Environmental Pollution 243 (2018) 553–562

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Perinatal exposure to low-dose decabromodiphenyl ethane increased the risk of obesity in male mice offspring☆

Sen Yan [a, 1], Dezhen Wang [a, 1], Miaomiao Teng [b], Zhiyuan Meng [a], Jin Yan [a], Ruisheng Li [a], Ming Jia [a], Chenyang Yao [c], Jing Sheng [c], Sinuo Tian [a], Renke Zhang [a], Zhiqiang Zhou [a], Wentao Zhu [a, *]

[a] Beijing Advanced Innovation Center for Food Nutrition and Human Health, Department of Applied Chemistry, China Agricultural University, Beijing, 100193, China
[b] Department of Applied Chemistry, China Agricultural University, Beijing, 100193, China
[c] College of Science, China Agricultural University, Beijing, 100193, China

ARTICLE INFO

Article history:
Received 31 May 2018
Received in revised form
7 August 2018
Accepted 23 August 2018
Available online 30 August 2018

Keywords:
Decabromodiphenyl ethane
Obesity
Metabolomics

ABSTRACT

Decabromodiphenyl Ethane (DBDPE), a kind of new brominated flame retardants (NBFRs) used to replace DecaBDE, has been frequently detected in the environment and human samples. In this study, we explored its toxic effects on male mouse offspring after perinatal exposure to DBDPE. During the perinatal period, pregnant ICR mice were exposed to DBDPE (100 μg/kg body weight) via oral gavage. After weaning, male offspring were fed on a low-fat diet and a high-fat diet, respectively. We measured and recorded body weight, liver weight, and epididymis fat mass, blood biochemical markers, metabolites changes in liver, and gene expression involved in lipid and glucose homeostasis. The results showed that perinatal exposure to DBDPE increased the risk of obesity in mouse offspring and affected triglyceride synthesis, bile secretion, purine synthesis, mitochondrial function and glucose metabolism, furthermore, the use of HFD feeding may further exacerbate these effects. All of these results show that early-life exposure to low doses of DBDPE can promote the development of metabolic dysfunction, which in turn induces obesity.

1. Introduction

There is growing concern that endocrine disrupting chemicals (EDCs), which are defined as substances that affect the biosynthesis, metabolism, or action of hormones, may pose a health threat (Diamantikandarakis et al., 2009). Among all ECDs, brominated flame retardants (BFRs) have drawn attention due to their potential toxicity, endocrine disrupting properties and widespread use (Ezechiáš et al., 2014). As the Stockholm Convention listed some traditional BFRs such as pentabromodiphenyl ether (Penta-BDE) and octabromodiphenyl ether (octa-BDE) as persistent organic pollutants (POPs) in 2009 and restricted their usage, some new brominated flame retardants (NBFRs) began to be produced and used. At present, the most used NBFRs in China are decabromodiphenyl ethane (DBDPE) (Covaci et al., 2011; Shi et al., 2016).

DBDPE, developed by the American company Albemarle in the early 90s of the last century, was used to replace DecaBDE (BDE209), the most widely used brominated flame retardant at that time (Kierkegaard et al., 2004). In China, it has been used to replace traditional BFRs since 2005, and the production of DBDPE is growing at a rate of 80% per year. The annual production of DBDPE in 2012 has reached 25,000 tons, accounting for one-fourth of the total production of BFRs in China and may have exceeded that of polybrominated diphenyl ethers (PBDEs) (Shi et al., 2016; Zhang and Gu, 2013; Zhang and Qi-Yong, 2011). Recent reports show that DBDPE has been detected in almost all environmental samples, including air (Olukunle et al., 2018; Tao et al., 2016), dust (Larsson et al., 2018; Wang et al., 2017), sludge (Lee et al., 2013), sediments (Klosterhaus et al., 2012), soils (Yadav et al., 2017) and animals (Cristale et al., 2013; Isobe et al., 2012). More importantly, DBDPE was detected in human foods such as aquatic food (12.4 ± 15.8 ng/g lw) and egg/egg products (8.15 ± 5.54 ng/g lw) and even in human milk (8.06 ± 5.46 ng/g lw) (Shi et al., 2016). In fact, there is evidence that for toddlers, the body burden of DBDPE is far higher than adults (Wang et al., 2017), which means that it is necessary to do

☆ This paper has been recommended for acceptance by Dr. Chen Da.
* Corresponding author. Yuanmingyuan west road 2, Beijing, 100193, China.
E-mail address: wentaozhu@cau.edu.cn (W. Zhu).
[1] Sen Yan and Dezhen Wang contributed equally to this paper.

https://doi.org/10.1016/j.envpol.2018.08.082
0269-7491/

some early exposure studies.

However, little is known about the toxicity of DBDPE. Limited evidence suggests that DBDPE may pose potential hazards especially endocrine disruptive effects. For example, previous research showed that male mice exposed to DBDPE after birth reduced epididymal sperm functions (Tseng et al., 2006). In the study of chicken embryos, the mRNA expression of type I iodothyronine 5′-deiodinase (DIO1) was increased after exposure to 0.1 μM DBDPE (Egloff et al., 2011). And DBDPE can interfere with the level of thyroid hormone mediated by agonizing aryl hydrocarbon receptor (AhR) and constitutive androstane receptor (CAR) signaling pathways and affect the balance of glucose metabolism in mice (Sun et al., 2018). Furthermore, there is evidence that some subclasses of EDCs such as perfluoroalkyl substances (PFAS) can disrupt hormone-regulated metabolic processes, especially if exposure occurs during early-life, a stage that is more sensitive to environmental pollutants, which leads to increased risk of obesity in offspring (Braun, 2016; Burton and Metcalfe, 2014; Heindel et al., 2017). Considering the endocrine disrupting properties of DBDPE, we speculated that DBDPE may be a potential obesogen. In addition, previous studies have shown that obesity is positively correlated with hepatic diseases (Jensen et al., 2018). Therefore, we believe that the health risks of DBDPE exposure in perinatal period should be carefully assessed.

In order to evaluate the health risk of DBDPE more comprehensively, we chose the research method of metabolomics. Metabolomics has been widely used in environmental toxicology for its comprehensive and rapid nature and ability to predict unknown mechanisms (Lankadurai et al., 2013). In combination with appropriate molecular biology methods, endogenous metabolites and differentially expressed genes that have changed in vivo after environmental changes can be identified, and biological pathways that may be affected by environmental pollutants can be found to explain complex toxicological mechanisms (Zhang et al., 2013).

In our study, we used ^{1}H-NMR-based metabolomics to assess metabolic changes in the mouse offspring after fetal exposure to DBDPE. Moreover, we used Q-PCR to determine the expressions of genes involved in lipid and glucose homeostasis. Furthermore, we also considered the combined effects of high-fat diets (HFD). Through these efforts, we hope to reveal the complex toxicity mechanism of DBDPE in offspring mice and provide reliable data support and scientific basis for subsequent safety evaluation and risk assessment.

2. Materials and methods

2.1. Chemicals

DBDPE (CAS: 84852-53-9; 96% purity) were purchased from J&K Scientific, Ltd. (Beijing, China), D_2O (99.9% in D) and Sodium 3-trimethylsilyl-2,-2,-3,-3-d4-propionate (TSP-d4) were obtained from Aladdin (Shanghai, China). All other reagents used were of analytical grade.

2.2. Animals and treatment

Primigravida pregnant ICR mice were purchased from Peking University Health Science Center and were separated into two groups (control and DBDPE treatments, seven to eight pregnant mice per group). All pregnant mice were housed individually in an environment maintaining the temperature of 25 ± 3 °C and the humidity of 50 ± 5% with 12hr/12hr light/dark cycle, and free access to water and food during feeding. After five days of acclimatization, the mice in the control group (corn oil, 5 mg/kg bw) and the DBDPE treatment group (corn oil solution of DBDPE, final concentration of DBDPE is 100 μg/kg bw) were gavaged every day from gestational day 6 (GD6) to postnatal day 21 (PND21). On the PND2, the litters were selected randomly to 8 pups. After weaning at PND21, male offspring of both groups were selected because some previous studies have demonstrated that male mice are more sensitive to the effects of ECDs (Giulivo et al., 2016). Males in each group were fed with low-fat diet (LFD: 10% calories from fat, Trophic Animal Feed High-tech Co., Ltd, China) or high-fat diet (HFD: 60% calories from fat, Trophic Animal Feed High-tech Co., Ltd, China) for 12 weeks. Therefore, four groups were obtained: vehicle + LFD (V+L), DBDPE + LFD (D+L), vehicle + HFD (V+H), and DBDPE + HFD (D+H). Body weights were measured weekly, epididymis fat, blood and liver samples were collected after overnight fasting on 15 weeks after birth and stored at −80 °C. The experimental design is shown in Fig. 1. All experimental procedures were approved by the independent Animal Ethical Committee of China Agricultural University.

2.3. Glucose and insulin tolerance test

Mice were fasted overnight prior to studies. For glucose tolerance tests, mice were intraperitoneally injected with D-glucose (2 g/kg bw). For insulin tolerance test, mice were intraperitoneally injected with insulin (0.75 IU/kg bw). Blood glucose levels were measured by glucose meter (Yicheng JSP-7, Beijing, China) at before and 20, 40, 60, 90, and 120 min after injection. Area under curve (AUC) were used to assess glucose tolerance and insulin resistance.

2.4. Clinical chemistry parameters assay

The activities of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using their standard kits (Nanjing Jiancheng Bioengineering Institute, China).

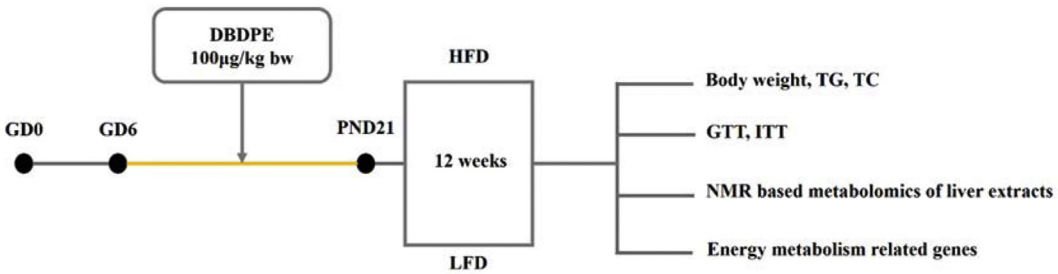

Fig. 1. Experimental design. From GD6 to PND21, pregnant mice were orally gavaged with corn oil (control group, vehicle) or DBDPE (100 μg/kg bw) corn oil solution. After weaning at day 21, male offspring were divided into two groups by providing them with LFD or HFD for 12 weeks.