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Phencyclidine (PCP) Self-Administration and Withdrawal in Rhesus Monkeys: Effects of Buprenorphine and Dizocilpine (MK-801) Pretreatment

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CARROLL, M. E., G. N. CARMONA AND J. S. RODEFER. *Phencyclidine (PCP) self-administration and withdrawal in rhesus monkeys: Effects of buprenorphine and dizocilpine (MK-801) pretreatment.* PHARMACOL BIOCHEM BEHAV **48**(3) 723-732, 1994.—The effects of dizocilpine and buprenorphine pretreatment on behavior reinforced by orally delivered phencyclidine (PCP) and saccharin, and on PCP withdrawal-induced disruptions in food-maintained responding were examined. Sixteen male rhesus monkeys were used in six different experimental protocols. Two groups of monkeys (N = 4-5) self-administered PCP (0.25 mg/ml) and water under concurrent FR 16 schedules, and were pretreated with IM injections of saline, and dizocilpine (0.001-0.1 mg/kg), or buprenorphine (0.003-0.8 mg/kg) 30 min before the 3-h sessions for 5 days. Two other groups (N = 5) were treated similarly except they had access to saccharin (0.03% or 0.3% w/v) and water under concurrent FR 16 schedules. In two other groups (N = 3), the effects of saline, dizocilpine (0.005-0.1 mg/kg), or buprenorphine (0.2 and 0.8 mg/kg) pretreatment were studied on PCP (0.25 mg/ml) withdrawal-induced disruptions in food-maintained responding. Dizocilpine and buprenorphine reduced both PCP (0.25 mg/ml) and saccharin (0.03% or 0.3% w/v) self-administration, especially at the 0.1-mg/kg dizocilpine dose and 0.2-mg/kg buprenorphine dose. Dizocilpine attenuated the PCP withdrawal effect, but buprenorphine had no effect on behavioral disruptions induced by PCP withdrawal. When dizocilpine was administered 2 days after PCP withdrawal began, the withdrawal effects were almost completely reversed. These results suggest that although drugs from the same and different pharmacological classes can suppress self-administration of drug and nondrug reinforcers, the same doses may produce an opposite effect or no effect on food-maintained behavior during PCP withdrawal.

Buprenorphine Dizocilpine MK-801 Monkeys Saccharin Self-administration Withdrawal

RECENT efforts in the behavioral analysis of drug abuse using animal models have focused upon the development of pharmacological means of reducing drug self-administration. A variety of treatment agents such as buprenorphine, a partial agonist at the mu opiate receptor (11,15,36-38), dopamine agonists such as bromocriptine (28), and several antidepressant medications such as fluoxetine (16,41) have been reported to reduce behavior reinforced by drugs such as amphetamine, cocaine, ethanol, and phencyclidine (PCP) in animal studies. There have been reports of varying efficacy when these pharmacological treatments are given in clinical studies (21-24,30,43).

One of the notable findings from this area of research is the lack of pharmacological specificity between treatment drug and self-administered drug. In fact, control group data indicate that treatment medications such as buprenorphine and fluoxetine also suppress behavior maintained by highly preferred nondrug reinforcers such as saccharin and glucose (11,15). The same doses of these drugs that decrease self-administration do not substantially alter food and water in-

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take, which suggests that treatment drugs are selectively interfering with the potent reinforcing effects of drugs and other substances or high rates of performance generated by these reinforcers, and that they are not producing a general suppression in behavior.

In most of the animal models used to investigate drug treatment, a steady-state level of drug self-administration is the baseline for analysis. The effect of drug treatment on transition states such as *acquisition* of drug self-administration, *withdrawal* effects that accompany termination of drug self-administration, or *relapse* have been largely unexplored. It was the goal of this experiment to investigate the effects of dizocilpine and buprenorphine on self-administration of orally delivered phencyclidine (PCP) and a nondrug reinforcer, saccharin, and on PCP withdrawal effects that occur when daily self-administration of the drug is discontinued. Treatment drugs were selected from the same and different pharmacological classes as the abused drug to determine whether the nonspecific treatment effects that have emerged in the self-administration paradigm also apply to alleviation of drug withdrawal effects.

The self-administered drug used in these studies was orally delivered PCP because steady rates of self-administration can be maintained over long periods of time, and withdrawal effects can be repeatedly demonstrated in a within-subjects design (7). Operant baselines of food-maintained responding were used to study PCP withdrawal because they detect withdrawal effects after discontinuation of low PCP doses (7), they are objective and quantifiable at doses that do not produce physical signs of withdrawal, and such operant baselines show an orderly time course in the recovery of drug withdrawal effects. Operant baselines have been reliably used to study withdrawal from PCP (3,7,33,45) and other drugs such as caffeine (6,12), cocaine (14,48), and nicotine (17) that do not produce observable signs of withdrawal when their access is abruptly terminated. They have also been used with drugs such as ethanol (1) and morphine (20,25,44) at doses too low to produce physical signs of withdrawal. Parametric behavioral studies of withdrawal have indicated that variables such as duration of access (7), dose and serum concentrations (45), and the relative amount of food satiation/deprivation (9) are related to the magnitude and duration of withdrawal effects. Schedule of reinforcement is a variable that has (9) and has not (33) been previously related to behavioral disruptions produced by drug withdrawal. Another variable that has received limited attention [cf. (2)] is cross-dependence or the effect of substituting a different drug during the withdrawal period. Beardsley and Balster (3) demonstrated that ketamine, a drug from a similar class, attenuated PCP withdrawal effects and Carroll (8) reported that (+)-*N*-allylnormetazocine, a benzomorphan opioid with psychotomimetic effects, reversed PCP withdrawal effects. It was a goal of the present study to further examine the specificity of cross-dependence by substituting a similar drug and a drug from another pharmacological class during PCP withdrawal.

The treatment drugs were buprenorphine and dizocilpine (MK-801). Dizocilpine has a mechanism of action that is similar to PCP (dizocilpine), a noncompetitive antagonist at the NMDA receptor complex. By blocking the excitatory and toxic actions of amino acids such as glutamate and aspartate, it has therapeutic potential for reducing brain damage in neurological disorders such as stroke; however, it may have damaging cellular and behavioral (dysphoria) side effects of its own (39,40). Like PCP, dizocilpine has been shown to function as a reinforcer via the IV route in monkeys (4,29,46).

Buprenorphine is a partial agonist at the mu opioid receptor. Buprenorphine is one of the few drugs that has been reported to have potential for treating cocaine abuse (30,36–38). Recently, buprenorphine has also been reported to suppress self-administration of cocaine base smoking in monkeys (11) and self-administration of orally delivered drugs such as PCP and ethanol (11), as well as nondrug substances such as saccharin in monkeys (11), and glucose and saccharin in rats (15). Buprenorphine has relatively weak reinforcing effects as demonstrated in self-administration studies with monkeys (32,35,48–50), conditioned place preference studies with rats (5), and lowered threshold of intracranial self-stimulation in rats (26).

The effects of buprenorphine and dizocilpine were also examined with respect to their effects on behavior maintained by a potent nondrug reinforcer, saccharin. An additional goal of the present study was to compare the effects of dizocilpine and buprenorphine on PCP-reinforced behavior with effects of these drugs on behavior maintained by a nondrug alternative reinforcer, saccharin. Thus, two pretreatment drugs, buprenorphine and dizocilpine, were compared in three behavioral paradigms: saccharin self-administration, PCP self-administration, and PCP withdrawal. Some of the monkeys used in these experiments had previously participated in a study of the effects of buprenorphine on self-administration of PCP, saccharin, and other drugs (8). Thus, data from the previous report are included for two of the six conditions; buprenorphine pretreatment/saccharin self-administration and buprenorphine pretreatment/PCP self-administration.

METHOD

Subjects

Sixteen adult male rhesus monkeys (*Macaca mulatta*) served as subjects with some monkeys participating in more than one experiment. A number of these monkeys had participated in previous experiments involving PCP and saccharin self-administration; others were experimentally naive. There were no differences in results between naive and experienced animals. Subjects were maintained at approximately 85% of their free-feeding weights with weights obtained every 2 weeks when their cages were steam cleaned. Monkey diets consisted primarily of high-protein monkey chow (Purina, No. 5045), but diets were supplemented with fresh fruits each day. Most of the monkeys had previous experience in drug self-administration procedures [e.g., (9,10)]. Monkeys were housed individually in rooms that were controlled for temperature (23°C) and humidity, with a 12 L : 12 D cycle (lights on at 0700 h). Animal care and housing was in accordance with regulations of the American Association for the Accreditation of Laboratory Animal Care. The care and use of monkeys in this experiment was approved by the University of Minnesota Institutional Animal Care and Use Committee under Protocol number 9002022.

Apparatus

Each monkey was housed in a custom-made stainless steel primate cage (Lab Products, Inc., Maywood, NJ). The cages (75 cm W × 88 cm H × 100 cm D) served as the experimental chambers and consisted of a solid side and back wall and a barred front. One side wall was modified to function with a work panel. The aluminum work panel (48.3 cm^2) was attached to the outside of the monkey cage by a thumb screw at each panel corner; the work panel contained two drinking

spouts, three stimulus lights (2.8 W), and a standard primate lever, all of which extended into the cage. The modified side wall contained circular holes for the drinking spouts (7.6 cm diameter) and stimulus lights (2.5 cm diameter), a rectangular hole (6 × 2.5 cm) for the primate lever, and a square opening (6.3 × 6.3 cm) to a recessed pellet receptacle. Each drinking spout was encased in a circular Plexiglas panel (7.5 cm diameter) with a corresponding green jeweled stimulus light located 11.5 cm above each spout that signaled the availability of water (constant light) or other liquid (pulsed 16 times/s). A standard primate lever was centered on the work panel 11.0 cm below the drinking spouts. A red jeweled stimulus light that signaled food availability was located 22 cm above the lever. Each individual chamber was controlled by a programmable microcomputer located in an adjacent room.

Liquids were stored in covered Nalgene reservoirs, which were located outside each cage and above each work panel. Liquids flowed through Tygon tubing attached to each drinking spout (2.7 cm length, 1.2 cm o.d., 0.2 cm i.d.). A drinking circuit was activated when a subject made lip contact with the spout. Successful contact was indicated to the subject by the illumination of lights located behind the Plexiglas panel holding the drinking spout. Four small lights (1.1 W) formed a diamond around the drinking spout, with two green lights (indicating drug) and two white lights (indicating water) on intersecting axes. When the fixed-ratio (FR) response criterion was achieved, a solenoid valve located at the base of the spout opened (approximately 120 ms) and dispensed 0.6 ml of liquid.

For the withdrawal study, food was delivered to some subjects from universal feeders (Ralph Gerbrands Co., Arlington, MA) into food hoppers at the base of the work panel after completion of an FR requirement. Subjects that were not required to lever press for food pellets received their daily allotment in a food hopper located on the front of the cage. The experimental chambers, microcomputers, work panel, and solenoid drinking spout have been described previously (19, 24,34).

Drugs

Phencyclidine HCl and buprenorphine HCl were obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Tap water and the PCP and saccharin solutions that were made from stock solutions (1.0 mg/ml) were presented at room temperature. Stock solutions were made weekly and the concentrations are expressed in terms of the salt. A PCP concentration of 0.25 mg/ml was used because it had been shown to be at the peak of the concentration-response function in earlier studies (18). Dizocilpine was donated by Merck & Co. (Rahway, NJ). Buprenorphine and dizocilpine were mixed with sterile distilled water in a stock solution of 8 mg/ml. Drug injection doses were: 0 (saline); 0.003, 0.012, 0.05, 0.2, and 0.8 mg/kg of buprenorphine; and 0, 0.001, 0.005, 0.01, 0.05, and 0.1 mg/kg of dizocilpine. Buprenorphine (11) and dizocilpine (44) doses were selected based on previous research. Saccharin (sodium salt) was purchased from the Sigma Chemical Co. (St. Louis, MO) and solutions were prepared in concentrations of 0.3% and 0.03% (w/v), depending upon which concentration generated the most drinking in each monkey.

Procedure

Two experimental protocols were used under different self-administration and pretreatment conditions. Two groups of monkeys (N = 4–5) self-administered PCP (0.25 mg/ml) and water under concurrent FR 16 schedules, and were pretreated with saline, dizocilpine (0.001, 0.005, 0.01, 0.05 and 0.1 mg/kg), or buprenorphine (0.003, 0.01, 0.05, 0.2 and 0.8 mg/kg) 30 min before the 3-h sessions for 5 consecutive days. Two other groups (N = 5) were treated similarly with saline, dizocilpine (0.005, 0.05, and 0.1 mg/kg), or buprenorphine at the same doses described above except they self-administered saccharin (0.03% or 0.3% w/v) and water under concurrent FR 16 schedules. The remaining two groups of monkeys were used to examine dizocilpine and buprenorphine pretreatment on PCP withdrawal effects. These groups self-administered PCP (0.25 mg/ml) and water under concurrent FR 16 schedules during three daily 6.5-h components. Delivery of a Purina Monkey Chow biscuit (5.5 g) from the universal feeder was contingent upon completion of 64 lever press responses (FR64) during three alternating 1-h components. Withdrawal effects were operationally defined as a suppression in food-maintained responding. Buprenorphine doses were tested in a nonsystematic order that was different for each monkey. At least 10 days of stable behavior preceded each 5-day buprenorphine treatment period.

PCP or Saccharin Self-Administration Procedure

Subjects had access to two liquids (PCP or saccharin and water), each under an FR 16 schedule, during the experimental session from 1000 to 1300 h every day. There was a 2-h timeout from 0800 to 1000 h each day when intersession water was removed from the reservoirs, measured, and replaced with the appropriate liquids for the daily experimental session. After reservoirs were filled, the daily liquids were first flushed through the tubing to ensure that the first liquid delivery would not be water from the previous intersession, and then measured to obtain an accurate initial volume. Following completion of the session, there was a 1.5-h timeout from 1300 to 1430 h when liquids were removed from the reservoirs, measured, and replaced with water. Water was then available under an FR 1 schedule during the intersession period from 1430 to 0800 h the following day. During both morning and afternoon timeouts, all chamber lights were extinguished, liquids were not available, and responding had no programmed consequences. At 1400 h subjects were fed predetermined amounts of pellets that maintained their weights at approximately 85% of their free feeding weights.

PCP Withdrawal Procedure

The withdrawal procedure used was one that was reported previously (7). According to this procedure PCP withdrawal effects were produced after three 6.5-h or three 3-h daily liquid access sessions, but not after three 1-h daily liquid access sessions. The parameters used were those that produced the most reliable PCP withdrawal in the previous experiment. Previous work had shown that withdrawal effects could be repeatedly produced using these procedures without an intensification or weakening of the effect (7,9). Two liquids (0.25 mg/kg PCP and water) and food were each made available three times daily, 7 days a week. Beginning at 1000 h each day, 1 h of food availability alternated with 6.5 h of liquid availability. This cycle lasted until 0830 h the following day. Food data were collapsed over the three 1-h access periods, although almost all of the food-maintained responding occurred during the first two food components. From 0830 until 1000 h there was a 1.5-h timeout period when all chamber lights were extinguished, no food or liquid was available, and responding had

no programmed consequences. During this timeout, liquids were removed from the reservoirs and consumption was measured. The tubing was flushed with the appropriate liquid to ensure that the first delivery at session or intersession onset contained the substance that was in the reservoir. Subsequently, reservoirs were filled with liquids appropriate for the day and universal feeders were refilled with Purina High Protein monkey chow biscuits (approximately 5.5 g each). All liquids were delivered under concurrent FR 16 schedules and the food was delivered under an FR 64 schedule. Previous research indicated that marked and consistent withdrawal effects occur when food is available under an FR 64 schedule (7,9). Completion of the required lever presses resulted in the delivery of one food pellet into the food hopper.

In the PCP withdrawal study, PCP (0.25 mg/ml) and water were concurrently available for 19.5 h each day except for periods of withdrawal when only water was available. Stability for 5 days, defined as no steadily increasing or decreasing pattern in liquid or food deliveries, was required before experimental manipulations began. When stable behavior was established, withdrawal was initiated by replacing PCP with water for 8 days. Subsequently, PCP was reinstated to measure recovery. The last 5 days preceding withdrawal served as a control period for the 8-day withdrawal period and subsequent 5-day recovery period. Following completion of PCP withdrawal, behavior was permitted to stabilize for an additional 5 days with normal PCP access. The minimum 10-day stabilization period often included part of the 5-day recovery period. The withdrawal sequence was repeated two or three times to establish that similar magnitudes of withdrawal were established over the replications. Injections of dizocilpine or buprenorphine were given only during the 8-day withdrawal period. Doses were given in nonsystematic order to minimize temporal effects. Dizocilpine or buprenorphine were administered IM twice a day at 0930 and 1600 h, to ensure adequate drug duration. The first dizocilpine or buprenorphine injection occurred 30 min before session onset, and the second injection was given 5 h into the liquid self-administration session. Although food or liquid access was available from 1000 each day to 0830 h the next day, most of the behavior typically occurred between 1000 and 2200 h. Thus, the rationale for the dosing regimen was to give two injections, one before session and one midway during the active cycle (1600 h).

RESULTS

The left panel of Fig. 1 illustrates the effect of dizocilpine dose on deliveries of PCP and water under the concurrent FR 16 schedules. Data are expressed as a mean for four monkeys. Mean baseline rates of PCP deliveries for the four monkeys ranged from 327.8 to 628. Saline pretreatment resulted in no change in PCP and water deliveries compared to when no pretreatment injections were given. As the dizocilpine dose increased from 0.0 (saline) to 0.1 mg/kg, there was a dose-related decrease in PCP deliveries. Intermediate effects occurred at the 0.0025- and 0.005-mg/kg doses; the 0.01-mg/kg dose had almost the same effect as a tenfold higher dose (0.1 mg/kg). Water deliveries remained at low levels across all dizocilpine doses, and they did not vary as a function of dizocilpine dose. The time course of dizocilpine's effect on PCP self-administration is not shown, but it was consistent across the four monkeys and five doses of dizocilpine. The greatest reduction in PCP self-administration occurred on the first day of pretreatment, followed by a reduced but stable level of self-administration over the remaining 4 days. When dizocilpine pretreatment was discontinued, PCP-reinforced responding returned to baseline levels within 1 or 2 days, and the rate of return to the PCP baseline was not a function of dizocilpine dose.

The right panel of Fig. 1 shows the effect of dizocilpine on concurrent saccharin (0.03% w/v) and water self-administration. Mean saccharin deliveries ranged from 243.6 to 1,027.4 across the group of five monkeys during the saline pretreatment period, and those levels of intake did not differ from the 5 days immediately preceding saline pretreatment when no injections were given. The mean saccharin deliveries during saline pretreatment (722.9) was considerably higher than mean PCP deliveries during saline injections (428.3); however, the effects of dizocilpine were comparable with both PCP and saccharin. Dizocilpine produced dose-related decreases in sac-

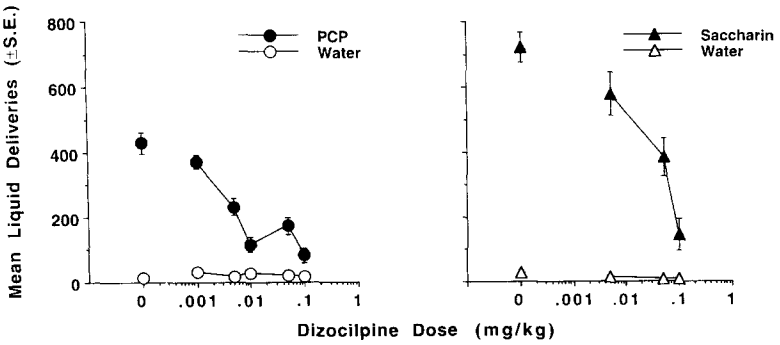

FIG. 1. Mean liquid deliveries (±SE) are presented as a function of dizocilpine dose (mg/kg) for a group of four monkeys that received access to PCP (0.25 mg/ml) and water under concurrent FR 16 schedules (left panel) and a group of five monkeys that received access to saccharin (0.03% w/v) and water under concurrent FR 16 schedules (right panel). The dizocilpine doses tested were: 0 (saline), 0.001, 0.005, 0.01, 0.05, and 0.1 mg/kg. Unconnected points refer to saline pretreatment. Filled circles represent PCP and saccharin deliveries and open circles refer to water deliveries. Each point represents a mean of five sessions. Vertical bars refer to the mean SEs for the 5 days across four or five monkeys.

charin self-administration, with a 92% reduction from saline baseline at the highest dose (0.1 mg/kg). Concurrent water deliveries were low and did not vary systematically with dizocilpine dose. As in the PCP group, the time course of dizocilpine's effects on saccharin self-administration was similar across monkeys and dizocilpine doses. The greatest suppression of saccharin intake was found on the first day, and recovery of baseline occurred within 1 or 2 days. The rate of return to baseline levels did not vary as a function of dizocilpine dose.

Mean pellet deliveries for the 8-day PCP withdrawal period and subsequent 5-day recovery are plotted in Fig. 2 for four monkeys as a function of the dizocilpine pretreatment dose: 0 (saline), 0.005, 0.05, and 0.1 mg/kg. The pellet deliveries for the 5 days immediately prior to PCP withdrawal were averaged to obtain the baseline level (designated as 100%), and pellet deliveries on the other days are expressed as a percentage of that baseline value. Day 1 was designated as the first 24-h period after water was substituted for PCP, and day 2 was the next 24-h period, etc. Thus, on day 1 water was substituted for PCP at 1100 h, and the next available food component began at 1730 h. The last time that PCP had been consumed between 0630 h the previous day until 1000 h on the morning of the withdrawal day or 10 to 16.5 h earlier. Thus, the first food session on day 1 occurred near the peak of the PCP withdrawal period. Generally, almost all of the food- and liquid-maintained responding occurred during the first two of three daily food and liquid components, and the reduction in pellet deliveries shown during PCP withdrawal was equally distributed between the first and second food component. There were almost no pellet deliveries during the third, as in the baseline condition.

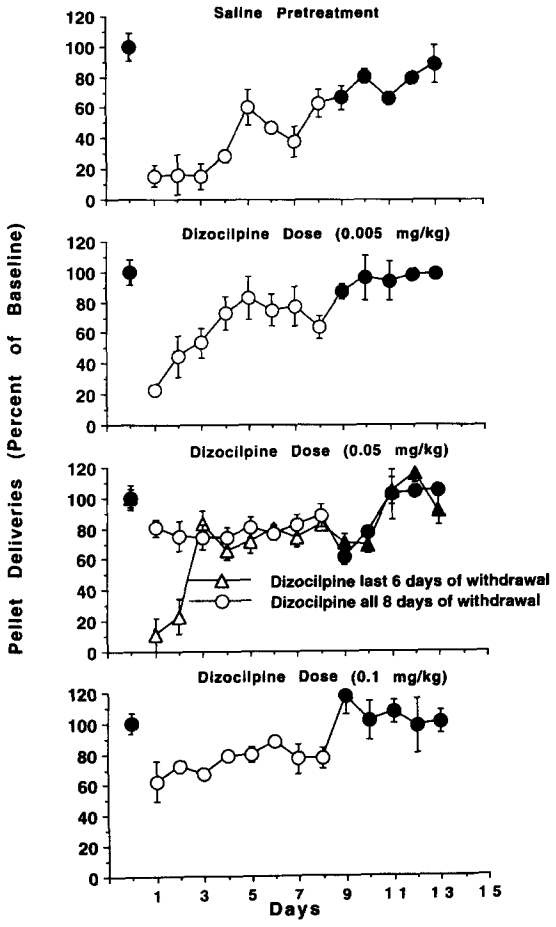

FIG. 2. Mean pellet deliveries (±SE) are presented as a percent of the 5-day baseline period before PCP withdrawal (unconnected filled symbols), as a function of 8 days of PCP withdrawal (open symbols) and 5 days of PCP reinstatement (connected filled symbols) for a group of three monkeys. In each panel the dizocilpine pretreatment dose (mg/kg) is indicated in parentheses. The doses tested were: 0 (saline), 0.005, 0.5, and 0.1 mg/kg. The dizocilpine was injected IM 30 min prior to the onset of the first food component (0930 h) and again 6.5 h later (1600 h) on each of the 8 days of PCP withdrawal. In the third panel triangles represent data from a replication of the PCP withdrawal-reinstatement sequence in which dizocilpine (0.05 mg/kg) pretreatments were begun after 2 days of PCP withdrawal had elapsed.

In the saline pretreatment condition (Fig. 2, top panel), pellet deliveries were suppressed to 18% of baseline levels during the first day of the PCP withdrawal period and continued to decline to 15% of baseline on days 2 and 3 of PCP withdrawal. By the end of PCP withdrawal, pellet deliveries had only recovered to approximately 65% of baseline levels, but they steadily increased to 90% of baseline after PCP was reinstated and dizocilpine treatment had ended. The second frame shows that when the low dose of dizocilpine (0.005 mg/kg) was administered, pellet deliveries fell to 23% of baseline on day 1 of withdrawal, and deliveries were at 73% of baseline by day 4 of withdrawal. Thus, the effects of the lowest dizocilpine dose were similar to the saline condition. During the postwithdrawal period, pellet deliveries approached baseline levels (>90% of baseline), and had nearly recovered fully by the second day of PCP reinstatement.

The intermediate dose of dizocilpine (0.05 mg/kg) resulted in a faster recovery from PCP withdrawal than found with saline or low dose dizocipline treatment (Fig. 2, third panel). When dizocilpine was administered beginning on day 1 of PCP withdrawal (circles), a distinct but much smaller decrease (87%) in pellet deliveries from baseline was observed compared with the lower dizocilpine dose or saline. However, when the dizocilpine administration was delayed 2 days (triangles), pellet deliveries were reduced to 11% of baseline on day 1 and 22% of baseline on day 2. When dizocilpine administration commenced on day 3 of PCP withdrawal, pellet deliveries returned to 80% of baseline. On the third day of PCP withdrawal, when all subjects were receiving dizocilpine, mean deliveries were similar regardless of whether dizocilpine treatment had begun on that day or 2 days before; thus, the 2-day delay of dizocilpine did not shift the recovery curve. There was a full recovery to 100% baseline by day 3 of PCP reinstatement under both the 6-day and 8-day dizocilpine treatment conditions. The high dose of dizocilpine (0.1 mg/kg) produced an amelioration of the PCP withdrawal effect that was nearly identical to that of the 0.05-mg/kg dose (Fig 2, bottom panel). With the initiation of PCP withdrawal, pellet deliveries fell to 60% of baseline with an increase to 76% of baseline over the 8 days of withdrawal. There was a complete recovery to baseline the first day PCP was reinstated. Generally, the intersubject variability was low, and there was little variability in food-maintained responding within monkeys from day to day. A higher dizocilpine dose (0.5 mg/kg) was tested, but it was discontinued when seizures occurred in two monkeys. The reduced withdrawal effect due to dizocilpine treatment was not a result of repeated withdrawal tests, as doses were given in nonsystematic order and monkeys tested

with a saline after the 0.05 or 0.1 mg/kg continued to show a pronounced withdrawal effect.

Liquid deliveries before, during, and after the 8-day PCP withdrawal period are presented in Fig. 3. The PCP deliveries during the 5-day baseline period were approximately 1600 during the 19.5-h daily liquid access components. This is more than three times higher than the baseline values from the 3-h sessions reported in Fig. 1 (e.g., 430 deliveries). When PCP was reinstated after the 8-day withdrawal period, deliveries returned to baseline levels (e.g., 1600). The baseline PCP deliveries were less than those reported earlier (7) due to the increase in liquid FR from 8 to 16 in the present experiment. Baseline water deliveries during the 19.5-h components were very low (e.g., 25) compared to concurrently available PCP deliveries (1600), indicating that PCP was functioning as a reinforcer. During the 8-day withdrawal period, water deliveries increased to approximately 600 when saline was given and returned to low levels when PCP was reinstated. These PCP reinstatement data also indicate that PCP was functioning as a reinforcer.

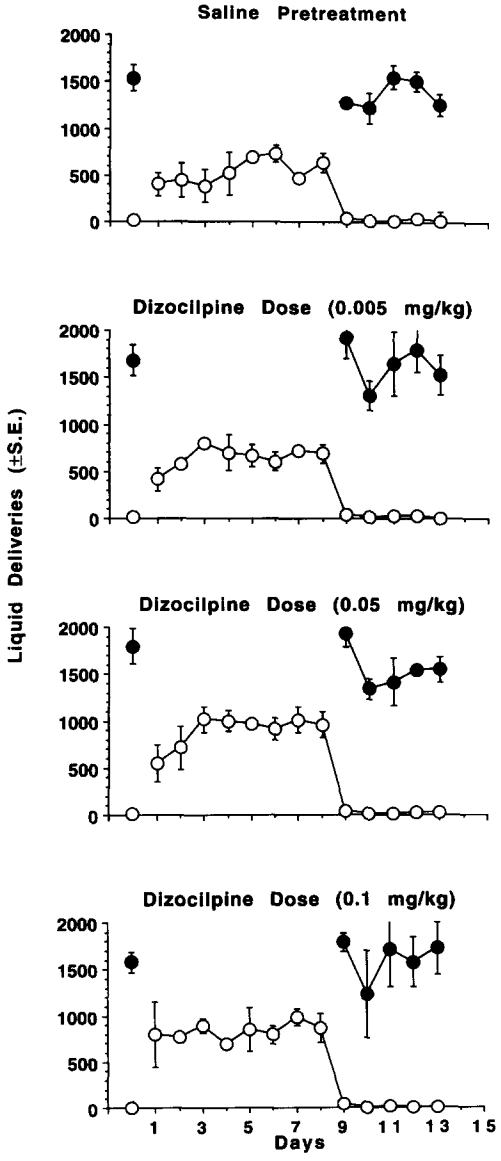

FIG. 3. Liquid deliveries are presented for the 5-day baseline period before PCP withdrawal (unconnected filled circles), during the 8 days of PCP withdrawl (open circles), and the 5 days of PCP reinstatement for a group of three monkeys. In each frame the dizocilpine pretreatment dose (mg/kg) is indicated in parentheses. The doses tested were 0 (saline), 0.005, 0.05, and 0.1 mg/kg. Dizocilpine was injected 30 min prior to the onset of the first food componet (0930 h) and again 6.5 h later (1600 h) on each of the 8 days of PCP withdrawal.

PCP withdrawal had little effect on water deliveries under the saline, 0.005- and 0.05-mg/kg dizocilpine treatment conditions. There was a slight suppression in water deliveries during the first 2 days of PCP withdrawal. This effect was not apparent at the high dizocilpine dose (0.1 mg/kg). These small decreases were not nearly the magnitude of decreases in pellet deliveries shown in Fig. 2. Thus, the reduction in pellet deliveries was not due to nonspecific decreases in all operant behavior. Dizocilpine treatment produced a slight elevation in water deliveries at the two higher doses (0.05 and 0.1 mg/kg). During saline and 0.005-mg/kg dizocilpine treatment water deliveries were approximately 600, the same as during buprenorphine treatment (Fig. 6). However, at the two higher dizocilpine doses water deliveries increased to approximately 850, indicating that dizocilpine enhanced water intake. When PCP was reinstated, PCP and water deliveries returned to baseline on the first day; however, there was a consistent decrease in PCP deliveries on the second day dizocilpine was discontinued and PCP was reinstated. This decrease on day 2 was followed by a recovery to baseline execpt at the 0.05-mg/kg dizocilpine dose.

Figure 4 (left panel) illustrates the effects of varying buprenorphine dose on PCP and water deliveries under the concurrent FR 16 schedules. Each data point represents a mean for five monkeys. Individual data, as well as these summary data, have previously been reported (11) and are presented here with an abbreviated description for comparison. The baseline PCP deliveries during saline pretreatment ranged from 278.0 to 418.2. At the 0.003-mg/kg buprenorphine dose, behavior was suppressed by 26% of the saline condition. It was reduced further to approximately 35% of the saline condition when the 0.2- and 0.8-mg/kg buprenorphine doses were given. Water deliveries were very low and unaltered by buprenorphine pretreatment. As reported previously (11), the greatest suppression due to buprenorphine pretreatment was found on the first day with a steady reduced amount of PCP deliveries (approximately 50% of baseline) on the remaining 4 days. When buprenorphine was discontinued, three of the five monkeys returned to baseline PCP deliveries within 5 days, but recovery of baseline did not occur in the other two monkeys until 7 or 10 days. There was a trend toward longer recovery of baseline with the higher buprenorphine doses.

Figure 4 (right panel) shows similar data for monkeys that had access to saccharin and water under concurrent FR 16 schedules. Each data point represents a mean for five monkeys. These summary data, as well as the individual data, have been previously published (11). As in the groups that were treated with dizocilpine, the saccharin baseline during saline pretreatment was nearly twice as high as the PCP deliveries. The range of mean saccharin deliveries across the five monkeys was 355.8 to 1060. Saccharin deliveries were reduced to about the same levels as PCP by buprenorphine; thus, reductions relative to baseline were much greater with saccharin. At the lowest buprenorphine dose (0.003 mg/kg), a decline from

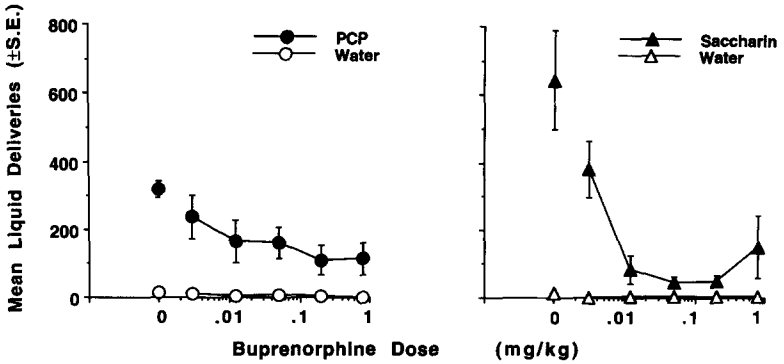

FIG. 4. Mean liquid deliveries (±SE) are presented as a function of buprenorphine dose (mg/kg) for a group of five monkeys that received access to PCP (0.25 mg/ml) and water under concurrent FR 16 schedules (left panel) and a group of five monkeys that received access to saccharin (0.03% w/v) under concurrent FR 16 schedules (right panel). The buprenorphine doses tested were 0 (saline), 0.003, 0.012, 0.05, 0.2, and 0.8 mg/kg. Unconnected points refer to saline pretreatment. Filled circles represent PCP and saccharin deliveries and open circles refer to water deliveries. Each point represents a mean of five sessions. Vertical bars refer to the mean SEs for the 5 days across five monkeys.

saline baseline of about 40% in saccharin deliveries is observed. The 0.2-mg/kg buprenorphine dose produced a near maximal decline (93% below baseline) in saccharin deliveries; this is the same dosage that was most effective in reducing PCP deliveries. Water deliveries remained low and stable, and unresponsive to buprenorphine dose. The time course of buprenorphine effects was characterized by an almost complete suppression of saccharin-reinforced responding on all 5 days of pretreatment. When lower dose buprenorphine pretreatment ended, all five monkeys returned to baseline levels within 2 to 6 days. Higher doses of buprenorphine resulted in a longer return to baseline (e.g., 5–10 days).

PCP withdrawal effects are shown for pretreatment with saline (0) or two doses of buprenorphine (0.2, 0.8 mg/kg) in Fig. 5. Mean data represent three monkeys. Intersubject variability was low, as was the variability in food-maintained responding from day to day. All three plots show that pellet deliveries were reduced substantially from baseline on the first day of PCP withdrawal (23.4%, 8.5%, and 14.2% of baseline for saline, 0.2, and 0.8 mg/kg, buprenorphine, respectively) and similar patterns of food-maintained responding emerged throughout PCP withdrawal. By the last day of PCP withdrawal, pellet deliveries were reduced to 34.5%, 52.8%, and 40.4% of baseline levels, respectively. Following PCP reinstatement, pellet deliveries continued to increase in all three groups, but an inverse relationship between buprenorphine dose and pellet deliveries became apparent. The mean pellet deliveries for the 5-day postwithdrawal period was 82.5%, 73.5%, and 66.2% of the prewithdrawal baseline for the saline, 0.2- and 0.8-mg/kg buprenorphine conditions, respectively. Water deliveries were low during when PCP was concurrently available. They increased only slightly during the 8-day PCP withdrawal period as described for the dizocilpine pretreatment study, and they returned to baseline levels when PCP was reinstated.

Figure 6 shows the liquid deliveries for a mean of 5 days before PCP withdrawal, during the 8-day withdrawal period, and the first 5 days of reinstatement. Baseline PCP deliveries were similar to those reported in Fig. 3 (approximately 1600). Concurrent water deliveries were very low (e.g., 40); however, when PCP was removed, water deliveries increased to approximately 650. Water deliveries were consistently lower on the first day of PCP withdrawal under the buprenorphine treatment conditions, indicating a possible suppressant effect of the drug that added to the PCP withdrawal effect. When PCP was reinstated, PCP and water deliveries returned to baseline levels. There was a decrease on the second day of reinstatement after buprenorphine treatment. There were no other differences in the magnitude or pattern of liquid intake due to buprenorphine treatments.

DISCUSSION

Injections of dizocilpine and buprenorphine reduced PCP and saccharin self-administration during 3-h sessions. Baselines of saccharin intake were nearly twice as high as those for PCP; however, the highest doses of dizocilpine and buprenorphine reduced responding maintained by PCP and saccharin to the same low levels. Lower doses of dizocilpine produced nearly the same percentage reductions in PCP deliveries as in saccharin deliveries, but lower buprenorphine doses produced greater percentage reductions in saccharin intake compared to that of PCP. The behavioral suppressions resulting from administration of these drugs were limited to the operantly reinforced PCP and saccharin deliveries. Concurrent water deliveries were near zero during the 3-h sessions, and water intake was not systematically altered by dizocilpine or buprenorphine. There was no reduction in postsession food and water intake, despite the fact that the effects of both dizocilpine and buprenorphine outlast the 3-h session. Furthermore, dizocilpine and buprenorphine had little effect on water deliveries during PCP withdrawal. These results concur with previous findings from other laboratories indicating that buprenorphine had a more marked effect on drug-rewarded behavior (e.g., cocaine) than on food-maintained behavior (38). These findings suggest that the suppression in drug and sac-

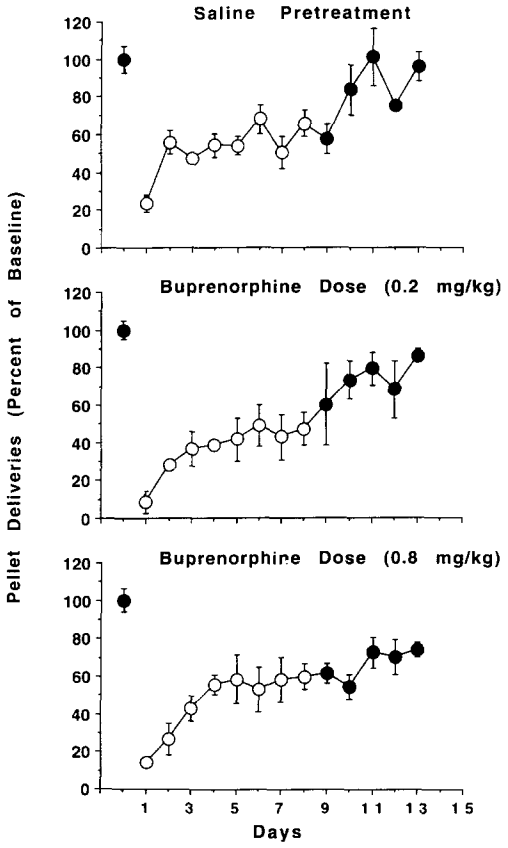

FIG. 5. Mean pellet deliveries (±SE) are presented as a percent of the 5-day baseline period before PCP withdrawal (unconnected filled circle) as a function of 8 days of PCP withdrawal (open circles) and 5 days of PCP reinstatement (connected filled circles) for a group of three monkeys. In each frame the buprenorphine pretreatment dose (mg/kg) is indicated in parentheses. The doses tested were 0 (saline), 0.2, and 0.8 mg/kg. Buprenorphine was injected IM 30 min prior to the onset of the first food component (0930 h) and again 6.5 h later (1600 h) on each of the 8 days of PCP withdrawal.

charin-reinforced behavior is not a general suppression in operant responding but a specific interaction with potent reinforcing substances.

The PCP withdrawal effect that was reported under baseline conditions (vehicle pretreatment) was similar to that reported in a previous study in which monkeys had daily 3-h access to PCP (7). As noted in the earlier study, this effect was not as severe as that reported earlier by Slifer and coworkers (42) when monkeys were maintained on continuous phencyclidine IV infusions prior to withdrawal of drug access. As reported earlier (7), the monkeys in the present study showed stable withdrawal effects after two or three cycles, with the severity of the disruption in food-maintained responding increasing from the first to second withdrawal test. This finding of increased sensitivity is in contrast to that reported by others (3,38) in which the magnitude of withdrawal effects diminished over successive withdrawal tests.

Although the effects of dizocilpine and buprenorphine on PCP and saccharin self-administration were quite similar, their effects on PCP withdrawal were very different. Dizocilpine suppressed PCP and saccharin self-administration at doses that restored food-maintained responding in the withdrawal paradigm. Water deliveries during PCP withdrawal actually increased during treatment with the higher dizocilpine doses. Buprenorphine markedly reduced PCP and saccharin-reinforced behavior, but it had no effect on food- and water-maintained behavior during PCP withdrawal. The differential effectiveness between dizocilpine and buprenorphine at attenuating PCP withdrawal is consistent with previous literature indicating that withdrawal effects may only be modified by substitution of a similar pharmacological agent (3,8).

The time course manipulation of treatment with dizocilpine 2 days after emergence of the PCP withdrawal effects indicated that PCP withdrawal effects could be rapidly reversed by dizocilpine. The dose of dizocilpine that was most effective at preventing and reversing the PCP withdrawal-induced disruptions in food-reinforced responding was 0.05 mg/kg, a dose that produced a 50% suppression in PCP- and saccharin-reinforced behavior. The highest dose (0.1 mg/kg) produced slightly less of an attenuation of the PCP withdrawal effect. This may have been due to mild acute intoxicating effects of

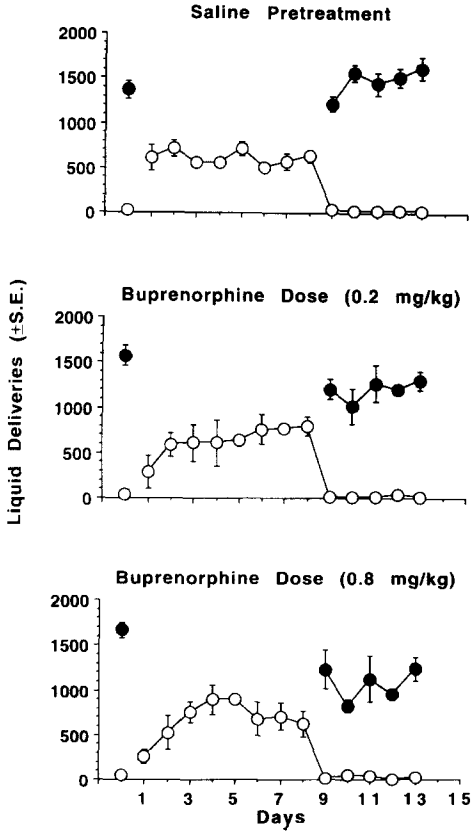

FIG. 6. Liquid deliveries are presented for the 5-day baseline period before PCP withdrawal (unconnected filled circles), during the 8 days of PCP withdrawal (open circles), and the 5 days of PCP reinstatement (connected filled circles) for a group of three monkeys. In each panel the buprenorphine pretreatment dose (mg/kg) is indicated in parentheses. The doses tested were 0 (saline), 0.2, and 0.8 mg/kg. Buprenorphine was injected 30 min prior to the onset of the first food component (0930 h) and again 6.5 h later (1600 h) on each of the 8 days of PCP withdrawal.

this high dose, as a higher dose (0.5 mg/kg) produced seizures in one monkey and ataxia in two others.

In summary, dizocilpine and buprenorphine both produced dose-dependent decreases in self-administration of orally delivered PCP and saccharin, but these drugs did not suppress water intake, or food-reinforced behavior that was maintained under an operant schedule and that had been suppressed by PCP withdrawal. These results suggest that drugs such as dizocilpine and buprenorphine nonspecifically suppress free operant behavior that is maintained by potent reinforcers (e.g., PCP, saccharin) and is under schedule and stimulus control. Dizocilpine and buprenorphine treatment of withdrawal effects indicated that only drugs from the specific drug class (e.g., dizocilpine) that is withdrawn (PCP) reinstate food-maintained behavior that has been suppressed by drug withdrawal.

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