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Effect modification of CPY2E1 and GSTZ1 genetic polymorphisms on associations between prenatal disinfection by-products exposure and birth outcomes☆

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ABSTRACT

Background: Prenatal disinfection by-products (DBPs) exposure is linked with adverse birth outcomes. Genetic susceptibility to DBP metabolism may modify the exposure-outcome associations.
Object: To investigate whether CYP2E1 and GSTZ1 genetic polymorphisms modified the associations of prenatal DBP exposures with adverse birth outcomes.
Methods: Two biomarkers of DBP exposures including trihalomethanes (THMs) in blood and trichloroacetic acid (TCAA) in urine were determined among 426 pregnant women from a Chinese cohort study. CYP2E1 (rs2031920, rs3813867, and rs915906) and GSTZ1 (rs7975) polymorphisms in cord blood were genotyped. Statistical interactions between prenatal DBP exposures and newborns CYP2E1 and GSTZ1 polymorphisms on birth outcomes (birth weight, birth length, and gestational age) were examined by multivariable linear regression with adjustment for potential confounders.
Results: We found that newborns CYP2E1 genetic polymorphisms (rs2031920 and rs3813867) modified the associations of maternal blood THMs or urinary TCAA levels with birth outcomes. However, these interactions were nonsignificant after Bonferroni correction for multiple comparisons, except for the interaction between maternal blood BrTHMs [sum of dibromochloromethane (DBCM), bromodichloromethane (BDCM), and bromoform (TBM)] and newborns CYP2E1 gene rs2031920 polymorphisms on birth weight (P for interaction = 0.003).
Conclusion: Newborns genetic variations of CYP2E1 rs2031920 may modify the impacts of prenatal BrTHM exposure on birth weight. This finding needs to be further confirmed.

1. Introduction

Chlorination disinfection is widely adopted for treatment of drinking water in public water supplies worldwide. Disinfection by-products (DBPs) can be formed as a side reaction of chlorine with organic precursors in water (Richardson, 2003). Numerous kinds of DBPs with various physicochemical properties constitute complex mixtures in drinking water. Trihalomethanes (THMs) and haloacetic acids (HAAs) are the most detectable DBPs in chlorinated drinking water (Lee et al., 2001; Sérodes et al., 2003). Exposure to DBPs is widespread for human beings through multiple pathways such as dermal absorption, ingestion, and inhalation (Nieuwenhuijsen et al., 2009a,b; Weisel and Jo, 1996). Concern on potential health hazards including adverse birth outcomes after

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exposure to DBPs has been raised.

Mounting evidence from toxicological studies have indicated that DBPs can cause developmental toxicities, including retarded fetal development, reduced fetal birth length and weight, delayed sexual maturation, as well as birth defects (Christian et al., 2002; Colman et al., 2011; Hunter et al., 1996; Murray et al., 1979; Ruddick et al., 1983; Schwetz et al., 1974). Also, some human studies have reported that specific THMs or HAA exposure during pregnancy is related to reduced birth weight and increased risks of intrauterine growth retardation and small for gestational age (SGA) (Cao et al., 2016; Grazuleviciene et al., 2011; Hinckley et al., 2005; Wright et al., 2003; Zhou et al., 2012). However, a meta-analysis showed no clear evidence of associations for exposure to THMs during pregnancy in relation to low birth weight (LBW) and preterm delivery (Grellier et al., 2010). Also, Kogevinas et al. (2016) reported null associations of prenatal exposure to THMs with LBW, SGA, and preterm delivery in a large European study. Genetic variations such as metabolic enzyme gene polymorphisms influencing DBP exposures across different populations may at least partly contribute to the heterogeneous results (Infante-Rivard, 2004).

Several key enzymes influencing the detoxification of DBPs include Cytochrome P450 (CYP) and Glutathione S-transferase (GST). Previous studies have demonstrated that CYP2E1 mediates the biological activation of bromodichloromethane (BDCM) and chloroform (TCM) (Gemmaet al., 2003; Zhao and Allis, 2002) and GST zeta-1 (GSTZ1) catalyzes the glutathione-dependent biotransformation of HAAs (Melnick et al., 2007; Saghir and Schultz, 2005). Human studies have also observed that inherited differences in CYP2E1 and GSTZ1 gene polymorphisms significantly affect the concentrations of blood and exhaled THMs and urinary trichloroacetic acid (TCAA) (Font-Ribera et al., 2016; Yang et al., 2016). However, limited studies focus on the role of genetic variations in these metabolic enzyme gene polymorphisms modulating the impacts of prenatal DBP exposures on adverse birth outcomes (Danileviciute et al., 2012; Infante-Rivard, 2004; Kogevinas et al., 2016; Levallois et al., 2016). Nevertheless, previous studies used the monitored drinking water DBP concentrations or combining individual's water-use activities as the external dose markers that may produce exposure misclassification and bias the observed results (Nieuwenhuijsen et al., 2009a,b; Savitz, 2012).

Here we utilized an established cohort study examining the impacts of maternal DBP exposures during later pregnancy on birth outcomes, where maternal elevated blood THM concentrations during late pregnancy were found to be associated with decreased birth weight and birth length (Cao et al., 2016). This study aimed to investigate whether newborns CYP2E1 (rs2031920, rs3813867, and rs915906) and GSTZ1 (rs7975) polymorphisms modified the associations of prenatal exposure to DBPs with birth outcomes (birth weight, birth length, and gestational age). Two biomarkers including THMs in blood and TCAA in urine were determined to enhance the exposure assessment of DBPs (Miles et al., 2002; Zhang et al., 2009a,b).

2. Materials and methods

2.1. Study population

Participants were selected from an established cohort study examining the impacts of maternal DBP exposures on birth outcomes in China (Cao et al., 2016). Briefly, pregnant women ($n = 1747$) during late pregnancy ($\geq$35 weeks) who waited for childbirth in a hospital per city (Wuhan and Xiaogan) were enrolled between 2011 and 2013. The pregnant women were eligible for inclusion if the participants: a) gave birth for a singleton live infants without birth defects, b) were >18 years of age, c) resided at the studied cities for more than 1 year. According to the inclusion criteria, 1184 pregnant women were retained in the cohort study. Of them, 893 participants provided both of urine and blood samples for the exposure analysis. Finally, a total of 426 pregnant women who had cord blood samples for the genotype analysis were retained in this study. The differences between the pregnant women included and excluded from this analyses in characteristics except for maternal age, study city, and time of showering/bathing were not statistically significant (Table S1). The research protocol was licensed by the Ethics Committee in Tongji Medical College, Huazhong University of Science and Technology. Each pregnant woman took part in this study with an informed consent.

2.2. Information collection

All the participants completed a study questionnaires conducted by the trained investigators to provide the detailed information on demographic characteristics (e.g., maternal age, parity, income, occupational exposure, education and smoking status, alcohol consumption, and water-use activities). No pregnant women reported that they were alcohol consumers and active smokers during pregnancy in our study population. The participants were considered as passive smokers if they had cigarette smoking exposure over 15 min per day at work and/or at home. Infant birth outcomes, including birth length (cm) and birth weight (g), were estimated by a nurse-midwife in the delivery room using an electronic scale. Gestational age (week) was calculated according to the last menstrual period through medical records and the date of childbirth.

2.3. Genotyping

Cord blood sample was immediately collected after delivery and stored in −80 °C until genotyping. The method for DNA extraction from cord blood has been presented previously (Yang et al., 2016). Genotyping for CYP2E1 (rs2031920, rs3813867, and rs915906) and GSTZ1 (rs7975) genes were measured using the TaqMan single nucleotide polymorphisms (SNP) Genotyping Assay. The ABI Prism 7900HT platform (Applied Biosystems, Foster City, CA, USA) were used to analyze the fluorescence data files. More than two no-template controls without DNA were included in all the genotyping assays. Also, we randomly selected approximately 5% of the samples to monitor the reproducibility of the assays, and the concordance was more than 99%. All candidate SNPs were in accord with Hardy-Weinberg equilibrium.

2.4. Exposure assessment

We collected blood and urine samples from each pregnant women when they presented to the prenatal care visit during late pregnancy [mean (±SD): 39.1 ± 1.1 weeks]. The sample collection, analysis method, and quality control for measurement of THM levels in blood have been detailed in our prior studies (Cao et al., 2016; Zeng et al., 2013). In short, 3 mL of peripheral blood was sealed with a 10 mL of headspace vial. Four individual THM compounds including BDCM, dibromochloromethane (DBCM), bromoform (TBM), and TCM were extracted using a solid phase micro-extraction (SPME). Then, the SPME fiber was shifted into the inlet of gas chromatography (GC) to desorb the targets. The targets were detected by an electron capture detector (ECD). The proportion of recoveries for the four individual THMs ranged from 82.04% to 93.58% and the relative standard deviation (RSD) was less than 10.00%. The limit of detections (LOD) for blood BDCM, DBCM, TBM, and TCM were 0.45, 0.68, 2.00, and 1.95 ng/L, respectively.