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Research review paper

Bisphenol A (BPA) and cell signaling pathways

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ABSTRACT

Bisphenol A (BPA; 4,4′-isopropylidenediphenol) is an endocrine disruptor that is used as a material for the production of phenol resins, polyacrylates, polyesters, epoxy resins, and polycarbonate plastics. Endocrine-disruptive or toxic effects of BPA on living organisms through a number of cell signaling pathways have been reported. BPA induces carcinogenesis, reproductive toxicity, abnormal inflammatory or immune response, and developmental disorders of brain or nervous system through various cell signaling pathways. This review considers the literature concerning BPA and its association with cancer-related cell signaling pathways, reproductive toxicity-related cell signaling pathways, inflammatory or immune response-related cell signaling pathways, and brain and nervous system-related cell signaling pathways.

1. Introduction

Bisphenol A (BPA; 4,4′-isopropylidenediphenol; CAS registry no. 80-05-7) is an organic compound composed of two phenol rings connected by a methyl bridge, with two methyl functional groups attached to the bridge (Fig. 1a). BPA is used as a material for the production of phenol resins, polyacrylates and polyesters, and principally for the production of epoxy resins and polycarbonate plastics (Kang et al., 2006b; Staples et al., 1998).

BPA is an endocrine disruptor. In some cases, its derivatives show higher toxicity or estrogenic potency than BPA itself. The estrogenic activity of a chlorinated derivative, 3,3′-dichlorobisphenol A (3,3′-diClBPA) (Fig. 1a), is higher than that of BPA (Tabata et al., 2004; Takemura et al., 2005). Tetrabromobisphenol A (TBBPA) (Fig. 1b) and 3,3′,5,5′-tetrachlorobisphenol A (3,3′,5,5′-tetraClBPA) (Fig. 1a) are more toxic than BPA (Kang et al., 2007; McCormick et al., 2010; Nakagawa et al., 2007).

BPA is detected in the water, air, and soil. For example, BPA is discharged into aquatic environments from the migration of BPA-based products into rivers and marine waters, and in the effluent from wastewater treatment plants and landfill sites (Kang et al., 2007). The environment can be one source of human BPA exposure, but the primary route of human exposure is foods (Kang et al., 2006b). Among foods, relatively high levels of BPA are detected in canned foods and its maximum concentration is 842 ng/g (Cao et al., 2010; Chen et al., 2016; Kang et al., 2006b; Noonan et al., 2011; Sajiki et al., 2007; Vandenberg et al., 2007a). After ingestion, BPA is rapidly metabolized to several inactive metabolites, such as BPA-glucuronide and BPA-sulfate. Free BPA is excreted mainly in feces (56–82%) and its metabolites are in urine (13–28%) (Kang et al., 2006a,b; Vandenberg et al., 2007a). In spite of rapid metabolism, free BPA is observed in the urine of adults and children (non-creatinine-adjusted concentration; < 0.1–822 ng/ml) (Calafat et al., 2008; Covaci et al., 2015; Zhang et al., 2011), as well as in the serum of pregnant women (< 0.1–154 ng/ml) (Schönfelder et al., 2002; Teeguarden et al., 2016; Unal et al., 2012), umbilical cord serum (< 0.05–52 ng/ml) (Gerona et al., 2013; Schönfelder et al., 2002; Unal et al., 2012), and breast milk (< 0.04–11 ng/ml) (Cao et al., 2015; Hines et al., 2015; Zimmers et al., 2014). In particular, the existence of free BPA in maternal and fetal serum and breast milk may result in long-term exposure to BPA during the fetal and neonatal period, and long-term harmful effects on the fetus and neonate.

The estimated daily intake of BPA by humans ranges from < 1 to 5 μg/kg body weight (BW)/day (Chen et al., 2016; Kang et al., 2006b; Thomson et al., 2003; Vandenberg et al., 2007a). It is very difficult to precisely estimate whether these levels of BPA can cause endocrine-disruptive or toxic effects in humans. However, several studies have reported adverse endocrine disruptive or toxic effects of BPA in animal models in the range of < 1 μg/kg BW/day (for review see refs. Vandenberg et al., 2012, 2013). For example, BPA exposure at doses as low as 0.025–0.25 μg/kg BW/day caused adverse effects, such as decreased daily sperm production and fertility in males exposed to 0.2 μg/kg BW/day (vom Saal et al., 1998; Chitra et al., 2003), altered development of mammary glands in female offspring (Muñoz-de-Toro et al., 2005) and fetuses (Vandenberg et al., 2007b) prenatally exposed to

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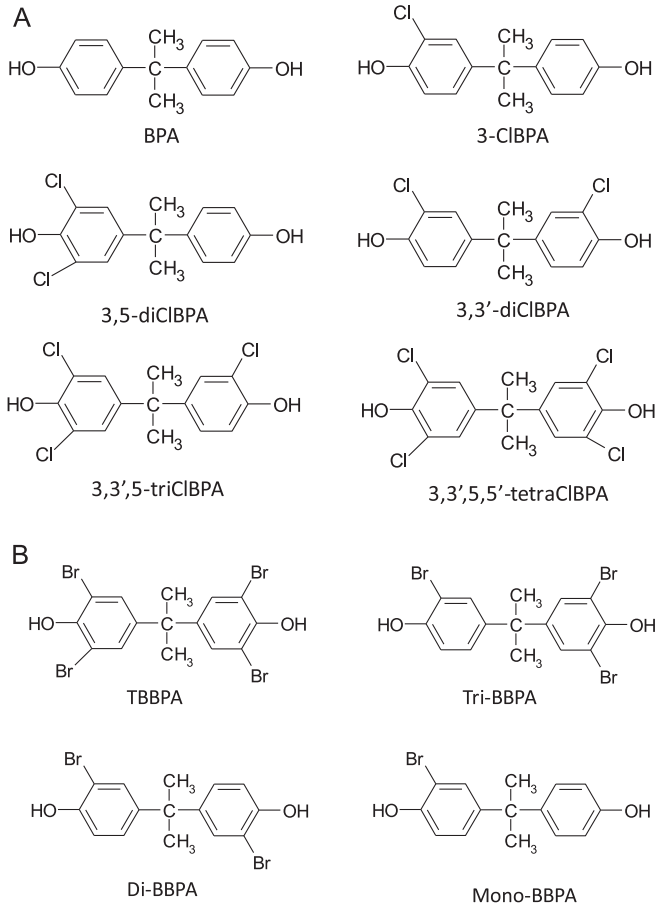

Fig. 1. (A) Chemical structure of BPA and its chlorinated derivatives produced by the reaction between BPA and free chlorine. (B) Chemical structure of brominated BPA analogs, tetrabromobisphenol A (TBBPA), tri-BBPA, di-BBPA, and mono-BPA. Fig. 1 was obtained from a previous study (Kang et al., 2007).

0.025–0.25 μg/kg BW/day, and disrupted global metabolism in male offspring prenatally exposed to 0.025–0.25 μg/kg BW/day (Cabaton et al., 2013).

Several cell signaling pathways are involved in endocrine-disruptive or toxic effects of BPA. BPA affects carcinogenesis, reproductive toxicity, inflammatory or immune response, and the brain and nervous system through various cell signaling pathways.

This review considers the literature concerning BPA and cancer-related cell signaling pathways, BPA and reproductive toxicity-relative cell signaling pathways, BPA and inflammatory or immune response-related cell signaling pathways, and BPA and brain and nervous system-related cell signaling pathways.

2. BPA and cancer-related cell signaling pathways

BPA is involved in the regulation of cancer cell growth, survival, proliferation, migration, invasion, and apoptosis, and anticancer drug resistance through several signaling pathways (Fig. 2). These regulations are activated by the binding of BPA to nuclear and membrane receptors, or by BPA-mediated stimulation of these receptors. These receptors include estrogen receptor α/β (ERα/β) (Dong et al., 2011; Hwang et al., 2013b; Kang et al., 2013; Park et al., 2009), androgen receptor (AR) (Wetherill et al., 2005), G protein-coupled estrogen receptor (GPER; also known as G protein-coupled receptor 30, GPR30) (Dong et al., 2011; Pupo et al., 2012), insulin-like growth factor-1 receptor (IGF-1R) (Hwang et al., 2013b; Kang et al., 2013), and estrogen-related receptor gamma (ERRγ) (Zhang et al., 2014a).

AR mutations in prostate cancer are associated with increased cancer progression and hormone therapy failure (Brooke and Bevan, 2009; Tan et al., 2015). BPA can activate functional mutant AR alleles, such as T877A, T877S, V715M, L701H, and K580R (Wetherill et al., 2005). BPA induces inappropriate AR-T877A activation and mitogenesis in prostate cancer cells (Lee et al., 2003; Wetherill et al., 2002). Activation of AR-T877A by BPA exposure (1 nM) can androgen-independently stimulate the proliferation of the androgen-dependent prostate cancer cell line LNCaP in the absence of androgen [5α-dihydrotestosterone (DHT)] (Hess-Wilson et al., 2007; Lee et al., 2003; Wetherill et al., 2002, 2005, 2006), but synergistically increases cell proliferation in the presence of DHT (1 nM) (Wetherill et al., 2005). However, high concentrations of BPA (10 μM) inhibited the proliferation of AR-positive/androgen-dependent prostate cancer cells, LNCaP (AR-T877A) and LAPC-4 (wild-type AR), but failed in AR-positive/androgen-independent 22Rv-1 cells (AR-H874Y) (Wetherill et al., 2005). On the other hand, BPA treatment (1 μM) enhances DHT-mediated AR-H874Y transactivation in 22Rv-1 cells (Wetherill et al., 2005).

Furthermore, BPA acts as an agonist for ERβ and has dual actions as an agonist and antagonist for ERα (Hiroi et al., 1999; Kurosawa et al., 2002). In cancer, BPA-mediated ERα activation is involved in cancer cell growth, survival, proliferation, migration, invasion, and apoptosis, and anticancer drug resistance. However, ERβ inhibits the function of ERα (Hayashi et al., 2003; Paruthiyil et al., 2004; Shaaban et al., 2003). For example, introducing ERβ to ERα positive breast cancer cells reduces cancer cell proliferation and cancer formation in a mouse xenograft model by inducing a G_2 cell cycle arrest (Paruthiyil et al., 2004). Furthermore, ERβ expression and the ERβ/ERα ratio decrease in the following order: normal breast lobules > usual ductal hyperplasia > ductal carcinoma *in situ* > invasive cancer (Shaaban et al., 2003). BPA exposure induces ERα expression in cancer cells, whereas ERβ expression is attenuated by BPA (Bolli et al., 2010; Dairkee et al., 2013; Hess-Wilson et al., 2007).

2.1. BPA and cancer cell growth and proliferation

BPA can stimulate growth and proliferation of cancer cells. Addition of BPA to ER-positive ovarian and breast cancer cells induces the activation of mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MARK/ERK1/2) (Dong et al., 2011; Park et al., 2009; Ptak and Gregoraszczuk, 2012; Song et al., 2015) and phosphoinositide 3-kinase/Akt (also known as protein kinase B)/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathways (Dairkee et al., 2013; Goodson et al., 2011; Hwang et al., 2013b; Kang et al., 2013; Ptak and Gregoraszczuk, 2012), which have key roles in cell growth and proliferation. Among the MAPK proteins, BPA-mediated activation of p38 MAPK in cancer cells has been reported in some studies (Park et al., 2009; Zhang et al., 2015). However, other studies suggested no or reduced BPA-mediated activation of p38 MAPK and/or Jun N-terminal kinase (JNK) (Bulzomi et al., 2012; Song et al., 2015). Furthermore, in spite of the use of the same BPA dose (10 nM) and ER-negative SkBr3 cell line, two research groups have reported different results on BPA-mediated activation of p38 MAPK. One group found increased p38 MAPK phosphorylation (Zhang et al., 2015), whereas the other reported no effect on p38 MAPK phosphorylation (Song et al., 2015).

Stimulation of cell cycle proteins including p53, cyclins, cyclin-dependent kinases (CDKs), and proliferating cell nuclear antigen (PCNA) by BPA exposure is associated with enhanced growth and proliferation of cancer cells through ER signaling (Dairkee et al., 2013; Hwang et al., 2013b; Kang et al., 2013; Lee et al., 2012a; Mlynarcikova et al., 2013; Song et al., 2015). For example, BPA notably increases proliferation-associated cell cycle proteins, such as cyclin A, cyclin D3, CDK2, CDK6, and PCNA, but decreases negative regulators, such as p53 and p21 (also designated WAF1/Cip1), in non-cancerous human high-risk donor breast epithelial cells (HRBECs) and T47D ER-positive breast cancer cells (Dairkee et al., 2013).

Furthermore, BPA treatment promotes the expression of ERα and