Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 76 (2003) 393–400
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Prior exposure to phencyclidine decreases voluntary sucrose consumption and operant performance for food reward

Sarah M. Turgeon[a,b,*], Stephen G. Hoge[b]

[a]Department of Psychology, Amherst College, Amherst, MA 01002, USA
[b]Neuroscience Program, Amherst College, Amherst, MA 01002, USA

Received 20 June 2003; received in revised form 28 July 2003; accepted 17 August 2003

Abstract

Prior exposure to the psychotomimetic drug phencyclidine (PCP) produces a number of schizophrenia-like behaviors in animals. The goal of the present study was to determine whether prior exposure to PCP produces decreased reward function, thereby modeling one aspect of negative schizophrenic symptomatology. To this aim, the consequences of prior exposure to PCP were assessed on two types of appetitive consumptive behavior. In the first set of experiments, the effects of PCP (15 mg/kg, 20 h before testing) on sucrose consumption were tested for three consecutive days under conditions of deprivation and nondeprivation. In the deprivation condition, animals were water deprived for 4 h prior to injection of PCP or saline (SAL). Twenty hours following the injection (24 h after the onset of water deprivation), animals were allowed access to either 5% sucrose or water for 30 min. In the nondeprivation condition, 5% sucrose consumption was measured for 30 min, 20 h after PCP or SAL injection and water consumption was measured during the 23.5 h preceding sucrose consumption. PCP decreased both sucrose and water consumption under deprivation conditions on the second and third day of testing but selectively decreased sucrose consumption under nondeprivation conditions on all three testing days. LiCl (50 mg/kg, 20 h before testing) did not significantly reduce sucrose consumption in the nondeprivation paradigm, indicating that the effect of PCP was not due to conditioned taste aversion. In the second experiment, PCP (15 mg/kg, 20 h before testing) decreased operant performance when animals were switched from a continuous reinforcement schedule of food delivery to a fixed ratio (FR4) schedule. Apomorphine (APO, 30 μg/kg, 30 min before testing), a positive control, induced a similar performance deficit. However, the PCP-induced deficit was not apparent until the third day of FR4 testing while the APO deficit was apparent on the first day. The effects of PCP on sucrose consumption demonstrate PCP-induced decreases in reward function. However, the delayed appearance of the PCP-induced decrease in operant performance suggests that these results may be better explained by a PCP-induced attentional deficit, also characteristic of schizophrenic psychopathology.

Keywords: Apomorphine; Anhedonia; Latent inhibition; Phencyclidine; Reward; Schizophrenia

1. Introduction

Phencyclidine (PCP) is a dissociative anesthetic that produces psychotomimetic symptoms in humans (Bakker and Amini, 1961; Allen and Young, 1978) and has been investigated for its usefulness in modeling the schizophrenic condition in animals (Javitt and Zukin, 1991; Jentsch and Roth, 1999). One of the reasons why PCP is touted as a good pharmacological model for schizophrenia is its ability to produce both positive and negative symptoms in humans (Javitt and Zukin, 1991). However, modeling the negative symptoms of schizophrenia in animals has proven to be somewhat difficult (Ellenbroek and Cools, 2000). Among the negative symptoms of schizophrenia is anhedonia, or a decrease in the experience of reward. A recent review of animal models of the negative symptoms of schizophrenia cited previous data from our lab as evidence that PCP does not produce anhedonia (Ellenbroek and Cools, 2000). In the context of a latent inhibition study, we demonstrated that prior exposure to PCP did not produce a decrease in sucrose preference 44 h after the last dose (Turgeon et al., 1998). However, reanalysis of these data suggested that PCP might decrease sucrose consumption 20 h following administration. In addition, a recent study reported elevated self-stimulation reward thresholds in animals following with-

* Corresponding author. Department of Psychology, Amherst College, P.O. Box 5000, Campus Box 2236, Amherst, MA 01002, USA. Tel.: +1-413-542-2625; fax: +1-413-542-2145.
E-mail address: smturgeon@amherst.edu (S.M. Turgeon).

0091-3057/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2003.08.019

drawal from acute (5 or 10 mg/kg) or chronic (10, 15, or 20 mg/kg/day for 14 days via osmotic minipump) PCP (Spielewoy and Markou, 2003), suggesting that prior exposure to PCP produces a decrease in reward function. Thus, the goal of the current study was to investigate the hypothesis that prior exposure to PCP produces behavioral changes reflective of decreased reward function.

A number of authors have relied upon decreases in sucrose consumption as an indicator of the presence of anhedonia (Papp and Moryl, 1994; Papp et al., 1991; Willner et al., 1994; Przegalinski et al., 1995; Zurita and Molina, 1999; Zurita et al., 1996, 2000; Sammut et al., 2001). In light of recent evidence suggesting PCP withdrawal-induced decreases in reward function (Spielewoy and Markou, 2003), the first set of experiments (Experiment 1) investigated the prediction that PCP would produce a decrease in voluntary sucrose consumption. In the first experiment, the effects of PCP on sucrose and water consumption were assessed separately under conditions of water deprivation. However, given the concern that water itself might be considered rewarding under deprivation conditions, the second experiment investigated the effects of PCP on sucrose and water consumption in nondeprived animals. In addition, a third experiment was conducted in which the effects of lithium chloride (LiCl) were assessed in the nondeprivation paradigm in order to rule out the possibility that PCP could be producing conditioned taste aversion (CTA) in this paradigm.

Drug-induced changes in operant responding for food reward have also been argued to represent an animal model for anhedonia (Carnoy et al., 1986a; Ellenbroek and Cools, 2000). In an attempt to investigate the ability for changes in dopaminergic transmission to produce negative schizophrenic symptomatology, Carnoy et al. (1986a) found that low doses of apomorphine (APO) induced a performance deficit when animals were switched from a continuous reinforcement schedule of food delivery to a fixed ratio (FR4) schedule. Given the hypothesis that prior exposure to PCP produces a decrease in reward function, Experiment 2 tested the prediction that prior exposure to PCP would produce a performance deficit similar to that seen following APO.

2. Experiment 1: The effects of PCP on voluntary sucrose intake

2.1. Methods

Animals for all experiments were male Sprague–Dawley rats (Charles River, Wilmington, MA). Animals arrived in the facility at least 5 days before experiments began, were housed individually, and were maintained on a 12-h reverse dark–light cycle (dark from 6:00 a.m. to 6:00 p.m.). All procedures were approved by the Amherst College Institutional Animal Use and Care Committee.

2.1.1. Experiment 1a: Effect of PCP on sucrose consumption in water-deprived rats

Twenty-four Sprague–Dawley rats were used Experiment 1a. All experiments were conducted in the home cage and all solutions were presented in graduated water bottles, which differed slightly from the usual water bottles in that they had longer spouts. On the first day of the experiment, animals were water deprived and only allowed access to water during the course of the experiment. Four hours after the onset of water deprivation, rats were injected with either PCP (15 mg/kg in 2 ml/kg saline [SAL], ip) or SAL (2 ml/kg, ip). On Day 2, 24 h after the onset of water deprivation (20 h postinjection), rats were given access to either 50 ml of a 5% sucrose solution (SUC) or 50 ml of tap water (H_2O) for 30 min such that four groups were generated: SAL–H_2O, SAL–SUC, PCP–H_2O, and PCP–SUC ($n=6$ per group). Rats were again injected with PCP or SAL 3.5 h after the end of the drinking session and then drinking was monitored 20 h postinjection (Day 3). Rats were injected again on Day 3 and drinking was monitored on Day 4. Daily consumption as a function of weight (ml/kg) was compared with a $2\times2\times3$ repeated-measures ANOVA with drug (PCP vs. SAL) and drink (H_2O vs. SUC) as between-subjects variables and day as the within-subjects variable. In order to examine drinking between groups on individual days, one-way ANOVAs were conducted with post hoc Student–Newman–Keuls tests.

2.1.2. Experiment 1b: Effect of PCP on sucrose consumption in nondeprived rats

Sixteen Sprague–Dawley rats were used in Experiment 1b. These included the six animals from Experiment 2a that received neither PCP nor sucrose (the SAL–H_2O group) evenly distributed between groups. Rats were allowed access to food and water ad lib throughout the experiment. Rats were trained to drink sucrose by replacing water bottles with sucrose for 30 min on at least three of the 7 days prior to the onset of the experiment. Two animals failed to drink sucrose and one animal knocked out his water bottle on Day 3 of the experiment and were thus excluded from the experiment.

On Day 1 of the experiment, animals were given access to 5% sucrose for 30 min (10:30–11:00 a.m.) and then sucrose bottles were replaced by water bottles (11:00 a.m.). On Day 2 of the experiment, rats were weighed and water consumption for the past 23.5 h was recorded at 10:30 a.m. Animals were then given access to sucrose for 30 min and consumption was recorded. Four hours after the end of the sucrose session (3:00 p.m.) on Day 2, rats were injected with either PCP (15 mg/kg in 2 ml/kg SAL, ip; $n=7$) or SAL (2 ml/kg, ip; $n=6$). On Days 3 and 4, 23.5 h water consumption and 30 min sucrose consumption were recorded and rats were again injected at 3:00 pm. On Day 5, 23.5 h water consumption and 30 min sucrose consumption were recorded. Daily consumption as a function of weight (ml/kg) is reported as a %-Day 2 consumption (prior to drug exposure).

Sucrose and water consumption were compared using separate repeated-measures ANOVAs with drug (PCP vs. SAL) as the between-subjects variable and day as the within-subjects variable. *T* tests were used to examine the effects of PCP on daily sucrose and water consumption.

2.1.3. Experiment 1c: Effect of LiCl on sucrose consumption

In order to ensure that PCP-induced taste aversion was not a plausible explanation for the decrease in sucrose consumption, the methods employed in Experiment 2b were repeated replacing PCP with 50 mg/kg LiCl, which should produce powerful CTA if conditioning was possible in this protocol (Parker, 1995; Turgeon et al., 1998). Ten rats were used in this experiment; one LiCl rat knocked his water bottle out on Day 1 and was thus excluded. As in Experiment 2b, rats were given access to 5% sucrose for 30 min on three occasions prior to the onset of the experiment. On Day 1 of the experiment, animals were given access to 5% sucrose for 30 min (10:30–11:00 a.m.) and then sucrose bottles were replaced by water bottles (11:00 a.m.). On Day 2, rats were weighed and water consumption for the past 23.5 h was recorded at 10:30 a.m. Animals were then given access to sucrose for 30 min and consumption was recorded. Four hours after the end of the sucrose session (3:00 p.m.) on Day 2, rats were injected with either LiCl (50 mg/kg in 10 ml/kg dH_2O, ip; $n=4$) or dH_2O (10 ml/kg, ip; $n=5$). On Day 3, 23.5 h water consumption and 30 min sucrose consumption were recorded. Days 4 and 5 were not tested as the need to subject the rats to further LiCl-induced malaise was deemed unnecessary. A *t* test was performed on Day 3 consumption (ml/kg) as a percentage of Day 2 consumption.

As a positive control for the effects of the LiCl, six additional rats were tested for LiCl-induced CTA. Immediately following their first exposure to sucrose (Day 1), rats were injected with either LiCl (50 mg/kg in 10 ml/kg dH_2O, ip; $n=3$) or dH_2O (10 ml/kg, ip; $n=3$) and sucrose consumption was tested 24 h later (Day 2). A *t* test was performed on Day 2 consumption (ml/kg) as a percentage of Day 1 consumption.

2.2. Results

2.2.1. Experiment 1a: Effect of PCP on sucrose consumption in water-deprived rats

A repeated-measures ANOVA revealed a significant effect of Day [$F(2,40)=35.9$, $P<.001$] and Drug [$F(1,20)=12.4$, $P<.005$], but not of Drink (Fig. 1). There were significant interaction effects of Day × Drink [$F(2,40)=17.8$, $P<.001$] and Day × Drug [$F(2,40)=7.1$, $P<.005$], but not of Drink × Drug. In addition, the three-way interaction of Day × Drink × Drug was not significant.

One-way ANOVAs conducted on each day revealed significant group effects on all three days [Day 2: $F(3,20)=13.5$, $P<.001$; Day 3: $F(3,20)=5.2$, $P<.01$; Day 4: $F(3,20)=5.1$, $P<.01$]. Student–Newman–Keuls post hoc tests revealed that on Day 2, the SUC groups drank significantly less than the H_2O groups; on Days 3 and 4, SAL–SUC was significantly different from PCP–SUC, whereas SAL–H_2O was not significantly different from PCP–H_2O.

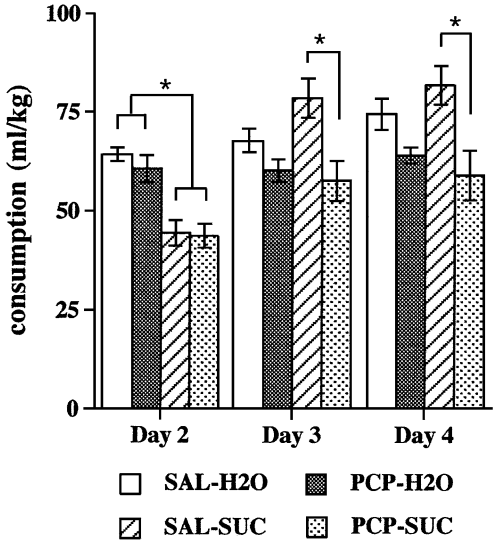

Fig. 1. Under conditions of water deprivation, animals offered 5% sucrose drank significantly less than animals offered water regardless of drug treatment on the first day of testing (Day 2). On the second and third days of testing, PCP (15 mg/kg, 20 h prior to testing) decreased sucrose consumption. However, a similar trend was observed for water consumption (see text). Data represent mean ± S.E.M. * $P<.05$.

2.2.2. Experiment 1b: Effect of PCP on sucrose consumption in nondeprived rats

Because sucrose and water were being measured over different time periods in the same animals, separate repeated-measures ANOVAs were run for sucrose and water consumption. For sucrose consumption, there were significant effects of Day [$F(2,22)=3.7$, $P<.05$] and Drug [$F(1,11)=20.23$, $P=.001$]. There was no significant Day × Drug interaction (Fig. 2a). For water consumption, there were no significant effects of Day, Drug, or Day × Drug (Fig. 2b). *T* tests conducted on individual days revealed a significant effect of PCP on sucrose consumption [Day 3: $t(11)=28.7$, $P<.005$; Day 4: $t(11)=4.1$, $P<.005$; Day 5: $t(11)=2.2$, $P<0.05$] but not water consumption [Day 3: $t(11)=-1.8$; Day 4: $t(11)=-0.8$; Day 5: $t(11)=-0.8$] on each day.

In order to ensure that the water deprivation experienced by the six animals used from Experiment 1a did not skew the data, another repeated-measure analysis was performed with an additional between-subjects factor of experiment. There was no significant effect of experiment or Experiment × Drug for either water or sucrose consumption. Despite the absence of a significant effect of experiment, *t* tests were also run on daily consumption in non-naive versus naive animals. The only significant difference uncovered was for Day 3 sucrose consumption in SAL-treated

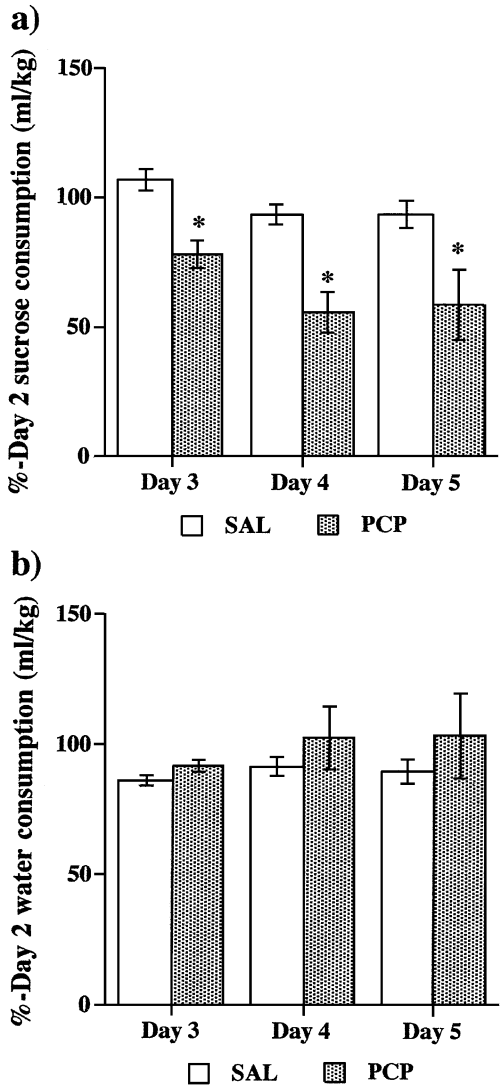

Fig. 2. Under nondeprived conditions, PCP (15 mg/kg, 20 h prior to testing) decreased 30-min sucrose consumption (a), but had no effect on 23.5 h water consumption (b). Data represent mean ± S.E.M. *$P < .05$ vs. SAL.

rats [naive = 114.8 ± 8.2; non-naive = 98.6 ± 1.3, $t(4) = -3.8$, $P < .05$]. However, the lower sucrose consumption in the non-naive animals would have led to an underestimation of the effect of PCP rather than an overestimation. In addition, despite the lower numbers, the difference in Day 3 sucrose consumption remained significant when analyzed in naive and non-naive groups separately [non-naive: $t(4) = 5.9$, $P < .005$; naive: $t(5) = 3.0$, $P < .05$]. Thus, the inclusion of animals used in Experiment 1a did not skew the results.

2.2.3. Experiment 1c: Effect of LiCl on sucrose consumption

LiCl was unable to produce a decrease in sucrose preference when administered in place of PCP [$t(7) = 1.3$; Fig. 3]. LiCl did induce CTA in the positive control. Animals treated with dH_2O drank 80.2 ± 17.5% of the sucrose consumed on the first day while animals treated with LiCl drank 6.7 ± 6.7% of the sucrose consumed on the first day [$t(4) = 3.92$, $P < .05$].

2.3. Discussion

In Experiment 1a, animals treated with PCP consumed less sucrose than animals treated with SAL. However, in any study that utilizes sucrose consumption as a measure of reward function, the results must indicate that the manipulation in question selectively decreases sucrose consumption without altering overall fluid consumption, so as to eliminate the possibility that the manipulation resulted in a motor deficit rather than a decrease in the rewarding properties of sucrose (Ellenbroek and Cools, 2000). While ANOVAs run on individual days in Experiment 1a indicate a significant effect of PCP on sucrose consumption in the absence a significant effect on water consumption, there was a clear trend toward PCP-induced decreases in water intake as well. In addition, the repeated-measures analysis did not reveal a significant Drug × Drink interaction, which would have been expected if there were an effect of PCP on sucrose consumption in the absence of an effect on water consumption. Thus, the results of this experiment do not convincingly demonstrate a selective PCP-induced decrease in sucrose consumption.

Under conditions of deprivation, both water and sucrose solutions have been shown to produce similar patterns of activation in certain populations of neurons within the nucleus accumbens (Roop et al., 2002). Thus, one possible explanation for the observed decreases in water and sucrose consumption in Experiment 1a is that both are rewarding to these animals and PCP induces a decrease in the reward value of both substances. In order to control for this possibility, Experiment 1b examined sucrose and water consumption in nondeprived animals.

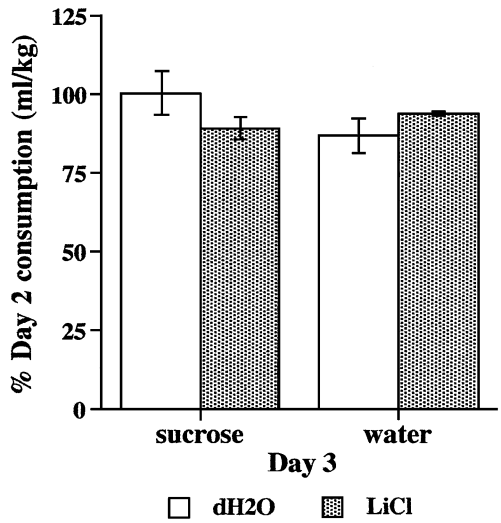

Fig. 3. Under nondeprived conditions, LiCl (50 mg/kg, 20 h prior to testing) failed to alter either sucrose or water consumption.

Experiment 1b revealed a significant effect of PCP on sucrose consumption but not water consumption in non-deprived animals. There was a small but significant effect of Day in the repeated-measures ANOVA for sucrose consumption, which appears to be driven by small overall decreases in consumption on Days 4 and 5. The reason for this decrease is not clear, but in the absence of a Drug × Day interaction, this result does not affect the interpretation of the effect of PCP.

The significant effects of Day in Experiment 1a appear to be driven by differences in drinking patterns on Day 2 as compared to Days 3 and 4. On Day 2, there was a significant effect of Drink as revealed in the significantly higher levels of consumption in the SAL–H_2O and PCP–H_2O groups as compared to the SAL–SUC and the PCP–SUC groups. However, the difference between SAL–SUC and PCP–SUC seen on Days 3 and 4 was not apparent. This effect is most likely due to the novelty of the sucrose solution on Day 2. Animals will drink less of a novel solution, presumably to avoid ingesting a harmful substance. However, another possible interpretation is that repeated exposure to PCP is required in order to see an effect on sucrose consumption. The first explanation seems to be the most likely as in Experiment 1b, where sucrose was not a novel stimulus, an effect of PCP was observed on the first day of testing.

In order to make the argument that the decrease in voluntary sucrose consumption reflects a decrease in the experience of reward, the possibility that PCP is inducing a CTA to sucrose needs to be ruled out. The 4-h gap between sucrose presentation and PCP injection was designed to reduce the likelihood of pairing between sucrose and PCP. However, in order to ensure that the PCP-induced decrease observed here was not due to a conditioned response, the effect of LiCl on sucrose consumption was tested. The dose of LiCl tested has been shown to produce profound CTA in this and other studies (Parker, 1995; Turgeon et al., 1998) when administered immediately following sucrose exposure in sucrose-naive animals. LiCl was unable to decrease sucrose consumption in this paradigm. Thus, the 4-h time gap, in combination with prior unpaired sucrose exposures, prevents conditioning from taking place.

Parker (1995) reported that following repeated pairings with sucrose, PCP, like a number of other drugs of abuse, produces a decrease in sucrose preference. However, this decrease is not accompanied by the presence of aversive taste reactivity, suggesting that it does not represent sickness-induced CTA. The absence of LiCl-induced CTA in this paradigm, combined with the absence of aversive taste reactivity in animals receiving repeated pairings of sucrose with a higher dose of PCP (20 mg/kg) than that used in this study, suggest that the PCP-induced decrease in sucrose consumption observed here is not due to CTA. In addition, the observation that PCP can produce a decrease in sucrose consumption in the absence of conditioning suggests that perhaps Parker's finding that prior pairings between a number of drugs of abuse and sucrose produce decrease in sucrose preference results from drug withdrawal-induced decreased reward function rather than conditioning.

As mentioned in the Introduction, a previously reported absence of an effect of PCP on sucrose consumption during a test for PCP-induced CTA (Turgeon et al., 1998) was cited as evidence against PCP-induced anhedonia (Ellenbroek and Cools, 2000). However, this test of PCP-induced CTA was run 44 h after the last PCP injection, as opposed to the 20-h delay at which we see the decrease in sucrose consumption in the present experiment. The possibility that the effects of prior exposure to PCP on reward function might be short lived is consistent with the finding that PCP-induced elevations in self-stimulation reward threshold seen following a single dose of PCP are evident at 24 but not 48 h postinjection (Spielewoy and Markou, 2003).

3. Experiment 2: Effect of PCP on operant performance for food reward

3.1. Methods

Twenty-one animals were used in Experiment 2. They received free access to water throughout the experiment but had restricted access to food beginning 24 h prior to the first day of training such that they were maintained between 80% and 85% of their normal body weight.

Training and testing were conducted in an operant chamber (21 × 30 × 21 cm; Lafayette Instruments, Lafayette, IN) centered in a black-walled testing room with red lighting. The chamber had a food receptacle centered on one wall 4 cm above the floor and a lever requiring 12 g of force to operate to the left of the receptacle. Rewards were 45 mg Noyes pellets. Animals were trained on a continuous reinforcement schedule of pellet delivery, receiving one pellet for every bar press, for 15 min a day for 14 days. Animals that had not acquired the continuous reinforcement response by the sixth day of training were trained by the experimenter on the seventh day. In all animals, a constant number of rewards (approximately 150 rewards/15 min session) was obtained for the last 4 days of training. Following 14 days of continuous reinforcement, animals were switched to a fixed ratio (FR4) schedule of reinforcement, receiving one pellet for every four bar pressess, and were tested under these conditions for 4 days.

Animals were injected with 15 mg/kg PCP ($n = 6$) in SAL (2 ml/kg, ip) 20 h before each FR4 session or 30 μg/kg APO ($n = 6$) in dH_2O (1 ml/kg, sc) 15 min before each FR4 session. Vehicle controls (VEH; $n = 9$) were injected with either SAL (2 ml/kg, ip) 20 h prior to FR4 sessions or dH_2O (1 ml/kg, sc) 15 min prior to FR4 sessions. No differences were observed between control groups so they were combined.

Comparisons between the performance of different groups over the 4-day FR4 testing period were made with

repeated-measures ANOVAs. Comparisons of the number of rewards obtained during 15-min training sessions between groups on individual days were made with one-way ANOVAs with post hoc Student–Newman–Keuls tests.

3.2. Results

There was no significant difference in the number of rewards obtained on Day 14 of continuous reinforcement training among different treatment groups (VEH = 150.2 ± 9.8, APO = 149.2 ± 11.3, PCP = 148.5 ± 13.4). During the 4 days of FR4 testing, a repeated-measures ANOVA revealed a significant effect of Group [$F(2,18) = 10.48$, $P < .005$] but not of Day or Day × Group. One-way ANOVAs conducted for each day revealed a significant effect of Group on each day [Day 1: $F(2,18) = 10.71$; Day 2: $F(2,18) = 5.56$; Day 3: $F(2,18) = 6.66$; Day 4: $F(2,18) = 5.65$]. Student–Newman–Keuls post hoc tests revealed significant differences between APO versus VEH and PCP on Day 1, APO versus VEH on Day 2, and APO and PCP versus VEH on Days 3 and 4 (Fig. 4).

3.3. Discussion

In this experiment, the effects of APO were assessed as a positive control for the procedure. The observation that APO produces a performance deficit replicates the findings of Carnoy et al. (1986a). Prior exposure to PCP was found to produce a similar performance deficit; however, the APO-induced deficit appeared on all four test days while the PCP-induced deficit did not appear until the third and fourth days of testing.

A variety of possible explanations for the observed PCP-induced performance deficit need to be considered. The effect of prior exposure to PCP could induce motor impairments that interfere with the animals' ability to respond under FR4 conditions. However, this explanation seems unlikely since Okuyama et al. (1995) reported no change in swimming ability, posture, or speed 24 h after 15 mg/kg PCP. Similarly, Haggerty et al. (1984) reported no effect on motor performance in a variety of tasks 12 to 16 h after PCP administration at doses up to 54.4 mg/kg. In addition, while there was a decrease in the number of rewards obtained following the switch from continuous reinforcement to FR4, the number of bar presses increased, suggesting that motor performance was not compromised by PCP. PCP could also be inducing appetite suppression that could interfere with performance. However, this seems unlikely as Fotlin (1989) found that overall food consumption was unchanged for a 24-h period following PCP treatment in baboons. In addition, PCP has not been found to interfere with memory of previously learned tasks (Handelmann et al., 1987), a result that seems to be mirrored in our study by the increase in bar pressing following the switch from continuous reinforcement to FR4 and the absence of an effect of PCP on Day 1 performance.

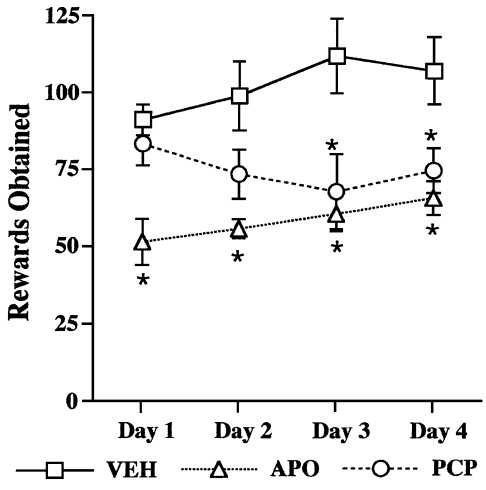

Fig. 4. Both APO (30 μg/kg, 15 min prior to testing) and PCP (15 mg/kg, 20 h prior to testing) produce a performance deficit during 4 days of an FR4 schedule of reinforcement following a switch from a continuous reinforcement schedule of reinforcement. The APO deficit was observed on all 4 days, while the PCP deficit was only significant on Days 3 and 4. Data represent mean ± S.E.M. * $P < .05$ vs. VEH.

Withdrawal from chronic PCP has been shown to decrease operant responding in both primates (0.05 mg/kg/h for 10 days; Slifer et al., 1984) and rodents (0.05 mg/kg/h for 10 days; Beardsley and Balster, 1987) (5.6, 10, or 17.8 mg/kg/day; Wessinger and Owens, 1991), which recovers upon reinstatement of PCP (Slifer et al., 1984; Beardsley and Balster, 1987). This decrease in operant responding has been argued to be indicative of behavioral dependence, defined as a state in which behavioral disruptions occur following withdrawal from chronic drug treatment. While these studies used chronic administration and higher cumulative doses, the effects of prior exposure to PCP on operant responding observed here could reflect similar processes. However, the decrease in responding seen following withdrawal from chronic PCP was apparent 6–12 h (Beardsley and Balster, 1987) or 24 h (Wessinger and Owens, 1991) after withdrawal. We did not observe an effect of PCP until the third day of testing, indicating that withdrawal from the single dose used here does not produce evidence of behavioral dependence. In addition, chronic (10 or 17.8 mg/kg/day for 10 days) PCP produced an initial decrease in operant responding on the first 3 days of treatment which recovered by the fourth day (Wessinger and Owens, 1991). The opposite pattern was observed here as the PCP-induced deficit was not seen until Day 3 and no recovery was evident on Day 4. However, given that the prior study used chronic infusion, these animals were currently receiving drug, whereas ours had not received a dose for 24 h. While the different methods of drug administration make comparison between the studies difficult, the pattern of the PCP-induced deficit seen here argues against behavioral dependence as an explanation.

Finally, PCP could be producing an attentional deficit that might be responsible for the observed behavioral

effect. As suggested as a possible explanation for the APO-induced deficit observed by Carnoy et al. (1986b), if PCP decreases the animals' ability to ignore the fact that three out of four presses are not being rewarded during the FR4 trials, they may decrease their level of response. Prior exposure to PCP has been shown to disrupt latent inhibition (Turgeon et al., 1998), a phenomenon whereby previous experience with a stimulus retards subsequent conditioning of that stimulus. A person or animal displaying disrupted latent inhibition will acquire a conditioned response to a stimulus which has been previously presented without consequence more easily than an individual with intact latent inhibition. In other words, individuals with disrupted latent inhibition switch too quickly from the old contingency of stimulus irrelevance to the new contingency of stimulus relevance (Weiner, 1990). The effect of PCP in the current experiment could be explained by a similar type of disruption; animals that have been trained on a continuous reinforcement schedule, upon being switched to an FR4 schedule, may attend to the association between bar pressing and *not* getting reward (three out of four times) more quickly than control animals and thus experience a mild extinction. The observation that the PCP-induced deficit did not appear until the third day of testing seems consistent with this explanation; a number of trials may be required to produce the hypothesized extinction.

4. General discussion

Taken together, these results support recent evidence that prior exposure to PCP is able to produce behaviors that model the schizophrenic state. The results of the first set of experiments clearly support the presence of PCP-induced decreased reward function and are thus in agreement with the recent results of Spielewoy and Markou (2003). Decreased reward function could conceivably contribute to the PCP-induced performance deficit observed in the second experiment; however, a more likely explanation for the deficit involves a PCP-induced attentional deficit similar to impaired latent inhibition. The results of Experiment 1b indicate that PCP can produce a decrease in sucrose consumption on the first day of testing, suggesting that the deficit observed in Experiment 2, which did not appear until the third day of testing, may not have resulted from PCP-induced decreases in reward function. The delayed appearance of the PCP-induced deficit in Experiment 2 is consistent with the argument that PCP produces an attentional deficit that leads to a gradual extinction of the response. Such attentional deficits also characterize schizophrenia; disruption of latent inhibition has been demonstrated to be present in certain subgroups of schizophrenic patients (Baruch et al., 1998; Gray et al., 1992; but see Swerdlow et al., 1996). Therefore, the PCP-induced deficit observed in Experiment 2 may reflect the induction of cognitive changes resembling those seen in schizophrenia.

PCP is a noncompetitive antagonist at the glutamate *N*-methyl-D-aspartate (NMDA) receptor (Anis et al., 1983; Javitt and Zukin, 1991), as well as a sigma receptor agonist (Sonders et al., 1988). The NMDA receptor antagonist MK-801 has been found to reverse stress-induced decreases in sucrose consumption (Papp and Moryl, 1994). This observation is consistent with evidence suggesting that acute PCP produces decreases in reward threshold (Carlezon and Wise, 1993; Spielewoy and Markou, 2003). In addition, rats will bar press for intracranial administrations of either PCP or MK-801, an effect that appears to be independent of any dopamine agonist action of PCP as it is not blocked by sulpiride (Carlezon and Wise, 1996b). Intracranial administration of MK-801 has also been shown to mimic PCP-induced potentiation of reward following lateral hypothalamic stimulation (Carlezon and Wise, 1996a). Taken together, these results suggest that PCP's action as an NMDA receptor antagonist is involved in the rewarding effects of acute PCP. However, it remains to be determined whether PCP's action as an NMDA receptor antagonist is responsible for the effects of prior exposure to PCP on sucrose consumption.

It has been suggested that the anhedonia associated with schizophrenia may be similar neurobiologically to anhedonia associated with depression (Markou and Kenny, 2002). In an attempt to examine depression-related decreases in reward function, a number of researchers have found that stress decreases sucrose consumption. While the precise mechanism is not clear, stress-induced decreases in sucrose consumption are reversed by low-dose AD treatment and have been found to involve opiates (Zurita and Molina, 1999; Zurita et al., 1996, 2000), DA (Willner et al., 1994), and 5HT (Przegalinski et al., 1995). Thus, PCP-induced decreases in sucrose consumption may involve changes in these systems as well.

Clearly, generalization from the observed decrease in sucrose consumption to the complex symptom of decreased reward function must be made with caution. Given the probability that the effect of PCP on operant performance reflects PCP-induced attentional deficits rather than decreased reward function, future studies need to verify the effects of PCP on reward function in a variety of behavioral procedures. However, while apparently reflecting different underlying processes, both of the present findings provide support for hypothesis that prior exposure to PCP produces behavioral changes that model the schizophrenic state.

References

Allen RM, Young SJ. Phencyclidine-induced psychosis. Am J Psychiatry 1978;135:1081–4.

Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-aspartate. Br J Pharmacol 1983; 79:565–75.

Bakker CB, Amini FB. Observations on the psychotomimetic effects of sernyl. Compr Psychiatry 1961;2:269–80.

Baruch I, Hemsley DR, Gray JA. Differential performance of acute and chronic schizophrenics in a latent inhibition task. J Nerv Ment Dis 1998;176:598–606.

Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther 1987;242:203–11.

Carlezon W, Wise R. Phencyclidine-induced potentiation of brain stimulation reward: acute effects are not altered by repeated administration. Psychophamacology 1993;111:208–402.

Carlezon W, Wise R. Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate medial forebrain bundle brain stimulation reward. Psychopharmacology 1996a;128:413–20.

Carlezon W, Wise R. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J Neurosci 1996b;16: 3112–22.

Carnoy P, Soubrie P, Puech AJ, Simon P. Performance deficit induced by low doses of dopamine agonists in rats: toward a model for approaching the neurobiology of negative schizophrenic symptomatology? Biol Psychiatry 1986a;21:11–22.

Carnoy P, Ravard S, Wemerman B, Soubrie P, Simon P. Behavioral deficits induced by low doses of apomorphine in rats: evidence for a motivational and cognitive dysfunction which discriminates among neuroleptic drugs. Pharmacol Biochem Behav 1986b;25:503–9.

Ellenbroek B, Cools A. Animal models for the negative symptoms of schizophrenia. Behav Pharmacol 2000;11:223–33.

Fotlin RW. Effects of anorectic drugs on the topography of feeding behavior in baboons. J Pharmacol Exp Ther 1989;249:101–9.

Gray NS, Hemsley DR, Gray JA. Abolition of latent inhibition in acute, but not chronic, schizophrenics. Neurol Psychiatry Brain Res 1992; 1:83–9.

Haggerty GC, Forney RB, Johnson JM. The effect of a single administration of phencyclidine on behavior in the rat over a 21-day period. Toxicol Appl Pharmacol 1984;75:444–53.

Handelmann GE, Contreras PC, O'Donohue TL. Selective memory impairment by phencyclidine in rats. Eur J Pharmacol 1987;140:69–73.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301–8.

Jentsch JD, Roth R. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1999;20:201–25.

Markou A, Kenny JP. Neuroadaptations to chronic exposure to drugs of abuse: relevance to depressive symptomatology seen across psychiatric diagnostic categories. Neurotoxicity Res 2002;4:297–313.

Okuyama S, Ogawa S, Nakazato A, Tomizawa K. Effect if NE-100, a novel sigma receptor ligand, on phencyclidine-induced delayed cognitive dysfunction in rats. Neurosci Lett 1995;189:60–2.

Papp M, Moryl E. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur J Phamacol 1994;263:1–7.

Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. Psychopharmacology 1991;104:255–9.

Parker LA. Rewarding drugs produce taste avoidance but not taste aversion. Neurosci Biobehav Rev 1995;19:143–51.

Przegalinski E, Moryl E, Papp M. The effect of 5HT1A receptor ligands in a chronic mild stress model of depression. Neuropharmacology 1995; 10:1305–10.

Roop R, Hollander J, Carelli R. Accumbens activity during a multiple schedule for water and sucrose reinforcement in rats. Synapse 2002; 43:223–6.

Sammut S, Goodall G, Muscat R. Acute interferon-α administration modulates sucrose consumption in the rat. Psychoneuroendocrinology 2001;26:261–72.

Slifer BL, Balster RL, Woolverton WL. Behavioral dependence produced by continuous phencyclidine infusion in rhesus monkeys. J Pharmacol Exp Ther 1984;230:399–406.

Sonders MS, Keana JFW, Weber E. Phencyclidine and psychotomimetic sigma opiates: recent insights into their biochemical and physiological sites of action. Trends Neurosci 1988;11:37–40.

Spielewoy C, Markou A. Withdrawal from chronic phencyclidine treatment induces long-lasting depression in brain reward function. Neuropsychopharmacology 2003;28:1106–16.

Swerdlow NR, Braff DL, Hartston H, Perry W, Geyer MA. Latent inhibition in schizophrenia. Schizophr Res 1996;20:91–103.

Turgeon SM, Auerbach AE, Heller MA. The delayed effects of phencyclidine (PCP) disrupt latent inhibition in a conditioned taste aversion paradigm. Pharmacol Biochem Behav 1998;60:553–8.

Weiner I. Neural substrates of latent inhibition: the switching model. Psychol Bull 1990;108:442–61.

Wessinger WD, Owens SM. Phencyclidine dependence: the relationship of dose and serum concentration to operant behavioral effects. J Pharmacol Exp Ther 1991;258:207–15.

Willner P, Lappas S, Cheeta S, Muscat R. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. Psychopharmacology 1994;115:454–62.

Zurita A, Molina V. Prior morphine facilitates the occurrence of immobility and anhedonia following stress. Physiol Behav 1999;65:833–7.

Zurita A, Murua S, Molina V. An endogenous opiate mechanism seems to be involved in stress-induced anhedonia. Eur J Pharmacol 1996;299:1–7.

Zurita A, Martijena I, Cuadra G, Brandao M, Molina V. Early exposure to chronic variable stress facilitates the occurrence of anhedonia and enhanced emotional reactions to novel stressors: reversal by naltrexone pretreatment. Behav Brain Res 2000;117:163–71.