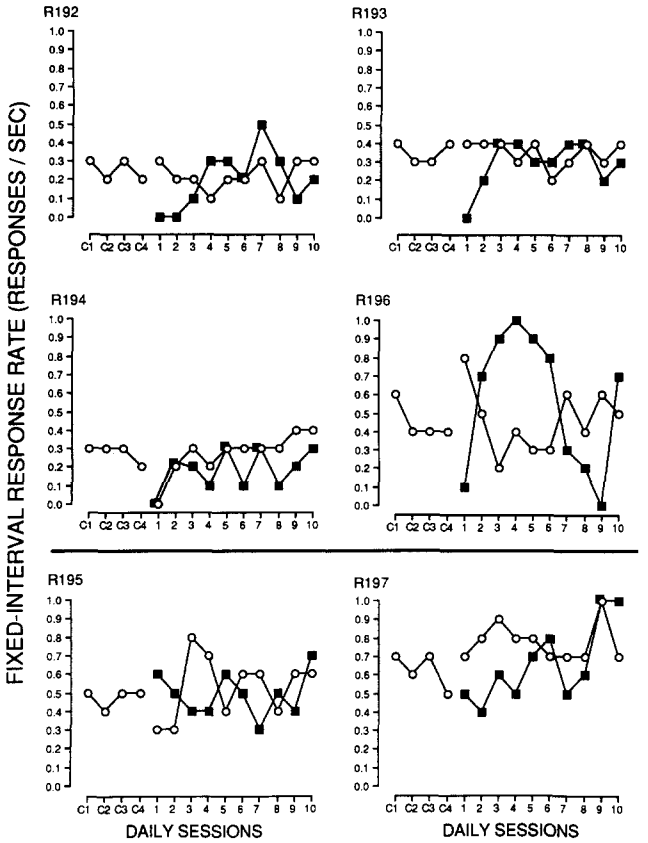


FIG. 3. Effects of chronic PCP administration (10.0 mg/kg/day) or saline administration, and the cessation of chronic administration on fixed-interval responding. Details are as in Fig. 2.

under the fixed-ratio component during chronic PCP administration, response rates fell to zero for 4 days after PCP was removed and never returned to control levels. R194 continued to not respond under the fixed-ratio component after the PCP pump was removed. The fixed-ratio response rates for the two subjects which received saline did not change appreciably after the pumps were removed.

The effects of chronic PCP administration (open circles) and its removal (filled squares) on fixed-interval response rates are shown in Fig. 3. Fixed-interval response rates in two of the four subjects receiving chronic PCP administration (R192 and R193) were not affected by the initiation of chronic PCP administration and these subjects continued to exhibit stable fixed-interval response rates throughout the duration of the 10-day chronic dosing period. R196 exhibited a slight increase in fixed-interval responding on the first day of chronic PCP administration and fixed-interval responding was variable for the remainder of the dosing period in this subject, but generally was within the range of control values. The other subject receiving chronic PCP (R194) exhibited a marked suppression of fixed-interval responding on the first day of chronic PCP administration with response rate returning to control levels by the second day. Fixed-interval responding in the subjects receiving chronic saline administration (R195 and R197) was not consistently altered during the initiation or continued administration of saline.

The cessation of chronic PCP administration disrupted fixed-interval responding in all four subjects receiving PCP. In R193 and R194, no responding under the fixed-interval component occurred on the day following removal of phencyclidine, but responding returned to control levels by the third day. Complete suppression of fixed-interval responding for 2 days following cessation of PCP administration was observed in R192, but responding returned to control levels by the fourth day. In R196, fixed-interval response rate was markedly suppressed on the day following PCP removal, but on the second day fixed-interval response rate was increased over control levels and remained at these higher rates until the seventh day. Fixed-interval responding remained variable in this subject (R196) throughout the remainder of the experiment. Fixed-interval response rate was not appreciably affected by the removal of saline pumps in either subject receiving chronic saline (R195 and R197).

The effects of chronic PCP administration and its cessation on fixed-interval quarter-life values are herein described but not shown. The chronic administration of PCP produced variable effects on quarter-life. In R193, quarter-life was not affected by chronic PCP administration. R196 and R192 show a decrease in quarter-life following initiation of chronic PCP administration. This decrease persisted for four days in R196, and for the duration of the dosing period in R192. Upon initiation of chronic PCP administration, R194 exhibited an initial increase in quarter-life value followed by a decrease in quarter-life value. Stable quarter-life values returned in this subject (R194) by the sixth day of PCP administration. Of the subjects which received chronic saline administration, R197 showed a decrease in quarter-life the day after initiation of chronic saline, however, by the second day quarter-life values were back to control levels and remained stable throughout the chronic dosing period. R195 exhibited unstable quarter-life values during the control days, however, this subject maintained very stable quarter-life performance throughout the duration of the chronic saline dosing period.

Cessation of chronic PCP administration produced disruptions in fixed-interval responding which was reflected in quarter-life values in all subjects. In R196, quarter-life was decreased for five days following cessation of PCP administration. Fixed-interval responding was suppressed by PCP removal in subjects R193, R194, and R192, but once fixed-interval responding resumed, quarter-life values were similar to those obtained on control days. The subjects receiving chronic saline (R195 and R197) did not exhibit any changes in quarter-life values following removal of the pumps.

## DISCUSSION

Drug dependence, as evidenced by observable signs and symptoms upon cessation of chronic administration, may be an important factor in the maintenance of drug self-administration (12). For example, in morphine-dependent rats, naloxone-precipitated withdrawal increased oral self-administration of morphine. Thus, the termination of a physical withdrawal syndrome may function as a reinforcer resulting in higher drug consumption (7). It is possible that the behavioral disruptions, in the absence of physical signs of withdrawal, may represent "subthreshold manifestations of physical dependence" (5). The behavioral disruptions observed following cessation of chronic PCP administration are alleviated by PCP readministration (3,9). It seems likely that behavioral dependence may contribute to the maintenance of PCP self-administration in the same manner that physical dependence contributes to the maintenance of opiate self-administration. Therefore, animal models of behavioral dependence using operant paradigms may contribute greatly to the understanding of the continued abuse of drugs that do not produce a physical dependence.

In the present study, the observation that upon acute administration, higher doses of PCP were required to produce response-

rate decreases during the fixed-interval component than in the fixed-ratio component, suggests that behavior under the fixed-interval component was less sensitive to the rate-decreasing effects of acute PCP administration. However, the temporal patterning of fixed-interval responding, as evidenced by quarter-life values, was affected at doses that did not decrease fixed-interval response rate. Thus, differential sensitivity to the effects of acute phencyclidine administration due to the schedule of reinforcement was not clearly evident in this study.

Under the multiple schedule of reinforcement employed in this study, there was no apparent differential sensitivity between the two components during chronic PCP administration. Under the fixed-ratio component, only one (R192) of the four subjects which received chronic PCP showed a marked change in response rate relative to control values. None of the subjects receiving PCP exhibited consistent changes in fixed-interval response rate during the chronic dosing period, although an initial suppression of responding was observed in one subject (R194) on the first day of PCP administration and variable responding up to the third day was exhibited by another subject (R196). However, the temporal patterning of responding during the fixed-interval component, as evidenced by quarter-life values, was affected by chronic PCP administration in three of the four subjects. One of the subjects receiving chronic PCP administration exhibited lowered quarter-life values throughout the duration of the dosing period. These effects are in agreement with the effects of PCP on quarter-life reported by others (6, 13, 14).

The data also do not suggest a differential sensitivity among components to the behavioral effects seen upon cessation of chronic PCP administration. A persistent disruption of fixed-ratio performance, precipitated by cessation of PCP administration, was observed in two subjects (R192 and R196). Persistent disruption of fixed-interval performance was observed in one subject, R196, following withdrawal of PCP.

At the schedule parameters used in this study, the schedule of reinforcement did not appear to influence the magnitude or the duration of the behavioral disruption observed upon cessation of chronic PCP administration. Although the magnitude of the behavioral disruptions seen upon discontinuation of chronic PCP were generally greater than that seen upon initiation of chronic drug administration, these response rate decreasing effects were similar in both components of the multiple schedule.

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