Effects of Prenatal Administration of Phencyclidine on the Learning and Memory Processes of Rat Offspring

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The effects of prenatal administration of phencyclidine (PCP) on the learning and memory processes of rat offspring were investigated at doses below the level for producing malformations. The offspring prenatally treated with PCP (10 or 20 mg/kg) on days 7 to 17, as well as on days 7 to 21 of gestation, showed disruption of the acquisition of passive avoidance response and pole-climbing avoidance response at the ages of 4 and 7 weeks, respectively. The brain weight of the offspring prenatally treated with PCP was significantly decreased. These results suggest that prenatal PCP administration impairs learning and memory processes of passive and active avoidance tasks and that more attention should be given to the developmental toxicity of PCP.

Keywords — phencyclidine; prenatal administration; perinatal administration; offspring; pole-climbing; avoidance response; passive avoidance behavior

Introduction

Phencyclidine (PCP) has been identified as a major drug of abuse.¹⁾ In this capacity, the chance of it being ingested by women of reproductive age is great, yet little information is available regarding its possible adverse effects on reproduction, development and subsequent behavioral activity in the offspring. However, Cooper *et al.*²⁾ have demonstrated that PCP administered to sows just prior to delivery crossed the placenta and remained in the plasma of the piglet for at least 48 h after delivery. Furthermore, the concentration of PCP in the plasma was almost ten times higher in the piglets than in the sows. In the human neonate with a mother having a documented history of PCP abuse, PCP was detected in the newborn's urine 7 d postpartum.³⁾ In addition, the concentration of PCP in the fetuses of mice was 7 times higher than in the plasma of dams.⁴⁾ Furthermore, in the fetuses PCP was hardly metabolized.⁴⁾ All of the above findings suggest that PCP is able to cross the blood-placenta barrier easily and remains in the fetal brain in high concentrations, adversely affecting the developing nervous systems.

Prenatal exposure to ethanol, another abused drug, reduces locomotor habituation using

open-field⁵⁾ and hole-board⁶⁾ techniques, avoidance performance using conditioned taste aversion,⁷⁾ one- and two-way active avoidance^{8,9)} and passive avoidance.¹⁰⁾ On the contrary, prenatal exposure to another abused drug, amphetamine, facilitated conditioned avoidance.^{11,12)} Recently, Nabeshima *et al.*¹³⁾ have reported that prenatal administration of a nonteratogenic dose of PCP produces a delay in the development of some behaviors, but perinatal PCP administration fails to produce toxicity of behavioral development. However, little information is available regarding its possible adverse effects on learning and memory processes on offspring. Thus, the effects of prenatal administration of a nonteratogenic dose of PCP on learning and memory processes of Sprague-Dawley rats were examined.

Materials and Methods

Animals — Twelve-week-old, sexually mature virgin female rats of the Sprague-Dawley substrain (Charles River Breeding Co., Japan) were used in this phase of the study. Proestrus females were individually caged overnight with 12-week-old males of the same substrain and those exhibiting spermatozoa in their vaginal lavage on the following morning were consid-

ered to be in day 0 of pregnancy. Pregnant females were caged individually in a climate-controlled facility and maintained on Oriental laboratory chow (Oriental Co., Japan) and tap water *ad lib*. The numbers of live pups were 210, 85, and 106 from 15 vehicle-, 6 PCP (10 mg/kg)- and 8 PCP (20 mg/kg)-treated dams, respectively. No significant difference was observed in the number of female and male pups. Litter size was standardized to 4 female and 4 male pups on day 4. Pups were bred by the same dam. The dam was removed from the litter on day 21 postpartum for weaning. Siblings of the same sex were housed together.

Drug Administration — The dose level of phencyclidine hydrochloride (10 or 20 mg/kg; PCP synthesized by us, identified by nuclear magnetic resonance (NMR) and infrared (IR)) used in the present study was selected on the basis of preliminary observations that PCP did not produce malformations at these doses. Two groups of dams were treated with PCP during different gestation periods: (1) an experimental group in which the animals received daily i.p. injections of PCP (10 and 20 mg/kg) at 9:00–10:00 a.m. on days 7–17 of gestation (PCP/G_{7–17}); (2) another experimental group received daily i.p. injections of PCP (10 mg/kg) on days 7–21 of gestation (PCP/G_{7–21}). Control groups of animals were given i.p. injection of saline. PCP or saline was injected into the shallow medial abdomen of the dam to avoid the womb. The mothers were weighed prior to every injection. At this time the mothers were also examined for evidence of poor physical health or behavioral disturbance which might indirectly affect fetal development apart from direct drug effects upon the fetuses. If a mother's health was poor, she was discarded from the study.

To investigate whether PCP-induced amnesia is related to the functional changes in the acetylcholinergic, serotonergic and opioidergic neuronal systems, normal female Sprague-Dawley rats were treated with PCP (12.5 mg/kg, i.p.) immediately after step-through passive avoidance task training at the age of 4 weeks. Physostigmine sulfate (Merk), ritanserin (Janssen-Kyowa) or naloxone (Endo Laboratories) was administered s.c. in combination with PCP.

Methods for Examining Learning and Memory Processes — At the age of 4 and 7 weeks, the ability to learn passive avoidance and pole-climbing avoidance behavior was measured, respectively. All behavioral experiments took place in a quiet room, at a temperature of 22–24 °C between 10:00 and 17:00.

a) **Step-down Type Passive Avoidance Task:** The passive avoidance (step-down) apparatus consisted of a plexiglass rectangular inner box (30 × 30 × 40 cm high) with a grid floor and a semi sound-proof wooden outer box (35 × 35 × 90 cm high) with a 15 W illumination lamp. The grid floor consisted of 30 parallel steel rods (0.3 cm in diameter) set 1.0 cm apart. In the center of the grid floor, a wooden platform (8 × 8 × 4 cm high) was set. Intermittent electric shocks (ES; 1 Hz, 0.5 s, 60 V D.C.) were delivered through the grid floor by an isolated stimulator (Nihon Kohden, Japan). Since the resistance, when an animal was placed in a test cage, varied between 100 to 250 kΩ, the rat received an electric footshock in the range of 0.24–0.6 mA. Each offspring was placed on the wooden platform. When the rat stepped down from the platform and placed all its paws on the grid floor, the ES was delivered for 15 s. The step-down latency (SDL) was measured, and the animals in the range of criteria (SDL 3–15 s) were used for the retention test. The non-ES group underwent the same procedure as the ES group except for the electric footshock. Twenty-four hours after the training, each pup was again placed on the platform, and the SDL was recorded.

b) **Step-through Type Passive Avoidance Task:** The experimental apparatus consisted of two compartments, one illuminated (25 × 15 × 15 cm high) and one dark (25 × 15 × 15 cm high), equipped with a grid floor. The two compartments are separated by a guillotine door. In the acquisition trial, a rat was placed in the illuminated compartment and allowed to enter the dark compartment; as soon as it did so, the door was closed and an unescapable footshock (1.0 mA, 3 s) was delivered through the grid floor. In the retention test, 24 h after the acquisition trial, the rat was again placed in the illuminated compartment and the latency to enter the dark compartment was measured. If the rat avoided

Fig. 1. Effects of Prenatal PCP Administration on Step-through Passive Avoidance Response in the Offspring

Dams were treated with PCP (10 and 20 mg/kg, i.p.) on days 7–17 of gestation. Step-through passive avoidance response of the offspring was observed at the age of 4 weeks. Figures in the columns show the number of animals.

a) $p < 0.01$ vs. vehicle-treated group (Mann-Whitney's U-test).

Fig. 2. Effects of Prenatal PCP Administration on Step-through and Step-down Passive Avoidance Response in the Offspring

Dams were treated with PCP (10 mg/kg, i.p.) on days 7–21 of gestation. Step-through and step-down avoidance response of the offspring was observed at the age of 4 weeks. Figures in the columns show the number of animals. a) $p < 0.05$, b) $p < 0.01$ vs. vehicle-treated group (Mann-Whitney's U-test).

entry for longer than 300 s, a ceiling score of 300 s was assigned.

c) **Pole-Climbing Task:** The pole-climbing apparatus (Takei Kiki Kohgyo, Japan) consisted of a vinyl chloride cylinder (30 cm diameter $\times$ 55 cm high) with a vinyl chloride pole (2 cm diameter $\times$ 50 cm) in the center and with a grid floor. A daily training session in the pole-climbing apparatus consisted of 15 trials, with an intertrial period of 120 s, during which time a sound signal was presented for 5 s. If the offspring did not climb the pole by 5 s after the presentation of the signal, a scrambled shock of 2 mA was delivered through the cage floor for 10 s. Rats were submitted to training for 5 d continuously.

d) **Brain and Body Weight:** Brain and body weights were measured at the age of 4 weeks. The brain was dissected into the cortex, hippocampus, striatum, brainstem and cerebellum following the method of Glowinski and Iversen.¹⁴⁾

Statistics — Behavioral data were evaluated using Mann-Whitney's U-test after the Krus-

Fig. 3. Effects of Prenatal PCP Administration on Pole-Climbing Avoidance Response in the Offspring

Dams were treated with PCP (10 mg/kg, i.p.) on days 7–17 and 7–21 of gestation. Pole-climbing avoidance response was observed for 5 d at the age of 7 weeks. Figures in parentheses show the number of animals. ○, vehicle; ●, PCP 10 mg/kg. a) $p < 0.01$ vs. vehicle-treated group (Mann-Whitney's U-test).

TABLE I. Effect of Prenatal Administration of PCP on the Brain and Body Weight (A) and on the Ratios of Brain to Body Weight (B) in Offspring at the Age of 4 Weeks (A)

	Brain and body weight (g)			
	Control	G ₇₋₁₇		G ₇₋₂₁
		PCP 10	PCP 20	PCP 10 (mg/kg)
Whole brain	1.54±0.02	1.36±0.02 <i>c</i>	1.33±0.03 <i>c</i>	1.36±0.02 <i>c</i>
Cortex	0.78±0.01	0.70±0.01 <i>c</i>	0.68±0.01 <i>c</i>	0.69±0.01 <i>c</i>
Hippocampus	0.11±0.00	0.09±0.00 <i>c</i>	0.09±0.00 <i>c</i>	0.10±0.00 <i>c</i>
Striatum	0.07±0.00	0.07±0.00	0.07±0.00	0.07±0.00
Brainstem	0.39±0.00	0.33±0.01 <i>c</i>	0.34±0.01 <i>c</i>	0.34±0.01 <i>c</i>
Cerebellum	0.21±0.00	0.19±0.00 <i>b</i>	0.19±0.01 <i>a</i>	0.18±0.00 <i>a</i>
Body	57.08±2.27	43.61±1.65 <i>c</i>	41.19±2.05 <i>c</i>	40.03±1.94 <i>c</i>

(B)

	(Ratio of brain to body weight) × 100			
	Control	G ₇₋₁₇		G ₇₋₂₁
		PCP 10	PCP 20	PCP 10 (mg/kg)
Whole brain	2.77±0.10	3.17±0.09 <i>b</i>	3.22±0.12 <i>b</i>	3.51±0.13 <i>c</i>
Cortex	1.40±0.05	1.63±0.05 <i>b</i>	1.72±0.07 <i>b</i>	1.78±0.07 <i>c</i>
Hippocampus	0.20±0.01	0.22±0.01	0.22±0.01	0.25±0.01 <i>c</i>
Striatum	0.12±0.01	0.16±0.01 <i>c</i>	0.17±0.01 <i>c</i>	0.18±0.01 <i>c</i>
Brainstem	0.70±0.02	0.79±0.03 <i>a</i>	0.83±0.03 <i>b</i>	0.88±0.03 <i>c</i>
Cerebellum	0.37±0.01	0.43±0.01 <i>c</i>	0.46±0.02 <i>c</i>	0.48±0.02 <i>c</i>

PCP (10 or 20 mg/kg, i.p.) was prenatally administered on days 7–17 and 7–21 of gestation. The brain and body weight was measured as described in Materials and Methods. *F* values of 1-way ANOVA in G₇₋₁₇ group were as follows: (A) whole brain: *F* (2.56)=24.845 *p* < 0.01, cortex: *F* (2.56)=20.360 *p* < 0.01, hippocampus: *F* (2.56)=37.266 *p* < 0.01, striatum: *F* (2.56)=0.478 *p* > 0.05, brainster: *F* (2.56)=37.856 *p* < 0.01, cerebellum: *F* (2.56)=4.357 *p* < 0.05, body: *F* (2.56)=18.314 *p* < 0.01, (B) whole brain: *F* (2.56)=7.755 *p* < 0.01, cortex: *F* (2.56)=8.280 *p* < 0.01, hippocampus: *F* (2.56)=2.608 *p* > 0.05, striatum: *F* (2.56)=18.266 *p* < 0.01, brainstem: *F* (2.56)=6.287 *p* < 0.01, cerebellum: *F* (2.56)=11.702 *p* < 0.01. Levels of significance: *a*) *p* < 0.05, *b*) *p* < 0.01, *c*) *p* < 0.001 vs. control (Student's *t* test or Cochran's *t* test).

kal-Wallis test or 2-way analysis of variance (ANOVA). The brain and body weight data were compared by using Student's *t* test or Cochran's *t* test after 1-way ANOVA.

Results

The Learning and Memory Processes in the Rat Offspring

a) Passive Avoidance Response — The step-through latencies in passive avoidance responses were significantly decreased in the offspring of rats prenatally treated with PCP (10 and 20 mg/kg, i.p.) on days 7 to 17 of gestation (PCP/G₇₋₁₇ group) at the age of 4 weeks, [Fig.

1, *H* (2)=29.013 *p* < 0.01 (Kruskal-Wallis test)]. As shown in Fig. 2, the step-through and step-down latencies in passive avoidance response were also significantly decreased in the offspring of the PCP/G₇₋₂₁ group, which were prenatally treated with PCP (10 mg/kg, i.p.).

b) Pole-Climbing Avoidance Behavior

The acquisition of pole-climbing avoidance behavior in the PCP/G₇₋₁₇ and PCP/G₇₋₂₁ groups was significantly poorer than that in the control group at the age of 7 weeks [Fig. 3, PCP/G₇₋₁₇: *F* (1,4)=259.394 *p* < 0.01, PCP/G₇₋₂₁: *F* (1,4)=94.016 *p* < 0.01 (2-way ANOVA test)].

Brain and Body Weight of the Rat Offspring

Fig. 4. Effects of Physostigmine, Ritanserin and Naloxone on PCP-Induced Amnesia in Young Adult Rats

Drugs were administered as described in Material and Methods. Figures in the columns show the number of animals.

a) $p < 0.01$ vs. vehicle (Veh)-treated group. b) $p < 0.05$ and c) $p < 0.01$ vs. PCP-treated group (Mann-Whitney's U-test).

As shown in Table IA, prenatal PCP administration decreased the brain and body weights of offspring at the age of 4 weeks. The decrease of the brain weight was significant in the cortex, hippocampus, brainstem and cerebellum, but not in the striatum. However, the ratios of whole brain and discrete brain area weights to body weight in the PCP-treated groups were significantly increased compared to the control group (Table IB).

Effects of Physostigmine, Ritanserin and Naloxone on PCP-Induced Amnesia in Rat

PCP (12.5 mg/kg, i.p.) decreased the step-through latencies when rats were treated with it immediately after the training (Fig. 4). Physostigmine and naloxone were administered s.c. in combination with PCP, because these drugs antagonize PCP-induced amnesia in mice.¹⁵ As shown in Fig. 4, both drugs also attenuated PCP-induced amnesia of rats in a dose-dependent fashion [physostigmine: $H(2) = 8.163$ $p < 0.05$, naloxone: $H(2) = 11.147$ $p < 0.01$ (Kruskal-Wallis test)]. Ritanserin, which antagonizes PCP-induced head-twitch responses,^{16, 17} also antagonized PCP-induced amnesia in a dose-dependent fashion [Fig. 4, $H(3) = 8.313$ $p < 0.05$ (Kruskal-Wallis test)]. Physostigmine,

ritanserin and naloxone alone did not show any effect on the step-through latencies at the doses used (data not shown).

Discussion

Little information is available on the potential embryotoxicity and teratogenicity of PCP in laboratory animals, although the chance of it being ingested as a drug of abuse by women of reproductive age is great. However, permanent changes in concentrations of 5-hydroxytryptamine (5-HT) have been noted in the brains of offsprings after male and female rats had received the chemical in their drinking water before and after mating and females had received it during the nursing period.¹⁸ In addition, Jordan *et al.*¹⁹ have reported that PCP administered prenatally in very high doses (25–40 mg/kg) possesses a definite teratogenic potential in the Sprague-Dawley rat. When given chronically as daily i.p. injections during the middle third of gestation, or acutely as i.p. injection during days 10–14, PCP at dose levels greater than 25 mg/kg produced a variety of malformations in a significant number of offspring. Marks *et al.*²⁰ have also reported that PCP ad-

ministered prenatally to the mouse produces a variety of gross structural defects but only at doses so high that the dam showed poor physical health and behavioral disturbance. Jordan *et al.*¹⁹⁾ and Goodwin *et al.*,²¹⁾ however, have reported behavioral effects among offspring prenatally exposed to a dose (5–10 mg/kg) below the level for producing malformations. In the offspring prenatally exposed to PCP, delay in development of locomotor and climbing skills in Sprague-Dawley rats¹⁹⁾ and a greater number of instances of rearing in Cox Swiss mice²¹⁾ have been observed. However, Hutching *et al.*²²⁾ could not confirm the developmental toxicity of PCP by measuring locomotor activity in Wistar rats at dose levels below the teratogenic threshold.

PCP administration at perinatal and nursing periods fails to develop behavioral toxicity (except for a delay in the development of separation of the eyelids), while prenatal PCP administration from days 7 to 17 and from days 7 to 21 of gestation produces varieties of behavioral toxicity such as delay in the development of spontaneous behavior in offspring.^{13,23)} Maternal behavior is affected by administration during perinatal and nursing periods, but not by prenatal administration. Therefore, Nabeshima *et al.* have concluded that the particular administration period is very critical in the developmental toxicity of PCP, although maternal behavior does not contribute to producing the toxicity.^{13,23)}

The present study was carried out to examine further the developmental toxicity of PCP. For this purpose, two different administration schedules and specific behavioral tests such as passive avoidance and pole-climbing avoidance behaviors were employed since prenatal PCP administration is more liable to produce developmental toxicity than to perinatal administration.

We have found a toxic effect of PCP on the learning and memory processes in the offspring. The prenatal administration of PCP disrupted the acquisition of pole-climbing avoidance behavior and the retention of step-through and step-down type passive avoidance behavior in the offspring. The impairment of learning and memory induced by the prenatal administration of PCP

did not relate to a change in the pain threshold of the offspring in the training, since there was no difference in tail-flick response between control and PCP-treated groups (data not shown). The PCP-induced deficit of learning and memory may not be due to delay of growth, although the body weight of offspring in the PCP-treated group was lower than that in the control group, because no differences in motor functions such as ambulation, rearing, bar holding, rope descent, negative geotaxis and cliff-drop aversion were observed between PCP-treated and control groups at the ages tested.¹³⁾ The decrease of brain weight induced by prenatal PCP administration may be responsible for the impairment of learning and memory processes. However, other possibilities such as permanent changes in neuronal functions in the brain of offspring may be more important, since the ratios of brain to body weight in the PCP treated groups were higher than those of the control group.

We have reported that PCP impairs the retention of step-down type passive avoidance behavior in adult mice.¹⁵⁾ In addition, it has been reported that PCP impairs the acquisition of one-way active avoidance learning and radial arm maze performance in adult rats.^{24, 25)} The mechanisms which might underlie the impairment of learning and memory processes among offspring prenatally treated with PCP are unknown. It is difficult to speculate on what might be the mechanism of the PCP-induced toxicity, because there might be some discrepancy between the acute and chronic transplacental effect of this drug. However, the opioidergic neuronal activity may be increased while the cholinergic neuronal activity may be decreased in the offspring since the impairment was recovered by treatment with naloxone and physostigmine in an experiment on adult mice¹⁵⁾ or rats. (Fig. 4) Furthermore, recent evidence suggests that one major factor in impairment of learning and memory processes may be hyperactivity in the serotonergic neuronal system.^{26–28)} Gillet *et al.* have reported that 5-HT inhibits acetylcholine release from rat striatum slices.²⁹⁾ We have suggested that PCP has 5-HT direct and indirect agonist action, since PCP interacts with 5-HT₂

receptor directly and releases 5-HT.^{16, 17, 30)} As mentioned above, prenatal administration of PCP produces permanent changes in the concentration of 5-HT in the brains of offspring.¹⁸⁾ As shown in Fig. 4, ritanserin, a 5-HT₂ receptor antagonist showed antagonism to PCP-induced amnesia. Taken together, the results raise the possibility that prenatal PCP administration impairs cholinergic neuronal function through an activation of the serotonergic neuronal system. Further work is required to identify the underlying mechanisms which can accommodate the impairment in both the pole-climbing avoidance response and passive avoidance behavior seen in the present study.

In conclusion, prenatal PCP administration produced impairment of learning and memory processes of passive and active avoidance tasks in the offspring.

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