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Phencyclidine (PCP) produces sexually dimorphic effects on voluntary sucrose consumption and elevated plus maze behavior

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ABSTRACT

Previous research in our laboratory indicates that the psychotomimetic drug phencyclidine (PCP) reduces voluntary sucrose consumption in male rats, potentially modeling the schizophrenic symptom of anhedonia. Given reports from the clinical literature that schizophrenia has a later age of onset and more favorable outcome in females, PCP might be expected to have sexually dimorphic effects in animal models of schizophrenia such as PCP-induced decreases in voluntary sucrose consumption. Young adult (66 days old) and adult (109 days old) male and female rats were trained to drink sucrose during a 30 min/day presentation protocol. On the day prior to the test day, animals were treated with PCP (15 mg/kg) or saline four hours after the onset of the sucrose presentation (20 h prior to the sucrose on the test day). PCP decreased sucrose consumption on the test day similarly in adult males and females, although females also showed decreased water consumption. In young animals, PCP decreased sucrose consumption in males but not in females. These results are consistent with the prediction that females will be less sensitive to the schizophrenia-like behavioral effects of PCP. In a separate study, the same animals were tested in an elevated plus maze one to two months after testing for voluntary sucrose consumption. Significant sex × drug interaction effects on a number of measures in the elevated plus maze indicated that prior exposure to PCP had an anxiolytic effect in females and an anxiogenic effect in males. While unexpected, this finding indicates an additional sexually dimorphic effect of PCP on behavior and its potential relevance to the PCP model of schizophrenia is discussed.

1. Introduction

Phencyclidine (PCP) is a psychotomimetic drug which produces a number of schizophrenia-like behaviors in animals, leading to its adoption as a major pharmacological model for schizophrenia. However, most studies examining the behavioral effects of PCP have used male animals. Human studies suggest that females have a later age of onset and a more favorable outcome than males following a diagnosis of schizophrenia (Grossman et al., 2006; Seeman and Lang, 1990; Tang et al., 2007). Females are less likely to suffer from the negative symptoms of the disease (Seeman and Lang, 1990; Tang et al., 2007) and more likely to show evidence of recovery (Grossman et al., 2006). These sex differences have been argued to result from cultural factors such as gender identity development (Nasser et al., 2002) and differences in diagnostic practice (Hoye et al., 2006) as well as biological factors such as hormones and rate of brain maturation (Seeman and Lang, 1990; Goldstein, 2006).

One of the few animal models for negative schizophrenic symptomatology is PCP-induced anhedonia. PCP pretreatment increases intracranial self-stimulation thresholds (Spielewoy and Markou, 2003) and decreases sucrose consumption (Turgeon and Hoge, 2003; Turgeon and Hulick, 2007; Baird et al., 2008), suggesting that PCP decreases reward function. However, all these of studies have examined the effects of PCP in males. Given the later age of onset and decreased prevalence of negative symptoms in women, the effect of PCP on reward might be predicted to appear earlier and be greater in males than in females. In order to test this prediction, the first experiment presented in the study examined the effect of PCP on voluntary sucrose consumption in male and female young and adult rats.

Between one and two months following inclusion in the sucrose study, the animals were used in an unrelated study examining sexual dimorphisms in elevated plus maze behavior. Prior data from our lab indicated that 14 days of 10 mg/kg/day PCP did not have demonstrable effects on elevated plus maze activity 24 h after the final injection (unpublished data), thus we did not predict that there would be an effect of prior PCP exposure on the behavior of the animals in this experiment. This assumption was also supported by a number of published findings including Lee et al. (2005) who reported that 3 mg/kg/day for 14 days

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did not alter behavior in either the open field or a light–dark emergence test 72 h later and Schwabe et al. (2006), who reported that 5 mg/kg/day for 7 days on P42–P48 did not alter either behavior in either the open field or the elevated plus maze on P70. However, significant interaction effects between drug and sex were observed for a number of behavioral measures, indicating that PCP had anxiolytic effects in females and anxiogenic effects in males. While not initially predicted, this observation of a long-lasting sexually dimorphic effect of PCP on behavior was striking and thus is reported here.

2. Methods

2.1. Experiment 1: effects of PCP on voluntary sucrose consumption

2.1.1. Animals

Forty-eight Sprague–Dawley rats, twenty-four males and twenty-four females, were obtained from Charles River Laboratories (Wilmington, MA). Rats were either 66 days old (12 males and 12 females) or 109 days old (12 males and 12 females) on Day 1 of the experiment. Animals arrived in the facility nine days before experiments began, were housed individually, and were maintained on a 12-h reverse dark–light cycle (dark from 6 am to 6 pm). Rats were allowed access to food and water ad lib throughout the experiment (except during sucrose training and testing, see below). All procedures were approved by the Amherst College Institutional Animal Use and Care Committee.

2.1.2. PCP

Phencyclidine hydrochloride (PCP) was obtained from Sigma (St. Louis, MO) and administered at a dose of 15 mg/kg in 2 ml/kg saline (ip). Vehicle controls were administered 2 ml/kg saline (ip). This dose was chosen as it has been shown to reliably decrease sucrose consumption in the past (Turgeon and Hoge, 2003; Turgeon and Hulick, 2007; Baird et al., 2008).

2.1.3. Sucrose training and testing

On Day 1 of the experiment, animals were weighed and given access to 5% sucrose for 30 min (10:00–10:30 am) after which sucrose bottles were replaced by water bottles (10:30 am). On Day 2 of the experiment, rats were weighed and water consumption for the past 23.5 h was recorded at 10:00 am. Animals were then given access to sucrose for 30 minutes and consumption was recorded. This was repeated on Days 4, 5 and 6 (rats were not offered sucrose on Day 3 for scheduling reasons). Four hours after the end of the sucrose session (2:30 pm) on Day 6, rats were injected with either PCP ($n=6$ 66-day old males, $n=6$ 66-day old females, $n=6$ 109-day old males and $n=6$ 109-day old females) or saline ($n=6$ 66-day old males, $n=6$ 66-day old females, $n=6$ 109-day old males and $n=6$ 109-day old females). On Day 7, 23.5 h water consumption and 30 minute sucrose consumption were recorded. Daily sucrose consumption was recorded as a function of weight (ml/kg) and reported as a percentage of pre-treatment consumption ((Day 7 consumption/(Day 6 consumption + Day 5 consumption/2))*100). Water consumption was also recorded as a function of weight and reported as a function of pre-treatment consumption ((Day 7 consumption/Day 6 consumption)*100). Weight on the test day was recorded and is reported as a percentage of pre-treatment weight ((Day 7 wt/((Day 6 wt + Day 5 wt)/2))*100).

2.1.4. Statistical analysis

Sucrose and water ratios were analyzed using a multivariate ANOVA with sex (male, female), drug (saline, PCP), and age (young, adult) as the between subjects variables. Given the observation of significant interaction effects with age, the data from the young and adult animals were analyzed separately using a 2×2 ANOVA with sex and drug as the between subjects variables. Within each age grouping, post-hoc *t*-tests were used to examine individual group differences between saline and PCP-treated males and females (male-saline vs male-PCP, female-saline vs female-PCP) as well as differences between males and females receiving the same treatment (male-saline vs female-saline and male-PCP vs female-PCP). In order to avoid the possibility of Type I error given the four comparisons done within each age grouping, the criterion for significance was set at $p<0.0.0125$. In addition, as an alternate form of analysis, repeated measures ANOVAs were conducted on absolute consumption data from before and after PCP injection with DAY as the within subjects variable and DRUG and SEX as between subjects variables (see Table 1). Weight ratios were also calculated ((Day 7 wt/((Day 6 wt + Day 5 wt)/2))*100) and analyzed with a multivariate ANOVA.

2.2. Experiment 2: effects of PCP on elevated plus maze behavior

2.2.1. Animals

The animals used in Experiment 1 were also used in Experiment 2. Animals were tested one to two months (36–74 days) after PCP administration. Animals had continued to be housed in the same conditions and were handled for 3–4 min on each of the three days prior to testing the elevated plus maze (EPM).

2.2.2. Elevated plus maze

The maze was located in a room with black walls and illuminated by a fluorescent light covered with red plastic. The maze had four arms (50 cm long×10 cm wide) extending at right angles off a central platform (10 cm×10 cm). Two arms were enclosed by walls (40 cm high). The walls were made of wood and the floor of the maze was made with black plexiglass. The maze was elevated 55 cm off the floor. A 40 W light bulb was affixed to the wall at a height of 55 cm above the maze and at a 45° angle from the outer edge of the open arms. Animals were placed in the center of the maze, facing an open arm, and their behavior was videotaped for 5 min. Videotapes were scored by an experimenter blind to the treatment condition for the amount of time spent in the open arms, closed arms, or on the center platform. The number full entries (all four paws) and partial entries (2 front paws) into the open and closed arms and the center platform were counted. In addition, the number of rears and the number of episodes of grooming behavior were assessed.

2.2.3. Statistics

Each of the behavioral variables was assessed with a 2×2 ANOVA with between subjects variables of drug (PCP, saline) and sex (male, female). For each behavior, post-hoc *t*-tests were used to examine individual group differences between saline and PCP-treated males and females (male-saline vs male-PCP, female-saline vs female-PCP) as well as differences between males and females receiving the same treatment (male-saline vs female-saline and male-PCP vs female-PCP). In order to avoid the possibility of Type I error given the four comparisons done for each behavior, the criterion for significance was set at $p<0.0.0125$. Initial analyses revealed the same statistical effects when full and partial open arm and center entries were calculated (there were no partial closed entries), partial and full entries were combined for the sake of brevity.

3. Results

3.1. Experiment 1: effects of PCP on voluntary sucrose consumption

3.1.1. Sucrose consumption

The multivariate ANOVA examining the effects of drug, age, and sex on sucrose ratio revealed significant effects of drug ($F(1,40)=19.2$, $p<0.01$), significant interaction effects between sex and drug ($F(1.40)=4.8$, $p<0.05$) and sex and age ($F(1,40)=4.5$, $P<0.04$) and drug and age ($F(1,40)=9.9$, $p<0.005$). There was also a three-way interaction effect between sex, drug and age ($F(1,40)=4.8$, $p<0.05$;

Fig. 1A). A 2×2 ANOVA in the young rats revealed a significant effect of sex ($F(1,20)=4.5$, $p<0.05$) and a significant sex×drug interaction ($F(1,20)=6.5$, $p<0.05$). Post-hoc *t*-tests revealed that PCP-treated males drank significantly less than saline-treated males ($t(10)=3.8$, $p<0.005$) and PCP-treated females ($t(10)=3.4$, $p<0.01$). In the adult rats, the 2×2 ANOVA revealed a significant effect of drug ($F(1,20)=17.9$, $p<0.001$) but no effect of sex and no sex by drug interaction. Post-hoc *t*-tests revealed that PCP-treated males drank less sucrose than saline-treated males ($t(10)=4.3$, $p<0.001$) and PCP-treated females drank less than saline-treated females ($t(10)=6.8$, $p<0.001$). Repeated measures analyses revealed the same pattern of results as %-change analysis with significant effects of sex, day×sex, and day×sex×drug in young animals and day and day×drug in adult animals (Table 1).

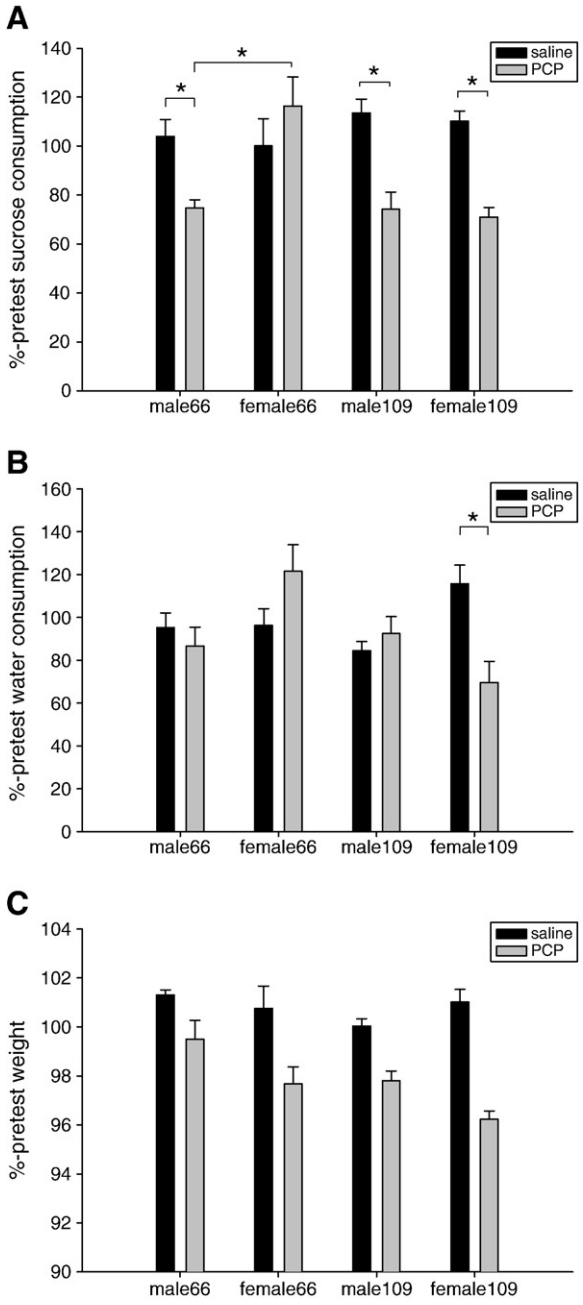

Fig. 1. PCP had similar effects on sucrose ratio in male and female adults; however, in young animals, PCP only decreased sucrose ratio in males (A). Water ratio was the same across groups in young animals; however, PCP decreased water ratio in adult females (B). PCP-induced decreases in weight ratios were greater in females than in males (C). *$p<0.0125$, student's *t*-test.

3.1.2. Water consumption

A multivariate ANOVA revealed significant interaction effects between drug and age ($F(1,40)=5.0$) and between sex, drug and age ($F(1,40)=13.0$, $p<0.005$; Fig. 1B). The separate 2×2 ANOVAs revealed no significant effects in the young rats; however there was a significant effect of drug ($F(1,20)=5.6$, $p<0.05$) and a significant sex by drug interaction ($F(1,20)=11.4$, $p<0.005$) in the adult rats. Post-hoc *t*-tests revealed that saline-treated females drank significantly more water than PCP-treated females ($t(10)=3.5$, $p<0.01$). Repeated measures analyses revealed the same pattern of results as %-change analysis with no significant effects in young animals and significant effects of sex, drug, day×drug, and day×sex×drug in adult animals (Table 1).

3.1.3. Weight

A multivariate analysis revealed significant effects of age ($F(1,40)=5.3$, $p<0.05$) and drug ($F(1,40)=42.9$, $p<0.001$), and a significant interaction between sex and drug (($F(1,40)=4.4$, $p<0.05$; Fig. 1C).

3.2. Experiment 2: effects of PCP on elevated plus maze behavior

Two-way ANOVAs revealed significant effects of sex for total entries ($F(1,43)=6.1$, $p<0.05$), percent open entries ($F(1,43)=9.6$, $p<0.005$), percent open time ($F(1,43)=10.9$, $p<0.005$), percent closed entries ($F(1,43)=5.4$, $p<0.05$), percent closed time ($F(1,43)=10.5$, $p<0.005$), and number of rears ($F(1,43)=7.1$, $p<0.05$; Fig. 2). Significant sex×drug interaction effects were observed for percent open entries ($F(1,43)=10.3$, $p<0.005$), percent open time ($F(1,43)=6.7$, $p<0.05$), percent closed entries ($F(1,43)=7.5$, $p<0.05$) and percent closed time ($F(1,43)=5.6$, $p<0.05$). In addition, there was a trend towards significant sex×drug interaction for total entries ($F(1,43)=3.9$, $p=0.054$). There were no significant differences in the percent center entries or center time. Post-hoc *t*-tests revealed significant differences between PCP-treated males and females for total entries ($t(22)=3.2$, $p<0.005$), percent open entries ($t(22)=5.2$, $p<0.001$), percent open time ($t(22)=4.3$, $p<0.001$), percent closed entries ($t(22)=3.1$, $p<0.01$), and percent closed time ($t(22)=4.2$, $p<0.001$). There were no significant differences between saline-treated males and females. Finally, PCP-treated males had a significantly higher percentage of closed arm time than saline-treated females ($p<0.005$; Fig. 2).

Table 1
Sucrose and water consumptions for young adult and adult animals during pretreatment (sucrose: average of Day 5 and Day 6 consumptions, water: Day 6 consumption) and post-treatment. Repeated measures ANOVAs revealed significant effects ($p<0.05$) shown in the table.

	Male-SAL	Male-PCP	Female-SAL	Female-PCP
Young (P66)				
Pretreatment sucrose (ml)	22.3±1.8	25.9±3.1	17.6±3.0	15.2±2.4
Post-treament sucrose (ml)	23.0±1.2	19.2±1.0	17.2±1.2	17.3±2.1
Sex: F(1,20)=25.9, day×sex: F(1,20)=5.2, day×sex×drug: F(1,20)=8.8				
Pretreatment water (ml)	36.5±3.6	37.2±3.6	34.0±6.2	24.0±2.9
Post-treatment water (ml)	34.0±2.1	32.5±4.7	31.8±4.7	27.7±2.9
Adult (P109)				
Pretreatment sucrose (ml)	24.5±4.1	29.9±4.2	17.1±3.6	22.6±1.6
Post-treatment sucrose (ml)	26.8±3.7	21.5±1.8	18.8±1.5	15.5±1.2
Sex: F(1,20)=10.4, day: F(1,20)=18.3, day×PCP: F(1,20)=54.0				
Pretreatment water (ml)	44.8±2.9	38.8±2.5	27.0±1.9	29.5±1.9
Post-treatment water (ml)	37.3±2.3	34.2±1.8	31.2±2.1	18.8±1.8
Sex: F(1,20)=50.7, day: F(1,20)=11.5, drug (F(1,20)=7.5, day×drug: F(1,20)=4.7, day×sex×drug: F(1,20)=10.7				

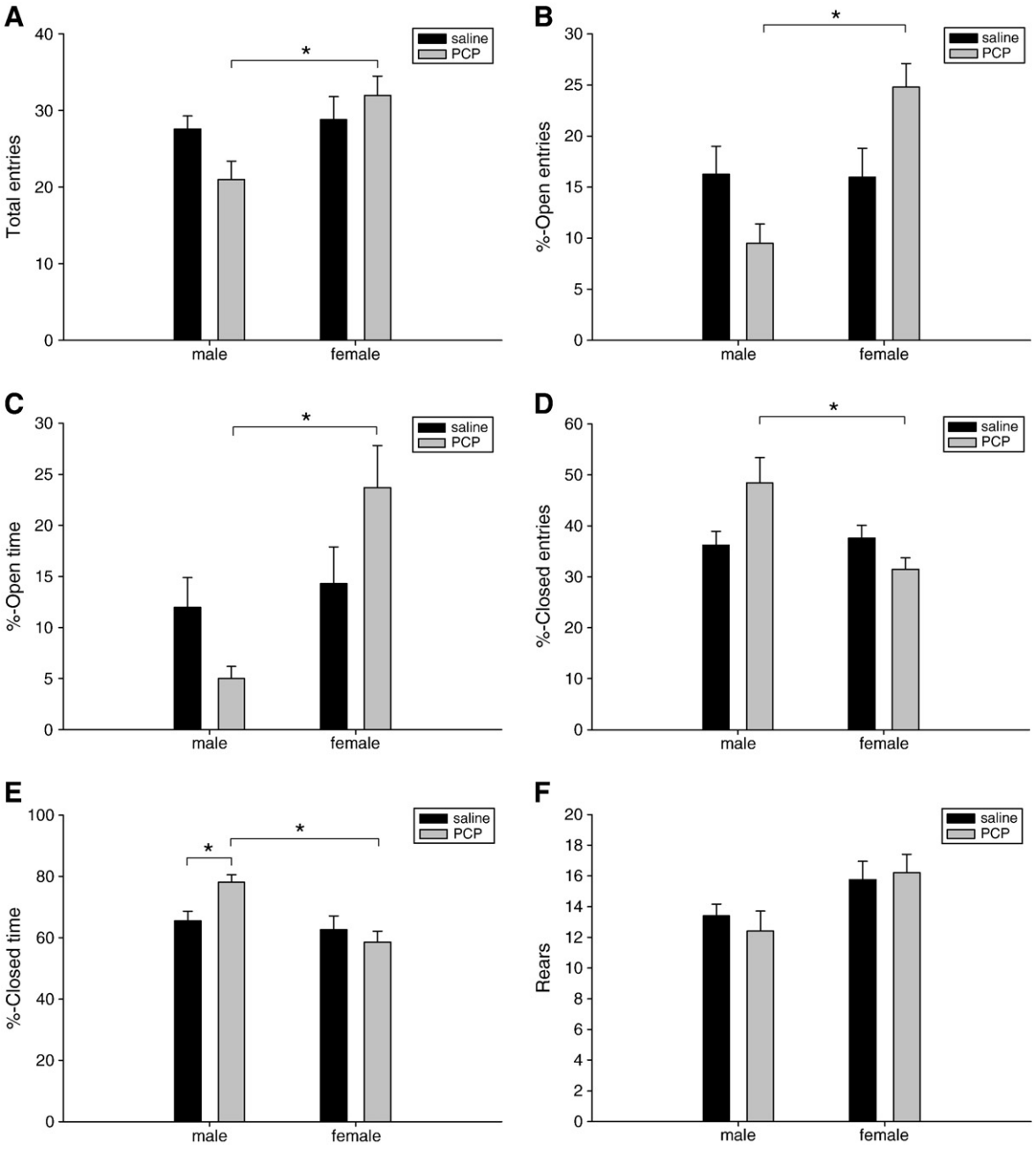

Fig. 2. PCP-treated males had fewer total entries (A), percent open entries (B) and percent open time (C), and more percent closed entries (D) and percent closed time (E) than PCP-treated females. Significant sex (male, female) by drug (saline, PCP) interaction effects were observed for measures B–E. PCP did not affect rearing behavior; however, females exhibited more rears than males (F). $^{*}p < 0.0125$, student's t-test.

4. Discussion

In young animals, PCP decreased sucrose consumption in males but not in females. In adults, PCP decreased sucrose consumption similarly in males and females; however, the effect in males was selective to sucrose whereas PCP also decreased water consumption in females. Generally, these data support an age and sex dependent effect of PCP on sucrose consumption, consistent with the observation that the onset of schizophrenic symptoms is later in females than males and that negative symptoms are more pronounced in males.

Given the observation that PCP induces anxiety in males reported in Experiment 2, the possibility that the sex difference in sucrose consumption is related to anxiety rather than anhedonia needs to be considered. However, repeated treatment with PCP (10 mg/kg for 14 days) did not produce a change in EPM behavior (unpublished data), suggesting that the effect of PCP on anxiety requires time to develop. In addition, PCP decreased anxiety in females and adult females also showed decreases in sucrose consumption, although this effect was not selective (see below). These observations, combined with previous effects of PCP noted on ICSS (Spielewoy and Markou, 2003), while not eliminating the possibility that sex differences in anxiety might play a role in sucrose consumption, support the suggestion that the effect of PCP on sucrose consumption reflects alterations in reward function.

The observation that the effect of PCP in adult females was not selective to sucrose consumption suggests that the effect of PCP may not simply reflect a decrease in reward function but may be related to a generalized decrease in fluid consumption. Should PCP be having a generalized effect on appetite, water consumption might be expected to follow from a decrease in chow consumption, which was not

measured. Fotlin (1989) reported that PCP decreased food consumption in male baboons for 8 h following administration, but that animals compensated for the decrease leading to no difference in consumption at 22 h; however, females were not assessed. Given the slower metabolism of PCP in females (see below), it is possible that the initial anorexic effect of PCP lasted longer in females and therefore lead to overall decreases in both sucrose and water intake. This possibility is consistent with the slightly greater weight loss in PCP-treated females versus males indicated by the significant sex x drug interaction effect. Thus while PCP does appear to have a similar effect on sucrose consumption in adult males and females, the effect in females may reflect a generalized anorexic effect rather than a specific effect on reward function.

It should be noted that sucrose and water consumption were not evaluated over the same time period. In order to evaluate water consumption over a 30 min period, animals would need to be water deprived. Prior data from our lab indicate that, while PCP does decrease sucrose consumption under conditions of deprivation, there are insignificant decreases in water consumption as well (Turgeon and Hoge, 2003). Given that water could be considered a rewarding stimulus under conditions of deprivation, it is difficult to interpret the selectivity of the effects of PCP on rewarding stimuli under deprivation conditions, leading to the present method of evaluation. The selectivity of the effect of PCP to rewarding stimuli is supported by recent data using microstructure analysis which demonstrated that the effect of PCP on brief access licking was limited to sucrose but not water or bitter quinine solutions (Baird et al., 2008).

A number of previous studies have examined sex differences in the effects of PCP. Females have been found to have greater behavioral sensitivity to acute PCP (Nabeshima et al., 1984a,b) and MK-801 (Honack and Loscher, 1993), as well as chronic infusions of PCP (Wessinger, 1995). These differences in the response to the acute effects of PCP may be due to sex differences in the pharmacokinetics of PCP as PCP has a longer half life in females, thought to be due to decreased metabolism (Shelnutt et al., 1999). However, Rasmussen et al. (2007) reported that males are slightly more susceptible to the effects of withdrawal from PCP on prepulse inhibition, a model for attentional deficits associated with schizophrenia. Male animals treated with a single injection of 10 mg/kg PCP at P45 and tested one week later demonstrated significantly reduced PPI whereas females showed an insignificant trend in the same direction. These results are consistent with our observation that PCP decreases sucrose consumption in males but not females at a young age. Withdrawal from higher doses of PCP has been argued to more accurately model schizophrenia than acute PCP (Jentsch and Roth, 1999). The finding that sex differences in schizophrenia-like behaviors seen following withdrawal from PCP mirrors the pattern of sex differences seen in human schizophrenics supports this notion.

The data from Experiment 2 demonstrate that prior exposure to a single dose of PCP produces long-lasting sexually dimorphic effects in elevated plus maze behavior. The observation that PCP-treated females showed greater open arm exploration and less closed arm exploration while males showed less open arm exploration and greater closed arm exploration indicates that PCP produces anxiolytic effects in females and anxiogenic effects in males. These findings are in agreement with those of Audet et al. (2007) who reported PCP-induced increases in anxiety in males one week after the cessation of treatment with 5 mg/kg bid for 7 days. In addition, our data suggest that this effect is quite long lasting, requires only a single exposure to PCP, and is sexually dimorphic.

The relevance of this finding to the PCP model of schizophrenia is not clear. Anxiety is not generally thought of as a diagnostic criterion for schizophrenia (Audet et al., 2007). However, Audet et al. (2007), suggest that PCP-induced increases in anxiety may reflect distorted emotional processing seen in schizophrenia. The clinical literature supports sexually dimorphic affective dysregulation in schizophrenia (Goldstein, 2006). To the extent that altered behavior in the EPM reflects the emotional disturbances characteristic of schizophrenia, the observation that PCP produces sexually dimorphic effects in the EPM is consistent with the clinical literature.

In addition to producing sex dependent effects on open versus closed arm exploration, PCP produced sexually dimorphic effects on the number of total arm entries, suggesting that PCP increased locomotor activation and/or exploration in females and decreased these measures in males. Withdrawal from PCP has been shown to increase (Jentsch et al., 1998) and decrease (Abdel-Naby Sayed et al., 2001; Turgeon et al., 2007) exploration of a novel environment in males. The current findings are consistent with PCP-induced decreases in males and suggest an opposite effect in females. These data are also consistent with prior data from our lab indicating that 10 mg/kg/day PCP for 14 days decreased total entries in males 24 h following the last injection (unpublished data). These PCP-induced differences in locomotion/exploration may reflect anxiety as well. Increases in line crossing have been associated with increased anxiety as assessed with an elevated plus maze (Butterweck et al., 2003) and rats bred for high anxiety exhibit decreased distance traveled in an open field (Liebsch et al., 1998). The observation that sex, but not PCP, had an effect on rearing suggests that rearing and total entries represent different aspects of locomotion/exploration. The current data are consistent with a sex difference in the number of rears in response to a novel environment (Gregory and Liebelt, 1967) as well as the absence of an effect of a single dose of PCP on rearing in males in an open field after a 24 h withdrawal (Turgeon et al., 2007).

With the exception of rearing, no sex differences were observed in the saline pretreated animals. Prior studies examining baseline sex differences in anxiety behaviors have produced mixed results. Lucion et al. (1996) reported that females exhibited a higher percentage of open arm entries than males and that this difference was dependent on perinatal testosterone exposure. Johnston and File (1991) found a similar sex difference in elevated plus maze behavior, but found that other tests produced evidence for greater anxiety in females. However, not all studies have found sex differences in EPM behavior (Steenbergen et al., 1990). Imhof et al. (1993) reported that females demonstrate less anxiety-like behavior at 45 and 90 days, but not at 120 and 150 days; thus the discrepancy in the literature may result from the use of animals of different ages. The animals in the present study were between 102 and 180 days at the time of testing, placing them largely above the range in which Imhof et al. (1993) observed sexually dimorphic effects. Thus our findings support an absence of sex differences in elevated plus maze behavior in adult animals.

The results of these two experiments establish sex differences in the susceptibility to PCP-induced behaviors in rats. The greater effect of PCP on sucrose consumption in males is consistent with human data suggesting that males are more likely to suffer from negative symptoms of schizophrenia such as anhedonia. The differential effect of PCP on EPM behavior is a bit more difficult to interpret; however, to the extent that altered EPM behavior reflects altered emotionality seen in schizophrenia, these data are consistent with a sexually dimorphic pattern of emotional disturbance. While the etiology of these sex differences remains to be determined, human studies have supported activational levels of gonadal hormones as a possible explanation for these sex differences (Seeman and Lang, 1990). In addition, sex differences in the hypothalamic pituitary–adrenal axis and other emotion-processing brain regions which are susceptible to organizational effects of gonadal hormones may be involved (Goldstein, 2006). Future studies will need to determine the role of gonadal hormones in the sexually dimorphic effects of PCP on these behaviors.

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