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Sex differences in the escalation of oral phencyclidine (PCP) self-administration under FR and PR schedules in rhesus monkeys

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Abstract *Rationale:* Studies with male rats indicate that long access (LgA) vs short access (ShA) to i.v. cocaine and heroin self-administration leads to an escalation of drug intake and a subsequent upward shift of the dose-response function. *Objective:* The purpose of this experiment was to extend these results to male and female rhesus monkeys and oral phencyclidine (PCP) self-administration under fixed-ratio (FR) and progressive-ratio (PR) schedules. *Methods:* Adult rhesus monkeys (seven females and nine males) orally self-administered PCP (0.25 mg/ml) and water under concurrent FR 16 FR 16 schedules during daily ShA 3-h sessions. Since females weighed less than males, each liquid delivery (0.6 ml) represented a higher unit dose mg/kg for females than males, but drug concentration mg/ml remained constant. Concurrent PR PR schedules were then used to obtain a concentration-response function (0.125, 0.25, 0.5, and 1.0 mg/ml). Next, PCP and water were available during LgA 6-h sessions under concurrent FR 16 FR 16 schedules for 21 days. The monkeys were then retested under the concurrent FR 16 FR 16 and PR PR conditions during ShA sessions. *Results:* Under the initial ShA concurrent FR 16 FR 16 schedules, females and males did not differ on PCP deliveries or intake (mg/kg); however, during LgA, males and females had more PCP deliveries compared with ShA. During LgA, males exceeded females in PCP deliveries, but females were higher than males in mg/kg PCP intake. Also, PCP (but not water) deliveries and mg/kg PCP intake significantly increased from the first 3 days to the last 3 days of the 21-day LgA period in both males and females. The subsequent ShA FR 16 FR 16 performance did not differ by sex, but it was significantly elevated above the first ShA period in both sexes. The con-

centration-response function for PCP break point under the PR PR schedules and PCP intake (mg/kg) were significantly shifted upward during the second (vs first) ShA period, and females' mg/kg intake significantly exceeded males'. *Conclusions:* Male and female rhesus monkeys both showed escalation of PCP self-administration during LgA to PCP and during ShA that occurred after (vs before) LgA. Both showed vertical upward shifts in the concentration×intake (mg/kg) function under the PR schedule, and females exceeded males on this measure. These findings with PCP and monkeys are consistent with vertical upward shifts of cocaine dose-response functions in previous escalation studies in male rats and reports of sex differences (F>M) during several other phases of drug abuse.

Keywords Escalation · Female · Long access · Male · Oral · PCP · Phencyclidine · Rhesus monkeys · Self-administration · Short access

Introduction

The escalation of drug use and eventual transition to dependence are defining features of drug addiction (Heyne and Wolffgramm 1998; Koob et al. 2004; Koob and Le Moal 2001; Lynch and Carroll 2001; Wolffgramm and Heyne 1995). Particularly with psychostimulant drug abuse, drug taking occurs in binges or repeated cycles of frequent use (Gawin and Kleber 1985; Gawin 1991). It is essential to identify factors that contribute to escalation and loss of control over drug intake and to apply this knowledge to more focused treatment efforts. There are several reliable methods for modeling the transition from moderate, stable drug use to excessive drug intake in the animal laboratory. Results of studies that have been primarily conducted in rats have identified factors that predict and/or increase excessive drug intake, and additional studies have investigated the underlying neurochemical mechanisms of this maladaptive behavior (Ahmed and Koob 2004a,b; Ahmed et al. 2003; Ben-Shahar et al. 2004; Koob et al. 2004). Escalation of drug intake can be characterized by an increase in consumption over time and/

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or an increase in consumption following a long access or binge period.

One of the factors that determines escalation of drug self-administration is the pharmacological class of drug. Generally in rats, long access (LgA 6 h) vs short access (ShA, 1 h) to stimulants (Ahmed and Koob 1998, 1999) and opioids (Ahmed et al. 2000) results in escalation and dysregulation (and potentially overdose); however, in a recent study with nicotine, escalation was not reported (Patterson and Markou 2004). Dose may explain discrepant findings, as some drugs may become aversive at high cumulative doses. In earlier studies of relatively unrestricted exposure to drugs (e.g., 24 h), when animals were given access to psychomotor stimulants or ethanol, they showed cyclic periods of rapid drug intake interspersed with episodes of self-imposed abstinence (e.g., Balster et al. 1976; Winger and Woods 1973; Wolffgramm et al. 2000; Yokel and Pickens 1974). The patterns reported for LgA to opioids (Deneau et al. 1969; Yanagita and Takahashi 1973) and dissociative anesthetics (Balster and Woolverton 1980, 1982) were more stable than stimulants on a daily basis, but intake increased over time.

Results of animal studies have revealed very different patterns of drug self-administration based on the length of access to drugs. Escalating and bingeing patterns of drug self-administration have recently been modeled in rats by increasing the daily duration of exposure to drugs from ShA, such as 1 or 2 h, to LgA, such as 6–12 h (Ahmed and Koob 1998, 1999; Ahmed et al. 2000; Mantsch et al. 2004; Morgan et al. 2004; Tornatzky and Miczek 2000), by increasing the number of exposures per day (Fitch and Roberts 1993; Lynch and Roberts 2004; Roberts et al. 1989), or by allowing the rats to self-select their drug dose by pressing one lever to increase unit dose and another lever to decrease it during LgA sessions (5 h) (Lynch et al. 1998; Lynch and Carroll 2001). In contrast, patterns of drug self-administration during ShA are characterized by well-regulated evenly spaced infusions with stable intake across days (Lynch and Carroll 2001; Tsibulsky and Norman 1999; Wise et al. 1995; Yokel and Pickens 1974).

Other factors contributing to escalation of drug taking are the presence of conditioned stimuli (Semenova and Markou 2003) and drug dose (Mantsch et al. 2003). Individual differences may also contribute to the pattern of bingeing and escalated intake. For example, rats that are high responders (HR) to novel environments show a greater high-dose escalation of cocaine self-administration than low responders (LR), and HR rats acquire amphetamine (Hooks et al. 1991; Piazza et al. 1989, 1990) and cocaine (Hooks et al. 1991; Mantsch et al. 2001; Piazza et al. 1998) self-administration more rapidly than LR rats at a low dose.

Recent preclinical studies have indicated that females exceed males in intake of several drugs of abuse; this sex difference may be subtle, and it is best revealed under low doses, when challenging behavioral schedules are used, and during transition states of addiction, such as acquisition and reinstatement (Carroll et al. 2004; Lynch et al. 2002; Roth et al. 2004). Other work suggests that estrogen plays an important role in these sex differences (Carroll

et al. 2004; Lynch et al. 2002; Roth et al. 2004). Sex and hormonal status influenced the extent to which the patterns of i.v. cocaine self-administration and dose self-selection became dysregulated, and intake escalated using a two-lever dose self-selection study in which responding on one lever increased the unit dose and responding on the other decreased it (Lynch et al. 2000). Female rats showed less precise dose (mg/kg/min) regulation than males (Lynch et al. 2000), and when phases of the estrous cycle were compared, cocaine dose dysregulation and intake (mg/kg) were highest during the estrus phase. Estrogen levels peak during proestrus, and they rapidly decline during estrus. It is believed that cascading gene effects due to this peak are related to the delayed increases in drug-seeking behavior after estrogen levels have peaked (Lynch et al. 2000). Results of another study indicated that female rats with LgA to cocaine escalated their intake to a greater extent than males, while there were no sex differences in ShA rats (Roth and Carroll 2004).

More men than women report problems with drug abuse (NSDUH 2003; SAMHSA 2003), although rates of drug abuse have increased faster in women than in men (Chen and Kandel 2002). Sex differences in humans may be linked to sex differences in opportunities to use drugs (Van Etten et al. 1999). Retrospective reports in humans also suggest that opioid-, cannabis-, and alcohol-dependent women may have an accelerated progression from initiation of use to treatment entry (Brady and Randall 1999; Hernandez-Avila et al. 2004; Lex 1991), suggesting an escalation effect that may be greater in women than in men.

In the present study, the investigation of escalation of drug self-administration was extended to male and female rhesus monkeys using the LgA vs ShA model similar to that described by Ahmed and Koob (1998, 1999) and oral self-administration of concurrently available phencyclidine (PCP) and water. Previous work with rhesus monkeys indicated that females exceeded males in the percent of animals per group meeting criteria for acquisition of oral PCP self-administration and total drug (mg/kg) consumed during the acquisition period (Carroll et al. 2000), and these results agreed with findings from rat studies using various i.v.-delivered drugs (see review by Roth et al. 2004). In the present study, female and male monkeys were compared on the effects of escalation by their FR and PR schedule performance before and after LgA, and concentration-response functions were obtained under the PR schedules. It was predicted that behavior would escalate under LgA conditions and remain elevated when ShA conditions resumed, as reported in rat studies with LgA vs ShA (Ahmed and Koob 1998, 1999; Roth et al. 2004). The monkeys used in the present study already had a long history of ShA (3 h) drug access that could serve as their baseline of behavioral stability. The PR schedule was used to assess changes in the reinforcing effectiveness of PCP or the motivation to seek the drug due to LgA. The concentration (mg/ml) of the PCP drinking solution was the same for males and females to control for taste factors, and the amount per delivery (0.6 ml) was the same for both sexes to promote similar drinking topographies, but the intake

data were presented per kilogram body weight (mg/kg) to allow for the fact that female rhesus monkeys weigh about 40% less than males. This allowed for a comparison of the dependent variable, total dose (mg/kg) self-administered per day, between males and females.

The mg/kg intake measure was used to account for differences in body weights between sexes and to control for the fact that males have the capacity to consume more liquid than females. Several measures point to the fact that consumption differences in females and males are proportional to differences in their body weights. For example, in an earlier study when monkeys (seven males and seven females) were allowed to self-administer water under concurrent FR 8 FR 8 schedules from the two drinking spouts for 3 h, the means of PCP deliveries (\pm SEM) were 504.14 (\pm 70.56) and 789.19 (\pm 63.18) for females and males, respectively, over 5 days. Also, recent data comparing males and females on PCP vs water intake show higher PCP and water deliveries in males vs females when liquids were available 3 h per day (Perry et al. 2004). In fact, in these studies, the proportion of water deliveries consumed in females vs males was 0.64, which is nearly the same as the female/male ratio of body weights (0.67). This proportion of female to male body weights is also similar to the ratio of PCP deliveries in females/males (0.66) during the first and last 3 days of the 21-day PCP and water access period that was conducted to stabilize behavior prior to this experiment under the FR schedules and 3-h sessions.

Materials and methods

Animals

Sixteen adult rhesus monkeys (*Macacca mulatta*), nine males and seven females, were used in this experiment. Data from an additional five monkeys (four males, one female) that were used in a pilot study are also included as a control for the repeated measures used in the present study. All monkeys had previous experience self-administering PCP at several doses under FR and PR schedules during 3-h sessions for several months. Immediately prior to the present experiment, the monkeys were maintained under concurrent FR 16 FR 16 schedules of PCP (0.25 mg/kg) and water and also served as a control for the extended exposure to PCP. The monkeys were maintained at 85% of their free-feeding body weights which ranged from 4.0 to 11.2 kg (mean 6.96, SEM 0.87) for the females and from 8.7 to 11.5 kg (mean 10.44, SEM 0.41) for the males throughout the experiment. The 85% weights were obtained by allowing the monkeys to free-feed until three consecutive biweekly weights were no longer increasing, and the mean of those three weights was multiplied by 0.85. The monkeys were then weighed monthly, and food amounts were adjusted to maintain the 85% weights (Teklad monkey chow, Bartonville, IL). The monkeys were fed at 1:30 P.M. each day, and they also received small amounts of fresh fruit, vegetables, trail mix, or other nutritious snacks several times per week for enrichment. After their daily drug sessions,

they also had Kong toys and movies for enrichment, and these activities did not interfere with drug self-administration sessions. The monkeys also had visual, auditory, and olfactory contact with nine to 11 monkeys that were housed in the room. The rooms were temperature- and humidity-controlled with a 12-h light/dark cycle that started with lights on at 6:00 A.M. Use of the monkeys for this protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (Protocol No. O112A14081). Laboratory facilities were accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), and recommended principles of animal care (National Research Council 2003) were followed.

Apparatus

The monkeys lived and were tested in individual stainless-steel units (Lab Products, Maywood, NJ) that were custom-made and modified to serve as operant conditioning chambers. The cages (83-cm width, 76-cm height, 100-cm depth) were two-tiered units, each with three solid walls, a barred front wall (and door), a grid floor, and primate perch. One of the side walls had cutouts through which response devices that were attached to an outside panel protruded into the cage. The response devices were two brass drinking spouts (1.2 cm in diameter) that extended 2.7 cm into the cage through circular cutouts in the wall about 45 cm above the cage floor. The two spouts were spaced equidistantly from the center and the sides of the cage. Jeweled green stimulus lights (3-cm diameter) also protruded from the panel through cutouts in the cage wall directly above the drinking spouts.

The green stimulus lights flashed (10 Hz) to indicate drug availability, or they were continuously on to signal water availability. The drinking spouts were surrounded by four stimulus lights (two green and two white) that were visible through a clear Plexiglas panel that faced against the circular cutout surrounding the drinking spout on the cage wall. The two green lights signaled lip contacts for PCP, and the two white lights signaled lip contacts for water. These lights were activated during lip contacts serving as feedback that a lip contact had been recorded because there was no noise or moving part (as with a lever press) when the lip contact response was made. When the monkeys made the required number of lip contact responses on the spout, a solenoid valve opened and allowed 0.6 ml of liquid to flow from 2,000-ml reservoirs that were suspended above and mounted to the outer panel that was attached to the cage. Data collection and programming of the experimental sessions and schedules were controlled by PC-compatible computers running MED-PC software (Med Associates, St. Albans, VT) in an adjacent room.

Drugs

Phencyclidine HCL was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research

Triangle Park, NC). The PCP solutions were mixed in tap water ~20 h before each session, and they were stored at room temperature.

Procedure

All monkeys had previously been trained to self-administer PCP and water under concurrent FR 16 FR 16 schedules during daily 3-h sessions that started at 10 A.M.. Under the concurrent FR 16 FR 16 schedules, there was no timeout after completion of each FR and the subsequent liquid delivery, and the ratio schedule on one spout was independent of that on the other spout. At the beginning of this experiment, this condition was conducted until responding met a stability criterion based on the last five sessions (days). Stability was defined as no steadily increasing or decreasing trend in the number of liquid deliveries over a 5-day period. Subsequently, the monkeys were changed to concurrent PR schedules that were similar to those used previously in this laboratory (Rodefer et al. 1999). The sequence of successive response/reinforcer ratios was 8, 16, 32, 64, 128, 178, 256, 356, 512, 712, 1,024, 1,424, 2,048, and 4,096. Three (0.15 log) increments were used (256, 712, and 1,424) because preliminary work indicated that some monkeys did not advance to the next ratio during training when the increment was 256, 512, or 1,024; however, with the intermediate values, monkeys go beyond those ratios and have often reached 2,048 and sometimes completed 4,096. This wider distribution of break points allows for a baseline that is more sensitive to group (e.g. M vs F) differences. Upon completion of each response requirement, 20 deliveries (0.6 ml each) were available contingent upon lip contact responses on the drinking spout. There was a 30-s limited hold to allow for consumption of the 20 deliveries, although the deliveries were consumed in only a few seconds. After the 20 liquid deliveries were obtained, the response requirement advanced in the sequence. There was no timeout after each liquid delivery, but the schedule terminated for the day when 30 min elapsed before the required ratio was completed or after 3 h, whichever occurred first. The last ratio requirement completed was designated as the break point (BP). Each day, the beginning ratio was reset to 8. The BP was not constrained by the 30-min limited hold, as previous data from this laboratory indicated that monkeys were able to make more than 4,096 responses in 30 min. In the present experiment, the monkeys did not exceed a ratio of 1,424. The PR schedule was also not constrained by the 3-h session because the BP was usually reached within 1.5 h. After the BP criterion was met, the end of the session was signaled by the light over the drinking device extinguishing and deactivation of the lip contact input and associated stimuli at the drinking device. The stability criterion for BP under the concurrent PR PR schedules was 5 days with no steadily increasing or decreasing trend. The time required for behavior to stabilize at each concentration change ranged from 5 to 9 days, and it was most often 5 or 6 days because monkeys adjust rapidly to concentration changes (Rodefer and Carroll 1999). After the BP stabilized with 0.25 mg/ml

PCP and concurrently available water for 5 days, the PCP concentration was changed to 0.125, 0.5, or 1.0, in non-systematic order, and BP was allowed to stabilize at each concentration for at least 5 days. Water was always concurrently available under the same but independent PR schedule as PCP, and BP criteria were reached separately on the drug and water drinking spouts. Switching between spouts did not affect the contingencies that were in effect on the other spout.

After the PR concentration-response curve was obtained, the monkeys were returned to the FR 16 schedules with PCP (0.25 mg/ml) and water, and that condition remained in effect until behavior met the stability criterion for five consecutive days. Subsequently, the session length was increased from 3 to 6 h, and the LgA condition remained in effect for 21 days. This session length was selected because it was similar to escalation procedures used with rats (Ahmed and Koob 1998, 1999; Mantsch et al. 2004; Morgan et al. 2004; Roth et al. 2004), and due to the time course of PCP-maintained behavior, it was assumed that a second drinking bout would occur after the first one that occurred between hours 1 and 2. Results from this LgA phase of the present experiment were compared to data that had been previously collected on these same animals (seven females, nine males) over a previous 21-day period of ShA (3 h) to PCP and water under a concurrent FR 16 FR 16 schedule. These 21 days were taken from a period of ShA concurrent FR 16 FR 16 schedules immediately before this experiment began. This comparison was made to determine whether the extended exposure (21 days) to ShA or the extended exposure (21 days) to LgA (6 h) was responsible for escalation of intake and subsequent elevations in PCP-maintained behavior. After the 21-day LgA period, the ShA condition was then reinstated, and the concurrent FR 16 FR 16 and PR PR (with 0.125, 0.25, 0.5, and 1.0 mg/ml PCP) conditions were conducted as described above. Hereafter, the concurrent FR 16 FR 16 and concurrent PR PR schedules will be referred to by the abbreviated terms FR and PR, respectively. The upper half of Table 1 summarizes the sequence of events in the present experiment. Since the design of this experiment was within subjects, and the behavior of interest, the post-LgA FR 16 and PR performance, may have been influenced by previous exposure to the PR schedule prior to LgA, data from animals that did not receive the pre-LgA PR condition were used for comparison. Four males and one female had been previously tested under this condition as a preliminary study before it was decided to obtain a pre-LgA PR baseline for within-subject comparison of PR performance before and after LgA. The five animals used in the pilot study were exposed to the same conditions as the 16 experimental subjects, except that they did not receive the pre-LgA PR condition (see Table 1).

Results

The left frame of Fig. 1 illustrates the mean (\pm SEM) PCP and water deliveries self-administered by females and

Table 1 Sequence of experimental events

Schedule		FR 16	PR	FR 16	FR 16	PR
Experimental animals (<i>N</i> =16)	PCP concentration (mg/ml)	0.25	0.125, 0.25, 0.5, 1.0	0.25	0.25	0.125, 0.25, 0.5, 1.0
	Session length (h)	3	3	6	3	3
	Condition duration	5 days	5 days	21 days	5 days	5 days
Control animals (<i>N</i> =5)	PCP concentration (mg/ml)	0.25	NT	0.25	0.25	0.125, 0.25, 0.5, 1.0
	Session length (h)	3	NT	6	3	3
	Condition duration	5 days	NT	21 days	5 days	5 days
		stability	stability		stability	stability
		stability			stability	stability

NT Not tested

males over the LgA period. For statistical analyses, 21-day LgA data were divided into seven blocks of 3-day means for each monkey, and a repeated-measures ANOVA of these sequential 3-day means for PCP deliveries revealed a significant main effect of sex ($F_{(1,111)}=4.38$, $p<0.05$), with the males obtaining more PCP deliveries than females. Subsequent Fishers LSD protected *t*-tests indicated that males' PCP deliveries exceeded females' during the second ($t=4.3031$, $p<0.01$), third ($t=4.465$, $p<0.01$), fourth ($t=3.8703$, $p<0.01$), sixth ($t=2.3534$, $p<0.05$), and seventh ($t=2.4511$, $p<0.05$) 3-day blocks as indicated by horizontal lines on the figure. There was no overall significant effect of time or a sex \times time interaction. However, when females and males were compared separately, and the mean PCP deliveries during the first 3 days of the 21-day LgA period were compared to the mean of the

last 3 days for each monkey, there was a significant increase in PCP deliveries in females ($t_{(6)}=1.9449$, $p<0.05$) and males ($t_{(8)}=2.0951$, $p<0.05$), as predicted, in a one-tailed *t*-test. The left panel of Table 2 also shows that females and males increased their PCP deliveries from the first to last 3 days of the 21 days by 35.43 and 32.78%, respectively, but there was no significant sex difference in these percentage increases. In contrast to the results of this 6-h access condition, there was no increase in PCP-maintained behavior over a 21-day segment of FR 16 maintained behavior with PCP and water available during 3-h sessions (ShA) that was conducted in these same animals prior to initiating the present experiment. In that earlier 21-day segment, the change in PCP deliveries from the first 3 days to the last 3 days of the 21 days was -0.5% in the seven females and -6.76% in nine males.

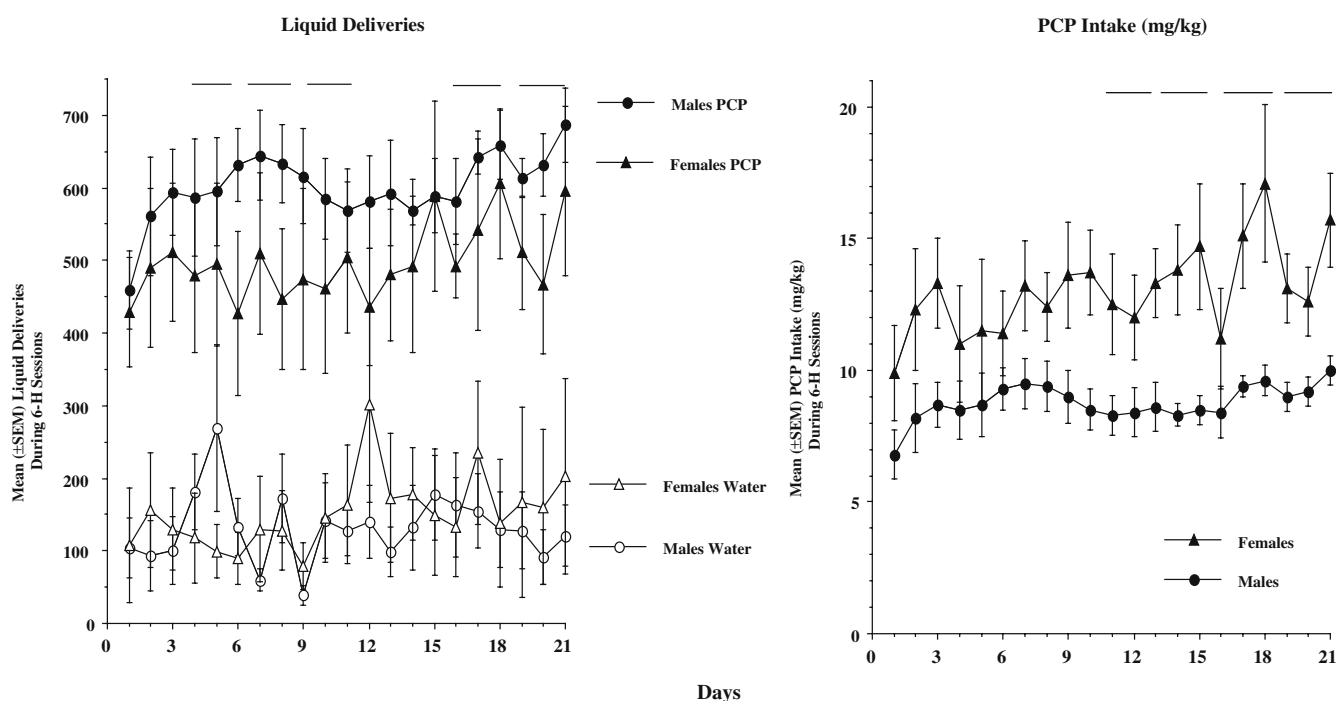


Fig. 1 Mean (\pm SEM) liquid deliveries (left frame) for drug (filled symbols) and water (open symbols) and mg/kg/PCP intake (right frame) are presented over the LgA period for males (circles) and females (triangles). Asterisks and brackets indicate the 3-day inter-

vals during which there were significant sex differences in drug deliveries and intake (mg/kg) ($p<0.05$). There were no sex differences in water deliveries

Table 2 Percent increase (\pm SEM) in PCP deliveries pre- vs post-LgA

	LgA FR 16, first 3 days vs last 3 days	ShA FR 16 pre-LgA, vs post-LgA, five stable days	ShA PR before LgA vs ShA PR after LgA, PCP concentration (mg/ml)			
			0.125	0.25	0.5	1.0
Females	35.43 (9.72)	42.29 (15.07)	20.84	43.84*	40.46*	48.84*
Males	32.78 (17.39)	56.04 (17.60)	23.96	34.92	13.07	7.14

*F>M, $p<0.05$

An overall analysis of variance of water deliveries in males and females over the seven blocks revealed a significant effect of time ($F_{(6,125)}=3.1307, p<0.05$), with intake increasing over time, but not a sex difference, and there was a significant sex \times time interaction ($F_{(6,48)}=2.4044, p<0.05$). However, there was no significant change in water deliveries in females or males from the first 3 days to the last 3 days of the 21-day period.

In the right frame of Fig. 1, PCP consumption data are expressed as mg/kg PCP intake to account for the substantially lower body weights in female monkeys compared with males. Statistical analyses of the seven sequential 3-day blocks of LgA for mg/kg PCP intake revealed a significant main effect of sex ($F_{(1,111)}=36.8, p<0.0001$), with the females consuming more PCP per unit of body weight (mg/kg) than the males. Subsequent Fishers LSD protected t -tests revealed that females consumed more PCP than males (mg/kg) during the fourth, fifth, sixth, and seventh 3-day blocks as indicated by the horizontal lines (t 's=2.49, 3.04, 2.77, and 2.61, respectively, p 's<0.05). There was no significant effect of time or a sex \times time interaction. Overall, males earned more PCP deliveries than females over the LgA, but due to their lower body weights, females consumed significantly more drug per body weight (mg/kg) than males. When PCP intake (mg/kg) was compared on the first and last 3 days of the 21-day period, PCP intake significantly increased in females ($t_{(6)}=1.8058, p<0.05$) and males ($t_{(8)}=2.4938, p<0.05$), as predicted, in a one-tailed t -test.

In Fig. 2, PCP intake (mg/kg) data are presented for males and females under the FR 16 schedules throughout different phases of the experiment. Mean (\pm SEM) FR 16 data for PCP intake (mg/kg) are presented for the last 5 days before LgA (left), during LgA (center), and the first 5 days of ShA after LgA (right). During ShA periods before LgA 6-h sessions, mean PCP intake (\pm SEM) during the last 5 days of stable behavior was similar in females (3.93 ± 0.60 mg/kg) and males (3.50 ± 0.62 mg/kg), and the means were not significantly different. The middle section of Fig. 2 shows that during the 21-day LgA period, mean PCP intake was significantly higher in females than in males ($t_{(14)}=2.4634, p<0.01$) as indicated by the plus sign. Females had an overall mean of $12.96 (\pm 0.63)$ mg/kg PCP intake, while in males, the mean was $8.76 (\pm 0.37)$ mg/kg. The right panel of Fig. 2 shows means of the last 5 days of stable behavior when PCP was again available for ShA sessions under FR 16 after the LgA period. PCP intake (mg/kg) was significantly elevated compared with the previous ShA condition in both groups, as indicated by asterisks, in both males ($t_{(8)}=3.711, p<0.01$) and females ($t_{(6)}=3.883, p<0.01$) indicating that the LgA significantly elevated subsequent FR 16 PCP

intake. However, there were no significant differences in ShA mean PCP intakes (mg/kg) after LgA between females (5.53 ± 0.76) and males (5.10 ± 0.58).

When the mg/kg intake data over the last 5 days of stable behavior were compared for these experimental animals and the pilot animals that did not have a pre-LgA PR condition (Table 3), the post-LgA PCP FR 16 intakes (mg/kg) for males (6.97 ± 9.2) and for the one female (8.57) over 5 days were very similar to the present results that are shown in Fig. 2, indicating that the increased intake was not due to prior exposure to the PR schedule.

Males and females showed an increase in PCP deliveries (ml) after compared to before LgA ($t_{(8),(6)}=3.498, 4.700, p_s<0.01$, respectively) but not in water deliveries (ml). These findings indicate that LgA selectively increased subsequent ShA PCP intake, and this increase was not explained by general increases in liquid intake, as ShA water intake did not increase after LgA.

Table 2 further summarizes the data shown in Fig. 2 for males and females by expressing the changes in behavior

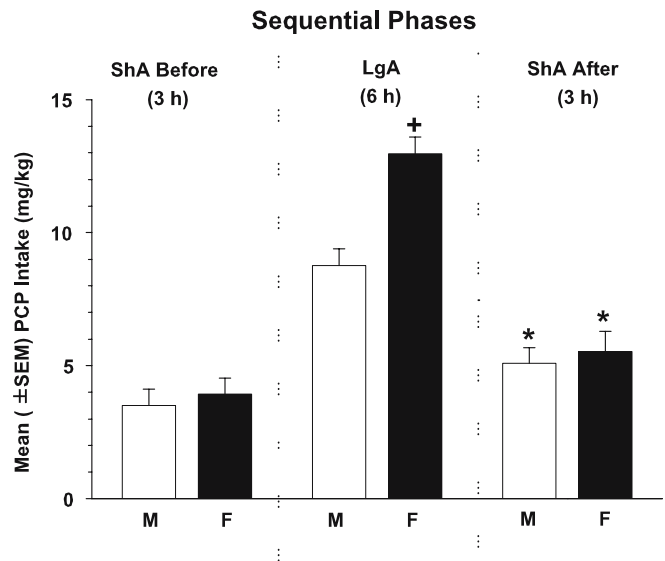


Fig. 2 Mean (\pm SEM) total mg/kg PCP intake per session is presented for the male (open bars) and female (shaded bars) groups before, during, and after the LgA period. The ShA before condition represents a mean of the last 5 days of stable behavior under ShA conditions (3 h) before session length was increased to 6 h. The LgA bars represent a mean of the 21 days of 6-h access, and the ShA after bars refer to a mean of the first 5 days of stable behavior with ShA after the LgA condition. The asterisks refer to significant increases from before to after the LgA condition, and the plus sign indicates significantly higher PCP intake in females (vs males) during LgA

Table 3 Mean PCP intake (mg/kg) in monkeys from a pilot study in which the procedure was identical to the present experiment except there was no pre-LgA PR condition

	Pre-LgA, ShA FR 16	LgA		Post LgA				
		First 3 days	Last 3 days	ShA FR 16	PR PCP Concentration (mg/ml)			
					0.125	0.25	0.5	1.0
Female ($N=1$)	6.38	12.94	14.61	8.57	1.59	3.25	7.45	11.49
Males ($N=4$)	3.50	9.45	10.52	6.97	1.16	2.89	4.78	8.94

(PCP deliveries earned) due to LgA as percent change in PCP deliveries (last five stable days) before vs after LgA for the ShA FR 16 condition. Males showed a slightly greater percent increase in ShA PCP deliveries than females when the post-LgA ShA condition was compared to pre-LgA data; however, these percent increases were not significantly different.

In summary, under FR schedules, both males and females showed significant escalation of PCP intake from the first 3 days to the last 3 days of the 21-day LgA period, from the first ShA to second (post-LgA) ShA period; however, there were no significant sex differences in the rate of escalation for either of these two comparisons. Water intake did not show an escalation effect under these measures.

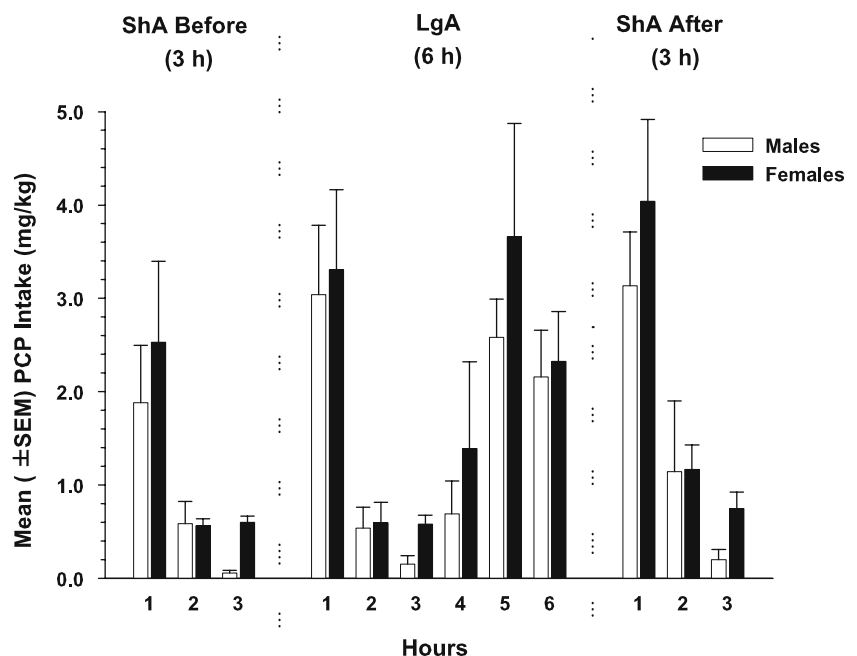
Figure 3 shows the hourly distribution of the mean PCP intake (mg/kg) in females and males that were shown collapsed across hours in Fig. 2 (collapsed across hours) before, during, and after the LgA condition when PCP and water were available under FR 16 schedules. Due to computer problems, time-course data were available for only four of the nine males and five of the seven females (compared with total N 's of 9 and 7, respectively, in Fig. 2); thus, Figs. 2, 3 are not directly comparable. Patterns of PCP self-administration during the first 3 h were similar before, during, and after the LgA period. Most of the drug was consumed during the first hour, and only small amounts

were recorded for hours 2 and 3. However, during the LgA condition, there was another peak in intake during hours 5 and 6 that was as high or higher than hour 1. This was not an artifact of averaging across monkeys, as all but one monkey showed the high intake in both hours 5 and 6. The one that did not fit this pattern was the smallest female (4 kg) who showed her second peak during hour 4.

When body weight was taken into account, and PCP intake was expressed in mg/kg, females generally consumed more PCP than males (mg/kg) overall, as shown in most of the hours. While there were significant hour effects within each of the three phases (ShA, LgA, ShA) ($F_{(2,29)}=15.7589$, $p<0.01$, $F_{(5,59)}=6.7894$, $p<0.001$, and $F_{(1,35)}=20.1132$, $p<0.001$, respectively), the sex difference did not reach statistical significance, probably due to the smaller N 's. A notable effect of the LgA condition was that it increased the hourly intake of PCP during the ShA condition that occurred after the LgA (right vs left panel) while the hourly distribution of responding remained the same. Analysis of this before vs after LgA comparison revealed a significant increase in mg/kg intake after LgA ($F_{(1,71)}=23.6249$, $p<0.005$), and females increased their post-LgA intake (mg/kg) significantly more than males ($F_{(1,71)}=6.3987$, $p<0.05$) before vs after LgA.

While males obtained more PCP deliveries than females during most hours (not shown), analysis of the deliveries

Fig. 3 Mean (\pm SEM) total hourly mg/kg PCP intake is presented for the male (open bars) and female (shaded bars), groups before, during, and after the LgA period. Time-course data were available for four males and five females



during the ShA before and after the LgA condition revealed significant hour effects ($F_{(2,29)}=15.3957, p<0.01$; $F_{(2,35)}=20.8709, p<0.001$), respectively; however, there were no significant sex differences. Hourly water deliveries were low and variable during the ShA and LgA sessions, and there were no significant time (before vs after), hour, or sex effects.

Figure 4 (upper frames) depicts the concentration-response functions for BP obtained with PCP and water under the PR schedules before (left) and after (right) LgA for females and males. Statistical analyses of the BP data revealed a main effect of time (before vs after the LgA condition), showing a significant upward shift in the BP dose-response curve in males ($F_{(1,71)}=17.585, p<0.001$) and females ($F_{(1,55)}=19.284, p<0.001$). However, there was no

significant main effect for concentration and no significant concentration \times time interaction. Although the males were slightly higher than the females on BP measures at most PCP concentrations, before and after the LgA period, a comparison of BP in females vs males before the LgA condition yielded no significant differences due to sex, concentration, or their interaction. In contrast, a comparison of BP after the LgA condition (upper right frame) indicated a significant concentration effect ($F_{(3,63)}=3.576, p<0.05$) but not a significant sex difference or concentration \times sex interaction.

The effect of repeated exposure to the PR schedule (pre-, post-LgA) was assessed by comparing these data to those of five monkeys previously tested under identical conditions except they did not have the pre-LgA PR. Table 3 shows that the PR data for these five monkeys at each

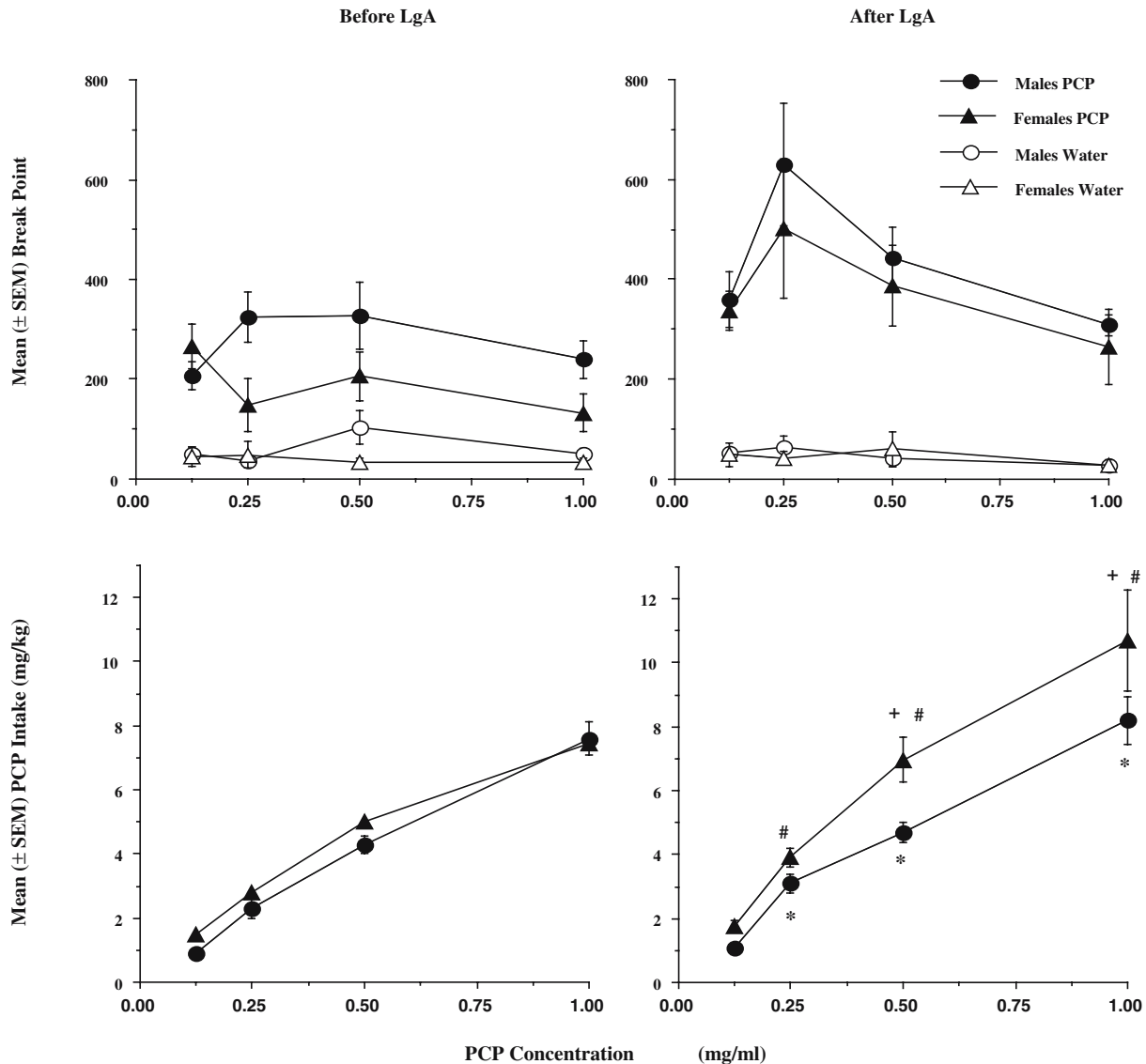


Fig. 4 Mean (\pm SEM) break point (*upper frames*) and mg/kg PCP intake (*lower frames*) under the PR schedule before (*left frames*) and after (*right frames*) the LgA condition. Four PCP concentrations (0.125, 0.25, 0.5, and 1.0 mg/ml) were tested in nonsystematic order until 5 days of stable behavior were obtained. Water was concurrently available with PCP under the same but independent PR

schedule. In the upper frames, BP for PCP are indicated by *filled symbols* and BP for water are shown in *open symbols*. Asterisks refer to significant increases in mg/kg intake after (vs before) the LgA sessions. Plus signs indicate significant increases in mg/kg intake after (vs before) the LgA sessions in females, and pound signs refer to significant sex differences

Table 4 Correlations (r^2) between body weight (kg) and post-LgA performance under the PR schedule

	PCP concentration (mg/ml)											
	0.125			0.25			0.5			1.0		
	DEL	mg/kg	%D	DEL	mg/kg	%D	DEL	mg/kg	%D	DEL	mg/kg	%D
Females	0.66	0.75*	0.16	0.75*	0.48	0.08	0.42	0.26	0.09	0.47	0.02	0.06
Males	0.23	0.00	0.49*	0.02	0.23	0.22	0.34	0.14	0.24	0.24	0.09	0.08
All monkeys	0.08	0.63	0.18	0.16	0.40	0.00	0.21	0.46*	0.00	0.25*	0.00	0.15

DEL PCP deliveries, mg/kg PCP intake, %D percent difference in PCP deliveries from pre- to post-LgA PR

* $p < 0.05$

PCP concentration were similar to the present data shown in Fig. 4; thus, LgA and not prior exposure to a PR concentration-response determination during 3-h ShA sessions was responsible for the elevated PR performance post-LgA.

The BP data for water were consistently lower than for PCP, illustrating the greater reinforcing effectiveness of PCP, and this contrast was greater after LgA than before. However, there were no significant sex, time, or concentration (concurrent PCP) effects for water BPs, and the five animals that were run in a pilot study without a pre-LgA PR had similar BPs for water (not shown). Overall, elevated PCP intake during the LgA sessions selectively increased the subsequent BP for PCP but not for water.

The lower frames of Fig. 4 represent the mg/kg intake under the PR schedule before (left) and after (right) the LgA condition. In males, there were significant main effects of concentration ($F_{(3,71)}=52.697$, $p < 0.0001$), time (before vs after) ($F_{(1,71)}=5.551$, $p < 0.05$), and a significant interaction between main effects ($F_{(3,71)}=73.728$, $p < 0.0001$). Subsequent contrasts (indicated by asterisks) revealed significant differences before and after the LgA condition at the 0.25 ($t=13.312$, $p < 0.01$), 0.5 ($t=2.591$, $p < 0.05$), and 1.0 mg/ml PCP concentrations ($t=6.522$, $p < 0.01$). Likewise, in females, there were significant main effects of concentration ($F_{(3,55)}=26.964$, $p < 0.0001$) and time ($F_{(1,55)}=19.100$, $p < 0.001$), but there was not a significant interaction. Paired comparisons in females revealed significant before/after effects at the 0.5 ($t=2.597$, $p < 0.05$) and 1.0 mg/ml PCP concentrations ($t=4.312$, $p < 0.01$) as indicated by plus signs.

Overall comparisons of mg/kg intake under the PR schedules before the LgA condition resulted in a significant concentration effect ($F_{(3,53)}=82.083$, $p < 0.0001$) but not a significant sex effect or concentration \times sex interaction. After the LgA condition, there was a significant main effect of sex in the mg/kg intake ($F_{(1,63)}=36.877$, $p < 0.005$), a significant main effect of concentration ($F_{(3,63)}=34.194$, $p < 0.0001$), and a significant sex \times concentration interaction ($F_{(1,63)}=24.221$, $p < 0.0001$). Subsequent contrasts revealed significant sex differences at the 0.25 ($t=4.760$, $p < 0.01$), 0.5 ($t=4.227$, $p < 0.01$), and 1.0 mg/ml concentrations ($t=6.554$, $p < 0.01$), indicated by pound signs. Thus, significant upward shifts in drug intake (mg/kg) occurred in both males and females after the LgA, but females showed a significantly greater elevation of the concentration-intake curve than males at the three highest PCP concentrations.

Table 2 also shows that in contrast to the FR schedule results, under the PR schedule, females significantly increased PCP deliveries more than males ($F_{(1,71)}=6.416$, $p < 0.05$) at concentrations of 0.25, 0.5, and 1.0 mg/kg, but there was no significant concentration effect or sex \times concentration interaction. Thus, the PR schedules were more sensitive to sex differences than the FR 16 schedules of PCP reinforcement. Percent changes in water deliveries before and after the LgA were not analyzed because they were small and highly variable, and the percent changes did not adequately represent patterns of the low water intake that occurred.

To examine the possibility that the differences in body weight (M>F) may have been responsible for the sex differences described above, the body weights in males and females were compared to their respective PCP deliveries, PCP intake (mg/kg), and percent increase in PCP deliveries in regression analyses for females and males separately and combined. Table 4 summarizes the results. Generally, body weight was not correlated with these measures; out of a total of 36 comparisons, seven had significant correlations while 29 did not. Four of the seven significant correlations were on the mg/kg measure, but no other trends were noted.

Discussion

The present results extend previous findings concerning the escalation of drug intake and its consequences into several new areas. Previous escalation studies have focused mainly upon male rats and psychomotor stimulants (Ahmed and Koob 1998, 2004a,b; Mantsch et al. 2001, 2003, 2004; Morgan et al. 2004; Patterson and Markou 2004; Roth and Carroll 2004) or opioids (Ahmed et al. 2000) and i.v. drug self-administration. These results extended the findings of escalation of drug self-administration to another drug class, an *N*-methyl-d-aspartate (NDMA) antagonist, PCP, to male and female rhesus monkeys, to the oral route of self-administration, and to a condition in which the drug vehicle (water) was concurrently available with the drug. As in previous rat studies (e.g., Roth et al. 2004), the present results did not reveal an overall significant daily increase in drug self-administration (due to the high variability from day to day), over the 21 days, but when the first 3 days were compared to the last 3 days of the LgA period, a significant increase in PCP deliveries and mg/kg intake was revealed in both males and females. This escalation

effect was not due to the extended PCP exposure over the 21 days because when the same monkeys' data were analyzed for a 21-day period of PCP and water availability under FR 16 schedules that occurred prior to the start of this experiment under ShA (3 h) conditions, their PCP deliveries did not increase during the 21 days of ShA. Rather, the increases over time resulted from the LgA (6 h) that gave the monkeys an opportunity for a second large bout of drinking (Fig. 3). In fact, the amount consumed during the 6-h period (LgA) was more than twice that consumed during 3-h (ShA) periods due to the larger second drinking bout.

The present study also showed an escalation in oral self-administration of PCP reflected in an increase in PCP deliveries and mg/kg intake after exposure to LgA sessions. After the LgA condition, PCP deliveries were elevated in ShA sessions compared with previous ShA under the FR schedule, and there was an upward shift in the PCP concentration-response curves under the PR schedule. Females exceeded males in mg/kg consumed; however, there were no sex differences in PCP deliveries. The elevated PR dose-response functions suggested that the motivation to self-administer PCP had increased as a result of LgA, and that effect (mg/kg increase) was greater in females than males. The present results concur with those of Ahmed and Koob (1998, 1999), showing that LgA (6 h) significantly influenced subsequent drug intake (cocaine) in male rats, and with Roth and Carroll (2004), who found this effect in females but not males. These discrepant results with males may be due to procedural differences, species, drug, dose, or other factors (see Roth and Carroll 2004). For instance, the ShA condition was 3 h in the present study compared with 1 h (Ahmed and Koob 1998, 1999; Roth and Carroll 2004) in previous studies. There were no elevations in water deliveries under ShA FR, or PR conditions after the LgA period, as there were for PCP, indicating that post-LgA increases in drug intake are not explained by general increases in liquid intake. Also, body weight was not highly correlated with PCP self-administration measures under the PR schedules (Table 4). Thus, sex differences in PR performance were not due to male–female body weight differences.

The hourly data shown in the present study over the LgA period are also similar to those reported in earlier studies (e.g., Ahmed and Koob 1998, 1999) in which there was increased drug consumption during the first hour of LgA. However, others have shown stable drug consumption across the 6- or 12-h daily sessions possibly due to differences in procedures or feeding conditions (e.g., Roth and Carroll 2004). In the present study, the elevated first hour responding occurred whether sessions were 3 or 6 h which was consistent with previous work (Carroll 1982a), and the LgA condition further enhanced this first hour responding when the monkeys were returned to ShA. The second peak in drug intake noted during hours 5 and 6 in the present study was different than the more steady intake during the end of the LgA interval reported in previous studies (Ahmed and Koob 1998, 1999; Roth and Carroll 2004). This may be specific to the oral route of self-administration and/or longer onset and duration of action of PCP (vs cocaine).

As in previous studies with rats and other drugs, escalation of PCP intake was also reflected in a significant upward shift in the subsequent PCP concentration-response curve, and this increase was greater in females than in males as in the previous rat study with cocaine (Roth and Carroll 2004). Females also consumed more PCP (mg/kg) than males during the LgA. In the present study, the elevations in PCP intake due to LgA persisted for at least several weeks while the post-LgA ShA FR and PR schedules were being tested. While long-term follow-up measures were not obtained with these monkeys, it appeared from initial results and those reported previously (Ahmed and Koob 1999) that the changes following LgA may last for months (Ahmed and Koob 1999). This behavioral persistence could be due to a behavioral history of increased responding due to LgA and/or to drug-induced changes in receptor sensitivity or other changes in neurochemical substrates due to long exposure to drug. There are previous reports of irreversible increases in baseline rates of behavior due to a history of behavioral schedules that required high response output (Barrett 1977; Carroll 1984; Morgan et al. 2002; Weiner 1970). However, a behavioral history explanation could have also predicted an enduring increase in water intake and accelerated first hour responding for water (as shown for PCP) when session length was returned to ShA (from LgA). That water intake was not affected by LgA could be due to baseline differences in PCP vs water intake, or it could support a drug-selective effect. It is possible that drug intake was more sensitive to behavioral history, or since the drug-maintained baselines were already higher than water, they may have shown proportionally greater increases. Another possible difference is that water is also available during the intersession period, and behavioral history may only affect intake of substances that are offered under limited access. An advantage of the oral procedure that was used in the present study is that the drug vehicle (water) was self-administered concurrently to rule out nonspecific behavioral effects.

Another interpretation of the effect of LgA on subsequent elevations in drug-seeking behavior is that the change is specific to the drug's pharmacological effect such as tolerance to the rate-suppressing effects of PCP or to its rewarding effects (e.g., Ahmed and Koob 1999; Koob et al. 2004). A small amount of tolerance has been reported to the disruptive effects of orally delivered PCP on a food-maintained schedule in rhesus monkeys, and it dissipated rapidly when access to the drug was terminated (Carroll 1982b); however, there is no evidence that this effect differs in males vs females. In contrast, in the present study, there were long-lasting effects on motivation to seek the rewarding effects of the drug in male and female monkeys under a ShA PR schedule. The reward allostasis hypothesis has been suggested, whereby prolonged exposure to the drug reduces reward sensitivity and the user becomes increasingly motivated to seek the rewarding effects of the drug (Ahmed and Koob 2004a,b). Thus, tolerance develops to the reward-facilitating effects of the drug rather than the disruptive effects on behavior. Hypotheses regarding the elevated drug intake after LgA to cocaine have

recently been extensively discussed in terms of reward allostasis, tolerance, and sensitization (Ahmed and Koob 2004a,b; Ben-Shahar et al. 2004; Katz and Higgins 2004; Koob and Le Moal 1997, 2001; Koob et al. 1998, 2004; Negus et al. 2004; Piazza and Deroche 2004; Robinson and Berridge 2004; Zernig et al. 2004).

The sex differences (F>M) found in the present study only became apparent when body weight was taken into account and/or when a challenging (PR) behavioral schedule was used. Each liquid delivery (0.6 ml) contained the same amount of PCP (e.g., 0.25 mg/ml) for males and females. Thus, since females weighed less than males, their unit dose for each liquid delivery was higher (mg/kg) than it was for males. However, these are very small unit doses that are not pharmacologically relevant until several hundred are obtained. Thus, the total daily dose (mg/kg) consumed was determined by how much the animal drank, and it is the dependent measure. Under ShA, females' total daily dose (mg/kg) consumed was higher than males'. The sex differences found in this study with PCP are consistent with those found in the one other escalation study with i.v. cocaine in which male and female rats were compared in a LgA/ShA i.v. cocaine self-administration paradigm (Roth and Carroll 2004). Higher PCP intake in female (vs male) rhesus monkeys has also been reported during an acquisition phase (Carroll et al. 2000), but not during maintenance (Cosgrove and Carroll 2003, 2004; Perry et al. 2004). The present results suggest that the typical ShA maintenance condition (FR 16, 3-h sessions) was not sensitive to sex differences; however, during a transition phase, such as the escalation of PCP self-administration that occurred during the LgA condition, sex differences in intake (mg/kg) emerged (F>M) when body weight was accounted for. In rat studies as well, transition phases of drug abuse such as acquisition of drug self-administration (Lynch and Carroll 1999), escalation of drug self-administration (Roth and Carroll 2004), the transition from regulation to dysregulation of drug self-administration (Lynch et al. 2000; Lynch and Carroll 2001), and reinstatement of extinguished drug-seeking behavior (Lynch and Carroll 2000) are more sensitive to sex differences (with females exceeding males) in drug self-administration compared to the steady-state, maintenance phase (Lynch and Carroll 1999; Roth et al. 2004). Body weights are already factored into these studies as i.v. doses are in mg/kg. The present results showing sex differences with the PR but not the FR schedule are also consistent with previous reports that sex differences are more apparent under more challenging reinforcement schedules (Donny et al. 2000).

It is also hypothesized that females are more sensitive to the long-term neurobiological changes that underlie the transition from steady use to escalated levels of intake. For example, dopamine release in brain areas that are related to drug abuse was greater after administration of stimulants in females than males (Becker 1999; Becker and Ramirez 1981). Dopamine release and uptake rates have been reported to be increased in the caudate in female (vs male) rats in both in vivo and in vitro studies (Walker et al. 2000). Other studies in gonadectomized rats have shown

developmental–organizational sex differences in male vs female rats that occur independently of circulating hormone levels (Hu and Becker 2003). Ovariectomized rats have been shown to have greater dopamine function in the striatum compared with castrated male rats (Bazzett and Becker 1994; Castner et al. 1993; McDermott et al. 1994). These findings may have relevance to the present study in regard to PCP's effects on the dopaminergic system, assuming the results generalize from rats to rhesus monkeys.

The neurobiological basis of the escalation-induced changes in cocaine intake has also been attributed to alterations in dopamine neurotransmission (Ahmed et al. 2002, 2003; Ahmed and Koob 2004a,b). For example, escalating cocaine (LgA) intake is associated with down regulation of dopamine D1/D2-like receptors compared with the ShA condition (Ahmed et al. 2003), and LgA rats are more sensitive than ShA rats to *cis*-flupenthixol, a highly selective dopamine (D1/D2) receptor antagonist. In another study, LgA animals had reduced c-Fos counts in several areas of the extended amygdala and a reduced locomotor response to cocaine compared with ShA rats (Ben-Shahar et al. 2004). Phencyclidine, an NMDA antagonist at the glutamate receptor, has some of the same effects on dopamine receptors as cocaine (Carroll and Comer 1994); however, there is no information on the interaction of NMDA glutamate receptor neurotransmitter and gonadal hormonal systems or under LgA vs ShA conditions.

Pharmacokinetic mechanisms may also play a role in the escalation and/or sex differences shown in the present study and the previous rat study with i.v. cocaine self-administration (Roth and Carroll 2004). However, sex differences in plasma cocaine have not been consistently reported (Carroll et al. 2004; Lynch et al. 2002; Mello et al. 2002). In rats, concentrations of PCP on the frontal and occipital cortex, midbrain, striatum, and medulla oblongata/pons were higher in female than male rats. Sex differences in response to NMDA antagonists may be due to differential pharmacokinetics or biotransformation (Nabeshima et al. 1984), and they may be modulated by gonadal hormones. However, there is no information on the pharmacokinetics of PCP self-administration in male vs female food-restricted rhesus monkeys.

In summary, the present results extend studies of the escalation of drug self-administration from rats to rhesus monkeys, to another class of abused drugs (dissociative anesthetics), to the oral route of self-administration, and to female as well as male animals. Both males and females escalated their PCP intake during the LgA period, and they showed an enduring elevation of FR-maintained performance and PR-maintained dose-response behavior during ShA sessions after (compared with before) LgA. As noted in a previous rat study, females showed a higher elevation of PR concentration-response functions that were greater than males (Roth and Carroll 2004). The concurrent availability of water (the PCP vehicle) under the same reinforcement schedule as PCP revealed no post-LgA effects indicating that the PCP findings were drug-specific and not due to a general increase in responding due to factors such as a behavioral history of elevated responding. The

present results confirm that females' drug self-administration patterns and intake (mg/kg) exceed those of the males, especially during transition phases of drug abuse (e.g., acquisition, escalation, reinstatement). Escalation of drug intake is thought to be one of the critical features of human drug abuse, and further consideration of sex differences during this transition phase may improve our understanding of the etiology of drug abuse and aid in designing gender-specific prevention and treatment strategies.

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