Journal of Steroid Biochemistry & Molecular Biology 127 (2011) 27–34

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

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

Bisphenol A: An endocrine disruptor with widespread exposure and multiple effects☆

Beverly S. Rubin*

Department of Anatomy and Cellular Biology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, United States

ARTICLE INFO

Article history:
Received 15 December 2010
Received in revised form 29 April 2011
Accepted 5 May 2011

Keywords:
BPA
Endocrine disruptors
Xenoestrogen developmental exposure
Perinatal exposure
Fetal basis of adult disease

ABSTRACT

Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide. This compound is a building block of polycarbonate plastics often used for food and beverage storage, and BPA is also a component of epoxy resins that are used to line food and beverage containers. Studies have shown that BPA can leach from these and other products in contact with food and drink, and as a result, routine ingestion of BPA is presumed. This compound is also found in an enormous number of other products that we come into contact with daily, and therefore it is not surprising that it has been detected in the majority of individuals examined. BPA is a known endocrine disruptor. Although initially considered to be a weak environmental estrogen, more recent studies have demonstrated that BPA may be similar in potency to estradiol in stimulating some cellular responses. Moreover, emerging evidence suggests that BPA may influence multiple endocrine-related pathways. Studies in rodents have identified adverse effects of BPA at levels at or below the current acceptable daily intake level for this compound. The various reported adverse effects of BPA are reviewed, and potential mechanisms of BPA action are discussed. Much more investigation is needed to understand the potential adverse health effects of BPA exposure in humans and to understand the multiple pathways through which it may act. Although many questions remain to be answered, it is becoming increasingly apparent that exposure to BPA is ubiquitous and that the effects of this endocrine disruptor are complex and wide-ranging.

1. Bisphenol A (BPA) is ubiquitous in our environment

BPA is one of the highest volume chemicals produced worldwide. Current estimates indicate that more than 8 billion pounds of BPA are produced annually and approximately 100 tons may be released into the atmosphere each year (for review see [1]). BPA is used in the manufacture of plastics and epoxy resins that are pervasive in our environment and in our daily lives.

BPA is a known endocrine disrupter. It was first synthesized by A.P. Dianin in 1891 and was investigated for potential commercial use in the 1930s during a search for synthetic estrogens (see [2] for review). Although BPA's estrogenic activity was confirmed, tests of a structurally related synthetic compound, diethylstilbestrol (DES), indicated that DES was a far more potent estrogen than BPA in a classical estrogenicity assay of vaginal cornification [3]. The use of BPA as a synthetic estrogen was therefore abandoned in favor of DES which was administered to pregnant women from the late 1940s through 1971 to prevent multiple pregnancy-related problems including miscarriage and premature births [4]. This treatment was stopped after links to vaginal and cervical cancers were identified in the exposed daughters. The studies of the children of those DES treated women as well as mouse models of early DES exposure have provided essential data and important insights regarding the fetal basis of adult disease [4–6]. Much of what was learned about windows of vulnerability and early action of estrogenic compounds by studying DES has proven relevant to the study of BPA. A comparison of the chemical structures of BPA, DES and estradiol are shown in Fig. 1. It should be noted that although DES and BPA have been shown to have similar actions in some parameters examined (e.g. [7,8]), their actions differ in others (e.g. [9,10]).

In the 1940s and 50s, a use for BPA was identified in the plastics industry. BPA is a building block of polycarbonate plastics often used in food and beverage containers, including baby bottles, and it is also used as an additive in other plastics. BPA is also a component of epoxy resins used for some dental materials, including dental sealants, and for the lining of food and beverage containers as well as numerous other products [11]. Additional uses for BPA include items that we come in contact with daily at home and in the workplace including the coating of CDs, DVDs, electrical and electronic equipment, automobiles, sports safety equipment, recycled

☆ Article submitted for the special issue on Endocrine disruptors.

* Tel.: +1 617 636 6694; fax: +1 617 636 6536.
E-mail address: Beverly.rubin@tufts.edu

0960-0760/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.jsbmb.2011.05.002

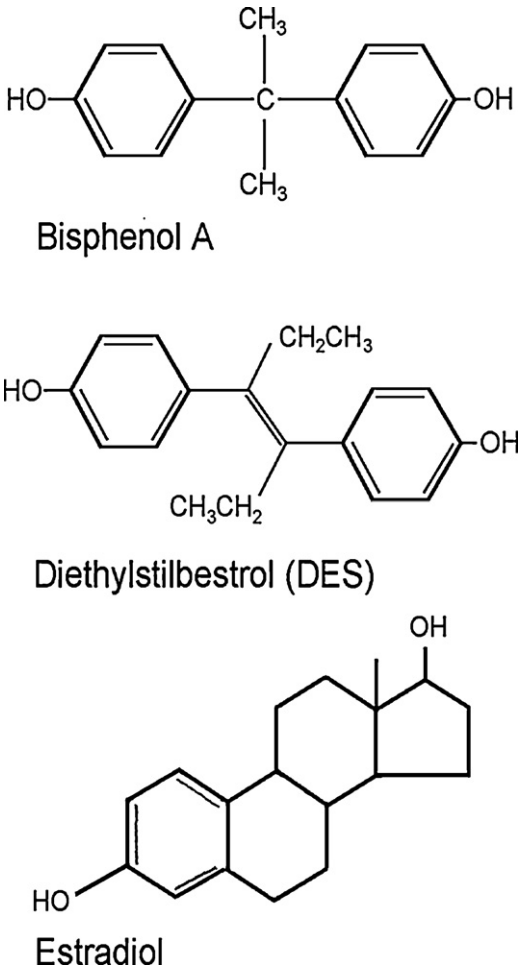

Fig. 1. Chemical structures of BPA, DES and estradiol reveal the structural similarity of BPA and DES.

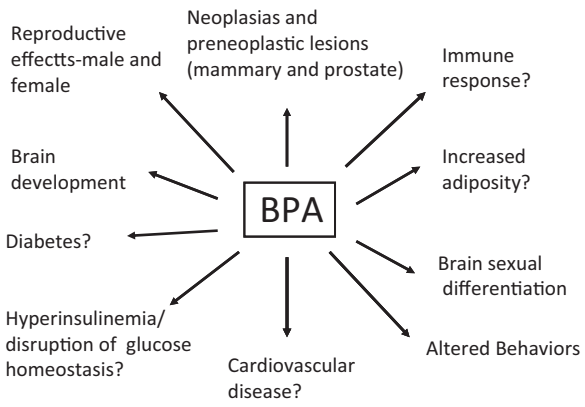

Fig. 2. Some of the proposed putative effects of BPA exposure are depicted here. As shown, the potential outcomes suggested to be influenced by BPA exposure are numerous, wide-ranging and complex. Some of these proposed relationships are still in the very in early stages of exploration.

paper and carbonless paper often used in register receipts. Polymerized, BPA molecules are linked by ester bonds that are subject to hydrolysis when exposed to high temperatures or to acidic or basic substances [12]. Studies have shown that BPA can leach from polycarbonate plastics and from epoxy resins and other products in contact with food and drink, and as a result, routine ingestion of BPA is presumed [13].

Given the prevalence of BPA in our environment, it is not surprising that measurable levels have been detected in the majority of individuals examined to date. Recent measurements by the Centers for Disease Control (CDC) revealed detectable levels of BPA in the urine samples of 92.6% of more than 2500 participants of the cross sectional NHANES (National Health and Nutrition Examination Survey) study [14]. The adjusted mean BPA levels reported were 4.5 ng/ml in children (6–11 years of age), 3.0 ng/ml in adolescents (12–19 years of age) and 2.5 ng/ml in adults (over 20 years of age). These exposure levels are in the range of those reported in other studies (for review see [1]). Children in the NHANES data set had the highest level of exposure, and statistical analysis revealed that children had higher BPA levels than adolescents ($p < 0.001$) who had higher levels than adults ($p = 0.003$). This is an important observation as data from animal studies demonstrate increased vulnerability to BPA exposure during development (reviewed in [15]). In this regard, BPA has been detected in pregnant women, human amniotic fluid, neonatal blood, placenta, cord blood and human breast milk (reviewed in [1,13]). Unfortunately, the NHANES data set did not include a cohort of children from birth through 5 years of age as very young children are predicted to have the highest BPA exposure level by body weight as estimated by the US National Toxicology Program [11]. Recent measurements of BPA in babies in the neonatal intensive care unit revealed levels that were an order of magnitude higher than the levels measured in the general US population (mean levels = 30.3 ng/ml), most probably due to the use of specific medical devices or products [16]. These data raise concerns about increased BPA exposure at a very sensitive time in development in these vulnerable infants, and they indicate a need for further detailed study of this population in childhood and beyond.

Relative to the number of studies that have measured BPA in urine, fewer have measured BPA in blood, and sample sizes in these studies are small. For many of these studies, the internal concentrations of unconjugated BPA were approximately 1 ng BPA/ml (for review see [1]). However, some controversy surrounds BPA measurements in blood stemming from concerns about assay sensitivity and the potential for cross contamination of samples. Additional studies will be required for detailed assessment of the range of circulating unconjugated BPA levels in the general population, and those studies could be greatly facilitated by the development of more sensitive methods of measurement.

Ingestion is considered the major route of BPA exposure in humans, and following ingestion, BPA is thought to be rapidly metabolized and excreted from the body in urine (reviewed in [1]). However, a recent reanalysis of BPA levels in adult subjects of the NHANES data set was performed to take into account the hours of fasting prior to sample collection. That analysis failed to demonstrate an inverse relationship between fasting times and BPA levels [17]. Therefore the data are not consistent with the current idea that BPA is rapidly cleared after ingestion and that ingestion is the major route of human exposure. Rather they suggest that (1) the half-life of BPA is longer than expected, and/or (2) BPA is stored in the body [18], and/or (3) ingestion is not the only route of exposure for BPA [17]. It is possible that humans may gain exposure to BPA through the air and by absorption through the skin. These routes of exposure have not received much attention to date; however, there are data to suggest that absorption of BPA through the skin is possible [19,20]. It is interesting to note that a recent study of BPA levels in the urine of pregnant women found the highest levels in cashiers [21]. This population would be expected to have the greatest exposure to carbonless receipts, a known source of BPA that could potentially be absorbed through the skin. Additional studies have identified BPA in dust, groundwater, and marine environments (reviewed in [13]), and recent measurements of BPA in the atmosphere have revealed significant levels in many regions tested [22]. Some of those high levels of BPA, particularly in south-

ern Asia, are considered to be related to the burning of plastics for waste disposal [22]. A thorough understanding of levels of human exposure requires that all potential sources of BPA be identified, and that the dose of BPA from food and beverages as well as from additional sources be assessed.

2. How much BPA is safe?

The lowest observed affect level (LOAEL) for BPA was established in a 2 year carcinogenesis study conducted in adult rodents exposed daily to high doses of BPA (reviewed in [2]). The established LOAEL (50 mg/kg body weight (BW)/day) was then divided by an uncertainty factor of 1000 in order to provide a safety margin below the LOAEL for the permitted daily exposure limits. Therefore, the first safety standard set by the EPA in 1988 and adapted by the FDA as a reference dose for BPA was calculated to be 50 μg/kg BW/day. This reference dose remains the current safety standard for BPA today despite new knowledge about BPA, including the numerous reports of non-monotonic dose response effects of BPA (reviewed in [23]), and the knowledge that low dose effects of BPA are not necessarily observed at high doses [12,24,25]. Moreover, the initial establishment of the acceptable human daily intake dose by studies in adult rodents did not take into account the knowledge that vulnerability to BPA exposure is dramatically increased during development relative to adulthood [23]. These two factors raise serious concerns about the method used to determine the safe dose for BPA exposure that has prevailed unchanged over the past 23 years.

3. The developing fetus and neonate are particularly vulnerable to BPA exposure

The effects of BPA vary with the dose and time of exposure. The prenatal and neonatal period represent the most vulnerable window of exposure (for review see [23]). Gestational, neonatal, and gestational and lactational exposure have all revealed effects of BPA in rodent models at doses below the established LOAEL (50 mg/kg BW/day). In addition, there are numerous examples of adverse effects of BPA at doses below, and in some cases far below the current acceptable human daily intake dose (50 μg BPA/kg BW). Some of the effects of developmental exposure to levels of BPA at or below the LOAEL or the human safe dose include the following: altered time of puberty [26,27]; altered estrous cycles [28,29]; prostate changes [30–32] including the development of neoplasias [30,33]; altered mammary gland development and evidence of intraductal hyperplasias and preneoplastic mammary gland lesions in adulthood [34–37]; changes in the uterus and ovary [7,38]; alterations in brain sexual dimorphisms [39–41]; additional changes in the brain [42] and in brain steroid receptor levels [10,43] and receptor transcripts [44]; changes in behavior including reports of hyperactivity [45,46]; increased aggressiveness [47]; altered sociosexual behavior [48]; altered cognitive and anxiolytic behaviors [49]; increased susceptibility to drugs of addiction [46,50]; altered body weight and body composition [26,28,51–54]; and altered glucose homeostasis [55]. Several recent reviews provide detailed summaries of findings from *in vivo* studies of BPA exposure [15,23,54,56] (Fig. 2).

4. What about effects of BPA exposure in adulthood?

Whereas the vulnerability of the fetus and neonate to the adverse effects of BPA has been established (for review see [15,23]), additional potential windows of vulnerability such as the peripubertal period have not been well studied. In some tissues, higher levels of BPA may be required in adults relative to the levels required during organogenesis and/or lactation to induce significant effects. For example, the levels of BPA required to induce a uterotrophic response (100 mg/kg BW) or an increase in uterine epithelial cell height (5 mg/kg BW) in ovariectomized female rodents were far greater than the doses capable of exerting lasting effects on the uterus when exposure occurred during gestation (0.025 μg or 0.250 μg BPA/kg BW/day to the pregnant dam) [38].

In contrast to the uterus, low levels of BPA exert effects on the adult pancreas [57]. A single exposure to 10 or 100 μg BPA/kg BW rapidly decreased glucose levels and increased plasma insulin levels in male mice. After 2 days of exposure pancreatic insulin content was increased, and after 4 days of treatment, the mice developed chronic hyperinsulinemia and altered glucose and insulin tolerance. Effects on glucose homeostasis were also observed in pregnant mouse dams exposed to similar doses of BPA on days 9–16 of gestation [55].

Effects of BPA on synaptogenesis have also been demonstrated in the brains of adult rats and nonhuman primates (reviewed in [58]). BPA was found to prevent the effects of estrogen and androgen on the induction of spine synapses in the hippocampus and prefrontal cortex. The reduction in the number of synapses observed in BPA-treated animals could have important implications for cognitive function and cognitive decline.

5. BPA exposure and human disease

In humans, increased levels of BPA in adults have been correlated with various diseases, health outcomes and medical conditions. To date, reported health complications associated with increased levels of BPA exposure include diabetes [59] which is consistent with the report that low levels of BPA inhibit adiponectin release from human adipose tissue [25], cardiovascular disease [59,60], and altered liver enzymes [59]. Also reported in women are correlations between increased BPA levels and recurrent miscarriages [61], and increased numbers of premature deliveries [62]. In women undergoing IVF, increased BPA levels are correlated with a decrease in peak estradiol levels and decreased oocyte retrieval numbers [63], and in postmenopausal women, increased BPA levels were associated with increased inflammation and oxidative stress [64]. Decreased semen quality and sperm DNA damage have been correlated with increased BPA levels in men [65,66]. The data from the above mentioned studies reveal associations between BPA levels and health issues in adults, but they cannot prove causality. They represent a first step in identifying potential human health effects of BPA and require further confirmation. Additional data that assesses associations between BPA levels in pregnant women, in cord blood, or in newborns and medical complications in childhood and later in life should be forthcoming from recently collected samples as well as samples currently being collected in human populations. Data from one recent study suggest that prenatal exposure to BPA (as assessed by measurements of maternal BPA levels) may be associated with increased aggression and hyperactivity at 2 years of age, primarily in females [67]. Prospective studies that correlate early exposure to BPA with various health outcomes in children as well as early markers or predictors of disease later in life are needed to fully understand the impact of BPA on human health.

6. Mechanisms of BPA action

6.1. BPA is a xenoestrogen

BPA was initially considered to be a weak environmental estrogen based on the relative binding affinity of BPA for the classical nuclear receptors ER alpha and ER beta which were estimated to be over 1000–10,000 fold lower than that of estradiol [68]. However,

more recent studies have demonstrated that BPA can stimulate some cellular responses at very low concentrations. In some cases, BPA is equivalent in potency to estradiol [8,24,25,69]. Some actions are attributed to BPA's ability to bind classical and non-classical membrane estrogen receptors [8,24,70] as well as the G-protein-coupled receptor 30 (GPR30) [71] and to act through non-genomic pathways [69,72,73]. Multiple cellular sites have been proposed as targets of BPA action [72]. In addition, it has been suggested that some metabolites of BPA may be more potent estrogens than the parent compound [74]. BPA has been shown to interact differently than estradiol with the ligand binding domain of the classical estrogen receptors [75], and differences have also been noted in the recruitment of transcriptional co-regulators [76] indicating that BPA is not merely an estrogen mimic.

When considering the effects of perinatal exposure to BPA, it is important to note that the fetal and neonatal liver produces high levels of alpha fetoprotein (AFP), the major estrogen binding plasma protein of the developing rodent. AFP is thought to protect tissues of the perinatal rodent from excessive exposure to estradiol [77]. In contrast to estradiol, BPA shows limited binding to serum proteins [78], and therefore, BPA may have increased access to estrogen sensitive tissues of the developing fetus or neonate. For this reason, BPA's actions during development may be greater than expected as BPA may act as an estrogen in tissues not normally exposed to estrogen at that time. This is particularly relevant to the brain. In rodents, steroidogenesis does not begin in the ovary until the second week of life whereas males have a testosterone surge, prior to and after birth, and that testosterone can be converted *in situ* to estradiol in the presence of aromatase. The conversion of testosterone to estrogen is an important mechanism for sexual differentiation of the rodent brain. We found that exposure of pregnant mice to very low levels of BPA (0.025 μg/kg BW/day and 0.25 μg/kg BW/day) resulted in masculinization of a brain region essential for cyclic gonadotropin release in their female offspring [40]. In addition, these female offspring showed masculinization of behavior in the open field. The significant sex differences observed in the control mice in these two parameters were obliterated in the BPA exposed offspring. These data suggest that BPA may have been acting as an estrogen in specific regions of the developing brain important for sexual differentiation.

It is interesting to note that in another study in which sex differences were attenuated or obliterated, early BPA exposure appeared to disrupt masculinization of the brain of male offspring [41]. It remains to be determined whether the acute high level of BPA exposure in these studies (neonatal pups were injected with approximately 100 mg BPA/kg BW/day for 2 days) may have interfered with the action of endogenous estrogens required for masculinization of the brain. Although BPA can and does act as an estrogen, particularly when administered under conditions of low endogenous estrogen levels, when administered in the presence of estradiol, BPA may act as an antiestrogen and interfere with the action of estradiol [25,69].

In addition to acting as an estrogen, early BPA exposure has been shown to alter estrogen sensitivity in a tissue specific manner long beyond the time of exposure. Perinatal BPA exposure altered the postnatal response to estradiol in the mammary gland [35,79]. In addition, perinatal BPA exposure altered ER alpha and ER beta mRNA levels in a tissue specific and sex specific manner [10,43].

6.2. Additional actions of BPA

6.2.1. BPA binds estrogen related receptor gamma

The most recently identified member of the estrogen-related receptor (ERR) family, ERRgamma, has been found to strongly bind BPA with high specificity and a binding affinity constant (K_D) of 5.5–5.7 nM [80,81]. The ERRs are nuclear receptors that do not directly bind estradiol. ERRgamma is present in the developing embryo and neonate, and therefore could be responsible for some of BPA's actions during development. ERRgamma is also highly expressed in the placenta and it has been suggested that it may promote accumulation of BPA in the placenta and facilitate exposure of the developing fetus to this compound [82]. A recent study has confirmed elevation of ERRgamma expression in several organs of fetuses and neonates of mothers exposed to 20 μg BPA/kg BW/day by oral gavage from gestational day 13 through gestational day 16 [9].

6.2.2. BPA may interfere with thyroid hormone pathways

Based on their studies of BPA and frog metamorphosis and the conservation of TH pathways, Heimeier and Shi have suggested that BPA may affect human embryogenesis and neonatal development through disruption or inhibition of thyroid hormone pathways [83]. BPA binds to thyroid hormone receptor and can act as an antagonist to inhibit transcriptional activity stimulated by thyroid hormone (triiodothyronine-T3) [84,85]. BPA displaced iodinated T3 from endogenous thyroid receptor (TR) with an inhibition constant of 200 μM, and Scatchard analysis revealed that BPA decreased the value for the association constant from 0.44 to 0.28×10^{-9} M [81]. The affinity of BPA for thyroid hormone receptor is lower than the affinity for the estrogen receptor suggesting that high levels of BPA would be required to antagonize thyroid hormone action; however, data from *in vitro* studies have demonstrated the ability of low levels of BPA to inhibit thyroid hormone receptor-mediated gene expression by enhancing recruitment of the co-repressor N-CoR to the thyroid hormone receptor [84]. Offspring born to rat mothers exposed via the diet to 1, 10, or 50 mg BPA/kg BW/day during gestation and lactation had increased circulating levels of thyroxine (T4) on postnatal day 15 and increased expression of a thyroid responsive gene in the brain. A loss of negative feedback via one thyroid hormone receptor isoform was hypothesized to be responsible for the increase in T4 levels [86]. Data from another *in vivo* study [87] demonstrated an elevation of thyroid hormone levels on PND 7 in male offspring of rat dams exposed to BPA in their drinking water (0.1 mg BPA/l) from gestational day 11. In any discussion of BPA and thyroid hormone action, it is important to note that the halogenated derivatives of BPA may be better competitors for the thyroid hormone receptor than BPA. Tetrabromobisphenol A and tetrachlorobisphenol A are commonly used as flame retardants for building materials, paints, textiles, electronic equipment and other items, and both compounds have been shown to inhibit binding of T3 to the thyroid hormone receptor [88]. Both agonist, and antagonist activities of halogenated BPA derivatives at the thyroid hormone receptor have been reported [88,89].

6.2.3. Can BPA act through the glucocorticoid receptor (GR)?

Data from a recent *in silico* study [90] indicate that BPA could bind to the human glucocorticoid receptor. Moreover, the mode of interaction and the binding energy of BPA were found to be similar to dexamethasone, and cortisol suggesting that BPA could be a GR agonist. In support of these predictions, a recent *in vitro* study demonstrated that BPA stimulated adipogenesis in 3T3-L1 cells by activation of the glucocorticoid receptor [91]. In addition, recent evidence suggests that early BPA exposure has sex dependent effects on corticosterone levels [92]. Adolescent female offspring of mothers exposed to BPA (40 μg/kg BW/day) during gestation and lactation showed increased baseline corticosterone levels with further increases following exposure to mild stress. Glucocorticoid receptor levels in the hippocampus were also affected. It is not yet known if these effects continue into adulthood. More work is needed to address the potential for early BPA exposure to permanently influence the hypothalamic–pituitary–adrenal axis.

6.2.4. Other endocrine related activities of BPA

Other endocrine related activities of BPA include potential action as an androgen receptor (AR) antagonist. Results of several *in vitro* studies have suggested that BPA may have antiandrogenic activity [93–96]. BPA also has been shown to bind the aryl hydrocarbon receptor (AhR) which is a ligand dependent transcription factor present in many tissues [96,97]. AhR can bind numerous chemicals and can indirectly affect metabolism of xenobiotics as well as steroid synthesis and metabolism, and cross talk is thought to exist between AhR and ER and AR as well as other nuclear receptors. BPA in the 10^{-5} M range elicited antagonist effects at the AhR whereas similar levels of BPA dimethacrylate (BPA-DM), another BPA monomer used in plastics and resins, elicited agonistic effects at the AhR (94). Finally, BPA has been found to inhibit aromatase activity [97] which would decrease the conversion of testosterone to estradiol and could have implications during development and in adulthood. Evidence of these additional activities, reveal the potential for BPA to affect more endocrine pathways and indicate the potential for BPA to act via multiple mechanisms and multiple pathways *in vivo*.

6.2.5. BPA and epigenetic modifications

Accumulating evidence indicates that developmental exposure to BPA may alter the epigenome. Several *in vivo* studies have demonstrated changes in DNA methylation following early exposure to BPA. Epigenetic alterations following early BPA exposure were reported in a study of viable yellow agouti (A^{vy}) mice exposed in utero and during lactation to BPA in the diet (50 mg BPA/kg diet) [98]. The BPA exposed mice revealed a shift in coat color toward yellow, and this shift was found to be associated with decreased DNA methylation in 9 cytosine-guanine dinucleotide (CPG) sites examined in the promoter region of the A^{vy} gene and in additional loci that were examined.

Additional evidence of BPA action through epigenetic alterations has been reported in studies of the prostate in rats exposed neonatally to BPA [30,33]. The methylation status of the phosphodiesterase type 4 variant 4 (PDE4D4) gene which encodes an intracellular enzyme important for degradation of cAMP and has been associated with cancer cell proliferation was examined in the prostate of BPA exposed males (10 μg BPA/kg BW injected on postnatal days 1, 3 and 5) [30]. Increasing methylation was noted with age in a cluster of cytosine-guanine (CG) sites in control males that reached 100% methylation by 7 months of age. In contrast, hypomethylation was noted in these same sites in males neonatally exposed to BPA. The inverse relationship between methylation status and PDE4D4 expression was confirmed and suggested that increased expression of this gene in BPA exposed males could contribute to their predisposition to hormonal carcinogenesis in adulthood.

Effects of maternal BPA exposure on the epigenome have also been reported in the developing mouse forebrain [99]. When pregnant mothers were exposed to BPA (20 μg/kg BW/day from the first day of pregnancy), changes in CpG methylation were observed in the forebrain of the fetuses at embryonic day 12.5 and 14.5.

Most recently, changes in DNA methylation of Hoxa10 was reported in the uterus of CD-1 mice exposed in utero to BPA (gestational days 9–16, 5 mg/kg BW/day) [100]. The hypomethylation of Hoxa10 following early BPA exposure altered developmental programming of gene expression and affected ER binding to the Hoxa10 ERE resulting in increased estrogen responsiveness of this gene. The authors of this study proposed that epigenetic alterations in ERE sensitivity to estrogen may represent a general mechanism through which endocrine disruptors could act.

7. BPA and female reproduction: multiple actions at multiple levels could contribute to impaired reproductive capacity of BPA exposed females

As discussed, BPA's actions are multiple and complex. BPA exposure exerts numerous tissue specific effects that are influenced by exposure period and dose. Our lab has devoted considerable attention to the effects of developmental exposure to low doses of BPA on endpoints important for female reproduction. Given its actions as an estrogen, it is not surprising that BPA should affect female fertility. The most recent study in our lab examined overall reproductive capacity of female CD-1 mice exposed perinatally to BPA to determine how the various changes reported in reproductive target tissues following BPA exposure may affect fertility and fecundity [101]. Although no differences were apparent during the first pregnancy, the females born to mothers exposed to 0.025 and 25 μg BPA/kg BW from day 8 of gestation through day 16 of lactation had fewer successful pregnancies and delivered fewer pups over the course of the 32 week study. The assorted and diverse effects of BPA that may contribute to an overall reduction in female reproductive capacity are illustrated by considering previously reported effects of BPA in rats and mice, some of which have already been mentioned.

To understand the role of early BPA exposure on female reproductive capacity, it is important to consider potential BPA-associated alterations at all levels of the hypothalamic–pituitary–ovarian axis (HPOA) as well as the reproductive tract and the mammary gland. Early BPA exposure has been reported to affect all of these components of female reproduction. Altered estrous cyclicity which has been reported in BPA exposed females [28,29,102] can represent a first indication of disruption of HPOA function. At the hypothalamic level, BPA exposure during the critical period of brain sexual differentiation is known to cause changes in the size and composition of the anteroventral periventricular nucleus (AVPV), a region essential for gonadotropin release [29,40,41]. Changes in gonadotropin release and hypothalamic/pituitary function have been reported in females following early exposure to BPA [28,103] and changes in ER levels in the hypothalamus and pituitary have also been reported [10,29,43]. Early BPA exposure is also known to have effects on the developing ovary [104,105]. In the uterus, developmental exposure to BPA can alter morphology [38] increase steroid receptor expression [38] and increase sensitivity to estrogen [100]. Finally, early BPA exposure has marked effects on mammary gland development [35,106], and it also promotes the development of intraductal hyperplasias and precancerous mammary lesions in adult rodents [36,37]. The changes known to occur at each of these levels of the reproductive axis and in reproductive tissues could contribute to the impaired fertility noted over time in female rodents exposed perinatally to BPA [101].

8. Evidence that early BPA exposure may promote obesity and its associated metabolic complications: an evolving story

Whereas the details of BPA action on reproductive endpoints in males and females have been unraveling over the past decade, new potential areas of BPA action are in the early stages of exploration. One area of increasing interest is the potential for BPA exposure to contribute to obesity and its associated metabolic complications. The idea that chemicals in our environment may act as obesogens [107] and may play some role in the meteoric rise in worldwide levels of obesity during the past 30–40 years [108] is an intriguing hypothesis (for review see [109,110]), and one that is currently actively being explored for various chemical compounds.

Prior to any formal study of BPA and body weight, data from some of the original *in vivo* studies of BPA revealed increased body weight in rats and mice exposed to this compound during gestation or gestation and lactation [26,28] (for review see [54]). Soon after those first *in vivo* observations, results of several *in vitro* studies of 3T3-L1 cells indicated that micromolar concentrations of BPA enhanced adipocyte differentiation and lipid accumulation in target cells in a dose dependent manner [111–113]. Additionally, bisphenol A was found to enhance basal glucose uptake in mature mouse 3T3-F443A adipocytes due to increased GLUT 4 protein [114]. Bisphenol A was also shown to increase gene expression of adipogenic transcription factors in 3T3-L1 preadipocytes [115], and it was subsequently shown that these actions were through a non-genomic pathway. It is now known that BPA may exert effects on adipogenesis *in vivo*. It is interesting to note that female fetuses of pregnant dams exposed to BPA (0.25 μg/kg BW/day), beginning on gestation day 8, showed evidence of accelerated maturation of the mammary fat pad when examined on gestation day 18 [106]. Other labs have reported that BPA exposure during gestation and lactation accelerated adipogenesis or increased fat pad weights at the time of or soon after weaning [51–53]. Somm and colleagues [51] recently confirmed an increase in the expression of adipogenic genes in adipose tissue at the time of weaning in BPA exposed rats. Increases in body weight following exposure to BPA have been reported most consistently in female rodents [26,28,51,53]. Thus far changes in body weight have been reported in animals exposed to BPA during gestation, or gestation and lactation, and in one study BPA exposure continued through PND 30 when animals were sacrificed [49]. To date, no studies have continued BPA exposure throughout life, and few have followed measurements of body weight and adiposity through adulthood and to later ages. It should be noted that a recent study reported increased body weight at the time of weaning in mice born to dams exposed to 0.25 μg BPA/kg BW during gestation and lactation; however, the increase was not observed at 16 weeks of age when the study ended [52]. Far more investigation is needed to understand the effects of BPA exposure on body weight and adiposity prepubertally and later in life and the mechanisms through which BPA may be acting. Given their potential roles in the regulation of body weight, it is possible that actions of BPA at the glucocorticoid receptor [90], and on thyroid hormone pathways [86], could be involved in some of the mechanisms through which perinatal BPA exposure may influence body weight and adiposity.

Contributing to the potential for altered metabolic homeostasis, as mentioned previously, BPA has been shown to alter glucose homeostasis [57]. Four consecutive days of BPA treatment (100 μg BPA/kg/day) increased pancreatic insulin content, produced hyperinsulinemia, and induced insulin resistance in adult male mice [57]. In addition, exposure of pregnant mouse dams to BPA (10 μg or 100 μg BPA/kg BW) from gestation day 9–16 resulted in decreased glucose tolerance, and increased plasma insulin, triglycerides and leptin concentrations relative to controls [55]. At 4 months postpartum, these same treated mothers had increased body weight, higher plasma insulin, leptin, triglyceride, and glycerol levels as well as increased insulin resistance revealing long term adverse consequences of exposure to BPA during pregnancy. Moreover, when examined at 6 months of age, the male offspring of the BPA-exposed dams had reduced glucose tolerance, increased insulin resistance, and altered blood parameters compared with offspring of control dams, further revealing the ability of BPA to alter pancreatic function and metabolic parameters. As discussed previously, positive correlations between BPA levels and diabetes, and BPA levels and cardiovascular disease have been reported in humans [59,60]. Moreover, BPA has been shown to decrease the release of the insulin sensitizing hormone adiponectin and to increase the release of inflammatory adipokines from human adipose tissue [116]. When considered together, the currently available data reveal a pressing need for further study, and they suggest that BPA may adversely affect metabolic homeostasis and may exacerbate or accelerate the development of diabetes and metabolic syndrome in at risk individuals [117].

In summary, the potential actions of BPA are multiple and complex, and they may involve several endocrine-related pathways, any number of which could be activated at a given time or during a specific susceptible window of exposure. Despite the huge increase in the number of research studies that have examined BPA during the last decade, many important questions about the mechanisms of BPA's actions remain to be answered. Controversies abound on the safety of BPA. Some level of uncertainty surrounds the levels of human exposure. Other controversies stem from discrepancies in data from different labs that may result from differences in study protocols, levels and routes of exposure, windows of exposure, and experimental subjects. Nonetheless, data from numerous studies have identified adverse effects in rodents exposed to BPA at levels below the current acceptable daily intake dose, particularly during development. Some effects observed in rodents have been observed in nonhuman primates as well [58]. Furthermore, human epidemiological studies have revealed a correlation between BPA levels and disease. Clearly additional basic and clinical research is required to understand the mechanism of action of BPA and the possible impact of BPA on human health. Although further investigation is required, there is currently sufficient evidence to raise concern and to warrant practice of the precautionary principle, particularly for protection of the developing fetus, neonate and young children as they may be the most vulnerable to adverse effects of this ubiquitous compound. It is also important to consider that BPA is only one of many endocrine disruptors that we are exposed to daily. As we continue to assess potential adverse effects of BPA in humans, the possibility of additive and synergistic effects of BPA with other prevalent endocrine disrupting compounds should not be overlooked.

Acknowledgements

The author was supported by ES018781 and ES013884 from the NIH.

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