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Effects of postnatal PCP treatment on locomotor behavior and striatal D_2 receptor

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Abstract

Exposing the developing brain to the *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) has been shown to cause deficits in neurobehavioral functions, particularly on learning and memory and seizure sensitivity. Besides acting as a noncompetitive NMDA antagonist, PCP at high doses is known to affect the dopaminergic system. The present study assessed the effect of postnatal PCP treatment on locomotor activity and striatal dopamine (DA) D_2 receptor. Male and female rat pups were injected intraperitoneally (ip) with one of three doses of PCP (1, 3 and 5 mg/kg) or saline from postnatal day (PD) 5 to PD 15. Control and PCP-treated rats were given a challenge dose of PCP (10 mg/kg) as adults, and their locomotor behaviors—locomotion, stereotypy and ataxia—were scored. Postnatal PCP treatment did not have any significant effect in either sex on any of the PCP-induced locomotor behavioral paradigms studied. Separate groups of male and female rats were treated daily with saline or PCP (5 mg/kg ip) from PD 5 to PD 15 and sacrificed either as juveniles (PD 21) or adults, and D_2 receptor binding was measured in their striata. Striatal D_2 receptor density in juvenile and adult male postnatal PCP-treated rats did not differ from saline-treated controls. Adult female PCP-treated rats showed a slight but significant reduction in the maximal binding of striatal D_2 receptors. There was no effect of postnatal PCP on striatal D_2 receptor binding in female juvenile rats. These results support the hypothesis that blocking the developing NMDA receptor minimally affects PCP-induced locomotor behavior and the striatal D_2 receptor.

Keywords: Brain development; Phencyclidine; Dopaminergic system; NMDA antagonist

1. Introduction

Earlier, we have shown that exposure to phencyclidine (1-phenylcyclohexylpiperidine; PCP) during the postnatal period causes long-term behavioral effects (Sircar et al., 1994; Sircar and Rudy, 1998). Daily single injections of PCP from postnatal days (PD) 5 to PD 15 produced both short-term and long-term alterations in seizure susceptibility (Sircar et al., 1994). In the short term, when rats were tested on PD 21, 6 days after the last injection, PCP-treated rats showed increased seizure sensitivity to an injection of pentylenetetrazol. This increase in seizure susceptibility disappeared by PD 45 and was replaced by a long-term reduction in seizure sensitivity that lasted into adulthood. When tested on PD 60 and PD 180, respectively, fewer PCP-treated rats had seizures compared to saline-treated controls, and the ones that did have seizures took significantly longer to have them. We have further shown that rats exposed to PCP from PD 5 to PD 15 had impairments in spatial memory when tested as juveniles on PD 28 (Sircar and Rudy, 1998) and as adults on PD 60 (Sircar, 2001, 2003). Behavioral effects of postnatal PCP tested in these investigations are known to be associated with the hippocampus, an area in the brain that has the highest density of PCP receptors (Sircar and Zukin, 1985), is crucially involved in spatial memory and is vulnerable to seizures. Besides affecting learning and memory and seizure generation, PCP has other behavioral consequences.

In adult rodents, PCP produces characteristic behavioral activation that includes increased locomotor activity, stereotypic behavior and ataxia (Castellani and Adams, 1981;

Abbreviations: PCP, phencyclidine; DA, dopamine; D_2, dopamine D_2 receptor; NMDA, *N*-methyl-D-aspartate.

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Chen et al., 1959; Kanner et al., 1975; Sturgeon et al., 1979; Tonge and Leonard, 1972). PCP-induced motoric activity is dose related. At lower dosages (5.0 mg/kg and under), PCP increases locomotion and induces stereotypic behavior and ataxia (Sturgeon et al., 1979). At dosages of 7.5–15.0 mg/kg, PCP induces moderate to high level of ataxia that results in significant impairment in locomotion. Whether PCP exposure during the postnatal period has long-term effects on PCP-induced motoric activity has not been studied.

PCP exerts its pharmacological effects through several neurotransmitter systems (Xu and Domino, 1999). Although the primary action of PCP is thought to be selectively mediated by the *N*-methyl-D-aspartate (NMDA) receptor channel complex (Anis et al., 1983; Fagg, 1987) since it interacts with the NMDA receptor with submicromolar affinity, at higher concentrations, it has been shown to interact with several other target sites. One molecular target responsible for PCP action is the dopamine (DA) receptor. Subanesthetic doses of PCP increase DA release (Carboni et al., 1989; Hondo et al., 1994; Verma and Moghaddam, 1996). Systemic administration of PCP activates dopaminergic neurons and increases DA output in the limbic-cortical areas (Hertel et al., 1996; Marcus et al., 2001). In this paper, we address two questions: (1) Are the behavioral effects of low-dose postnatal PCP exposure mediated by neurotransmitter receptors other than the NMDA receptor? and (2) Could other behaviors, besides learning and memory and seizure susceptibility, be affected by low-dose postnatal PCP treatment? The actions of PCP are known to be dose sensitive. At relatively low concentrations (5 mg/kg and under), PCP interacts almost exclusively with the channel blocking site in the NMDA receptor complex (Sircar et al., 1987); however, at higher concentrations, it also interacts with other receptor systems (Javitt and Zukin, 1991), particularly the σ receptor (Sircar et al., 1986; Noda et al., 2001) and the dopaminergic system (Doherty et al., 1980; Deutch et al., 1987; Verma and Moghaddam, 1996; Adams and Moghaddam, 1998). Previously, we have shown that postnatal PCP treatment does not affect the σ receptor (Sircar and Li, 1994). Here, we test the hypotheses that repeated low-dose postnatal PCP treatment does not alter the dopaminergic system, particularly the D_2 receptor, or the hyperlocomotion induced by a high-dose PCP (10 mg/kg) challenge injection.

2. Materials and methods

2.1. Animal

Time-pregnant female Sprague–Dawley rats (between days 17 and 21 of gestation) were obtained from Taconic farms (Germantown, MD) and housed in our animal institute with a 12 hour light/12 hour dark cycle and at a room temperature of 22 °C. Food and water were provided ad libitum. Mothers were left undisturbed until the day after birth. On PD 1 (day of birth was considered as PD 0), litters were culled to 10 pups: 5 males and 5 females. Pups were numbered by injection of India ink into their paws. All pups were weaned on PD 21 and housed by sex in groups of three to four rats per cage. Behavioral testing was carried out between PD 70 and PD 120. Each rat was behaviorally tested only once. Both male and female rats were used in this study. Groups of control and PCP-treated rats were sacrificed as juveniles on PD 21 or as adults, respectively, for biochemical studies. One male and one female pup per litter were used for behavior or biochemical testing. All experimental protocols were approved by the Animal Institute Committee of the Institute for Animal Care at the Albert Einstein College of Medicine and were in compliance with the NIH Guide for the Care and Use of Laboratory Animals (Publication 85-23, revised 1985).

2.2. Drug treatment

Starting on PD 5, pups were injected between 8:00 and 11:00 AM with one of three doses of PCP (1, 3 and 5 mg/kg) intraperitoneally (ip) and continued daily until PD 15. Control pups received saline (10 ml/kg ip) for the same period. All pups from the same litter received the same treatment. To compensate for difference in weight gain between PCP- and saline-treated rats, the size of saline-injected control litters was increased by the introduction of two to four pups of the same age, from separate nonhandled, nontreated litters maintained specifically for this purpose, on the first day of injection and removed 1 day after the last injection (Sircar and Li, 1994; Sircar, 1995). These foster pups were not injected with drug or saline. They were not marked with India ink to separate them from animals to be used for further experimentation.

2.2.1. Drug solutions

Fresh solutions of PCP in physiological saline were prepared for each batch of rats. Drug dosages refer to the hydrochloride salt. Drug solutions were refrigerated after injections and warmed to room temperature prior to injections.

2.3. PCP levels in blood and brain

Male and female Sprague–Dawley rat pups were given a single intraperitoneal PCP (5 mg/kg ip) injection on PD 15 (acute) or daily intraperitoneal injections (5 mg/kg ip) from PD 5 to PD 15 (chronic). Under Metophane® anesthesia, blood samples (100–200 μl) were collected directly from the heart at predetermined time points (30 min, 6 hours and 24 hours) after PCP administration. Rats were then sacrificed by decapitation and brains were removed quickly, weighed and immediately frozen in liquid nitrogen. Blood samples were allowed to clot, centrifuged at $1500 \times g$ for 5 min to obtain serum specimens, frozen immediately on dry ice and used for PCP level determination. All serum and brain samples were stored at −80 °C until analyzed. PCP con-

centrations in serum and brain were determined using the PCP-specific radioimmunoassay (Proksch et al., 2000; Valentine and Owens, 1996).

2.4. Locomotor behavior testing

2.4.1. PCP challenge

On the day of the experiment, adult saline- and PCP-treated rats were removed from their home cages to a sound-attenuated room and placed in individual clear plastic cages with metal grid top that contained bedding at approximately 1 cm depth. Rats were allowed to habituate to the environment for 1 hour before a single intraperitoneal injection of saline or PCP (10 mg/kg) was given. Each rat was used for one treatment level (dosage) only. Treatments were administered to individual rats in a random single-blind manner. Behavioral ratings were made beginning 5 min after drug injection and every 10 min thereafter. Each subject was observed for 1 min and ratings were recorded for each of the three behavioral rating scales during the next 15–20 s. Total duration of each test session was 95 min. Behavioral recordings were made 5 min before PCP/saline injection and again starting at 30 min postinjection and continued for the next 60 min.

2.4.2. Behavioral rating

PCP has been shown to increase locomotor activity and produce stereotypic behavior and ataxia. A modified rating scale of Sturgeon et al. (1979) that concurrently assesses all three dimensions of PCP behavior was used to elucidate the behavioral actions of PCP (Table 1).

Table 1
Modified Sturgeon et al. (1979) PCP behavior rating scale

Rating	Description of behavior
Locomotor activity	
0	Stationary, with little or no movement
1	Movement within localized area of cage, intermittent activity at low rate
2	Movement over a small area of cage, intermittent activity at low-moderate rate
3	Movement over a small area of cage, intermittent activity at a moderate-rapid rate
4	Movement over a large area of cage, intermittent activity at low-moderate rate
5	Movement over a large area of cage, continuous activity at moderate-rapid rate
Stereotypic behavior	
0	Inactive or in-place nonrepetitive activity
1	Locomotor activity, sniffing and grooming more frequent than normal
2	Gagging, weaving, nondirected movements, intermittent grooming, occasional reciprocal forepaw treading (RFT), higher frequency of rearing or sniffing than in 1
3	Moderate and intermittent turning, packpeddling, praying, RFT, nondirected movements, sniffing, weaving, gagging
4	Rapid rate and continuous turning, backpedaling, praying, sniffing, weaving, gagging
5	Dyskinetic extension and flexion of limbs, head and neck, gagging and weaving
Ataxia	
0	Inactive or in-place activity, coordinated movement
1	Unusual, awkward or jerky movements, loss of balance during rearing, occasional falling on side
2	Awkward or jerky movements, moderate rate of falling on side while rearing or moving about
3	Frequent falling on back and/or side when moving, partial impairment of antigravity reflexes
4	Cannot move beyond a restricted area, antigravity reflexes greatly impaired, may support weight on haunches or abdomen
5	Unable to move except for twitching/convulsive movements, occasional rolling on side or raising of head.

2.5. D_2 receptor binding

Groups of postnatal PCP-treated (5 mg/kg) and control rats were sacrificed on PD 21 or as adults, and their striata were dissected out and frozen immediately on crushed ice. Crude synaptosomal membranes were prepared from control and experimental brain regions. D_2 receptor binding was measured using [^{125}I]RTI-55 (2200 Ci/mmol; Perkin-Elmer NEN, Boston, MA) as the radioligand. Aliquots of synaptic membranes were incubated with [^{125}I]RTI-55 (0.01–0.11 nM) for 1 hour at 4 °C in 55.2 mM sodium phosphate buffer pH 7.4. Fifty nanomoles of imipramine were added to the incubation buffer to block the serotonin transporter. Nonspecific binding was carried out under identical conditions but in the added presence of 20 μM mazindol. Protein analysis was performed using the Lowry method (Lowry et al., 1951). Saturation analysis was carried out and the final data were fit to a two-parameter logistic equation to determine the best fit.

2.6. Statistical analysis

Behavioral data were analyzed using a two-way ANOVA analysis (Drug × Sex). One-way ANOVA was performed to compare groups within the same sex followed by Tukey test for post-hoc comparisons. Binding data were statistically evaluated using the Student's *t* test. The level of significance was set at $P < .05$.

3. Results

As reported earlier, body weights of postnatal PCP-treated rats did not differ from large litter saline-treated control rats

(Sircar and Li, 1994; Sircar and Rudy, 1998). There was no delay in the appearance of developmental landmarks in postnatal PCP-treated rats, such as appearance of fur and opening of eyes and ears. Visual inspection of postnatal PCP- and saline-treated rats did not reveal any apparent difference in behavior either on PD 21 or on PD 60.

3.1. Postnatal PCP clearance

3.1.1. PCP level in serum and brain following a single drug injection

To test the hypothesis that the behavioral effects of acute and repeated postnatal PCP treatments were not due to the persistent presence of PCP in rats, we measured the levels of PCP in serum and brain at several time points after PCP injection. Thirty minutes following an acute PCP injection, the level of PCP in the serum of male and female rats was lower than in same-sex brain levels (Table 2). PCP levels in both serum and brain had dropped significantly by 6 hours. In the serum, levels dropped by 74% in males and 71% in females and in the brain by 87% in males and 75% in females. By 24 hours of PCP injection, no PCP was found in the serum and the levels of PCP in the brain were barely detectable.

3.1.2. PCP level in serum and brain following daily repeated drug injections

In the repeated PCP injection group, PCP levels in the serum of male and female rats were similar to those following acute PCP injections (Table 3). However, in the brain, the levels following repeated PCP injections were lower in both male and female rats than after an acute PCP injection (Table 3). At 6 hours, both serum and brain PCP levels were lower compared to those at 30 min postinjection. Also, in the repeated PCP treatment group, drug levels in the brain were lower than after acute administrations. At 24 hours, as in the acute PCP group, following repeated PCP injections, no drug was found in the serum of either male or female rats, and in the brain, only 1–2 ng/mg tissue of PCP was present. These data indicate that the pharmacokinetics of PCP disposal in postnatal rat is similar to that in adult rat. PCP administered to postnatal rat is readily metabolized and within 24 hours of injection almost completely eliminated. Therefore, the long-term neurobehavioral consequences of postnatal PCP administrations are unlikely due to the residual levels of PCP present in the system.

Table 2
PCP level following a single injection of PCP (5 mg/kg ip) on PD 15

Postinjection time	Gender	Serum level (ng/ml)	Brain level (ng/g)
30 min	M	523	937
30 min	F	533	723
6 hours	M	137	121
6 hours	F	153	181
24 hours	M	UD	2.9
24 hours	F	UD	2.43

UD = undetectable (< 1 ng/ml).

Table 3
PCP level following repeated injections of PCP (5 mg/kg ip) from PD 5 to PD 15

Postinjection time	Gender	Serum level (ng/ml)	Brain level (ng/g)
30 min	M	518	406
30 min	F	457	347
6 hours	M	72	25
6 hours	F	52	18
24 hours	M	UD	1.53
24 hours	F	UD	1.33

UD = undetectable (< 1 ng/ml).

3.2. Postnatal PCP treatment and PCP-induced locomotor behavior in adults

3.2.1. Locomotor activity

The behavioral ratings of PCP-induced locomotor activity were measured in adult rats treated postnatally with saline or PCP. Postnatal saline-treated rats given an acute saline injection had an average locomotor score of 1.75 ± 0.48 for males and 1.67 ± 0.88 for females, respectively. In male rats, after a challenge injection of PCP (10 mg/kg), locomotor activity ratings increased significantly in both postnatal saline-treated and PCP-treated animals, but there was no effect of postnatal PCP treatment (Fig. 1). Locomotor activity in rats treated postnatally with 5 mg/kg dose was no greater than in 3 mg/kg PCP, 1 mg/kg PCP or saline-injected rats [$F(3,32) = 1.304$, $P = 0.2900$]. In female rats, PCP also increased locomotor activity following postnatal saline and PCP treatment (Fig. 1). PCP-induced behavioral ratings were higher in female rats than in male rats, particularly in the 1 and 3 mg/kg PCP groups, indicating that locomotor activating effect of PCP was greater in females than males. Again, as with the males, there was no effect of postnatal PCP treatment on locomotor activity in female rats [$F(3,48) = 0.5427$, $P = 0.6554$].

3.2.2. Stereotypic behavior

The ratings of PCP-induced stereotypic behaviors were averaged within treatment groups at 10 min intervals and presented in Fig. 2. No male or female postnatal saline- or PCP-treated rat showed any stereotypic behavior following an acute saline injection. Injecting adult rats, treated postnatally with saline or PCP, with a challenge PCP injection increased their stereotypic scores. Female control and experimental rats had higher stereotypic scores than similarly treated male rats. Postnatal saline-treated and 5 mg/kg PCP-treated adult male rats injected with PCP scored significantly lower than female rats (Fig. 2). Male [$F(3,32) = 2.110$, $P = 0.1184$] and female [$F(3,48) = 1.744$, $P = 0.1705$] PCP-treated rats did not differ in their stereotypic scores from same-sex saline-treated controls (Fig. 2).

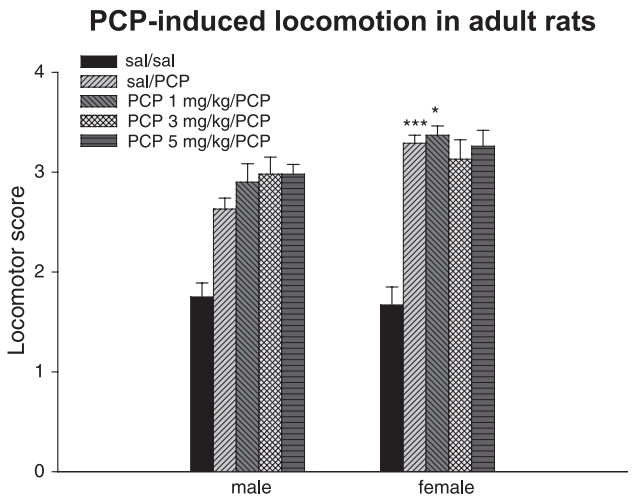

Fig. 1. Male and female rats were treated postnatally with one of three doses of PCP (1.0, 3.0 and 5.0 mg/kg) or equivalent volume of saline from PD 5 to PD 15. As adults, all postnatal PCP- and saline-treated rats were challenged with one dose of PCP (10 mg/kg ip). PCP-induced locomotor activity was scored during the 60 min observation period following injection using the modified Sturgeon et al. (1979) scale. A mean score was assigned to each rat. Female (saline- and PCP-treated) rats were more sensitive to PCP compared to similarly treated male rats ($*P<.05$, $***P<.001$ compared to males). There was no effect of postnatal PCP treatment on locomotor activity in either sex. Values are mean ± S.E.M. sal/sal, postnatal saline injection with adult saline challenge. sal/PCP, postnatal saline injection with adult PCP (10 mg/kg) challenge. PCP 1 mg/kg/PCP, postnatal PCP (1 mg/kg) injection with adult PCP (10 mg/kg) challenge. PCP 3 mg/kg/PCP, postnatal PCP (3 mg/kg) injection with adult PCP (10 mg/kg) challenge. PCP 5 mg/kg/PCP, postnatal PCP (5 mg/kg) injection with adult PCP (10 mg/kg) challenge.

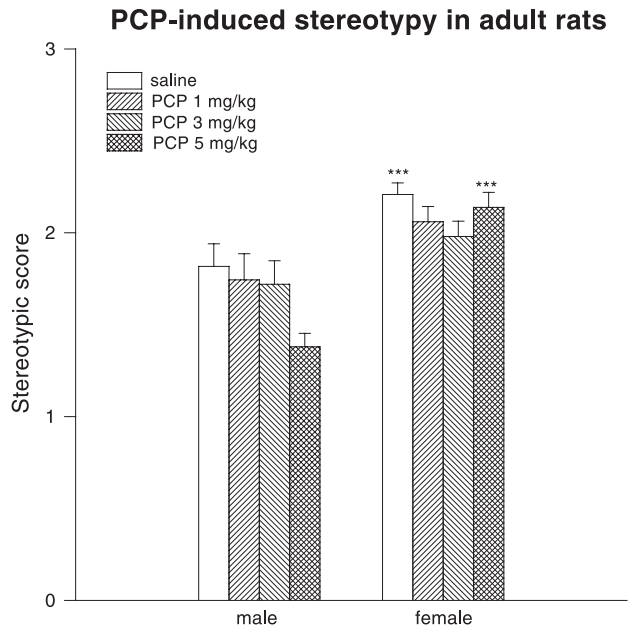

Fig. 2. Postnatal treatments were as described in Fig. 1. PCP-induced stereotypic behavior was scored during the 60 min observation period following a single injection of PCP (10 mg/kg) using the modified Sturgeon et al. (1979) scale. A mean stereotypic score was calculated for each rat. Female saline- and PCP-treated rats were more sensitive to PCP-induced stereotypic behavior compared to male rats ($***P<.005$ compared to males). Postnatal PCP-treated male and female rats did not differ from same-sex saline-treated controls. Values are mean ± S.E.M.

3.2.3. Ataxia

Adult male and female rats treated postnatally with saline or varying doses of PCP (1, 3 and 5 mg/kg ip) were given a single injection of PCP (10 mg/kg) and ataxia score was scored using the modified Sturgeon rating scale (Table 1). All postnatal saline-treated male and female rats injected with saline had an ataxic score of 0 (data not shown). PCP challenge injection increased ataxic scores in both male and female saline and PCP-treated rats. There was no effect of postnatal PCP on ataxic score in either male [$F(3,33)=2.538$, $P=0.075$] or female [$F(3,46)=0.6782$, $P=0.5698$] rats. As with the locomotor activity and stereotypic scores, ataxia scores in female rats were higher than in male rats (Fig. 3).

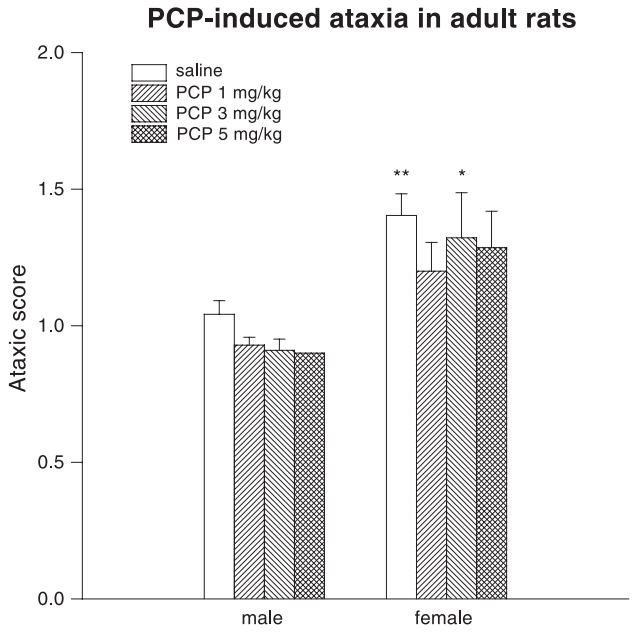

Fig. 3. For details of postnatal treatments, see legend in Fig. 1. PCP-induced ataxic behavior was scored during the 60 min observation period using the modified Sturgeon et al. (1979) scale, and a mean ataxic score was determined for each rat. Female saline- and PCP-treated rats were more sensitive to PCP-induced ataxia compared to male rats ($*P<.05$, $**P<.005$ compared to males). Postnatal PCP-treated rats of either sex did not differ from same-sex saline-treated rats. Values are mean ± S.E.M.

3.3. Postnatal PCP and striatal D_2 receptor

3.3.1. [^{125}I]RTI-55 binding in striatal membranes

Saturation D_2 receptor binding experiments were carried in the striata from adult rats treated postnatally with saline or the highest dose of PCP used in the behavioral study (5 mg/kg). Additional groups of male and female saline-treated and PCP-treated rats were sacrificed on PD 21. [^{125}I]RTI-55 binding was measured in synaptic membranes prepared from drug- and saline-treated juvenile and adult male and female

Table 4
[^{125}I]RTI-55 maximal binding in postnatal PCP- and saline-treated rats

Condition	PD 21 M	PD 21 F	Adult M	Adult F
Saline	205.62 ± 48.93	265.25 ± 31.70	537.00 ± 60.82	570.33 ± 30.34
PCP 5	191.20 ± 30.94	341.73 ± 34.36	530.00 ± 66.48	472.25 ± 22.91 *

Values are mean ± S.D. and are in fmol/mg protein.
PCP 5 refers to PCP 5 mg/kg.
* $P < .05$ compared to same-sex saline-treated rat.

rat striata, and saturable binding analyses were carried out. Under the binding conditions used, Scatchard analysis of [^{125}I]RTI-55 binding data revealed that the ligand bound with high affinity to a single class of binding sites (mean K_d of 0.98 ± 0.27 nM, range of 0.76–1.66 nM). Postnatal PCP treatment did not alter striatal D_2 receptor maximal binding in juvenile rats (PD 21) of either sex (Table 4). In adult male rats, postnatal PCP administration did not have any effect on striatal D_2 receptor binding. In adult female PCP-treated rats, there was a mild but significant 17% reduction in maximal binding (Table 4). K_d values did not vary with treatment or sex.

4. Discussion

The dosage of PCP used for injections in this study was restricted to 5 mg/kg or less (1 and 3 mg/kg). These doses of PCP were specifically chosen to study the behavioral and biochemical effects of the drug at low doses. In adult animals, the effects of low-dose PCP are thought to be primarily mediated by the NMDA receptor, whereas at relatively higher doses (10 mg/kg and more) PCP interacts with several different receptor types such as the σ receptor and D_2 receptor. Earlier, we have shown that low-dose PCP injections in postnatal rats do not affect the σ receptor (Sircar et al., 1995). In this study, whether low-dose PCP in postnatal rat alters the D_2 receptor was examined. Also, the effects of low-dose postnatal PCP treatment on locomotor behavior were studied.

The present study demonstrates that repeated administrations of low-dose PCP in postnatal rats did not alter PCP (10 mg/kg)-induced locomotor behavior—stereotypy, locomotion or ataxia—in both adult male and female rats. Another important finding is that postnatal PCP treatment minimally altered striatal D_2 receptor regulation in a gender-specific manner.

4.1. PCP levels in serum and brain

One reason for the effects of postnatal PCP on adult animal behavior could be due to the lingering effects of PCP released from lipophilic sources. To rule out this possibility, PCP levels in blood and brain were measured at several time points following a single PCP injection and after repeated PCP injections in postnatal rats. In our experiments, 24 hours after a single PCP injection or the last chronic PCP injection, no PCP was found in the blood. At 24 hours, PCP levels in the brain were barely detectable at 2–3 ng/mg tissue (level of detection was 1 ng/mg tissue). The most parsimonious explanation is that PCP is metabolized in postnatal rats and that no accumulation of PCP occurs in the developing brain. In adult rats, elimination half-life of PCP ranges between 2 and 16 hours (Cook et al., 1982; Woodworth et al., 1985). Wessinger and Owens (1991a) chronically infused adult rats with 10 mg/kg PCP intravenously for 10 days and found that after infusions were terminated the log PCP concentrations declined in a linear fashion over time, with an average $T_{1/2}$ of 4.6 hours. Fico and Vanderwende (1988) injected pregnant mice with PCP (20 mg/kg sc) for 7 days (G12–G18) and measured the levels of PCP and its metabolites in fetal mice brain at several time points after the last injection. Peak concentration of PCP in G18 fetal brain (1.11 μg/g fetal brain) was reached 30 min after the last injection and the $T_{1/2}$ of PCP was 27 min. These data indicate that, as with adult rats, perinatal rats rapidly metabolize PCP and the idea that PCP persists over a long period of time to cause neurobehavioral deficits is not true. An interesting finding was that following an acute PCP injection, PCP levels in the brain were higher than after repeated PCP injections. This observation needs further examination.

4.2. Postnatal PCP and locomotor behavior in adult rats

PCP induces a characteristic syndrome of hyperactivity, stereotypy and ataxia (Sturgeon et al., 1979; Castellani and Adams, 1981; Wessinger and Owens, 1991b). Behavioral effects of PCP are dose dependent. Sturgeon et al. (1979) reported that a dose of 7.5 mg/kg or less induces significant locomotor activity and at dosages of 10 mg/kg and higher, produces significant ataxia. Stereotypic behavior, particularly PCP-induced sniffing, is also more predominant at doses of PCP above 10 mg/kg. PCP-induced stereotypies begin with sniffing and exploration and progress through gagging, head weaving, reciprocal forepaw treading, turning, back peddling and "praying" and end with dyskinetic extension and flexion of limbs, head and neck (Sturgeon et al., 1979). The lack of postnatal PCP treatment on adult PCP-induced locomotor behavior (stereotypic behavior, ataxia and locomotor activity) seen in the present study is consistent with our hypothesis that low-dose PCP (5 mg/kg and under) in postnatal rats selectively alters some behaviors, particularly those associated with cortical and limbic NMDA receptors, but not others. Earlier, we have shown that behaviors, such as seizure susceptibility (Sircar et al., 1994) and learning and memory (Sircar and Rudy, 1998; Sircar, 2001, 2003), are significantly affected by low-dose postnatal PCP treatment.

4.3. Postnatal drug treatment and malnutrition

Postnatal PCP treatment had minimal effects on locomotor behavior in adult rats. These data although in agreement with those reported by Gorter and de Bruin (1992) differ from other studies (Facchinetti et al., 1994; Semba et al., 2001). Gorter and de Bruin (1992) injected rats from PD 8 to PD 19 with the PCP-like drug MK-801 and found no difference in the open field activity between MK-801-treated and control rats. Other groups have reported changes in stereotypic behavior (Semba et al., 2001) and spontaneous locomotor activity (Facchinetti et al., 1994). Semba et al. (2001) injected rats with 5 and 10 mg/kg PCP daily from PD 1 to PD 14 and found that PCP dose-dependently reduced methamphetamine-induced stereotypic behavior. In a study by Facchinetti et al. (1994), rats were treated with escalating doses of the competitive NMDA receptor antagonist CGP 39551 from PD 1 to PD 22 (1.5 mg/kg from PD 1 to PD 5, 3 mg/kg from PD 6 to PD 10, 4 mg/kg from PD 11 to PD 14, 5 mg/kg from PD 15 to PD 18 and 6 mg/kg from PD 19 to PD 22). When tested between PD 55 and PD 75, CGP 39551-treated rats exhibited increased spontaneous locomotor activity compared to saline-treated controls. In these studies (Semba et al., 2001; Facchinetti et al., 1994), body weights of drug-treated rats were significantly lower than controls. Semba et al. (2001) commented that the severe neonatal undernutrition (31% reduction in body weight) induced by injections of PCP may account for the altered mesolimbic dopaminergic system and locomotion. The dopaminergic system is known to be particularly vulnerable to undernutrition (Marichich et al., 1979; Ramanamurthy, 1977). Shoemaker and Wurtman (1971) induced restricted malnutrition during the postnatal period and reported hypofunctioning of the dopaminergic system. This raises the possibility that some of the developmental sequelae of postnatal drug exposure seen by Semba et al. (2001) and Facchinetti et al. (1994) might be a result of undernutrition and its associated consequences. Several techniques have been used to control for weight gain in pups such as restricted feeding of mothers during lactation (Lewis et al., 1979), split-litter treatment (pups are foster cared by nonlactating, maternalized virgin females (‘‘aunts’’) for varying periods of time per day and artificial rearing (pups are reared in a standardized artificial manner (Tonkiss et al., 1987). In the present study, the large litter rearing method for reducing weight gain in control rats was used (Dobbing et al., 1971; Zagon and McLaughlin, 1982). Control pups were exposed to daily handling, injections and separation from their mothers and subjected to equivalent levels of undernutrition as the PCP-treated pups. On PD 5, two to four foster pups from separate litters were added to the saline litter. These additional pups were removed from the foster cage on PD 16, a day after the last drug injection. Pups used to increase the litter size were not marked (with food pad India ink injection) or injected with any drug or saline. In the past, we have used this protocol to control for PCP-induced loss of body weight gain in pups (Sircar et al., 1994, 1996; Sircar and Li, 1994; Sircar and Rudy, 1998). Controlling for PCP-induced reduction in body weight appeared to ameliorate any significant effect of postnatal PCP treatment on rat locomotor behavior.

4.4. PCP behavioral effects and dopaminergic system

The stimulant effect of PCP on locomotor activity has been thought to be mediated by the dopaminergic system (Doherty et al., 1980; Freeman and Bunney, 1984). Systemic administration of PCP increases DA turnover and metabolism in the mesolimbic and mesocortical DA systems (Deutch et al., 1987) and striatal DA overflow (Mele et al., 1998). Noncompetitive (PCP and MK-801) as well as competitive antagonists of the NMDA receptor channel complex activate dopaminergic neurotransmission (Adriani et al., 1998; Hiramatsu et al., 1989; Liljequist et al., 1991; Schmidt et al., 1991; Tomić et al., 1997). Others have reported that NMDA antagonist-induced hyperlocomotion is not due to an increase in the levels of DA in the striatum (Druhan et al., 1996), and in adult rats, corticolimbic DA neurotransmission has been shown not to be associated with the locomotor effects of PCP (Adams and Moghaddam, 1998).

DA is the predominant catecholamine neurotransmitter in the brain and is associated with a variety of functions including locomotor activity (see review by Missale et al., 1998). Pharmacological, biochemical, physiological and anatomical receptor distribution patterns indicate that DA interacts with two families of receptors—the D_1-like family (D_1 and D_5 receptors) and the D_2-like family (D_2, D_3 and D_4 receptors). Unlike D_1 receptors that are expressed widely (substantia nigra pars reticulata, nucleus accumbens, olfactory tubercle, thalamus, hypothalamus, striatum and limbic areas) and in high levels in the brain, D_2 receptors are found mainly in the striatum, the olfactory tubercle and the core of the nucleus accumbens. Activation of D_2 receptor decreases DA release and decreases locomotor activity, whereas postsynaptic D_2 receptors slightly increase locomotion. Activation of D_1 receptors has little or no effect on locomotor activity, but for maximal locomotor stimulation, synergistic interaction between D_1 and D_2 receptor is necessary (Gershanik et al., 1983; Missale et al., 1998). In the present study, the effect of repeated postnatal PCP administration on D_2 receptor activity in the striatum was examined. In adult animals, D_2 receptor antagonists have been shown to reduce PCP-induced locomotion (Freed et al., 1980; Kitaichi et al., 1994) and ameliorate behavioral impairment by ketamine, a PCP-like drug (Krystal et al., 1995). Chronic administration of MK-801, another more potent PCP-like drug, in adult rats has been reported to decrease D_2 receptor number in the striatum (Dall’Olio et al., 1992; Gandolfi and Dall’Olio, 1993). Semba et al. (2001) reported that neonatal PCP treatment attenuated mesolimbic dopaminergic function. Dall’Olio et al. (1994) treated neonatal rats with the com-

petitive NMDA antagonist CGP 39551 from PD 1 to PD 22 and studied the kinetics of striatal DA receptors. Chronic neonatal treatment with CGP 39551 increased the maximal number of [^{3}H] spiroperidol-labeled D_2 receptors in the striatum of adult rats. Dall'Olio et al. (1994) found no effect of neonatal NMDA antagonist administration on [^{3}H]SCH 23390 binding to the D_1 receptor, either on maximal binding or on binding affinity. Our data did not show any biochemical alteration in the striatal D_2 receptor functioning following postnatal PCP treatment in juvenile and adult male rats, and only a slight reduction in maximal binding in adult female rats. Whether postnatal PCP treatment alters other DA receptor types in the striatum, or elsewhere in the brain, needs further investigation. Regions besides the striatum, such as the subthalamic nucleus, entopeduncullar nucleus or substantia nigra, may be important in the PCP-induced increased locomotor output in rats and need to be further investigated.

Repeated low-dose postnatal PCP administrations selectively alter behaviors such as seizure generation and spatial learning and memory (Sircar et al., 1994; Sircar and Rudy, 1998), but not others (drug-induced locomotor activity). Since PCP affinity for the NMDA receptor complex is much greater than its ability to inhibit DA uptake (Mele et al., 1998), it appears that the former mechanism may be a more critical determinant of the behavioral actions of postnatal PCP treatment. Although PCP interacts with a variety of cellular substrates including the σ receptor (Sircar et al., 1986, 1995), nicotine cholinergic receptor muscarinic cholinergic receptor (Vincent et al., 1978) and voltage-dependent K^+ channel (Bartschat and Blaustein, 1986), its low-dose behavioral properties are mediated primarily through the blockade of the NMDA receptor-mediated neurotransmission.

4.5. Postnatal PCP and gender-specific neurochemical effects

Our data suggest that the PCP challenge-induced behavioral effects are sexually dimorphic in nature, with adult females showing a more robust response than adult males. Female rats are known to be more sensitive to NMDA receptor blockade than males (Honack and Loscher, 1993). Sex difference in neural responses to NMDA receptor antagonists have been reported (D'Souza et al., 1999; Giordano and Mejía-Viggiano, 2001). Male rats treated with low-dose MK-801 had little or no effect on locomotor, stereotypic and ataxic behavior, but the same dose in female rats caused stereotypy (head bobbing and thrashing), hyperactivity and uncoordinated movements (D'Souza et al., 1999). Giordano and Mejía-Viggiano (2001) reported that female rats showed two to three times more locomotor activity (mean total distance traveled) than male rats treated with 0.25 mg/kg MK-801. In male rats, MK-801 has been shown to have negligible effects on the expression of the immediate early c-*fos* gene, whereas in female rats it causes large inductions of c-*fos* in several brain regions (D'Souza et al., 1999). MK-801 in female rats with lesions in the striatum, unlike male rats, failed to stimulate locomotor activity, suggesting that normal striatal function is important for the expression of MK-801 effects only in female rats (Giordano and Mejía-Viggiano, 2001). These gender effects may result from direct hormonal influences on striatal functions (Emerich et al., 1991) or from sexual dimorphism in the organization of the striatum (Becker, 1999). In the present study, postnatal PCP treatment caused a slight down-regulation of striatal D_2 receptors in adult female rats but not male rats.

In conclusion, adult rats treated postnatally with low-dose PCP have dysfunction in the NMDA neurotransmission (Sircar and Li, 1994; Sircar et al., 1996). They do not show any alterations in PCP-induced locomotor behavior and have minimal gender-specific changes in the density of D_2 receptors in the striatum.

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References

Adams B, Moghaddam B. Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. J Neurosci 1998;18:5545–54.

Adriani W, Felici A, Sargolini F, Roullet P, Usiello A, Oliverio A, et al. *N*-methyl-D-aspartate and dopamine receptor involvement in the modulation of locomotor activity and memory processes. Exp Brain Res 1998;123:52–9.

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

Bartschat DK, Blaustein MP. Phencyclidine in low-doses selectively blocks a presynaptic voltage-regulated potassium channel in rat brain. Proc Natl Acad Sci U S A 1986;83:189–92.

Becker JB. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol Biochem Behav 1999;64:803–12.

Carboni E, Imperato A, Perezzani L, Di Chiara G. Amphetamine, cocaine, phencyclidine and nomifensin increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 1989;28:653–61.

Castellani S, Adams PM. Acute and chronic phencyclidine effects on locomotor activity, stereotypy and ataxia in rats. Eur J Pharmacol 1981; 73:143–54.

Chen G, Ensor CR, Russel D, Bohnier B. The pharmacology of (1-(phenylcyclohexyl) piperidine HCl. J Pharmacol Exp Ther 1959;127:241–50.

Cook CE, Brine DR, Jeffcoat AR, Hill JM, Wall ME, Perez-Reyes M, et al. Phencyclidine disposition after intravenous and oral doses. Clin Pharmacol Ther 1982;31:625–34.

Dall'Olio R, Gandolfi O, Montanaro N. Effect of chronic treatment with dizocilpine (MK-801) on the behavioral response to dopamine receptor agonists in the rat. Psychopharmacology 1992;107:591–4.

Dall'Olio R, Facchinetti F, Contestabile A, Gandolfi O. Chronic neonatal blockade of *N*-methyl-D-aspartate receptor by CGP 39551 increases dopaminergic function in adult rat. Neuroscience 1994;63:451–5.

Deutch AY, Tam S-Y, Freeman AS, Bowyers Jr MB, Roth RH. Mesolimbic and mesocortical dopamine activation induced by phencyclidine: contrasting pattern to striatal response. Eur J Pharmacol 1987;134:257–64.

Dobbing J, Hopewell JW, Lynch A. Vulnerability of developing brain: VII. Permanent deficit of neurons in cerebral and cerebellar cortex following early mild undernutrition. Exp Neurol 1971;32:439–47.

Doherty J, Simonovic M, So R, Meltzer H. The effects of phencyclidine on dopamine synthesis and metabolism in rat striatum. Eur J Pharmacol 1980;65:139–49.

Druhan JP, Rajabi H, Stewart J. MK-801 increases locomotor activity without elevating extracellular dopamine levels in the nucleus accumbens. Synapse 1996;24:135–46.

D'Souza DN, Harlan RE, Garcia MM. Sexual dimorphism in the response to *N*-methyl-D-aspartate receptor antagonists and morphine on behavior and c-*fos* induction in the rat brain. Neuroscience 1999;93: 1539–47.

Emerich DF, Zubrycki EM, Shipley MT, Norman AB, Sanberg PR. Female rats are more sensitive to the locomotor alterations following quinolinic acid-induced striatal lesions: effects of striatal transplants. Exp Neurol 1991;11:369–78.

Facchinetti F, Dall'Olio R, Ciani E, Sparapani M, Virgili M, Contestabile A, et al. Long lasting effects of chronic neonatal blockade of *N*-methyl-D-aspartate receptor through the competitive antagonist CGP 39551 in rats. Neuroscience 1994;60:343–53.

Fagg GE. Phencyclidine and related drugs bind to the activated *N*-methyl-D-aspartate receptor-channel complex in rat brain membranes. Neurosci Lett 1987;76:221–7.

Fico TA, Vanderwende C. Phencyclidine during pregnancy: fetal brain levels and neurobehavioral effects. Neurotoxicol Teratol 1988;10: 349–54.

Freed WJ, Weinberger DR, Bing LA, Wyatt RJ. Neuropharmacological studies of phencyclidine (PCP)-induced behavioral stimulation in mice. Psychopharmacology 1980;71:291–7.

Freeman AS, Bunney BS. The effects of phencyclidine and *N*-allylnormetazocine on midbrain dopamine neuronal activity. Eur J Pharmacol 1984;104:287–93.

Gandolfi O, Dall'Olio R. Chronic treatment with MK-801 decreases D_2 dopamine receptor function in rat striatum. Pharmacol Biochem Behav 1993;4:683–7.

Gershanik O, Heikkila RE, Duvoisin RC. Behavioral correlations of dopamine receptor activation. Neurology 1983;33:1489–92.

Giordano M, Mejía-Viggiano MC. Gender differences in spontaneous and MK-801-induced activity after striatal lesions. Brain Res Bull 2001; 56:553–61.

Gorter JA, de Bruin JPC. Chronic neonatal MK-801 treatment results in an impairment of spatial learning in adult rat. Brain Res 1992;580: 12–7.

Hertel P, Mathé JM, Nomikos GG, Iurlo M, Mathé AA, Svensson TH. Effects of D-amphetamine and phencyclidine on behavior and extracellular concentrations of neurotensin and dopamine in the ventral striatum and the medial prefrontal cortex of the rat. Behav Brain Res 1996;72: 103–14.

Hiramatsu M, Cho AK, Nabeshima T. Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. Eur J Pharmacol 1989;166:359–66.

Honack D, Loscher W. Sex differences in NMDA receptor mediated responses in rats. Brain Res 1993;620:167–70.

Hondo H, Yonezawa T, Nakahata T, Nakamura K, Hirano M, Uchimura H, et al. Effect of phencyclidine on dopamine release in the rat prefrontal cortex; an in vivo microdialysis study. Brain Res 1994;633: 337–42.

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

Kanner M, Meltzer HY, Davis JM. Pharmacologic aspects of the locomotor stimulation produced by phencyclidine in the rat. SFN Neurosci Abstr 1975;1:366.

Kitaichi K, Yamada K, Hasegawa T, Furukawa H, Nabeshima T. Effects of risperidone on phencyclidine-induced behaviors: comparison with haloperidol and ritanserin. Jpn J Pharmacol 1994;66:181–9.

Krystal J, Karper L, Bennett A, Abi-Saab D, Souza C, Abi-Dargham A, et al. Modulating ketamine-induced thought disorder with lorazepam and haloperidol in humans. Schizophr Pre 1995;15:156.

Lewis P, Patel AJ, Balázs R. Effect of undernutrition on cell generation in the rat hippocampus. Brain Res 1979;168:186–9.

Liljequist S, Ossowska K, Grabowska-Anden M, Anden NE. Effect of the NMDA receptor antagonist MK-801 on locomotor activity and on the metabolism of dopamine in various brain areas of mice. Eur J Pharmacol 1991;195:55–61.

Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265–75.

Marcus MM, Mathé JM, Nomikos GG, Svensson TH. Effects of competitive and non-competitive NMDA receptor antagonists on dopamine output in the shell and core subdivisions of the nucleus accumbens. Neuropharmacology 2001;40:482–90.

Marichich ES, Molina VA, Orsingher OA. Persistent changes in central catecholaminergic systems after recovery of perinatally undernourished rats. J Nutr 1979;109:1045–50.

Mele A, Thomas ND, Pert A. Different mechanisms underlie MK-801 and dopamine agonist induced locomotor activity. Neuroscience 1998; 82:43–58.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiol Rev 1998;78:189–225.

Noda A, Noda Y, Ichihara K, Mamiya T, Nagai T, Sugiura S, Furukawa H, Nabeshima T. Phencyclidine impairs learning in mice: interaction between glutamatergic systems and σ receptors. Neuropsychopharmacol 2001;24:451–60.

Proksch JW, Gentry WB, Owens SM. The effect of rate of drug administration on the extent and time course of phencyclidine distribution in rat brain, testis, and serum. Drug Metab Dispos 2000;28:742–7.

Ramanamurthy PS. Maternal and early postnatal malnutrition and transmitter amines in rat brain. J Neurochem 1977;28:253–4.

Schmidt WJ, Zadow B, Kretschmer BD, Hamber W. Anticataleptic potencies of glutamate-antagonists. Amino Acids 1991;1:225–37.

Semba J, Tanaka N, Wakuta M, Suhara T. Neonatal phencyclidine treatment selectively attenuates mesolimbic dopamine function in adult rats as revealed by methamphetamine-induced behavior and c-*fos* mRNA expression in the brain. Synapse 2001;40:11–8.

Shoemaker W, Wurtman R. Perinatal undernutrition: accumulation of catecholamines in rat brain. Science 1971;171:1017–9.

Sircar R. Chronic postnatal phencyclidine administration in female rat delays onset of puberty but has no effect on pentylenetetrazol-induced seizure-susceptibility. Brain Res 1995;694:318–21.

Sircar R. Postnatal phencyclidine treatment in rats dose-dependently affects spatial learning and memory. SFN Abstr 2001;31:319.6.

Sircar R. Postnatal phencyclidine-induced deficit in adult water maze performance is associated with *N*-methyl-D-aspartate receptor upregulation. Int J Dev Neurosci [in press].

Sircar R, Li C-S. PCP/NMDA receptor-channel complex and brain development. Neurotoxicol Teratol 1994;16:369–75.

Sircar R, Rudy JW. Repeated neonatal phencyclidine treatment impairs performance of a spatial task in juvenile rats. Ann N Y Acad Sci 1998; 844:303–9.

Sircar R, Zukin SR. Quantitative localization of [^{3}H]TCP binding in rat brain by light microscopy autoradiography. Brain Res 1985;344:142–5.

Sircar R, Nichtenhauser R, Ieni JR, Zukin SR. Characterization and autoradiographic visualization of (+)[^{3}H]SKF10,047 binding in rat and

mouse brain: further evidence for phencyclidine/"σ opiate" receptor commonality. J Pharmacol Exp Ther 1986;237:681–8.

Sircar R, Rappaport M, Nichtenhauser R, Zukin SR. The novel anticonvulsant MK-801: a potent and specific ligand of the brain phencyclidine/σ-receptors. Brain Res 1987;435:235–48.

Sircar R, Veliskova J, Moshe SL. Chronic neonatal phencyclidine treatment results in age-related changes in pentylenetetrazol-induced seizures. Dev Brain Res 1994;81:185–91.

Sircar R, He H-J, Li C-SD. Chronic postnatal phencyclidine treatment on [^{3}H](+)pentazocine binding in juvenile rat brain. Dev Brain Res 1995; 88:224–6.

Sircar R, Follesa P, Ticku MK. Chronic neonatal PCP differentially regulates mRNA levels for NMDA receptor subunits. Mol Brain Res 1996; 40:214–20.

Sturgeon RD, Fessler RG, Meltzer HY. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. Eur J Pharmacol 1979;59:169–79.

Tomić M, Vukosavić S, Joksimović J. Acute amphetamine and/or phencyclidine effects on the dopamine receptor specific binding in rat brain. Eur Neuropharmacol 1997;7:295–301.

Tonge SR, Leonard BE. Partial antagonism of the behavioral and neurochemical effects of phencyclidine by drugs affecting monoamine metabolism. Psychopharmacologia 1972;24:516–20.

Tonkiss J, Smart JL, Massey RF. Effects of early life undernutrition in artificially reared rats: 2. Subsequent behavior. Physiol Behav 1987; 41:555–62.

Valentine JL, Owens SM. Antiphencyclidine monoclonal antibodies significantly change phencyclidine concentrations in brain and other tissues in rats. J Pharmacol Exp Ther 1996;278:717–24.

Verma A, Moghaddam B. NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alteration performance in rats: modulation by dopamine. J Neurosci 1996;16:373–9.

Vincent JP, Cavey D, Kamenka JM, Geneste P, Lazdunski M. Interactions of phencyclidines with the muscarinic and opiate receptors in the central nervous system. Brain Res 1978;152:176–82.

Wessinger WD, Owens SM. Chronic administration of phencyclidine of phencyclidine: pharmacokinetic comparison of intravenous and subcutaneous infusions in Sprague–Dawley rats. Drug Metab Dispos 1991a; 19:719–21.

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

Woodworth JR, Owens SM, Mayersohn M. Phencyclidine disposition kinetics in dogs as a function of dose and route of administration. J Pharmacol Exp Ther 1985;234:654–61.

Xu X, Domino EF. A further study on asymmetric cross-sensitization between MK-801 and phencyclidine-induced ambulatory activity. Pharmacol Biochem Behav 1999;63:413–6.

Zagon IS, McLaughlin PJ. Comparative effects of postnatal undernutrition and methadone exposure on protein and nucleic acid contents of the brain and cerebellum in rats. Dev Neurosci 1982;5: 385–93.