Developmental exposure to Bisphenol A : a contributing factor to the increased incidence of obesity ?

Julie Fudvoye, Marie-Christine Lebrethon, Anne-Simone Parent

Department of Pediatrics, University Hospital of Liège

jfudvoye@chuliege.be

Keywords

Endocrine disruptors, perinatal exposure, Bisphenol A, adipose tissue, hypothalamus

Abstract

Recent data suggest a possible involvement of endocrine disruptors in the current trend of increased incidence of metabolic syndrome and/or obesity. Indeed, by altering hormonal environment, endocrine disruptors can affect homeostatic mechanisms involved in the regulation of metabolism and the control of adipocyte function.

According to Barker's hypothesis, prenatal and early postnatal life are critical periods for future health. Exposure to endocrine disruptors perinatally could be associated with disorders of energy balance throughout subsequent life.

Bisphenol A is a widespread endocrine disruptor, commonly found in food and beverages stored in polycarbonate plastic and epoxy resin containers. Humans are exposed to Bisphenol A through dietary intake but also through non food sources (transdermal exposure from skin contact with thermal paper; dental materials, medical devices). More than 90% of the Belgian population has detectable levels of Bisphenol A in their urine, illustrating the widespread exposure.

In this article, we will first describe animal studies suggesting the potential role of early exposure to Bisphenol A in the alteration of energy balance, through peripheral as well as central effects on circuits involved in the regulation of energy homeostasis. The second part of the article will be dedicated to human data currently available.

Introduction

The rise in obesity, diabetes and metabolic disease incidence during the last 50 years is attributed to genetic factors associated with increased caloric intake, decreased physical activity, sleep deficit and aging (1). However, other environmental factors, among which endocrine disrupting chemicals (EDCs), seem to play a significant role in the global deterioration of metabolic health.

The concept of developmental origin of health and disease has been first developed by Barker. He showed that lower birth weight was associated with a higher risk of cardiovascular disease and premature death in young adult (2). The potential impact of early exposure to endocrine disruptors has been dramatically illustrated by the story of diethylstilbestrol (DES), a pharmaceutical oestrogen prescribed to pregnant women to avoid pregnancy complications. Daughters of mothers treated with DES presented an increased incidence of vaginal adenocarcinoma and benign reproductive lesions but also diabetes and cardiovascular disease and hypercholesterolemia (3,4). Those examples highlight the critical role of intra-uterine and early postnatal life for future health and suggest that the increased incidence of obesity and metabolic syndrome could be explained in part by early alteration of early hormonal environment through EDCs exposure. Many rodent studies have addressed this hypothesis, examining the effects of early (foetal and neonatal) exposure to endocrine disruptors on adiposity and metabolic control. Data in human are scarce but a few longitudinal studies is currently available. Bisphenol A (BPA) was initially synthetized as an estrogenic compound but is now used in polycarbonate plastic and epoxy resin. In Belgium, its use is forbidden in food containers for children under 3 years of age. However, the vast majority of the population is constantly exposed (5).

Several endocrine disrupters are now considered to be obesogens (table 1). In this article, we will use BPA to illustrate some important concepts regarding obesogenic EDCs as it is one of the most widespread and studied chemicals.

Table 1: list of potential obesogens

Name	Use
Dibutyltin	Polyvinyl chloride (PVC) plastics
Bisphenol A	Plasticizer
Bisphenol F, bisphenol S	Plasticizers
Acrylamide	Manufacture of paper and dye, byproduct of carbohydrate-containing food (frying, baking, roasting)
Dioctyl sodium sulfosuccinate	Dietary emulsifier
Carboxymethylcelluclose, P-80	Dietary emulsifier
Dichloro-diphenyl-trichloroethane (DDT)	Pesticide
Methoxyclor	Pesticide
Imidacloprid	Insecticide
Glyphosate	Herbicide
Quizalofop-p-ethyl	Herbicide

Animal studies

Animal studies have shown that early exposure to BPA predisposes individuals to weight gain and accelerated growth rate. A study by Howdeshell *et al* revealed that pups prenatally exposed to low dose of BPA (2,4 µg/kg/day) were heavier than control pups before puberty (6). This finding was confirmed in 2001, by Rubin, who showed that male and female offspring exposed to BPA *in utero* and through lactation (0.1 mg BPA/kg body weight (bw)/day or 1.2 mg BPA/kg bw/day) had increased body weight. The increase started soon after birth and was more persistent in females than males (7). Additional studies confirmed the link between perinatal exposure to BPA and increased body weight (8-11). However, heterogeneity of the results is high and explained by periods of exposures, doses and animal strains. Many studies have reported nonmonotonic effects on weight gain and insulin resistance. Thus, BPA is an obesogenic EDC whose effects needs to be further characterized.

Following initial evidence of alterations of energy balance caused by BPA, many studies have focused on the effects of perinatal and lactational exposure to BPA on specific tissues involved in the regulation of energy homeostasis. We will first summarize the central effects of early BPA exposure on the

hypothalamus. We will then focus on data illustrating the impact of BPA on adipose tissue and pancreas.

Effect of BPA on hypothalamus

The hypothalamus is connected to the hindbrain and plays a central role in the control of energy homeostasis and feeding behaviour (12). Regulation of energy intake in the hypothalamus takes place in the arcuate nucleus (ARC) where two neuronal populations with antagonistic effects coexist: neuropeptide Y (NPY) and agouti- related protein (AgRP) expressing neurons have an orexigenic action and proopiomelanocortin (POMC), cocaine expressing neurons and amphetamine-regulated transcript protein (CART) expressing neurons have an anorexigenic action. The establishment of such central control of feeding behaviours takes place both in utero and neonatally. Thus, it seems that the metabolic impact of EDC exposure during this critical period may be significantly greater (13).

Males perinatally exposed to BPA exhibit reduced POMC fibre density into the paraventricular nucleus of the hypothalamus during adulthood, when fed a high-fat diet, suggesting that BPA exposure could make them more susceptible to diet-induced obesity or metabolic disease (14). The pattern of oestrogen receptor alpha expression in POMC neurons in females exposed to BPA was similar to that seen in males, suggesting a masculinizing effect of BPA. Interestingly, female exposed to BPA gained more weight, and ate more calories daily compared to control without any effect on energy expenditure whereas male exposed to BPA and high fat diet exhibited decreased energy expenditure compared to control, illustrating a sexually dimorphic effect of early BPA exposure on energy homeostasis.

Perinatal exposure of mice to BPA also disrupts the action of leptin on the hypothalamus. Leptin is an adipokine hormone that interacts with POMC and neuropeptide Y / agouti- related protein neurons in the ARC to control food intake and plays a crucial role in the establishment of those hypothalamic circuits postnatally. Male and female mice exposed to BPA are less sensitive to leptin effects on POMC expression and weight loss compared to controls. The postnatal leptin surge is delayed in mice exposed to BPA, suggesting permanent alterations of the neurocircuitry involved in the metabolic homeostasis (15).

Effects of BPA on adipose tissue

BPA enhances differentiation of pre-adipocytes into adipocytes *in vitro* and causes higher accumulation of triglycerides and lipoprotein lipase in target cells (16,17). Additionally, BPA has been shown to increase mRNA expression and enzymatic activity of 11β-HSD1, an enzyme which converts inactive cortisone into cortisol in adipose tissues and promotes adipogenesis (17). A concentration of 100nM also activates glucocorticoid receptors and thereby increases lipid accumulation and expression of adipocytic proteins in mature adipocytes (18). Basal glucose uptake in mature mouse 3T3-F443A adipocytes is enhanced after BPA exposure, in relation with an increased expression of the GLUT 4 protein (19). Some studies *in vivo* showed evidence of similar actions of BPA on adipocytes differentiation and function: gestational and lactational exposure to BPA leads to adipocyte hypertrophy in female pups and increased expression of adipogenic markers such PPAR-γ, SREBP-1C, SCD-1 and C/EBP-ALPHA I (20). Notably, BPA at low doses (1 and 10 nM) also inhibits adiponectin secretion from human adipose tissue (21). Adiponectin is an adipocyte-specific hormone that increases insulin sensitivity and reduces tissue inflammation while the release of IL-6 and TNF alpha, two inflammatory cytokines involved to obesity, is stimulated by BPA exposure (22,23).

Effects of BPA on the pancreas

Exposure to BPA has been shown to affect different aspects of β-cell function. *In vivo*, a single dose exposure to BPA in adulthood has been shown to increase insulin release and glucose stimulated insulin secretion in an estrogen-receptor–dependent manner (24). When exposure occurs *in utero*, BPA reduces glucose tolerance and increases insulin resistance in male offspring at 6 months of age (25). These opposite effects illustrate the disruption of foetal programming caused by BPA which could predispose mice to metabolic disorders. Interestingly, some studies suggest that these changes in glucose regulation are persistent in adult offspring and are worsened if the offspring is fed with a high fat diet (26). The pregnant mice exposed to BPA during gestation also develop profound glucose intolerance and impaired insulin sensitivity. Those mice remain heavier several months after delivery and show impaired beta-cell function and mass (27).

Transgenerational effects of BPA exposure on obesity

Developmental exposure to EDCs is associated with epigenetic alterations that can be passed from one generation to another and persist in adulthood (28). Animals born from female exposed to a mixture containing BPA and phthalates have a higher incidence of obesity throughout the third generation (29). Mechanisms involved in such transmission remain to be elucidated. It was proposed that obesogen exposure can permanently reprogram mesenchymal stem cells to favor the adipose lineage (30). Thus EDCs could promote epigenomic changes favoring the development of obesity (30).

Human studies:

The potential effects of BPA exposure on energy balance in children and adolescents have been investigated in recent epidemiological studies. Trasande *et al* have shown that higher urinary BPA concentrations in children and adolescents were associated with increased incidence of obesity (31). Another cross sectional study in school-age children in Shangai, reported that incidence of overweight was increased amongst girls aged 9-12 who had higher urinary BPA concentrations (32). Interestingly, this association was not found in boys, suggesting a sexually dimorphic effect of BPA exposure. In contrast, the association between higher urinary BPA levels and incidence of obesity was predominantly observed in American boys (33). Increased BPA concentrations have been also linked to abnormal waist circumference-to-height ratio in the US population (34). More recently, a study performed on a small number of Iran children has shown that, in addition to the increased body mass index and waist circumference, it appears that systolic and diastolic blood pressure as well as fasting blood glucose were increased in children with higher urinary BPA levels (35).

In all those studies, BPA exposure is assessed by the measure of BPA concentrations in one urinary sample. Given the short half-life of BPA, the use of a single urine sample to categorize exposure is an important limitation for data interpretation (36). Moreover, drawing conclusions from those cross sectional studies remains difficult because obese children ingest more BPA contaminated food such as canned sodas or have greater adipose stores of BPA which would explain the higher urinary concentrations.

Only a few longitudinal human studies focused on the effects of early exposure to BPA on metabolic health later in life. One prospective study in a Spanish birth cohort showed a positive association between prenatal exposure to BPA (assessed by urine BPA concentration during the first and the third trimester of pregnancy) and the risk of obesity at 4 years of age. This association was not present at earlier ages (37). In contrast, other prospective studies have demonstrated an inverse correlation between early exposure to BPA and BMI in childhood (38, 39). Once again, a sexually dimorphic effect of early BPA exposure has been suggested since the inverse correlation was only present in girls (38). Currently, it remains difficult to draw any conclusions from prospective studies aiming at evaluating the effects of early BPA exposure on metabolic health in children and large prospective birth cohorts with multiple measurements of urinary BPA concentrations during pregnancy are needed.

Conclusion:

In conclusion, the perinatal period is a crucial window for the organization of the control of energy balance. While many animal studies indicate that developmental exposure to BPA disrupts the central and peripheral control of energy balance, large longitudinal studies are needed to explore the metabolic consequences of BPA in children.

Factors such as the gut microbiome composition, stress and disrupted circadian rhythms have been recently identified as playing a role in metabolic disease. As these factors are targeted by EDCs, further studies will need to focus on such interactions.

BPA is slowly being phased out and replace by other chemicals such as BPS (Bisphenol S) which appear to have endocrine disrupting properties. Thus effects of replacement chemicals as well as mixture on obesity will need to be further explored.

REFERENCES:

1. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr Rev. 2017; 38: 267-296.
2. Barker DJP., Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. The Lancet 1986; 1: 1077-1081.
3. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N. Engl. J. Med. 1971; 284: 878-881.
4. Troisi R, Hyer M, Hatch EE, Titus-Ernstoff L, Palmer JR, Strohsnitter WC et al. Medical conditions among adult offspring prenatally exposed to diethylstilbestrol. Epidemiology 2013; 24: 430-438.
5. Pirard C, Sagot C, Deville M, Dubois N, Charlier C. Urinary levels of bisphenol A, triclosan and 4-nonylphenol in a general Belgian population. Environ. Int. 2012; 48: 78-83
6. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. Exposure to bisphenol A advances puberty. Nature 1999; 401: 763-4.
7. Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity and plasma LH levels. Environ. Health Perspect. 2001; 109: 675-680.
8. Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara Net al. Effects of maternal xenoestrogen exposure on development of the
9. reproductive tract and mammary gland in female CD-1 mouse offspring. Reprod.
10. Toxicol. 2004; 18: 803-11
11. Patisaul and Bateman. Neonatal exposure to endocrine active compounds or an ER beta agonist increases adult anxiety and aggression in gonadally intact male rats. Horm. Behav. 2008; 53: 580-8
12. Newbold RR, Jefferson WN, Padilla-Banks E. Long term adverse effects of neonatal exposure to BPA on the murine female reproductive tract. Reprod. Toxicol. 2007; 24: 253-8
13. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. J Atheroscler Thromb. 2007; 14: 245-252
14. Waterson MJ, Horvath TL. Neuronal Regulation of Energy Homeostasis: Beyond the Hypothalamus and Feeding. Cell Metab. 2015; 22: 962-70.
15. Walley S and Roepke T. Perinatal exposure to endocrine disrupting compounds and the control of feeding behavior- an overview. Horm. Behav. 2018; 101: 22-28.
16. Mackay H, Patterson ZR, Khazall R, Patel S, Tsirlin D, Abizaid A. 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 2013;154: 1465-75.
17. MacKay H, Patterson ZR, Abizaid A. Perinatal Exposure to Low-Dose Bisphenol-A Disrupts the Structural and Functional Development of the Hypothalamic Feeding Circuitry. Endocrinology. 2017;158: 768-777.
18. Masuno L., Kidani., Sehiya K., Sakayama K., Shiosaka T., Yamamoto H.et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. J. Lipid. Res. 2002; 43: 676-684
19. Masuno H., Iwanami J., Kidani, T., Sakayama K., Honda K. Bisphenol A accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. Toxicol. Sci. 2005; 84: 319–327.
20. Sargis RM., Johnson DN., Choudhuryl RA., and Bradyl MJ. Endocrine Disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. Obesity 2010; 18: 1283-1288.
21. Sakurai K, Kawazuma M, Adachi T, Harigaya T, Saito Y, Hashimoto N et al.
22. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. Br. J. Pharmacol. 2004;141: 209-14.
23. Somm E., Schwitzgebel VM., Toulotte A., Cederroth CR., Combescure C., Nef S et al. Perinatal exposure to bisphenol A alters early adipogenesis in the rat. Environ. Health Perspect. 2009; 117: 1549-1555.
24. Hugo ER., Brandebourg TD., Woo JG., Loftus J., Wesley Alexander J., and Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Environ. Health Perspect. 2008; 116: 1642-1647
25. Whitehead JP., Richards AA., Hickman IJ., Macdonald GA., Prins JB. Adiponectin- a key adipokine in the metabolic syndrome. Diabetes Obes. Metab. 2008; 8: 264-280
26. Ben-Jonathan N., Hugo ER., and Brandebourg TD. Effects of bisphenol A on adipokine release from human adipose tissue: implications for the metabolic syndrome. Mol. Cell. Endocrinol. 2009; 304: 49-54
27. Alonso-Magdalena P1, Morimoto S, Ripoll C, Fuentes E, Nadal A. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ Health Perspect. 2006; 114: 106-12.
28. Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ. Health Persp. 2010; 118: 1243-1250.
29. Wei J, Lin Y, Li Y, Ying C, Chen J, Song et al. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. Endocrinology 2011; 152: 3049-3061.
30. Alonso-Magdalena P, García-Arévalo M, Quesada I, Nadal Á. Bisphenol-A treatment during pregnancy in mice: a new window of susceptibility for the development of diabetes in mothers later in life. Endocrinology. 2015;156: 1659-70.
31. Mclachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. Endocrin. Rev. 2001; 22: 319-341
32. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One. 2013;8 :e55387.
33. Egusquiza R.J., Blumberg B. Environmental Obesogens and Their Impact on Susceptibility to Obesity: New Mechanisms and Chemicals. Endocrinology 2020; 161: 1-14
34. Trasande L., Attina TM., Blustein J. Association Between Urinary Bisphenol A Concentration and Obesity Prevalence in Children and Adolescents. JAMA 2012; 308: 1113-1121.
35. Li D.K., Miao M., Zhou Z. Urine bisphenol-A level in relation to obesity and overweight in school-age children. PLoS One. 2013; 8(6): e65399.
36. Bhandari R, Xiao J, Shankar A. Urinary bisphenol A and obesity in U.S. children. 2013; 177 :1263-70
37. Eng D., Lee J.M., Gebremariam A., Meeker J.D., Peterson K., Padmanabhan V. Bisphenol A and Chronic Disease Risk Factors in US Children. Pediatrics 2013; 132: e637–e645.
38. Amin M., Ebrahim K., Hashemi M. Association of exposure to Bisphenol A with obesity and cardiometabolic risk factors in children and adolescents. Int. J. Environ. Health Res. 2018; 29: 94-106.
39. Thayer K., Doerge D., Hunt D. Pharmacokinetics of Bisphenol A in Humans Following a Single Oral Administration. Environ Int. 2015; 83: 107–115.
40. Valvi D., Casas M., Mendez M. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiology. 2013; 24: 791-9.
41. Vafeiadi M., Roumeliotaki T., Myridakis A. Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood. Environ Res. 2016; 146: 379-87.
42. Braun J.M., Lanphear B.P., Calafat A.M. Early-life bisphenol A exposure and child body mass index: a prospective cohort study. Environ. Health Perspect. 2014; 122: 1239–1245