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Effects of Prenatal and Perinatal Administration of Phencyclidine on the Behavioral Development of Rat Offspring

TOSHITAKA NABESHIMA, KAZUMASA YAMAGUCHI, MASAYUKI HIRAMATSU, KAZUHIRO ISHIKAWA, HIROSHI FURUKAWA* AND TSUTOMU KAMEYAMA

*Department of Chemical Pharmacology and *Department of Medicinal Chemistry Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan*

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NABESHIMA, T., K YAMAGUCHI, M HIRAMATSU, K ISHIKAWA, H FURUKAWA AND T KAMEYAMA *Effects of prenatal and perinatal administration of phencyclidine on the behavioral development of rat offspring* PHARMACOL BIOCHEM BEHAV **28**(3) 411–418, 1987 —The effects of prenatal and perinatal administration of a nonteratogenic dose of phencyclidine (PCP) on the behavioral development of Sprague-Dawley rats were examined In the offspring prenatally treated with PCP (10 mg/kg) between days 7 and 17 of gestation, a decrease in maternal body weight in the gestation period, a decrease in fetal body weight and body length, a decrease in viability of offsprings, and a decrease in the body weights of the offspring in the nursing period were observed Furthermore, PCP pups had difficulty performing the rota-rod task at 4 weeks and exhibited a decrease in sensitivity to challenged PCP at 5 weeks (female) In the offspring prenatally treated with PCP between days 7 and 21 of gestation, a decrease in the body weights of dams, fetuses and offspring, and a decrease in the viability of offsprings were observed PCP pups showed an increase in the score for head-twitch response (male), a delay in the development of ambulation, negative geotaxis (male), bar holding and rope-descending behavior (female) However, the PCP administration during prenatal (between days 17 and 21 of gestation) and nursing periods showed only a decrease in viability and body weight of offspring, and a delay in the development of the separation of eyelids These results suggest that more attention should be given to the developmental toxicity of PCP

Phencyclidine Prenatal and perinatal administration Behavioral development Developmental toxicity Offsprings Rota-rod performance

PHENCYCLIDINE (PCP) has been identified as a major drug of abuse [4]. 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 offspring. However, Cooper *et al* [2] 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 hr 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 days postpartum [8] In addition, the concentration of PCP in the fetuses of mice was 7 times higher than in the plasma of dams Furthermore, in the fetuses PCP was not metabolized [14] All of the above suggest that PCP is able to cross the blood-placenta barrier easily and remains in the fetus brain in high concentrations, and that PCP has the potential to adversely affect the developing nervous system. However, little information is available regarding its possible adverse effects on behavioral activity in offspring To this end, the effects of prenatal and perinatal administration of a nonteratogenic dose of PCP on the behavioral development of Sprague-Dawley rats were examined

METHOD

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 the following morning were considered 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.

Drug Administration

The dose level of phencyclidine hydrochloride (10 mg/kg· PCP synthetized by us, identified by NMR and IR) used in the present study was selected on the basis of preliminary observations that PCP did not produce malformations at this dose. Three groups of animals were treated with PCP during different gestation periods (Fig. 1): (1) an experimental group in which the animals received daily IP injections of PCP (10 mg/kg) between 9:00–10.00 a.m. on days 7–17 of gestation (PCP/G_{7-17}); (2) on days 7–21 of gestation (PCP/G_{7-21}); (3) on

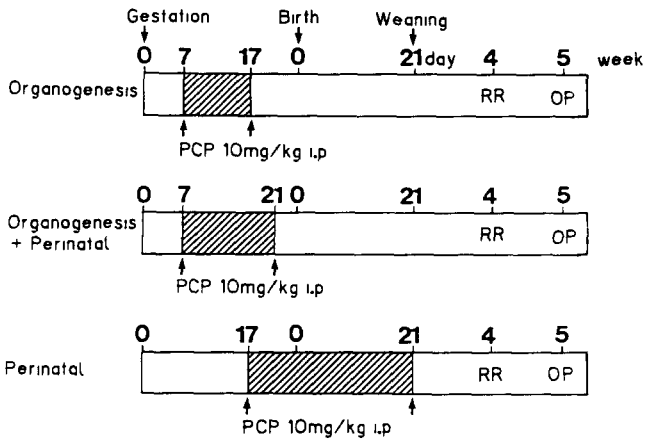

FIG 1. Administration schedule RR Rota-rod test, OP Open-field test

days 17–21 of gestation and nursing period (PCP/G_{17}-N_{21}). Control groups of animals were treated with IP injection of saline PCP or saline was injected into the shallow medial abdomen of dams to avoid the womb The mother's weights were taken 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 effects of drugs upon the fetuses If a mother's health was poor, she was discarded from the study

Reproduction

On day 21 of gestation, some part of the dams were killed by ether overdosage and the live fetuses removed, weighed, sexed and examined for external malformations In addition, the number of corpora lutea, the number and position of implantation sites, and the number of dead and resorbed fetuses were recorded

Neonate Development

The presence of new-born pups was checked daily at approximately 9·00 a.m. and 3:00 p.m in the plastic home cage The day of birth was designated as day 0 of age The body weight of the pups was measured on day 0 (at birth), 4, 7, 14 and 21 postpartum On day 4, 4 males and 4 females were culled from each litter whenever possible

Postnatal Tests of Physical Development

Auricule Test pups were examined daily for the day on which the auditory canals fully opened bilaterally.

Dorsal hair Test pups were examined daily for the day of appearance of dorsal hair

Eye opening The pups were examined daily for the day on which their eyelids opened bilaterally

Incisor eruption Test pups were examined daily for the day of bilateral appearance of lower incisors.

The pups were examined daily from day 4 (auricle and dorsal hair) and day 14 (eye opening and incisor eruption) postpartum until all test members of the litter were positive for the trait.

Preweaning Test of Neurobehavioral Development

Righting reflex Test pups were tested daily for righting to reorient from a supine to a prone position If the righting reflex was observed within 35 sec in one trial, the pup was considered positive The pups were examined daily from day 4 postpartum until all test members of the litter were positive for the trait

Walking Test pups were observed daily for the day of appearance of locomotion in the fore- and hindlimbs with abdomen not contacting the ground The pups were examined daily from day 14 postpartum until all test members of the litter were positive for the trait.

Free fall Test pups were dropped upside down from a height of 60 cm onto a sponge mat. Righting responses in mid-air and mode of landing were recorded The mid-air righting response consists of a sequence of orderly movements proceeding in the rostrocaudal direction head rotation appears first, rotation of hindlimbs last. The pups were examined daily from day 21 postpartum until all test members of the litter were positive for the trait

Cliff-drop aversion Test pups were placed on the edge of a wooden platform with their noses and fore feet over the edge and then tested for whether they turn or crawl away from the edge Adult animals can turn or back away from the edge within 1 sec The pups were examined from day 3 to 21 postpartum and the observational rating scales were as follows. 0, no response, 1, backing within 10 sec; 2, backing within 3 sec, 3, backing within 1 sec

Negative geotaxis Test pups were placed on an inclined (45°) board (which has a surface consisting of 1-mm thick nylon mesh) with their heads pointing downward and then tested to see whether the pups turn to face upward. Adult animals can climb the inclined board after a turn of 180° upward The pups were examined from day 2 to 21 postpartum and the observational rating scales were as follows· 0, falling from the inclined board; 1, supporting of body weight but no turn on the inclined board, 2, an incomplete turn of less than 180° upward, 3, a turn of 180° upward; 4, climbing after a turn of 180° upward.

Bar holding. Test pups were suspended by their forepaws on a thin (2 mm thick) wire which was extended horizontally at a height of 40 cm from floor level and then tested to see whether the pups attempted to chin with the forepaw, and support their bodies with their hindlimbs. When the pups let go of the wire, they were caught in hand gently. The pups were examined from day 1 to 21 postpartum and the observational rating scales were as follows 0, falling from a thin wire; 1, supporting body with their forelimbs, 2, grasping the wire with one or both of the hindlimbs within 30 sec in one trial

Rope descent Test pups were made to grasp a 7-mm diameter woolen rope with their heads pointing upward and then tested to see whether the pups would fall or descend from the rope. The pups were examined from day 12 to 21 postpartum and the observational rating scales were as follows· 0, falling from the rope, 1, supporting body with their fore- and hindlimbs and /or climbing the rope, 2, trying to descend, but not releasing grip with paws; 3, turning around on the rope and trying to descend, but falling from the rope, 4, descending with the head in the leading position until the end of the rope

Open-field test The open-field used for the pre-weaning rats was a gray box (38 cm wide × 75 cm long × 15 cm high) The floor of the apparatus was divided in 18 equally sized

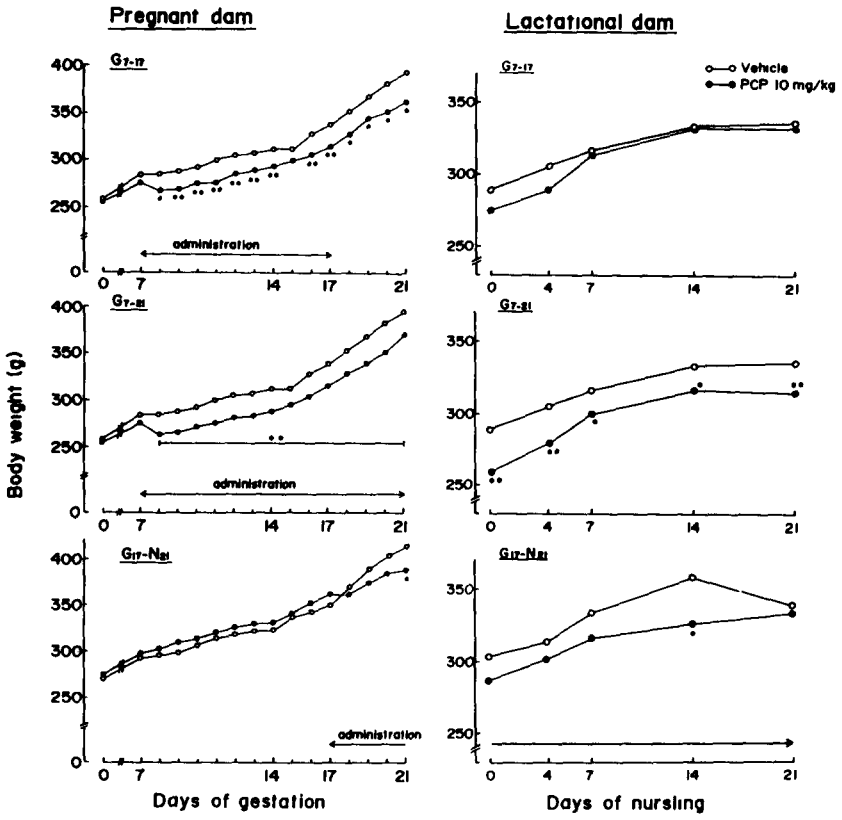

FIG 2 Mean body weight of pregnant and lactational dams treated with phencyclidine (PCP) from day 7 of gestation to day 21 postpartum N=6–15 per data point, $*p<0.05$, $**p<0.01$ vs vehicle

squares by black lines The pup was placed in the central area of the box and following behavioral items were checked during 3-min sessions from day 1 to 21 postpartum. (a) head-twitch (rapid lateral twitch of head similar to pinna reflex), (b) head-weaving (slow lateral weaving of head without elevating the chest), (c) pivoting (turning the body more than 90° using the forelimbs, with the pelvis as a pivot), (d) head-up (lifting the head while elevating the chest), (e) ambulation (the number of complete squares traversed by the rats on all fours), (f) rearing (standing only on the hindlimbs with the forelimbs not contacting the ground), (g) face-washing (washing the face or head while sitting), (h) paw-licking (licking the forelimbs or washing the mouth area while lying or sitting down). In addition to recording the results of the above test, we also recorded the onset time as the duration (sec) from placement in the center of the box to the occurrence of ambulation The apparatus was cleared of odors in between animals in all tests

Postweaning

Rota-rod performance. Pups were weaned on day 21 postpartum and siblings of the same sex were housed together Rota-rod performance was measured at 4 weeks of age using a plastic rota-rod with diameter of 3 5 cm and the rough surface (Nihon Ikakikai, Japan). A pup was put on the rota-rod revolving at 14 rpm and the number of falls from the rota-rod were totalled during a 3-min observation period.

Open-field test Open-field measures were taken at 5 weeks of age by two "blind" observers. The open-field apparatus (110 cm wide × 110 cm long × 24.5 cm high) was painted gray, and divided into 25 equally sized squares by black lines. The pup was placed into a corner square and the number of squares crossed was recorded by one "blind" observer and the number of instances of rearing, fur-licking, face-washing, urination and defecation was recorded by a second "blind" observer for a 3-min period Each observer measured the number of the same behavioral events in all tests. The open-field was cleaned after each trial and before another animal was put into it [6]

Statistics

In order to perform statistical assessments of differences among the groups, behavioral data from all animals in each group were averaged for each time period. The behavioral score represents the mean value in each group.

Frequency data were analyzed using Fisher's Exact Probability Test or Wilcoxon's Rank Sum Test on a litter basis, e.g., the proportion of implantation sites, malformations, resorptions, viability, physical development. The data from the preweaning test of neurobehavioral development were analyzed using a two-factor analysis of variance (ANOVA) with repeated measuring of both factors (drug × day × subject). All other parameters were analyzed using the two-tailed Mann-Whitney U-test or the two-tailed Student's

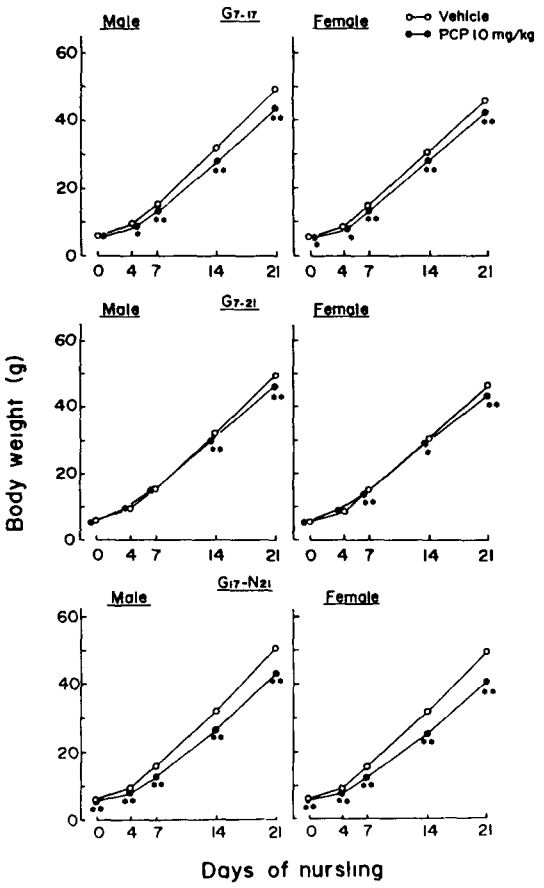

FIG 3 Mean body weight of nursling from dams treated with phencyclidine (PCP) from day 7 of gestation to day 21 postpartum N=20–111 per data point, *$p<0.05$, **$p<0.01$ vs vehicle

TABLE 1

MATERNAL AND FETAL FINDING ON DAY 21 OF GESTATION BY LAPAROTOMY OF PREGNANT RATS TREATED WITH PHENCYCLIDINE (PCP) ON DAYS 7–21 OF GESTATION (G_{7-17})

	Vehicle	PCP 10 mg/kg
No of dams	11	24
Corpora luta		
Total	185	412
Mean ± S E	16 8 ± 1 0	17 2 ± 0 4
Implants		
Total	135	377
Mean ± S E	12 3 ± 1 3	15 7 ± 0 5*
	73 0	91 5
No of live fetuses	133	358
Mean ± S E	12 1 ± 1 4	14 9 ± 0 5
No of dead fetuses	2	19
(total %)	(1 5)	(5 0)
Implanation sites	0	0
Early resorption	2	18
Late resorption	0	0
Dead	0	1
Fetal body weight (g)	5 42 ± 0 10	5 00 ± 0 05*
Sex ratio (male/female × 100)	105	94
Weight of placenta (g)	0 48 ± 0 02	0 47 ± 0 01
Body length of fetuses (cm)	4 14 ± 0 03	3 96 ± 0 02*
Brachydactyly of forelimbs	0	1

*$p<0.01$ vs vehicle (two-tailed Student's *t*-test)

TABLE 2

VIABILITY OF PUPS ON 21 DAY OF WEANING FROM DAMS TREATED WITH PHENCYCLIDINE (PCP) ON DAYS 7–17 (G_{7-17}) AND DAYS 7–21 (G_{7-21}) OF GESTATION AND ON DAYS 17–21 OF GESTATION AND NURSING PERIOD (G_{17}–N_{21})

	G_{7-17}		G_{7-21}		G_{7}–N_{21}	
	Vehicle	PCP 10 mg/kg	Vehicle	PCP 10 mg/kg	Vehicle	PCP 10 mg/kg
No of dams	15	6	15	14	8	9
No of live pups Day 0	210	85	210	173	122	128
Day 4						
Before culling	206	63	206	137	122	100
After culling	114	43	114	103	64	66
Day 7	114	43	114	103	64	66
Day 14	114	43	114	103	64	66
Day 21	114	43	114	102	64	65
Viability index (%)*	98 1	74 1‡	98 1	79 2‡	100	78 1‡
Weaning index (%)†	100	100	100	99 0	100	98 5

*(No of live pups on day 4/No of pups born alive) × 100
†(No of live pups on day 21/No of live pups on day 4) × 100.
‡$p<0.01$ vs vehicle (Wilcoxon's rank sum test)

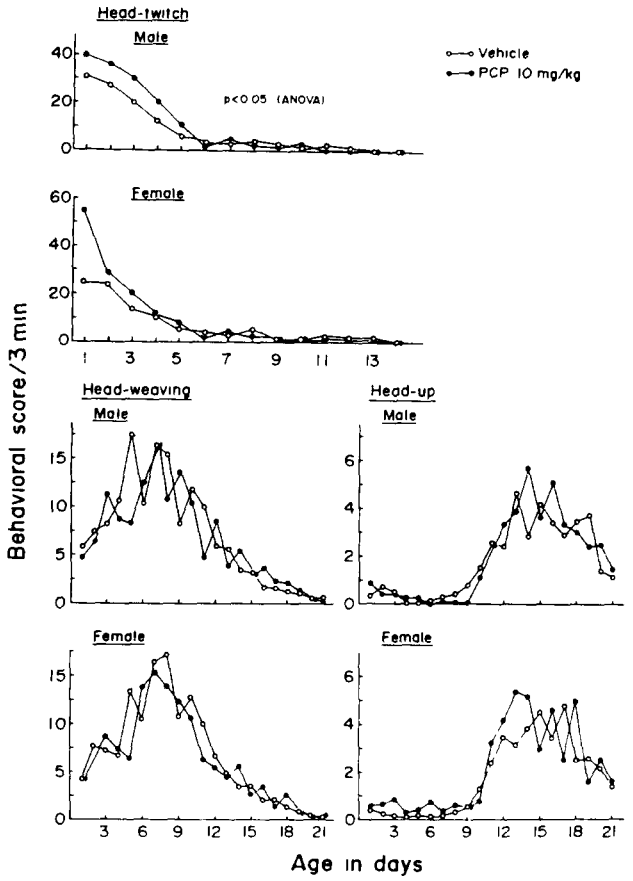

FIG 4 Development of head responses in pups from dams treated with phencyclidine (PCP) from day 7 to 21 of gestation N=19–51 per data point

t-test The difference between two comparable sets of results was considered significant when $p<0$ 05

RESULTS

Effect of Prenatal and Perinatal PCP Administration on the Body Weight of Dams and Offspring in the Gestation and Nursing Periods

The body weights of dams in the PCP/G_{7-17} and PCP/G_{7-21} groups decreased significantly compared to the control group during the gestation period, but not in the PCP/G_{17}-N_{21} group (Fig. 2). The decrease in body weight of dams was observed only in the PCP/G_{7-21} group during the nursing period (Fig 2)

The body weights of offspring in the nursing period decreased significantly in all of the PCP-treated groups (Fig. 3). The fetal body weights and body lengths by day 21 of gestation had been significantly decreased by the prenatal PCP administration (day 7–17 of gestation) (Table 1). In addition, the viability of offspring in all of the PCP-treated groups was significantly decreased on day 4 postpartum (Table 2).

Effect of Prenatal and Perinatal PCP Administration on the Maturational Landmarks and Simple Behavioral Development Tasks in Offspring

Physical development before weaning There was no significant difference in the development of separation of auricule, appearance of dorsal hair, separation of eyelids, eruption of lower incisors, righting reflex, walking and free fall between the control and all of the PCP-treated groups, except for a delay in the separation of eyelids in the PCP/G_{17}-N_{21} group. Separation of eyelids of all animals was observed on day 15 and 16 of postpartum in the control and PCP/G_{17}-N_{21} groups, respectively

Neurobehavioral development before weaning. The score for the head-twitch response was highest at birth and gradually decreased, thereafter it was not observed 2 weeks postpartum In the offspring of the PCP/G_{7-21} group, the score for head-twitch response was significantly increased compared to that of the control group (Fig. 4).

There was no clear difference in the development of head-weaving and head-up response between the control and PCP/G_{7-21} group

PCP produced a delay in development in open-field behavior Prenatal PCP administration (day 7–21 of gestation) retarded the development of ambulation in the open-field, although PCP failed to affect the onset of ambulation (Fig. 5) A delay in the development of rearing was found in the offspring derived from the dams treated with PCP (day 7–21 of gestation), but not a significant one No differences in the development of pivoting, face-washing and paw-licking were observed between the control and PCP-treated group (Fig 5)

In the prenatal PCP-treated male offspring (day 7–21 of gestation), the development of negative geotaxis was retarded, but not cliff-drop aversion behavior. On the contrary, in the female offspring of the dams treated with PCP, a delay in the development of bar-holding and rope-descending behavior was observed (Fig 6)

The frequency of face-washing in the male offsprings of PCP/G_{7-17} and male and female offsprings of PCP/G_{7-21} groups and that of ambulation in the female offsprings of PCP/G_{17}-N_{21} group was significantly higher, compared to the control group, at the age of 5 weeks (Table 3).

Neurobehavioral development after weaning. The number of drops from the rota-rod was significantly high in the female offspring of the PCP/G_{7-17} group at the age of 4 weeks There was no difference in the rota-rod performance between the control and PCP/G_{17}-N_{21} groups (Fig. 7).

DISCUSSION

Little information is available on the potential embryotoxicity and teratogenicity of PCP in laboratory animals, although the chance of it being ingested by women of reproductive age is great [8]. However, permanent changes in concentrations of 5-hydroxytryptamine have been noted in the brains of offspring after male and female rats have been administered the chemical in their drinking water before and after mating, and to females during the nursing period [15]. In addition, Jordan *et al* [6] have reported that PCP administered prenatally in very high doses (25–40 mg/kg) possesses definite teratogenic potential in the Sprague-Dawley rat When given chronically as single daily IP injections during the middle third of gestation, or acutely as a single IP injection during days 10–14, in dose levels greater than 25 mg/kg, PCP produced a variety of malformations in a significant number of offsprings Marks *et al* [9] have also reported that PCP administered prenatally to the mouse produces a variety of gross structural defects but only at doses that are highly toxic to the dam. Jordan *et al.* [6] and

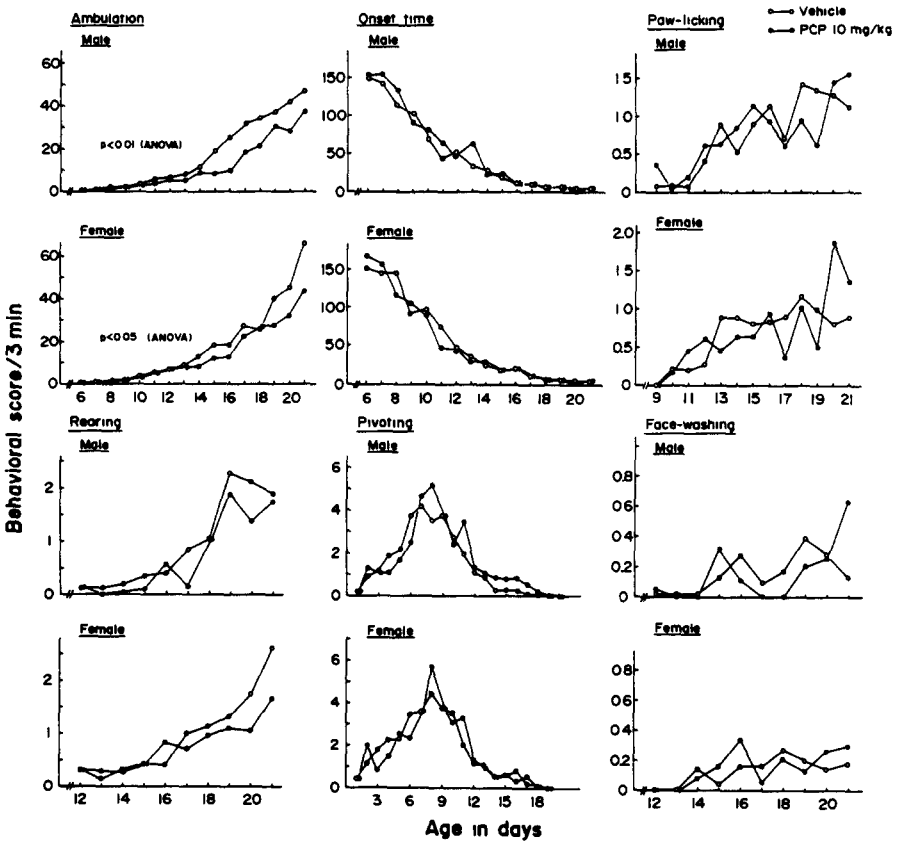

FIG 5 Development of open-field behavior in pups from dams treated with phencyclidine (PCP) from day 7 to 21 of gestation N=19–51 per data point

TABLE 3

OPEN-FIELD BEHAVIOR IN 5-WEEK-OLD PUPS FROM DAMS TREATED WITH PHENCYCLIDINE (PCP) ON DAYS 7–17 OF GESTATION

		G_{7-17}		G_{7-21}		G_7–N_{21}	
Behaviors	Sex	Vehicle	PCP 10 mg/kg	Vehicle	PCP 10 mg/kg	Vehicle	PCP 10 mg/kg
Locomotor	male	33 1 ± 8 0	38.7 ± 5 0	36.1 ± 4 2	34 8 ± 6 2	31 3 ± 7 9	36 1 ± 7 5
	female	24 9 ± 6 5	17 9 ± 5 6	43 3 ± 5 4	43 7 ± 9 3	36 3 ± 6.8	60 3 ± 4 3*
Rearing	male	4 4 ± 0 9	8 5 ± 0 9*	10 2 ± 1 3	13 5 ± 2 8	8 5 ± 2.1	6 7 ± 1 4
	female	3 4 ± 1 0	3 3 ± 1 0	10 3 ± 1 4	13 3 ± 2 1	6 8 ± 2.0	7 0 ± 1 3
Face-washing	male	0 5 ± 0 3	1 5 ± 0 3*	0 9 ± 0 3	5 6 ± 0 8†	2 1 ± 0.2	1 6 ± 0 3
	female	1 6 ± 0 5	2 0 ± 0 4	0 5 ± 0 3	2 8 ± 0 6†	1 9 ± 0.6	2 0 ± 0 3
Fur-licking	male	0	0 1 ± 0 1	0 2 ± 0 1	0 4 ± 0 2	0 5 ± 0 3	0 1 ± 0 1
	female	0 1 ± 0 1	0 1 ± 0 1	0 4 ± 0 3	0	0 1 ± 0 1	0 1 ± 0 1
Urination	male	0 6 ± 0 2	0 5 ± 0 2	1 4 ± 0 7	0 4 ± 0 2	0 8 ± 0 3	0 6 ± 0 3
	female	0 7 ± 0 2	0 3 ± 0 2	1 0 ± 0.5	0 3 ± 0 2	0 8 ± 0 4	0 6 ± 0 4
Defecation	male	2 4 ± 0 8	2 1 ± 0 6	1 0 ± 0.4	1 5 ± 0 7	2 8 ± 0 7	2 3 ± 0 7
	female	2 4 ± 0 5	2 2 ± 0 8	0 5 ± 0 3	1 7 ± 0 8	1 9 ± 0 4	0 9 ± 0 4

Values are the mean ± S E *$p<0.05$, †$p<0.01$ vs vehicle (Mann-Whitney's U-test)

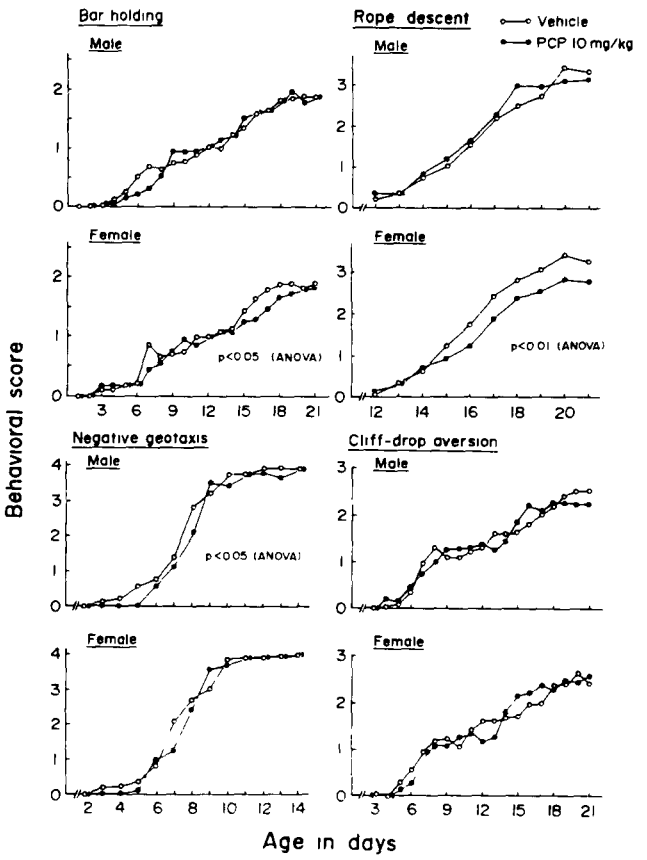

FIG 6 Development of bar holding, rope descending, negative geotaxis and cliff-drop aversion behavior in pups from dams treated with phencyclidine (PCP) from day 7 to 21 of gestation N=19–51 per data point

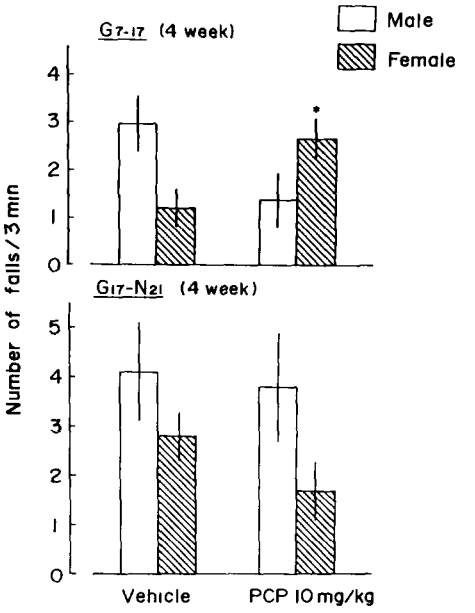

FIG 7 Rota-rod performance in 4-week-old pups from dams treated with phencyclidine (PCP) from day 7 of gestation to day 21 postpartum N=19–51 per data point, *$p<0.05$ vs vehicle

Goodwin *et al.* [3], however, have reported behavioral effects among offspring prenatally exposed to a dose below the level (5–10 mg/kg) for producing malformations In the offspring prenatally exposed to PCP, delay in development of locomotor and climbing skills in Sprague-Dawley rats [6] and a greater number of instances of rearing in Cox Swiss mice [3] have been observed However, Hutching *et al.* [5] could not confirm the developmental toxicity of PCP by measuring locomotor activity in Wistar rats at dose levels below the teratogenic threshold.

The present study was carried out to further examine the developmental toxicity of PCP since previous authors examined PCP toxicity only at one phase of gestation For this purpose, three different administration schedules were employed. PCP administration at prenatal, perinatal and nursing periods failed to develop toxicity (except for the delay in the developmental of separation of eyelids), while prenatal PCP administration from day 7 to 17 and from day 7 to 21 of gestation produced varieties of behavioral toxicity in offspring Maternal behavior was affected by administration during perinatal and nursing periods, but not by the prenatal administration schedule (data not shown) Therefore, the particular administration period is very critical in the developmental toxicity of PCP, although maternal behavior does not contribute to producing the toxicity.

Prenatal PCP administration from day 7 to 21 of gestation produced delays in the development of locomotion in males and females, and in bar-holding and rope-descending behavior in female offspring of Sprague-Dawley rats. The differences in both behavioral parameters were not observed at a later time and the PCP groups eventually caught up with the control groups These would be consistent with the results of Jordan *et al* [6] in Sprague-Dawley rats These findings, however, are inconsistent with the report of Hutchings *et al* [5] using Wistar rats The rat strain may have contributed to the discrepancies in these results since our methodology and the age of our animals at testing, as well as the prenatal dosing schedules are very similar to those of Hutchings *et al.* [5]. The intensity of stereotyped behavior induced by PCP at the same dose levels was greater in Sprague-Dawley rats than in Wistar rats, while the ability to metabolize PCP was greater in the Wistar strain than in the Sprague-Dawley strain (unpublished results) Therefore, the Wistar strain may be more tolerant to PCP toxicity than the Sprague-Dawley strain.

The present experiments showed that PCP delayed the development of negative geotaxis in male offsprings. In addition, an increase in the score for the head-twitch response was observed in the male offsprings prenatally treated with PCP. The differences in both behavioral parameters were observed only in the early period after birth As mentioned in the Introduction, the newborn animal is not able to metabolize PCP [14] Furthermore, it is well known that PCP produces motor incoordination [10] and head-twitch response [13]. Taken together, the effects of PCP on the negative geotaxis and head-twitch response may be due to a direct effect of the residual presence of PCP

After weaning, the rota-rod performance and the open-field behavior of pups at the age of 4 and 5 weeks were investigated Consistent results showing PCP-toxicity were not obtained, however, the number of locomotor counts was increased in the female pups of PCP G_{17}-N_{21} group. Furthermore, the frequency of face-washing in the open-field was increased in the 5-week-old pups of the PCP G_{7-21} group The female pups of the same group showed an increased

number of drops from the rota-rod. The emotionality of the pups of PCP G_{7-21} group might be increased, since the number of instances of face-washing is one of the indicators of emotionality [1] Other parameters of emotionality did not change in the PCP G_{7-21} groups Therefore, we should further investigate this point.

To our knowledge, a study demonstrating sex differences in the development of toxicity of PCP in laboratory animals has not been published. In adult rats, we have reported that sex differences in the intensity of PCP-induced behavior and the metabolic rate of PCP do exist, and that these sex differences are related to sex-hormones [11,12]. One mechanism which may account for the difference in sensitivity to PCP's toxicity in male and female offspring is the effect of PCP on the balance of the neonatal hormonal milieu. Clearly, however, whether the more complex alterations in neurobehavioral function observed following prenatal PCP administration may be accounted for by early hormonal imbalances awaits a more through understanding of the interactions of the early endocrine, neural, and metabolic environment.

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