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Perinatal polychlorinated biphenyl 126 exposure alters offspring body composition

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Abstract. Polychlorinated biphenyls (PCBs) are ubiquitous environmental contaminants whose exposure levels are associated with various health hazards. We hypothesized that in utero and lactational exposure to PCBs can cause changes in body composition and obesity in a mouse model. Pregnant mice were exposed biweekly to two concentrations of PCB 126 via oral gavage. Maternal PCB exposure did not result in heavier offspring, however, dose-dependent and sex specific changes in body composition were observed. Female offspring displayed the most susceptibility to PCB-induced alterations in body composition, having less percent lean body mass and increased adiposity compared to females born to control dams, and these effects were largely dose-dependent. In contrast to females, and independent of the exposure level of PCB 126, male offspring had reduced lean body mass but no change in fat mass compared to males born to control dams. In conclusion, perinatal PCB 126 exposure did not affect body weight, but rather modulated body composition in a dose-dependent and gender-specific manner.

Keywords: Programming, obesity, persistent organic pollutants, mice, aryl hydrocarbon receptor, coplanar

1. Introduction

Polychlorinated biphenyls (PCBs) were produced in the United States (US) until their ban in 1976 upon realization of their many hazards to human health [1]. Although production of PCBs has long ceased, environmental contamination remains, and PCBs are found in over 29% of hazardous waste sites in the US [1]. Primary sources of PCB exposure for the general population include contact with ground water or contaminated soil due to inappropriate disposal of materials containing PCBs, food contamination from food storage in silos with PCB-coated interiors, and consumption of fish from contaminated waterways [1]. Additionally, PCBs resist biodegradation, are lipophilic, and consequently bioaccumulate in the environment and in the food chain, thus exposing millions of Americans to these toxic compounds [2].

There are 209 possible congeners depending upon the extent and position of chlorination within the two phenyl rings which comprise PCBs. Those with coplanar conformations are referred to as dioxin-like PCBs in that, like dioxin, these PCBs are aryl hydrocarbon receptor (AhR) agonists [3]. The strongest AhR agonist among PCB congeners is 3, 3', 4, 4', 5 pentachlorobiphenyl (PCB 126) [4].

PCBs are ubiquitous and persistent environmental pollutants whose presence in utero perturbs fetal development. The developmental origins of health and disease hypothesis, derived from the thrifty phenotype hypothesis put forth by Barker and Hales in 1992 [5], postulates that low birth weight offspring can result from insufficient nutrition in the intrauterine environment, leading to metabolic and other health derangements later in life [5−10]. In fact, maternal serum PCB levels in humans negatively correlate with infant birth weight and gestational age [11−17]. A meta-analysis comparing prenatal PCB exposure and

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birth weight effects across 12 European birth cohorts found a significant negative correlation between cord blood PCB levels and birth weight [11]. Multiple studies have confirmed that low-level PCB exposure during the perinatal period can significantly affect fetal growth and birth weight [12,14−19], although other studies found that PCBs have minimal or no effect [20,21]. Nonetheless, the decreased body weight can persist to preschool ages and is concomitant with hypotonia and diminished physical activity [22,23]. A recent paper suggests that catch-up growth may occur by six years of age and prenatal organochlorine levels contribute to gender-specific overweight incidence in children [24].

Exposure to environmental pollutants can contribute to the pathology of obesity [25], and recent human studies support our hypothesis that perinatal exposure to PCBs is associated with overweight offspring [11, 24]. Thus, the purpose of our experiment was to study gender-specific differences in body composition of offspring born to PCB exposed dams.

2. Materials and methods

2.1. Animals and diets

At 2 months of age, female ICR mice were bred and subsequently produced one litter at Taconic (Hudson, NY) prior to their purchase and shipment to the University of Kentucky at roughly 4 months of age. The following studies were carried out at the University of Kentucky according to an approved Institutional Animal Care and Use Committee protocol. Females were housed 4 mice per cage for a 2 week acclimation period prior to mating. Female mice were fed a semi-purified diet containing 10% kcal from fat (D12450B, Research Diets, New Brunswick, NJ) ad libitum for the duration of the study. Male ICR sires (Taconic) were fed standard chow (#2018, Teklad Global 18% Protein Rodent Diet) during a 7 day acclimation period then mated to dams for 7 days, 1 sire per 2 dams. In order to equilibrate nutrient availability, litters were culled to 6 pups on postnatal day 3. Pups from litters with more than 6 pups that were born on the same day were cross-fostered to dams nursing less than 6 pups. Body weight and maternal food intake were monitored weekly throughout weaning. Pups were weaned on postnatal day (PND) 21 onto standard chow, and male and female offspring were housed 3 and 5 mice per cage, respectively.

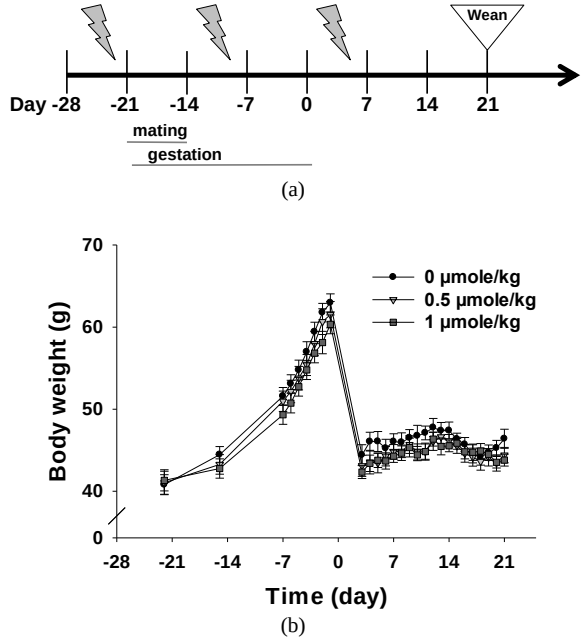

Fig. 1. Maternal PCB 126 Exposure and Body Weight. (a) Schematic diagram of exposure model. Dams were administered 0, 0.5 or 1.0 µmole of PCB 126 per kg body weight via oral gavage every 14 days beginning 48 hours prior to mating until approximately postnatal day 7, for a total of 3 exposures. Females were allowed to mate for 7 days; therefore, the exact developmental day of exposure was unknown. Day 0 signifies date of birth. Litters were delivered over a span of 7 days. Mice were weaned on postnatal day 21. (b) Maternal body weight. Dam body weights were taken weekly prior to mating. During mating and gestation, dam body weights were taken daily until birth and again beginning on postnatal day 3 until weaning. There were no differences in maternal body weight between treatment groups ($p = 0.459$).

2.2. PCB exposure

3, 3', 4, 4', 5-pentachlorobiphenyl (PCB 126) was purchased from AccuStandard (C-126N, New Haven, CT). PCB 126 was dissolved in tocopherol stripped safflower oil (#403952, Dyets, Bethlehem, PA). Female mice were orally gavaged with 0, 0.5 or 1.0 µmole of PCB 126 per kg body weight at a frequency of once per 14 days. The frequency was such that the dams were exposed to PCB 48 hours prior to mating, once during gestation, and once during lactation (Fig. 1).

2.3. Body composition

At 7 weeks of age, nuclear magnetic resonance (EchoMRI; EchoMedical Systems; Houston, TX) was employed to quantify fat mass and lean body mass in

Table 1
Litter number, size and mean pup body weight

Dose of PCB 126 (μmole/ kg)	Number of litters[a]	Mean # pups per litter	Mean pup weight (g) per litter (s.e.m.)					
		PND[b] 3	PND 3	PND 7	PND 14		PND 21	
					Male	Female	Male	Female
0	13	10.46 (0.78)	2.45 (0.10)	5.47 (0.16)	11.43 (0.36)	11.30 (0.26)	17.08 (0.49)	16.24 (0.39)
0.5	15	9.13 (0.65)	2.53 (0.08)	5.34 (0.15)	11.01 (0.31)	11.03 (0.26)	15.87 (0.40)	15.51 (0.33)
1	13	7.92* (0.56)	2.60 (0.13)	5.46 (0.26)	10.90 (0.47)	11.90 (0.37)	15.28 (0.72)	16.23 (0.71)
p[c]	–	0.043	0.617	0.794	0.615	0.123	0.083	0.433

[a]Out of 15 breeding females; [b]Postnatal day; [c]p value from ANOVA; *Significantly different from 0 μmole/kg control following post hoc analysis, $p < 0.05$.

Table 2
Seven week old female offspring body composition

Dose of PCB 126 (μmole/kg)	n	Body weight[a] (s.e.m.)	Fat mass[a] (s.e.m.)	Fat % (s.e.m.)	Lean mass[a] (s.e.m.)	Lean % (s.e.m.)
0	12	29.33 (0.80)	5.76 (0.52)	19.37 (1.21)	20.52 (0.39)	70.23 (1.09)
0.5	15	30.43 (0.71)	6.91 (0.45)	22.45* (0.92)	20.69 (0.31)	68.23 (0.81)
1	10	31.56 (1.41)	8.57** (0.94)	26.54** (1.93)	20.33 (0.59)	65.00** (1.70)
p[b]	–	0.298	0.015	0.003	0.830	0.017

[a]Body weight, fat mass and lean mass are reported in grams. [b]p value for ANOVA; *,**Significantly different from 0 μmole/kg control following post hoc analysis, $p < 0.05$ and $p < 0.01$, respectively.

Table 3
Seven week old male offspring body composition

Dose of PCB 126 (μmole/kg)	n	Body weight[a] (s.e.m.)	Fat mass[a] (s.e.m.)	Fat % (s.e.m.)	Lean mass[a] (s.e.m.)	Lean % (s.e.m.)
0	10	39.58 (1.64)	6.72 (1.05)	16.35 (1.91)	28.51 (0.64)	72.59 (1.83)
0.5	11	37.69 (0.91)	7.20 (0.73)	18.80 (1.61)	26.15* (0.39)	69.66 (1.49)
1	13	36.82 (1.45)	6.76 (0.42)	18.28 (0.77)	25.68** (0.91)	69.96 (0.82)
p[b]	–	0.368	0.876	0.476	0.024	0.286

[a]Body weight, fat mass and lean mass are reported in grams. [b]p value for ANOVA; *,**Significantly different from 0 μmole/kg control following post hoc analysis, $p < 0.05$ and $p < 0.01$, respectively.

both female and male offspring born to vehicle or PCB exposed dams. Although many tissues contribute to the lean mass output, there are undetectable components such as bone mineral content, hair, and claws. Body composition measurements in Tables 2 and 3 include data from only one female and one male offspring per litter, respectively. Body weight was measured just prior to body composition analysis.

2.4. Statistics

Overall differences in maternal body weight were determined by repeated measures ANOVA using IBM SPSS statistics 20 software. The remaining analyses were completed using SigmaPlot 12.0 software. One-way ANOVA was used to make comparisons between groups for the remaining comparisons in Tables 1–3.

Fisher LSD Method was used for post hoc comparisons. Upon the event of a failed Shapiro-Wilk normality test, data were transformed using natural log. Kruskal-Wallis ANOVA on Ranks was used when the data failed the equal variance test or failed normality following transformation.

3. Results

3.1. Maternal effects of biweekly PCB 126 exposure and pup body weight

Figure 1a illustrates the perinatal exposure model used in the current study. Exposure at concentrations of 0.5 and 1 μmole PCB per kg body weight did not affect pregnancy rate (Table 1), maternal body weight (Fig. 1b) or food intake (data not shown) when compared to vehicle controls. In order to promote successful rearing, litters were not disturbed until postnatal day 3, at which time pups per litter were enumerated. The 1 μmole/kg dose led to significantly decreased litter size compared to control. There was no significant difference in pup body weight although there was a trend toward decreased body weights in male offspring maternally exposed to PCB 126 compared to those from control dams at postnatal day 21 ($p = 0.083$) (Table 1).

3.2. Body composition analysis

At 7 weeks of age, body composition was analyzed by EchoMRI, and the data are presented in Tables 2 and 3 for the female and male offspring, respectively. Perinatal PCB exposure resulted in gender specific differences in body composition. Females born to PCB exposed dams had similar body weights, yet displayed significantly increased adiposity compared to females born to vehicle treated dams. Females perinatally exposed to 0.5 μmole/kg and 1 μmole/kg PCB 126 showed a dose-dependent 15.9% and 37.0% increase in percent body fat compared to females born to control dams ($p = 0.044$ and $p < 0.001$, respectively). The largest effect was seen in the high exposure group as these offspring additionally displayed significantly elevated fat mass and a 7.4% reduction in percent lean body mass ($p = 0.004$ and $p = 0.005$, respectively).

For male offspring at 7 weeks of age, there was no significant effect of perinatal PCB exposure on body weight ($p = 0.368$). In contrast to that which was observed in females, male offspring born to PCB exposed dams showed no difference in adiposity taken as either weight of fat mass or when expressed as a percentage of body weight ($p = 0.876$ and $p = 0.476$, respectively). There was, however, a significant reduction in grams of lean mass between the groups; specifically, males perinatally exposed to 0.5 μmole/kg and 1 μmole/kg PCB 126 showed significant reductions in lean mass (8.3% and 9.9%, respectively). However, there was no significant difference in percent lean mass ($p = 0.268$).

4. Discussion

The current study focused on the effects of perinatal PCB exposure on gender-specific body compositional changes in the offspring. Because many studied causes of low birth weight are due to intrauterine growth restriction resulting from maternal undernutrition [5,26–28], it is important to note that neither maternal body weight nor food intake was affected by PCB exposure. It is uncertain whether or not the congener dosing and frequency used in this experiment caused low birth weight because initial pup weights were not measured until postnatal day 3 instead of day 0 in order to promote successful rearing. Nonetheless, there was no difference in body weight between pups born to control or PCB exposed dams at the first measurement of offspring body weight at postnatal day 3. In fact, pup body weights were comparable throughout weaning. When mice were sexed at postnatal day 14, there was also no difference in body weight between treatment groups within each gender. In the event that low birth weight had occurred, it is unlikely that catch up growth would have occurred 3 days post-partum [29, 30]. It is important to note that decreased pup weight was observed throughout the nursing period in a separate experiment in which dams were gavaged with 1 μmole PCB 126 /kg body weight weekly totaling five doses. The pregnant dams also gained significantly less weight late during pregnancy (data not shown).

Possible toxicity of our dosing regimen was evidenced by reduced litter size in the 1 μmole/kg PCB 126 dose compared to control. The observed reduction in litter size is a likely consequence of poor rearing because unpublished data from our laboratory revealed no differences in fetal number at embryonic

day 18 when dams were administered 1 μmole/kg PCB 126 similar to the current exposure model (data not shown). Studies in humans have shown conflicting effects of maternal PCB exposure on fecundity, and specifically time to pregnancy [31−36].

In the present study, at 7 weeks of age, there was still no effect of perinatal PCB exposure on offspring body weight in these mice. Hertz-Picciotto and colleagues [13] showed that in humans, in utero PCB exposure of males was associated with low birth weight and body weight for gestational age in boys, while in girls, in utero exposure was associated with shorter gestation. Within the same study, at five years of age, prenatal PCB exposure was associated with increased growth in girls but not boys [13]. Additionally, a recent prospective study conducted in humans revealed a significant positive correlation between cord blood concentrations of PCBs and overweight in females 6.5 years of age [24]. The males in that study did not exhibit such an association, although there was a trend toward a negative correlation between moderate prenatal PCB exposure and overweight. Our current experiment shows similar trends (Tables 2 and 3), such that perhaps with an increased sample size, we too would have observed statistically significant dose and gender-specific effects of maternal PCB exposure on body weight. Interestingly, when Valvi and colleagues [24] adjusted for birth weight, the association between overweight and PCBs strengthened, and the findings still held true even when only normal birth weight offspring were included, suggesting that prenatal PCB exposure in the absence of low birth weight may still contribute to the overweight phenotype. It was assumed that increased weight at 6.5 years of age was caused by increased adiposity, but confirmation was not provided [24].

In the current experiment, body composition analyses showed female offspring born to PCB exposed dams had increased adiposity as well as reduced lean body mass compared to offspring from vehicle treated dams despite comparable body weights. The observed adiposity is consistent with published data in mice which demonstrated coplanar PCB 77 augmented body weight gain, adiposity, and adipocyte differentiation [37]. There are previous reports in humans of PCB levels correlating with decreased muscle tone, and from these studies it appears hypotonia occurs preferentially in females [38−40]. Also, there is evidence that while in utero exposure correlates with later life neurocognitive impairments, it is lactational exposure that better associates with hypotonia [22,38, 39]. In the present study, male offspring displayed no such increased adiposity. In contrast to females, male offspring born to dams exposed to 1 μmole PCB 126/kg body weight had decreased lean body mass compared to control males (Table 3).

Timing of maternal exposure may be important in PCB-induced abnormal development, and consequently future studies will include cross-fostering of pups born to PCB-treated dams with those of vehicle-treated dams to further clarify compositional changes induced by exposure to PCB. Cross-fostering will allow us to establish whether PCB exposure in utero or during lactation precipitates these aberrant changes in body composition.

Results from the presented experiment are similar to findings in humans, thus supporting current and future use of this exposure model to assess effects of maternal PCB exposure on altered body composition in the offspring. Moreover, this model can be utilized to determine mechanisms causing or regulating long-term outcomes in body composition. Future studies will allow for aging of exposed offspring to determine the extent to which altered body composition persists, as well as the impacts these changes will have on metabolic disease risks. Because skeletal muscle and adipose tissue are key sites of glucose disposal, one would suspect the observed differences in body composition of female mice perinatally exposed to PCBs may predispose them to impaired glucose tolerance. Our data clearly demonstrate that perinatal PCB exposure impacts body composition in young females, increasing adiposity and reducing lean body mass. Later life implications of such early PCB exposure and the development of obesity-associated pathologies remain uncertain.

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