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ORIGINAL INVESTIGATION

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Acquisition of oral phencyclidine self-administration in rhesus monkeys: effect of sex

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Abstract *Rationale:* There are increasing reports of sex differences in the etiology of drug abuse in humans. A nonhuman primate model is useful for examining sex as a variable in drug abuse. *Objectives:* To determine whether there are sex differences in the acquisition of oral phencyclidine (PCP) self-administration and to compare the effect of altered feeding conditions on drug self-administration in male and female monkeys. *Methods:* Acquisition of orally delivered PCP was studied using 7 female and 11 male adult rhesus monkeys. Initially, the monkeys were not food restricted, and they were given access to water under concurrent fixed-ratio (FR) 1 schedules during daily 3-h sessions. Each lip-contact response on a drinking spout resulted in a 0.3 ml liquid delivery. After baseline levels of water intake were obtained for 5 days, water was replaced with PCP (0.125 mg/ml) at both drinking spouts. Body weights were then reduced to 85% of free-feeding weights, and the monkeys were fed 30 min before the session began. The FR value was increased from 1 to 2, 4, and 8, at both drinking spouts. As a final step in the procedure, water and PCP were concurrently available at the two spouts under FR 8 schedules. Acquisition of PCP-reinforced behavior was considered to have occurred if PCP intake was consistently greater than water intake. *Results:* Lip-contact responses and liquid deliveries were not significantly different between the females and males throughout the acquisition period, but there was a significant increase in responding and decrease in liquid intake as FR increased, and a significant increase in PCP consumption due to food restriction that did not differ in males and females. On a milligram per kilogram basis, female monkeys consumed nearly twice as much PCP as the males; however, this effect was not significant. The females showed significantly higher PCP than water intake while the males consumed approximately equal amounts of PCP and water. Of the seven females, 100% met the acquisition criterion of significantly greater PCP than water intake, while only 36.4% of the males met the criterion. *Conclusion:* These results concur with previous rat studies and indicate that female monkeys are more likely than males to acquire drug-reinforced behavior.

Key words Acquisition · Drug self-administration · Oral phencyclidine · PCP · Rhesus monkey · Sex

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Introduction

Women initiate drug use sooner than men (Griffin et al. 1989; Lex 1991; Weiss et al. 1997; Carise et al. 1999), and they take less time than men to become addicted to cocaine, opioids, and alcohol after initial use (for a review see Lex 1991). Thus, studies of acquisition of drug self-administration in drug-naive animals are important to our understanding of factors that affect vulnerability to drug abuse in humans. Most investigations of acquisition processes have been conducted in rats. Factors that have been found to facilitate this stage of the addiction process include food restriction (Carroll and Lac 1993, 1997), repeated pretreatment with the drug (Piazza et al. 1989), and stress (Piazza et al. 1990; Goeders and Guerin 1994; Tidey and Miczek 1997). Conversely, factors that retard drug acquisition behavior include food satiation (Carroll 1982), nondrug alternative reinforcers (Carroll 1982; Carroll and Lac 1993), and low drug doses (Carroll and Lac 1997). Previous research regarding pharmacological and environmental factors that influence acquisition of drug taking indicates that an environment enriched with alternative activities inhibits the acquisition of drug self-administration, and stress and impoverished environments enhance the development of drug abuse. However, there are striking individual differences in vulnerability to drug abuse. Sex and hormonal status may contribute to these differences.

Much of the research involving animal models of drug self-administration has focused primarily on males. However, recent data suggest that sex may influence different phases of drug addiction. For example, drug-expe-

rienced female rodents self-administer more cocaine (Morse et al. 1993), morphine (Alexander et al. 1978; Hill and Powell 1976; Craft and Stratmann 1999), fentanyl (Klein et al. 1997), and alcohol (Hill and Powell 1976; Lancaster and Spiegel 1992) than males. Sex has also been shown to influence the initiation of drug self-administration. For example, drug-naive female rats more readily acquired i.v. cocaine self-administration than males (Lynch and Carroll 2000c). Similarly, female rats showed greater re-initiation or reinstatement of extinguished cocaine-reinforced responding than males (Lynch and Carroll 2000b). Examination of sex as a variable in drug self-administration in nonhuman primates is very limited. Oral ethanol self-administration was compared in male and female juvenile (Pakarinen et al. 1998) and adult (Grant and Johanson 1988) rhesus monkeys, but no statistically reliable sex differences were found. There are also negative findings of sex differences in rats (Stewart et al. 1996). It may be that there is only a subtle difference in drug self-administration due to sex, that is observed under particularly sensitive conditions such as acquisition of drug self-administration in drug-naive animals and/or at threshold or low reinforcing drug doses.

The purpose of the present study was to investigate the effects of sex on the acquisition of oral self-administration of phencyclidine (PCP) in rhesus monkeys, and to observe differences in the maintenance levels of drug intake once they had acquired. An additional goal of this experiment was to compare PCP self-administration in females and males under conditions of food satiation and restriction. Previous work in males indicated a nearly twofold increase in intake of PCP during food restriction compared with satiation (Carroll 1982); however, this effect has not been studied in females. Lower drug concentration and access to a nondrug alternative reinforcer (saccharin) are factors that reduced acquisition of oral PCP self administration in male rhesus monkeys (Campbell et al. 1998). In general, there are few comparisons of acquisition of drug self-administration and factors controlling the behavior between male and female nonhuman primates. The present experiment will extend the use of a standard acquisition procedure (Carroll 1982; Campbell et al. 1998) to female monkeys, and this will serve as a baseline to later test variables affecting acquisition. This acquisition procedure is a gradual process in which drinking (water) is induced by offering the daily food allotment before the session. Drug then replaces water, and the response requirement under a fixed-ratio (FR) schedule is gradually increased. Eventually food is given after the session and the vehicle, water, is added concurrently to demonstrate that if drug drinking persists in excess of water drinking, with the absence of food prior to the session, then the drug is functioning as a reinforcer. The concentrations and volumes used have previously been shown to be behaviorally active, as signs of slight ataxia have been noted postsession (Carroll 1982). Since it is important for the success of this process to introduce the drug (PCP) at a low behaviorally active concentration, the concentration and volume were held constant for males and females.

In the present study, data from seven male monkeys used in the Campbell et al. (1998) study were compared with data from seven new female monkeys. To control for possible order effects from testing males first, then females, and for the fact that the initial males were tested in an all male environment, four new males were added and tested with the females to equal a total of 11 males and 7 females. The acquisition procedure was identical to that used in the previous study (Campbell et al. 1998). Based on reports that female rats are more sensitive to the reinforcing effects and other pharmacological effects of drugs (Roberts et al. 1989; Shelnutt et al. 1999; Lynch and Carroll 2000c), a low dose of PCP that produced acquisition in less than 50% of the males (Campbell et al. 1998) was used. It was hypothesized that more females than males would acquire oral PCP self-administration and that females would consume greater amounts (mg/kg) of drug. The same PCP concentration (0.125 mg/ml) was used at the lower volume/delivery (0.3 ml) that was used in the previous study (Campbell et al. 1998) for both males and females to equate the taste of the drug solution. However, since females weighed less than males, they received a greater amount of PCP (mg/kg) per delivery. There are three variables – concentration, volume, and mg/kg – that determine dose/delivery, and with a comparison between animals of different weights, only two of the three can be equated. Since taste and other oral stimuli are important variables in addition to the drug effect, concentration and volume were held constant. The monkeys could determine their milligrams-per-kilogram intake by taking more or fewer deliveries, which were easily available under low FR schedules over the 3-h sessions. An alternative approach would have been to keep the dose constant by scaling concentrations or volume to the body weights.

Materials and methods

Subjects

Eighteen young adult rhesus monkeys (*Macaca malatta*) served as subjects. There were seven gonadally intact, normally cycling females (M-A3, M-G3, M-L2, M-M4, M-P2, M-R3, and M-S3) and eleven males (M-B3, M-CR, M-C2, M-D1, M-J1, M-R4, M-T1, M-D2, M-E1, M-M5, and M-S2). The first seven males had been part of a previous experiment regarding acquisition of oral PCP self-administration (Campbell et al. 1998), and the last four males were added later and tested at the same time as the females. Although the first group of seven males was housed in an all-male colony, and the latter group of four was housed in the same rooms with female monkeys, the data from the two groups did not differ with regard to their mean responses, liquid intake (ml), and body weights; thus, they were combined. All monkeys were drug- and experimentally naive at the start of the acquisition experiment, except that M-R4 had brief exposure to cocaine base smoke. The monkeys were initially tested under conditions of food satiation, and their free-feeding weights ranged from 3.9 kg to 8 kg for females and 5.0 kg to 13 kg for males. During part of the acquisition phase, they were reduced to approximately 85% of their free-feeding body weights by slightly limiting their access to food (100–120 g). The 85% body weights ranged from 3.2 kg to 7.4 kg for females and 4.7 kg to 10 kg for males. The monkeys also received small treats such as fruit, trail-mix, a fourth of a peanut

Table 1 Sequence of experimental conditions

Step	Liquid(s) available	Fixed ratio	Feeding conditions	Days of stable responding
1.	Water at both spouts	1	Food ad libitum	5
2.	PCP at both spouts	1	Food ad libitum	10
3.	PCP at both spouts	1	Food restricted, fed 30 min after session	10
4.	PCP at both spouts	1	Food restricted, fed 30 min before session	10
5.	PCP at both spouts	2	Food restricted, fed 30 min before session	5
6.	PCP at both spouts	4	Food restricted, fed 30 min before session	5
7.	PCP at both spouts	8	Food restricted, fed 30 min before session	5
8.	PCP at both spouts	8	Food restricted, fed 30 min after session	5
9.*	Concurrent PCP and water	8	Food restricted, fed 30 min after session	5

*Test for reinforcement

butter and jelly sandwich, or movies each afternoon. The occurrence of these enrichment activities was nonsystematic and in small amounts that did not interfere with drug self-administration performance during the 3-h test sessions each morning. Subjects were housed individually in their experimental cages in temperature- (24°C) and humidity-controlled rooms. Each room contained 12–14 monkeys arranged in a circular pattern to allow proximity to other animals as well as visual, auditory, and olfactory contact with other monkeys. Each room was on a 12-h/12-h light/dark cycle with the lights on from 0700–1900 hours. The use of these animals was approved by the University of Minnesota Animal Care and Use Committee (protocol number 9812A00041). Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and accepted principles of laboratory animal care (National Research Council 1996) were followed.

Apparatus

Each monkey was housed in a custom-made, stainless-steel primate cage (Lab Products, Inc., Maywood, N.J.) that served as the experimental test chamber. The cages had grid floors, barred front walls, and solid stainless-steel side, top and back walls. There was a swinging perch and access to Kong® toys or hanging polycarbonate mirrors for enrichment. An operant chamber response panel was attached to a side wall of each cage from the outside. Holes punched through the wall allowed two drinking devices and associated stimulus lights mounted on a panel that was attached on the outside of the side wall to protrude through to the inside of the cage. The brass drinking spouts were 2.7 cm long and spaced 30 cm apart, located approximately at the level of the animal's mouth (45 cm from the floor). The drinking devices were operated by lip contacts. The experimental procedure required a specific number of lip contacts under a FR schedule, to produce a liquid delivery. The liquid was delivered when a solenoid valve opened long enough to allow a fixed amount (0.3 ml) to flow by gravity from an elevated reservoir outside the cage through the spout. Liquids were placed in 2000-ml Nalgene reservoirs before each daily session, and they flowed through Tygon tubing. If the monkey removed its mouth from the spout while the solenoid valve was open, it closed, and the liquid delivery was terminated.

Above the drinking devices were green jeweled LED stimulus lights 2.5 cm in diameter. The lights flashed at 10 Hz to signal PCP availability and remained constantly on when water was available. Each drinking device also had four smaller stimulus lights behind its clear Plexiglas mounting. Two of these lights (green) were illuminated each time a lip contact was made and PCP was available, and two others (white) were lit during lip contacts when water was available. The solid green light above the drinking device and two white lights behind it were also activated when water was available during the intersession period. The behavioral schedules were programmed and data were recorded using MED-PC (Med Associates, St. Albans, Vt.) interfaces and IBM-compatible computers.

Drugs

Phencyclidine HCl (PCP) was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, N.C.). The PCP salt was mixed with water to form concentration of 0.125 mg/ml, and stored at room temperature at least 18 h before use.

Procedure

The monkeys had access to PCP and/or water each day (7 days per week) during daily 3-h sessions (1000–1300 hours). Each session was preceded by a 2-h timeout and followed by a 1.5-h timeout period when liquids were changed and consumption from the previous period (intersession or session, respectively) was measured. During the 17.5-h intersession period, the monkeys had access to water from both drinking spouts. The daily food allotment was placed in food hoppers over an opening on the front of the chambers at 1330 hours during the postsession timeout.

As described in the subjects section, two groups of subjects were tested using identical procedures. The acquisition procedure is shown on Table 1 and also under the x axes of Fig. 1 and Fig. 2. Thus, the acquisition procedure consisted of nine steps that included these gradual changes. Previous research has shown that acquisition of oral drug self-administration is accomplished by a gradual reduction in body weight during introduction of the drug and a gradual increase in the FR requirement. In addition, it is important to first establish reliable drug self-administration under at least FR 8 or 16 before the vehicle (e.g., water) is added in a concurrent schedule:

1. Initially, water was available from both spouts, and the monkeys were maintained under food satiation conditions. Each lip-contact response produced one liquid delivery of 0.3 ml under a FR 1 schedule.
2. After 5 days of stable responding were obtained, PCP was substituted for water at both spouts. The concentration was held constant at 0.125 mg/ml, and volume per delivery was 0.3 ml, yielding 0.0375 mg per delivery for at least 10 days. This yielded a higher unit dose (mg/kg) for females than the males that weighed more. However, it is not possible to equate all parameters – concentration, volume, and dose (mg/kg). The monkeys were maintained on relatively low FRs, the concentration and volume were the same for males and females, and there were no limits on drinking except for the 3-h session. Thus, dose (mg/kg) was determined by the intake of the animal.
3. After 10 days of stable behavior were obtained, the postsession food allotment was limited to 75–100 g/day until the monkeys reached 85% of their free-feeding body weights, and they were then fed amounts needed to keep them at the 85% levels for the remainder of the experiment.
4. Food was then given to the monkeys in the food hoppers on the front of their cages 30 min before the session began. Food was usually consumed within the first 10 min. The feeding conditions were then held constant for 10 days at the FR 1 condition.

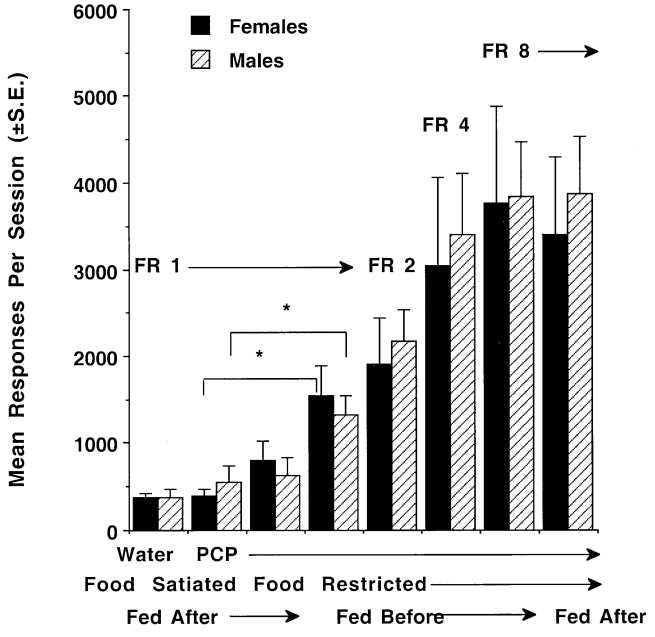

Fig. 1 Mean responses (±SEM) per 3-h session are shown for the male and female groups. Each phase of the acquisition procedure is presented sequentially from left to right. Fixed ratio (FR) values are shown *above the bars*, and water, phencyclidine (PCP), and food conditions are depicted along the *x axis*. *Solid bars* represent data from the females while *striped bars* refer to males. The specified liquid was available from both left and right spouts. Thus, each *bar* represents the total amount of liquid consumed from both spouts. Each *bar* is a mean of the last 5 days of stable responding under each condition. *Asterisks* and *brackets* indicate statistically significant comparisons ($P<0.05$)

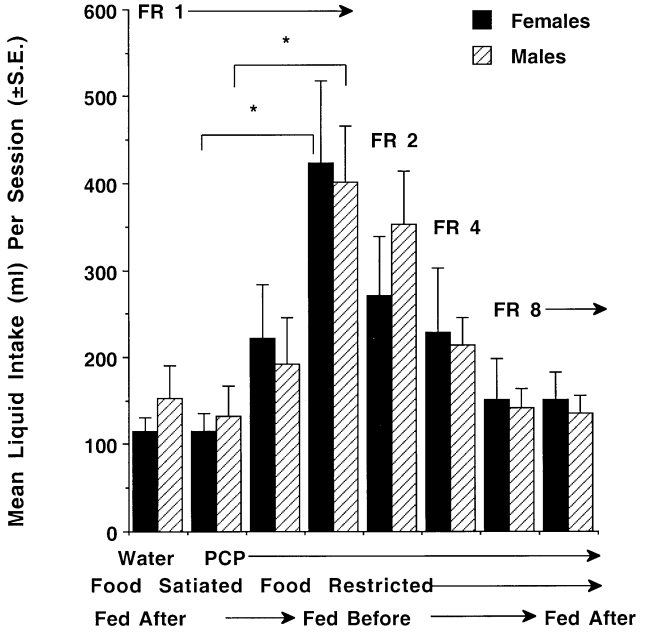

Fig. 2 Mean liquid intake in milliliters (±SEM) is presented for the male and female groups. Each phase of the acquisition procedure is presented sequentially from left to right. Fixed ratio (FR) values are shown *above the bars*, and water, phencyclidine (PCP), and food conditions are depicted along the *x axis*. *Solid bars* represent data from the females while *striped bars* refer to males. The specified liquid was available from both left and right spouts. Thus, each *bar* represents the total amount of liquid consumed from both spouts. Each *bar* is a mean of the last 5 days of stable responding under each condition. *Asterisks* and *brackets* indicate statistically significant comparisons ($P<0.05$)

5–7. The monkeys were then tested at FR 2, 4, and 8 schedules of liquid delivery. Each FR condition was held constant until 5 days of stable responding were obtained. Stability was defined as no steadily increasing or decreasing trend in the level of liquid deliveries over five successive days. Generally, it required 5–7 days to obtain stable data.
8. After 5 days of stable data were obtained under FR 8, food access was shifted to 30 min after the session to determine whether drug intake would persist in the absence of the food, and behavior was allowed to stabilize for 5 days.
9. In the final step of the procedure, the feeding conditions remained the same, but PCP and water were available concurrently at the two drinking spouts, with side positions reversed daily, under concurrent FR 8 schedules instead of PCP at both spouts. This served as a test for whether or not PCP was functioning as a reinforcer. This condition was again held constant until behavior stabilized for at least 5 days. The criterion for reinforcement was the consistent consumption of more PCP than water under concurrent FR 8 schedules when food was available after session.

Data analysis

Lip-contact responses, PCP intake (ml and mg/kg), and water intake (ml) served as the dependent measures. The FR value was a within-subjects factor, and sex was the independent variable. A repeated measures factorial analysis of variance was used to compare differences between and within groups, since FR was a discrete rather than a continuous variable. Post-hoc comparisons were made with Bonferroni-corrected *t*-tests. Under conditions where monkeys had concurrent access to PCP and water (FR 8), paired *t*-tests were used to determine whether drug intake exceeded water intake. Values of $P<0.05$ were considered to be statistically significant.

Results

Figure 1 shows the mean responses per 3-h session at the various phases of the acquisition procedure (x axis labels and Table 1) for male and female monkeys. When water or PCP was available under food satiation conditions or when food was restricted and the monkeys were fed after the session, responding was relatively low, approximately 400–500 responses per 3-h session (first three pairs of bars). When water and PCP-maintained responses were compared with *t*-tests under food satiation conditions (first two pairs of bars), there were no significant differences for males or females. Food restriction and feeding the animals before the session resulted in a twofold increase in responses per session in both males and females. The females' responding was slightly higher than males'. Paired *t*-tests revealed no significant increases in PCP responses due to food restriction under FR 1 (2nd vs 3rd pairs of bars) for either males or females when the monkeys were fed after session; however, there was a significant increase in responding when the food satiation condition was compared with food restriction when

they were fed before the session (bar 2 vs bar 4) for both males (t=2.62, df=21, P<0.05) and females (t=2.68, df=13, P<0.05).

Under the food-restricted fed-after conditions, both males and females increased responding as the FR value increased to a maximum of approximately 4000 at FR 8. This increase due to FR value was statistically significant (F=10.2, df=3, P<0.05). However, there was no significant difference between the male and female groups during these steps of the acquisition process and no significant FR value by sex interaction. There is a low observed power for analyses of interaction effects between sex and FR size (0.049) and between-sex differences (0.063). However, a markedly higher power is observed for tests of change within subjects (0.996). The low observed power is most likely due to high variability between subjects. For example, the FR 8 conditions show male responses from 565 to 7559 and female responses from 1982 to 10,194. There was also no significant difference in responses between males and females when restricted food amounts were given after the session (last pair of bars) under the FR 8 schedule. In summary, there was a significant increase in responding as FR increased and a significant increase in responding due to food restriction (vs satiation) when the monkeys were fed before session. However, there were no sex differences in any of the other comparisons of response measures.

Figure 2 illustrates mean liquid intake (ml) during the 3-h sessions over the last 5 days of stable behavior. As the FR increased, liquid intake significantly decreased (F=20.48, df=3, P<0.05). However, there were no significant differences due to sex or a sex by FR value interaction. When water and PCP intake (ml) were compared with t-tests under food satiation conditions (first two pairs of bars), there were no significant differences either in females or in males. Paired t-tests also revealed no significant increases in PCP intake due to food restriction when the monkeys were fed after the session under FR 1 (2nd vs 3rd pairs of bars) for either males or females. When the monkeys were fed before session, however, there was a significant increase in PCP intake (ml) when the food satiation condition was compared with the food restriction condition (bar 2 vs bar 4) for both males (t=3.73, df=10, P<0.05) and females (t=2.5, df=6, P<0.05). In summary, there was a significant decrease in PCP intake (ml) as FR increased and a significant increase in PCP intake (ml) due to food restriction (vs satiation) when the monkeys were fed before the session. There were no sex differences in the intake (ml) measures when PCP was available from both spouts.

Figure 3 shows PCP intake expressed as milligrams per kilogram for the male and female groups under seven of the nine components of the acquisition process when PCP was available. Female monkeys consumed more milligrams per kilogram of PCP under all seven conditions; however, due to the large intersubject variability, this trend did not reach significance. There was a significant decrease in milligrams per kilogram PCP intake as the FR size increased from 1 to 8 under conditions of restricted amounts of food given before the sessions (F=18.48, df=3, P<0.05), but there was no significant sex by FR size interaction. Variability among monkeys, as shown by the low power of analyses (0.364), may have resulted in the failure to find statistical significance. Paired t-tests between food satiation (first pair of bars) and food restriction (second pair of bars) conditions under the FR 1 schedule revealed no significant increase in PCP intake (mg/kg) due to food restriction when food was available after the session in either males or females. However, when monkeys were fed before session (bar 1 vs bar 3) there was a significant increase in PCP intake (mg/kg) in males (t=3.04, df=10, P>0.05) and females (t=3.02, df=6, P<0.05). Under the FR 8 schedule when restricted food was given before the sessions, the females consumed nearly twice the amount of PCP (mg/kg) as males; however, again due to the high variability this effect was not statistically significant. In summary, there was a significant decrease in PCP intake (mg/kg) as FR increased and a significant increase in mg/kg intake due to food restriction when the monkeys were fed before session. There were no sex differences in any of the intake (mg/kg) measures shown in Fig. 3.

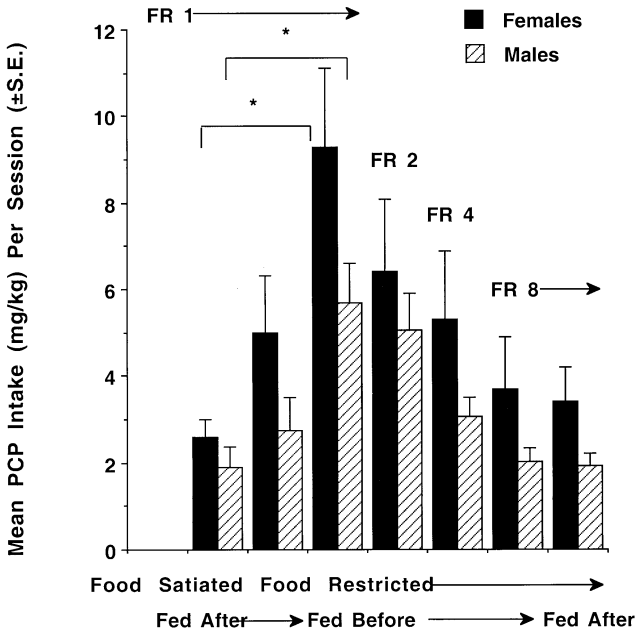

Fig. 3 Mean phencyclidine (PCP) intake (mg/kg) per 3-h session (±SEM) is presented for the male and female groups. Each phase of the acquisition procedure is presented sequentially from left to right. Fixed ratio (FR) values are shown *above the bars*, and water, PCP, and food conditions are depicted along the *x axis*. *Solid bars* represent data from the females while *striped bars* refer to males. The specified liquid was available from both left and right spouts. Thus, each *bar* represents the total amount of PCP consumed (mg/kg) from both spouts. Each *bar* is a mean of the last 5 days of stable responding under each condition. *Asterisks* and *brackets* indicate statistically significant comparisons (P<0.05)

Figure 4 (left frame) illustrates the results of the test of PCP reinforcement when PCP and water were available concurrently during the 3-h sessions, with side posi-

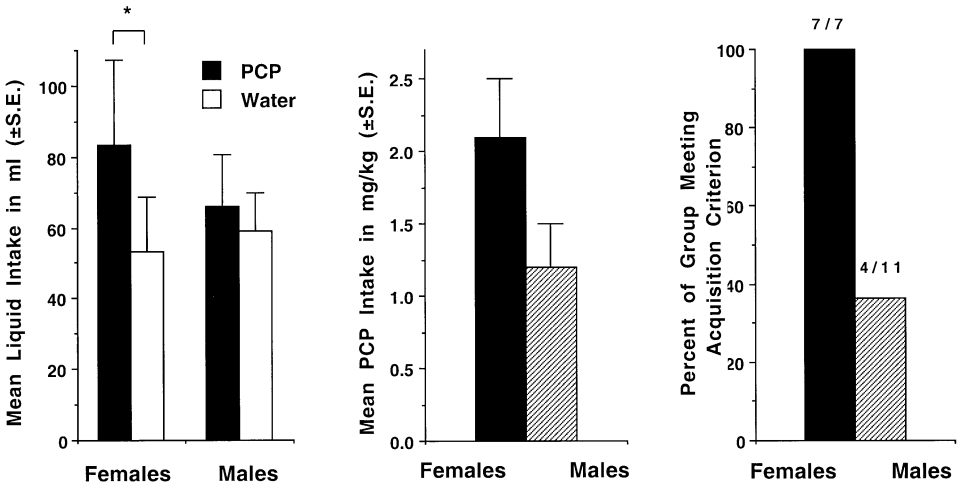

Fig. 4 In the *left frame*, mean liquid intake (ml) per 3-h session (±SEM) is presented for the male and female groups. Data represent the test for reinforcement when phencyclidine (PCP) and water were concurrently available under fixed ratio (FR) 8 schedules. The *solid bar* refers to PCP intake while the *open bar* refers to water intake. Each *bar* is a mean of the last 5 days of stable responding for the FR 8, concurrent PCP and water condition. The *asterisk* and *bracket* indicates a statistically significant comparison ($P<0.05$). The *center frame* shows mean PCP intake (mg/kg) per 3-h session (±SEM) for the male and female groups. The test for reinforcement when PCP and water were concurrently available under FR 8 schedules. The *solid bar* represents data from the females, while the *striped bar* refers to the males. Each *bar* is a mean of the last 5 days of stable responding for the FR 8, concurrent PCP and water condition. The *right frame* illustrates the percentage of each group meeting the acquisition criterion of greater drug than water intake. Data were compared over the last 5 days of stable session responding when PCP and water were concurrently available under FR 8 schedules. The *solid bar* represents the female group while the *striped bar* represents the male group

tions reversed daily. Concurrent and independent FR 8 schedules were used for PCP and water, food intake remained restricted, and the monkeys were fed after the session. The females showed significantly greater PCP intake (ml) than water intake ($t=2.14$, df=6, $P<0.05$). There was no significant difference between drug and water intake in males. The pattern of PCP and water self-administration over the 3-h session was similar for males and females, and it was similar to that reported previously (Carroll 1982). Drinking began immediately at the start of the session and continued at a steady negatively accelerated rate for about the first hour. Often water and drug were initially sampled, and then the remaining session intake occurred on the PCP spout, indicating that taste of the drug solution had become associated with its reinforcing effects.

Mean PCP intake (in mg/kg) per 3-h session was approximately 75% higher for females than for males. However, due to the high variance in intake values between monkeys, a *t*-test showed no significant difference. Figure 4 (center frame) illustrates this comparison. One-tailed, paired *t*-tests were also conducted for each individual monkey over the last 5 days of stable behavior under the concurrent PCP and water condition. A significant difference indicated that the acquisition criterion had been met. All of the seven female monkeys met the criterion for PCP reinforcement under FR 8 conditions (100%), while only 4 of the 11 (36.4%) monkeys met the criterion. Thus, Fig. 4 (right frame) shows that a greater percentage of females than males met the acquisition criterion for PCP self-administration.

Discussion

In the present study, the acquisition of oral PCP self-administration was defined by PCP intake in excess of water intake when both liquids were available under concurrent FR 8 schedules, and the monkeys were fed after the session. Of the seven females tested, 100% met the acquisition criterion, while only 36.4% of the males met the criterion. The number of lip-contact responses and liquid deliveries (ml) were nearly identical across all experimental conditions. Similarly, under all seven experimental conditions when PCP was available, female monkeys showed milligram-per-kilogram intakes that were not significantly different than males; although they were consistently higher than males in seven of the seven conditions when PCP was available. A lack of statistical significance may have been due to the high level of intersubject variability. When the males and females were compared under the FR 8 concurrent PCP and water condition with food available after the session, females consumed significantly greater amounts (ml) of PCP than water, while males did not show a significant difference between PCP and water intake (ml).

Previous work with rodents indicates that females do not metabolize PCP as well as males (Shelnutt et al. 1999). If this is true for rhesus monkeys, it may explain why the females were more sensitive to the reinforcing effects of this low dose of PCP than males. Further work would be needed to adjust dose to body weight (mg/kg) in males and females to determine whether the higher milligram-per-kilogram intake in females was due to sex differences in metabolism.

Food restriction produced significant increases in PCP intake in both male and female monkeys, and these increases were proportionally the same across groups. There are no previous reports regarding sex differences in response to food restriction in monkeys. However, male and female rats increase i.v. heroin self-administration by proportionally similar amounts when food access is temporarily restricted (Carroll and Heideman, unpublished observations).

The present results with the four newly added males are in close agreement with the previous results from the seven males that participated in the previous study (Campbell et al. 1998). Thus, testing the four additional male monkeys at a later time and under conditions in which males and females were housed together compared with males housed only with males was not likely to influence the present finding of sex differences in the acquisition of PCP self-administration. However, females were not tested in two groups, alone and with males, thus it is not known whether the housing conditions would have affected their behavior.

The present results agreed with one study of greater ethanol intake in female (vs male) vervet monkeys (Juarez et al. 1993); however, they differed from previous studies of the acquisition of ethanol self-administration in rhesus monkeys. For example, Grant and Johanson (1988) found no sex differences in the acquisition of ethanol self-administration in rhesus monkeys. In a more recent study, Pakarinen and coworkers (1998) tested 12 male and 12 female juvenile monkeys on the acquisition of oral ethanol self-administration. Groups consisted of two levels of food restriction, with six monkeys per group. They did not find a significant sex difference, but there was a significant interaction among sex, ethanol concentration, and feeding condition. Since these were juvenile monkeys, and gonadal hormones would be at lower levels, sex differences may not have emerged in this study. Differences in i.v. cocaine self-administration in males relative to females are related to the phase of the estrus cycle or estrogen levels (Roberts et al. 1989; Lynch and Carroll 2000a). Caffeine intake is also greater in female rats but only under conditions of food restriction (Heppner et al. 1986), a finding that agrees with the sex by feeding condition interaction (Pakarinen et al. 1998).

The present results agree with previous reports of sex differences and acquisition of cocaine (0.2 mg/kg) and heroin (0.015 mg/kg) self-administration in rats (Lynch and Carroll 2000c). Females met the acquisition criterion more quickly than males in both the cocaine and heroin groups. In the cocaine groups, only 30% of the males met the criterion within the maximum time allowed (30 days) compared with 70% of the females. Once cocaine self-administration stabilized, females continued to significantly self-administer more cocaine than males, but male and female rats that acquired heroin self-administration eventually self-administered similar amounts. In this rat study, the dose per animal (mg/kg) was equated for males and females, and taste and other oral stimuli were not factors. Thus, increased drug self-administration in females relative to males may be due to sex differences in metabolism.

These results are consistent with those of other studies that have reported a significant sex difference in which female mice self-administered slightly greater levels of cocaine than male mice (Hill and Powell 1976; Morse et al. 1993). They also concur with reports of greater alcohol (Lancaster and Spiegel 1992), morphine (Alexander et al. 1978), and fentanyl (Klein et al. 1997) intake in female than male rats. In a study of regulation of cocaine self-administration using a procedure that allowed rats to increase or decrease their infusion dose by responding on two levers, Lynch and Carroll (2000a) found sex differences. Regulation was defined as the correlation between interdose interval and preceding dose size. The correlation coefficient was usually in the r=80–90 range, accounting for 60–80% of the variance. They found that females regulated their cocaine intake less precisely than males. Further examination of regulation during different phases of the estrous cycle in female rats indicated that large increases in responding for high doses of cocaine occurred during estrus, the phase of the estrous cycle when estrogen levels are lowest. During this phase, regulation of cocaine intake was significantly disabled. Female rats also demonstrated reinstatement of extinguished cocaine reinforced responding compared with males (Lynch and Carroll 2000b). When given one priming injection of cocaine (0.32, 1.0, or 3.2 mg/kg) after saline had been substituted for cocaine, females showed significant reinstatement responding (relative to a saline priming injection) at a lower cocaine priming dose (0.32 mg/kg) than males. Data from the present and previous studies showed that females are more responsive to the acquisition, maintenance, and reacquisition (relapse) of drug self-administration, and that they consume more drug than males.

There are also rat studies in which no sex differences in drug self-administration were reported. For example, Stewart and coworkers (1996) compared male and female rats using four heroin doses (0.006, 0.013, 0.025, and 0.05 mg/kg) presented in ascending order. All animals rapidly acquired heroin self-administration and stabilized within 8 days; however, a ceiling effect may have overshadowed sex differences. The previous cocaine acquisition study by Lynch and Carroll (2000c) used an autoshaping procedure with a delay (Messing et al. 1986) between lever presentation, retraction, and the noncontingent priming infusions to slow acquisition, and the difference in procedures may have revealed the faster acquisition in females. Two other studies also reported no sex difference in cocaine intake in rats (Roberts et al. 1989; Haney et al. 1995). Overall, the present results and previous literature indicate that when sex differences are found, females are more sensitive to the reinforcing effects of drugs than males. The finding of no differences may be due to a higher drug dose, drug history, age or to other aspects of the experimental setting. It appears that sex differences are more consistently apparent in the

transition phases of drug addiction, such as acquisition or relapse (or reinstatement), than in the steady-state, maintenance phase.

In summary, the results of the present investigation revealed that female and male monkeys made similar numbers of lip-contact responses for PCP and water under FR schedules, and similar amounts of liquid were consumed. Male and female monkeys also showed the same increase in PCP self-administration when food access was restricted. Since the adult females weighed less, they consumed more PCP per body weight (mg/kg) than males; however, this difference was not statistically significant. Additionally, with the low concentration of PCP (0.0375 mg/delivery) that was used in the present experiment, a much greater proportion of females (100%) than males (36.4%) met the acquisition criterion (a significantly greater number of PCP versus water deliveries for 5 days of stable behavior when PCP and water were available under concurrent FR 8 schedules, and the monkeys were fed after the session). Under these conditions the female group consumed significantly more PCP than water while males did not. This is the first demonstration of sex differences in the acquisition of drug self-administration in rhesus monkeys, and the results concur with rat i.v. drug self-administration studies (Lynch and Carroll 2000b), indicating that under low-dose (or concentration) conditions, a greater percentage of females (vs males) acquire drug self-administration.

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