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Effect of acute and chronic olanzapine treatment on phencyclidine-induced behavioral sensitization in rats with neonatal dopamine loss

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Abstract

In agreement with previous work, adult rats given selective lesions to dopamine (DA)-containing neurons as neonates exhibited a greater behavioral sensitization to repeated phencyclidine (PCP) treatment in comparison to sham-lesioned controls. Acute administration of olanzapine (1–5 mg/kg ip) or clozapine (15 mg/kg ip) decreased sensitized PCP-induced activity in both lesioned and control animals. Acute haloperidol (0.5 mg/kg ip) had no impact on PCP responsiveness in lesioned animals, but significantly antagonized PCP effects in sham-lesioned controls. Ketanserin, a selective 5-HT_{2A}/5-HT_{2C}-receptor antagonist, significantly reduced PCP activation in both lesioned and control rats, suggesting that the efficacy of atypical antipsychotics against PCP-induced sensitized responses may be mediated by one of the 5-HT_2-receptor subtypes. A 6-week chronic regimen of orally administered olanzapine, clozapine, or haloperidol failed to block the sensitization induced by repeated PCP exposure. However, a 10-month oral olanzapine treatment significantly blunted the behavioral sensitization to repeated PCP exposure in lesioned animals, even after withdrawal from chronic olanzapine for more than 3 weeks. A 10-month oral haloperidol treatment had no effect on the sensitization induced by repeated PCP dosing. The persistent effect of chronic olanzapine administration on PCP sensitization may be relevant to the chronic therapeutic efficacy of atypical antipsychotics treating schizophrenia—a clinical syndrome linked to enhanced sensitivity to *N*-methyl-D-aspartate (NMDA)-receptor antagonists.

Keywords: Acute olanzapine; Acute haloperidol; Behavioral sensitization; Ketanserin; Neonate-6-hydroxydopamine lesion; Phencyclidine; Chronic olanzapine; Chronic haloperidol

1. Introduction

Rats given selective lesions of dopaminergic neurons very early in life exhibit changes in pharmacological and behavioral profiles indicative of fundamental adaptive alterations in brain function (Breese et al., 1984, 1985; Criswell et al., 1989b). For example, in comparison to normal animals, these neonate-lesioned rats show supersensitive behavioral responsiveness to *N*-methyl-D-aspartate (NMDA)-receptor antagonists, including MK-801 (Criswell et al., 1993) and phencyclidine (PCP; Moy and Breese, 2002). The robust behavioral sensitization in the neonate-lesioned rats to repeated administration of NMDA antagonists has been termed "priming" (Criswell et al., 1989b, 1993; Moy and Breese, 2002). It is notable that neuropathology in schizophrenia has been linked to a sensitization process (Lieberman et al., 1997), and schizophrenics evidence enhanced susceptibility to the actions of NMDA antagonists (Javitt and Zukin, 1991; Lahti et al., 1995; Malhotra et al., 1997b). Additionally, the neonate-lesioned rats at adulthood demonstrate abnormalities in habituation, startle responses, and sensory gating

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(Moy et al., 1994; Schallert et al., 1989; Schwarzkopf et al., 1992, 1996), functional deficits which have been previously associated with some types of schizophrenia (Parwani et al., 2000; for review, see Geyer et al., 1990).

The present studies were designed to define the acute dose–effect action of olanzapine, an atypical antipsychotic, on locomotor responses to PCP in sensitized neonate-lesioned and control animals. Results were compared to the acute actions of clozapine and haloperidol against sensitized responses to PCP. Because both olanzapine and clozapine are antagonists for particular 5-HT (serotonin) receptor subtypes (Bymaster et al., 1996), the efficacy of ketanserin, a serotonergic antagonist selective for 5-HT_{2A} and 5-HT_{2C} receptors, was also tested against the stimulant action of PCP in neonate-lesioned and control animals. Finally, because extended antipsychotic treatment is required to alleviate symptoms of schizophrenia (Baldessarini, 1990), it was determined whether the adaptive changes induced by chronic antipsychotic drug treatments would minimize the sensitization process induced by repeated PCP administration to adult rats with early dopamine (DA) loss.

2. Method

2.1. Subjects

Rat pups were derived from Sprague–Dawley breeding stock (Charles River Laboratories, Raleigh, NC). For the 10-month chronic treatment experiment, an additional set of adult control animals was also obtained from Charles River Laboratories; these rats gave identical results to sham-lesioned control animals. Rats were housed in groups of two or three, except for a small number of males that were housed singly when they showed signs of home-cage aggression. Rats were given free access to water and food (Purina Rat Chow, supplemented with apples), and maintained on a 12-h light–dark cycle in a temperature-controlled environment. All procedures involved in this work were in strict compliance with the policies on animal welfare of the National Institutes of Health and the University of North Carolina (stated in the *Guide for the Care and Use of Laboratory Animals*, Institute of Laboratory Animal Resources, National Research Council, 1996 edition), and approved by the Institutional Animal Care and Use Committee of the University of North Carolina.

2.2. Procedure for neonatal DA lesions

On Day 3 after birth, male and female rat pups were given desipramine (20 mg/kg ip) to protect norepinephrine-containing neurons. One hour later, animals were anesthetized with ether and were injected intracisternally with 100 μg (free base) 6-hydroxydopamine (6-OHDA) in 10 μl saline (0.5% ascorbic acid; Breese et al., 1984). Control animals underwent this same procedure, except that vehicle was injected intracisternally, rather than 6-OHDA. Pups were returned to their dams following recovery from the ether anesthesia. The 6-OHDA treatment typically leads to a more than 90% reduction of striatal DA, without a concomitant loss of norepinephrine, but with a significant elevation of striatal serotonin (Breese et al., 1984).

2.3. Drugs

PCP (Sigma, St. Louis, MO) was dissolved in saline. Olanzapine (a gift from Lilly Research Laboratories, Indianapolis, IN) was dissolved in a minimal amount of 1.0 N HCl, then diluted with sterile water, with the pH adjusted between 5.0 and 6.0 with 1.0 N NaOH. Clozapine (a gift from Novartis, Basil, Switzerland) was dissolved in a minimal amount of glacial acetic acid, then diluted with sterile water, with the pH adjusted between 5.0 and 6.0 with 1.0 N NaOH. Haloperidol (Research Biochemicals, Natick, MA) was dissolved in 0.1% tartaric acid, with the pH adjusted between 5.0 and 6.0 with 1.0 N NaOH. Ketanserin (Research Biochemicals) was dissolved in sterile water. Injection volume was 1 ml/kg body weight, administered intraperitoneally.

For the chronic treatment regimens, antipsychotic drugs were administered in the water bottles of each cage. Drugs were first dissolved as described above. The drug solutions were prepared as 1-mg/ml stock solutions, with a pH between 5.0 and 5.5. Stock solutions were kept refrigerated and were used within 1 week of preparation. The final concentration of the olanzapine, clozapine, and haloperidol solutions was determined weekly for each of the treatment groups, based on average weight and water consumption by the particular group. The stock solutions were then diluted with water to an appropriate concentration. Animals were not given an alternate source of water from the drinking bottles containing the antipsychotic drug solutions, and therefore, were motivated to drink the solutions by thirst.

2.4. Activity measurement

For all of the experiments, locomotor activity was measured in circular locomotor chambers, each with six photocells arranged around the periphery. Scores were derived from breaks in the photobeams crossing the chambers. Each test session began with a 50-min habituation period, followed by a 150-min testing period. For every session, either saline vehicle or PCP (5 mg/kg ip) was administered 10 min before the testing period. There were at least 4–7 days between each drug test session, as specified for each experiment.

2.5. Effects of acute antipsychotic and ketanserin treatment on PCP-induced locomotor activity

2.5.1. Test with olanzapine and haloperidol

The first experiment investigated the effects of olanzapine and haloperidol on PCP-induced responses in neonatal-

lesioned rats and sham-lesioned controls. Animals were not tested until at least 60 days of age. The procedure involved a repeated-measures design, in which subjects were assessed for activity following the administration of vehicle or drug treatment, with at least 5 days between each drug session. Before beginning the investigation of the effect of antipsychotic pretreatment, all subjects for the study were first sensitized to PCP by a chronic dosing regimen (method reported in Moy and Breese, 2002). In brief, the animals were given four to five treatments with PCP (5 mg/kg ip), with at least 5 days between each test session, to insure sensitized drug responses. Activity measures were taken after each test.

Following this initial phase, the PCP-sensitized rats were first assessed for levels of activity after vehicle, and (at least 5 days later), tested for activity following PCP (5 mg/kg ip). The subsequent three test sessions examined the antagonistic potency of the atypical antipsychotic olanzapine (1, 3, and 5 mg/kg ip) against PCP-induced locomotion, with the three doses of olanzapine tested in an ascending order. In a final test session, the typical antipsychotic haloperidol (0.5 mg/kg ip) was tested against the effects of PCP. Administration of antipsychotic compounds occurred 20 min before the PCP treatment.

2.5.2. Test with clozapine

For the next study, a subset of the animals used in the first experiment was further tested on whether the atypical antipsychotic clozapine would block the stimulant effects of PCP. During the first test session, all animals were reassessed for activity levels following vehicle injections. Next, subjects were again tested for the effects of PCP alone (5 mg/kg ip) in a second test session. At least 5 days later, all of the subjects were tested with the same dose of PCP following a 20-min pretreatment with clozapine (15 mg/kg ip).

2.5.3. Test with ketanserin

For the next study, a separate group of experimentally naive female subjects, both lesioned and control, was sensitized to PCP (5 mg/kg ip) by four treatments, given once every 4 days. Animals were returned to their home cages following each injection, and no activity measures were taken across this period. Three weeks later, all animals were measured for activity levels following vehicle injections. Next, subjects were tested for the effects of PCP alone (5 mg/kg ip), and then the same dose of PCP following a 20-min pretreatment with ketanserin (1 or 2 mg/kg ip), with at least 4 days between each testing session.

2.6. Effects of chronic antipsychotic treatment on sensitization to PCP

2.6.1. Six-week regimen with olanzapine, clozapine, or haloperidol

The fourth experiment investigated the effect of a 6-week regimen of antipsychotic administration on sensitization to PCP. The effects of chronic antipsychotic treatments were assessed only in female animals, because previous work has established that females are more sensitive than males to the stimulant effects of NMDA antagonists (Criswell et al., 1993; Honack and Loscher, 1993). Naive, lesioned female rats, aged 45 to 55 days, were distributed across treatment groups (olanzapine, clozapine, haloperidol, or tap water), based on litter and weight. Sham-lesioned control rats were not included in this experiment. Olanzapine (5 mg/kg/day; oral), clozapine (30 mg/kg/day; oral), and haloperidol (2.5 mg/kg/day; oral) were administered in the drinking water. Appropriate drug concentrations in water were determined weekly, based on average weight and water consumption by the particular group (see Section 2.3). The chronic administration regimen was continued for 6 weeks.

Subjects were tested for activity following vehicle administration 6 days after withdrawal from the 6-week antipsychotic regimen. The first test session with PCP (5 mg/kg ip) was conducted 2 days later (8 days following withdrawal from the chronic treatment). Three subsequent tests with PCP (5 mg/kg ip) were then given across the next 3 weeks, one test per week, for a total of four treatments.

2.6.2. Ten-month regimen with olanzapine or haloperidol

In the final study, the effects of a 10-month chronic protocol of antipsychotic treatment on PCP sensitization were assessed. Female lesioned and control animals (2 months of age, all experimentally naive) were distributed across treatment groups based on litter, weight, and behavioral responses to a D_1-DA agonist (SKF-38393). Previous work has shown that lesioned animals, but not controls, evidence repeated sniffing, locomotion, and other indices of dopaminergic stimulation with SKF-38393 (Breese et al., 1985). In this case, all animals were first administered a "priming" dose of 9 mg/kg SKF-38393 (Criswell et al., 1990), and returned to their home cages. One week later, the rats were given a lower dose (3 mg/kg), and observed for signs of hyperactivity or stereotyped responses for 1 h following the injection. The lesioned rats were classified as high or moderate responders to the D_1-DA receptor agonist, and divided across the experimental groups. This procedure allowed us to ascertain that all of the lesioned rats did, indeed, show lesioned-like behavioral responses from the very beginning of the long-term study. As reported before, all of the nonlesioned control rats were classified as low responders to the D_1-DA receptor agonist (Breese et al., 1985). For this study, the control groups consisted of both sham-lesioned rats ($n = 13$) and a set of normal, age-matched rats ($n = 5$), also divided as equally as possible across the experimental groups. Across a 10-month period, all animals received either olanzapine (3 mg/kg/day; oral), haloperidol (1.5 mg/kg/day; oral), or tap water in their drinking bottles for a 10-month period.

During the 10th month of chronic antipsychotic treatment, female subjects were tested for baseline locomotor activity and then, 3 days later, given the first test session

with PCP (5 mg/kg ip). Four days later, the animals were withdrawn from the chronic antipsychotic treatment. The second test session with PCP (5 mg/kg ip) was conducted 3 days following withdrawal (1 week after the first dose of PCP). All subjects were then given three subsequent tests with PCP (5 mg/kg ip) across the next 3 weeks, one test per week, for a total of five treatments. In addition, one group of subjects given chronic haloperidol was not withdrawn from the long-term antipsychotic treatment during the PCP sensitization procedure, to determine if continuous haloperidol administration would have an inhibitory impact on the effects of PCP.

2.7. Statistical analysis

Locomotor measures were first analyzed using an overall repeated-measures analysis of variance (ANOVA), testing for effects of lesion, drug treatment, and sex (when applicable). Separate repeated-measures ANOVAs, testing for effects of lesion and drug treatment, were run for males and females. In addition, separate repeated-measures ANOVAs for the lesioned and control groups were used to test for effects of drug treatment within each experimental group. One-way ANOVAs were used to test for the effects of chronic antipsychotic treatment (either the 6-week or 10-month regimen) at a single time point (the fourth dose of PCP). Fisher's Protected Least Significant Difference (PLSD) Tests were conducted on group means only when a significant F value was found. Regression analyses were performed on the data from the three doses of olanzapine (the first experiment) to test for linear trends within each experimental group (sorted by lesion and gender). Significance was set at $P < .05$.

3. Results

3.1. Effects of acute antipsychotic and ketanserin treatment on PCP-induced locomotor activity

3.1.1. Test with olanzapine

As previously observed (Moy and Breese, 2002), the loss of DA early in development led to a profound supersensitivity to the locomotor effects of repeated exposure to PCP [Fig. 1; post hoc tests following repeated-measures ANOVA; significant main effects of lesion, $F(1,31) = 46.131$; $P < .0001$; sex, $F(1,31) = 5.697$; $P = .0233$; drug treatment (the repeated measure), $F(4,124) = 69.914$, $P < .0001$, and significant interactions between lesion and drug treatment, $F(4,124) = 14.707$, $P < .0001$); and sex and drug treatment, $F(4,124) = 6.223$, $P = .0001$]. These significant effects of lesion and PCP treatment were confirmed in the males [post hoc tests following repeated-measures ANOVA; significant main effect of lesion, $F(1,14) = 15.006$, $P = .0017$; drug treatment, $F(4,56) = 20.867$, $P < .0001$, and interaction between lesion and drug treatment, $F(4,56) = 9.394$, $P < .0001$] and in the females [post hoc tests following repeated-measures ANOVA; significant main effect of lesion, $F(1,17) = 36.66$, $P < .0001$; drug

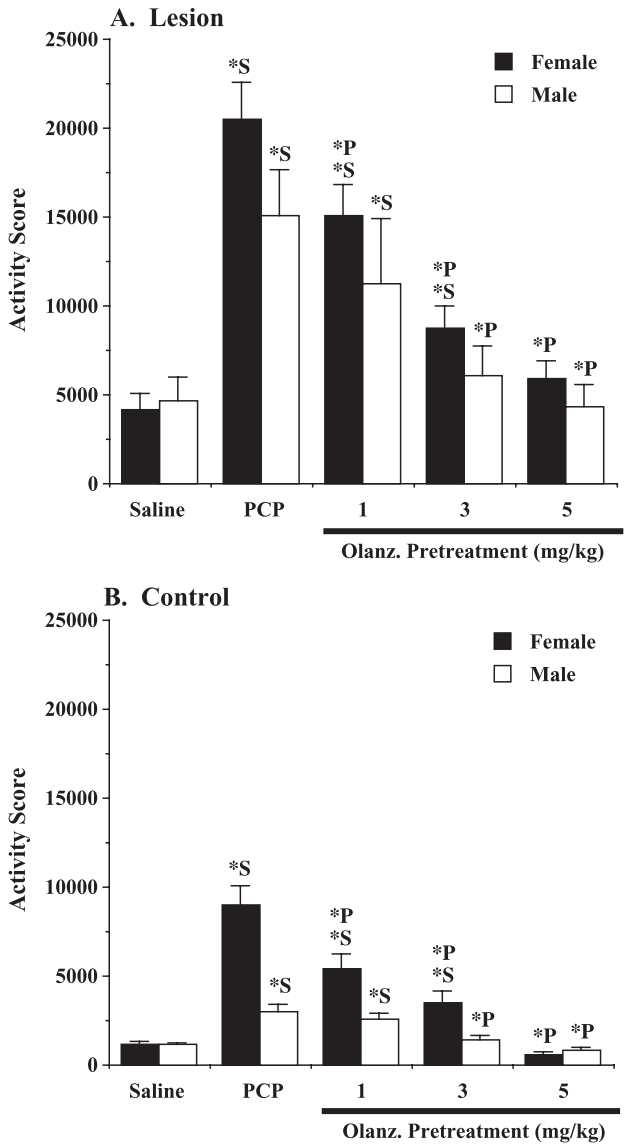


Fig. 1. Effect of pretreatment with olanzapine (Olanz) on PCP-induced locomotor activity in rats given early dopamine lesions (A) and controls (B). Data presented are mean (+S.E.M.) for each group, taken across a 150-min. testing session, with at least 5 days between each drug session. Drug treatments were given in the order shown in the figure. The subjects for the study had been previously sensitized to the effects of PCP. In the lesioned group, n=10 for female rats and n=7 for male rats; in the control group, n=9 for both female and male rats. Olanzapine doses (1–5 mg/kg ip) were administered 20 min before PCP (5 mg/kg ip). Regression analyses for locomotor scores after the three doses of olanzapine indicated significant linear trends for the female lesioned animals [R^2=.441; $F(1,28)$=22.049; P<.0001], female control animals [R^2=.547; $F(1,25)$=30.346; P<.0001], and control males [R^2=.499; $F(1,25)$=24.878; P<.0001], while the linear trend for the male lesioned rats approached significance [R^2=.428; $F(1,19)$=4.262; P=.0529]. *S: P<.05, drug treatment versus respective saline score; *P: P<.05, drug treatment versus respective score for PCP alone, Fisher PLSD Tests following significant F values with repeated-measures ANOVA.

treatment, $F(4,68) = 54.434$, $P < .0001$, and interaction between lesion and drug treatment, $F(4,68) = 6.53$, $P = .0002$]. The significant effects for sex found in the overall ANOVA confirm previous observations that PCP has enhanced stimulant effects in female animals, in comparison to males (Criswell et al., 1993; Honack and Loscher, 1993).

Examination of the dose–response relationship of olanzapine against the sensitized responses to PCP revealed that olanzapine was remarkably effective at blocking the stimulant impact of PCP in both the sensitized neonate-lesioned (Fig. 1A) and control (Fig. 1B) animals. For each group, the highest dose of olanzapine (5 mg/kg) led to a return to saline levels of activity. Regression analyses for locomotor scores after the three doses of olanzapine indicated significant linear trends for all groups except the male-lesioned rats, where the linear trend approached significance ($P = .0529$; see Fig. 1 caption for F values). These results reflect the progressive impact of increasing doses of olanzapine against the hyperlocomotion induced after sensitization with PCP.

3.1.2. Test with clozapine

A subset of the animals used in the first experiment was further tested to investigate the effects of another atypical antipsychotic, clozapine. As shown in Fig. 2, clozapine (15 mg/kg) had an action on sensitized responses to PCP comparable to that of the high dose of olanzapine in both lesioned and control rats (Fig. 1), confirming the marked potency of atypical antipsychotic agents against PCP-induced responses [repeated-measures ANOVA, significant main effect of lesion, $F(1,27) = 32.884$, $P < .0001$; significant effect of drug treatment (the repeated measure), $F(2,54) = 44.085$, $P < .0001$; and significant interaction between lesion and drug treatment, $F(2,54) = 15.538$, $P < .0001$]. In both lesioned and control groups, pretreatment with clozapine decreased the PCP-induced activity to levels observed after saline administration. This pattern was evident in both the male and female rats (F values in Fig. 2 caption).

3.1.3. Test with ketanserin and haloperidol

Clozapine and olanzapine have effects on both dopaminergic and serotonergic receptors (Bymaster et al., 1996). For this reason, the effect of ketanserin, a serotonergic antagonist selective for the 5-HT_{2A} and 5-HT_{2C} receptor types, was compared to the action of haloperidol, primarily a D_2-DA antagonist, against PCP-induced activity in female neonate-lesioned and control animals (Fig. 3). Ketanserin decreased locomotor activity in a dose-dependent fashion in the neonate-lesioned females. For the control females, only the higher dose (2 mg/kg) of ketanserin produced a significant reduction of the stimulant effects of PCP (F values in Fig. 3 caption).

Haloperidol, at a relatively high dose of 0.5 mg/kg, was also tested against PCP in a separate group of animals (the female subjects from Fig. 1), in which the levels of PCP-induced hyperlocomotion prior to treatment with haloperidol were not significantly different from those for the animals tested with ketanserin. In agreement with earlier work (Moy and Breese, 2002), haloperidol did not significantly decrease PCP-induced activity in the female-lesioned rats, yet returned locomotion in the control animals to saline levels (F values for separate haloperidol analysis in Fig. 3 caption).

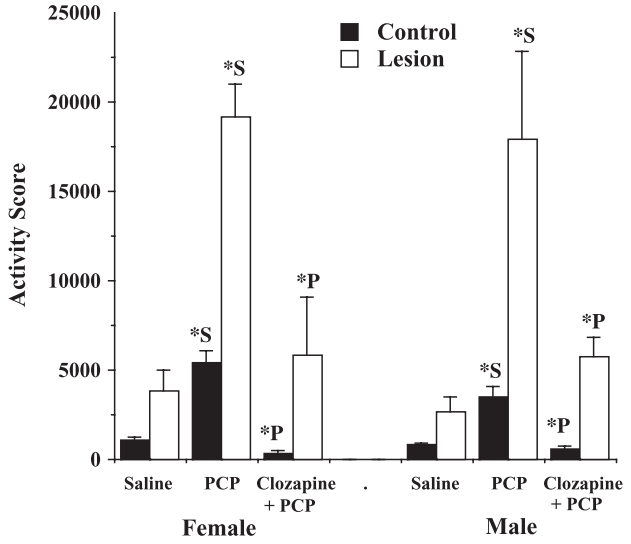


Fig. 2. Effect of pretreatment with clozapine (15 mg/kg ip) on PCP-induced locomotor activity in rats given early dopamine lesions and controls. Data presented are mean (+S.E.M.) for each group, taken across a 150-min testing session, with at least 5 days between each drug session. Drug treatments were given in the order shown in the figure. The subjects for the study had been previously sensitized to the effects of PCP. Clozapine was administered 20 min before PCP (5 mg/kg ip). $n = 8$ for female control rats and $n = 9$ for female lesioned rats. $n = 8$ for male control rats and $n = 6$ for male lesioned rats. The data analysis indicated significant main effects of lesion [females, $F(1,15) = 18.06$, $P = .0007$, and males, $F(1,12) = 15.4$, $P = .002$], drug treatment (the repeated measure) [females, $F(2,30) = 26.858$, $P < .0001$, and males, $F(2,24) = 18.47$, $P < .0001$], and significant interactions between lesion and drug treatment [females, $F(2,30) = 7.31$, $P = .0026$, and males, $F(2,24) = 8.41$, $P = .0017$]. *S = $P < .05$, drug treatment versus respective saline score; *P = $P < .05$, drug treatment versus respective score for PCP alone, Fisher PLSD Tests following significant F values with repeated-measures ANOVA.

3.2. Effects of 6-week or 10-month chronic antipsychotic treatment on sensitization to PCP

3.2.1. Effects of chronic antipsychotic treatment on responses to the fourth dose of PCP

Lesioned animals given 6 weeks of antipsychotic treatment demonstrated the same progressive increase in PCP responsiveness as observed in the water-treatment group (response after fourth dose of PCP presented in Fig. 4). For this procedure, the first test session with PCP (5 mg/kg) was conducted 8 days following withdrawal from the chronic treatment. The individual chronic antipsychotic regimens

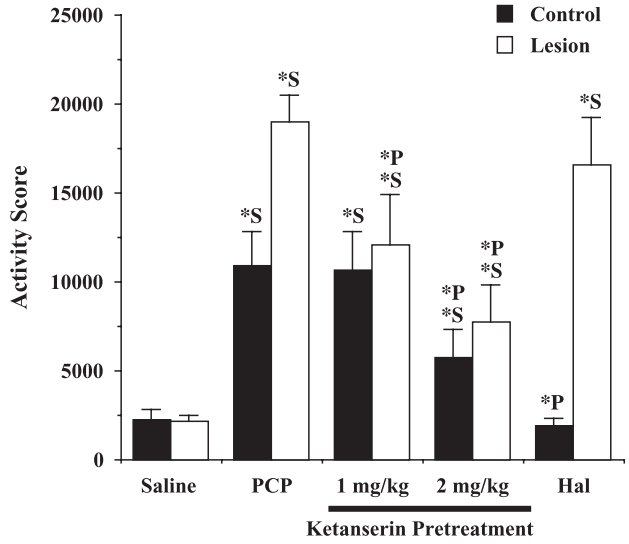


Fig. 3. Effect of pretreatment with ketanserin (1 or 2 mg/kg ip) or haloperidol (0.5 mg/kg ip) on PCP-induced locomotor activity in female lesioned and control rats. Data presented are mean (+S.E.M.) for each group, taken across a 150-min testing session, with at least 5 days between each drug session. The subjects for the study had been previously sensitized to the effects of PCP. Ketanserin or haloperidol was administered 20 min before PCP (5 mg/kg ip). Data analysis for the ketanserin groups ($n=6$ for both control and lesioned groups) revealed a significant effect of drug treatment (the repeated measure) [$F(3,30)=35.113$, $P<.0001$], and a significant interaction between lesion and drug treatment [$F(3,30)=3.7$, $P=.0225$]. Results for the haloperidol test were from a separate group of female animals ($n=10$ for the lesion group and $n=9$ for the control group), with saline and PCP scores shown in Fig. 1. The separate repeated-measures ANOVA for these animals revealed a significant main effect of lesion [$F(1,17)=44.017$, $P<.0001$], drug treatment (the repeated measure) [$F(2,34)=34.466$, $P<.0001$], and interaction between lesion and drug treatment [$F(2,34)=8.589$, $P=.001$]. *S = $P<.05$, drug treatment versus respective saline score; *P = $P<.05$, drug treatment versus respective score for PCP alone, Fisher PLSD Tests following significant F values with repeated-measures ANOVA.

[haloperidol (2.5 mg/kg/day), olanzapine (5 mg/kg/day), and clozapine (30 mg/kg/day)] did not significantly change the subsequent sensitized response to PCP. In contrast, the 10-month olanzapine regimen resulted in a marked reduction in responsiveness to PCP sensitization following repeated treatment, in comparison to the water-exposed group (see Fig. 4 caption for F values). The extended chronic treatment with haloperidol did not have an inhibitory effect against the sensitized response to PCP.

3.2.2. Ten-month regimen with olanzapine or haloperidol

Fig. 5 presents the time course of responsiveness for each PCP dose administered following the 10-month treatment regimens with olanzapine, haloperidol, or tap water. For this determination, the neonate-lesioned rats and controls were given the first dose of PCP during the final week of the long-term antipsychotic treatments. The majority of animals were then withdrawn from the chronic regimen, and tested with the second injection of PCP 3 days later (and 1 week after the first test). Three additional tests with PCP were conducted at weekly intervals.

An overall repeated-measures ANOVA was conducted for all of the experimental groups, excluding the one set of lesioned rats that was never withdrawn from the haloperidol treatment (the Hal/No WD group on the lower panel of Fig. 5). As shown in the previous experiments, there were significant effects of lesion [$F(1,48)=26.064$, $P<.0001$] and PCP treatment (the repeated measure) [$F(5,240)=18.824$, $P<.0001$] as well as a significant interaction between lesion and PCP treatment [$F(5,240)=8.791$, $P<.0001$]. These findings reflected the progressive increases in locomotor activity evident during the repeated PCP regimen, with an enhanced sensitization clearly present in the lesioned groups, in comparison to the nonlesioned control rats. However, no overall impact from the different antipsychotic treatments was observed (nonsignificant effect of chronic treatment), although there was a significant interaction between lesion and chronic treatment [$F(2,48)=3.471$, $P=.0391$].

Further analysis of the data from only the lesioned groups (water, olanzapine-withdrawal, or haloperidol-withdrawal) confirmed the significant effect of the PCP treat-

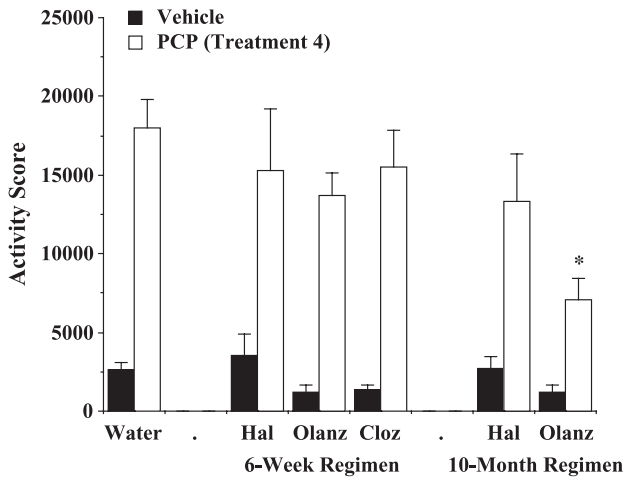
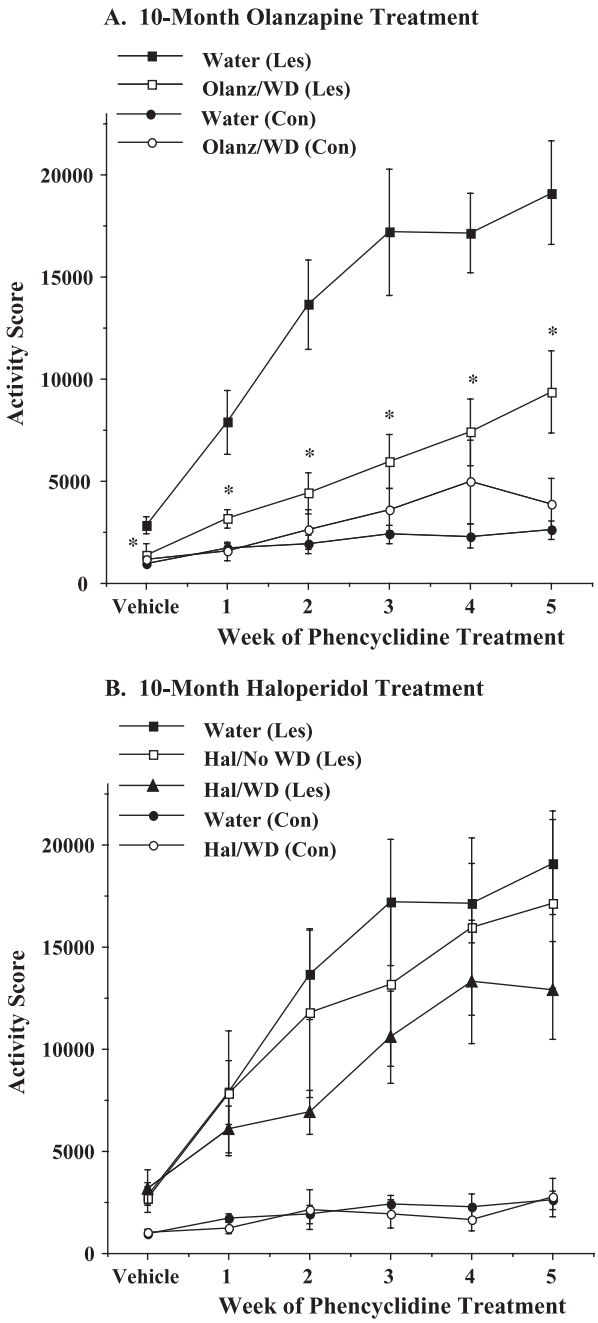


Fig. 4. Summary of the effects of chronic treatment with haloperidol (Hal), olanzapine (Olanz), or clozapine (Cloz) for either 6 weeks or 10 months on PCP (5 mg/kg) sensitization in lesioned female rats. Data presented are mean (+S.E.M.) for each group, taken across a 150-min testing session. Animals were tested for baseline activity with vehicle, and then given one dose of PCP per week (results from the fourth dose are presented). Water groups were combined for the figure depiction, but not for statistical analysis (overall $n=24$). For the groups tested after 6 weeks of treatment, there were no effects of the antipsychotic regimens [nonsignificant effect of treatment on PCP-induced responses at fourth dose, $F(3,33)=0.676$, $P=.5726$]. For the group tested after 10 months of treatment, only olanzapine significantly reduced activity levels [Fisher PLSD Test following significant effect of treatment, $F(2,33)=4.836$, $P=.0144$]. Subject sizes for the 6-week group were $n=8$ for the water group, $n=10$ for the olanzapine group, $n=10$ for the clozapine group, and $n=9$ for the haloperidol group. Subject sizes for the 10-month group were $n=16$ for the water group, and $n=10$ for both the olanzapine and haloperidol groups. * $P<.05$, comparison to water group PCP score.

ment [$F(5,165)=27.835$, $P<.0001$]. In fact, although the animals were over 1 year in age when the sensitization procedure for PCP was initiated, the neonate-lesioned group that received water during the 10-month treatment regimen still evidenced a progressive increase in locomotor activity with repeated PCP doses (Fig. 5A and B). The level of the activity in the older lesioned rats approached that observed in the younger female neonate-lesioned rats depicted in Fig. 1. Control female rats also showed evidence of PCP sensitization with repeated dosing [significant effect of repeated measure, $F(5,75)=7.131$, $P<.0001$], but overall levels of activity induced by PCP across time were considerably lower than those in the lesioned rats.



The same lesioned groups (water, olanzapine-withdrawal, or haloperidol-withdrawal) also evidenced significant effects of the long-term antipsychotic treatment [$F(2,33)=6.524$, $P=.0041$] and a significant interaction between the antipsychotic treatment and the PCP treatment (the repeated measure) [$F(10,165)=2.3$, $P=.0149$]. The lesioned animals given chronic exposure to olanzapine showed a marked reduction in PCP sensitization, in comparison to the animals given only water, at every dose during the PCP regimen (Fig. 5A, post hoc tests following repeated-measures ANOVA comparing water group and olanzapine group; see figure caption for F values). There was no significant impact of the extended treatment with olanzapine on PCP-induced changes in locomotion in the control rats.

In contrast to the effects of olanzapine in the neonate-lesion animals, the 10-month haloperidol treatment did not lead to an attenuated PCP sensitization, in comparison to the water-alone regimen (Fig. 5B). This same lack of effect on PCP responsiveness was also observed in an additional set of neonate-lesioned female rats that were given haloperidol for the 10-month period, but not withdrawn from antipsychotic treatment during the PCP sensitization regimen [repeated-measures ANOVA comparing the water group to the haloperidol–no withdrawal group, nonsignificant effect of antipsychotic treatment, significant effect of PCP treatment (the repeated measure), $F(5,130)=24.084$, $P<.0001$]. Likewise, the 10-month haloperidol treatment did not affect PCP sensitization in the control rats.

4. Discussion

The present studies confirm that early loss of dopaminergic neurons leads, in adulthood, to an enhanced sensitivity to repeated exposure to NMDA-receptor antagonists

Fig. 5. Time course for the effect of a 10-month regimen of antipsychotic treatment on PCP (5 mg/kg ip) sensitization in lesioned (Les) and control (Con) female rats. (A) Mean ± S.E.M. for groups given water or olanzapine (Olanz; 3 mg/kg/day; oral) for 10 months. (B) Mean ± S.E.M. for groups given water (presented again for comparison) or haloperidol (Hal; 1.5 mg/kg/day; oral) for 10 months. WD (withdrawal): groups that were withdrawn from the 10-month antipsychotic regimen 4 days after the first PCP dose and 3 days before the second PCP dose. No WD (no withdrawal): group in panel B that remained on the haloperidol treatment regimen during the period of PCP testing. Activity measures were taken across a 150-min testing session, with one dose of phencyclidine given per week. For the lesioned subjects, $n=16$ for the water group, $n=10$ for the olanz/WD group, $n=10$ for the hal/WD group, and $n=12$ for the hal/No WD group. For the control subjects, $n=5$ for the water group, $n=6$ for the olanz/WD group, and $n=7$ for the hal/WD group. As shown in panel A, the olanz/WD (Les) group had significantly lower levels of activity to PCP, in comparison to the water (Les) group [repeated-measures ANOVA; significant main effect of antipsychotic treatment, $F(1,24)=11.315$, $P=.0026$; significant effect of repeated PCP treatment, $F(5,120)=21.920$, $P<.0001$, and significant interaction, $F(5,120)=3.732$, $P=.0036$]. $^*P<.05$, drug treatment versus respective score for water group; Fisher PLSD Tests following significant F values with repeated-measures ANOVA.

(Criswell et al., 1993; Moy and Breese, 2002). The results also confirm earlier work demonstrating PCP sensitization in rodents (Nabeshima et al., 1983; Xu and Domino, 1994). The effects of the neonatal lesion proved to be persistent across time, because the increased responsiveness to repeated PCP administration was clearly evident in lesioned rats 1 year in age. Previous studies have suggested that a component of the stimulant action of MK-801 or PCP in normal animals is mediated through effects on dopaminergic systems (Gleason and Shannon, 1997; Loscher and Honack, 1992; Martin et al., 1997), a premise consistent with the finding from the present study that haloperidol can fully block the sensitized response to PCP in control animals. However, the neonate-6-OHDA-treated rats show even greater locomotor effects from MK-801 and PCP, despite having markedly reduced levels of DA (Breese et al., 1984). These enhanced responses are not blocked by haloperidol (0.5 mg/kg) or the D_1-DA receptor antagonist, SCH-23390 (0.3 mg/kg; Criswell et al., 1993; Moy and Breese, 2002, present study), suggesting a nondopaminergic mechanism for PCP sensitization in lesioned animals. In respect to this conclusion, others have provided evidence for a nondopaminergic neurotransmission being involved in selected actions of NMDA antagonists (Carlsson and Carlsson, 1989; Corbett et al., 1995; Swanson and Schoepp, 2002).

In contrast to the nominal efficacy of haloperidol, the acute administration of either olanzapine or clozapine minimized PCP-induced sensitized locomotor activity in the neonate-lesioned rats. A greater efficacy of atypical antipsychotic compounds, in comparison to haloperidol, has previously been reported for PCP-induced locomotion (Gleason and Shannon, 1997), social withdrawal (Corbett et al., 1995), deficits in prepulse inhibition (Bakshi and Geyer, 1995; Geyer et al., 2001; Linn et al., 2003; Swerdlow et al., 1996), and changes in neural activity (Ninan et al., 2003; Wang and Liang, 1998). It is notable that clozapine (Malhotra et al., 1997a), but not haloperidol (Lahti et al., 1995), has been reported to reduce the cognitive and psychotomimetic impact of ketamine, an NMDA antagonist, in schizophrenics. Because the acute administration of olanzapine minimizes sensitized responses to PCP, a question raised is whether testing drugs against PCP effects in the neonate-lesioned rats can be used to screen for agents with potential usefulness in treating schizophrenia.

In contrast to haloperidol, which is mainly characterized by a potent action on D_2-DA receptors, atypical antipsychotics have diverse receptor affinity profiles, including effects on 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors (Bymaster et al., 1996; Kuoppamaki et al., 1995; Schotte et al., 1996). Work measuring functional responses from receptor-transfected cells has confirmed the high potency of olanzapine as an antagonist of 5-HT_{2A} and 5-HT_{2C} receptors (Bymaster et al., 1999), and the impact of olanzapine on these serotonergic receptors is markedly greater than its potency at the D_1-DA receptor site (Zhang and Bymaster, 1999). Importantly, the same dose of olanzapine or clozapine that can fully block the action of PCP has only a partial effect against comparable activity levels induced by a selective D_1-DA receptor agonist in lesioned rats (Criswell et al., 1989a; Moy et al., 2001). At the same time, the selective D_1-DA antagonist, SCH-23390, is not an effective blocker of MK-801- and PCP-induced stimulant effects (Criswell et al., 1993; Moy and Breese, 2002). These observations diminish the possibility for D_1-DA receptor involvement in atypical antipsychotic inhibition of PCP.

An increase in central serotonergic tone has been linked to NMDA antagonist-induced hypermotility (Martin et al., 1997). Lesioning dopaminergic neurons early in development provokes a robust hyperinnervation of neostriatal serotonergic neurons (Berger et al., 1985; Breese et al., 1984). An increase in striatal 5-HT_{2A} receptors has also been reported in neonate-lesioned rats (Radja et al., 1993). Kostrzewa et al. (1998) have suggested that the unique characteristics of neonate-lesioned animals may depend upon alterations in serotonergic function. Therefore, an action of olanzapine and clozapine on serotonergic function could be an explanation for their reduction of PCP-induced activity in the lesioned rats. To investigate the possible role of 5-HT_2-receptor function in the inhibitory action of these antipsychotics, ketanserin, an antagonist selective for both the 5-HT_{2A}- and 5-HT_{2C}-receptor subtypes, was tested against sensitized responses in neonate-lesioned and control rats. Ketanserin (1 and 2 mg/kg) reduced PCP activation in neonate-lesioned rats, whereas only the higher dose of ketanserin (2 mg/kg) was capable of minimizing the stimulant effect of PCP in control animals. These findings agree with previous studies showing that ketanserin blocks PCP-induced activity in normal animals (Gleason and Shannon, 1997; Krebs-Thomson et al., 1998) and in α-methyl-*p*-tyrosine-treated animals (Swanson and Schoepp, 2002). It is notable that an antagonist selective for the 5-HT_{2a} receptor, M100907, has been found to be effective in reducing the stimulant action of PCP in normal animals (Gleason and Shannon, 1997; Higgins et al., 2003; Martin et al., 1997; Maurel-Remy et al., 1995), as well as preventing PCP-induced antagonism of NMDA responses from pyramidal cells in the prefrontal cortex (Wang and Liang, 1998). In a recent investigation, a drug selective for the 5-HT_{2C}-receptor subtype was not found to inhibit PCP-induced activity (Higgins et al., 2003), pointing to the 5-HT_{2a} receptor being critical for the action of ketanserin to reduce PCP stimulant effects. Nonetheless, the 5-HT_3 antagonist, zatosetron, has also been found to reverse PCP-induced activity in control mice (Gleason and Shannon, 1997), implicating the involvement of yet another serotonin receptor in PCP action.

It is held that chronic administration of antipsychotic drugs is needed to attain full beneficial impact of antipsychotic treatment for schizophrenia (Baldessarini, 1990). Yet, work in normal animals has shown that a 3-week regimen with haloperidol or clozapine does not have persistent effects on activity induced by PCP (Sams-Dodd, 1998).

Therefore, it was determined if longer chronic antipsychotic treatments would modify behavioral sensitization induced by repeated treatment with PCP, even after withdrawal from chronic exposure. A treatment regimen of 6 weeks with either olanzapine, clozapine, or haloperidol failed to have a significant effect on PCP-induced sensitization. However, a 10-month regimen of olanzapine produced a significant inhibition of PCP sensitization that was still apparent almost a month following withdrawal from the chronic treatment. The 10-month exposure to haloperidol did not affect sensitization to PCP effects in the neonate-lesioned rats. The finding that prolonged treatment with olanzapine, but not haloperidol, can have persistent effects against the induction of sensitization to repeated PCP exposure may be relevant to treating the worsening symptoms of schizophrenia over the extended course of this disease.

The enhanced susceptibility to NMDA antagonists observed in schizophrenia has led to the proposal that a state of NMDA receptor hypofunction may be inherent to this psychiatric disorder (Javitt and Zukin, 1991; Jentsch and Roth, 1999; Olney et al., 1999). Consequently, the exacerbated responsiveness to NMDA antagonists in the neonate-lesioned rats could serve as a model of the NMDA hypofunction in schizophrenia. The neonate-lesioned animals have also been shown to have impaired habituation and alterations in startle responses and sensory gating (Moy et al., 1994; Schwarzkopf et al., 1992, 1996), as well as a marked susceptibility to the stimulant impact of pharmacological challenges and environmental stressors (Moy et al., 1994; Schallert et al., 1989). These characteristics are also similar to those observed in schizophrenia (Javitt and Zukin, 1991; Jentsch and Roth, 1999; Malhotra et al., 1997b; Olney et al., 1999). Therefore, the neonate-lesioned rat may be a valuable model to investigate the neural basis for the behavioral and pharmacological abnormalities, including enhanced responsiveness to NMDA-receptor antagonists that characterize at least some forms of schizophrenia.

In summary, the present data suggest that neonate-lesioned rats can provide a model of enhanced NMDA-antagonist sensitivity and a means to differentiate classes of antipsychotic drugs. The reduction in PCP activity with ketanserin suggests a serotonergic involvement in its action. Therefore, atypical antipsychotic action on serotonergic 5-HT_2 receptors, rather than DA receptors, may be responsible for the observed inhibition of NMDA-antagonist-induced activity. Nonetheless, it is possible that other forms of neurotransmission are also mediators of the observed effects on PCP and are involved in the chronic actions of atypical antipsychotic agents. For example, an mGlu2/3 receptor agonist has been shown to block the acute action of PCP (Clark et al., 2002; Moghaddam and Adams, 1998; Swanson and Schoepp, 2002), and a compound that enhances glutamate uptake and inhibits glutamate release can block the behavioral sensitization to the stereotypy induced by repeated PCP administration (Abekawa et al., 2002a,b). Given the persistent effects of olanzapine against PCP sensitization, the therapeutic efficacy of chronic antipsychotic treatment in schizophrenia may depend upon correcting central maladaption(s) of serotonergic, as well as glutamatergic, function (Breese et al., 2002). Certainly, testing this view should be the focus of future investigations.

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