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Research Progress on Cardiovascular Toxicity of Poly Brominated Diphenyl Ethers

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Abstract

As we were known,Poly Brominated Diphenyl Ethers (PBDEs) is a group of common brominated flame retardant from our surrounding environments. Because it is effective on fire retarding, it has been used widely in the manufacture of electronic products, plastics, rubber products, decorative materials and textiles. It is also one of the persistent organic pollutants (POPs) as well. It was known that PBDEs is hard to be broken down into small molecules for its more higher lipopholicity and bioaccumulation. Therefore, it was reported that PBDEs might have potentially deleterious effects on human organs and systems including cardiovascular system. More and more studies of animal experiments have showed that PBDEs can induce serious damages in the cardiovascular systems of animals.It was reported that severe congested blood capillaries,swelling mitochondrial, disordered myofibrils, karyopyknosis and karyolysis were occurred in the group of rats exposure to PBDEs. Present experimental results have showed that PBDEs could damage the structure and function of cardiovascular system by down-regulating the expression of microRNAs. A brief review was made about primary research on cardiovascular toxicity and their potential mechanism of PBDEs in the past over 20 years.

Key Words: Polybrominated Diphenyl Ethers(PBDEs), Cardiovascular System, Toxicity, Review

PBDEs is a group of aromatic compounds containing bromine atoms. According to the position and number of binding bromine atoms on the benzene ring, 209 kinds of isomers have been found in all till now[1]. Most of PBDEs have not been permitted or restricted to be used in the developed countries for their potential biological toxicity. Only tetrabromobiphenyl ether, pentabromobiphenyl ether, hexabromobiphenyl ether and ocabromobiphenyl ether were banned to used permanently and written into the Stockholm Convention by United Nations Environment Programme in 2009 as a persistent organic pollutants. However, due to short biological half-time and its relatively large molecular mass of Decabromodiphenyl Ether (BDE209), it is less known if biological toxicity of due to the short biological half-life of , which makes it difficult to penetrate cell membranes (Zhu Chun yan,2012).

A great deal of scientific research proved that PBDEs have been discovered widely in Environmental media and some organisms, such as in the atmosphere, soil, water, sediments, fish, birds, and humans, and with increasing levels of PBDEs exponentially[2]. Current experimental studies have shown that for humans, the toxicity of PBDEs is mainly manifested in developmental neurotoxicity and endocrine toxicity;For rats, it is mainly manifested in liver toxicity and tumors[3];For fish, the toxicity of PBDEs is mainly manifested in neurotoxicity [4] and oxygen stress[5]. However,less research was made on the cardiovascular system.Therefore we focus on the effects of PBDEs on the cardiovascular system and their potential mechanism.

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1. Effects of PBDEs on the cardiovascular system

As we have known, PBDEs have the toxic effect on the cardiovascular system,but most of them made from animal experiments, few of them made from the large-scale epidemiological investigation of human beings.

1.1 epidemiological investigation

Only few research of PBDEs was made by the way of epidemiological investigation. Gump BB .et [6]have tested the levels of four PBDE homologue (BDE-28, -47, -99, and -100) in blood from 43 children(females16,males27). They found that there were some links between the levels of PBDE homologue and risk factors of Cardiovascular diseases. The results indicated that there was notable correlation between the blood levels of BDE-28 and BDE-100 and idiopathic hyperdynamic heart syncirome.

Zhu et al.(2012) have proved that there was the correlation between the blood levels of PBDEs and the incidence of acute lymphoblastic leukemia.There was the difference between the blood levels of PBDEs of the normal group and two groups of children with acute lymphoblastic leukemia,of which the blood levels of PBDEs of sick children were higher than those of the normal group .The differences were statistically significant.

1.2 Animal experiments

More and more studies of animal experiments have showed that PBDEs can induce damages in the cardiovascular systems of animals.

1.2.1 Effect PBDEs on the Heart

Lema et al.[7]have reported that the cardiac functions of Zebrafish larvals were damaged when they were exposed to PBDE-47 at different levels of 500 and 5000 μg/l, including a significant increase in the beat rates of the atrium and ventricle. Tachycardia of fish larvae were reported firstly earlier from 72 to 96h after being fertilized, which has a positive positive correlation with the levels of PBDE. Moreover ,the tachycardia might worse into arrhythmia at the higher level of PBDE-47 (5000ug/l),which was observed by different degrees of atrioventricular conduction blocks. The mechanism of arrhythmia was known that it was involved in the formation and Abnormal conduction of impulse, which were caused by changing mRNA to affect gene expression and function of ion channels. Xiong et al.[8] reported that the heart rates of daphnia magna increased significantly after being administrated BDE-47 of 200μg/ L($p<0.05$),and different levels of BDE-209. They also they also found the mixtures of BDE-209 and BDE-47 made the heart rates of daphnia magna beat so fast. But McClain et al.[9] found that the rates of atrial and ventricular of zebrafish decreased badly when exposure to 8μM BDE 49.At the same time ,the severe physical stress appeared.it is nut sure if the occurrence of death is associated with decreased rates. But McClain et al. found that the rates of atrial and ventricular of zebrafish decreased badly when exposure to 8μM BDE 49.At the same time ,the severe physical stress appeared. It is not sure if the occurrence of death is associated with decreased rates. The studies showed that the different levels of PBDEs had the toxic effects on conduction of impulse and heart rate ,of which BDE-209 was more toxical on construction and function of rat hearts.

Li et al.[10]found that the marked pathological changes of the rat heart cells morphologically and structurally occurred in the groups of rats after administrated orally with BDE-209 of 5, 50 and 500 mg / kg /day for 28days.As compared to the control group, the congested blood capillaries between the muscles were found in both groups of rats exposure to BDE-209 of 5 and 50 mg / kg /day, while both the congested blood capillaries and fibers disruption were seen in the group of rats treated by BDE-209 50 / kg /day. As gradual increase of doses of BDE-209, ultrastructurally, more severe congested blood capillaries, karyopyknosis, karyolysis and swelling myocardial cells occurred in the group of rats exposure to BDE-209 500 mg / kg /day, even if slight damages of myofibrila, swelling mitochondrial, disordered mitochondrial cristae were found in both groups of rats exposure to BDE-209 of 5 and 50 / kg /day. The worse histopathological changes also were found in the group of rats exposure to BDE-209 500 mg / kg /day, such as loss of the striated pattern of their myofibrils, swelling and disordered mitochondrial and vacuolation of mitochondrial cristae, and so on. As we have known, the basic structures for the hearts to keep functioning properly are myocardial cells including

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their subcellular structure. The heart failure will be developed inevitably if the subcellular structures were damaged badly for something toxic. Therefore, it is the key point for us to make clear how BDE-209 damaged myocardial cells, is it working by damaging mitochondrial directly, or at the same time, injuring other parts of myocardial cells, such as cell membrane, cell nucleus or caused disorder of their functioning. The further studies need to be done.

In addition, Zhou et al.(2018) have reported that the Cardiac Indexes of experimental rats at the different ages of 1-2 ,5 and 6 weeks were higher than those of control group($P<0.01$) when the continuous low-dose PBDE-209 was administrated orally to the rats of three groups before and after pregnant rats and lactation rats. The results above indicated that PBDE-209 had developmental toxicity in development and differentiation of myocardial cells of rat fetuses.

Moreover, Blanco et al.[11]have found that BDE-99 caused delayed ossification, hypertrophy of the heart and enlarging the ventricles of rat fetuses.

1.2.2 Effects of PBDEs on blood vessels

Li et al.[10] found that the marked morphological changes of the rat blood vessels also occurred in the groups of rats after administrated orally with BDE-209 of 5,50 and 500 mg / kg /day for 28days.As compared with normal abdominal aortas of rats in the control group ,it was found that the different degrees of elastic fibres damages of abdominal aortas intima occurred in rats of the experimental groups administrated 5,50 and 500mg/kg bw/day, such as disorders of elastic fibres arrangement, proliferation of smooth muscle cells, the broken troponin. As gradual increase of doses of BDE-209, ultrastructurally, more severe disruption could be seen including enlarged nucleuses of endothelial cells, the wide space between endothelial cells and elastic fibers , irregular outline of smooth muscle cells with hollow membrane surface. It suggests that PBDEs had the toxic effects on both endothelial cells and smooth muscle cells of abdominal aortas, then resulted in functioning improperly .Chen et al.[12]reported that obvious toxic effects of BDE-209 were found on new blood vessel forming and cardiovascular diseases when zebra fish larvae of 6 days after fertilization was exposed to the mixture of BDE-209(200 μ g/ L)and Pb(20 μ g/ L). These worse effects included formation of blood clots blocking to block blood flow and afterwards causing the increases of genes transcription of factor II receptor following that . Xing et al.[13] have indicated that there were so many harmful effects of BDE-47 on the development of vessels in zebra fish embryos ,such as stopping common cardinal vein growth, delaying common cardinal vein rebuilding and changing genes express of vessels growth and rebuilding. More and more studies show that mRNA, VEGF and PDG may be involved in the progress of damages and repair of vessels.it must be helpful for us to make the further investigation about how PBDEs effect on expression of them above.

2. Possible mechanism of cardiovascular toxicity of PBDEs

2.1 Affecting miRNA expression

As we had known, the expression of cardiovascular disease(CVD)-related genes were regulated by specific microRNA(miRNA) [14],which consisted of some endogenous and non-coding RNAs that regulated gene expressions at the posttranscriptional level[15]. Data from both vivo and vitro experiments indicated that some CVD of related-endothelial function might be associated with the expression of different characteristics of miRNAs,while the expression of intercellular adhesion molecule-1(ICAM-1) associated with the types of of miRNAs. The previous studies showed that the PBDE congeners of BDEs-28,−47, −99 and −100 with the lower brominated level were statistically related with certain markers of CVD or its risk factors. Zhi et al.[16]found the increasing adhesion between monocyte endothelial cell and endothelial cell when exposures to 6.25, 12.5 and 25μM of BDE-209 dose dependently in cultured human aortic endothelial cells. The possible mechanism of that was known it might down regulate the expression of miRNA-141,while resulting in following up-regulating of the expression of ICAM-1.Therefore ,we believe that the toxical effect of BDE-209 on cardiovascular diseases may work by down-regulating of the expression miRNA-141 and then to cause the increasing level of ICAM-1 expression.

Recent studies showed that the level of specific miRNA-1 expression. of myocardial cells closely related to the growth and differentiation of cardiomyocytes .When the expression level of miRNA-1 was lower, it was beneficial for the myocardial cells to grow and differentiate during embryonic period. Then the expression level of miRNA-1 increased gradually and suppress the expression of Hand-2 protein to keep growing and developing of the heart properly. Zhao eat al. reported that the 1/6 mice of the experimental group died so fast for suffering from enlarging hearts, pulmonary embolism, and severe heart failure after knocking out of miRNA-1-2[17].As we have known, miRNA-126 one of angiogenesis-promoting factors. After miR-126 was knocked out, severe vascular defects and the vascular endothelium cells damage were found in the mice of experimental groups. It suggested that miRNA-126 might be the key targets and regulatory sites of angiogenesis signal when the mice were blocked the blood flow and caused ischemic. Some studies also confirmed that the lasting exposure of the high level of PBDE-209 to the arts of the fetal rats caused increase of cardiac index, and evident edema and hypertrophy of myocardial cells(Zhou Jun,2018).

2.2 Inducing Inflammatory Reaction

As we know, although there could be different causes inducing the heart diseases, the inflammatory reaction plays a very important role in the development of many cardiovascular diseases, such as myocarditis, atherosclerosis, hypertension, acute myocardial infarction and heart failure. Previous studies have shown that BDE-47-treated mice could be observed inflammatory cell infiltrating and gathering to liver, increasing levels of pro-inflammatory cytokines and chemokines, and inducing inflammation[18]. TNF-a, IL-1 b, IL-6, and IL-10 elaborate an important action in regulating the inflammatory reaction, which excessive production of these factors can induce inflammatory reaction. Among these pro-inflammatory cytokines, found TNF-a was found more important and up-regulated in most of cardiovascular diseases as an indicator of inflammation[19]. There were also experimental studies suggesting that TNF-α plays an important role in many oxidative stress-related diseases, including diabetes, different cancers, cardiac hypertrophy and cardiomyopathy[20-23]. Some updated evidence suggested that another crucial cytokine IL-1 b also played an important role in the occurring and progression of acute myocarditis[24-25], which reducing production of IL-1b improved autoimmune myocarditis in rats[26]. As it was known,IL-6 was one of more important cytokines that was secreted by T lymphocytes and macrophage with both effects of pro-inflammatory and anti-inflammatory. It was found that was involved in the process of infection and wound healing. The recent studies have shown that the early inflammatory reaction mediated by IL-6 signaling pathway and promoted the myocardial infarction healing of zebra fishes. IL-6 also promoted the proliferation and differentiation of satellite cells and regeneration of skeletal muscle cells injury[27-28]. Besises,IL-6 is crucial for inducing the inflammation reaction during the acute phase and related to some kinds of cardiovascular diseases closely[29]. IL-10 is another inflammation cytokines with multiple effects. It was found to keep increasing in patients with the acute myocarditis. It indicated that the lasting inflammation of myocarditis in patients with the acute myocarditis might be associated with the elevated level of IL-10[30]. Li et al. [10]found that BDE-209 exposure to experimental groups of rats can significantly increase the levels of IL-1b, IL-6 and TNF-a of treated rats, indicating that BDE-209 induced a severe inflammatory reaction. The further investigation of their mechanisms will be needed more.

2.3 Oxidative stress

Experimental studies in vivo and in vitro suggest that oxidative stress might be a common mechanism of PBDEs causing toxic effects on different cells, organs and systems of animals[11,31]. It was reported that BDE-47 disrupted redox equilibrium in mice cells through production of reactive oxygen species[35]. there were also some finding oxidative stress to play an important role in the toxic effects on earthworms inducing by BDE-209[33]. As it was known, with excessive accumulation of oxygen free radicals in cells, the unsaturated fatty acids in membrane lipid will cause peroxidation reaction, which will damage the membrane structure and induce apoptosis(Kang Pinfang,2014). Superoxide dismutase (SOD) is an important

antioxidant enzyme that can specifically scavenge superoxide anion free radicals as a natural scavenger of oxygen free radicals. The lower of the SOD activity, the worse of its ability to scavenge oxygen free radicals in cells will be. MDA, a product of membrane lipid peroxidation, used to detect the damaging degree of cell membranes as a mark. The higher level of Malondialdehyde (MDA) means the more severe damaging in cell membranes. Like SOD, glutathion(GSH) is also an endogenous antioxidant existed in cells, which can prevent oxidative stress from damaging cell components. After investigating the induction effect of MDA, the activity of antioxidant enzymes SOD and GSH PX, and the content of GSH , Li et al.[12] found that BDE-209 exposure increased the level of MDA significantly in the heart and abdominal aorta of rats, and decreased the SOD activity and GSH level. These results indicated that BDE-209 could induce oxidative stress in the heart and abdominal aorta. Therefore, oxidative stress was known as the crucial factor causing damage of heart and blood vessels.

2.4 Mitochondria damaging and dysfunction

As we had known, mitochondria is the important place where the oxidative reaction in eukaryotes carry out , that is, energy producing and releasing by the aerobic oxidation of sugars, fats and amino acids finally. Animal experiments show that BDE-209 exposure can damage mitochondrial structures of heart cells in rats, making their crista vacuolized and disorganization[10]. Therefore, we infer that BDE-209 might disturb mitochondrial functions, then disrupting the stability of myocardial cells, following damaging heart functioning. More experimental studies will be needed to make sure how PBDEs act on mitochondria and impair their functions.

2.5 Affect the expression of VEGF

As was reported, angiogenesis was regulated by particular genes of relating to remodeling[34]. It was found that vascular endothelial growth factor (VEGF) is a growth factor from supergene family derived platelet, which plays a very important role in the regulation of angiogenesis and lymphangiogenesis. VEGF-A regulates the proliferation, migration, permeability and secretion of endothelial cells by binding with two tyrosine kinase (TK) receptors of VEGFR-1 (Flt-1) and VEGFR-2 (KDR / Flk-1). VEGF-A was found more important than other growth factors of which exists in VEGF family because it could bind two tyrosine kinase (TK) receptors of VEGFR-1 (Flt-1) and VEGFR-2 (KDR / Flk-1) to regulate the proliferation, migration, permeability and secretion of endothelial cells. The further study also indicated that the homozygous embryo mice of VEGF-A knockout and hybrid mice (VEGF-A + / -) might die of the delaying the formation of mature blood vessels. So it is needed for the proper concentration of VEGF in the embryo to be controlled strictly and regulated for the normal blood vessel development[35]. Besides, Lobov et al.[36] reported that vascular endothelial growth factor receptor-2(VEGFR-2) induced pre-angiogenesis signal by activating thymidine kinase (TK) intensively.As it was known, Delta-like ligand 4 (Dll4) is a regulatory molecule of VEGF signal transduction induced by VEGF to stop excessive growing and developing of blood vessels by regulating angiogenesis negatively. Some results from animal experiments showed that the mRNA levels of VEGFA, VEGFR1, VEGFR2 and Dll4 decreased dose-dependently manner in the zebrafish larvae treated with BDE-47 at 48 hpf. Therefore, it was presumable that BDE-47 exposure inhibited growing and developing of blood vessels finally by down regulating related signals to VEGF and then affecting the expression of VEGF gene.

2.6 Impact PBDEs on other systems

In addition to effects above, there were other systems involved in that and damaging cardiovascular system ,such as the nervous system and endocrine system. One of them is the effect on thyroid gland. As is well known that thyroid hormone (TH) were found to promote tissue differentiation, growing and developing by taking part in many of physiological and biochemical functions of cells, tissues and organs. Previous studying results suggested that cardiovascular system is one of the most important targets of which thyroid hormone recognizes and binds. It is noted that excessive thyroid hormone might cause a series of cardiac arrhythmia and deteriorating cardiac functioning, including symptoms of sinus tachycardia, palpitations atrial fibrillation, declining exercise endurance, even dyspnea on exertion,

angina and heart failure, etc[37]. Instead, decreasing level of thyroid hormone makes the heart rate beat slower, myocardial contractility weaker, and peripheral resistance increased. Animal research shows that the exposure to PBDEs caused decreasing level of thyroxine(T4) concentration in adult and puberty animals significantly, but no obvious change of triiodothyronine (T3) and thyroid-stimulating hormone (TSH) concentration. It is presumable that the possible mechanism of animals arrhythmia or heart rate changes caused by PBDEs might be PBDEs had disrupted the normal function of the thyroid gland and thyroid hormone secretion before the hearts were damaged by PBDEs.

Herein, the following three levels of mechanisms were used to explain how PBDEs disturbed the functioning of the thyroid gland (Kang Pinfang,2014). Firstly, the thyroid tissue was attacked and damaged by PBDEs directly. Secondly, the transport and metabolism of thyroid hormones(TH) was disturbed by PBDEs and resulted in biological activity changing of thyroid hormones. Thirdly, hormonal function and regulation were interrupted by PBDEs binding thyroid hormone receptor, as well as the balance between thyroid hormones was destroyed by PBDEs binding other related thyroid hormone receptors indirectly. Therefore, the further research will be needed to make clear how PBDEs act on and poison the thyroid gland and then induce toxic effects of PBDEs on the hearts and interrupt the heart functioning properly.

3.Conclusions

In conclusions, the toxic effects of PBDEs on the cardiovascular system might not act as a single mechanism, but the results of combing multiple mechanisms together. Just less mechanisms were discussed above, it will be needed for us to investigate the more complex and thorough reasons how and why PBDEs damage the cardiovascular system.

(1) The related gene homeostasis inducing cardiovascular diseases is controlled by specific miRNA[17].Many experimental results confirmed that PBDEs damage the structure and function of cardiovascular system by down-regulating the expression of miRNAs. However, there are so many homologs of PBDEs up to 209 discovered till now. So it will be needed to know more about how they induce different cardiovascular diseases by regulating different miRNA expressions.

(2) It was known that mitochondria play a crucial role in the survival of myocardial cells. It was reported that PBDEs caused mitochondrial damages by many different ways. They included destroying mitochondrial inner membranes to break electron transport in ATP synthesis, causing oxidative damages by disrupting mitochondrial antioxidant defense system to induce excessive ROS production, stopping electron delivery by inhibiting complexes of respiratory chain, inducing the opening of mitochondrial permeability transition pore (MPTP);disturbing mitochondrial DNA directly and so on(Liu Zaoling,2012). Above all, it is more significant that which way is more important for us to explore the real reason of which PBDEs damage cardiovascular systems.

(3) There was little experiments done about interaction between PBDEs and other pollutants in the environment. As one of environmental harmful pollutants, undoubtedly, PBDEs could interact on other pollutant constantly. Chen et al.[15] found that the mixed BDE-209 and Pb could accelerate uptake of Pb in the blood of zebrafish larvae even if decreasing uptake and debromination of BDE-209 . At the same time, it was found that there were both of lower scavenging activity and higher accumulation of Pb in zebrafish larvae. Therefore, we get to know both BDE-209 and Pb might be more toxical and dangerous to organisms than that of single one.

(4) Less researches were done about interaction between PBDEs homologues, which will be still necessary to make further studies afterwards. The adding effects of mixed BDE-209 and BDE-47 on Daphnia hearts were found stronger significantly than that of the single one when making researches to compare two results of single or the combined effect of BDE-47 and BDE-209[10].

(5) At present, most of the results of previous researches from different kinds of animal experiments,

It will be still needed for us to do some epidemiological studies from a large-scale population research.

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