The Toxicity of Bisphenol A and Its Analogues on Human

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Abstract. With the development of human society, technology and medicine have been widely discovered. Bisphenol A (BPA) is a kind of substance widely used in industrial production, mainly used in the production of polycarbonate, epoxy resin and other polymer materials. Many analogues of BPA like BPS, BPF and BPAF have been used as substitutes for BPA. However, BPA and its analogues exposure in daily life has been found to be harmful to people's health. In this paper, the toxicity of BPA and its analogues in the environment exposed with different concentrations, exposure time, ages, genders has been discussed. In addition, the effects of BPA and its analogues on biological endocrine system, immune system, reproductive system and nervous system have been introduced by studying the endocrine organs of animal models. Results reveal that DNA can be severely damaged at certain BPA concentration, and that BPA may act directly on the ovary due to its similar structure to secreted estrogen Besides, BPA exerts a bi-directional regulatory effect on the mouse immune system, and when exposed to BPA for a long time, activity of immune system can be suppressed. Researches on BPA and its analogues' effects on organs and systems can give some suggestion on the use as materials for the production.

Keywords: Bisphenol A, analogues, toxicity.

1. Introduction

Bisphenol A (BPA) is a very prevalent industrial material in manufacturing polycarbonate plastics and resins [1]. The plastics can be used as containers or packings for the common foods sold in the supermarkets [1]. This chemical can also migrate into the environment and accumulate through the food chain, thus providing an exposure pathway for humans [1]. The BPA can also be existed in the air and dust [1].Thus, BPA is so ubiquitous that human can be easily exposed to the chemicals. The chemical structure of BPA is similar to estrogen so it is believed to antagonize the estrogen receptor (ER). Many researches have found that BPA can also disrupt androgen receptors (AR) and thyroid hormone receptor (THR) [2]. It will lead to the problems on human's reproduction, immunity, neurodevelopment and so on.

Other bisphenols like BPB, BPF, BPS and BPAF have the similar chemical structures of BPA. It means they will have the similar biological properties are usually used as the alternatives of BPA [1]. Therefore, they also need to be carefully evaluated before putting them into the long term use.

Many researches have investigated the effects of BPA and its analogues on reproduction of human via toxicokinectic models, like a pregnancy sheep model, an ovine materno-feto-placental model or a PBPK model as a predictive model to evaluate the concentration of BPs in zebrafish embryos [3-5]. Those models are used to describe how the chemicals get into the next generations and generate the adverse effects. They can be further used to stimulate the toxicokinectics of the alternatives of BPA and make some assessments. Many of the models based on the animals so the further studies will pay more efforts to make sure the models can be valid if used for human.

BPA can cause damage on the testicular organs and sperms in animals and human. It becomes a reason for the lower quality of sperms of man. BPA can cause oxidative stress in the red blood cells [1]. A research on 111 women who underwent unexplained recurrent spontaneous abortion. The result has showed that BPA could induce the oxidative stress and lead to immunity imbalance [6]. The two conclusions can call the attention of BPA's damage on the immunity, especially for the group that

have some potential diseases. Some researches have revealed that children's early exposure of BPA would have neurodevelpoment problems like ADHD [7]. There are also other damages that caused by BPA and its analogues which will be presented in this review. It can help to have a quick and wide depiction of BPA and to know how to choose safer substitutes of the BPA for the future manufacture.

2. Bisphenol A's Effect on Endocrine System

Due to the widespread use of BPA, its environmental impact and its security have attracted great attention in the public. BPA is a recognized environmental endocrine disruptor, which can interfere with the endocrine system of animals and humans. In a study on the endocrine system of mice[8], BPA toxicity had certain effects on the survival rate of mouse testicular cells, and the activity of DNA damage enzymes and organ coefficient.

Table 1. Effects of different dose BPA on survival rates in the mouse testis cells($\bar{x}$±s)

Groups	n	Survival rate(%)
NC	6	1.074±0.020
DMSO	6	0.969±0.023①
10^{-8}mol/L	6	0.944±0.013①
10^{-7}mol/L	6	0.902±0.039①②
10^{-6}mol/L	6	0.902±0.028①②
10^{-5}mol/L	6	0.864±0.0052①②
10^{-4}mol/L	6	0.853±0.029①②
Annotate:①compare with NC p<0.05, ②compare with DMSO p<0.05.		

Testis are part of the endocrine system, with the increase of BPA's concentration, the survival rate of mouse testicular cells decreased significantly and was lower than that of the control group. In the detection of DNA damage induced by BPA toxicity, and the tailing rate of DNA in alkaline electrophoresis solution increased significantly with the increase of the BPA concentration. DNA tailing does not occur when the cell is not damaged. When the cell is damaged, the double strand of DNA will unspin and the single strand will break into fragment. Fragments, intracellular RNA, and proteins move toward the anode, while DNA moves toward the negative electrode, creating a trail. As shown in table 1, the higher the BPA concentration was, the more serious the DNA was damaged, and the more serious the DNA damage appeared in 10-5mol/L and 10-6mol/L groups, indicating sever DNA damage. The organ coefficients of testis, uterus, kidney and thyroid of mice exposed to BPA were higher than those of the control group, but different concentrations of BPA had little effect on organ coefficients. BPA can damage endocrine organs, causing congestion and edema. The results showed that when the dose of BPA increased, the activity of lactate dehydrogenase was lower than that of the control group. Lactate dehydrogenase in the testis is produced by sperm. When sperm is defective, lactate dehydrogenase cannot be produced or its activity is reduced. BPA caused damage to testicular cells and inhibited the activity of lactate dehydrogenase. The low lactate dehydrogenase index was closely related to the endocrine system.

In the study of maternal mice exposure to BPA during pregnancy, the abortion rate of maternal mice and the survival rate of offspring mice were also affected. 60 mice were divided into groups A, B, C, D, E and F with group A as the control, and the remaining groups were given 2.5 ,5, 10, 20, 40mg/kg BPA [9]. Table 2 shows that with the increase of BPA concentration, the abortion rate of maternal mice also increased, and the abortion rate could reach 50%~60% at 20 and 40mg/kg concentrations. At 2.5 and 10mg/kg BPA concentrations, the survival rate of the offspring mice decreased significantly compared with the control group A. At 20 and 40mg/kg BPA concentrations, the survival rate was extremely low.

Table 2. BPA's effect on the abortion rate of maternal mice

Group	Number of abortions	Unaborted number	Total	Abortion rate(%)
A	0	10	10	0
B	3	7	10	30
C	3	7	10	30
D	4	6	10	40
E	5	5	10	50
F	6	4	10	60

Polycystic ovary syndrome (PCOS) is a common endocrine disease, which is closely related to endocrine. In a study of BPA on polycystic ovary syndrome, 51 PCSO patients were given drugs for ovulation, and follicular fluid samples were collected [10]. The content of BPA in the follicular fluid of the patients was determined. The results showed that the BPA content in the follicular fluid of the patients was much higher than that of the control group. After that, female PCSO rats were injected subcutaneously with BPA which was dissolved in 1mg corn oil per day from 0 to 9 days after birth, and a control group was injected with the same dose of corn oil. The rats were put to death on the 81st day of feeding. Through the hematoxylin and eosin - staining, it has shown that the ovaries of the BPA-exposed rats were polycystic compared with the control group, and the free androgen index (FAI) in the blood of the BPA-exposed rats was significantly higher than that of the control group, and the hormone levels in the rats were unstable. The structure of BPA is very similar to that of estrogen, so BPA can compete with estrogen to produce antagonistic effect. BPA can affect enzymes in the ovaries, interfere with estrogen production and cause a host of problems.

3. Bisphenol A's Effect on Immune System

The toxicity of BPA may also affect the immune systems of humans and animals. In an animal study, 25 red carp were divided into five groups exposed to 0.1, 1, 10, 100, and 1000μg/L BPA for 30 days, and one red carp from each group served as a control group [11]. Respiratory burst activity is a measure of the immune system of fish. Measurements of respiratory burst activity showed that it increased with increasing BPA concentrations, but decreased at concentrations up to 100μg/L. The immune system of red carp was disturbed by long-term exposure to BPA. Serum lysozyme is one of the non-specific immune factors in the body, which can inactivate the virus to achieve the antibacterial and anti-inflammatory effect. In the test of serum lysozyme, the activity of serum lysozyme was the highest when the concentration of BPA reached 1μg/L, which could activate the immune system of red carp to some extent. However, the levels dropped again at 10μh/L, and long-term exposure to high levels of BPA could suppress the immune system of red carp.

A mouse experiment also demonstrated the bidirectional regulatory effect of BPA on the immune system of mice [12]. The concentrations of BPA were 7,20,30 g/L with corn oil, and 40 mice in 4 groups were given gavage for 7 days, and macrophage phagocytotic function and hemolysis plaque test were performed on the last day.

Table 3. Comparison of immune function in different dose groups ($\bar{x}$±s,n=10)

Group	The number of plaques formed (unit per 10^6)	DTH(mm)	MΦPhagocytosis rate(%)	MΦphagocytic index
Control	936±165	0.41±0.097	57.9±4.7	0.73±0.060
low-dose	1431±177**	0.63±0.090**	65.9±7.0*	0.76±0.059
middle-dose	349±98**	0.83±0.025	54.6±7.1	0.64±0.065**
high-dose	274±87**	0.33±0.062	50.6±30*	0.56±0.035**
Annotate: compared with control group,*p<0.05,**p<0.01.				

The Table 3 showed that the results in the low dose group (7g/L) were slightly higher than those in the control group and the medium(20g/L) and high (30g/L) dose groups. At low concentrations of BPA, mice were stimulated to boost their immune systems, while at medium and high concentrations, measurements decreased significantly. This suggests that high concentrations of BPA can inhibit the phagocytosis of macrophages, leading to a decrease in immune system function.

The phagocytosis function of macrophages can effectively understand the specific and non-specific immune status of the body.

Lymph is one of the important immune organs. In a study on the effect of BPA on crucian carp lymphocytes, crucian carp blood lymphocytes were separated and prepared into cell suspension, 50μL cell suspension was added into 5 holes, and a series of BPA concentrations were added to each hole in order to determine the cell proliferation (BPA concentration 0 was the control group) [13]. With the increase of BPA concentration, the optical density of each group is higher than that of the control group. BPA can effectively stimulate the growth of crucian carp lymphocytes, and the concentration of BPA at 540ng/mL can stimulate the growth of lymphocytes to the greatest extent.

4. Bisphenols' Effect on Reproduction

It is believed that the BPA in the environment will affect the endocrine that correlates to the fertility both in females and males.

For males' fertility, BPA is considered as an endocrine disruptor, which makes an adverse effect on the androgen receptor(AR) signaling pathway via antagonizing the transcriptional activity of AR[2].This will decrease the binding of androgen to the AR, which leads to the inhibition to the sex organ development [2].The coregulator peptides that mostly have a negative effect on the transcription level of AR are induced by BPA-bound AR[2].The coregulators recruitment of BPA analogues like BPAF and BPS that bind to AR both show significantly different from the androgen-bound AR [2].The assay indicated that BPAF-bound AR recruited nearly the same coregulator peptides as the BPA-bound AR and the BPA-bound AR recruited very different peptides from BPA/BPAF-bound AR[2].The mechanism of the coregulator peptides recruitment of the BPA analogues still need further study.

Ullah A et al. performed *in vitro* and *in vivo* studies on the rats' sperms and testicular tissues, which showed BPA and its analogues, BPS, BPF and BPB had increased the oxidative stress on male rats' reproduction tissues[14].However, Castellin C et al. conducted an experiment on the human sperms exposed BPA and BPA's analogues including BPS and BPF for 4 h to determine how the BPs affect the motility and viability of human sperms. and the result shows BPS and BPF did not damaged the function of human sperms and could be safer substitutions to BPA [15]. The time of exposure needs to be longer for the further study of the effect of the BPS and BPF on the human sperms. Rehfeld A et al. also indicated that BPS, BPF have no effect on inducing the Ca^{+} signaling that will cause adverse effect on sperms [16].

BPA not only effects the androgen signaling pathway but also affects the estrogen signaling pathway as an estrogen-like chemical [2]. There are also lots of toxicokinectic models on BPA and its analogues. Gingrich J et al. used a pregnancy sheep model to demonstrate that transfer of the BPS and BPF from the maternal placenta to fetu, entering the amnion as well as the BPA[3]. Flore C et al. investigated toxicokinetics of BPs in the ovine materno-feto-placental unit and indicate that although the less concentration of BPS transfer from maternal compartment to fetus compared to BPA, it will have an accumulation of BPS if materno keeps being exposed to the BPS, which will cause toxic effect on the fetus [4]. Many researches have shown that BPAF could have a more efficiently adverse effect on the reproduction and BPF, BPF might have less toxic effect than BPA [16,17].

Yuqing W et al. did a research on the association between BPA, BPS, BPF and sex hormones among children and adolescent [18]. The result showed a high association between BPs and female adolescents [18]: BPs had non-monotonic effects on the sex hormones. It may suggest that BPs as an estrogen like chemicals will have more significant effects on female.

Melanie H et al. have investigated the relationship between BPs and postpartum depression (PPD) [19]. PPD as a result of the fluctuations of the sex hormones, it may be induced by endocrine disruptor, BPs [19]. Despite the research lacks the psychiatric mechanism, it does demonstrate the exposure of BPs during pregnancy has a potential effect on causing the PPD [19]. As the mechanism of the BPA and its analogues is very complex. Various concentrations of BPAs, different genders, ages and other conditions should be considered in the future study about this.

5. Bisphenols' Effect on Nervous System

Kim J.I et al. observed 619 children aged 4-8 also detected the influence of BPA, BPS and BPF to determine the association of BPs with ADHD [7]. The conclusion is that BPA, BPS and BPF were highly associated with ADHD at age 6. The more concentration children were exposed, the more obvious symptom of ADHD would be [7]. The conclusion also indicates that girls at that age are more susceptible for BPs exposure [7]. Here it can be found that BPs are more likely to influence female in both reproduction and neurodevelopment.

Kim J.K et al. used rats to examine the effect of BPA and found that BPA would increase the loss of vitamin D3 in blood which could cause neurodevelopment disorders [20].

6. Bisphenols' Other Effects

There is a research to test bisphenols' effect on growth: the BPA and its analogues' effect on osteoclast differentiation in rats [21]: BPA, BPF, and TMBPF have presented a negative effect on the osteoclast differentiation, which indicates that these chemicals will inhibit the homeostasis in bone.

There is another research on the association of BPA and BPF with the pigmentation [22]: the investigators indicated that in the molecule's dynamics of experiment that BPA and BPF can both be ligands to zebrafish and human Tyr family protein, which means they can have a depigmentation effects. It shows a risk of skin pigmentation interference of these chemicals.

7. Conclusion

As the endocrine disrupting chemicals, BPA and its analogues have been studied in many literatures. It can be seen that BPA can disrupt the reproduction in animals and human. As substitutes of BPA, BPF and BPS are be safer to some extent. In addition, BPA will cause more adverse effect on females than males in terms of neurodevelopment, and the mechanisms of how BPA affects the reproduction of women and men are different. For men, the BPA's toxicity will show in the testicular tissues and sperms while for women it shows in the placentas and ovary. The chemical might have the effect on women's mental health which can lead to PPD. There are many other symptoms that caused by BPA need to be explored, and the comparison of the BPA and its analogues should be considered in many aspects. Therefore, it is of great significance to developing less toxic alternatives.

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