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Zoological Research

Effects of Intraperitoneal Injection of Polychlorinated Biphenyls During Pregnancy on Sexual Behavior of F1 Rats

WANG Xiong-qing*, DAI Min, LUO Ying

(Key Laboratory for Molecular Biology and Biopharmaceuticals, Institute of Applied Animal Technology Mianyang Normal University, Mianyang, Sichuan 621000, China)

Abstract: 50 time-mated pregnant rats were divided into five groups and injected daily from gestational days 7 to 18 with either 2,2′,4,4′-tetrachlorobiphenyl (PCB 47) at the dosage of 1.00 or 20.00 mg/kg body weight; or 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) at the dosage of 0.25 or 1.00 mg/kg body weight; or sesame oil (control) to investigate the effects of fetal and lactational PCB exposure on reproductive behavior in male and female laboratory rats. Offspring were then tested for male sexual behavior: mount frequency, MF; mount latency, ML; intromission frequency, IF; intromission latency, IL; ejaculation latency, EL; post ejaculatory interval, PEI; hit rate and female sexual behavior; approach latency, AL; mount return latency, MRL; intromission return latency, IRL; post ejaculatory refractory period, PER; lordosis quotient, LQ. Measures were made at the age of postnatal days 70 to 91, and 97 to 101, respectively. The results showed that exposure to both PCB 77 and PCB 47 significantly reduced the LQ (84.4% for control, 76.0%, 67.8% for PCB 47 groups and 64.4%, 53.3% for PCB 77 groups; $P < 0.05$) in the female offspring. There were no significant effects on AL, MR, IRL, PER ($P > 0.05$) of the female offspring, or on MF, ML, IF, IL, EL, PEI and hit rate ($P > 0.05$) of the male offspring.

Key words: PCB; Rat; Sexual behavior

妊娠期腹腔注射多氯联苯对大鼠性行为的影响

王雄清，代 敏，罗 英

(绵阳师范学院 动物应用技术研究所 分子生物学与生物制药重点实验室，四川 绵阳 621000)

摘要：将50只同期怀孕的大鼠分为5组，在怀孕第7—18 d，每天分别给两组大鼠腹腔注射1.00和20.00 mg/kg体重2，2′，4，4′-四氯联苯(PCB 47)；分别给另两组注射0.25和1.00 mg/kg体重3，3′，4，4′-四氯联苯(PCB 77)；对照组注射0.10 mL芝麻油。幼鼠出生后第70—91 d、97—101 d测试F_1代雌鼠的接近时间(AL)、爬跨后返回时间(MRL)、插入后返回时间(IRL)、射精后不应期(PER)、脊柱前凸系数(LQ)和雄鼠的爬跨频率(MF)、爬跨等待时间(ML)、插入频率(IF)、插入等待时间(IL)、射精等待时间(EL)、射精后不应期(PEI)、插入率等性行为。结果显示，妊娠期腹腔注射PCB 47和PCB 77显著降低F_1代雌鼠的LQ(对照组为84.4%；PCB 47组分别为76.0%、67.8%；PCB 77组分别为64.4%、53.3%；$P > 0.05$)，但对雌鼠的AL、MRL、IRL、PER和雄鼠的MF、ML、IF、IL、EL、PEI和插入率无显著影响($P > 0.05$)。

关键词：多氯联苯；大鼠；性行为
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Polychlorinated biphenyls (PCBs), a family of global environmental pollutants, have been shown to disrupt a wide array of physiological and behavioral systems, including reproduction and brain development.

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* Corresponding author(通讯作者), E-mail: wangxq193@126.com
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PCBs are reported to decrease female fertility by reducing implanted ova and increasing the degeneration rate of embryos in mice (Orberg & Kihlstrom, 1973; Kholkute et al, 1994). A possible mechanism for this effect is through the change of the biochemical environment of the ovaries and uterus during oogenesis or pregnancy (Torok, 1976; Spencer, 1982). PCBs also affect male fertility by depressing the reproductive organs (Sanders et al, 1977; Sager et al, 1987) and by reducing sperm production (Sager et al, 1987). Further, androgen metabolism was altered in males (Sanders et al, 1977; Derr & Dekker, 1979; Haake-McMillan & Safe, 1991), and progesterone synthesis was disrupted in female rats (Johnson et al, 1976), following exposure to PCBs.

Perinatal treatment with the PCB mixtures, Aroclor 1221 (A 1221) and Aroclor 1254 (A 1254), has been shown to decrease sexual behavior in female rats (Chung & Clemens, 1999; Chung et al, 2001). These commercial PCB mixtures are composed of different concentrations of coplanar and noncoplanar PCBs. Therefore, some PCBs, such as the commercial mixture A 1221, may act as endocrine disrupters because of their affinity for estrogen receptors (Bitman & Cecil, 1970). However, other PCB mixtures, such as A1254, exhibit minimal binding to estrogen receptors, and some of their metabolites may even have antiestrogenic activity (Bitman & Cecil, 1970; Moore et al, 1997).

In this study, we used rat as a model to evaluate the effects of prenatal exposure to the dioxin-like PCB congener 3, 3′, 4, 4′-tetrachlorobiphenyl (PCB 77), and the noncoplanar di-ortho-substituted PCB congener, 2,2′,4,4′- tetrachlorobiphenyl (PCB 47), on the development of sexual behavior in the laboratory rat. Both of these congeners have been shown to alter brain dopamine levels (Brouwer et al, 1995; Seegal et al, 1997), a neurotransmitter that plays an important role in mediating male and female sexual behavior (Pfaff et al, 1994; Meisel & Sachs, 1994). PCB 77 is also reported to have estrogenic and antiestrogenic activity (Jansen et al, 1993; Nesaretnam et al, 1996).

1 Materials and Methods

1.1 Animals

Fifty time-mated Long-Evans female rats (*Rattus norvegicus*) were purchased from the Harlan-Sprague Dawley Inc. (Indianapolis, IN, USA). Upon arrival, the rats were divided into five groups and one female was housed to a plastic cage (50 cm × 25 cm × 20 cm). These animals were maintained in an air-conditioned room at 23 ± 2 ℃ under a 12:12 light/dark cycle with lights on from 19:00 to 07:00 and a relative humidity of 55%. Food (Harlan Teklad 22/5 rodent diet #8640, Madison, WI, USA) and tap water were available *ad libitum*.

At birth, litters were culled to four male and four female pups within the first 24 h after birth. When necessary, additional offspring from identically treated dams were used to maintain the desired sex ratio and the number of pups per litter. The dams that donated pups provided them to a single litter. At weaning, the animals were segregated by sex and treatment, and housed in plastic cages (50 cm × 25 cm × 20 cm).

1.2 Drugs and injections

Both PCB 47 and PCB 77 were purchased from AccuStandard (New Haven, CT, USA) and dissolved in sesame oil (Sigma, St. Louis, MO, USA). The dams were injected daily with either PCB 47 at the dosage of 1.00 or 20.00 mg/kg body weight or PCB 77 at the dosage of 0.25 or 1.00 mg/kg body weight or sesame oil (control group) from gestational days 7 to 18. These treatment levels were adapted from studies showing developmental effects of these congeners on brain dopamine (Seegal et al, 1997). While the dose levels used in this experiment parallel those used by Seegal et al (1997), the routes of administration differed. We administered the PCBs through intraperitoneal injections, as was done in other behavioral studies using PCB mixture (Chung & Clemens, 1999; Chung et al, 2001). The dams were weighed every 3 days during gestation and the amount of PCB was adjusted in accordance with changes in body weight.

1.3 Ovariectomy and hormone treatment

The sexual behavior of the experimental animals was evaluated by testing them with nonexperimental males or females, referred to as stimulus animals. Stimulus females, used to test the experimental males, were Long-Evans females ovariectomized (OVX) at 60 days of age. Prior to each test, they were treated with estrogen and progesterone to bring them into sexual receptivity. The surgical procedures and hormone treatments were identical to those described below for the experimental females. Untreated, sexually experienced Long-Evans male rats (stimulus males) were used to test the experimental females. At the beginning of the experiment, these stimulus males were approximately 90 days of age.

At 60 days of age, experimental females were OVX under ketamine and xylazine anesthesia (81.50

mg ketamine/ mL and 18.50 mg xylazine/mL; Fort Dodge Animal Health, Fort Dodge, IA, USA), housed in groups of three rats per cage, and left undisturbed for 1 week. These OVX experimental females were brought into sexual receptivity by intramuscular injections of 0.50 mg of estradiol benzoate (EB; Sigma, St. Louis, MO, USA) dissolved in 0.10 mL of the sesame oil vehicle. The injections were given 72, 48, and 24 h prior to the behavioral test. Additionally, 4 h prior to the start of testing, a single intramuscular injection of 0.50 mg of progesterone (Sigma, St. Louis, MO, USA) in 0.10 mL of the sesame oil vehicle was administered. Hormone treatments were given once a week. To familiarize the females with the test apparatus, each female was placed in the testing chamber for 5 min after each hormone injection.

1.4 Female sexual behavior tests

Female sexual behavior was evaluated with two separate test paradigms: a pacing test was used to determine the female's willingness to approach the male and a standard lordosis test was used to obtain measures of the lordosis response. The two tests were performed on the same days with the pacing test first followed by the lordosis test. In the pacing test, females were placed in a Plexiglas chamber that was divided into two arenas by a Plexiglas barrier. The female chamber (also called the escape chamber) was 21.5 cm × 44.5 cm × 48.3 cm, and the main chamber was 33.5 cm × 44.5 cm × 48.3 cm. A series of four-square holes (4.0 cm × 4.0 cm) along the bottom of the barrier allowed the female to pass through the barrier freely but prevented the larger male from following her. This testing situation allowed the female to control the timing of copulation. The female was introduced into the escape chamber 5 min after the male was placed in the main chamber. The time course of the behavior was recorded with a computer using an event-recording program. Two experienced investigators, who were not kept blind to the treatment received by the experimental animals, collected all the behavioral data. Several latency measurements were used to assess the temporal pattern of female sexual behavior. Approach latency (AL) was defined as the time from the introduction of the female into the escape chamber to her crossing the barrier to approach the male (Yang & Clemens, 1996, 1997). Mount return latency (MRL), intromission return latency (IRL), and postejaculatory refractory period (PER) were the measures of time that the female spent in the escape chamber after each male copulatory event (mount, intromission, or ejaculation, respectively) (Yang & Clemens, 1996, 1997). The behavioral tests began 4 h after the progesterone injection (at 13:00 h). Testing occurred once a week for 3 weeks from postnatal days (PND) 70 to 91. Tests were conducted under dim red light. Behavioral data were collected only on the third or last test. The first two tests served only to provide animals with sexual experience.

Sexually receptive females respond to mounts by a male by exhibiting a pronounced arching of the back, lordosis. To evaluate this aspect of the female's sexual receptivity, each female was tested in standard lordosis test (Beach, 1976) immediately following the pacing test. Testing was conducted in a Plexiglas observation chamber, which had no barrier in it, thus providing the male with unrestricted access to the female. Following treatment with EB and progesterone, sexual receptivity was measured by counting the number of times the female responded to the male with lordosis in 10 mounts (lordosis quotient, LQ). Only full lordosis responses, which included tilting of the head, arching of the back, and deflection of the tail, were counted. The male rat was placed in the testing arena (57.0 cm × 44.5 cm × 48.3 cm) 5 min before the female rat was introduced into the test chamber. The test ended after the male mounted the female 10 times.

1.5 Male sexual behavior tests

Male sexual behavior tests were conducted in a Plexiglas observation chamber (57.0 cm × 44.5 cm × 48.3 cm), where the male had free access to the sexually experienced OVX stimulus female that was brought into sexual receptivity with injections of EB and progesterone. We recorded male sexual behaviors including mount frequency (MF; number of mounts before ejaculation), intromission frequency (IF; number of intromissions before ejaculation), hit rate (number of intromissions/number of intromissions plus number of mounts), mount latency (ML; the interval from the female's entry into the chamber to the first mount), intromission latency (IL; the interval from the female's entry into the chamber to the first intromission), ejaculation latency (EL; the interval from the first intromission to ejaculation), and postejaculatory interval (PEI; the interval from ejaculation to the next intromission) (Yang & Clemens, 1997). The behavioral tests began 4 h after the OVX stimulus females were given the progesterone injection (at 13:00 h). The tests were performed once a week for 3 weeks from PND 97 to 101 under dim red light. As with the females, behavioral data were collected only on the third or last test, with the first two tests serving to provide animals with sexual

experience.

1.6 Data analyses

For each treatment group, the mean for each behavioral measure was calculated from the means of the appropriate litters. Latencies, frequencies, PEIs and PERs were analyzed by one-way ANOVA. Student-Newman-Keuls tests were performed between the control and PCB-treated groups when there was a significant ($P < 0.05$) overall difference between treatments. The lordosis quotients and hit rate scores were analyzed using chi-square tests.

2 Results

2.1 Female behavioral results

Prenatal exposure to PCB 77 significantly decreased sexual receptivity in female rats as measured by LQ (Tab. 1); however, treatment with PCB 47 had a significant effect only in the 20.00 mg/kg group Tab. 1). Exposure to PCB 77 significantly decreased the AL of the females ($F_{2,26} = 4.905$, $P < 0.05$; Tab. 2) in both the 0.25 and 1.00 mg/kg groups compared with that of the control group. Treatment with PCB 47 did not significantly affect AL. MRL, IRL, and PER were not significantly affected by prenatal exposure to either PCB 47 or PCB 77(Tab. 2).

2.2 Male behavioral results

Treatment with either PCB 47 or PCB 77 did not significantly affect the males' sexual behavior as measured by MF, IF, ML, EL, PEI, and hit rate (Tabs. 1 and 3).

3 Discussion

Our results demonstrate that prenatal exposure to both the coplanar congener PCB 77 and the ortho-chlorinated congener PCB 47 at subtoxic doses reduces sexual receptivity of female rats as measured by the LQ. This effect was seen at both doses for the coplanar PCB, but only at the relatively high dose in the case of PCB 47. Other aspects of female sexual behavior including the pacing of copulation were relatively normal in the PCB-treated females, with one interesting exception. Compared to controls, females exposed to the coplanar PCB showed significantly shorter approach latencies at the beginning of the pacing tests. Short approach latencies are commonly taken as evidence of enhanced sexual motivation on the part of the female (Erskine et al, 1989), therefore, considering the reduction in LQ seen in the females from the PCB 77 groups, the AL data seem paradoxical. Although there are examples of manipulations that differentially affect motivational and performance aspects of mammalian sexual behavior, e.g., lesions of the preoptic area in females (Whitney et al, 1986), there are other possible interpretations for these apparently conflicting observations.

Tab. 1 Effects of prenatal exposure to PCBs on sexual behavior of rats

	PCB 47		PCB 77		Control ($n = 10$)
	1.00 mg ($n = 10$)	20.00 mg ($n = 10$)	0.25 mg ($n = 9$)	1.00 mg ($n = 10$)	
Lordosis quotient(%)	76.0	67.8*	64.4*	53.3***	84.4
	$df = 2$, $n = 30$, $\chi^2 = 6.868$		$df = 2$, $n = 29$, $\chi^2 = 20.365$		
Hit rate(%)	32.3	32.7	30.2	29.6	33.4
	$df = 2$, $n = 30$, $\chi^2 = 0.094$		$df = 2$, $n = 29$, $\chi^2 = 1.305$		

* $P < 0.05$, *** $P < 0.001$ vs. control.

Tab. 2 Effects of prenatal exposure to PCB 47 and PCB 77 on sexual behavior of female rats

	PCB 47		PCB 77		Control ($n = 10$)
	1.00 mg ($n = 10$)	20.00 mg ($n = 10$)	0.25 mg ($n = 9$)	1.00 mg ($n = 10$)	
AL(s)	14.8 ± 7.2	18.1 ± 9.8	5.82 ± 0.7*	4.3 ± 0.4*	12.3 ± 3.2
	$F_{2,27} = 0.153$		$F_{2,26} = 4.905$		
MRL(s)	10.7 ± 3.5	16.1 ± 7.0	11.2 ± 5.3	13.8 ± 2.1	20.1 ± 4.3
	$F_{2,27} = 0.722$		$F_{2,26} = 1.253$		
IRL(s)	24.5 ± 5.6	51.0 ± 35.2	19.1 ± 5.9	16.4 ± 6.5	29.3 ± 5.5
	$F_{2,27} = 0.498$		$F_{2,26} = 1.218$		
PER(s)	76.7 ± 13.1	55.5 ± 11.2	63.4 ± 19.9	49.7 ± 9.8	51.4 ± 9.0
	$F_{2,27} = 1.411$		$F_{2,26} = 0.276$		

Data were represented as mean ± SEM; * $P < 0.05$ vs. control.

AL: Approach latency; MRL: Mount return latency; IRL: Intromission return latency; PER: Postejaculatory refractory period.

Tab. 3 Effects of prenatal exposure to PCB 47 and PCB 77 on sexual behavior of male rats

	PCB 47		PCB 77		Control (n = 10)
	1.00 mg (n = 10)	20.00 mg (n = 10)	0.25 mg (n = 9)	1.00 mg (n = 10)	
MF	11.9 ± 2.1	13.6 ± 2.0	14.3 ± 6.0	13.8 ± 3.0	10.5 ± 1.9
	$F_{2,27}$ = 0.584		$F_{2,26}$ = 0.292		
ML(s)	43.0 ± 12.6	39.3 ± 17.1	62.7 ± 43.2	17.8 ± 3.3	14.0 ± 2.3
	$F_{2,27}$ = 1.635		$F_{2,26}$ = 1.314		
IF	10.9 ± 1.1	12.8 ± 1.4	10.9 ± 1.5	10.0 ± 1.2	10.6 ± 1.3
	$F_{2,27}$ = 0.856		$F_{2,26}$ = 0.115		
IL(s)	64.1 ± 25.5	91.8 ± 38.3	110.7 ± 57.5	26.1 ± 3.7	51.8 ± 19.7
	$F_{2,27}$ = 0.503		$F_{2,26}$ = 1.672		
EL(s)	396.8 ± 64.8	534.6 ± 63.8	505.3 ± 122.2	519.0 ± 92.6	368.6 ± 27.3
	$F_{2,27}$ = 2.628		$F_{2,26}$ = 0.928		
PEI(s)	322.8 ± 13.4	336.7 ± 20.6	330.0 ± 16.7	362.1 ± 15.7	322.3 ± 9.2
	$F_{2,27}$ = 0.286		$F_{2,26}$ = 2.358		

Data were represented as mean ± SEM (standard error of means);
MF: Mount frequency; ML: Mount latency; IF: Intromission frequency; IL: Intromission latency; EL: Ejaculation latency; PEI: postejaculatory interval.

It is possible that the short latencies to cross the partition are the result of an increase in general activity due to exposure to PCB 77. Gestational treatments with PCB 77 increase general activity in rats (Hany et al, 1999) and mice (Agrawal et al, 1981; Tilson et al, 1990) when tested as adults. We did not include a condition in which the latency to cross the partition between the two chambers was determined in the absence of the male. Therefore, we cannot exclude the possibility that a nonspecific increase in activity, rather than a change in female sexual motivation, was responsible for the short approach latencies shown by the PCB 77 groups.

While both putative hyperactivity and deficits in sexual behavior may be mediated by actions of the PCBs on dopaminergic systems that facilitate lordosis (Mermelstein & Becker, 1995) and modulate general activity (Agrawal et al, 1981), strong support for that notion is lacking in this experiment. Perinatal treatments with PCB 77 and PCB 47 using an oral route of administration have been reported to induce lasting changes in the dopamine levels of some brain regions (Seegal et al, 1997), but the changes induced by each PCB were in opposite directions, PCB 77 raising dopamine levels and PCB 47 lowering them. In the present experiment, both treatments interfered with normal sexual receptivity. Consequently, we regard it as unlikely that the PCB-related behavioral changes reported here are a reflection of PCB-induced variations in brain dopamine. In addition, perinatal exposure of rats to the PCB mixture Aroclor 1221, using the intraperitoneal route of administration of the present study, also results in deficits in lordosis without producing any detectable changes in hypothalamic dopaminergic systems (Chung & Clemens, 1999). Thus, PCBs may interfere with the normal development of female sexual behavior by acting on central and peripheral sites other than the brain dopaminergic systems (Chung et al, 2001), and the effects of perinatal exposure to PCBs on the development of central dopaminergic systems may depend upon route of administration.

Different from the effects seen in females, male sexual behavior were not affected by any of the treatments. For PCB 77, this is consistent with the report by Faqi et al (1998). In that study, PCB 77 administered on day 15 of pregnancy did not disrupt sexual behavior and did not affect anogenital distance or the ratio of anogenital distance to body length in the male offspring. However, Faqi et al (1998) found a significant reduction in testosterone levels in the adult male offspring of mothers that received PCB 77 during gestation.

Based on the data summarized here, it appears that fetal (and lactational) exposure to PCB 77 or PCB 47 results in a decrease in sexual receptivity in the adult rat. In contrast, male offspring of PCB-treated dams showed no deficits in male sexual responding as adults. Whether the behavioral deficits in the female reflect a direct action of androgens during early development, an effect of estrogenic metabolites or direct PCB stimulation of estrogen receptors is unclear.

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