Hormones and Behavior 102 (2018) 129–138

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Bisphenol-A inhibits improvement of testosterone in anxiety- and depression-like behaviors in gonadectomied male mice

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ARTICLE INFO

Keywords:
Bisphenol-A
Anxiety
Depression
Androgen
GABA(A)a2 receptor

ABSTRACT

Bisphenol-A (BPA) is a well-known environmental endocrine disruptor. Developmental exposure to BPA affected a variety of behaviors in multiple model organisms. Our recent study found that exposure to BPA during adulthood aggravated anxiety- and depression-like states in male mice but not in females. In this study, 11-w-old gonadectomied (GDX) male mice daily received subcutaneous injections of testosterone propionate (TP, 0.5 mg/kg), TP and BPA (0.04, 0.4, or 4 mg/kg), or vehicle for 45 days. BPA (0.4 or 4 mg/kg) did not affect the elevated plus maze task of GDX mice but shortened the time on open arms and decreased the frequency of head dips of sham and TP-GDX mice. In forced swim task, BPA prolonged the total time of immobility of both sham and TP-GDX mice but not GDX mice. In addition, BPA reduced the levels of T in the serum and the brain of sham and TP-GDX mice. Western blot analysis further showed that BPA reduced the levels of androgen receptor (AR) and GABA(A)α2 receptor of the hippocampus and the amygdala in sham and inhibited the rescue of TP in these proteins levels of GDX mice. Meanwhile, BPA decreased the level of phospho-ERK1/2 in these two brain regions of sham and TP-GDX mice. These results suggest that long-term exposure to BPA inhibited TP-improved anxiety- and depression-like behaviors in GDX male mice. The down-regulated levels of GABA(A)α2 receptor and AR and an inhibited activity of ERK1/2 pathway in the hippocampus and the amygdala may be involved in these process.

1. Introduction

Bisphenol-A (BPA), widely used in polycarbonate plastics, epoxy resins and some dental sealants, is a well-known environmental endocrine disruptor (EED). BPA has a low affinity for estrogen receptors (ERs) and exerts weak estrogenic properties by competing with the endogenous estrogens at receptor level (Erler and Nova, 2010; Vandenberg et al., 2012). Fetal and/or neonatal exposure to BPA influenced sexual differentiation of brain and behavior during early development and permanently impacted the behaviors of adult animals, including memory and emotion (Fujimoto et al., 2006, 2013; Gonalves et al., 2010; Jones and Watson, 2012; Wolstenholme et al., 2011; Xu et al., 2012). A growing body of evidence indicated that exposure to low levels of BPA has adverse effects on anxiety- and depression-like behaviors though the outcomes were incongruent (Beronius et al., 2013; Gioiosa et al., 2013). Early development and adolescent exposure to BPA increased anxiety- and depression-like behaviors of rodents independent of sex (Jašarevic et al., 2011; Weinstein et al., 2013; Xu et al., 2012). Male and female mice from dams ingesting BPA did not display sex differences of anxiety state in elevated plus maze (EPM) but controls did (Gioiosa et al., 2007). Other researchers reported that BPA-induced anxiogenic effects were mainly detected in adolescent or adult females but not males (Farabollini et al., 1999; Poimenova et al., 2010). Maternal BPA diet induced anxiety-like behavior in female juvenile (Luo et al., 2014). Females exposed from gestation to weaning had reduced time spent in the open arms of EPM in C57/BL-6 mice (Ryan and Vandenbergh, 2006). More data showed the anxiogenic effects of BPA in male rodents (Cox et al., 2010; Fujimoto et al., 2013; Jašarević et al., 2013; Kumar and Thakur, 2017; Luo et al., 2013, 2017; Matsuda et al., 2012; Patisaul and Bateman, 2008). Epidemiological investigations also showed an association between high maternal urinary BPA during gestation and anxiety and depression in childhood (Mustieles et al., 2015). Gestational exposure to BPA increased hyperactivity, anxiety, and depression in girls but decreased hyperactivity among boys

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https://doi.org/10.1016/j.yhbeh.2018.05.012
Received 4 January 2018; Received in revised form 20 April 2018; Accepted 15 May 2018
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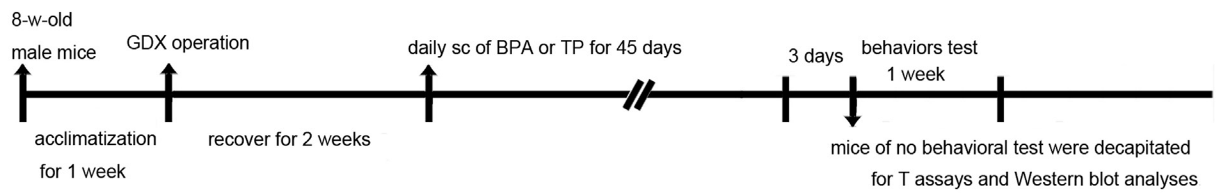

Fig. 1. The overall experimental timeline.

(Braun et al., 2011). Prenatal BPA exposure is associated with more symptoms of anxiety and depression in boys but not in girls at age 3–12 years, and there was substantial co-occurrence of anxiety and depressive symptoms in these samples (Evans et al., 2014; Harley et al., 2013; Perera et al., 2012, 2016). Our recent study found that long-term exposure to BPA during adolescence and adulthood sex-specifically affected anxiety- and depression-like behaviors, with aggravating anxiety- and depression-like states in male mice but not or anxiolytic in female mice (Xu et al., 2011, 2015).

Given the well known weak estrogen activity, the earlier studies of BPA focused on its estrogenic disruption on the development, function, and morphology of the brain (MacLusky et al., 2005; Xu et al., 2010a,b). Recent evidence from ligand competition assays revealed that BPA at 50 nM inhibited dihydrotestosterone (DHT), a 5α-reduced metabolite of testosterone (T), binding to androgen receptor (AR) by 40% (Lee et al., 2003) and antagonized DHT-induced transcriptional activity (Xu et al., 2005). Furthermore, the serum level of T was reduced in male BPA-rats (Chen et al., 2014; Nakamura et al., 2010; Xu et al., 2015). Because androgens are just as critical in the cognitive function and emotion in males as estrogens are in females (Domonkos et al., 2017; Hajszan et al., 2007), we speculated that anti-androgenic effect of BPA may be involved in the influence of BPA on emotional behavior of males. In this study, using the castrated male mice, we investigated whether or not BPA disrupted the modulation of T in anxiety- and depression-like behaviors of male mice.

Gamma-amino-butylic acid neurotransmission (GABAergic), a main inhibitory neurotransmitter system in the brain, participates in anxiety and depression behavior. It was found that α2-containing GABA(A) (GABA(A)α2) receptor, highly expressed in limbic regions such as the hippocampus and the amygdale, is involved in the pathophysiology of anxiety and depression disorders (Mohler, 2012). The anxiolytic effect of benzodiazepine drugs is mediated by GABA(A)α2 receptors (Löw et al., 2000). Depressive-like state in the forced swim and the tail suspension test was aggravated in GABA(A)α2 receptor-knockout mice (Vollenweider et al., 2011). Picrotoxin and bicuculline, noncompetitive and competitive antagonists of GABA(A) receptors respectively, blocked the anxiolytic effects of T (Aikey et al., 2002), suggesting that anxiolytic effect of T was mediated by GABA(A) receptors. Our recent study found that BPA exposure inhibited the protein level of GABA(A)α2 receptor in hippocampus of males but not of females (Xu et al., 2015).

In addition, the activity of the extracellular signal-regulated kinases (ERKs), one of the most important mitogen-activated protein kinases (MAPKs) cascades, is a critical regulator of emotional responses (Sweatt, 2001). It was found that brain-derived neurotrophic factor ameliorated depressive-like behavior in learned helplessness and the forced swim test via activating ERKs/MAPK pathway (Shirayama et al., 2002). Antidepressant fluoxetine increases the activity of ERKs-CREB (cAMP-response element binding protein) signal system and alleviates the depressive-like behavior in rats exposed to chronic forced swim stress (Qi et al., 2008). These data suggest that ERK1/2 are involved in the molecular pathophysiology of depression. Therefore, the present study further examined the levels of GABA(A)2α receptor and p-ERK1/2 in the hippocampus and the amygdala to explore the molecular mechanism underlying the anti-androgenic effect of BPA on anxiety- and depression-like behaviors of male mice.

2. Materials and methods

2.1. Animals

Eight-week-old male ICR mice were from the Experimental Animal Center, Zhejiang Academy of Medical Science, and kept under standard laboratory conditions in a 12-h light, 12-h dark cycle, with free access to food and water. To minimize the background exposure to BPA, mice were housed in white poly-propylene cages with water provided in glass bottles and an autoclaved conventional diet (P1200, Slaccas, Shanghai, China) containing 9.7% wet, 4.5% fat, 21% protein, 52.5% nitrogen free extract, 4% coarse fibre, 1.2% calcium, and 0.75% total phosphorus (total 3.45 kJ/g) ad libitum. All experiments in current study were conducted in according to the Care and Use Standard of the Laboratory Animal (China Ministry of Health publication). The mice were divided into 3 groups with 96 animals each group: sham, GDX, and GDX plus testosterone propionate (GDX-TP). Each group was divided into four treatments: BPA (0.04, 0.4, 4 mg/kg/d) or vehicle. Twenty-four animals each treatment were kept in 3 cages: 10 mice were kept in a cage for behavior testing, 8 mice in a cage were for testosterone (T) assays, and 6 mice in a cage for Western blotting analyses.

2.2. Surgery

After acclimatization for 1 week, sham or gonadectomy (GDX) operation was performed under deep anesthesia with a ketamine-xylazine mixture (containing 25 mg/mL ketamine, 1.2 mg/mL xylazine, and 0.03 mg/mL acepromazine dissolved in saline; 3 mL/kg, im) (Fig. 1). A 0.5 cm ventral incision was then made in the scrotum and the skin was cut to expose tunica. The tunica was pierced, and gap was stretched with blunt forceps. The testes were exposed by applying mild pressure to the pelvic region. The spermatic artery was clamped and cauterized, and the testes then were removed. Sham-operated animals were exposed to the entire procedure noted above except removing the testes (with the aim of measuring possible stress induced by surgery). Later, all animals were allowed to recover for two weeks.

2.3. Drug treatments

Compared with approximately 2 ng/mL unconjugated serum BPA reported in multiple human studies, the average unconjugated serum BPA concentration of 0.5 ng/mL in both monkeys and mice after a 0.4 mg/kg oral dose demonstrates that total daily human exposure is via multiple routes including oral or dermal exposures, inhalation exposure to BPA on dust, iatrogenic exposures from medical devices, and also sublingual absorption from food while in the mouth (Taylor et al., 2011). The serum concentration of BPA after continuous sc of BPA was similar to values reported in human biomonitoring studies suggests sc is an appropriate human exposure model (vom Saal et al., 2014).

Two weeks after surgery, the mice were treated with daily subcutaneous injections (sc) of BPA (0.04, 0.4, 4 mg/kg/d) or the sesame oil vehicle (50 μL/d) for 45 days (n = 24 animals each treatment), respectively. GDX-TP group treated with daily sc TP (0.5 mg/kg/d) and BPA (0.04, 0.4, 4 mg/kg/d) or the sesame oil vehicle (50 μL/d) for 45 days (n = 24 animals each treatment), respectively. These dose of BPA converted to humans equivalent dose based on the body surface

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