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Differential effects of acute and subchronic clozapine and haloperidol on phencyclidine-induced decreases in voluntary sucrose consumption in rats

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Abstract

Prior exposure to the psychotomimetic drug phencyclidine (PCP) decreases voluntary sucrose consumption in rats. This may be indicative of reduced reward function, a phenomenon associated with negative schizophrenic symptomatology. Given that atypical antipsychotics have been shown to ameliorate negative symptoms of schizophrenia more effectively than typical neuroleptics, this effect should be reversed by clozapine but not haloperidol. PCP (15 mg/kg) or saline was administered 20 h prior to testing for voluntary sucrose consumption in non-deprived rats. In the acute experiments, rats were treated with clozapine (5 mg/kg), haloperidol (0.2 mg/kg), or vehicle 45 min prior to testing. In the subchronic experiments, rats were treated with clozapine (3 mg/kg, bid), haloperidol (0.5 mg/kg, bid), or vehicle for 10 days prior to PCP administration. Acute clozapine exacerbated the PCP-induced decrease in sucrose consumption without altering water consumption. Acute haloperidol produced an overall decrease in sucrose consumption in both PCP-pretreated and control groups. Subchronic treatment with clozapine, but not haloperidol, reversed PCP-induced decreases in sucrose consumption. The synergistic effect of acute clozapine and PCP may reflect a PCP-induced increase in the reward-reducing properties of CLZ, normally seen only at higher doses. The observation that subchronic clozapine, but not haloperidol, reversed PCP-induced decreases in sucrose consumption supports the hypothesis that this effect of PCP represents a plausible animal model for negative schizophrenic symptomatology.

Keywords: Anhedonia; Clozapine; Haloperidol; Phencyclidine; Reward; Schizophrenia; Sucrose

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). Among the negative symptoms of schizophrenia is anhedonia, or a decrease in reward function. Withdrawal from acute or subchronic PCP has been shown to produce elevated self-stimulation reward thresholds (Spielewoy and Markou, 2003). In addition, we have recently shown that prior exposure to a single injection of PCP produces decreases in voluntary sucrose consumption (Turgeon and Hoge, 2003). These findings suggest that prior exposure to PCP may lead to decreases in reward function.

The negative symptoms of schizophrenia have generally been found to be refractory to typical antipsychotic medications such as chlorpromazine (Kane et al., 1988) and haloperidol (Breier et al., 1994). However, the atypical antipsychotic drug clozapine has been found to be effective in treating negative symptoms (Kane et al., 1988; Meltzer et al., 1991), and anhedonia in particular (Breier et al., 1994). Clozapine and haloperidol have been investigated for their ability to reverse schizophrenia-like behaviors in animal models of the disease. Both drugs reverse amphetamine-induced disruption of latent inhibition (Russig et al., 2003) and PPI (Swerdlow and Geyer, 1993). On the other hand, subchronic PCP-induced decreases in

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exploration of novel objects in mice are reversed by subchronic administration of clozapine, but not haloperidol (Hashimoto et al., 2005). Likewise, clozapine but not haloperidol has been found to reverse PCP-induced alterations in NMDA receptor function in the medial prefrontal cortex (Ninan et al., 2003). Clozapine inhibits PCP-induced decreases in social interaction, whereas haloperidol does not (Sams-Dodd, 1996; Qiao et al., 2001). In addition, clozapine has been observed to reverse the reward attenuating effects of nicotine and amphetamine withdrawal (Semenova and Markou, 2003). Consistent with clinical findings regarding the efficacy of antipsychotic medications, behaviors modeling negative symptoms of schizophrenia tend to be sensitive to clozapine but not haloperidol, whereas behaviors modeling positive symptoms seem to be sensitive to both. Therefore, should PCP-induced decreases in sucrose consumption be modeling the negative schizophrenic symptom of anhedonia, we would predict that clozapine, but not haloperidol, would be able to reverse the effect of PCP on sucrose consumption.

2. Methods

The effects of acute and subchronic clozapine and haloperidol were assessed in four separate experiments. Male Sprague–Dawley rats, weighing between 300 and 400 g at the onset of the experiments, were allowed access to food and water ad lib throughout the experiment except when water was replaced by sucrose solution (food was still available).

Thirty-five rats were used to assess the effects of acute clozapine on PCP-induced decreases in voluntary sucrose consumption. Rats were trained to drink sucrose by replacing water bottles with sucrose for 30 min on three or four of the seven days prior to the onset of the experiment. On Day 1 of the experiment, animals were given access to 5% sucrose for 30 min (11–11:30 am) and then sucrose bottles were replaced by water bottles. On Day 2 of the experiment, rats were weighed and water consumption for the past 23.5 h was recorded at 11 am. Animals were then given access to sucrose for 30 min and consumption was recorded. Four hours after the end of the sucrose session (3:30 pm) on Day 2, rats were injected with either PCP (15 mg/kg in 2 ml/kg saline, ip) or saline (2 ml/kg, ip). On Day 3, 45 min prior to the sucrose session (10:15 am), rats were injected with clozapine (5 mg/kg in 1 ml/kg HCl, pH=5.5, ip) or vehicle (1 ml/kg HCl, pH=5.5, ip). Sucrose was then provided from 11:00 to 11:30. Four treatment groups were generated: VEH–VEH (n=8), VEH–CLZ (n=9), PCP–VEH (n=9), PCP–CLZ (n=9). Consumption on the Test Day (Day 3) is reported as %-Day 2 consumption (prior to PCP exposure). Water consumption assessed on Days 2 (between 11:30 on Day 2 and 11:00 on Day 3) and 3 (between 11:30 on Day 3 and 11:00 on Day 4) is reported as %-Day 1 (between 11:30 on Day 1 and 11:00 on Day 2) consumption. Water consumption on Day 3 was inadvertently not measured for 12 of the animals (3 in V–C, P–V, and P–C and 2 in V–V).

Twenty-nine male rats were used to assess the effects of acute haloperidol. All the methods were the same as those described above for clozapine except that rats were treated with haloperidol (0.2 mg/kg in 1 ml/kg lactic acid, pH=5.5) or vehicle (1 ml/kg lactic acid, pH=5.5, ip) 45 min prior to testing for sucrose consumption such that four groups were generated: VEH–VEH (n=8), VEH–HAL (n=6), PCP–VEH (n=9), PCP–HAL (n=6). Water consumption on Day 3 was inadvertently not measured for 5 of the animals (2 in V–V and 3 in V–H). These doses of clozapine and haloperidol were chosen for the acute experiments based on the observation that they prevented amphetamine-induced disruption of latent inhibition in a conditioned taste aversion paradigm (Russig et al., 2003).

The methods used to assess the effects of subchronic clozapine treatment on PCP-induced decreases in voluntary sucrose consumption were the same as described above for acute clozapine except that following the training period, rats were treated with either clozapine (3 mg/kg in 1 ml/kg HCl, pH=5.5, ip) or vehicle (1 ml/kg HCl, pH=5.5, ip) twice a day for 10 days without sucrose exposure. They were then allowed access to sucrose for 30 min on 3 days prior to Day 1 of the experiment. Twenty-four rats were run in an initial experiment with n=6 per group. Examination of the data revealed what appeared to be two subsets of responders in the PCP–CLZ group (see Discussion). In an attempt to determine whether this was accurate, an additional 12 animals were added to yield the following groups: VEH–VEH (n=6), CLZ–VEH (n=6), VEH–PCP (n=9), CLZ–PCP (n=15). This dose of clozapine was chosen based on the observation that it reduced increases in

Table 1
Sucrose and water consumption and body weights in the acute clozapine and haloperidol experiments

	V–V	V–C	P–V	P–C
Day 2 sucrose (ml)	24.8±1.9	24.8±2.2	23.9±1.4	23.5±1.5
Day 3 sucrose (ml)	25.2±2.2	24.4±1.7	18.7±1.9	9.1±2.4
PCP: $F(1,31)=13.1$, DAY×PCP: $F(1,31)=24.1$, DAY×CLZ: $F(1,31)=6.2$, DAY×PCP×CLZ: $F(1,31)=4.3$				
Day 1 water (ml)	43.1±2.5	35.2±4.1	42.8±2.9	40.6±4.0
Day 2 water (ml)	39.5±2.1	41.3±1.1	41.4±2.9	38.2±4.2
Day 3 water (ml)	34.7±1.8	32.3±1.5	32.3±3.5	35.8±5.1
DAY: $F(2,40)=8.3$				
Day 2 weight (g)	439.4±3.4	433.6±5.7	440.6±9.1	440.9±11.8
Day 3 weight (g)	444.0±4.1	438.8±6.7	428.0±8.9	427.3±10.7
DAY×PCP: $F(1,33)=47.0$				
	V–V	V–H	P–V	P–H
Day 2 sucrose (ml)	25.3±2.6	24.3±2.8	24.0±1.4	24.2±0.6
Day 3 sucrose (ml)	23.8±2.9	14.3±1.5	17.7±2.5	10.5±3.0
HAL: $F(1,25)=5.4$, DAY×HAL: $F(1,25)=12.2$, DAY×PCP: $F(1,25)=3.5$, $p=0.07$				
Day 1 water (ml)	39.1±14.0	34.3±7.7	36.8±8.6	32.4±3.7
Day 2 water (ml)	37.9±9.2	39.1±5.7	38.8±10.0	34.4±5.8
Day 3 water (ml)	30.0±7.3	29.2±6.2	26.7±6.2	27.6±2.3
DAY: $F(2,40)=25.6$				
Day 2 weight (g)	470.0±41.0	387.5±7.8	492.0±35.7	416.2±10.6
Day 3 weight (g)	473.5±40.0	394.5±6.9	480.8±33.5	412.8±10.3
DAY×PCP: $F(1,27)=17.1$				

Repeated measures ANOVAs revealed significant effects ($p<0.05$, unless otherwise indicated) shown in the table.

Table 2
Sucrose and water consumption and body weights in the subchronic clozapine and haloperidol experiments

	V–V	C–V	V–P	C–P
Day 2 sucrose (ml)	22.2±2.4	22.3±2.3	24.2±1.7	22.9±0.9
Day 3 sucrose (ml)	24.2±2.4	23.3±2.8	18.4±2.0	21.5±1.0
DAY×PCP: $F(1,32)=18.6$, DAY×PCP×CLZ: $F(1,32)=5.6$				
Day 1 water (ml)	46.0±3.0	49.7±5.8	36.8±1.7	39.9±2.3
Day 2 water (ml)	40.0±1.8	40.5±4.2	37.7±4.5	36.7±3.5
DAY: $F(1,32)=5.0$				
Pretmt weight (g)	404.2±6.2	396.0±5.9	390.2±6.6	393.5±4.2
Day 2 weight (g)	461.0±7.9	425.7±6.1	440.8±7.8	429.5±6.2
Day 3 weight (g)	462.2±8.8	425.2±5.7	433.2±7.2	422.2±6.7
DAY×CLZ (Pretmt vs Day 2): $F(1,34)=13.9$, DAY×PCP (Day 2 vs Day 3): $F(1,32)=18.2$				

	V–V	H–V	V–P	H–P
Day 2 sucrose (ml)	22.8±2.1	19.2±2.0	21.8±2.1	17.5±1.7
Day 3 sucrose (ml)	23.2±1.1	21.2±2.7	17.7±2.4	13.7±1.3
PCP: $F(1,20)=8.2$, DAY×PCP: $F(1,20)=8.2$, HAL: $F(1,20)=4.0$, $p=0.06$				
Day 1 water (ml)	35.3±2.1	34.3±1.1	37.2±2.3	33.8±2.0
Day 2 water (ml)	33.8±3.4	32.2±1.4	36.7±2.6	32.5±1.8
Pretmt weight (g)	377.2±6.2	387.8±8.0	395.2±7.9	374.2±7.2
Day 2 weight (g)	422.7±5.9	429.5±12.2	434.8±10.2	402.3±5.7
Day 3 weight (g)	423.3±6.9	432.2±12.0	412.3±19.2	415.5±7.1
DAY×PCP (Day 2 vs Day 3): $F(1,20)=3.5$, $p=0.075$				

Repeated measures ANOVAs revealed significant effects ($p<0.05$, unless otherwise indicated) shown in the table.

ICSS threshold following nicotine withdrawal (Semenova and Markou, 2003).

Twenty-four male rats were used to assess the effects of subchronic haloperidol treatment. All the methods were the same as described for subchronic clozapine except that following the training period, rats were treated with either haloperidol (0.5 mg/kg in 1 ml/kg lactic acid, pH=5.5, ip) or vehicle (1 ml/kg lactic acid, pH=5.5, ip) twice a day for 10 days without sucrose exposure. Four groups were generated: VEH–VEH ($n=6$), HAL–VEH ($n=6$), VEH–PCP ($n=6$), HAL–PCP ($n=6$). This dose of haloperidol was chosen based on the observation that, when administered via subcutaneous mini-pump, it blocked apomorphine-induced disruption of prepulse inhibition (Martinez et al., 2000).

The sucrose and water consumption data were analyzed using a 2×2 ANOVA with main factors of PCP (PCP vs VEH) and antipsychotic (CLZ vs VEH or HAL vs VEH). Post-hoc Student's *t*-tests were also conducted to look for individual group differences. In addition, as an alternate form of analysis, repeated measures analyses were conducted on absolute consumption data from Day 2 and Day 3 with DAY as the within subjects variable and PCP and antipsychotic as the between subjects variables (see Tables 1 and 2). In the acute experiments, the effects of PCP on body weight were analyzed on Day 2 (before PCP) and Day 3 (after PCP, but before antipsychotic treatment) using a repeated measures analysis with PCP (PCP vs VEH) as the between subjects factor. In the subchronic experiments, the effects of antipsychotic treatment on body weight were assessed by comparing body weight on the first day of subchronic antipsychotic treatment and Day 2 of the experiment using a repeated measures analysis with antipsychotic treatment (CLZ vs VEH or HAL vs VEH) as the between subjects variable. The effects of PCP on body weight, as well as interaction effects between PCP and CLZ or HAL were also analyzed on Days 2 and 3 using a repeated measures analysis with PCP (PCP vs VEH) and antipsychotic (CLZ vs VEH or HAL vs VEH) as between subjects variables. Finally, given the observation that there were some effects of drugs on body weight, all %-Day 2 sucrose analyses were rerun adjusting for body weight (calculating %-Day 2 based on ml/kg consumed).

3. Results

Treatment with acute clozapine did not alter sucrose consumption on its own; however, it did exacerbate PCP-induced decreases in sucrose consumption (Fig. 1a). A 2×2

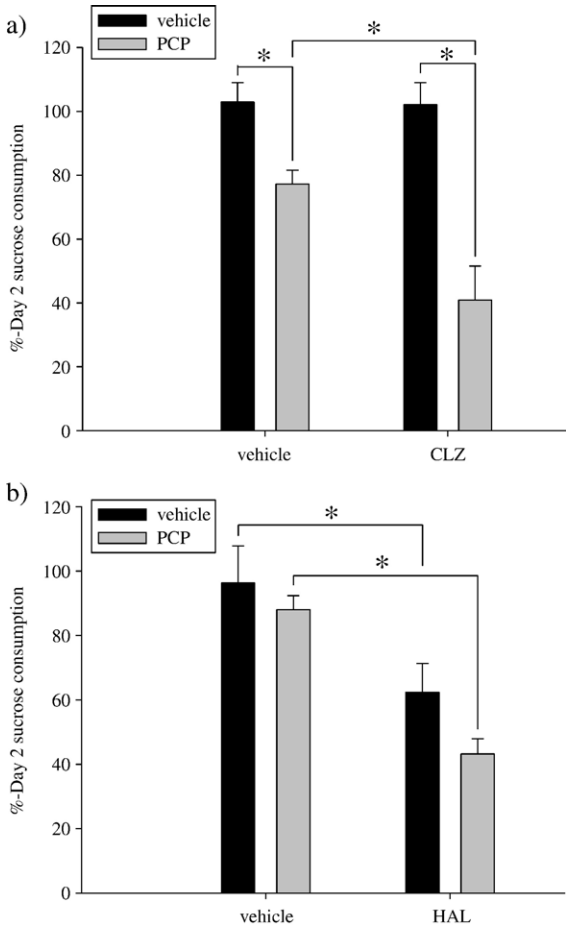

Fig. 1. Acute clozapine exacerbated PCP-induced decreases in sucrose consumption while acute haloperidol decreased sucrose consumption overall. Sucrose consumption (mean±SEM) on the test day (Day 3) as a % of Day 2 consumption (prior to PCP) in animals treated with acute clozapine (a) or haloperidol (b). For clozapine, a 2×2 ANOVA revealed significant effects of PCP and CLZ and a significant PCP×CLZ interaction effect. For haloperidol, a 2×2 ANOVA revealed significant effects of PCP and HAL but no interaction effect. *$p<0.05$ post-hoc Student's *t*-test.

ANOVA revealed significant main effects of PCP ($F(1,31)=33.9$, $p<0.001$) and CLZ ($F(1,31)=6.2$, $p<0.05$), as well as a significant interaction effect ($F(1,31)=5.7$, $p<0.05$). Post-hoc *t*-tests revealed differences between V–V and P–V ($t(16)=3.1$, $p<0.01$), V–C and P–C ($t(16)=4.8$, $p<0.001$), and P–V and P–C ($t(16)=3.1$, $p<0.01$). Significant effects of DAY × PCP, DAY × CLZ, and DAY × PCP × CLZ were also revealed in the repeated measures ANOVA conducted on absolute sucrose consumption; however, there were no significant effects of drugs on water consumption on either Day 2 or Day 3 (Table 1).

In the acute haloperidol experiment, PCP produced an overall decrease in sucrose consumption as revealed by a significant main effect of PCP ($F(1,25)=5.1$, $p<0.05$). Acute haloperidol did not affect PCP-induced decreases in sucrose consumption but did decrease sucrose consumption on its own as revealed by a significant main effect of HAL ($F(1,25)=21.1$, $p<0.005$) but no interaction effect (Fig. 1b). Post-hoc *t*-tests revealed differences between V–V and V–H ($t(12)=2.5$, $p<0.05$) and P–V vs P–H ($t(13)=2.3$, $p<0.05$). A significant effect of DAY × HAL and a trend toward a significant DAY × PCP effect were also revealed in the repeated measures ANOVA conducted on absolute sucrose consumption (Table 1). There were no significant effects of drugs on water consumption on either Day 2 or Day 3 of the experiment; however, there was a trend toward decreased water consumption on both days in both haloperidol treated groups (Table 1).

The initial study of 24 animals failed to support an effect of subchronic CLZ on PCP-induced changes in sucrose consumption. However, examination of the data suggested the possibility that there may have been two subsets of animals in the CLZ–PCP group (see Discussion for details). A second experiment comparing just VEH–PCP ($n=3$) to CLZ–PCP ($n=9$) did not support this hypothesis but instead revealed a significant reversal of the PCP-induced deficit in the CLZ–PCP group (VEH–PCP = 82.9 ± 3.6; CLZ–PCP = 105.0 ± 5.4, $t(10)=-2.25$, $p<0.05$). When both groups of CLZ–PCP animals were combined, there were no statistical outliers, so all animals were included in the final analysis. When all the data were combined, a 2 × 2 ANOVA revealed a significant main effect of PCP ($F(1,32)=12.2$, $p<0.005$) and a significant PCP × CLZ interaction effect ($F(1,32)=5.0$, $p<0.05$; Fig. 2a). Post-hoc *t*-tests revealed differences between V–V and V–P ($t(13)=4.2$, $p<0.005$) and V–P and C–P ($t(22)=2.6$, $p<0.05$). Significant effects of DAY × PCP and DAY × PCP × CLZ were also revealed in the repeated measures ANOVA conducted on absolute sucrose consumption (Table 2). There were no effects of CLZ or PCP on water consumption and there was no effect of subchronic CLZ on Day 2 sucrose consumption (Table 2).

In the subchronic haloperidol experiment, PCP produced an overall decrease in sucrose consumption as revealed by a significant main effect of PCP ($F(1,20)=7.4$, $p<0.05$). Subchronic haloperidol did not alter PCP-induced decreases in sucrose consumption and post-hoc *t*-tests revealed a significant difference between H–V and H–P ($t(10)=2.3$, $p<0.05$; Fig. 2b). A significant effect of DAY × PCP was also revealed in the repeated measures ANOVA conducted on absolute sucrose consumption (Table 2). There were no effects of either PCP or HAL on water consumption on Day 2 (Table 2); however, there was an effect of chronic haloperidol on Day 2 sucrose consumption (VEH = 22.3 ml ± 1.4 ml; HAL = 18.3 ml ± 1.3 ml, $t(22)=2.1$, $p<0.05$). Because the effect of haloperidol on Day 2 consumption (prior to PCP) could have altered the outcome of the 2 × 2 ANOVA on %-Day 2 consumption (Day 3 / Day 2 * 100), raw Day 3 consumption values were also compared. As with the %-Day 2 values, the 2 × 2 ANOVA on Day 3 raw consumption revealed a significant effect of PCP ($F(1,20)=10.7$, $p<0.005$) but no effect of HAL and no interaction effect.

PCP did produce slight decreases in body weight, as compared to slight increases in control groups, from Day 2 to Day 3 in Experiments 1–3 and a similar trend in Experiment 4, as demonstrated by significant DAY × PCP interaction effects (Tables 1 and 2). In addition, rats treated subchronically with CLZ, but not HAL, experienced a smaller increase in weight than controls from the first day of subchronic treatment until Day 2 as demonstrated by a significant DAY × CLZ effect (Table 2). There were no significant interaction effects with the antipsychotic treatments in the comparison of Day 2 and Day 3

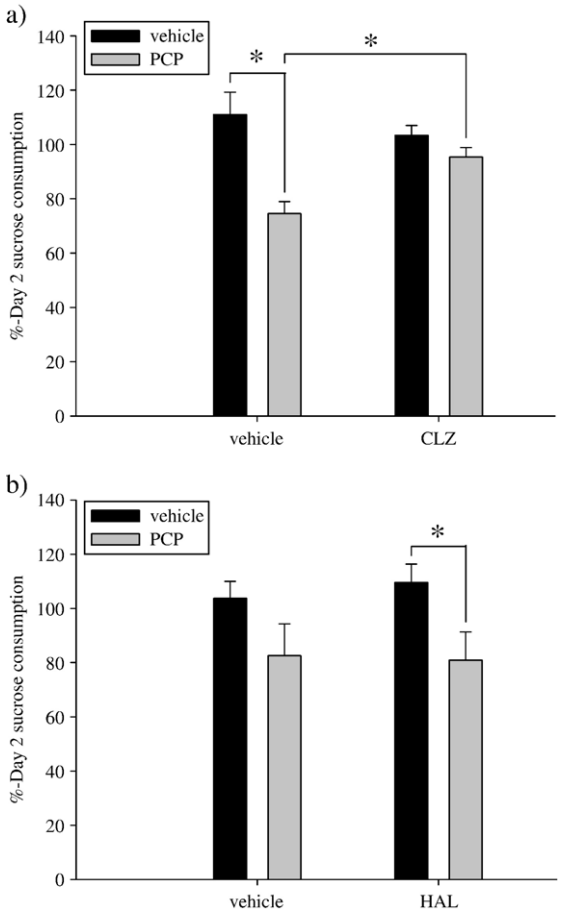

Fig. 2. Subchronic treatment with clozapine, but not haloperidol, reversed PCP-induced decreases in voluntary sucrose consumption. Sucrose consumption (mean ± SEM) on the test day (Day 3) as a % of Day 2 consumption (prior to PCP) in animals treated with chronic clozapine (a) or haloperidol (b). For clozapine, a 2 × 2 ANOVA revealed a significant effect of PCP and a significant PCP × CLZ interaction effect. For haloperidol, a 2 × 2 ANOVA revealed a significant effect of PCP. *$p<0.05$ post-hoc Student's *t*-test.

weights. Because the drug treatments had an effect on body weight, all %-Day 2 sucrose analyses were rerun using ml/kg consumed. All the analyses that were significant using raw consumption values remained significant using ml/kg values.

4. Discussion

Acute clozapine potentiated PCP-induced decreases in voluntary sucrose consumption without having any effect on sucrose consumption on its own. The dose of clozapine tested (5.0 mg/kg) is within a range (1.5 mg/kg–6.0 mg/kg) that has been reported to have no significant effect on brain stimulation reward threshold using intracranial self-stimulation (ICSS; Semenova and Markou, 2003). The absence of an effect of clozapine on voluntary sucrose consumption in vehicle pretreated rats is consistent with the absence of an effect on ICSS. However, this dose of clozapine has also been shown to prevent amphetamine-induced disruption of LI in a conditioned taste aversion paradigm (Russig et al., 2003). Thus, a dose of clozapine that reverses a psychotomimetic effect of amphetamine appears to exacerbate the reward-reducing properties of PCP as assessed in this paradigm. Acute clozapine has been shown to decrease lever pressing for food, thought to result from sedative effects of the drug (Salamone et al., 1996). While this does not seem to be a plausible explanation for decreased consumption in the PCP–CLZ group here given the absence of an effect of clozapine on sucrose consumption in vehicle pretreated rats, a potentiative effect of the two drugs cannot be ruled out. Higher doses of clozapine (9–12 mg/kg) have been reported to elevate reward thresholds (Semenova and Markou, 2003; although see Wiley and Porter, 1990), suggesting reduced reward function. Given that both drugs have been shown to elevate ICSS thresholds, the enhanced decrease in sucrose consumption seen in the PCP–CLZ group may reflect a synergistic interaction between reward-reducing effects of PCP and CLZ.

There has been another report of clozapine-induced exacerbation of a PCP-induced behavioral effect. Schwabe et al. (2005) reported that acute PCP-induced disruption of prepulse inhibition (PPI) is exacerbated by clozapine in animals that have been pretreated with subchronic PCP. Schwabe et al. (2005) suggested that the effects of clozapine on PPI could be mediated via chronic PCP-induced changes in NMDA receptors that enhance clozapine's ability to act as an NMDA receptor agonist. Thus clozapine would be better able to open the NMDA channel, allowing an acute exposure to PCP to act more efficiently as an antagonist. While this precise explanation would not apply here given the differences in the pattern of drug exposure, Schwabe et al. (2005) also reported that acute clozapine reduced PPI in animals pretreated, but not challenged, with PCP (final PCP injection administered the day before clozapine and test). This administration pattern approximates ours more closely as we also administered PCP the day before CLZ and test. Thus the synergistic effect of PCP and CLZ observed in the current study may involve a PCP-induced enhancement of the reward-reducing properties of clozapine, previously only seen with higher doses of clozapine (Semenova and Markou, 2003), mediated by a PCP-induced increase in the ability for CLZ to bind to the NMDA receptor. In support of the hypothesis that NMDA receptor activation could lead to decreased reward, Corbett (1989) found that NMDA receptor antagonists potentiate the rewarding effects of ICSS.

Acute haloperidol produced a reduction in sucrose consumption in both vehicle and PCP-pretreated animals. Neuroleptics have been repeatedly shown to decrease operant responding for reinforcing stimuli which were originally ascribed to neuroleptic-induced motor deficits (see Wise, 1982). However, Wiley and Porter (1990) used an alleyway reacquisition paradigm to demonstrate that haloperidol administered prior to alleyway running for a food reward does not decrease food consumption, but prevents reacquisition of alleyway running on the following day when the motor effects of the drug had worn off. This finding was argued to support the anhedonia hypothesis which suggests that decreased reward function contributes to neuroleptic-induced decreases in operant behavior (Wise, 1982). Subsequent studies found that doses of haloperidol which did not decrease preference of preferred food in a free choice paradigm decreased operant responding for food reward in food-deprived rats while increasing consumption of freely available less preferred food (Salamone et al., 1991). This finding suggests that haloperidol-induced decreases in dopamine activity do not remove the motivation to eat palatable food but may decrease the willingness to work for it. More recently, haloperidol has been found to attenuate conditioned taste aversion produced by either amphetamine or lithium chloride, suggesting that the valence of the stimuli is not relevant and that dopamine is involved in weakening the impact of the conditioned stimulus (Huang and Hsiao, 2002). Finally, the role of dopamine in sucrose preference has been called into question by the observation that mice without DA still prefer sucrose (Cannon and Palmiter, 2003). Our data suggest that dopamine function contributes to maintaining normal levels of sucrose consumption in sated rats; however, it does not rule out the possibility that other factors are involved as well.

The observation that this dose of haloperidol was able to reduce sucrose consumption in the VEH–HAL group was surprising given that it has been previously shown to be without effect. In examining the effect of haloperidol on amphetamine-induced disruption of latent inhibition using a conditioned taste aversion paradigm, Russig et al. (2003) reported that this dose of haloperidol did not decrease sucrose consumption during pre-exposure and conditioning. This may be due to the fact that rats in the current study were given access to sucrose in their home cages whereas rats in the prior study were given access to sucrose in separate testing cages. Previous experiments in our lab have been unable to replicate the effect of PCP on sucrose consumption in separate lickometer cages (unpublished data), suggesting that the attenuating effects of PCP and haloperidol on sucrose consumption may be dependent upon home cage testing.

Russig et al. (2003) did report that this dose of haloperidol was able to reverse amphetamine-induced disruption of latent inhibition. The observation that haloperidol was able to reverse amphetamine-induced disruption of LI is consistent with the observation that disruptions in LI in schizophrenic humans are typical of the acute phase of the disorder and are reversed by neuroleptic treatment (Baruch et al., 1998; Gray et al., 1992).

While it is difficult to interpret the effect of haloperidol on PCP-induced decreases in sucrose consumption given the effect of haloperidol alone, the apparent absence of an effect of haloperidol on PCP-induced decreases in sucrose consumption is not surprising given the observation that negative symptoms are less likely to be sensitive to treatment with classical neuroleptics (see Introduction).

Subchronic treatment with clozapine reversed PCP-induced decreases in sucrose consumption. This dosing schedule of clozapine has been found to reduce increases in ICSS threshold following nicotine withdrawal (Semenova and Markou, 2003). However, this effect was only revealed when animals found to have high levels of initial sensitivity to clozapine were excluded (50% of the rats). The authors argue that the variability in response to clozapine in their study may reflect the fact that only 30–60% of schizophrenic patients treated with clozapine respond to the drug. Our initial data set revealed what appeared to be a similar pattern of results; of the six rats in the CLZ–PCP group, two had sucrose values over 100%, whereas none of the remaining rats in that group were over 83%. This led us to speculate that subchronic clozapine was effective in reversing PCP-induced decreases in sucrose consumption in a subset of rats. In order to test the hypothesis that there were two subsets of animals in the CLZ–PCP group, we increased the number of animals in the CLZ–PCP group (as well as the VEH–PCP group as a control, see Methods). All of the CLZ–PCP animals in the second set of rats had sucrose levels above 90% (mean = 105%), suggesting that there were no non-responders in that experiment. When all the animals were included in the analysis, CLZ clearly reversed the PCP-induced decrease in sucrose consumption. The four CLZ–PCP animals with low %-Day 2 sucrose consumption may represent non-responders; however, their number appears to be less than the 50% observed in the Semenova and Markou (2003) study.

Subchronic treatment with haloperidol failed to alter PCP-induced changes in sucrose consumption. However, sucrose consumption on Day 2 (prior to PCP) was significantly lower in the haloperidol pretreated groups than in vehicle treated groups. Thus both acute and subchronic haloperidol appear to reduce voluntary sucrose consumption. The observation that subchronic haloperidol decreased sucrose consumption 5 days after the end of treatment is consistent with the report that subchronic treatment with haloperidol (1 mg/kg for 12 days) leads to increases in ICSS threshold that last for at least 3 weeks post-treatment (Borowski and Kokkinidis, 1992).

When administered for 10 days, this dose of haloperidol (1 mg/kg/day) administered via subcutaneous minipumps was found to block apomorphine-induced disruption of prepulse inhibition (PPI). In addition, PCP-induced disruption of PPI was not affected following 7 days of haloperidol but was decreased at 14 days (Martinez et al., 2000). In combination with our findings, these observations are consistent with the notion that behaviors modeling positive symptoms of schizophrenia, such as disrupted PPI, are sensitive to treatment with haloperidol whereas those modeling negative symptoms are not. However, it should be noted that only a single dose of haloperidol was tested in the current study and this dose was administered subchronically rather than chronically, as in the Martinez et al. (2000) study. Thus it remains possible that haloperidol administered chronically or at higher doses might be able to alter PCP-induced decreases in voluntary sucrose consumption.

Our prediction that clozapine, but not haloperidol, would reverse PCP-induced decreases in sucrose consumption was supported; however, this was only the case for subchronic administration of clozapine. This finding supports the use of PCP-induced decreases in voluntary sucrose consumption as an animal model for negative schizophrenic symptomatology. The mechanism by which acute clozapine exacerbates PCP-induced decreases in sucrose consumption remains uncertain; however, PCP-induced alterations in the sensitivity of NMDA receptors to clozapine represent a plausible hypothesis.

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