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Phencyclidine During Pregnancy in the Rat: Effects on Locomotor Activity in the Offspring[1]

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HUTCHINGS, D. E., S. R. BODNARENKO AND R. DIAZ-DeLEON. *Phencyclidine during pregnancy in the rat: Effects on locomotor activity in the offspring.* PHARMACOL BIOCHEM BEHAV 20(2) 251–254, 1984.—Either 5 or 10 mg/kg of phencyclidine hydrochloride (PCP) was administered by gastric intubation to gravid rats during the last two weeks of gestation. Intubation controls received the vehicle and all offspring were fostered to untreated controls at birth. PCP produced a decrement in maternal weight gain and a small but nonsignificant reduction in birth weight that was no longer evident at weaning. There were no maternal deaths nor were resorptions or stillbirths increased by PCP exposure. Offspring were tested for differences in locomotor activity from birth to weaning at 30 days of age and during adulthood. No behavioral differences were found among the preweanling or adult offspring. Results are compared with other prenatal studies of PCP toxicity and teratogenicity.

Phencyclidine Prenatal Developmental toxicity Locomotor activity Behavioral teratology

AS with most drugs of abuse, studies of toxic effects in the developing organism typically lag well behind those of the adult; phencyclidine (PCP) is no exception. The abuse problem of PCP is well known and thoroughly documented [8], yet studies of its possible developmental toxicity, particularly during the prenatal period, are meager [2]. Pediatric studies suggest abstinence-like effects in the newborn [6] and one case report described a possible PCP-related facial dysmorphogenesis [1]. PCP administered prenatally to the mouse [7] and rat [5] produces a variety of gross structural defects but only at doses that are highly toxic to the dam. Jordan *et al.* [5], however, reported behavioral effects among offspring prenatally exposed to a dose below the level for producing malformations. The present study was carried out to further examine the developmental toxicity of PCP. Two dose levels, both below the teratogenic threshold, were administered during the last two weeks of gestation. Treated and control litters were fostered and tested for differences in the ontogeny of locomotor behavior from birth to 30 days of age and activity level in adulthood.

METHOD

Individual nulliparous Wistar females (Hilltop Lab Animals, Inc., Scottdale, PA) were paired with males of the same strain in cages containing raised grid floors. The date of finding a mating plug was designated Day 1 of gestation. Gravid dams were housed 2–3 to a cage on sterile wood chips with Purina Lab Chow and water provided ad lib.

The dose levels of phencyclidine hydrochloride (obtained through the NIDA drug supply program) used in the present study were selected on the basis of preliminary observations with groups of non-pregnant females administered either 5, 10, or 30 mg/kg. Within 5–7 min after administration, animals receiving the two highest doses became hyperactive but then showed hypoactivity, ataxia, hypotonicity, a reduced startle response and side-to-side head oscillations. These symptoms lasted several hours and were equally severe in both the 10 and 30 mg/kg groups. By comparison, animals administered 5 mg/kg showed symptom onset within 12–15 min and included only mild hyperactivity and ataxia, side-to-side head oscillations that were less pronounced and less frequent and a startle response that appeared normal. The 5 mg/kg animals were considerably less affected, both in magnitude and duration of response.

Thus, beginning on Day 8 of gestation, either 5 or 10 mg/kg of PCP dissolved in sterile water was administered to two groups of gravid dams (PCP5; PCP10) once daily by gastric intubation between 1000 and 1400 hr. Both dose-level groups received daily drug administration through Day 22 of gestation, approximately 24 hr prior to expected parturition. The behavioral symptoms observed for each dose-level group were identical to those described above for the 5 and 10 mg/kg non-pregnant groups. An intubation control group (IC) received 1.0 ml of sterile water on the same gestation days as the treated groups.

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TABLE 1
OFFSPRING EFFECTS

	IC	PCP5	PCP10
No. of Litters	7	7	6
Mean Implantation Sites/Litter*	14.0 ± 0.72	13.86 ± 0.51	13.0 ± 0.45
Stillborn (%)	0	2.06%	1.26%
Resorptions (%)	7.14%	7.22%	3.85%
Total Prenatal Mortality (%)	7.14%	9.28%	5.13%
No. Live Born	91	88	74
Mean Litter Size	13.0 ± 0.49	12.57 ± 0.87	12.33 ± 0.67
Mean Birthweight (g)			
♂	7.58 ± 0.07	6.90 ± 0.27	7.02 ± 0.26
♀	7.15 ± 0.11	6.48 ± 0.26	6.52 ± 0.26

*All mean data are expressed as Mean ± SEM.

Two days before parturition all animals were separated and housed individually. Within 1 to 5 hours after birth, all treated and control offspring were sexed and weighed. Litters were culled when necessary to 12 pups; none contained fewer than 8. Offspring were fostered to normal dams of the same strain that had delivered approximately 24 hr earlier. All treated and control dams were sacrificed and autopsied to determine the number of implantation sites.

Testing for the ontogeny of locomotor behavior was carried out using a 6-channel electronic activity monitor with 6 remote sensors, each measuring 25.4×48.3×10.2 cm (Cat. No. 31409, Stoelting Co., Chicago, IL). The 6 sensors are driven by a single oscillator and are cross-calibrated allowing comparison of data between sensors. The operating principle of the activity monitor has been previously described [3].

The 6 sensors were stacked 40.6 cm apart in a vertical metal rack with the metal shelving acting as an insulator between the respective sensor fields. Testing revealed no "cross-talk" (i.e., heterodyning) between sensors. For the present study, the threshold reset time was placed in the "normal" mode and the activity level and Ma controls set at 15 and 0.7, respectively. Activity counts were collected at 60-sec intervals and recorded by electronic printing counters.

Locomotor activity was measured in the adult using an automated figure-eight maze (New Standard Systems, Cincinnati, OH). The maze, with a clear Plexiglas cover and wire mesh floor, consists of two circular stainless steel alleys connected in the center by an open area accessing two blind alleys located on either side. Locomotor activity is detected by 8 infra-red photo cells, three located in each circular arm and one in each blind alley. An electronic counter/control unit determines the preset session length, scans the sensors and displays total activity counts/session.

There were a total of 7 IC, 7 PCP5 and 6 PCP10 litters in the study. The day of birth was designated as Day 0 of life. Treated and control litters were tested between 1000 and 1400 hr at 5-day intervals from Day 1 through 30 days of age when offspring were weaned. On each test day the intact litter was removed from its mother and home cage and immediately placed in a huddle in the center of a standard 48.3×26.7×20.3 cm polycarbonate cage on approximately 1.5 cm of sterile wood chips. The cage, with its wire top in place, was then placed on one of six monitors and recording began for a test period of 60 min. Neither food nor water was provided during testing.

Beginning at 60 days of age, offspring were tested for 10 min on each of three successive days in one of two figure-eight mazes between 0900 and 1700 hr. Individual animals were placed in the maze through a guillotine door located in one of the blind alleys and at the end of the test period, removed through an opening over the maze center. Throughout the experiment, laboratory lights automatically came on at 0600 hr and went off at 1800 hr.

RESULTS

There were no maternal deaths among any of the PCP-treated or control dams. From conception to term the IC, PCP5, and PCP10 dams gained a mean of 177.0, 148.7 and 129.0 g, respectively. A 1-way analysis of variance (ANOVA) revealed a significant treatment effect, $F(2,17)=8.37$, $p<0.01$.

For the analysis of offspring body weight, the mean weight of the male and female offspring for each litter was used as the unit of analysis. Table 1 shows that the birthweights of the male and female offspring from both the PCP5 and PCP10 groups were lower than the male and female ICs. A 2-way ANOVA comparing the PCP-treated and control birthweights revealed a significant effect for sex, $F(1,34)=6.42$, $p<0.005$, whereas drug treatment was not significant. Similarly, at weaning, there were no differences in body weight between any of the treated and control groups.

The mean activity data for the PCP-treated and control litters is shown in Fig. 1. Overall, activity level was lowest for all groups on Day 1 followed by a steady increase until Day 10. Thereafter, activity level slowly declined until Day 20 and then rapidly increased until Day 30. A 2-way ANOVA was performed using the activity data from individual animals with age and drug treatment tested as main effects. A highly significant effect was obtained for age, $F(6,102)=71.1$, $p<0.001$, whereas drug treatment failed to reach significance.

Maze activity data from male and female adult offspring are shown in Fig. 2. Over the three test days, mean activity

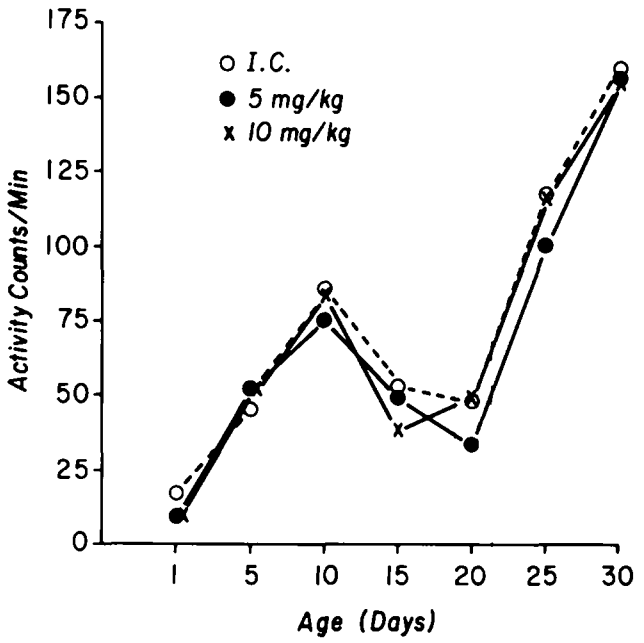

FIG. 1. Activity counts/min for PCP-treated and control offspring from 1 through 30 days of age.

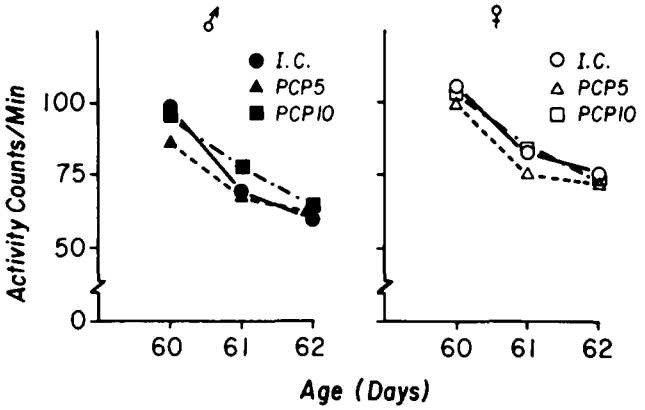

FIG. 2. Activity counts/min for PCP5 males (N=42) and females (N=36), PCP10 males (N=40) and females (N=29) and IC males (N=38) and females (N=45).

of both the males, shown on the left, and the females, shown on the right, steadily declined with the females being consistently more active than the males. There were no differences, however, between the PCP5, PCP10 and the control offspring of either sex. A 3-way ANOVA revealed significant effects for test days, $F(2,68)=109.6$, $p<0.001$, and sex, $F(1,34)=5.56$, $p<0.025$; drug treatment was not significant.

DISCUSSION

PCP has been found to produce malformations in the mouse [7] and rat [5] but only at doses that approximate the maternal LD50. For example, Jordan *et al.* [5], found a variety of malformations in the rat at a dose range of 25–60 mg/kg IP but dose levels between 10 and 20 mg/kg had little effect on offspring mortality or fetal weight. A non-teratogenic dose of 10 mg/kg administered on Days 6–15, however, produced a decrement in maternal weight gain but only during the period of drug administration. Although the inclusion of a large number of sub-groups obscured clear effects, birthweights appeared normal but offspring tended to show a decrement in preweaning weight gain and delays in behavior development.

In the present study, 5 and 10 mg/kg of PCP administered during the last two weeks of gestation produced dose-related behavioral effects in the dams and a corresponding decrement in maternal weight gain. Both dose levels produced a small but non-significant reduction in birthweight and at weaning, these differences were no longer evident. Neither dose, however, produced maternal death, increased resorptions or stillbirths. These results along with previous findings [5,7] indicate that PCP, at doses that produce mild toxicity but are well below the maternal LD_{50}, produces little if any embryotoxicity and does not appear teratogenic.

The ontogenetic change in activity level found for both the PCP-treated and control litters replicates previous observation from our laboratory for both nontreated and intubation control litters [4]. The observed behavior is characterized by an initial peak in activity at 10 days of age, a decline to a low level between 15–20 days and a sharp increase until the end of testing at 30 days of age. Although neither dose of PCP produced a developmental delay or altered activity level on this measure, it would be premature to conclude that the compound is without functional effects early in life. In studies with prenatally administered methadone, we found that the preweaning activity measure used here was sufficiently sensitive to detect behavioral effects during the first week of life [4]. This same 60-min test, however, failed to detect methadone effects during the third and fourth postnatal week of life, but extending the observation period to 8 hr revealed potent effects characterized by hyperactivity, increased state lability and sleep disturbance [3].

Similarly, on the adult measure of activity, the PCP5 and 10 male and female offspring were no different from controls; all groups were alike in overall activity level and, following initial exposure, showed habituation on subsequent trials. Like the preweaning measure, however, this test measures a relatively simple behavioral parameter that may not reflect other long-term effects produced by PCP. These findings suggest that sub-teratogenic doses of PCP that are sufficiently high to produce in the dam pronounced behavioral toxicity and a significant decrement in gestational weight gain, do not alter preweaning or adult locomotor activity in the offspring. It remains to be determined, however, whether or not early PCP exposure has effects on more complex behavioral processes.

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