

Prenatal Exposure to BPA and Offspring Outcomes: The Diabetogenic Behavior of BPA

Dose-Response:
An International Journal
April-June 2015:1-8
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DOI: 10.1177/1559325815590395
dos.sagepub.com



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Abstract

Obesity and type 2 diabetes mellitus (T2DM) are the most common metabolic disorders, with prevalence rates that are reaching epidemic proportions. Both are complex conditions affecting virtually all ages and with serious health consequences. The underlying cause of the problem is still puzzling, but both genetic and environmental factors including unhealthy diet, sedentary lifestyle, or the exposure to some environmental endocrine disrupting chemicals (EDCs) are thought to have a causal influence. In addition, the impact of early environment has recently emerged as an important factor responsible for the increased propensity to develop adult-onset metabolic disease. Suboptimal maternal nutrition during critical windows in fetal development is the most commonly studied factor affecting early programming of obesity and T2DM. In recent years, increasing experimental evidence shows that exposure to EDCs could also account for this phenomenon. In the present review, we will overview the most relevant findings that confirm the critical role of bisphenol-A, one of the most widespread EDCs, in the development of metabolic disorders.

Keywords

bisphenol-A, diabetes, obesity, metabolic disorders

Introduction

Metabolic disorders remain the leading causes of morbidity and mortality in the modern world. Type 2 diabetes mellitus (T2DM), obesity, and associated cardiovascular diseases are on the rise which makes them one of the most important public health challenges.

According to the World Health Organization (WHO, 2014), worldwide obesity has nearly doubled since 1980. In 2008, more than 1.4 billion adults were overweight, and of these 200 million men and approximately 300 million women were obese. In 2012, more than 40 million children under the age of 5 were overweight or obese.

In a similar manner, the global prevalence of diabetes is rapidly increasing with an estimated number of 285 million cases of diabetes worldwide, 90% of whom have T2DM. According to the predictions, this number will rise to 439 million by 2030 (Chen et al., 2011).

The connection between both diseases is firmly established with obesity as one of the single more important risk factors for the development of T2DM. Epidemiological studies show that 60% to 90% of all patients with T2DM are or have been obese (Halpern & Mancini, 2005; Stumvoll et al., 2005).

Nevertheless, the problem is even more complex, and there is also a high incidence of T2DM in normal weight individuals. This is the case of Asian population with one of the highest prevalence of T2DM in a population with the lowest body mass index (Yoon et al., 2006). This phenomenon came to coin the term of “metabolically obese” which revealed that the key factor in the development of this pathology is the appearance of insulin resistance independent of overweight (Chen et al., 2011).

In the etiology of these disorders, there is a strong genetic component; however, their rapidly increasing incidence seems

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difficult to explain just as a result of genetic changes, which comes to emphasize the important contribution of the environmental factors (Qatanani & Lazar, 2007; O'Rahilly, 2009). Of note, novel environmental factors such as endocrine disrupting chemicals (EDCs) are emerging as key players. The EDCs are defined as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action and consequently causes adverse health effects in an intact organism, or its progeny" (Diamanti-Kandarakis et al., 2009). According to a more recent definition reported by an Endocrine Society Statement, "An endocrine disrupting chemical (EDC) is an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" (Zoeller et al., 2012). Studies in animal models as well as human epidemiological studies have shown that some EDCs can have a diabetogenic behavior (Alonso-Magdalena et al., 2011; Casals-Casas & Desvergne, 2011; Hectors et al., 2011).

In addition to that, increasing evidence supports the theory commonly named "developmental or fetal origins of adult disease," which states that adverse influences early in the development and particularly during intrauterine life are related to subsequent physiological disturbances in adulthood, resulting in an increased risk of developing chronic disease in adult life (Barker, 1998). This paradigm establishes a relationship between a nonoptimal gestational environment and an increased propensity to develop adult-onset metabolic disease.

Strong support for this idea comes from studies that show a positive correlation between low birth weight and increased risk of cardiovascular disease, hypertension, and T2DM (Gilbert & Epel, 2009). High birth weight or an excessive gestational weight gain has been shown to predispose to higher obesity risk later in life (Oken & Gillman, 2003; Catalano et al., 2009).

The underlying causal mechanisms still remain unknown, but altered maternal–fetal nutrition and increased glucocorticoid exposure have been proposed to be decisive (Warner & Ozanne, 2010). In addition, the exposure to environmental hazards during critical periods of development has recently been highlighted as an important contributor. Increased incidence of breast cancer (Munoz-de-Toro et al., 2005), genital tract abnormalities (Skakkebaek et al., 1998), and fertility problems (Sharpe & Skakkebaek, 1993) are some of the most common abnormalities associated with early EDCs exposure. In addition, prenatal treatment with bisphenol-A (BPA) has been related to the development of obesity and diabetes (Heindel, 2003; Newbold et al., 2009; Alonso-Magdalena et al., 2010). In this review, we will analyze the experimental and epidemiological findings that point to BPA as an important risk factor in the adult origin of metabolic diseases.

Bisphenol-A

Bisphenol-A was first synthesized by Dianin in 1891 and then reported to be a synthetic estrogen in the 1930s (E.C. Dodds & Lawson, 1936). In the 1950s, BPA was introduced in the plastic

industry and used as the base compound in the manufacture of polycarbonate plastic and the resin lining of food and beverage cans. It is also used as an additive in other widely used plastics such as polyvinyl chloride and polyethylene terephthalate. Numerous studies have found that BPA can leach from polycarbonate containers. Heat and either acidic or basic conditions accelerate the hydrolysis of the ester bond linking BPA monomers, leading to a release of BPA with the concomitant potential human exposure (Kang et al., 2006; Vandenberg et al., 2007). BPA has been detected in 93% of urine samples in the United States (Calafat et al., 2005). It has been found to be present in amniotic fluid, neonatal blood, placenta, cord blood, and human breast milk (Vandenberg et al., 2007). Its concentration in human serum ranges from 0.2 to 1.6 ng/mL (0.88–7.0 nmol/L; Sajiki et al., 1999; Takeuchi & Tsutsumi, 2002).

According to the Environmental Protection Agency (EPA), the lowest adverse effect level for BPA was established at 50 mg/kg/d. Based on that, the reference dose, which is considered an estimate of a daily exposure to the human population that is supposed to be without an appreciable risk of deleterious effects during a lifetime, is 50 µg/kg/d (EPA, 1993).

In 2006, the European Food and Safety Authority (EFSA) set the tolerable daily intake (TDI) as 50 µg/kg/d. In 2013, the authority again evaluated this level of exposure. In January 2014, EFSA identified likely adverse effects on liver and kidney as well as on the mammary gland as being linked to exposure to this chemical. As a result they recommended that the current TDI to be lowered from its current level of 50 µg/kg bw/d to 5 µg/kg bw/d (EFSA, 2014).

There are already hundreds of *in vivo* studies concerning low-dose effects of BPA published in peer-reviewed journals. A large number of them have demonstrated deleterious effects below the established reference dose. These effects include among others alteration of mammary gland development, behavioral effects, abnormalities in the prostate growth, alterations of sexual maturation, altered immune system function, detrimental effects on glucose homeostasis and insulin sensitivity, and so on (vom Saal & Hughes, 2005; Richter et al., 2007).

Experimental Evidence for the Obesogenic Behavior of BPA

In the last decade, experimental research conducted in animals has shown that the exposure to BPA, as well as others EDCs, during critical developmental stages can influence lipid and energy balance promoting adipogenesis. Based on that, it has been predicted that environmental pollutants can contribute to the epidemic of obesity (Grun & Blumberg, 2007; Heindel & vom Saal, 2009).

In 1999, Howdeshell and collaborators demonstrated that the treatment of pregnant CF-1 mice fed with BPA at a dose of 2.4 µg/kg on days 11 to 17 of gestation provoked an increased body weight on postnatal day 22. Curiously, the effect was dependent on fetus position in such manner that it

was higher in those fetuses positioned between 2 female fetuses (Howdeshell et al., 1999).

When the administration occurred via drinking water, the effects on adipogenesis have also been reported. Offspring from rats exposed to BPA 0.1 mg/kg or 1.2 mg/kg from day 6 of pregnancy through the period of lactation showed an increase in body weight that resulted evident soon after birth and seemed to continue into adulthood (Rubin et al., 2001). Also, the BPA exposure from day 10 of gestation throughout the lactation period, but at lower doses (1 $\mu\text{g}/\text{mL}$ or 10 $\mu\text{g}/\text{mL}$), resulted in an increment of adipose tissue and body weight (Miyawaki et al., 2007). Changes in the expression of some important adipogenic genes including PPAR- γ (peroxisome proliferator activated receptor gamma), SREBP-1C (sterol regulatory element binding protein-1C), SCD-1 (stearoyl-CoA desaturase 1) and C/EBP- α (CCAAT/enhancer-binding protein alpha) have been also observed in female offspring at 21 days of age after perinatal exposure to 1 mg/L BPA (Somm et al., 2009). Shorter subcutaneous exposures to BPA (0.5 or 10 mg/kg) in pregnant CD-1 mice also result in an accelerated body weight gain in female offspring (Nikaido et al., 2004). Interestingly, the effects of BPA exposure during pregnancy are restricted not only to changes in body weight but also to other characteristic symptoms that encompass the metabolic syndrome. One of the major studies that address this problem was conducted by Angle and collaborators in 2013 (Angle et al., 2013). The authors showed in an elegant manner that the administration of BPA in a range from 5 to 50 000 $\mu\text{g}/\text{kg}/\text{d}$ disrupts energy balance, with maximal responses at doses from 5 to 500 $\mu\text{g}/\text{kg}/\text{d}$. In general terms, they observed an increased postnatal body weight; changes in adipocyte number and volume of abdominal fat; and glucose intolerance together with alterations of leptin, insulin, and adiponectin levels in serum when animals reach 19 weeks old (Angle et al., 2013). According to this, BPA exposure during gestation and lactation (0-3000 $\mu\text{g}/\text{kg}/\text{d}$) led to increased body weight in males after weaning, effect that persisted until adulthood, as well as increased liver weight. Curiously, the effect in females was opposite to that in males, with a dose-dependent decrease in body weight, liver, muscle, adipocyte number, and serum lipids. In addition, females showed increased expression of UCP1 and lipid accumulation in brown adipose tissue (van Esterik et al., 2014). In another study, the perinatal exposure to 50 ng, 50 μg , and 50 mg BPA/kg of diet resulted in an overall increase in energy expenditure in both males and females (Anderson et al., 2013). Higher doses of BPA via drinking water along with fructose promoted no changes in body weight or volume adipocyte but an increased liver fat content (Ronn et al., 2013).

When combining BPA exposure with a metabolic stressor, such as a high-fat diet (HFD), there is an exacerbation of the underlying metabolic disorders that accounts for BPA action. This is the case of the study reported by Wei and collaborators, in which pregnant rats were orally exposed to BPA (50, 250, or 1250 $\mu\text{g}/\text{kg}/\text{d}$) during both gestation and lactation. Later on, pups were fed with normal diet or HFD. The results showed that under a normal diet, BPA was able to promote glucose intolerance and

increased body weight and insulin levels in male offspring, at least under the dose of 50 $\mu\text{g}/\text{kg}/\text{d}$. Interestingly, these effects were clearly aggravated by the administration of a HFD which resulted in dyslipidemia, obesity, glucose intolerance, and structural damages in pancreatic β -cells (Wei et al., 2011). Subcutaneously, BPA administration (10 $\mu\text{g}/\text{kg}/\text{d}$) from day 9 to 16 of gestation has also marked effects in lipid metabolism in male offspring. Remarkably, the body weight of BPA-treated animals reached levels comparable to those animals fed with HFD unexposed to BPA when reaching 20 weeks old. Changes in the messenger RNA expression of genes involved in glucose and lipid metabolism in adipose tissue, liver, and muscle resembled that of HFD-fed animals. Major changes were observed in genes involved in fatty acid metabolism such as SREBPC1, PPAR α (peroxisome proliferator activated receptor alpha), and CPT 1 β (carnitine palmitoyltransferase 1 β). A diminished expression of Cd36 was also observed (Garcia-Arevalo et al., 2014).

Changes in the hypothalamic energy balance system were also found when combining oral perinatal exposure to BPA (from 0.19 to 7.2 $\mu\text{g}/\text{kg}/\text{d}$) with HFD, when reaching adulthood in a sex-dependent manner (Mackay et al., 2013).

As regards other periods of exposure, it has been shown that the treatment with 50 $\mu\text{g}/\text{kg}$ of BPA for 4 days just after birth provoked an increase in body weight that was apparent on postnatal day 68 (Patisaul & Bateman, 2008). In contrast, the effects of BPA on energy balance during adulthood still remain unclear. The administration of BPA to ovariectomized rats at a dose of 4 or 5 mg/d during 15 days has been reported to decrease body weight gain (Nunez et al., 2001), although treatment with lower doses (8.9 or 88 μg BPA/d for 3 months) showed no effect (Seidlova-Wuttke et al., 2005).

In Vitro Studies and Mechanisms Proposed

In vitro experiments also reveal the obesogenic behavior of BPA. Most of the studies leading to that conclusion have been performed in the adipocyte cell line 3T3-L1 or in human adipose stromal/stem cells. Masuno and collaborators demonstrated that the treatment of 3T3-L1 cells in the presence of BPA in the range dose of $\mu\text{mol}/\text{L}$ promoted an increase in triglyceride content and adipogenesis (Masuno et al., 2002; Masuno et al., 2005). This phenomenon was later confirmed in the same cell line at a concentration of 10 to 100 nmol/L, although no induction of adipogenesis was observed in mesenchymal stromal stem cells (Chamorro-Garcia et al., 2012). Other studies observed BPA-mediated adipogenic differentiation processes in human adipose stromal/stem cells (Ohlstein et al., 2014). Interestingly, environmental relevant doses of BPA (from 0.1 to 1 nmol/L) have been shown to inhibit adiponectin release and increase the release of interleukin 6 and tumor necrosis factor α in human explants which has special relevance since adiponectin has been reported to be a protective factor for metabolic syndrome (Hugo et al., 2008; Ben-Jonathan et al., 2009).

The adipogenic effect of BPA has been proposed to be mediated by an estrogen receptor (ER)-dependent mechanism with enhanced expression of DLK (leucine zipper-bearing

kinase), IGF-1 (insulin-like growth factor-1), C/EBP α , or PPAR γ among other factors (Ohlstein et al., 2014; Riu et al., 2014). In adipose tissue samples from children, it has been reported that BPA promotes adipogenesis by increasing expression of 11 β -hydroxysteroid dehydrogenase type 1 and enzyme activity (Wang et al., 2013). Recent studies also suggest the implication of the thyroid receptor/retinoic X receptor or mammalian target of rapamycin signaling pathways (Boucher et al., 2014).

In addition to that, BPA has been proposed to increase triglyceride content and lipid accumulation in a hepatoma cell line associated with a decreased expression of some genes involved in lipid oxidation (Grasselli et al., 2013).

Epidemiological Evidence for the Obesogenic Behavior of BPA

Several epidemiological studies have established a link between BPA levels and obesity. One of the first cross-sectional studies that addressed this association was based on the pooled data from the 2003/04 and 2005/06 National Health and Nutrition Examination Surveys (NHANES). The authors found in adults that urinary BPA concentration was positively associated with general and central obesity, with a slight higher correlation in men than in women (Carwile & Michels, 2011). These results were lately confirmed in another study based on NHANES data in which, additionally, it was reported that the association between BPA and obesity was independent of other factors such as age, education, smoking, physical activity, or alcohol intake among others (Shankar et al., 2012). This positive association was also found in a small sample of Chinese (Wang et al., 2012b) and Korean adults (Ko et al., 2014) as well as in a subpopulation of American women (Song et al., 2014).

An even more worrying fact is that, this phenomenon has been observed not only in adults but also in children and adolescents. A representative cross-sectional study using the data from 2003 to 2008 NHANES evaluated the levels of urinary BPA in participants aged 6 through 19 years and found that the rates of obesity were increased in the second, third, and fourth quartiles of urinary BPA concentration (Trasande et al., 2012). In subsequent analysis, a strongest positive correlation was observed in boys and in non-Hispanic white children (Bhandari et al., 2013). In a Chinese children population study, BPA was found in 84.9% of urine samples, with an estimated mean of 0.45 ng/mL. Linear regression analysis showed that increasing BPA concentrations were related to higher body mass index values (Wang et al., 2012a). Curiously, in a Shanghai population, BPA concentration was associated with obesity in female children from 9 to 12 years old but not in male (Li et al., 2013).

New epidemiological studies are being published, in which prenatal exposure to BPA and later outcomes in adiposity are discussed. The first one was performed in a Mexican American population and published in 2013. The authors reported different effects depending on the prenatal or postnatal period. Thus, BPA levels in urine was correlated with a decrease in adiposity in girls at the age of 9 but not in boys, while in accordance with the previous findings, higher levels of urinary BPA were

correlated with increased odds of obesity in both girls and boys at the age of 9 (Harley et al., 2013). Similar findings as regards early-life BPA exposure have been reported in more recent studies (Braun et al., 2014).

Experimental Evidence for the Diabetogenic Behavior of BPA

Prenatal exposure to BPA in different animal models has been shown to result in a wide range of effects in glucose metabolism observed during postnatal life. Offspring of mice exposed to BPA injections 10 μ g/kg/d during days 9 to 16 of pregnancy displayed glucose intolerance, insulin resistance, hyperinsulinemia, and altered insulin release from pancreatic β -cells compared to control mice when reaching 6 months of age. Exposure of mice to a higher dose of BPA (100 μ g/kg/d) during days 9 to 16 of pregnancy produced a different phenotype in the male offspring at 6 months of age, characterized by glucose intolerance but normal insulin sensitivity and a mild alteration in β -cell function (Alonso-Magdalena et al., 2010). When pregnant mice were fed with BPA at doses from 5 to 50 000 μ g/kg during gestational days 9 to 18, similar effects on glucose tolerance were observed. At the age of 18 weeks, all BPA dose groups, except for the highest one, showed an impairment of glucose tolerance measured as an increased area under the curve for the glucose tolerance test. In addition, at the dose of 5 and 50 μ g/kg/d, animals showed decreased insulin sensitivity and higher plasma insulin levels in the first group (Angle et al., 2013).

A larger study in regard to periods of exposure to BPA (doses 100 μ g/kg/d) was conducted by Liu and collaborators. The authors analyzed different critical windows of exposure including preimplantation, fetal, and neonatal as well as the combination of fetal and neonatal exposure. They found an impairment of glucose tolerance in all periods of exposition in male offspring at the age of 3 months, phenomenon that persisted to 8 months in those males that have been exposed to BPA during the fetal period. Insulin secretion and sensitivity were also reduced with no changes in β -cell mass. The effects were less pronounced in female offspring (Li et al., 2013).

When combining prenatal BPA exposure with later HFD treatment, parameters of glucose and lipid metabolism were severely impaired (Wei et al., 2011; Garcia-Arevalo et al., 2014) as well as decreased pancreatic β -cell function and mass (Wei et al., 2011; Ding et al., 2014). Interestingly, the administration of BPA (50 μ g/kg/d) in rats throughout gestation and lactation was associated with hepatic epigenetic modifications that were proposed to be responsible for the metabolic alterations, insulin resistance, and impaired glucose tolerance, developed in the postnatal life (Ma et al., 2013).

Evidence now exists indicating that in adults BPA also provokes adverse metabolic consequences. Experiments performed in male OF-1 mice showed that a single subcutaneous injection of 10 μ g/kg of BPA produces a rapid decrease in blood glucose that occurred in parallel to an increase in plasma insulin levels (Alonso-Magdalena et al., 2006). Prolonged exposure to this compound also have effects on glucose homeostasis.

The administration of BPA at a dose 100 $\mu\text{g}/\text{kg}$ for a period of 4 days resulted in postprandial hyperinsulinemia, impaired glucose tolerance, and marked insulin resistance (Alonso-Magdalena et al., 2006). This insulin resistance may be explained by a disruption of insulin signaling in skeletal muscle and liver. The BPA treatment led to decreased phosphorylation of insulin receptor tyrosine, followed by reduced Akt phosphorylation on the residue Thr³⁰⁸ in the skeletal muscle. In addition, there is an impairment of insulin-induced ERK (extracellular-signal-regulated kinase) phosphorylation in that tissue. In the liver, the effects were lower with decreased insulin-stimulated tyrosine phosphorylation of the insulin receptor (Batista et al., 2012). Longer exposure to BPA in adults impaired hepatic glucokinase activity and function (Perreault et al., 2013), meanwhile chronic BPA administration during a period of 8 months provoked increased adipose tissue, glucose intolerance, higher levels of cholesterol, and overexpression of key genes involved in cholesterol biosynthesis (Marmugi et al., 2014).

In Vitro Studies and Mechanisms Proposed

It is well known that environmental relevant doses of BPA can affect pancreatic α - and β -cell physiology. At a concentration of 1 nmol/L, BPA inhibits calcium oscillations in α -cells, a key event in the glucagon secretion process. This action is characterized by a rapid onset and involves a pertussis toxin-sensitive G-protein, nitric oxide synthase, guanylate cyclase, and PKG (protein kinase G) (Alonso-Magdalena et al., 2005). As regards β -cells, BPA affects pancreatic β -cell function in 2 different manners in the range doses 100 pmol/L to 10 nmol/L. On one hand, it rapidly provokes the closure of the K_{ATP} channel of β -cells, increasing the frequency of $[\text{Ca}^{2+}]$ oscillations, which finally results in a rapid increased insulin secretion. Genetic and pharmacological tools demonstrated that this effect is mediated by the activation of ER β out of the nucleus (Nadal et al., 2000; Soriano et al., 2012). On the other hand, BPA can affect insulin gene transcription and biosynthesis after binding extranuclear ER α (Alonso-Magdalena et al., 2008; Alonso-Magdalena et al., 2012).

Moreover, it has been shown that BPA can affect glucose transport in adipocyte cell models, in a mechanism that includes an increase in the basal and insulin-stimulated glucose transport due to an increased amount of GLUT4 (glucose transporter type 4; Sakurai et al., 2004).

More recently, it has been reported that cultured human adipocytes in the presence of BPA 1 nmol/L showed decreased insulin-stimulated glucose utilization, with no changes in GLUT4 levels. However, an increased basal glucose uptake was observed in this cellular model which was related to increased levels of GLUT1 (Valentino et al., 2013).

Epidemiological Evidence for the Diabetogen Behavior of BPA

Increasing epidemiological evidence establishes a connection link between BPA levels (predominantly in urine) and incidence

of T2DM. The first one was the cross-sectional analysis performed in a representative sample of the adult population of the United States in 2003/2004 (NHANES) which showed that higher urinary levels of BPA were associated with abnormal levels of the liver enzymes γ -glutamyl-transferase, alkaline phosphatase, and lactate dehydrogenase. The authors also established a significant relationship between BPA concentration and T2DM and cardiovascular disease (Lang et al., 2008).

A similar study was carried out using later NHANES data from 2005/2006. The authors found that urinary BPA concentrations were significantly lower in 2005/2006 (1.79 ng/mL) than in the population of 2003/2004 (2.49 ng/mL). A correlation between urinary BPA concentrations and an increased prevalence of coronary heart disease was still present. With regard to the prevalence of diabetes and liver enzyme abnormalities, the association with urinary BPA was not significant but the pooled estimate remained significant (Melzer et al., 2010). Data from 2003/2008 confirmed the association of urinary BPA levels with T2DM in the 2003/04 pool but not in the 2005/06 pool (Silver et al., 2011).

Similar studies based on NHANES 2003 to 2008, but taking into consideration fasting glucose levels, as well as glycosylated hemoglobin to define diabetes mellitus, reported a positive association between increasing BPA levels and the incidence of diabetes, which was independent of other factors such as age, gender, or body composition (Shankar & Teppala, 2011). A positive correlation with prediabetes was also observed (Sabanayagam et al., 2013). In a representative Chinese adult population, similar findings were observed with a significant relationship between urinary BPA levels and prevalence of insulin resistance (Wang et al., 2012b). Other studies show the same association between BPA and insulin resistance as well as hyperinsulinemia which was more evident in male than in female (Beydoun et al., 2014). Curiously, a new prospective study established a correlation between BPA concentrations and risk of T2DM in middle-aged but not older women, after adjusting by body mass index (Sun et al., 2014).

Concluding Remarks

The data reviewed earlier support the notion that the environmental estrogen, BPA, is involved in the metabolic programming of metabolic disorders such as obesity and T2DM. Exposure to low doses of BPA during critical periods of development has been shown to increase body weight (obesogenic action), alter glucose homeostasis (diabetogenic action), or both (diabesogenic action). In adult humans, epidemiological evidence also shows a positive relationship between BPA levels and the incidence of both diseases. More mechanistic insides are, nonetheless, required in order to completely understand the molecular basis of the obesogenic, diabetogenic, and diabesogenic actions of BPA.

References

Alonso-Magdalena P, Laribi O, Ropero AB, Fuentes E, Ripoll C, Soria B, and Nadal A. (2005). Low doses of bisphenol A and

- diethylstilbestrol impair Ca^{2+} signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ Health Perspect* **113**, 969-977.
- Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E, and Nadal A. (2006). The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. *Environ Health Perspect* **114**, 106-112.
- Alonso-Magdalena P, Quesada I, and Nadal A. (2011). Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nat Rev Endocrinol* **7**, 346-353.
- Alonso-Magdalena P, Ropero AB, Carrera MP, Cederroth CR, Baquie M, Gauthier BR, Nef S, Stefani E, and Nadal A. (2008). Pancreatic insulin content regulation by the estrogen receptor ER alpha. *PLoS One* **3**, e2069.
- Alonso-Magdalena P, Ropero AB, Soriano S, Garcia-Arevalo M, Ripoll C, Fuentes E, Quesada I, and Nadal A. (2012). Bisphenol-A acts as a potent estrogen via non-classical estrogen triggered pathways. *Mol Cell Endocrinol* **355**, 201-207.
- Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, and Nadal A. (2010). Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect* **118**, 1243-1250.
- Anderson OS, Peterson KE, Sanchez BN, Zhang Z, Mancuso P, and Dolinoy DC. (2013). Perinatal bisphenol A exposure promotes hyperactivity, lean body composition, and hormonal responses across the murine life course. *FASEB J* **27**, 1784-1792.
- Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, Welshons WV, Besch-Williford CL, Palanza P, Parmigiani S, vom Saal FS, and Taylor JA. (2013). Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reprod Toxicol* **42**, 256-268.
- Barker DJ. (1998). In utero programming of chronic disease. *Clin Sci (Lond)* **95**, 115-128.
- Batista TM, Alonso-Magdalena P, Vieira E, Amaral ME, Cederroth CR, Nef S, Quesada I, Carneiro EM, and Nadal A. (2012). Short-term treatment with bisphenol-A leads to metabolic abnormalities in adult male mice. *PLoS One* **7**, e33814.
- Ben-Jonathan N, Hugo ER, and Brandebourg TD. (2009). Effects of bisphenol A on adipokine release from human adipose tissue: Implications for the metabolic syndrome. *Mol Cell Endocrinol* **304**, 49-54.
- Beydoun HA, Khanal S, Zonderman AB, and Beydoun MA. (2014). Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among U.S. adults. *Ann Epidemiol* **24**, 90-97.
- Bhandari R, Xiao J, and Shankar A. (2013). Urinary bisphenol A and obesity in U.S. children. *Am J Epidemiol* **177**, 1263-1270.
- Boucher JG, Husain M, Rowan-Carroll A, Williams A, Yauk CL, and Atlas E. (2014). Identification of mechanisms of action of bisphenol A-induced human preadipocyte differentiation by transcriptional profiling. *Obesity (Silver Spring)*.
- Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, and Venners SA. (2014). Early-Life Bisphenol A Exposure and Child Body Mass Index: A Prospective Cohort Study. *Environ Health Perspect*.
- Calafat AM, Kuklennyik Z, Reidy JA, Caudill SP, Ekong J, and Needham LL. (2005). Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environ Health Perspect* **113**, 391-395.
- Carwile JL and Michels KB. (2011). Urinary bisphenol A and obesity: NHANES 2003-2006. *Environ Res* **111**, 825-830.
- Casals-Casas C and Desvergne B. (2011). Endocrine disruptors: from endocrine to metabolic disruption. *Annu Rev Physiol* **73**, 135-162.
- Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, de Mouzon SH, and Amini SB. (2009). Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr* **90**, 1303-1313.
- Chamorro-Garcia R, Kirchner S, Li X, Janesick A, Casey SC, Chow C, and Blumberg B. (2012). Bisphenol A diglycidyl ether induces adipogenic differentiation of multipotent stromal stem cells through a peroxisome proliferator-activated receptor gamma-independent mechanism. *Environ Health Perspect* **120**, 984-989.
- Chen L, Magliano DJ, and Zimmet PZ. (2011). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nat Rev Endocrinol* **8**, 228-236.
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, and Gore AC. (2009). Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev* **30**, 293-342.
- Ding S, Fan Y, Zhao N, Yang H, Ye X, He D, Jin X, Liu J, Tian C, Li H, Xu S, and Ying C. (2014). High-fat diet aggravates glucose homeostasis disorder caused by chronic exposure to bisphenol A. *J Endocrinol* **221**, 167-179.
- Dodds E.C. and Lawson W. (1936). Synthetic estrogenic agents without the phenanthrene nucleus. *Nature* **137**, 996.
- Efsa. (2014). <http://www.efsa.europa.eu/en/topics/topic/bisphenol.htm>.
- EPA. (1993). (<http://www.epa.gov/iris/subst/0356.htm#reforal>).
- Garcia-Arevalo M, Alonso-Magdalena P, Rebelo Dos Santos J, Quesada I, Carneiro EM, and Nadal A. (2014). Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering glucose homeostasis and gene expression in adult male mice. *PLoS One* **9**, e100214.
- Gilbert S and Epel D. (2009). Ecological Developmental Biology: Integrating Epigenetics, Medicine and Evolution.
- Grasselli E, Cortese K, Voci A, Vergani L, Fabbri R, Barmo C, Gallo G, and Canesi L. (2013). Direct effects of Bisphenol A on lipid homeostasis in rat hepatoma cells. *Chemosphere* **91**, 1123-1129.
- Grun F and Blumberg B. (2007). Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Rev Endocr Metab Disord* **8**, 161-171.
- Halpern A and Mancini MC. (2005). Diabetes: are weight loss medications effective? *Treat Endocrinol* **4**, 65-74.
- Harley KG, Aguilar Schall R, Chevrier J, Tyler K, Aguirre H, Bradman A, Holland NT, Lustig RH, Calafat AM, and Eskenazi B. (2013). Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. *Environ Health Perspect* **121**, 514-520, 520e511-516.

- Hectors TL, Vanparys C, van der Ven K, Martens GA, Jorens PG, Van Gaal LF, Covaci A, De Coen W, and Blust R. (2011). Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. *Diabetologia* **54**, 1273-1290.
- Heindel JJ. (2003). Endocrine disruptors and the obesity epidemic. *Toxicol Sci* **76**, 247-249.
- Heindel JJ and vom Saal FS. (2009). Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. *Mol Cell Endocrinol* **304**, 90-96.
- Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenberg JG, and vom Saal FS. (1999). Exposure to bisphenol A advances puberty. *Nature* **401**, 763-764.
- Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, and Ben-Jonathan N. (2008). Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. *Environ Health Perspect* **116**, 1642-1647.
- Kang JH, Kondo F, and Katayama Y. (2006). Human exposure to bisphenol A. *Toxicology* **226**, 79-89.
- Ko A, Hwang MS, Park JH, Kang HS, Lee HS, and Hong JH. (2014). Association between Urinary Bisphenol A and Waist Circumference in Korean Adults. *Toxicol Res* **30**, 39-44.
- Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, and Melzer D. (2008). Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA* **300**, 1303-1310.
- Li DK, Miao M, Zhou Z, Wu C, Shi H, Liu X, Wang S, and Yuan W. (2013). Urine bisphenol-A level in relation to obesity and overweight in school-age children. *PLoS One* **8**, e65399.
- Ma Y, Xia W, Wang DQ, Wan YJ, Xu B, Chen X, Li YY, and Xu SQ. (2013). Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood. *Diabetologia* **56**, 2059-2067.
- Mackay H, Patterson ZR, Khazall R, Patel S, Tsirlin D, and Abizaid A. (2013). Organizational effects of perinatal exposure to bisphenol-A and diethylstilbestrol on arcuate nucleus circuitry controlling food intake and energy expenditure in male and female CD-1 mice. *Endocrinology* **154**, 1465-1475.
- Marmugi A, Lasserre F, Beuzelin D, Ducheix S, Huc L, Polizzi A, Chetivau M, Pineau T, Martin P, Guillou H, and Mselli-Lakhall L. (2014). Adverse effects of long-term exposure to bisphenol A during adulthood leading to hyperglycaemia and hypercholesterolemia in mice. *Toxicology* **325C**, 133-143.
- Masuno H, Iwanami J, Kidani T, Sakayama K, and Honda K. (2005). Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci* **84**, 319-327.
- Masuno H, Kidani T, Sekiya K, Sakayama K, Shiosaka T, Yamamoto H, and Honda K. (2002). Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res* **43**, 676-684.
- Melzer D, Rice NE, Lewis C, Henley WE, and Galloway TS. (2010). Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06. *PLoS One* **5**, e8673.
- Miyawaki J, Sakayama K, Kato H, Yamamoto H, and Masuno H. (2007). Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb* **14**, 245-252.
- Munoz-de-Toro M, Markey CM, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, and Soto AM. (2005). Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocrinology* **146**, 4138-4147.
- Nadal A, Ropero AB, Laribi O, Maillet M, Fuentes E, and Soria B. (2000). Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor alpha and estrogen receptor beta. *Proc Natl Acad Sci U S A* **97**, 11603-11608.
- Newbold RR, Padilla-Banks E, and Jefferson WN. (2009). Environmental estrogens and obesity. *Mol Cell Endocrinol* **304**, 84-89.
- Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara N, and Tsubura A. (2004). Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. *Reprod Toxicol* **18**, 803-811.
- Nunez AA, Kannan K, Giesy JP, Fang J, and Clemens LG. (2001). Effects of bisphenol A on energy balance and accumulation in brown adipose tissue in rats. *Chemosphere* **42**, 917-922.
- O'Rahilly S. (2009). Human genetics illuminates the paths to metabolic disease. *Nature* **462**, 307-314.
- Ohlstein J, Strong AL, McLachlan JA, Gimble JM, Burow ME, and Bunnell BA. (2014). Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells. *J Mol Endocrinol*.
- Oken E and Gillman MW. (2003). Fetal origins of obesity. *Obes Res* **11**, 496-506.
- Patisaul HB and Bateman HL. (2008). Neonatal exposure to endocrine active compounds or an ERbeta agonist increases adult anxiety and aggression in gonadally intact male rats. *Horm Behav* **53**, 580-588.
- Perreault L, McCurdy C, Kerege AA, Houck J, Faerch K, and Bergman BC. (2013). Bisphenol A impairs hepatic glucose sensing in C57BL/6 male mice. *PLoS One* **8**, e69991.
- Qatanani M and Lazar MA. (2007). Mechanisms of obesity-associated insulin resistance: many choices on the menu. *Genes Dev* **21**, 1443-1455.
- Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, Vandenberg JG, Walser-Kuntz DR, and vom Saal FS. (2007). In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol* **24**, 199-224.
- Riu A, McCollum CW, Pinto CL, Grimaldi M, Hillenweck A, Perdu E, Zalko D, Bernard L, Laudet V, Balaguer P, Bondesson M, and Gustafsson JA. (2014). Halogenated bisphenol-A analogs act as obesogens in zebrafish larvae (Danio rerio). *Toxicol Sci* **139**, 48-58.
- Ronn M, Kullberg J, Karlsson H, Berglund J, Malmberg F, Orberg J, Lind L, Ahlstrom H, and Lind PM. (2013). Bisphenol A exposure increases liver fat in juvenile fructose-fed Fischer 344 rats. *Toxicology* **303**, 125-132.
- Rubin BS, Murray MK, Damassa DA, King JC, and Soto AM. (2001). Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect* **109**, 675-680.

- Sabanayagam C, Teppala S, and Shankar A. (2013). Relationship between urinary bisphenol A levels and prediabetes among subjects free of diabetes. *Acta Diabetol* **50**, 625-631.
- Sajiki J, Takahashi K, and Yonekubo J. (1999). Sensitive method for the determination of bisphenol-A in serum using two systems of high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl* **736**, 255-261.
- Sakurai K, Kawazuma M, Adachi T, Harigaya T, Saito Y, Hashimoto N, and Mori C. (2004). Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. *Br J Pharmacol* **141**, 209-214.
- Seidlova-Wuttke D, Jarry H, Christoffel J, Rimoldi G, and Wuttke W. (2005). Effects of bisphenol-A (BPA), dibutylphthalate (DBP), benzophenone-2 (BP2), procymidone (Proc), and linurone (Lin) on fat tissue, a variety of hormones and metabolic parameters: a 3 months comparison with effects of estradiol (E2) in ovariectomized (ovx) rats. *Toxicology* **213**, 13-24.
- Shankar A and Teppala S. (2011). Relationship between urinary bisphenol A levels and diabetes mellitus. *J Clin Endocrinol Metab* **96**, 3822-3826.
- Shankar A, Teppala S, and Sabanayagam C. (2012). Urinary bisphenol A levels and measures of obesity: results from the national health and nutrition examination survey 2003-2008. *ISRN Endocrinol* 2012, 965243.
- Sharpe RM and Skakkebaek NE. (1993). Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* **341**, 1392-1395.
- Silver MK, O'Neill MS, Sowers MR, and Park SK. (2011). Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003-2008. *PLoS One* **6**, e26868.
- Skakkebaek NE, Rajpert-De Meyts E, Jorgensen N, Carlsen E, Petersen PM, Giwercman A, Andersen AG, Jensen TK, Andersson AM, and Muller J. (1998). Germ cell cancer and disorders of spermatogenesis: an environmental connection? *Apmis* **106**, 3-11; discussion 12.
- Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combesure C, Nef S, Aubert ML, and Huppi PS. (2009). Perinatal exposure to bisphenol A alters early adipogenesis in the rat. *Environ Health Perspect* **117**, 1549-1555.
- Song Y, Hauser R, Hu FB, Franke AA, Liu S, and Sun Q. (2014). Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women. *Int J Obes (Lond)*.
- Soriano S, Alonso-Magdalena P, Garcia-Arevalo M, Novials A, Muhammed SJ, Salehi A, Gustafsson JA, Quesada I, and Nadal A. (2012). Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor beta. *PLoS One* **7**, e31109.
- Stumvoll M, Goldstein BJ, and van Haefen TW. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* **365**, 1333-1346.
- Sun Q, Cornelis MC, Townsend MK, Tobias DK, Eliassen AH, Franke AA, Hauser R, and Hu FB. (2014). Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. *Environ Health Perspect* **122**, 616-623.
- Takeuchi T and Tsutsumi O. (2002). Serum bisphenol A concentrations showed gender differences, possibly linked to androgen levels. *Biochem Biophys Res Commun* **291**, 76-78.
- Trasande L, Attina TM, and Blustein J. (2012). Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. *JAMA* **308**, 1113-1121.
- Valentino R, D'Esposito V, Passaretti F, Liotti A, Cabaro S, Longo M, Perruolo G, Oriente F, Beguinot F, and Formisano P. (2013). Bisphenol-A impairs insulin action and up-regulates inflammatory pathways in human subcutaneous adipocytes and 3T3-L1 cells. *PLoS One* **8**, e82099.
- van Esterik JC, Dolle ME, Lamoree MH, van Leeuwen SP, Hamers T, Legler J, and van der Ven LT. (2014). Programming of metabolic effects in C57BL/6JxFVB mice by exposure to bisphenol A during gestation and lactation. *Toxicology* **321**, 40-52.
- Vandenberg LN, Hauser R, Marcus M, Olea N, and Welshons WV. (2007). Human exposure to bisphenol A (BPA). *Reprod Toxicol* **24** (2), 139-177.
- vom Saal FS and Hughes C. (2005). An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ Health Perspect* **113**, 926-933.
- Wang HX, Zhou Y, Tang CX, Wu JG, Chen Y, and Jiang QW. (2012a). Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study. *Environ Health* **11**, 79.
- Wang J, Sun B, Hou M, Pan X, and Li X. (2013). The environmental obesogen bisphenol A promotes adipogenesis by increasing the amount of 11beta-hydroxysteroid dehydrogenase type 1 in the adipose tissue of children. *Int J Obes (Lond)* **37**, 999-1005.
- Wang T, Li M, Chen B, Xu M, Xu Y, Huang Y, Lu J, Chen Y, Wang W, Li X, Liu Y, Bi Y, Lai S, and Ning G. (2012b). Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J Clin Endocrinol Metab* **97**, E223-227.
- Warner MJ and Ozanne SE. (2010). Mechanisms involved in the developmental programming of adulthood disease. *Biochem J* **427**, 333-347.
- Wei J, Lin Y, Li Y, Ying C, Chen J, Song L, Zhou Z, Lv Z, Xia W, Chen X, and Xu S. (2011). Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology* **152**, 3049-3061.
- WHO. (2014). (<http://www.who.int/mediacentre/factsheets/fs311/en/>).
- Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, and Son HY. (2006). Epidemic obesity and type 2 diabetes in Asia. *Lancet* **368**, 1681-1688.
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ, and Vom Saal FS. (2012). Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology* **153**, 4097-4110.