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Bisphenol A: Perinatal exposure and body weight

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Abstract

Bisphenol A (BPA) is a component of polycarbonate and other plastics including resins that line food and beverage containers. BPA is known to leach from products in contact with food and drink, and is therefore thought to be routinely ingested. In a recent cross sectional study, BPA was detected in urine samples from 92.6% of the US population examined. The potential for BPA to influence body weight is suggested by *in vitro* studies demonstrating effects of BPA on adipocyte differentiation, lipid accumulation, glucose transport and adiponectin secretion. Data from *in vivo* studies have revealed dose-dependent and sex dependent effects on body weight in rodents exposed perinatally to BPA. The mechanisms through which perinatal BPA exposure acts to exert persistent effects on body weight and adiposity remain to be determined. Possible targets of BPA action are discussed.

Keywords

Endocrine disruptors; Obesity; Perinatal exposure; Fetal and neonatal exposure; Xenoestrogens; Body weight regulation; Fetal basis of adult disease

1. Introduction

1.1. Facts about Bisphenol A (4,4'-dihydroxy-2,2-diphenylpropane)

Bisphenol A (BPA) is a known endocrine disruptor that is prevalent in our environment. It was first synthesized by A.P. Dianin in 1891, and BPA was further investigated in the 1930s during a search for synthetic estrogens. Although BPA's estrogenic activity was confirmed at that time, tests of a related synthetic compound, diethylstilbestrol (DES), indicated that DES was a far more potent estrogen than BPA as determined in a classical estrogenicity assay of vaginal cornification (Dodds and Lawson, 1936). The use of BPA as a synthetic estrogen was 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 (Rubin, 2007). This practice was stopped after the treatment was linked to vaginal and cervical cancers 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 (McLachlan, 2006; Newbold et al., 2006; Rubin, 2007). The chemical structures of BPA, DES and estradiol are shown in Fig. 1.

Based on the relative binding affinity of BPA for the classical nuclear receptors ER alpha and ER beta which is estimated to be over 1000–10,000 fold lower than that of estradiol (Kuiper et al., 1998), BPA was initially considered to be a weak environmental estrogen. However, more recent studies have revealed that BPA can stimulate cellular responses at very low

concentrations and that BPA is equipotent to estradiol in some of its effects (Alonso-Magdalena et al., 2005, 2008; Hugo et al., 2008; Zsarnovszky et al., 2005). Some of BPA's actions are attributed to its' ability to bind classical and non-classical membrane estrogen receptors (Alonso-Magdalena et al., 2005, 2008; Watson et al., 2005) as well as the G-protein-coupled receptor 30 (GPR30) (Thomas and Dong, 2006) and to act through non-genomic pathways (Leranth et al., 2008; Ropero et al., 2006; Zsarnovszky et al., 2005). Multiple cellular sites in addition to the nucleus and membrane have been proposed as targets of BPA action (Ropero et al., 2006). In addition, it has been suggested that some metabolites of BPA may be more potent estrogens than the parent compound (Ben-Jonathan and Steinmetz, 1998). BPA has been shown to interact differently than estradiol with the ligand binding domain of the classical estrogen receptors (Gould et al., 1998), and differences have also been noted in the recruitment of transcriptional coregulators (Routledge et al., 2000) lending support to the idea that BPA is not merely an estrogen mimic.

In the 1940s and 1950s, a use for BPA was identified in the plastics industry. BPA is the building block for polycarbonate plastic, and it is a component of other plastics as well. BPA is also a component of epoxy resins used for some dental materials and for the lining of food and beverage containers (<http://www.bisphenol-a.org>; <http://www.ourstolenfuture.org/NewScience/oncompounds/bisphenola/bpauses.htm>, NTP-CERHR, 2008). 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, and carbonless paper. When polymerized, BPA molecules are linked by ester bonds that are subject to hydrolysis when exposed to high temperatures or to acidic or basic substances (Welshons et al., 2006). 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 (Vandenberg et al., 2007a). Although ingestion is considered the major route of exposure, it is likely that humans also gain exposure to BPA through the air and by absorption through the skin.

BPA is one of the highest volume chemicals in use today. And therefore it is not surprising that BPA is ubiquitous in our environment and can be detected in the majority of individuals examined in the US. Recent measurements by the Centers for Disease Control (CDC) revealed detectable levels of BPA in urine samples from 92.6% of more than 2500 participants of the cross sectional NHANES (National Health and Nutrition Examination Survey) study (Calafat et al., 2008). Because BPA is thought to be rapidly metabolized and excreted from the body, the data from the NHANES study is suggestive of continuous exposure to the compound. The youngest individuals included in the NHANES data set were children between the ages of 6–12 years of age, and they showed the highest levels of exposure. This is an important finding as the data from animal studies indicate increased vulnerability to BPA exposure during development (for review see Richter et al., 2007). In this regard, BPA has been detected in amniotic fluid, neonatal blood, placenta, cord blood and human breast milk (for review see Vandenberg et al., 2007a). Unfortunately the NHANES data set did not include samples from children from birth to 6 years of age. This is the population with the highest expected exposure level per body weight as estimated by the US National Toxicology Program from the currently available human data (NTP-CERHR, 2008).

In the 1980s, the lowest-observable-adverse-effect-level (LOAEL) for BPA was determined at 50 mg/kg BW/day, and the US Environmental Protection Agency (EPA) calculated a “reference dose” or safe dose of 50 µg BPA/kg BW/day. Since that time, data from many animal studies have revealed significant effects of exposure to doses of BPA below the calculated safe levels particularly in response to fetal, neonatal or perinatal exposure. To date, the reported effects of perinatal exposure to BPA include: altered time of puberty (Honma et al., 2002; Howdeshell et al., 1999); prostate changes (Gupta, 2000; Prins et al., 2007; Timms

et al., 2005); altered mammary gland development and evidence of intraductal hyperplasias and preneoplastic mammary gland lesions in adulthood (Markey et al., 2001; Munoz de Toro et al., 2005; Murray et al., 2007; Vandenberg et al., 2008); changes in the uterus and ovary (Markey et al., 2005; Newbold et al., 2007a); alterations in brain sexual dimorphisms (Kubo et al., 2003; Rubin et al., 2006); changes in brain steroid receptor levels (Khurana et al., 2000; Ramos et al., 2003); changes in behavior including reports of hyperactivity (Ishido et al., 2004; Jones and Miller, 2008), increased aggressiveness (Kawai et al., 2003), altered sexual behavior (Farabollini et al., 2002), and increased susceptibility to drugs of addiction (Jones and Miller, 2008; Mizuo et al., 2004). A review by Richter and colleagues provides a comprehensive account of the findings from *in vivo* studies of BPA exposure (Richter et al., 2007).

1.2. Early exposure to BPA and body weight

In our initial studies to examine the effects of perinatal BPA exposure on the reproductive axis and reproductive tract tissues, we noted that at some exposure levels, animals showed increased body weight (BW) relative to controls (Rubin et al., 2001). This observation was first made in offspring born to Sprague Dawley rat dams that were exposed to bisphenol A in their drinking water from day 6 of pregnancy through the period of lactation. Pregnant dams were exposed to approximately 0.1 mg BPA/kg BW/day (Low Dose) or 1.2 mg BPA/kg BW/day (High Dose) and the body weights of their offspring were measured at intervals from birth through 110 days of age. Both BPA exposed males and females showed an increase in body weight; however, the increase was more persistent in females than males. Moreover, in females, the effect was dose-dependent as the lower exposure dose increased body weight in the offspring while the higher exposure dose did not (see Fig. 2). This pattern is typical of the non-monotonic dose-response curves that have been reported for many actions of BPA (Vandenberg et al., 2006; Alonso-Magdalena et al., 2008; Hugo et al., 2008; Vandenberg et al., 2009).

Subsequent to our first observations in Sprague Dawley Rats (Rubin et al., 2001), we noted that the original cohort of CD-1 mice, generated to study the effects of perinatal BPA exposure on hypothalamic–pituitary–ovarian axis function also showed evidence of dose-dependent effects on body weight (unpublished observations). A more thorough examination of the link between early BPA exposure and body weight regulation is currently underway in our lab. To date, the data suggest that exposure of pregnant CD-1 mouse dams to 0, 0.25, 2.5 or 25 µg BPA/kg BW/day from gestational day 8 through day 16 of lactation via osmotic minipumps resulted in dose-dependent and gender-dependent effects on body weight of the offspring (manuscript in preparation).

A review of the currently available literature reveals additional reports of increased body weight in offspring of mothers exposed to BPA during gestation, or gestation and lactation, or in rodents administered BPA during the early postnatal period. With regard to prenatal exposure to BPA, increased body weight was reported at the time of weaning in female CD-1 mice born to mothers that received an oral dose of 2 µg BPA/kg BW /day on gestational days 11–17 (Howdeshell et al., 1999). The difference in body weight was most pronounced in females positioned between two females in the uterine horn during gestation. This finding suggests that the magnitude of BPA's effects on body weight were influenced by subtle differences in the hormone environment *in utero*. In a study examining xenoestrogen effects on estrogen target organs, increased body weight was also reported in the female offspring of CD-1 mothers treated with 0.5 or 10 mg BPA/kg BW/day on days 15–18 of gestation (Nikaido et al., 2004). Although not apparent at 4 or 8 weeks of age, differences in body weight were obvious at 12 and 16 weeks of age in this paradigm. Females born to mothers exposed to the lower dose of BPA were heavier in adulthood than those born to mothers exposed to the higher dose. As in other studies, the effects of BPA revealed a non-monotonic dose–response. Additionally,

preimplantation exposure to BPA was reported to effect body weight at weaning (Takai et al., 2001). When mouse embryos were cultured at the two cell stage in 1 nM BPA, 100 μ M BPA, or 0.1% ethanol (the solvent used to prepare the BPA solutions), no differences in pup weight were noted at birth. However at the time of weaning on PND 21, offspring from embryos exposed to either dose of BPA were significantly heavier than control offspring.

With regard to postnatal BPA exposure, male rat pups were injected with 50 μ g BPA/kg BW/day for 4 days beginning on the day of birth, to study the effects of BPA exposure on anxiety. When their body weights were recorded on postnatal day (PND) 68, the BPA treated males were significantly heavier than controls (Patisaul and Bateman, 2008). In another study, CD-1 female mice were treated daily from PND 1 through PND 5 with 10 μ g BPA/kg BW to study the effects on the reproductive tract. At 18 months of age, the only time point reported, body weights were 11% higher in the BPA treated females relative to the controls (Newbold et al., 2007a). Finally, in a study designed to examine the potential relationship between early BPA exposure and obesity, pregnant ICR mouse dams fed a high fat diet were exposed to BPA from day 10 of gestation through the period of lactation. After weaning the pups continued to be exposed to BPA and the high fat diet through PND 31 when they were killed (Miyawaki et al., 2007). BPA was administered in the drinking water, and exposure levels in the pregnant dams were estimated at approximately 0.26 mg BPA/kg BW/day in the low dose and 2.7 mg BPA/kg BW/day in the high dose group. Body weights and adipose tissue weights were increased in 31 day old male and female offspring exposed to BPA. Both sex-dependent and dose-dependent differences were observed, and a non-monotonic dose-response was noted in some of the parameters reported. In this study, animals were examined prior to adulthood and BPA exposure was ongoing at the time of sacrifice.

The initial observations in our lab (Rubin et al., 2001) and others (Howdeshell et al., 1999) linking prenatal or perinatal BPA exposure to increased body weight long after the time of exposure were intriguing. Data gleaned from the studies that followed provided additional evidence of increased body weight following perinatal exposure to BPA (Nikaido et al., 2004; Patisaul and Bateman, 2008; Newbold et al., 2007a; Miyawaki et al., 2007). The accumulating evidence linking perinatal BPA exposure to increased body weight was particularly interesting due to growing reports in the literature revealing effects of other endocrine disruptors on body weight (Heindel, 2003). For example, neonatal DES administration was found to increase body weight and adiposity in adulthood (Newbold et al., 2007b). Organotins were also reported to exert effects on adipocyte differentiation and body weight (Grun and Blumberg, 2006). Recent analysis of NHANES data revealed an age-dependent and gender-dependent association between urinary phthalate metabolite concentrations and body mass index and waist circumference in humans (Hatch et al., 2008). Furthermore, a prospective study in humans revealed a correlation between hexachlorobenzene levels in cord blood at birth and increased body mass index at 6.5 years of age (Smink et al., 2008). In addition to contributions from diet, and exercise, emerging data from studies of endocrine disruptors lend support to the hypothesis that the increase in industrial chemicals in our environment has contributed to the significant increase in body weight over the past 40 years (Baillie-Hamilton, 2002).

1.3. Possible mechanisms of action of BPA in body weight regulation

How perinatal exposure to BPA may exert lasting effects on body weight remains to be determined. Some potential targets of BPA action in this regard are discussed in the paragraphs that follow.

1.3.1. BPA action on preadipocytes—Results of several *in vitro* studies of 3T3-L1 cells have indicated that micromolar concentrations of BPA enhance adipocyte differentiation and

lipid accumulation in target cells in a dose-dependent manner (Masuno et al., 2002, 2005; Wada et al., 2007). Additionally, bisphenol A was found to enhance basal glucose uptake in mature mouse 3T3-F443A adipocytes due to increased GLUT 4 protein (Sakurai et al., 2004). Most recently Bisphenol A was shown to increase gene expression of adipogenic transcription factors in 3T3-L1 preadipocytes (Phrakonkham et al., 2008). If similar actions of BPA occur *in vivo*, they would be expected to contribute to increased adiposity and increased body weight. Whether BPA may exert similar dose-dependent effects on adipocyte differentiation perinatally, and whether such effects contribute to increased adiposity later in life remains to be determined. It is interesting to note that female fetuses of pregnant dams exposed to BPA (0.25 µg/kg BW/day), beginning on gestational day 8, showed evidence of accelerated maturation of the mammary fat pad when examined on gestational day 18 (Vandenberg et al., 2007b).

1.3.2. BPA as an estrogen—BPA's actions as an estrogen may contribute to effects on body weight. Sex-dependent and dose-dependent differences in body weight in response to early postnatal exposure to DES, an estrogenic compound with structural similarities to BPA have been reported (Newbold et al., 2008). Those studies demonstrated increased body weight at 4 months of age in females exposed to DES (1 µg DES/day) from postnatal days 1 through 5. In contrast, males exposed to DES during that time period demonstrated a decrease in body weight relative to controls at 4 months of age. The administration of another estrogenic compound, the soy isoflavone, genistein to 4 week old male and female mice (in doses of 50–200,000 µg/kg/day for 15 days) also revealed dose and sex-dependent effects on adipose tissue deposition (Penza et al., 2006). In this specific paradigm, the males proved to be more sensitive to the effects of genistein showing increased adipose tissue deposition following treatment with nutritional doses of genistein and a significant decrease in fat pads when they were treated with pharmacological doses of the compound. It is intriguing to note that continuous exposure of male mice from conception through adulthood to a high phytoestrogen diet (containing high levels of genistein as well as diadzein) resulted in decreased adiposity, increased energy expenditure, and improved glucose and lipid metabolism (Cederroth et al., 2007, 2008). These data further suggest the importance of the dose and the precise timing of exposure to estrogenic compounds as well as the compounds themselves in determining their effects on adiposity and glucose homeostasis.

As mentioned previously, BPA may bind the classical nuclear estrogen receptors as well as classical and non-classical membrane estrogen receptors and GPR-30 (Alonso-Magdalena et al., 2005, 2008; Kuiper et al., 1998; Thomas and Dong, 2006; Watson et al., 2005). Data from *in vitro* studies have revealed similarities between the action of estrogen and BPA on the gene expression of adipogenic transcription factors (Phrakonkham et al., 2008). In addition, both BPA and estradiol were reported to inhibit adiponectin secretion from human adipocyte explants in a (non-monotonic) dose-dependent manner (Hugo et al., 2008). There is also evidence from *in vivo* studies to suggest that neonatal estrogenization can increase body weight (Ruhlen et al., 2008). In addition, as discussed above neonatal exposure to DES, which is typically considered a more potent estrogen than BPA, can increase body weight and adiposity in females (Newbold et al., 2008). When considering 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 (Toran-Allerand, 1984). Because BPA shows limited binding to serum proteins (Milligan et al., 1998), relative to estradiol, BPA may have increased access to the tissues of the developing fetus or neonate, and as a result, its' actions as an estrogen may be greater than expected.

The role of estrogens in body weight regulation is complex and not yet well understood. Although perinatal exposure to estrogenic compounds can lead to increased body weight,

estradiol acts via multiple mechanisms later in life to reduce body weight and adiposity (Wade et al., 1985). Clearly the adipogenic effect of estrogen observed *in vitro* and in response to perinatal exposure differs from the anti-adipogenic effects observed when estrogens are administered to ovariectomized females in adulthood (D'Eon et al., 2005). In this regard, the administration of very high levels of BPA (4–5 mg/day) to ovariectomized rats for a period of 15 days has also been reported to reduce body weight gain (Nunez et al., 2001). However, body weight gain was not significantly reduced in ovariectomized rats in response to a lower level of BPA supplementation (8.9 µg or 88 µg BPA/day for 12 weeks (Seidlová-Wuttke et al., 2005).

The long-term loss of estrogen action increases body weight and adiposity in both males and females. Aromatase knockout mice show increased gonadal fat pad weights after sexual maturation (Fisher et al., 1998; Jones et al., 2008). Estrogen action through ER alpha appears to be essential for body weight regulation as ER alpha knockout mice, but not ER beta knockout mice, have markedly increased adiposity in adulthood (Heine et al., 2000; Ohlsson et al., 2000). Additionally, the targeted silencing of ER alpha in the ventromedial nucleus of the hypothalamus, a region known to be involved in food intake and energy homeostasis, increased adiposity and body weight in rats (Musatov et al., 2007).

1.3.3. Perinatal BPA exposure may permanently alter sensitivity to 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 (Munoz de Toro et al., 2005; Wadia et al., 2007). In addition, perinatal BPA exposure altered ER alpha and ER beta mRNA levels in a tissue specific and sex specific manner (Khurana et al., 2000; Ramos et al., 2003), and increased ER alpha expression in the uterus (Markey et al., 2005). Both ER alpha expression and the relative abundance of ER alpha transcript variants were altered in the brains of female Wistar rats in a dose-dependent manner following neonatal exposure to BPA (Monje et al., 2007). Lasting tissue specific alterations in ER expression may contribute to the persistent effects of early exposure to BPA on body weight. Data from a recent study confirm gene expression of both classical estrogen receptors in human adipose tissue (Hugo et al., 2008).

1.3.4. Estrogen-related receptor gamma—It is of interest that the most recently identified member of the estrogen-related receptor (ERR) family, ERRgamma, has been found to strongly bind BPA (Matsushima et al., 2008; Okada et al., 2008). The ERR's are nuclear receptors that do not directly bind estradiol. Although the functions of ERRgamma have not yet been delineated and no endogenous ligand has been identified, ERRgamma is known to be present in adipose tissue (Giguere, 2008; Hugo et al., 2008). Recent data suggests that ERR gamma along with the other two known ERRs, ERRalpha and ERRbeta, plays an important role in the transcriptional control of energy homeostasis and normal mitochondrial biogenesis and function (Giguere, 2008). It remains to be determined whether early exposure to BPA may exert lasting effects on body weight regulation that are mediated through ERRgamma and its target genes. ERRgamma is known to be present during mammalian development (Heard et al., 2000; Hermans-Borgmeyer et al., 2000).

1.3.5. BPA and thyroid hormone pathways—In addition to its estrogenic activities, BPA has been reported to bind to thyroid hormone receptor and to act as an antagonist to inhibit transcriptional activity stimulated by thyroid hormone, triiodothyronine (T3) (Moriyama et al., 2002; Zoeller, 2005). Although the affinity of BPA for thyroid hormone receptor is lower than the affinity for the estrogen receptor, 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 (Moriyama et al., 2002). *In vivo* studies have revealed that 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 levels of thyroxine (T4) on postnatal day 15 and increased expression of a thyroid responsive gene in the brain. The increased T4 levels were hypothesized to result from a loss of negative feedback via one thyroid hormone receptor isoform (Zoeller et al., 2005). Data from another *in vivo* study (Xu et al., 2007) demonstrated a transient elevation of thyroid hormone levels on PND 7 in male offspring of rat dams exposed to BPA in their drinking water (0.1 mg/liter) from gestational day 11 through PND 21. Of interest, measurements of free T4 levels in the lactating dams were significantly decreased relative to controls on PND 0 and PND 7 leading to the suggestion that the increase in T4 levels in the offspring might have been a compensatory response for the lower hormone levels in their mothers. It is conceivable that effects of perinatal BPA exposure on thyroid hormone action during development or on the development of the thyroid hormone axis could be a factor in its ability to exert long-term effects on body weight given the important role of thyroid hormone in energy homeostasis.

It is important to note that the halogenated derivatives of BPA appear to be better competitors for the thyroid hormone receptor than BPA. Tetrabromobisphenol A and tetrachlorobisphenol A are commonly used worldwide 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 (Kitamura et al., 2002). Both agonist, and antagonist activities at the thyroid hormone receptor have been attributed to halogenated BPA derivatives (Ghisari and Bonefeld-Jorgensen, 2005; Kitamura et al., 2002).

1.3.6. Circuits that regulate food intake and metabolism—Development and maturation of brain circuits involved in the regulation of food intake and metabolism occur during the perinatal period (Grove et al., 2005; Simerly, 2008; Xiao et al., 2007). Therefore, they could be potential direct or indirect targets of BPA action during perinatal exposure. Numerous studies have confirmed the ability of BPA to affect the developing brain (for review see Richter et al., 2007) even at very low doses (Rubin et al., 2006; Zsarnovszky et al., 2005), indicating that the brain is a very sensitive target organ for BPA action.

1.3.7. Glucose regulation—Mounting evidence reveals that BPA can influence pancreatic function *in vitro* and *in vivo*. BPA has been found to exert effects on the insulin secreting beta cells as well as glucagon secreting alpha cells of the pancreas (Ropero et al., 2008). The ability of BPA to increase insulin mimics that of estradiol and appears to act through the ERalpha receptor (Alonso-Magdalena et al., 2008). *In vivo* studies have revealed that treatment of adult male mice with BPA for a period of 4 days results in overexpression of insulin which leads to hyperinsulinemia and then to insulin resistance (Alonso-Magdalena et al., 2006; Ropero et al., 2008). These data indicate that exposure to BPA and/or other estrogenic endocrine disruptors in adulthood can disrupt normal glucose homeostasis and could be a factor contributing to the development of type 2 diabetes. It is not yet known whether BPA exposure during the perinatal period may alter pancreatic development in the neonate. In humans, fetal and neonatal life are known to be important periods for the development of the beta cells of the pancreas (Ozanne and Hales, 2002). One of the first examples of exposure *in utero* to a chemical pollutant that led to increased body weight was reported in the offspring of women who smoked during pregnancy (Power and Jefferis, 2002). Prenatal exposure to nicotine has been reported to alter the developing pancreas (Holloway et al., 2005; Somm et al., 2008).

1.3.8. BPA and peroxisome proliferator-activated receptor gamma (PPARGamma)—Some endocrine disruptors including the organotins and phthalates have been proposed to influence body weight via a mechanism that involves perturbed PPARGamma signaling (Grun and Blumberg, 2006, 2007). PPARGamma is important for the differentiation of both brown and white adipocytes and is highly expressed in adipose tissue. It plays an important role in the control of energy balance and lipid homeostasis (for review see Tontonoz

and Spiegelman, 2008). The role of PPARgamma in adipocyte differentiation and fat storage is illustrated by the marked obesity observed in individuals with a gene mutation that results in constitutive PPARgamma activation (Ristow et al., 1998). In contrast, decreased body weight and impaired adipocyte development and function have been observed in mice with impaired PPARgamma function (Freedman et al., 2005).

The BPA derivative, bisphenol A diglycidyl ether (BADGE), which is a component of epoxy resins, has been used extensively as a PPARgamma antagonist. BADGE is a ligand for PPARgamma that reportedly has no ability to induce transcriptional activity but can antagonize the ability of agonist ligands to activate the transcriptional and adipogenic action of this receptor (Wright et al., 2000). Whereas BPA and 8 derivatives of BPA were able to accelerate terminal adipocyte differentiation of 3T3-L1 cells, BADGE was not (Masuno et al., 2005). BADGE was also reported to block hormone-mediated adipocyte differentiation in 3T3-L1 and 3T3-F442 cell lines (Wright et al., 2000); however, as mentioned previously, BPA has been reported to increase adipocyte differentiation in both of these cell lines (Masuno et al., 2002, 2005; Sakurai et al., 2004; Wada et al., 2007). When examined along with BADGE, BPA was unable to antagonize PPARgamma action in the paradigm tested (Wright et al., 2000). Taken together these data suggest that BPA and BADGE may differentially affect PPARgamma. Additional detailed studies are needed to determine the relationship between BPA and its derivatives and PPARgamma signaling and the possibility of dose-related or cell specific differences in BPA's actions. It should be noted that in addition to its' action as an antagonist, BADGE has been reported to act as an agonist of PPARgamma in a cell line derived from ECV 304 cells suggesting that the regulation of PPARgamma activity by BADGE may be cell specific (Bishop-Bailey et al., 2000).

2. In summary

Given the potential of BPA to exert pleiotropic effects, it is likely that early BPA exposure can influence several mechanisms important for body weight regulation, including adipocyte deposition, glucose uptake and homeostasis, and the development and maturation of pathways and circuits important for energy homeostasis (see Fig. 3). The specific pathways and mechanisms affected by perinatal BPA exposure may be dependent upon the dose and the precise time of exposure as well as other factors such as circulating endogenous hormone levels present during exposure.

It is paramount that the potential effects of early BPA exposure on body weight regulation, adipose deposition, and glucose homeostasis in adulthood be further investigated. As mentioned previously, the results of the latest CDC evaluation of BPA exposure confirmed detectable levels of BPA in the urine of 92.6% of the US NHANES population examined (Calafat et al., 2008). If one considers that BPA is thought to be rapidly metabolized and excreted from the body, these data suggest continuous exposure to the compound. However, a recent publication has presented evidence that BPA may be stored in human adipose tissue (Fernandez et al., 2007). More recent analysis of the NHANES data set has revealed that higher levels of urinary BPA were associated with diabetes and cardiovascular disease (Lang et al., 2008). The results of this analysis are particularly interesting in light of the recent report of the ability of low levels of BPA to decrease adiponectin release from human adipose tissue explants (Hugo et al., 2008) as adiponectin is known to play an important role in insulin sensitivity and a positive role in cardiovascular health. Although the NHANES data are correlative and cannot prove causality, the trend identified is troubling and one that warrants further study. Finally, given the extensive literature showing that fetuses and neonates are generally more vulnerable to BPA exposure than the adult, it is extremely important to decipher effects of BPA on body weight that can be attributed to perinatal exposure and those that result from adult exposures as well as the mechanisms of action involved in each.

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Bisphenol A

Diethylstilbestrol (DES)

Estradiol

Fig. 1. Chemical structures of BPA, DES and estradiol. Structurally, bisphenol A and DES are more similar to each other than they are to estradiol. DES is typically considered a more potent estrogen than BPA.

Fig. 2.

Body weights of female offspring of Sprague Dawley rat dams exposed to bisphenol A. Body weights of female offspring born to mothers exposed to approximately 0.1 mg BPA/kg BW (low dose BPA, 4) or 1.2 mg BPA/kg BW (high dose BPA, !) via their drinking water (control, 0 BPA, $\diamond$). Exposure to BPA was from gestational day 6 through the period of lactation. Female offspring born to mothers exposed to low dose BPA were significantly heavier than offspring born to control mothers or mothers exposed to high dose BPA (adapted from Rubin et al., 2001).

Fig. 3.

Proposed actions of perinatal BPA exposure that may influence body weight. Bold typeface denotes potential influences supported by current data. Regular typeface denotes additional possibilities for BPA action.