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Association of maternal serum concentration of hydroxylated polychlorinated biphenyls with maternal and neonatal thyroid hormones: The Hokkaido birth cohort study

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ABSTRACT

Background: Evidence on the toxicity of hydroxylated metabolites of polychlorinated biphenyls (OH-PCBs) for thyroid hormones (TH) is limited, and the underlying mechanism remains unknown.
Objectives: We aimed to investigate the effects of environmental prenatal exposure to OH-PCBs and maternal and neonatal TH levels, taking the maternal-fetal TH transfer into account.
Methods: In this prospective birth cohort (the "Hokkaido study") we included 222 mother-neonate pairs. We measured five OH-PCB isomers in maternal serum samples either during pregnancy or within 5 days of delivery. Thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were obtained from maternal blood samples at an early gestational stage (median; 11.1 weeks) and from heel prick samples of neonates between 4 and 7 days after birth. Multiple linear regression analysis and structural equation modeling (SEM) were performed to investigate the associations between maternal OH-PCB and maternal and neonatal TH levels.
Results: Median concentration of ΣOH-PCBs was 25.37 pg/g wet weight. The predominant isomer was 4-OH-CB187, followed by 4-OH-CB146 + 3-OH-CB153. In the fully adjusted linear regression analysis, maternal ΣOH-PCBs was positively associated with maternal FT4, and 4-OH-CB187 was positively associated with both maternal and neonatal FT4 levels. Maternal OH-PCBs showed no significant association with TSH among mothers and neonates. Path analysis indicated the indirect pathway from 4-OH-CB187 exposure to increased neonatal FT4, via maternal THs and neonatal TSH.
Conclusions: These findings suggest that maternal exposure to OH-PCBs during pregnancy may increase both maternal and neonatal FT4 levels. Neonatal FT4 is presumed to be increased by prenatal 4-OH-CB187 indirectly, and this process may be mediated by maternal THs and neonatal TSH.

1. Introduction

During the last decade, the advances in technology have made it possible to detect the metabolites of polychlorinated biphenyl (PCBs). Hydroxylated PCBs (OH-PCBs) are the predominant metabolites of PCBs, and are mainly formed by cytochrome P450 oxidation of PCBs

Abbreviations: AGFI, adjusted goodness of fit index; AMC, antimicrosome antibody; ATG, antithyroglobulin antibody; CFI, comparative fit index; CI, confidence interval; FT4, free thyroxine; GFI, goodness of fit index; IQR, interquartile range; LC/MS/MS, liquid chromatography-tandem mass spectrometry; LOD, limit of detection; OH-PCBs, hydroxylated polychlorinated biphenyl; PCBs, polychlorinated biphenyl; T4, thyroxine; THs, thyroid hormones; TSH, thyroid stimulating hormone; TTR, transthyretin

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(Letcher et al., 2000). There is increasing evidence that OH-PCBs accumulate in the environment, in animals, and in humans, at detectable levels (Bergman et al., 1994; Hovander et al., 2002; Park et al., 2007; Soechitram et al., 2004). They are water-soluble and therefore rapidly eliminated via the urine or excreta (Soechitram et al., 2004). However, a recent study reported that some OH-PCB congeners showed longer half-lives than the parent PCBs, with evidence of retention in the human blood for several years (Quinete et al., 2017). Furthermore, previous studies have reported that the ratio of ΣOH-PCB/ΣPCBs in cord blood was higher than that in maternal blood (Kawashiro et al., 2008; Park et al., 2008; Soechitram et al., 2004). These reports indicate that OH-PCBs have a higher ability than PCBs in passing through the placenta and reaching the fetus. Although the adverse effects of prenatal exposure to PCBs on the health of children has been extensively reported (Bell, 2014), there is a possibility that those effects may have been caused by OH-PCBs, and not PCBs. However, there are limited studies examining OH-PCB toxicity.

Thyroid hormones (THs) are crucial for fetal and neonatal neurodevelopment (Haddow et al., 1999; Zoeller et al., 2002). OH-PCBs are reported to possess a higher binding affinity for transthyretin (TTR) than thyroxine (T4) (Brouwer et al., 1998; Lans et al., 1993), which may disrupt TH levels. Animal studies previously reported that maternal exposure to 4-OH-CB107 was associated with decreased total and free T4 (FT4) levels and elevated thyroid stimulating hormone (TSH) in fetal plasma among rats (Meerts et al., 2002). Additionally, one study among hooded seal pups showed that 4-OH-CB107 and 3-OH-CB138 were inversely associated with FT4: free triiodothyronine (FT3) and Total T3: FT3 ratios, respectively (Gabrielsen et al., 2011). As for human, three epidemiological studies involving Dutch and Japanese participants reported a significant association between prenatal exposure to OH-PCBs and neonatal or infant THs (Hisada et al., 2013; Otake et al., 2007; Soechitram et al., 2017). However, a Canadian study examining Inuit women and their infants found no significant association (Dallaire et al., 2009b). These findings suggest the adverse influence of OH-PCBs on newborn and infant THs; however, the findings, based on small sample sizes (under 100 participants) are controversial. Moreover, maternal THs are transferred to the fetus throughout pregnancy to support fetal development. The fetus is completely dependent on maternal TH supply during the first trimester of pregnancy, before fetal TH synthesis and secretion develops (Vulsma et al., 1989). Maternal hypothyroxinemia during early pregnancy may be an important risk factor for impaired infant development (de Escobar et al., 2004; Pop et al., 1999). Therefore, disruption of maternal TH homeostasis in the early stages of pregnancy may impair fetal development. Early gestational screening tests for maternal THs have been implemented in many parts of the world to prevent abnormal fetal development. Nevertheless, few studies have investigated the association of exposure to OH-PCBs during pregnancy and neonatal TH concentration, taking the possibility of disruption of maternal THs by OH-PCBs into account.

The aim of this study is to determine whether maternal exposure to OH-PCBs at environmental levels is associated with TH levels in mothers and neonates. We also aim to investigate the indirect effect of maternal THs, affected by OH-PCB exposure, on neonatal TH levels, using path analysis.

2. Material and methods

2.1. Study design and population

This prospective birth cohort study was based on data from mothers and their neonates delivered at the Sapporo Toho Hospital in Sapporo, Hokkaido, Japan (Sapporo cohort in Hokkaido Study on Environment and Children's Health). Details regarding the study population, data collection, and the questionnaires have been previously described (Kishi et al., 2011, 2013, 2017). In brief, pregnant women at 23–35 weeks of gestation and planning to deliver at one obstetric hospital, Toho Hospital, in Sapporo city were recruited between July 2002 and October 2005. All participants were native Japanese women residing in Sapporo and surrounding areas. Their children have been followed up as subjects in the prospective cohort. Out of a total of 514 women, we excluded those who experienced miscarriage, stillbirth, relocation, or voluntary withdrawal (n = 10), and those who delivered twins (n = 7). The following exclusion criteria were applied to the remaining 497 mother-neonate pairs: current maternal treatment for thyroid disease (n = 14), lack of data on maternal OH-PCB levels (n = 238), lack of data on both maternal and neonatal serum TH levels (n = 23). Finally, data on 222 mother-neonate pairs were included in this analysis. The protocol for this study was approved by the ethics review board for epidemiological studies at the Hokkaido University Graduate School of Medicine and the Hokkaido University Center for Environmental and Health Sciences (14-10-1), and the study conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

2.2. Data collection

At enrollment, participants completed a self-administered questionnaire to obtain relevant sociodemographic, medical, and behavioral information, as described previously (Kishi et al., 2011, 2013, 2017). In brief, the questionnaire extracted information related to medical history of thyroid diseases, dietary habits fish consumption, intake of seaweed and intake of iodine including supplements/eggs, smoking status, alcohol intake, household income, and educational levels, during pregnancy. We also obtained information from medical records on maternal age, maternal height, maternal pre-pregnancy weight, parity, pregnancy complications, gestational age, sex of the child, birth weight, and birth length.

2.3. Measurement of OH-PCB levels in maternal serum

Forty milliliters of maternal peripheral venous blood under non-fasting condition were collected during the third trimester at the time of the hospital examination following recruitment (Mean of gestational weeks: 35.95 ± 3.99) or within 5 days of delivery, and were stored at − 80 °C until analysis. We used the simultaneous measurement method for the concentration of OH-PCBs and their parent PCBs, polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) in the same maternal blood in Fukuoka Institute of Health and Environmental Sciences. The procedure of the measurement has been described in previous reports (Tobiishi et al., 2013). In brief, each 5 g of maternal blood sample was loaded into an extraction cell filled with Isolute. After freeze-drying, OH- [$^{13}C_{12}$]-PCBs was added as internal standards. Acetone: n-hexane was used as the extraction solvent for an accelerated solvent extractor. After the extract was evaporated to near dryness, it was dissolved in n-hexane and treated with sulfuric acid overnight. The separated hexane layer was applied to a silver nitrate/silica gel column. Following the first fraction containing PCDDs, PCDFs and Co-PCBs, OH-PCBs were eluted with 15 mL of 50% dichloromethane/n-hexane as the second fraction. The eluate was concentrated to near dryness with a multiple sample concentrator, and dissolved in 2 mL of methanol. After the methanol solution was loaded onto an Envi-18 cartridge with 4 mL of methanol, the eluate was concentrated under nitrogen flow and transferred to an LC injection vial with 0.2 mL of methanol.

OH-PCBs concentrations in maternal serum were measured via liquid chromatography-tandem mass spectrometry (LC/MS/MS) at the Fukuoka Institute of Health and Environmental Sciences. The following isomers of OH-PCBs were measured in this study: 4-OH-CB107, 4-OH-CB146 + 3-OH-CB153, 4-OH-CB172, and 4-OH-CB187. We calculated the concentration of ΣOH-PCB as the sum of five congeners. Peaks of 4-OH-CB107, 4-OH-CB172, and 4-OH-CB187 were detected clearly, but 4-OH-CB146 and 3-OH-CB153 could not be separated in this analytical