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Chapter 6

Low-Dose Exposure to Bisphenol A in Early Life

Yeon-Pyo Hong and Yun-Jung Yang

Additional information is available at the end of the chapter

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Abstract

Bisphenol A (BPA) has lower estrogenic potency than 17b-estadiol. The reference dose of BPA is defined as 50 ug/kg bw/day by the Environmental Protection Agency. The lower doses of BPA than no observable effect level are considered safe. However, early life exposure to low-dose BPA may increase the risk of developing adult onset disease. The harmful effects caused by low-dose BPA in fetus and newborns can transmit to third or fourth generations. The suggested mechanism of transgeneration is epigenetic changes. In addition, simultaneous exposure to various chemicals can induce combined effects. Low-dose effects of BPA are ongoing controversy because the animal test results will be the same in humans. Epidemiologic evidences are needed to provide the human health effects from exposure to low dose of BPA.

Keywords: bisphenol A, low dose, early life

1. Introduction

Bisphenol A (BPA, CAS #80-05-7) is widely used in manufacturing polycarbonate plastics, epoxy resins, and thermal paper including food containers, baby bottles, dental sealant, and store receipts. BPA can produce the estrogenic activity through binding with estrogen receptor [1] and can also exert the actions through androgen receptor, peroxisome proliferator-activated receptor γ, and others [2]. Thus, BPA is classified as an endocrine disruptor (ED) because of the estrogenic potency.

Traditional toxicology considers that the effect would consistently increase with the amount of treatment. The dose levels of BPA below low observed adverse effects level (LOAEL) at 50 mg/kg/day [3] are regard as safe. However, recent studies describe the nonmonotonic dose response relationship of BPA. Perinatal exposure to lower dose of BPA than LOAEL has been reported the harmful effects on endocrine system including reproductive

system [4–7], immune system [8–10], pituitary gland [11–20], and metabolic system [21–24]. Because, the fetus and neonates are extremely sensitive to perturbation by hormone like chemicals, early life exposure to low dose BPA probably is able to affect the epigenetic mechanism. The epigenetic changes caused by BPA may explain the increased risk of developing adult onset diseases.

The mixed exposure to several low-level EDs should be tested because humans are exposed to various EDs simultaneously. Mixture can produce significant adverse effects, even when each chemical is present at low doses that individually do not induce observable effects in reproductive system [4, 25] neuroendocrine system [26], and endocrine system [27, 28].

Therefore, this chapter describes the harmful effects on adulthood caused by exposure to low-dose BPA during early life stage.

2. Exposure to bisphenol A

BPA is a chemical compound used to produce polycarbonate plastic and epoxy resins. Therefore, humans are exposed to BPA throughout their life. The predominant source of BPA exposure to general population is ingestion of food and beverages [29, 30]. Humans can also be exposed to BPA through nondietary routes including inhalation [31, 32] and skin contact [33].

2.1. Human exposure levels

BPA levels have been measured in human biological samples due to the widespread use of BPA-containing products. Unconjugated BPA levels in humans were measured as a wide range from 0.2 to 20 ng/ml in serum [32, 34]. BPA also detected in amniotic fluid [35], breast milk [36, 37], and maternal amniotic fluid and fetal plasma [38, 39]. These studies indicate that BPA is able to easily transverse the placental barrier and affect the fetal development.

The estimation of BPA exposure in the general population can be based on the presence of BPA levels in the biological sample and the amount of daily food intake. Based on urinary excretion levels of BPA metabolites, the estimated amounts of BPA in general population are up to 0.16-μg/kg body weight (bw) in the USA and 0.04–0.08 μg/kg bw in Japan [40]. Daily intake levels of BPA to human have been estimated from 0.2-μg/kg bw/day in 3-month-old breasted infants up to 13-μg/kg bw/day in 6-to-12-month-old infants. The estimates of potential dietary exposure in young children and adults were respectively 5.3 and 1.5 μg/kg bw/day based on conservative migration values of BPA and conservative estimates of consumption of commercial foods and beverages [41]. This report shows that infants and children are the highest intake group because they eat, drink, and breathe more than adults and play or bite with the plastic toys.

2.2. Metabolism

The orally administered BPA could rapidly metabolize to the bisphenol A-glucuronide carried out by the uridine 5′-diphospho-glucuronyl transferase (UGT) in the liver and gut. The metabolic process is called as glucuronidation. Unconjugated parent BPA is converted into other substances such as sulphate conjugate [37]. The conjugated form of BPA does not bind to the estrogen receptors and is excreted in urine [42–44]. It suggests that the conjugates have relatively less estrogenic potency than unconjugated form because of the less binding affinity to nuclear receptors and rapid excretion. The estimated half-life of BPA was about 6 h in the human body [45–47]. In addition, BPA metabolisms in liver cells from rats, mice, and humans showed similar pattern across the species [48].

The metabolic process of BPA is different depending on the route of exposure. The highest concentration of BPA was measured at 1 h after oral or intraperitoneal administration and at 4 h after subcutaneous administration [44]. More than 60% of the glucuronidated BPA were excreted through urine, and unconjugated form of BPA was mainly excreted in the feces [44]. It suggested that the oral route was recommended for appropriated risk assessment of BPA because the predominant exposure route of BPA to human is dietary ingestion [40].

In pharmacokinetic studies, BPA metabolites were measured in human urine and blood after ingestion of 5 mg deuterated (d6)-BPA [46]. Besides, the maximum unconjugated d6-BPA concentration in human serum was detected at 1.6 h after ingestion of the BPA-contained soup [49].

The fetus and newborns are not fully developed in the ability of glucuronidation [50]. In experimental studies, neonates showed higher free BPA levels in blood compared to older animals when given a same level of BPA [50, 51]. Despite the glucuronidation enzymes have not been identified in human, neonates and infants may be vulnerable to BPA exposure compared to adult human.

3. Health effects of low dose bisphenol A

Until recently, the studies on BPA mainly focused on the nuclear mechanisms of estrogen response through bind with estrogen receptors (ERs). The binding affinity of BPA to ERβ is about 10 times higher than that of ERα [52, 53]. BPA showed 10,000–100,000 weaker estrogenic potencies compared to 17β-estradiol [54]. It has been considered that BPA has relatively weak estrogenic potency due to the low binding affinity with ERs and the low estrogenic potency compared to estradiol.

However, recent studies reported a variety of molecular pathways including androgen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, which are associated with hormones of the endocrine and other systems in the body [34, 55]. The disrupted nuclear hormone receptors can interfere with the secretion and function of endocrine system.

3.1. Low dose effects of bisphenol A

The low dose was defined in the U.S. Environmental Protection Agency (EPA), the National Toxicology Program (NTP) assembled a group of scientists in 2001 as any biological effects occurring in the range of typical human exposures or occurring at doses lower than those typically used in traditional toxicology assessment [56]. Traditional toxicology considers that the dose makes poison. Thus, toxicological studies have been focused on identifying the concentrations at which chemicals can cause biological changes, and below that levels are not harmful to health.

According to the definition of NTP, the cutoff doses of low-dose BPA might be the range of general public exposure except for occupational exposure and the levels less than 50 mg/kg/day of LOAEL [3, 54]. However, diethylstilbestrol (DES), which was used to prevent premature births and miscarriages of pregnant women, is one of the endocrine disruptor and is caused endocrine disrupting activity to exposed women and developing babies [57]. Thus, the safety levels of EDs may not exist.

Many experimental studies have been reported on low dose effects of BPA [1, 58, 59]. Epidemiologic studies also showed that exposure to environmental relevant levels of BPA are associated with the disorders in human [60–62]. However, there is still controversy over the low-dose effects of BPA because of the difficulty to replicate. Thus, the necessity of the reevaluation of human safety daily intake limits is raised.

Low dose is not the same as nonmonotonicity. Monotonic dose response relationship is the basic approach in traditional toxicology. In contrast to traditional toxicological approach, recent studies suggest that EDs may show the nonmonotonicity including biphasic, U- or inverted U-shape dose–response curve (**Figure 1**) [63]. The lack of monotonic dose-response relationship makes it difficult to predict the health effects at low dose using the result from high-dose endocrine disruptors.

Exposure to environmental relevant doses of BPA to pregnant mice moved the timing of vaginal opening and first estrous cyclicity up in their offspring [58]. BPA below reference dose affects the structure and functions of brain through interfering with the hormones and neuro hormone receptors [64]. It may be caused by the disruption on brain-gonads-pituitary

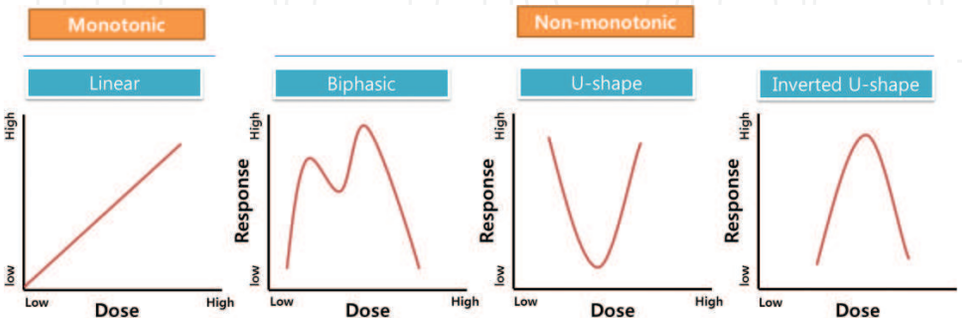

Figure 1. Examples of monotonic and non-monotonic dose response curve.

gland axis function. However, BPA exposed male and female rats showed no changes of body weight, reproductive morphology, and fertility of their female offspring [65].

In epidemiologic studies, the associations were observed between internal BPA concentrations and endocrine hormones. The BPA concentrations in the urine of men in the fertility clinic were showed inverse correlation with the estradiol:testosterone ratio [66]. Urinary BPA concentrations in human from Italy were positively associated with ERα and ERβ [67].

Recent study showed that BPA at low doses decreased estradiol level and inhibited growth of follicles isolated from wild-type and aryl hydrocarbon receptor (AHR) knock-out mice through interfering with the AHR [55]. They suggested that AHR signaling pathway might not be a major route through BPA exert its toxic effect on ovarian follicles.

The low-dose effects of BPA may associate with the genetic susceptibility, i.e., a gene-environment interaction. Transgenerational inheritance may associate with the epigenetic changes caused by low-dose BPA exposure. Without understanding the gene-environment interactions, there is a limit to understand the low dose effects. Low-dose effects of BPA should be validated through epidemiologic studies.

Exposed environmental factors during fetal or neonatal life can interact with the genome and influence the onset of diseases in their adulthood including cancer, infertility, precocious puberty, and obesity [68]. This theory is called "the developmental origins of health and disease" [69]. DES, a synthetic estrogen, is well documented that fetal exposure to DES causes the severe malformations and cancers of the reproductive tract [57].

Perinatal exposure to low-dose BPA may produce the adverse effects including brain function, reproduction, pituitary gland, and immunity (**Table 1**). The harmful effects are persisted and transferred to the fourth generation that was not directly exposed to BPA. BPA exposed fetus during their gestational period showed neoplasia and changes in mammary tissue [70].

Organ developing period as the first trimester in fetus is the critical period, which means they are extremely sensitive to low-dose effects of EDs than adult organisms. Thus, gestational exposure to EDs may induce the harmful effects on the offspring and can transfer to the subsequent generation. This process is called as "epigenetic transgenerational inheritance." The attention has been increasing to the role of epigenetic changes in the development of disease because it is considered as one of the mechanisms for explaining of low-dose effects.

When epigenetic changes are induced by EDs, those can regulate the gene expression by silencing or activating the gene. The mechanisms of regulation are classified as (1) DNA methylation, (2) histone modification, and (3) RNA-associated silencing. Because epigenetic changes do not modify the gene sequence but affect the gene expression, it may reflect the plausible association between exposure to endocrine disruptors and alteration of gene expression, which resulted into the development of disease.

Classification	Animal model	Administration (dose)	Exposure duration	Effects (offspring)	References
Reproductive system	Pregnant rats	Gavage (50 μg/kg bw/day)	GD 6–PND 21	Reduction of semen quality	[4]
Reproductive system	Medaka (Oryzias latipes)	Water tank (200 ng/ml)	Lifelong, development, neurogenesis, sex differentiation	Transgenerational effects	[71]
Reproductive system	Pregnant rats	Drinking water (3 μg/kg bw/day [estimated average dose of exposure])	GD 0–PND 21	Increase LH, estradiol levels in serumAbnormal ovary histology	[5]
Reproductive system	Pregnant rats	Gavage (2.5, 25, 260, 2700 ug/kg bw/day)	GD 6–GD 21 (Dam gavage)/ PND 0–PND 21 (Pup gavage)	Alters estrogen receptor expression	[7]
Pituitary system/Brain	Pregnant rats	Gavage (2.5, 25, 2500 μg/kg bw/day)	GD 6–GD 21 (Dam gavage)/ PND 0–PND 21 (Pup gavage)	Effects on anxiety or exploratory activity No consistent effects	[12]
Pituitary system/Brain	Pregnant rats	Oral (440,400 μg/kg bw/day)	GD 6–PND 21	Alters NCS proliferation and differentiation	[11]
Pituitary system/Brain	Pregnant rats	Oral (40 μg/kg bw/day)	GD 0–PND 21	Cause anxiety like alteration	[13]
Pituitary system/Brain	Pregnant rats	SC injection (10 μg/kg bw/day)	GD 12–PND 21	Disruption in dopamine- and serotonin-related genes	[14]
Pituitary system/Brain	Pregnant rats	Oral (5 μg/kg bw/day)	GD 1–PND 100	Adverse development and behavior effects on F1 and F2	[17]
Reproduction disorders	Pregnant rats	Drinking water (3 μg/kg bw/day [estimated average dose of exposure])	GD 0–PND 21	Increase FSH, LH levels in serum Abnormal testis histology	[6]
Pituitary system/Brain	Pregnant rats	Diet (40 μg/kg bw/day)	GD 0–PND 21	Abnormal adrenal histology Alters the basal and stress induced activity	[15]
Pituitary system/Brain	Pregnant rats	Drinking water (0.1 mg/L BPA)	PND 0–PND 21	Alters the ERα signaling and behavioral deficit	[16]
Pituitary system/Brain	Pregnant rats	Gavage (10, 100, 1000, 10,000 μg/kg bw/day)	GD 10–PND 10	Alters brain development	[18]

Classification	Animal model	Administration (dose)	Exposure duration	Effects (offspring)	References
Pituitary system/Brain	Pregnant rats	Gavage (5, 10 μg/kg bw/day)	GD 6–GD 21	Alters brain development	[19]
Pituitary system/Brain	Four week old mice (male and female)	Gavage (40, 400 μg/kg bw/day)	8 weeks	Sex difference of behaviors: locomotion, exploration, anxiety, learning-memory in adult	[20]
Immune system	Pregnant rats	Gavage (5 μg/kg bw/day)	GD 15–PND 21	Alters immune response	[8]
Immune system	Pregnant rats	Gavage (0.5, 5, 50, 500 μg/kg bw/day)	GD 6–PND 21	Induce allergic inflammation	[9]
Immune system	Pregnant mice	Gavage (50 μg/kg bw/day)	GD 6–PND 21	Affect immune response	[72]
Immune system	Pregnant mice	Drinking water (10 μg/ml)	GD −28 (One week before mating)–PND 22	increase the development risk of asthma	[10]
Metabolic system	Female mice (4-week-old)	Diet (50 μg/kg bw/day)	Before mating–7 weeks after birth	Alters metabolism	[21]
Metabolic system	Pregnant mice	Diet (Prenatal: 0.19, 3.49 μg/kg bw/day Postnatal: 0.36, 7.2 μg/kg bw/day)	GD 0–PND 21	Control food intake and energy expenditure	[22]
Metabolic system	Pregnant rats	Drinking water (0.01, 0.1, 1.0 C31 mg/L)	GD 11–PND 21	Increase the preference for sweet taste Sexual difference (female>male)	[23]
Metabolic system	Pregnant rats	Drinking water (1 mg/L BPA (estimated 70 μg/kg bw/day))	GD 6–PND 21	Increase adipogenesis: gene expression	[24]

Table 1. Low-dose studies of BPA in early life stage.

3.2. Mixed exposure

Traditional risk assessment approaches are focused on the single chemical. Individual NOAEL does not reveal about the possible risk for the multiple exposure of EDs. Simultaneous exposure to multiple endocrine disruptors (mixed exposure) can generate combination effects even lower than their NOAEL [73, 74].

The crucial definitions for assessment of mixture exposure are classified as synergisms, antagonisms, or additivity: synergism means that the observed effects are stronger than expected; likewise, if they are weaker than expectations, there is antagonism. The combination effects are similar to the effect of individual agents are called additivism [75].

Combined effects have been reported when treated with mixture of BPA and other EDs simultaneously. *In vitro* studies, synergistic/additive effects are showed in case of simultaneous exposure of two or more chemicals [76, 77]. Perinatal exposure to low dose of BPA and paraben showed the additive effects on the downregulated semen quality in adult male offspring compared to individual exposure [4]. Mixture of BPA and other plastic-derived chemicals, despite of higher dose than environmental relevant levels, promoted epigenetic transgenerational inheritance of adult onset disease including obesity, testis, and ovary disease [78].

4. Conclusion

BPA in daily life are considered safe; however, low-dose effects are observed in experimental studies. Early life exposure to low-dose BPA may increase the risk of developing adult onset of disease, and the biological changes can transmit to the third or fourth generation. Therefore, EFSA propose the tolerable daily intake levels of BPA from 50 to 4-ug/kg bw/day. Low-dose effects of BPA are ongoing controversy because of the inconsistent results. Epidemiologic evidences such as nested case control studies are needed to provide the human health effects caused by exposure to low dose of BPA.

Author details

Yeon-Pyo Hong[1]* and Yun-Jung Yang[2]

*Address all correspondence to: hyp026@cau.ac.kr

1 Department of Preventive Medicine, College of Medicine, Chung-Ang University, Seoul, South Korea

2 Institute for Integrative Medicine, International St. Mary's Hospital, Catholic Kwandong University, Gangneung, South Korea

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