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Sex Differences in Physical Dependence on Orally Self-Administered Phencyclidine (PCP) in Rhesus Monkeys (*Macaca mulatta*)

Jennifer L. Perry, Lisa M. Normile, Andrew D. Morgan, and Marilyn E. Carroll
University of Minnesota

Withdrawal from orally self-administered phencyclidine (PCP) has been shown to alter operant baselines of food-maintained responding. The goal of the present study was to determine whether there are sex differences in these alterations. Seven female and 7 male rhesus monkeys (*Macaca mulatta*) were given concurrent access to PCP and water under fixed ratio (FR) 8 schedules during 2 daily sessions that alternated with 2 sessions during which pellet deliveries were contingent on lever presses under an FR 64 schedule. After operant responding stabilized, PCP was replaced by water for 10 days, and food access remained under the same schedule. Subsequently, concurrent PCP and water access was reintroduced for 10 days. This procedure was repeated with 3 PCP concentrations (0.125, 0.25, and 0.50 mg/ml) and 3 FR requirements for food-reinforced responding (64, 128, and 256). Disruptions in operant responding for food served as a quantitative measure of withdrawal severity. During PCP withdrawal, males showed a greater suppression of food-maintained behavior than females at the 2 highest PCP concentrations and the lowest FR requirement tested. Males responded more than females for PCP; however, when weight was taken into consideration, PCP intake (milligrams per kilogram) in males and females was equal. The data suggest that males may experience more severe withdrawal effects than females, and the duration of the adverse effects of withdrawal lasts longer in males than in females. This study is the 1st to use nonhuman primates to document sex differences in withdrawal severity as measured by a quantifiable baseline.

Keywords: operant baselines, phencyclidine, physical dependence, sex differences, withdrawal

Recent research in animals indicates that females are more vulnerable to the reinforcing effects of drugs of abuse than males during several phases of drug abuse (for reviews, see Carroll, Lynch, Roth, Morgan, & Cosgrove, 2004; Lynch, Roth, & Carroll, 2002). For example, female rats acquired cocaine (Carroll, Morgan, Lynch, Campbell, & Dess, 2002; Lynch & Carroll, 1999), heroin (Lynch & Carroll, 1999), fentanyl (Klein, Popke, & Grunberg, 1997), methamphetamine (Roth & Carroll, 2004), and nicotine (Donny et al., 2000) self-administration at a faster rate than males. Females also showed less precise dose regulation (Lynch, Arizzi, & Carroll, 2000) and more bingelike patterns (Morgan, Brebner, Lynch, & Roberts, 2002) of cocaine self-administration than males. Female rats maintained higher rates of responding during extinction and reinstatement, which indicates that they may be more persistent in their drug-seeking behavior and more vulnerable to relapse than males (Lynch & Carroll, 2000).

Despite the differences seen between males and females in many phases of drug abuse (e.g., acquisition, dysregulation, extinction), few studies have been conducted to examine sex differences in physical dependence and withdrawal. Sex differences in physical dependence are becoming an increasingly important area of study, because even though more men report problems with drug abuse than women, the gender gap appears to be closing (Substance Abuse and Mental Health Services Administration [SAMHSA], 2004). In 2003, men age 18 and older were more likely to be classified with substance dependence than women of a similar age; however, rates of substance dependence in those aged 12–17 were similar for boys and girls (SAMHSA, 2004).

Laboratory studies of sex differences in physical dependence have mainly used rat models, and the results have been mixed. For example, females showed more physical signs of withdrawal (e.g., weight loss, convulsions) than males during withdrawal from pentobarbital (Suzuki, Koike, Yoshii, & Yanaura, 1985) and methaqualone (Suzuki, Koike, & Misawa, 1988). However, Wessinger (1995) found no sex differences in the effect of phencyclidine (PCP) withdrawal on operant responding for food after 10

Jennifer L. Perry, Lisa M. Normile, Andrew D. Morgan, and Marilyn E. Carroll, Department of Psychiatry, University of Minnesota.

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Correspondence concerning this article should be addressed to Jennifer L. Perry, Department of Psychiatry, Division of Neuroscience, University of Minnesota Medical School, MMC 392, Minneapolis, MN 55455. E-mail: perry050@umn.edu

days of chronic PCP exposure. In a study of morphine withdrawal in rats by Cicero, Nock, and Meyer (2002), males demonstrated more severe physical withdrawal signs than females. Additionally, male rats showed greater withdrawal from ethanol than female rats, as manifested by increased seizure susceptibility and delayed recovery to control levels of seizure susceptibility (Devaud & Chadda, 2001) and by increased anxiety in social interactions (Varlinskaya & Spear, 2004) and in an elevated plus maze (Gatch & Lal, 2001). In a study of alcohol withdrawal in humans, men had more signs and symptoms of physiological dependence than women (Woodstock-Striley, Cottler, & Ben Abdallah, 2004). Taken together, these studies are equivocal, and the majority of them examine sex differences in one species, rats. Thus, a goal of the present study is to extend previous investigations of sex differences in spontaneous drug withdrawal using PCP and another species, rhesus monkeys. The present study also extends previous work to conditions under which the drug is self-administered and functions as a reinforcer.

PCP is an effective reinforcer when delivered either intravenously (Balster, Johanson, Harris, & Schuster, 1973; Pickens, Thompson, & Muchow, 1973) or orally (Carroll & Meisch, 1980). We chose orally delivered PCP for the present study because it maintains steady rates of responding over long periods of time and a range of concentrations in rhesus monkeys and because we could use a within-subject design to measure withdrawal effects without order effects or serious adverse consequences (Carroll, 1987). Furthermore, PCP withdrawal effects have previously been reported in human and animal studies. In humans, PCP withdrawal has been associated with reports of depression, irritability, drug craving, and increased need for sleep (Burns & Lerner, 1981). Laboratory studies in animals have also reported physiological (Balster & Woolverton, 1980) and behavioral (Beardsley & Balster, 1987; Carroll, 1987; Carroll & Carmona, 1991; Carroll, Carmona, & Rodefer, 1994; Slifer, Balster, & Woolverton, 1984) manifestations of PCP withdrawal.

Alterations in operant baselines of food-maintained responding have previously been used as a quantitative measure of withdrawal severity. Baselines of food-maintained responding were sensitive to withdrawal from low levels of PCP intake (Carroll, 1987). They produced quantifiable and objective indicators of withdrawal at levels of PCP intake that did not produce physical signs of withdrawal, and they showed a protracted time course in the recovery of drug withdrawal effects (Carroll et al., 1994). Previous studies have indicated that the magnitude and duration of withdrawal effects are related to duration of access (Carroll, 1987), dose and serum concentrations of the maintenance drug (Wessinger & Owens, 1991), and the amount of food restriction (vs. satiation; Carroll & Carmona, 1991). Schedule of reinforcement has (Carroll & Carmona, 1991) and has not (Massey & Wessinger, 1990) been related to behavioral disruptions seen during PCP withdrawal. Thus, a second goal of the present study is to compare disruptions in food-maintained responding in male and female monkeys following withdrawal under three fixed ratio (FR) schedules of food-maintained responding and with three different concentrations of PCP, including the peak of the concentration–response curve.

In the present study, we examine the effects of PCP withdrawal in male and female rhesus monkeys using a within-subject design. Orally delivered PCP and water were concurrently available contingent on lip-contact responses on drinking spouts during two sessions each day that alternated with two sessions in which food pellets were available, contingent on lever presses. After operant responding for food stabilized, PCP was replaced with water for 10 days, whereas food access remained under the same schedule. Subsequently, PCP access was reintroduced for 10 days. Withdrawal effects due to the termination of PCP access were inferred by disruptions in the baseline for food-maintained responding. We examined sex differences in PCP withdrawal under three different concentrations of PCP (0.125, 0.25, and 0.50 mg/ml) under the FR 64 schedule for food to evaluate withdrawal severity as a function of PCP intake and at the 0.25 mg/ml PCP concentration with three different FR requirements for food (64, 128, and 256) to examine the effect of schedule of reinforcement and relative amounts of food satiation (i.e., FR 64) and restriction (i.e., FR 256) on PCP withdrawal. To control for taste and tactile factors, we kept the concentration of the PCP solution (milligrams per milliliter) and amount of liquid per delivery (0.60 ml) constant for males and females so that they would have similar drinking topographies. We calculated the PCP intake data in milligrams per kilogram body weight to account for weight differences in males and females and to control for higher rates of liquid consumption in males (vs. females).

Method

Subjects

In this experiment, subjects were 7 adult male and 7 adult female rhesus monkeys (*Macaca mulatta*). Previously, all subjects had self-administered PCP under different FR and progressive ratio (PR) schedules for several months. Immediately prior to this experiment, all monkeys had daily 3-hr sessions with concurrent access to water and PCP (0.25 mg/ml), and we restricted food intake to maintain each monkey at 85% of its free-feeding weight. During the experiment, food intake increased as monkeys earned all of their food during experimental sessions under various food FR schedules, and monkey weights approached free-feeding values. We measured body weights every 4 weeks. The mean (plus or minus standard error of the mean) 85% body weight for females was 6.80 ($\pm$ 0.88) kg, and for males it was 10.56 ($\pm$ 0.49) kg. The mean (plus or minus standard error of the mean) free-feeding body weights that occurred during this study were 7.54 ($\pm$ 0.95) kg for females and 12.10 ($\pm$ 0.70) kg for males. Monkeys were individually housed in their experimental chambers in a temperature- (24°C) and humidity-controlled room under a 12-hr light–dark cycle (lights on at 6 a.m.). For enrichment, we gave monkeys fruit, trail mix, and other small snacks at 1:30 p.m., and they had access to toys and movies when not in session. They were also housed in rooms that allowed them visual, auditory, and olfactory cues from 9–11 other monkeys. Use of animals for this protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (Protocol 0112A14081). Laboratory facilities

were accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, and we followed recommended principles of laboratory animal care (National Research Council, 2003).

Apparatus

Monkeys were individually housed in custom-made stainless steel primate cages (Lab Products, Inc., Maywood, NJ) with a work panel mounted to the outside of one wall (for more details on the cage and operant panel, see Carroll, Batulis, Landry, & Morgan, 2005). In brief, the panel consisted of two brass drinking spouts spaced 30 cm apart 45 cm above the floor on either side of a centrally located lever. A lip contact on the spout resulted in solenoid operation for approximately 120 ms, and 0.60 ml of liquid was released from the spout. Each spout was mounted on a clear Plexiglas plate that was fitted up to circular holes in the side of each monkey's cage. Two pairs of green and white feedback lights were attached behind clear Plexiglas support plates, and illumination of green lights signaled a lip contact resulting in PCP delivery, whereas illumination of white lights coincided with a lip contact leading to water delivery. Two covered reservoirs on the outside of the work panel contained water and PCP.

The panel also contained three stimulus lights located 12 cm above the lever and each drinking spout. These lights provided visual cues corresponding to experimental events. Responses on the lever during food components activated a Universal Feeder (Ralph Gerbrands Co., Arlington, MA) and resulted in the delivery of a full pellet (Harlan Tekland Monkey Chow, Madison, WI) for males (approximately 12.50 g) and a half pellet for females (approximately 6.25 g) into a receptacle approximately 10 cm below the lever. The stimulus lights, spouts, lever, and food receptacle protruded through holes in the side of the cages to allow for easy removal and cleaning of the experimental panel. Experiments were programmed and data were recorded via PCs and Med-PC software (Med Associates, 1998, St. Albans, VT).

Drug

PCP hydrochloride (HCl) was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC), and we prepared stock solutions weekly. Solutions used for experiments were prepared from stock solution 20 hr before use, and both PCP and water were presented at room temperature. The PCP concentrations (0.125 mg/ml, 0.25 mg/ml, and 0.50 mg/ml) refer to the HCl salt.

Training Procedure

Prior to the start of this study, monkeys responded under concurrent FR 16 schedules of PCP (0.25 mg/ml) and water delivery during daily 3-hr sessions. When the present experiment began, response requirements for PCP and water deliveries were reduced from FR 16 to FR 8 schedules. Table 1 summarizes the daily sessions.

PCP (0.25 mg/ml) and water were concurrently available during two daily sessions lasting 1.5 hr each. Liquid sessions started at 12 p.m. and 4:30 p.m. and were signaled by the onset of the green stimulus lights directly above the spouts. To signal water availability, the stimulus light above one spout remained continuously lit, and to signal PCP availability, the stimulus light above the other spout flashed at a rate of 10 Hz.

Two daily 1-hr food sessions (10 a.m. and 2:30 p.m.) alternated with the liquid sessions. The red stimulus light above the centrally located lever illuminated at the onset of each food session and remained illuminated for the duration of each session. At the onset of the experiment, responding on the lever under an FR 1 schedule resulted in a single food pellet for males and a half pellet for females. Preliminary data indicated that males responded more than females for full food pellets, as they did not become satiated as quickly. The pellet size in females was half that used in males because females consumed half the total amount of food. Therefore, to avoid a potential floor effect in females because of low rates of baseline responding and to avoid possible response rate–dependent effects (for reviews, see McKearney & Barrett, 1978; Thompson, 1984), we used different pellet sizes to maintain similar baseline levels of responding for food despite differences in body size and food intake between males and females. At the beginning of the experiment, we increased response requirements for food (FR 2, 4, 8, 16, 32, 64) until consistent responding under FR 64 occurred. Food and liquid components were separated by 1-hr time-outs, during which stimulus lights remained extinguished and the spouts and feeder were inactive. From 6 p.m. to 8 a.m., there was an intersession period, during which water was available from both spouts under a concurrent FR 1 schedule.

We followed this daily sequence of events under each condition until 5 consecutive days of stable behavior occurred. We defined stability as no steadily increasing or decreasing daily responses for food or PCP over a 5-day period, and this constituted the baseline period (Table 2 shows baseline numbers of pellet deliveries under each condition). Subsequently, water was substituted for PCP for 10 days, keeping the FR 8 schedule for liquid deliveries and the FR 64 schedule for food deliveries as they were. PCP was then reintroduced for 10 days. Subsequently, we repeated the procedure using two other PCP concentrations (0.125 mg/ml and 0.50 mg/ml) under an FR 64 schedule for food-reinforced responding and two other FR schedules (FR 128 and FR 256) with a single PCP concentration (0.25 mg/ml). Each monkey was first tested using an FR schedule for food-reinforced responding and 0.25 mg/ml PCP. Subsequently, we nonsystematically mixed the order of FR schedules and PCP concentrations across animals, and we repeated the entire procedure (i.e., the 5-day baseline period, the 10-day withdrawal period, and the 10-day reintroduction period) under each condition.

Data Analysis

Food pellet deliveries werw expressed as a percentage of the 5-day baseline period to account for initial between- and within-group differences in food intake. For statistical analyses, we transformed these data into a normal distribution using a natural log transformation. We analyzed the percentage of change in pellet

Table 1
Summary of Daily Session Times and Events

Session time	Event
8 a.m. to 10 a.m.	Time-out
10 a.m. to 11 a.m.	Food component
11 a.m. to 12 p.m.	Time-out
12 p.m. to 1:30 p.m.	Liquid component
1:30 p.m. to 2:30 p.m.	Time-out
2:30 p.m. to 3:30 p.m.	Food component
3:30 p.m. to 4:30 p.m.	Time-out
4:30 p.m. to 6 p.m.	Liquid component
6 p.m. to 8 a.m.	Intersession[a]

[a] During intersession, only water was available.

Table 2
Mean Pellets Earned During Experimental Phases

PCP concentration	FR for food reinforcement	Baseline average		Withdrawal				Reinstatement average	
				Day 1		Last 5 days			
		M	*SEM*	*M*	*SEM*	*M*	*SEM*	*M*	*SEM*
Males									
0.125	64	24.48	2.98	19.50	4.25	18.84	0.78	20.63	1.39
0.250	64	27.30	2.33	16.75	2.09	15.43	0.22	24.05	4.01
0.500	64	23.91	2.68	12.00	1.94	13.92	0.70	19.19	1.14
0.250	128	22.15	1.88	12.50	2.31	18.48	0.96	21.58	2.10
0.250	256	18.94	1.82	15.63	1.97	17.90	0.56	19.50	1.30
Females									
0.125	64	26.91	3.36	22.43	3.48	23.50	0.91	26.79	2.53
0.250	64	24.14	2.54	17.43	4.99	20.66	1.02	21.97	2.87
0.500	64	26.31	3.13	21.29	3.40	28.37	1.37	25.17	3.56
0.250	128	23.81	2.33	19.86	1.72	22.14	1.14	20.97	2.66
0.250	256	19.37	2.55	16.86	2.41	17.25	0.87	17.67	1.80

Note. Note that pellet size for females was half that for males. PCP = phencyclidine; FR = fixed ratio; SEM = standard error of the mean.

deliveries over the withdrawal period using a two-way (sex, day) repeated measures analysis of variance (RMANOVA), and we made post hoc comparisons with adjustments for multiple comparisons using Fisher's least significant difference (LSD) protected *t* tests (GB Stat School Pak 1997, Dynamic Microsystems, Inc., Silver Spring, MD). The average percentage of reductions in pellet deliveries between males and females across PCP concentrations and FRs for food-reinforced responding were compared using a two-way (sex, condition) RMANOVA, and we used Fisher's LSD protected *t* tests with adjustments for multiple comparisons for post hoc comparisons.

We compared the number of liquid deliveries during each day of the baseline and PCP reintroduction periods using three-way (sex, day, type of liquid) RMANOVAs. We used percentage of baseline to analyze food data but not liquid data, because food pellets were different sizes for males and females, whereas liquid deliveries were the same size for both sexes. Water deliveries during withdrawal and PCP intake (milligrams per kilogram) during the baseline and PCP reintroduction periods were compared using two-way (sex, day) RMANOVAs. The average PCP intake during the baseline and PCP reintroduction periods was compared using two-tailed *t* tests (Sigmastat, Version 2.03, Systat Software, Inc., Point Richmond, CA). We analyzed PCP intake across the PCP concentrations tested using a 3 (concentration) × 2 (sex) analysis of variance. We considered results statistically significant if $p < .05$.

Results

Mean daily pellet deliveries during PCP withdrawal and reintroduction are shown as a percentage of the mean pellet deliveries during the 5-day baseline period in the left panels in Figure 1. The upper left panel represents pellet deliveries when the concentration of PCP during the baseline and reinstatement periods was 0.125 mg/ml. There were no significant differences during 0.125-mg/ml PCP withdrawal or reintroduction.

The middle left panel shows pellet deliveries as a percentage of baseline for the 0.25-mg/ml PCP concentration. Over the 10-day withdrawal period, there was a significant Sex × Day interaction, $F(9, 139) = 1.98$, $p < .05$. Pellet deliveries in males decreased significantly over the PCP withdrawal period ($p < .05$), whereas pellet deliveries increased in females ($p < .05$). There were no sex differences in pellet deliveries on Withdrawal Days 1–6, but on Days 7, 8, and 9, males earned significantly fewer pellets than females ($p < .05$). When 0.25 mg/ml PCP was reintroduced, both males and females increased their pellet deliveries over the 10-day period, $F(9, 139) = 2.16$, $p < .05$. During withdrawal, males generally showed a greater magnitude and duration of suppression in food-maintained behavior than females, but when PCP was reintroduced, males and females had similar patterns of food intake.

The lower left panel shows percentage of baseline pellet deliveries when 0.50 mg/ml PCP was available during the baseline and reintroduction periods. During PCP withdrawal, males earned significantly fewer pellet deliveries as a percentage of baseline than females on each day of the withdrawal period, $F(1, 139) = 10.22$, $p < .01$. There were no significant differences when 0.50 mg/ml PCP was reintroduced.

The comparison of average withdrawal disruptions in males and females across the different PCP concentrations is summarized in the right panels in Figure 1. The average (plus or minus standard error of the mean) percentage of change in pellet deliveries as a percentage of baseline during withdrawal as a function of PCP concentration is presented for males and females at each PCP concentration. Males experienced significantly greater average reductions in pellet deliveries than females across all three PCP concentrations, $F(1, 41) = 22.82$, $p < .01$.

The number of pellet deliveries for males and females under each condition is shown in Table 2. Males and females earned similar amounts during the baseline periods, but males earned consistently fewer pellet deliveries on Day 1 of withdrawal and on the last 5 days of withdrawal

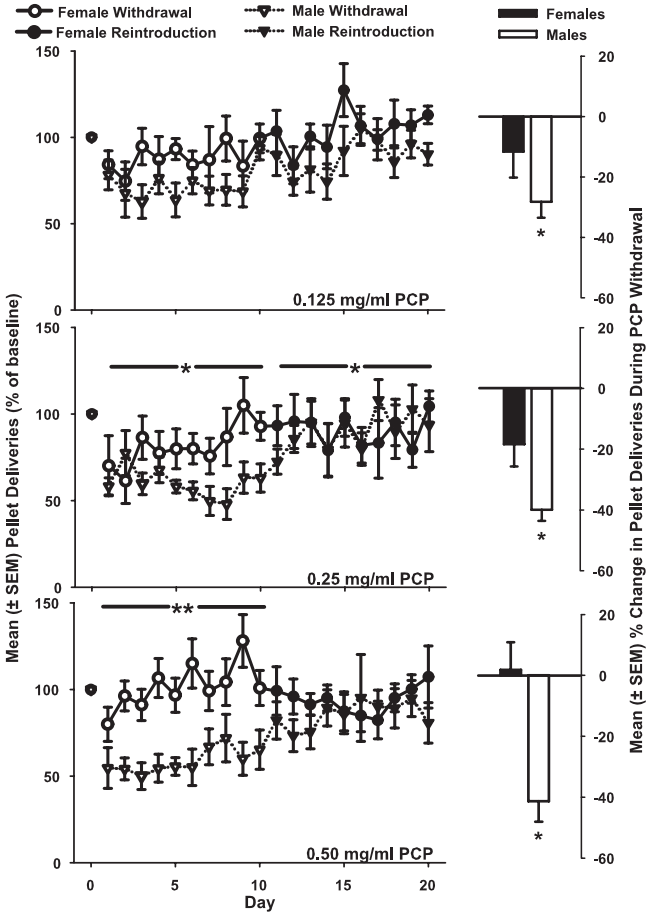

Figure 1. Left panels: Average pellet deliveries (plus or minus standard error of the mean) as a percentage of the average number of pellets earned during the 5-day baseline period. The upper panel shows pellet deliveries when the concentration of phencyclidine (PCP) available was 0.125 mg/ml. In the middle panel, 0.25 mg/ml PCP was available before and after the withdrawal period, and in the bottom panel, 0.50 mg/ml PCP was available. During the withdrawal period, only water was available; during the reintroduction period, water and PCP were available concurrently. Right panels: Average (plus or minus standard error of the mean) percentage of change in pellet deliveries during withdrawal (compared with the baseline period) when the PCP concentration available for self-administration before and after the withdrawal period was 0.125 (upper), 0.25 (middle), and 0.50 (lower) mg/ml. Males showed significant decreases compared with females at all PCP concentrations. * $p < .05$. ** $p < .01$.

(except at FR 256). During PCP reintroduction, males and females earned similar amounts of pellet deliveries. Females' food intake (in grams) was approximately half that of males; however, the females used in this experiment weighed only slightly more than half of what the males in this study weighed (females/males = 0.62).

Figure 2 shows the average (plus or minus standard error of the mean) PCP and water deliveries for male and female monkeys over the 5-day baseline, the 10-day withdrawal, and the 10-day PCP reintroduction periods. The upper panel shows liquid deliveries when the concentration of PCP available was 0.125 mg/ml. During the baseline and reintroduction periods, males consumed significantly more PCP deliveries than females, $F(1, 139) = 4.58$, $p < .05$, and $F(1, 279) = 4.92$, $p < .05$, respectively, and both sexes consumed more PCP than water, $F(1, 139) = 41.61$, $p < .01$, and $F(1, 279) = 75.31$, $p < .01$, respectively.

When the PCP concentration was 0.25 mg/ml (middle panel of Figure 2), males earned more PCP deliveries than

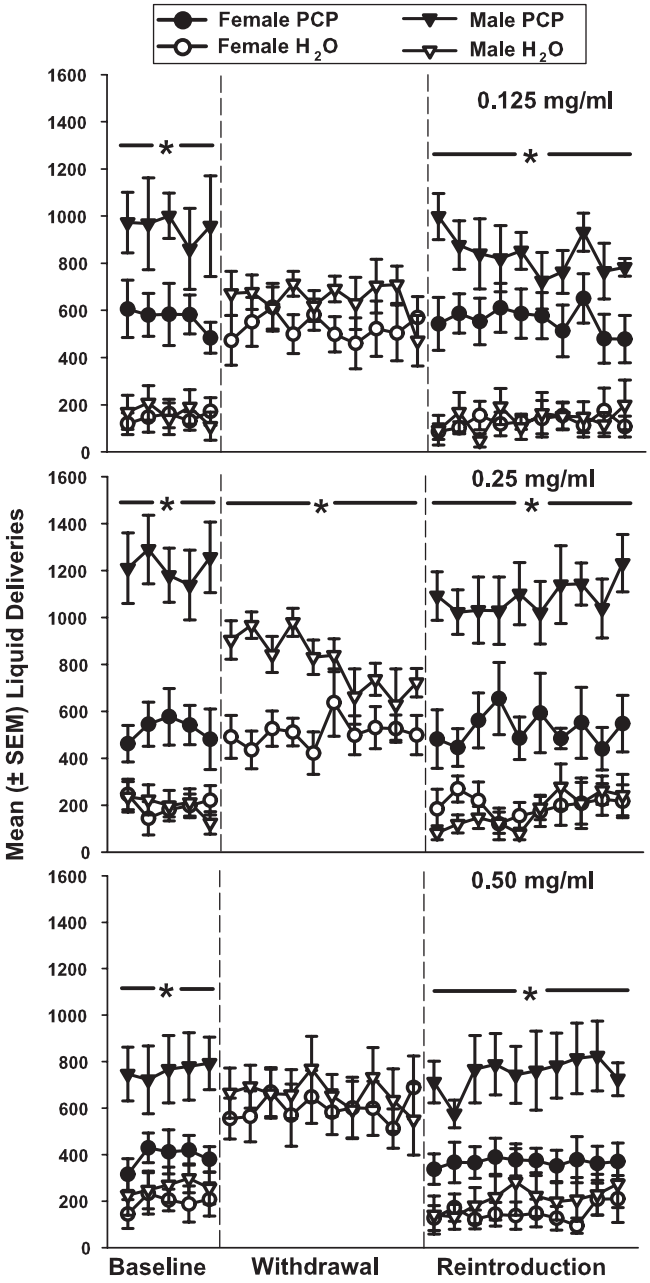

Figure 2. Liquid deliveries during the baseline, withdrawal, and reintroduction periods when the concentration of phencyclidine (PCP) available was 0.125 (upper panel), 0.25 (middle panel), and 0.50 (lower panel) mg/ml. H_2O = water.* $p < .05$.

females, $F(1, 139) = 16.91$, $p < .01$, and $F(1, 279) = 12.29$, $p < .01$, respectively, and all monkeys consumed more PCP than water, $F(1, 139) = 62.91$, $p < .01$, and $F(1, 279) = 65.39$, $p < .01$, during the 5-day baseline and 10-day PCP reintroduction periods, respectively. During withdrawal from 0.25 mg/ml PCP, males earned more water deliveries than females, $F(1, 139) = 13.39$, $p < .01$. The number of water deliveries self-administered by males decreased over the 10-day withdrawal period, whereas the number of water deliveries self-administered by females remained constant, $F(9, 139) = 2.45$, $p < .05$.

The lower panel shows liquid deliveries during the baseline, withdrawal, and reintroduction periods when the concentration of PCP available was 0.50 mg/ml. During the baseline and reintroduction periods, males consumed more PCP deliveries than females, $F(1, 139) = 6.62$, $p < .05$, and $F(1, 279) = 7.15$, $p < .05$, respectively, and both sexes consumed more PCP than water, $F(1, 139) = 17.03$, $p < .01$, and $F(1, 279) = 21.17$, $p < .01$, respectively. In summary, during the baseline and reinstatement periods at all three PCP concentrations, males earned significantly more PCP deliveries than females, and both males and females self-administered significantly more PCP than water, which indicates that PCP served as a reinforcer in these animals. There were no sex differences in water deliveries during the baseline and PCP reintroduction periods.

When we averaged each monkey's PCP intake in milligrams per kilogram over the 5-day baseline period, we found, as the upper panel in Figure 3 shows, that there were no significant differences between males and females at any of the three PCP concentrations tested. However, in both males and females, PCP intake increased as a function of PCP concentration, $F(2, 41) = 22.26$, $p < .01$.

Figure 4 shows daily pellet deliveries during PCP withdrawal and reintroduction as a percentage of the average number of pellet deliveries during the 5-day baseline period for the three food FR values. The upper left panel shows pellet deliveries as a percentage of baseline when the FR for food-reinforced responding was 64. These data are presented in the middle left panel in Figure 1. In brief, there was a significant Sex × Day interaction, $F(9, 139) = 1.98$, $p < .05$, over the 10-day withdrawal period, with males' pellet deliveries decreasing and females' pellet deliveries increasing. When PCP was reintroduced, there was a significant effect of day, $F(9, 139) = 2.16$, $p < .05$, with pellet deliveries decreasing in females and increasing in males.

Pellet deliveries as a percentage of baseline when the FR for food-reinforced responding was 128 are shown in the middle left panel of Figure 4. There were no significant day or sex differences in pellet deliveries as a percentage of baseline during the withdrawal period, but when PCP was reintroduced, females showed a decrease in pellet deliveries, whereas males generally increased their pellet deliveries, $F(9, 139) = 2.07$, $p < .05$.

The lower left panel of Figure 4 depicts pellet deliveries as a percentage of baseline when the FR for food-reinforced responding was 256. There were no significant effects of sex or day during withdrawal; however, there was a significant effect of sex during PCP reintroduction, $F(1, 139) = 4.99$, $p < .05$. Males had significantly more pellet deliveries than females on Days 7–9 ($p < .05$).

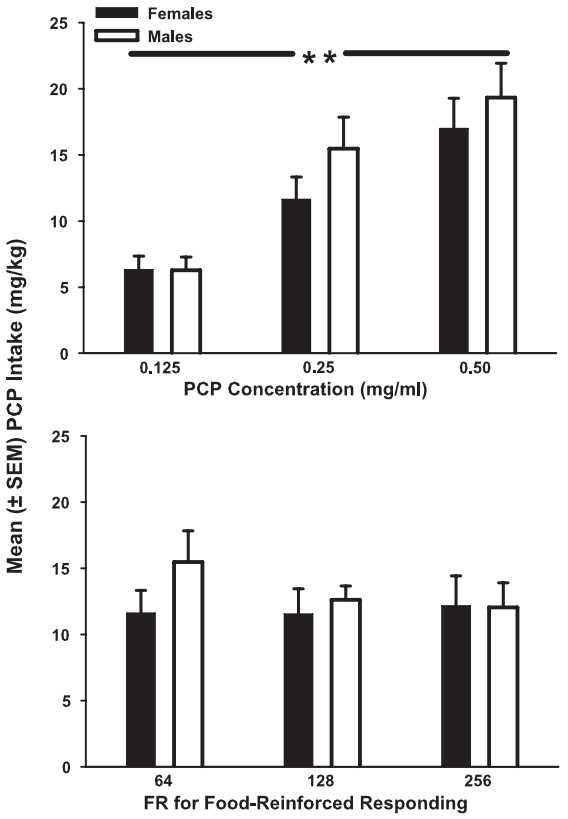

Figure 3. Average (plus or minus standard error of the mean) baseline phencyclidine (PCP) intake for male and female monkeys when the concentration of PCP available was 0.125, 0.25, and 0.50 mg/ml and the fixed ratio (FR) for food-reinforced responding was 64 (upper panel) and when the FR for food-reinforced responding was 64, 128, and 256 and the concentration of PCP was 0.25 mg/ml (lower panel). Note that the bars representing intake when the PCP concentration was 0.25 mg/ml and the FR for food-reinforced responding was 64 are presented in both panels. There were no significant differences in average PCP intake in milligrams per kilogram under any of the conditions tested; however, in both males and females, PCP intake increased as a function of PCP concentration. ** $p < .01$.

The right panels in Figure 4 summarize the withdrawal effects as a function of FR value by presenting the average (plus or minus standard error of the mean) percentage of change in pellet deliveries during withdrawal in males and females over the three FRs. Overall, the reductions in pellet deliveries were inversely related to FR value—this was a significant effect, $F(2, 41) = 4.29$, $p < .05$—and males showed significantly greater reductions in pellet deliveries across all FRs, $F(1, 41) = 5.89$, $p < .05$.

Figure 5 shows the average (plus or minus standard error of the mean) PCP and water deliveries for male and female monkeys over the 5-day baseline, the 10-day PCP withdrawal, and the 10-day reintroduction periods. The upper panel shows liquid deliveries when the FR for food-rein-

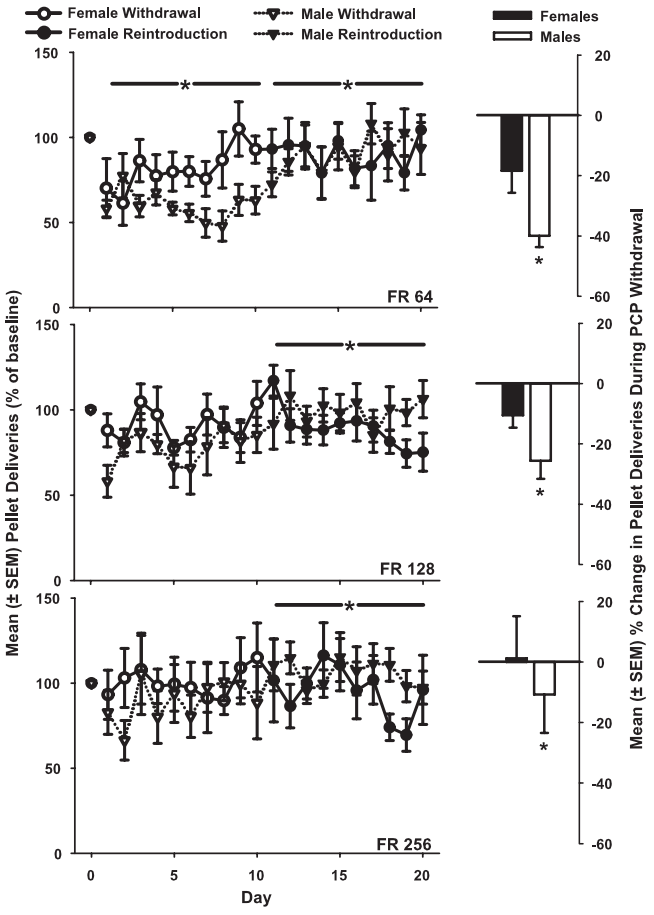

Figure 4. Left panels: Average pellet deliveries (plus or minus standard error of the mean) as a percentage of the average number of pellets earned during the 5-day baseline period. The upper panel represents pellet deliveries that were contingent on lever pressing under a fixed ratio (FR) 64 schedule. In the middle panel, pellets were delivered under an FR 128 schedule, and in the lower panel, pellets were delivered under an FR 256 schedule. During the withdrawal period, only water was available; during reintroduction; water and phencyclidine (PCP) were available concurrently. Right panels: Average (plus or minus standard error of the mean) percentage of change in pellet deliveries during withdrawal (compared with the baseline period) when pellet deliveries were contingent on lever pressing under FR 64, 128, and 256 schedules. Males showed a significant decrease compared with females under each FR for food-reinforced responding, and both males and females showed a significant reduction in pellet deliveries during withdrawal at lower (vs. higher) FRs for food-maintained responding. *$p < .05$.

forced responding was 64, and these are the same data as presented in Figure 3 for the 0.25-mg/ml PCP concentration. In brief, males consumed more PCP deliveries than females, and both sexes consumed more PCP than water during the baseline and reintroduction periods. During withdrawal from PCP, males consumed significantly more water deliveries than females, and the number of water deliveries earned by males decreased over the withdrawal period. In contrast, the number of water deliveries self-administered by females remained constant.

The middle panel of Figure 5 shows that when the FR for food-reinforced responding was raised to 128, males consumed more PCP deliveries than females, $F(1, 139) = 6.03$, $p < .05$, and $F(1, 279) = 6.27$, $p < .05$, respectively, and both sexes self-administered more PCP than water, $F(1, 139) = 58.19$, $p < .01$, and $F(1, 279) = 39.10$, $p < .01$, during the baseline and PCP reintroduction periods, respectively.

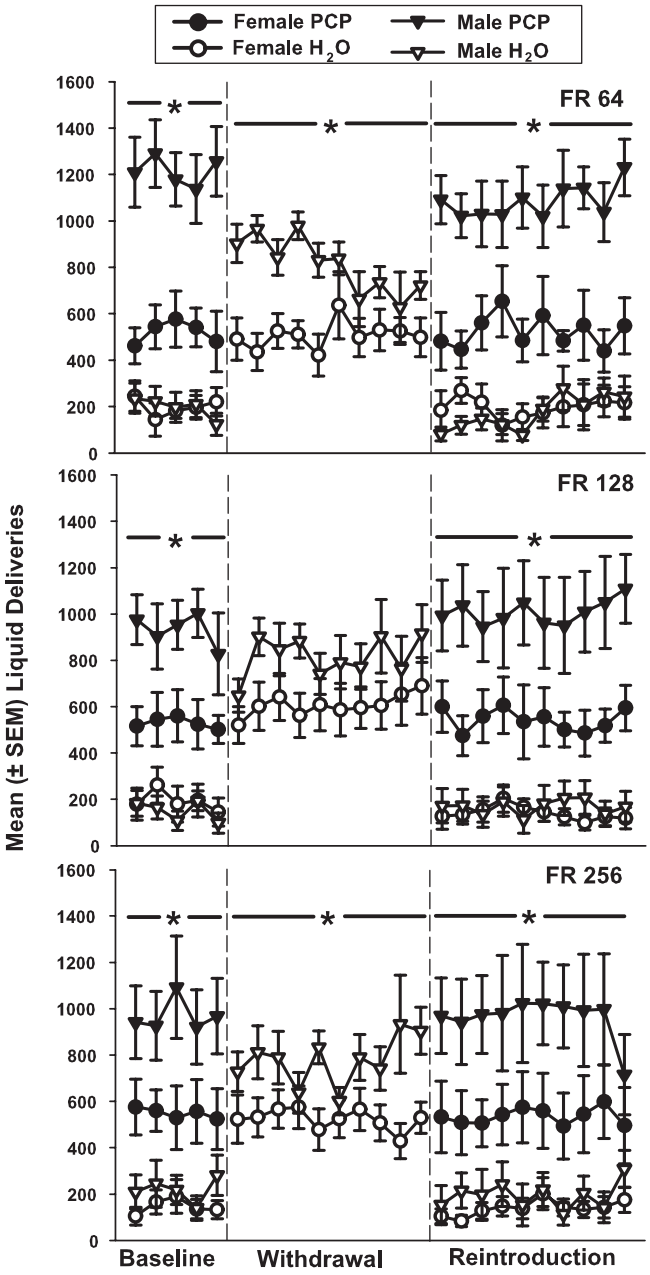

Figure 5. Liquid deliveries during the baseline, withdrawal, and reintroduction periods when the fixed ratio (FR) for food-reinforced responding was 64 (upper panel), 128 (middle panel), or 256 (lower panel). PCP = phencyclidine; H_2O = water.* $p < .05$.

The lower panel of Figure 5 shows liquid deliveries when food was available under FR 256. During the 5-day baseline period, males earned more PCP deliveries than females, $F(1, 139) = 5.04$, $p < .05$, and all monkeys consumed more PCP than water, $F(1, 139) = 27.61$, $p < .01$. During withdrawal, males earned more water deliveries than females, $F(1, 139) = 6.51$, $p < .05$. Both males and females self-administered more PCP than water, $F(1, 279) = 24.15$, $p < .01$, but there were no sex differences in the number of liquid deliveries during reintroduction of PCP.

In summary, during the baseline period for all three FRs tested, males earned significantly more PCP deliveries than females, and both males and females self-administered significantly more PCP deliveries than water. Although water deliveries in males and females were indistinguishable during the baseline period, males consumed significantly more water deliveries during withdrawal than females at the lowest and highest FRs. During reinstatement, both males and females self-administered more PCP deliveries than water deliveries, and there were no sex differences in water deliveries at any FR. At the highest FR, there were no sex differences in number of PCP deliveries earned; however, at the lower FRs, males earned significantly more PCP deliveries than females. When we averaged PCP intake in milligrams per kilogram over the 5-day baseline period, we found, as the lower panel in Figure 3 shows, that there were no significant differences in PCP intake at any of the three FRs tested.

Discussion

In this study, we used disruptions in operant responding for food to indicate severity of withdrawal from PCP. At the highest PCP concentration, females maintained significantly higher levels of food-maintained responding than males over the 10-day withdrawal period. At the second highest PCP concentration and the lowest FR for food-maintained responding, males experienced more protracted withdrawal, as measured by decreases in food-maintained responding, than females. The results indicate that under certain conditions, males experience more severe withdrawal effects than females, and the duration of the adverse effects of withdrawal may be longer in males than in females.

The present results confirm previous reports that behavioral changes in operant responding were not accompanied by obvious physiological signs of withdrawal from orally self-administered PCP (Carroll, 1987, 1988; Carroll & Carmona, 1991; Carroll et al., 1994). The results from this study also concur with findings that baselines of food-maintained responding were sensitive to withdrawal from lower levels of PCP intake (Carroll, 1987). They produced quantifiable and objective indicators of withdrawal at PCP intakes (5–20 mg/kg) that did not produce physical signs of withdrawal, and they showed a protracted time course in the recovery of drug withdrawal effects (Carroll et al., 1994). The length of disruptions in food-maintained responding is not surprising given that previous studies have shown that reductions in food-reinforced responding persisted as long as 24 days after cessation of PCP self-administration (Carroll, 1987).

In this study as well as a previous study (Wessinger & Owens, 1991), the magnitude and duration of withdrawal effects were related to the dose of the drug. The present findings indicate that food-maintained responding was more disrupted during withdrawal from the highest PCP concentration (0.50 mg/ml) than during withdrawal from the lowest concentration (0.125 mg/ml) in males; however, the magnitude of withdrawal effects was not related to PCP concentration in females. Moreover, at the highest PCP concentration, females increased their food intake above baseline during withdrawal. The amount of food restriction and schedule of reinforcement also appeared to affect withdrawal-induced disruptions in food-maintained responding, as they had in a previous study (Carroll & Carmona, 1991). In the present study, food-maintained responding was less disrupted by withdrawal under higher FRs (128 and 256), when the amount of food earned was typically lower (indicating greater food restriction) than it was at the lowest FR (64). Thus, as the monkeys had to work harder to earn amounts of food that would maintain their body weight, the motivation to respond for food increased, conflicting with the reduction in food-motivated behavior during PCP withdrawal. In the present study, total liquid deliveries were also suppressed during PCP withdrawal in males but not in females. This is consistent with previous studies in which total liquid deliveries decreased during PCP withdrawal in male monkeys (Carroll, 1987, 1988; Carroll & Carmona, 1991; Carroll et al., 1994).

The results of the present study add to a growing body of literature on sex differences in drug addiction, and they expand previous studies of sex differences in withdrawal to another species, rhesus monkeys. This study adds to the generality of previous withdrawal studies by showing a sex difference in operant responding as an indicator of withdrawal severity and under conditions whereby the drug is self-administered. Operant responding has been used to study sex differences in PCP withdrawal in only one previous study, with rats, and no sex differences in operant responding for food were found (Wessinger, 1995). The present study differs from that study in several ways. First, in the present study PCP was orally self-administered and functioned as a reinforcer, whereas in the study by Wessinger (1995) experimenter-administered PCP was used. Second, the monkeys in the present study had an extensive history of PCP self-administration, whereas the rats in the Wessinger (1995) study were only allowed 10 days of PCP exposure prior to withdrawal. Furthermore, there is a very narrow concentration–response function for self-administered PCP (Rodefer & Carroll, 1996). Withdrawal effects may occur after the rewarding effects of a drug are discontinued. If an experimenter-administered drug is at a high dose that is aversive, the contrasting effect may be positive when drug administration is terminated.

In the present study, males showed elevated levels of responding for PCP deliveries compared with females during the baseline and reintroduction periods under almost all

conditions tested. When body weight was considered, however, males and females had the same average PCP intake during baseline periods under all conditions. These results concur with a previous study from this laboratory that revealed sex differences in oral PCP self-administration during an acquisition phase (females > males) but no sex differences in intake during a maintenance phase (Carroll, Roth, Voeller, & Nguyen, 2000). This finding suggests that the differences in food-maintained responding in males and females during withdrawal are not due to differences in PCP consumption prior to withdrawal. Additionally, in the present study, responding for PCP in males and females was significantly higher than responding for water during the baseline and reintroduction periods, which indicates that PCP was functioning as a reinforcer in these animals. Males self-administered significantly more water deliveries during withdrawal than females at the 0.25-mg/ml PCP concentration and under the FR 64 and FR 256 response requirements for food, possibly because of the larger size of the males compared with the females.

The sex differences in food-maintained responding seen at the highest two concentrations of PCP tested and the lowest FR tested could be due to motivational differences in males and females. Previous studies using PR schedules in males and females have found that female rats reach higher PR break points for intravenous cocaine (Carroll et al., 2002; Roberts, Loh, & Vickers, 1989), methamphetamine (Roth & Carroll, 2004), nicotine (Donny et al., 2000), and fentanyl (Klein et al., 1997) self-administration. However, these may be drug-specific effects and may be unrelated to the increased food intake in females compared with males during withdrawal. In one study with rats, van Hest, van Haaren, and van de Poll (1988) found that males and females reached the same break point for food self-administration under a PR schedule.

Sex differences in pharmacokinetics of PCP or neurotransmission prior to or during the withdrawal phase (for reviews, see Carroll et al., 2004; Lynch et al., 2002) could also have influenced food-maintained responding. Additionally, PCP has a longer half-life in females compared with males because of decreased metabolic clearance of PCP (Nabeshima et al., 1984; Shelnutt, Gunnell, & Owens, 1999). This finding coincides with reports that PCP has a longer duration of action and a greater magnitude of behavioral effects and toxicity in female rats than in males (Nabeshima et al., 1984; Wessinger, 1995). In the present study, we observed no differences in the behavioral effects of PCP in males and females while PCP was available. This could have been due to several differences between the present study and previous studies, such as species, acute versus chronic PCP, or experimenter- versus self-administration of PCP.

Differences in responding for food during PCP withdrawal could have been influenced by ovarian hormones. Estrogen has been implicated to play a role in several key phases of the addiction process (for reviews, see Carroll et al., 2004; Lynch et al., 2002). In the present study, estrogen could have influenced factors such as motivation, hunger, or the hedonic value of the food, which would cause the females to have increased food-maintained responding compared with males. To our knowledge, estrogen's effects on drug withdrawal have been examined in only one study. In this study, researchers used ovariectomized and intact female rats to examine the effect of ethanol withdrawal on bicuculline-induced seizures (Devaud, Morrow, & Nguyen, 2000). There were no differences in ethanol withdrawal due to ovariectomy; however, the measure of withdrawal used in that study might not have been as sensitive to individual differences as the procedure used in the present study. Future studies should assess the effects of the estrous cycle on withdrawal, using disruptions in food-maintained responding as a quantitative measure of withdrawal severity.

Alternatively, differences in body weight or reinforcing efficacy of PCP could underlie the apparent sex differences noted in this study. Previous studies noted diminished behavioral effects of PCP injections in high-weight (vs. low-weight) rats, and this was associated with lower brain levels of PCP (Coveney, Neal, & Sparber, 1990; Woolverton, Martin, & Balster, 1980). The researchers suggested that differences in brain levels of PCP and behavioral effects of PCP were due to differences in amount of adipose tissue in the two groups (Woolverton et al., 1980). In the present study, there did not appear to be a trend in the relation between disruptions in operant baselines during withdrawal and body weight, which suggests that even though the average weight for males was higher than that for females, these differences were not related to severity or length of behavioral disruptions in withdrawal. Additionally, although the number of PCP deliveries in males was larger than that in females, both males and females had similar PCP intake when we took body weight into account. We note, however, that the body composition of females is higher in adipose tissue than that of males (for a review, see Roth, Cosgrove, & Carroll, 2004). PCP may accumulate more in the adipose tissue in females than in males, resulting in a slower release of PCP in females compared with males. If the differences in adiposity in females and males were underlying the sex differences in withdrawal in this study, we would expect that females would experience more severe disruptions in food-maintained responding after several days of withdrawal. In the present study, however, females experienced the greatest disruptions in food maintained responding in the first 2 days of withdrawal. This suggests that although other variables (i.e., body weight, PCP deliveries, adiposity) might have accompanied sex differences, the influence of these variables on the results of this study was minimal.

Present treatment strategies are focused on reducing the adverse effects of drug withdrawal; therefore, it is important to understand sex differences in this phase of addiction. The present results indicate that males display more severe and protracted withdrawal-induced disruptions in operant behavior baselines than females under higher concentrations of PCP and lower FRs for food-maintained responding. A better understanding of factors affecting the duration and severity of drug withdrawal will aid in developing measures to reduce the negative aspects of this phase, which may lead to relapse.

References

Balster, R. L., Johanson, C. E., Harris, R. T., & Schuster, C. R. (1973). Phencyclidine self-administration in the rhesus monkey. *Pharmacology Biochemistry and Behavior, 1,* 167–172.

Balster, R. L., & Woolverton, W. L. (1980). Continuous-access phencyclidine self-administration by rhesus monkeys leading to physical dependence. *Psychopharmacology, 70,* 5–10.

Beardsley, P. M., & Balster, R. L. (1987). Behavioral dependence upon phencyclidine and ketamine in the rat. *Journal of Pharmacology & Experimental Therapeutics, 242,* 203–211.

Burns, R. S., & Lerner, S. E. (1981). The effects of phencyclidine in man: A review. In E. F. Domino (Ed.), *PCP (phencyclidine): Historical and current perspectives* (pp. 449–469). Ann Arbor, MI: NPP Books.

Carroll, M. E. (1987). A quantitative assessment of phencyclidine dependence produced by oral self-administration in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 242,* 405–412.

Carroll, M. E. (1988). Oral self-administration of N-allylnormetazocine (SKF-10,047) stereoisomers in rhesus monkeys: Substitution during phencyclidine self-administration and withdrawal. *Pharmacology Biochemistry and Behavior, 30,* 493–500.

Carroll, M. E., Batulis, D., Landry, K., & Morgan, A. D. (2005). Sex differences in the escalation of oral phencyclidine (PCP) self-administration under FR and PR schedules in rhesus monkeys. *Psychopharmacology, 180,* 414–426.

Carroll, M. E., & Carmona, G. (1991). Effects of food FR and food deprivation on disruptions in food-maintained performance of monkeys during phencyclidine withdrawal. *Psychopharmacology, 104,* 143–149.

Carroll, M. E., Carmona, G. N., & Rodefer, J. S. (1994). Phencyclidine (PCP) self-administration and withdrawal in rhesus monkeys: Effects of buprenorphine and dizocilpine (MK-801) pretreatment. *Pharmacology Biochemistry and Behavior, 48,* 723–732.

Carroll, M. E., Lynch, W. J., Roth, M. E., Morgan, A. D., & Cosgrove, K. P. (2004). Sex and estrogen influence drug abuse. *Trends in Pharmacological Sciences, 25,* 273–279.

Carroll, M. E., & Meisch, R. A. (1980). Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. *Journal of Pharmacology & Experimental Therapeutics, 214,* 339–346.

Carroll, M. E., Morgan, A. D., Lynch, W. J., Campbell, U. C., & Dess, N. K. (2002). Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: Phenotype and sex differences. *Psychopharmacology, 161,* 304–313.

Carroll, M. E., Roth, M. E., Voeller, R. K., & Nguyen, P. D. (2000). Acquisition of oral phencyclidine self-administration in rhesus monkeys: Effect of sex. *Psychopharmacology, 149,* 401–408.

Cicero, T. J., Nock, B., & Meyer, E. R. (2002). Gender-linked differences in the expression of physical dependence in the rat. *Pharmacology Biochemistry and Behavior, 72,* 691–697.

Coveney, J. R., Neal, B. S., & Sparber, S. B. (1990). Food deprivation alters behavioral and plasma corticosterone responses to phencyclidine in rats. *Pharmacology Biochemistry and Behavior, 36,* 451–456.

Devaud, L. L., & Chadda, R. (2001). Sex differences in rats in the development of and recovery from ethanol dependence assessed by changes in seizure susceptibility. *Alcoholism: Clinical & Experimental Research, 25,* 1689–1696.

Devaud, L. L., Morrow, A. L., & Nguyen, U. T. Q. (2000). Ovariectomy has minimal effects on neuroadaptations associated with ethanol dependence in female rats. *Neurochemistry International, 37,* 433–442.

Donny, E. C., Caggiula, A. R., Rowell, P. P., Gharib, M. A., Maldovan, V., Booth, S., et al. (2000). Nicotine self-administration in rats: Estrous cycle effects, sex differences and nicotinic receptor binding. *Psychopharmacology, 151,* 392–405.

Gatch, M. B., & Lal, H. (2001). Animal models of the anxiogenic effects of ethanol withdrawal. *Drug Development Research, 54,* 95–115.

Klein, L. C., Popke, E. J., & Grunberg, N. E. (1997). Sex differences in effects of predictable and unpredictable footshock on fentanyl self-administration in rats. *Experimental and Clinical Psychopharmacology, 5,* 99–106.

Lynch, W. J., Arizzi, M. N., & Carroll, M. E. (2000). Effects of sex and the estrous cycle on regulation of intravenously self-administered cocaine in rats. *Psychopharmacology, 152,* 132–139.

Lynch, W. J., & Carroll, M. E. (1999). Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. *Psychopharmacology, 144,* 77–82.

Lynch, W. J., & Carroll, M. E. (2000). Reinstatement of cocaine self-administration in rats: Sex differences. *Psychopharmacology, 148,* 196–200.

Lynch, W. J., Roth, M. E., & Carroll, M. E. (2002). Biological basis of sex differences in drug abuse: Preclinical and clinical studies. *Psychopharmacology, 164,* 121–137.

Massey, B. W., & Wessinger, W. D. (1990). Effects of terminating chronic phencyclidine on schedule-controlled behavior in rats. *Pharmacology Biochemistry and Behavior, 36,* 117–121.

McKearney, J. W., & Barrett, J. E. (1978). Schedule-controlled behavior and the effects of drugs. In D. E. Blackman & D. J. Sanger (Eds.), *Contemporary research in behavioral pharmacology* (pp. 24–36). New York: Plenum Press.

Morgan, D., Brebner, K., Lynch, W. J., & Roberts, D. C. (2002). Increases in the reinforcing efficacy of cocaine after particular histories of reinforcement. *Behavioral Pharmacology, 13,* 389–396.

Nabeshima, T., Yamaguchi, K., Yamada, K., Hiramatsu, M., Kuwabry, Y., Furukawa, H., et al. (1984). Sex-dependent differences in the pharmacological actions and pharmacokinetics of phencyclidine in rats. *European Journal of Pharmacology, 97,* 217–227.

National Research Council. (2003). *Guidelines for the care and use of mammals in neuroscience and behavioral research*. Washington, DC: National Academies Press.

Pickens, R., Thompson, T., & Muchow, D. C. (1973). Cannabis and phencyclidine self-administration by animals. In L. Goldberg (Ed.), *Psychic dependence* (pp. 78–86). New York: Springer-Verlag.

Roberts, D. C., Loh, E. A., & Vickers, G. (1989). Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. *Psychopharmacology, 97,* 535–538.

Rodefer, J. S., & Carroll, M. E. (1996). Progressive ratio and behavioral economic evaluation of the reinforcing efficacy of orally delivered phencyclidine and ethanol in monkeys: Effects of feeding conditions. *Psychopharmacology, 128,* 265–273.

Roth, M. E., & Carroll, M. E. (2004). Sex differences in the acquisition of IV methamphetamine self-administration and subsequent maintenance under a progressive ratio schedule in rats. *Psychopharmacology, 172,* 443–449.

Roth, M. E., Cosgrove, K. P., & Carroll, M. E. (2004). Sex differences in the vulnerability to drug abuse: A review of preclinical studies. *Neuroscience & Biobehavioral Reviews, 28,* 533–546.

Shelnutt, S. R., Gunnell, M., & Owens, S. M. (1999). Sexual dimorphism in phencyclidine in vitro metabolism and pharmacokinetics in rats. *Journal of Pharmacology & Experimental Therapeutics, 290,* 1292–1298.

Slifer, B. L., Balster, R. L., & Woolverton, W. L. (1984). Behavioral dependence produced by continuous phencyclidine infusion in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 230,* 399–406.

Substance Abuse and Mental Health Services Administration. (2004). *Results from the 2003 National Survey on Drug Use and Health: National findings* (DHHS Publication No. SMA 04–3964, NSDUH Series H-25). Washington, DC: Author.

Suzuki, T., Koike, Y., & Misawa, M. (1988). Sex differences in physical dependence on methaqualone in the rat. *Pharmacology Biochemistry and Behavior, 30,* 483–488.

Suzuki, T., Koike, Y., Yoshii, T., & Yanaura, S. (1985). Sex differences in the induction of physical dependence on pentobarbital in the rat. *Japanese Journal of Pharmacology, 39,* 453–459.

Thompson, T. (1984). Behavioral mechanisms of drug dependence. In T. Thompson, P. B. Dews, & J. E. Barrett (Eds.), *Advances in behavioral pharmacology* (Vol. 4, pp. 10–45). Orlando, FL: Academic Press.

van Hest, A., van Haaren, F., & van de Poll, N. E. (1988). The behavior of male and female Wistar rats pressing a lever for food is not affected by sex differences in food motivation. *Behavioral Brain Research, 27,* 215–221.

Varlinskaya, E. I., & Spear, L. P. (2004). Acute ethanol withdrawal (hangover) and social behavior in adolescent and adult male and female Sprague–Dawley rats. *Alcoholism: Clinical & Experimental Research, 28,* 40–50.

Wessinger, W. D. (1995). Sexual dimorphic effects of chronic phencyclidine in rats. *European Journal of Pharmacology, 277,* 107–112.

Wessinger, W. D., & Owens, S. M. (1991). Phencyclidine dependence: The relationship of dose and serum concentrations to operant behavioral effects. *Journal of Pharmacology & Experimental Therapeutics, 258,* 207–215.

Woodstock-Striley, C., Cottler, L. B., & Ben Abdallah, A. (2004, June). *Females have less physiological dependence to alcohol than men*. Paper presented at the meeting of the College of Problems on Drug Dependence, San Juan, Puerto Rico.

Woolverton, W. L., Martin, B. R., & Balster, R. L. (1980). Modification of the behavioral effects of phencyclidine by repeated drug exposure and body weight changes. *Pharmacology Biochemistry and Behavior, 12,* 761–766.

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