PRENATAL EXPOSURE TO OH-PCBs IN RELATION TO PHYSICAL DEVELOPMENT IN A BIRTH COHORT (T-Child) AT 5 YEARS OF AGE

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Introduction

In recent years, obesity in children has become a growing health concern in most countries. The number of obese and overweight is growing rapidly. In the U.S., the rate of obesity increased from 6.5% to 19.6% between 1976- 1980 and 2007- 2008, respectively, among children aged 6-11[1]. In Japan, the rate of obesity and overweight children has increased by 2-3 times in the past decade (Ministry of Education, Culture, Sports, Science and Technology, Japan, 2008).

The concept of an "Environmental Obesogen" has been proposed, and a concern for the possibility of the involvement of an endocrine disruptor that affects obesity related programming has been growing[2]. The proposed mechanisms of the environmental obesogen include effects on the thyroid and steroid hormones and activation of peroxisome proliferator-activated receptors (PPARs)[3].

Hydroxylated PCBs (OH-PCBs) may act as environmental obesogens since OH-PCBs perturb thyroid hormone homeostasis[4] and some OH-PCB congeners act as estrogen and anti-estrogen[5, 6].

In a previous study, we measured OH-PCBs in preserved umbilical cords from subjects of a prospective cohort study (T-Child) to estimate the prenatal exposure to OH-PCBs[7]. We reported that body weight and height at 2 years old for all toddlers were significantly associated with total OH-PCBs and 4M187. For males, body weight at 2 years old was significantly associated with total OH-PCBs, 4M107, and 4M187.

In the present study, to examine whether such effects persist into later age, we investigated the associations between prenatal exposure to OH-PCBs and the physical development of children at 5 years of age.

Materials and methods

Study population. The Tokyo Children's Health, Illness, and Development (T-CHILD) cohort study recruited about 1,600 women in early pregnancy from 2003 to 2005 at the National Center for Child Health and Development, Setagaya, Tokyo, Japan. In 2007 and 2008, we asked 910 cohort participants to offer their children's umbilical cords stored at home for the analysis of hydroxylated PCBs (OH-PCBs). A total of 126 participants, including 10 who had children with neurodevelopmental disorders (cases), agreed to

provide their children's umbilical cords. One mother-infant pair was excluded from further analysis because of low birth weight (1,540g).

At 5 years of age, 110 (55 male, 55 female) of the 125 children (88%) of the original cohort participants whose umbilical cords had been provided, were weighed and measured for height.

Analytical procedures. About 1/2 – 1/3 of the umbilical cords (0.0317g – 0.1180g) were used for analysis. The umbilical cords were powdered using a multi-bead shocker, and PCBs were extracted in hexane after alkaline degradation with a KOH/ethanol solution. The alkaline phase containing OH-metabolites was acidified and extracted with hexane. This organic phase was purified with sulfuric acid, and a hydroxyl group was then methoxylated with tetramethylsilyl diazomethane. The clean-up process of the OH-PCB and PCB fraction was performed using silica gel chromatography and a multilayer silica gel column, respectively.

In this study, 35 selected OH-PCBs and PCBs in the umbilical cords were analyzed using a gas chromatograph (6890 series, Agilent Technologies, USA) and high-resolution mass spectrometry (resolution > 10,000; Autospec- Ultima, Micromass, England). An RH12ms column (INVENTx, USA) and an HT8-PCB column (SGE Analytical Science, Australia) were used to separate the OH-PCB and PCB congeners, respectively. The results of the PCB analysis were expressed as the sum of the congeners grouped by number of chlorines.

Data analyses. Multiple regression models were used to examine the association between physical development (body weight, height, and BMI) and OH-PCB congener levels in the umbilical cords in the quartile. All statistical analyses were performed using SAS statistical software (version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

Results and discussion

The Japanese traditionally keep a small portion of their baby's umbilical cord in a wooden box as a keepsake. This tradition provides a unique opportunity to monitor, after birth, the chemical exposure during fetal life.

Relatively higher concentrations were observed for 4'-OH-2,3',4,5,5'-pentachlorobiphenyl (4PM120), 4'-OH-2,2',4,5,5'-pentachlorobiphenyl (4PM101), 4-OH-2,3,3',4,5'-pentachlorobiphenyl (4M107), 3-OH-2,2',4,4',5,5'-hexachlorobiphenyl (3M153), 4-OH-2,2'3,4',5,5'-hexachlorobiphenyl (4M146), 3'-OH-2,2',3,4,4',5'-hexachlorobiphenyl (3PM138), 4'-OH-2,3,3',4,5,5'-hexachlorobiphenyl (4PM159), 4'-OH-2,3,3',4',5,5'-hexachlorobiphenyl (4PM162), 4-OH-2,2',3,4',5,5',6-heptachlorobiphenyl (4M187), and 4'-OH-2,2',3,3',4,5,5'-heptachlorobiphenyl (4PM172). Except 4PM159, these congeners were detected in most of the samples. The median concentration of total OH-PCBs was 375 pg/g dry weight (Fig. 1).

In the present study, on the basis of the median concentration (pg/g dry weight), the order of dominant congeners was 3PM138 (59) > 4M146 (54) > 4M187 (53) > 4PM162 (32) > 4PM159 (31) > 3M153 (28) > 4M107 (25) > 4PM120 (25) > 4PM101 (25) > 4PM172 (24). There is no previous data to compare with the present results. Kawashiro et al. measured 9 OH-PCBs in fresh frozen umbilical cords from 6 Japanese mother-infant pairs[8]. The two dominant OH-congeners in the cords were 4M146 (1.6) and 4M187 (1.5), followed by 3PM138 (0.84) and 4M109 (0.76) on the basis of the median concentration (pg/g wet weight). In the present study, 3PM138 was relatively higher than the results in Kawashiro's study. The reason for this difference is not understood, as the dietary habits of the two populations were most likely similar.

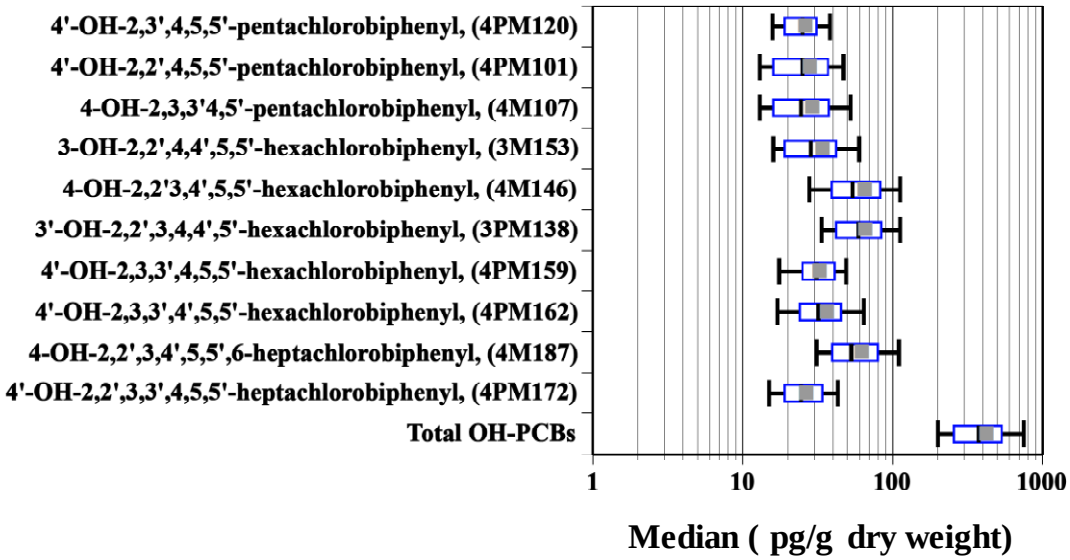

Fig. 1. Levels of major OH-PCB congeners in preserved umbilical cords

At 5 years old, the mean body weight, height and BMI for boys and girls were 17.5 kg, 107.1 cm, and 17.5 and 17.0 kg, 106.8 cm, and 17.0, respectively.

Body weight at 5 years old for all children was significantly associated with total OH-PCBs, 4PM101, 3M153, 3PM138 and 4M187. For males, body weight at 5 years old was significantly associated with 3M153 and 4M187. For females, body weight at 5 years old was neither significantly associated with total OH-PCBs nor any OH-PCB congeners. The associations between prenatal exposure to OH-PCBs and BMI were almost the same as those observed in body weight. Height at 5 years old was significantly associated with neither total OH-PCBs nor any OH-PCB congeners.

In a previous report, we reported that body weight and height at 2 years old for all toddlers were significantly associated with total OH-PCBs and 4M187[7]. For males, body weight at 2 years old was significantly associated with total OH-PCBs, 4M107, and 4M187. The associations between prenatal exposure to OH-PCBs and body weight at 2 years old persisted at 5 years old.

In our study, the associations between prenatal exposure to OH-PCBs and body weight were observed only in boys. A strong association was observed for 4M187 ($p < 0.01$). As 4M187 is a potent inhibitor of the human estrogen sulfotransferase (hEST)[5], this inhibition would result in estrogenic effects, which may explain the gender-specific effects of OH-PCBs on body weight. However most prospective studies suggest that prenatal PCB exposure may have a larger impact on weight development among girls than among boys[9]. The difference in the gender-specific effects on body weight may partly attributable to chemicals, i.e., PCBs vs. OH-PCBs. Further study is needed to elucidate the mechanisms involved in the obisogenic effects of PCBs and OH-PCBs.

In summary, this study suggests that prenatal OH-PCB exposure may be associated with being overweight in children and that sex may influence susceptibility.

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