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In vitro cytotoxicity of decabrominated diphenyl ether (PBDE-209) to human red blood cells (hRBCs)

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HIGHLIGHTS

- Effect of PBDE-209 on the anti-oxidative defense system, structure and function (ATP enzyme activity) of hRBCs is assessed.
- Affected activity (content) of SOD, CAT, GSH-Px, GSH, MDA in hRBCs cause decline in function of antioxidant defense system.
- The PBDE-209 can result in the cytoplasmic projections and structure deformation of the hRBCs.
- The relative ATPase activity can be decreased by the PBDE-209.

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ABSTRACT

This work presents the effect of decabrominated diphenyl ether (PBDE-209) on the anti-oxidative defense capacity, and ATPase activity (structure and function) of human red blood cells (hRBCs). The results show that the PBDE-209 influences the activity and content of typical biomolecules (SOD, CAT, GSH-Px, GSH and MDA) in hRBCs, causing a decline in the function of the antioxidant defense system. The PBDE-209 with a concentration of 10 μmol/L resulted in the cytoplasmic projections and structure deformation of the hRBCs. When its concentration exceeds 25 μmol/L, the relative ATPase activity was decreased to 20% of the initial activity. Since the discovered effects of PBDE-209 on hRBCs are in cell level, this study may offer some information to advise the related *in vivo* cytotoxicity works.

1. Introduction

Polybrominated Diphenyl Ethers (PBDEs) are organobromides widely used as flame retardants in industry (Darnerud et al., 2001). The PBDEs can easily enter the environment through volatilization, exudation, etc., resulting in severe pollution (Siddiqi et al., 2003). Since the PBDEs are difficult to degrade naturally and have high lipid-solubility, they can be biologically accumulated and magnified in food chain. In recent years, PBDEs with noticeable concentrations have been observed in environmental media (up to mg/kg dry weight and μg/L levels) (Chen et al., 2012; Newton et al., 2015), animals (up to mg/kg lipid weight and μg/L levels) (Shang et al., 2016; Van den Steen et al., 2007), and human body (such as blood, fat tissue and breast milk, at μg/kg lipid weight level, higher for occupational exposure, tens or even hundreds of the general population) (Herbstman et al., 2010; Leonetti et al., 2016; Nguyen et al., 2016; Shen et al., 2010). The main detected PBDEs homologues are PBDE-47, PBDE-99, PBDE-100, PBDE-153, PBDE-154, PBDE-183 and PBDE-209, where their ecological toxicity and potential hazard to human health have attracted widespread attention.

Previous studies have reported that the PBDEs are toxic to the liver activity (Zhou et al., 2002), thyroid and reproduction systems

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(Yu et al., 2015), nervous system (Costa et al., 2014) and immune system (Lv et al., 2015). Though some highly-toxic PBDEs have been banned in many countries, other PBDEs with relatively lower toxicity, such as BDE-209, are still largely produced and used in the world (Chen et al., 2012; Akortia et al., 2016). Although the concentration of PBDEs in the human blood is generally low in most places, it has been reported that the concentrations of PBDEs in the human blood of workers can reach significantly high levels in many heavily polluted areas (Jin et al., 2009; Makey et al., 2016).

Red blood cells (RBCs) are the largest number of cells in blood which play important roles of O_2/CO_2 transport, blood-pH control and body immunity (D'Alessandro et al., 2010). It is important to study the influences of PBDEs on RBCs for a comprehensive understanding of the toxicology of PBDEs, on which few studies have been reported. An early study reported by Tjarnlund et al. has showed that the PBDEs can affect the hematocrit in the blood of rainbow trout but has no significant influence on its hemoglobin content (Tjarnlund et al., 1998). In 2010, Van den Steen et al. have reported that the PBDEs have no significantly influence on the hematological indicators (hemoglobin content and hematocrit) of female starlings (*Sturnus vulgaris*) (Van den Steen et al., 2010). Since their results showed that the PBDEs do not affect the RBCs activity much based on the animal studies, the toxicity of PBDEs to the RBCs of human may be underestimated. To the best of our knowledge, the toxicity of PBDEs to the RBCs of human has not been studied in cell levels yet.

In this paper, the effects of PBDEs on the structure and function of human RBCs are studied in cell levels. The toxicity of PBDEs is assessed regarding the activity of human RBCs during blood transportation. This work may provide some theoretical guidance for risk assessment or early diagnosis of PBDEs in the environment.

2. Materials and methods

2.1. Reagents and apparatus

EDTA-K_2 (Tianjin Kermel Chemical Reagent Co., Ltd.) stabilized blood samples were obtained from Weihai Blood Center (Weihai, China). A solution of PBDE-209 was prepared by dissolving 2,2′,3,3′,4,4′,5,5′,6,6′-decaBDE (Shanghai Yubo Biotech Co., Ltd.) in normal saline to achieve different concentrations. Glutaraldehyde, isoamyl acetate, ethanol, osmium tetroxide, and PBS buffer (pH 7.4) were purchased from Sigma.

All UV–visible absorption spectra and absorption value were measured on a UV-2450 spectrophotometer (SHIMADZU, Kyoto, Japan). Automatic balance centrifuge (LDZ4-2, Jiangsu Jintan Medical Instrument Factory) was used for centrifugation. Vortex mixer (vortex-6) was purchased from Kylin-Bell Lab Instruments Co., Ltd. Digital dry bath incubator (HB-100, Hangzhou Bioer Technology Co., Ltd) was used to control temperature of the samples.

Ethics statement: The study was approved by the Ethics Committee of Weihai Blood Center (Weihai, China).

2.2. In vitro cytotoxicity of PBDE-209 to hRBCs

2.2.1. In vitro measurements of typical biomolecules in hRBCs

The antioxidant defense capacity of hRBCs was showed by measuring the activity and content of hRBC-related biomolecules, according to the protocol reported by Chi et al. (2014). The hRBC-related biomolecules were SOD (superoxide dismutase), CAT (catalase), GSH-Px (glutathione peroxidase), GSH (glutathione) and MDA (malondialdehyde), where their relative activity or content was measured using the detection kits (Nanjing Jiancheng Bioengineering Institute). In a typical measurement, the fresh blood sample (1 mL) was washed by PBS solution (2 mL) for three times with centrifugation for 10 min at 1500 rpm. The purified hRBCs sample was diluted to 5 mL with PBS solution. 1 mL of the diluted hRBCs sample was mixed with 1 mL PBDE-209 solution of different concentration (0, 10, 20, 30, 40, 50 and 60 μmol/L) by votexing, and then incubated at 37 °C for 2 h. After centrifugation for 10 min at 1500 rpm, the supernatant of the hRBCs sample was discarded and the sample was refilled with pure water to achieve hemolysis for the activity measurement. 0.1 mL of the hemolytic blood sample was used to measure the activities of SOD, CAT and GSH-Px, and the relative contents of GSH and MDA, respectively, regarding the procedures of the detection kits. The relative SOD activity was calculated using the following formula: relative SOD activity $= (A_{control} - A_1)/(A_{control} - A_0) \times 100\%$, where $A_{control}$ is the absorbance of the control tube, A_1 and A_0 are the absorbances of the testing tube of hRBCs with and without PBDE-209, respectively. In this study, for each biomolecule, three independent experiments have been done, and data have been presented as means ± SD (standard deviation).

2.2.2. Scanning electron microscopy (SEM) preparation

The fresh blood sample (1 mL) was washed by PBS solution (2 mL) for three times with centrifugation for 10 min at 1500 rpm, and then diluted by 20 times with PBS solution. 0.5 mL of the diluted hRBCs sample was incubated with 1.5 mL PBDE-209 solution of different concentration (0, 10 and 40 μmol/L) at 37 °C for 2 h. After a centrifugation for 10 min at 1500 rpm, the supernatant of hRBCs sample was discarded. The hRBCs sample was then added with 2% glutaraldehyde and incubated at 37 °C for 6 h to recover. The hRBCs sample was washed with PBS buffer and then fixed in osmium tetroxide solution (1%) for 60 min. After washing with pure water, dehydration of the hRBCs sample was performed with increasing concentrations of ethanol (40%, 60%, 85%, 95% and 100%). The hRBCs sample was then replaced in pure isoamyl acetate solvent for 10 min and dried by critical point drying. The hRBCs sample was platinum-coated using the sputtering coater (Eiko IB5) and measured with the scanning electron microscope (SEM, Hitachi S570).

2.2.3. ATPase activity measurement

The fresh blood sample (1 mL) was washed by PBS solution (2 mL) for three times with centrifugation for 10 min at 1500 rpm. The purified hRBCs sample was diluted to 5 mL with PBS solution. 1 mL of the diluted hRBCs sample was mixed with 1 mL PBDE-209 solution of different concentration (0, 5, 10, 15, 20, 25 and 30 μmol/L, considering the actual concentration in blood, especially for occupational exposure) by votexing, and then incubated at 37 °C for 2 h. After centrifugation for 10 min at 1500 rpm, the supernatant of the hRBCs sample was discarded and the sample was refilled with pure water to achieve hemolysis for the activity measurement. 0.1 mL of the hemolytic blood sample was used to measure the ATPase activity, regarding the procedure of the detection kit. Three independent experiments have been done, and data have been presented as means ± SD (standard deviation).

3. Results and discussion

3.1. Effects of PBDE-209 on antioxidant defense capacity of hRBCs

The enzymatic antioxidant system of human body can prevent the uncontrolled formation of reactive oxygen species and inhibit reactions of reactive oxygen species with biological structures. Three main functional enzymes are SOD, CAT and GSH-Px in the enzymatic antioxidant system (Roversi et al., 2006), where their balance is important to maintain a good antioxidant function

(Hachul de Campos et al., 2006). In this study, the relative SOD activity (Fig. 1a) and CAT activity (Fig. 1b) increased from 100% (initial) to 105% and 115%, respectively, when the concentration of PBDE-209 in the hRBCs samples increased from 0 to 30 μmol/L. On the contrary, the relative GSH-Px activity (Fig. 1c) decreased from 100% (initial) to 86%, when the concentration of PBDE-209 in the hRBCs samples increased from 0 to 30 μmol/L. However, although the activities of SOD, CAT and GSH-Px have been largely changed, it is hard to conclude whether the dose of PBDE-209 increased the activity of body's enzymatic antioxidant system for the following reasons. The increase in SOD activity enhances the removal of superoxide anion radical (Herken et al., 2001). The increase in CAT activity enhances the degradation of hydrogen peroxide to water and oxygen (Mecocci et al., 2000). The decrease in GSH-Px activity can reduce the reaction of hydrogen peroxide with GSH (Yuan et al., 2015).

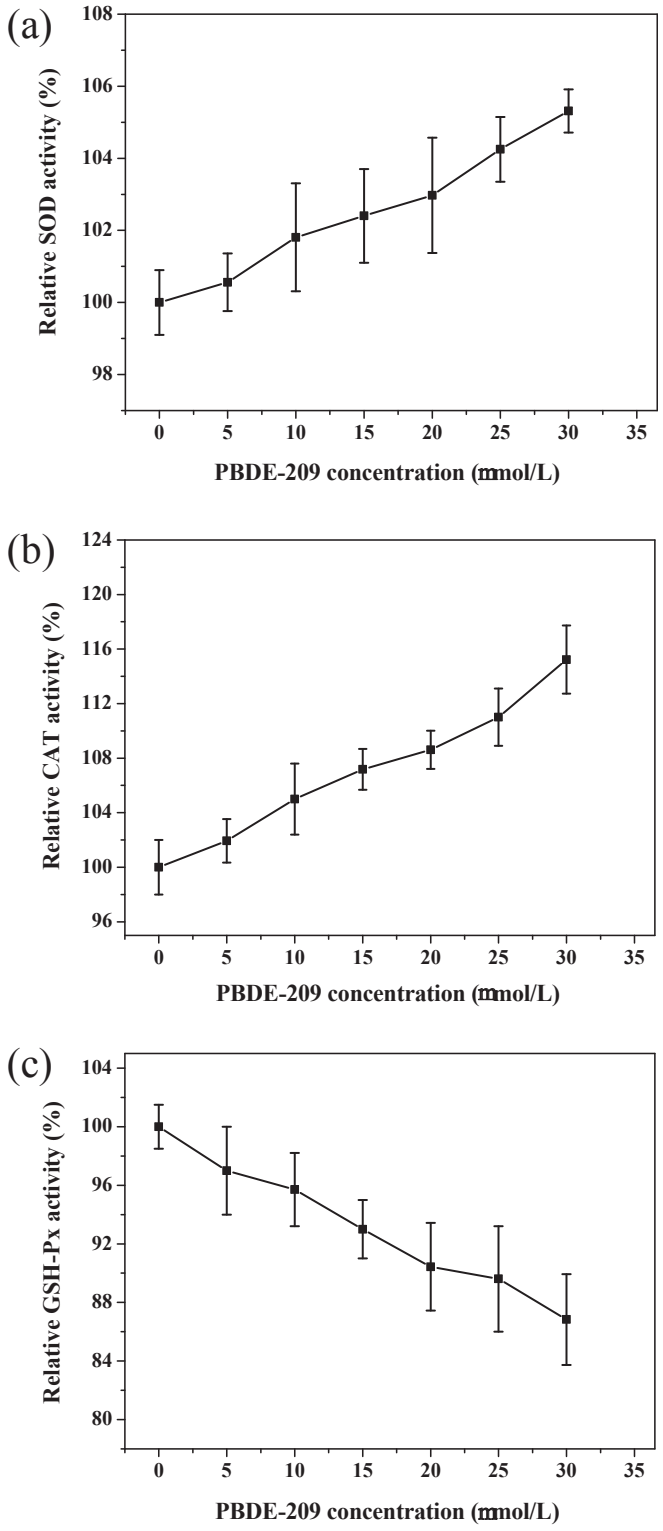

Fig. 1. Effect of PBDE-209 on the activity of SOD (a), CAT (b) and GSH-Px (c) in hRBCs. Data represent the mean ± SD of three independent experiments.

Apart from the enzymatic antioxidant system, the non-enzymatic antioxidant system also plays an important role in the defense aspect of oxidative damage (Anandan et al., 2013). GSH, as a typical non-enzymatic antioxidant, is capable of maintaining the redox equilibrium in hRBCs (van't Erve et al., 2014). Fig. 2a shows that the relative GSH content decreases with the PBDE-209 concentration increases. When the concentration of PBDE-209 is 30 μmol/L, the relative GSH content is reduced to 83% of its initial concentration, showing a decrease of the activity of GSH-related non-enzymatic antioxidant system.

The MDA content indicates the level of oxidative stress in hRBCs, since the MDA is a degradation product of lipid peroxidation induced by oxidative injury (Das et al., 2000; Sies, 2015). As shown in Fig. 2b, the relative MDA content increases to 280% of its initial concentration, when the concentration of PBDE-209 in the hRBCs sample increases from 0 to 30 μmol/L. Since a high MDA content means a high level of oxidative stress, the PBDE-209 has been experimentally proven to be toxic to the antioxidant defense system of hRBCs.

PBDEs can disrupt the normal biological functions of liver, neural and endocrine systems in animal and *in vitro* studies, with oxidative stress as one of the pathways, reported in previous works (Gao et al., 2009; Raldúa et al., 2008). Here we found that PBDE-209 can also cause oxidative stress in hRBCs, may affecting the cell structure and function.

3.2. Effects of PBDE-209 on the morphology of hRBCs

The effect of PBDE-209 on the morphology of hRBCs was studied by SEM. Fig. 3 shows the morphology of hRBCs samples reacted with different PBDE-209 concentration. The RBCs have a diameter of about 6 μm. The morphology of hRBCs without addition of PBDE-209 shows a smooth surface (Fig. 3a), consisting of a lipid bilayer membrane (Manrique-Moreno et al., 2010). Fig. 3b shows the cytoplasmic projections and a slightly deformed structure of the hRBCs, with the PBDE-209 concentration at 10 μmol/L. When the concentration of PBDE-209 was 40 μmol/L, the hRBCs received more damage that the cellular structure significantly changed (Fig. 3c). Due to the bilayer-couple hypothesis (Sheetz et al., 1976), the possible mechanism may be related to the intercalation of PBDE-209 in the monolayers of cell membrane, resulting in severe damages to the membrane receptors, molecule channels and cell pressure. Since the membrane structure plays a key role in cellular bioactivity, the structure deformation has high potential to cause the cell death of hRBCs (Zhao et al., 2011).

3.3. ATPase activity study

The ATPase is an important enzyme controlling the decomposition of ATP into ADP. As showed in Fig. 4, the relative ATPase activity significantly decreased to 20% of its initial activity, when the concentration of PBDE-209 in the hRBCs sample increased from 0 to 25 μmol/L. The relative ATPase activity remained at a low level (20% of the initial activity), when the PBDE-209 concentration further increased to 30 μmol/L. Since the ATPase controls the in-

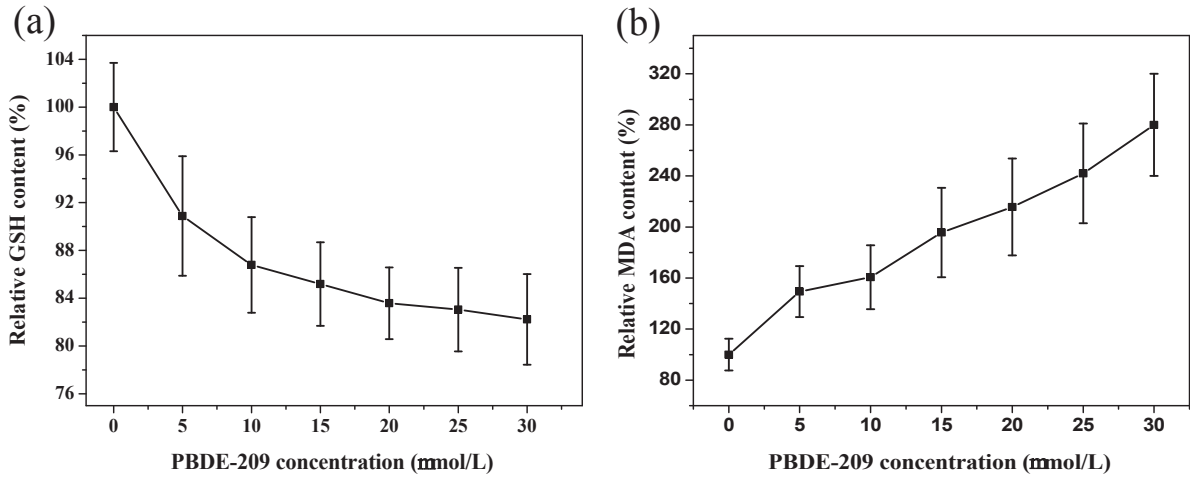

Fig. 2. Effect of PBDE-209 on the GSH content (a) and MDA content (b) in hRBCs. Data represent the mean ± SD of three independent experiments.

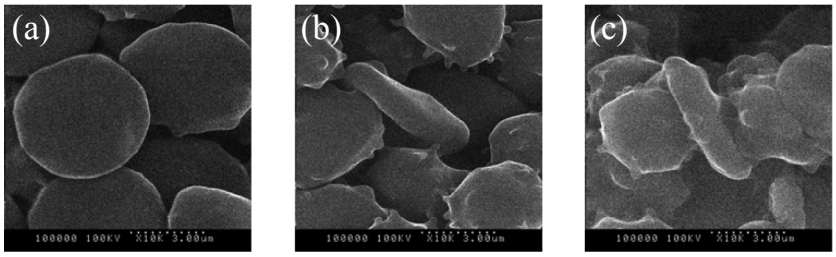

Fig. 3. SEM images of the hRBCs reacted with PBDE-209 of 0 (a), 10 (b) and 40 (c) μmol/L.

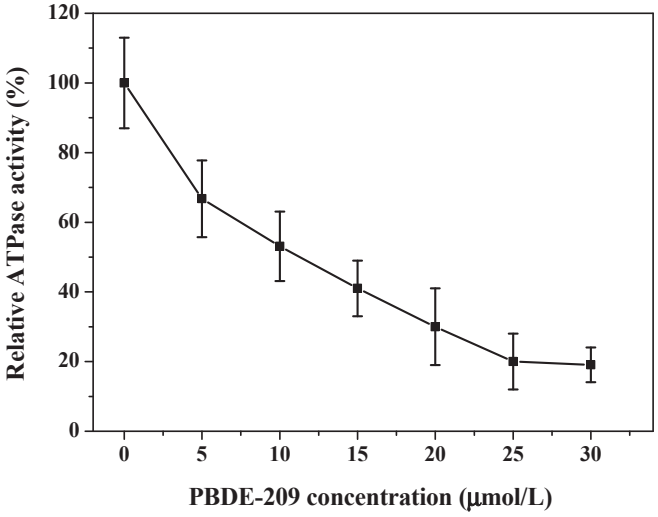

Fig. 4. Effect of PBDE-209 on the ATPase activity of hRBCs. Data represent the mean ± SD of three independent experiments.

cellular metabolism (Shan, 2016), such a low ATPase concentration of 20% is not sufficient to maintain the cellular bioactivity, again indicating a high cytotoxicity of PBDE-209 to hRBCs.

4. Conclusions

This work studied the effect of PBDE-209 on the anti-oxidative defense system biomolecules (SOD, CAT, GSH-Px, GSH and MDA) and the ATPase activity (structure and function) of human red blood cells (hRBCs). When the PBDE-209 concentration increased, the SOD activity and the CAT activity increased while the GSH-Px activity and the GSH content decreased, showing a destroyed balance of the enzymatic and non-enzymatic antioxidant defense system. The dose of 30 μmol/L PBDE-209 caused a decline in the function of the antioxidant defense system of hRBCs, where the MDA content largely increased to 280% of its initial concentration. The PBDE-209 with a concentration of 10 μmol/L resulted in the cytoplasmic projections and structure deformation of the hRBCs. The relative ATPase activity significantly decreased to 20% of its initial activity, when the PBDE-209 concentration reached 25 μmol/L.

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