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Is Bisphenol A an environmental obesogen?

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ABSTRACT

Bisphenol a (BPA) is an endocrine disruptor with an estrogenic activity that is widely produced for the manufacture of polycarbonate plastic, epoxy resin and thermal paper. Its ubiquitous presence in the environment contributes to broad and continuous human exposure which has been associated with deleterious health effects. Despite numerous controversial discussions and a lack of consensus about BPA's safety, growing evidence indicates that BPA exposure positively correlates with an increased risk of developing obesity. An updated analysis of the epidemiological, *in vivo* and *in vitro* studies indicates that BPA should be considered an obesogenic environmental compound. Precisely, BPA exposure during all life stages correlates with increased body weight and/or body mass index (BMI). Developmental periods that include prenatal, infancy and childhood appear to be critical windows with increased sensitivity to BPA effects. Finally, blood analysis and *in vitro* data clearly demonstrate that BPA promotes adipogenesis, lipid and glucose dysregulation and adipose tissue inflammation, thus contributing to the pathophysiology of obesity. Future prevention efforts should now be employed to avoid BPA exposure and more research to determine in depth the critical time windows, doses and impact of long-term exposure of BPA is warranted in order to clarify its risk assessment.

INTRODUCTION

Although 600 million people are currently facing energy deficits exposing them to undernutrition, 1.9 billion people worldwide are overweight, with 600 million of those classified as obese [1]. The growing rate of overweight and obese individuals clearly characterizes the current worldwide “nutrition paradox”. Whereas undernutrition has declined since 2007, obesity is now considered an epidemic and affects both adults and children [1]. An increase in caloric intake and a decrease of energy expenditure are the main risk factors for developing obesity. However, this energy imbalance, as well as genetic predispositions, do not seem to be fully responsible for the epidemiological rise of obesity worldwide [2]. Growing evidence strongly suggests that environmental chemicals, and particularly endocrine disruptors (EDs), are an additional risk factor explaining the global obesity epidemic [3–5]. The term “endocrine disruptor” was first mentioned in the 1990s and is historically associated with the field of developmental organs, reproductive toxicology and wildlife biology [6]. An ED is precisely defined as a substance or an exogenous mixture that is able to interfere with the endocrine system and consequently cause adverse effects in a healthy organism, its progeny, or other subpopulations [7]. Through the secretion of adipokines, adipose tissue is considered an endocrine organ and can be targeted by EDs, thus potentially leading to adipose tissue dysfunction and inflammation. These biological disorders appear during the pathophysiology of obesity and confirm the causative link between ED exposure and the “obesogen hypothesis” [3,8–10]. Obesogens are defined as chemicals that inappropriately alter metabolic functions such as lipid homeostasis and fat storage, energy balance, regulation of appetite and satiety in order to increase fat accumulation and, eventually, lead to the development of obesity [11–13]. Bisphenol a (BPA) was one of the first compounds identified as an obesogen alongside pesticides, heavy metals, polychlorinated bisphenyls (PCBs) [3,5,14]. BPA is a plastic and thermal paper component ubiquitously present in the environment and possesses estrogenic activity. Numerous controversial discussions concerning the impact of BPA exposure on human health are still debated despite emerging data demonstrating that BPA is associated with infertility, cancer and metabolic disorders like obesity [8,9].

The aim of this review is to provide an updated analysis of the literature focusing on the association between BPA exposure and the development of obesity.

OBESOGENIC ACTIVITY OF BISPHENOL A

1 – BPA

BPA (4,4'-isopropylidenediphenol or 2,2'-bis(4-hydroxyphenyl)-propane, CAS 80-05-7) is a white crystalline compound with a molecular weight of 228.29 g/mol, a melting-point of 156 °C and a water-octanol partition coefficient (logP) of 3.32, and is relatively soluble in lipophilic phases with low solubility in water (Figure 1) [15].

Figure 1: Molecular structure of BPA

BPA is one of the most widely produced compounds worldwide for the manufacture of polycarbonate plastic and epoxy resin with an estimated annual production that reached 6.8 million tons in 2013 [16]. BPA is found in pipes, food containers, bottles, toys, soaps, lotions, shampoo, nail polish, sunscreen, electronic equipment, car equipment, car tires, flame, retardants and more [17,18]. It is also used for its stabilizing and antioxidant properties and in thermal and carbonless paper manufacturing [19].

In 2010, after growing evidence suggested an association between BPA exposure and deleterious effects for human health, most notably in infants, France prohibited BPA in plastic infant feeding bottles as a precautionary measure. This prohibition was then applied in all of Europe in 2011. Since 2015, BPA has been prohibited in all food contact materials in Europe and the European Food Safety Authority (EFSA) defined the maximum tolerable daily intake (TDI) for BPA at 4 µg/kg of body weight *per* day [20].

In the USA, the Food and Drug Administration (FDA) banned the presence of BPA in products designed for infants and toddlers in 2012 and in 2014 published a draft assessment of the available literature and data on BPA. This draft assessment indicated that the “no observed adverse effect level” (NOAEL) was 5 mg/kg of body weight per day without any definition of a total daily intake (TDI). In contrast, Japan adopted a similar TDI as the EFSA [21]. After a study reviewing the health risk assessment of BPA from food packaging applications in 2013, the Minister of Health of Canada recommended that the general principle

of ALARA (as low as reasonably achievable) should be applied to continue efforts to limit BPA exposure[22].

Therefore, despite that the majority of health authorities in the world have enacted policies limiting BPA exposure in their populations, there is a clear lack of international harmonization concerning the BPA limit of exposure. This lack, as mentioned by the WHO, is due in part to a lack of data from experimental animal studies that are suitable for risk assessment, but also to design and analysis issues in epidemiological studies and their resulting controversial results [23].

2 - BPA exposure

Due to the ubiquitous presence of BPA in the environment, all routes of exposure need to be considered to identify all sources of BPA, which is difficult process. Oral exposure seems to be the most frequent source of BPA exposure in the literature, notably through food contamination by containers. For example, aluminum cans can release BPA in food after the pasteurization process. In addition, it has been demonstrated that increased temperature and extended use of plastic baby bottles can increase polycarbonate hydrolysis and lead to a release of BPA in the bottle contents [24]. All plastic baby bottles containing BPA are now prohibited in numerous countries in Europe, as well as Canada, USA and China.

BPA can also be released from epoxy resin lining of pipes leading to an increase of BPA levels in drinking water [25]. Consequently, BPA has been found in drinking water at concentrations ranging from 0.014 to 0.317 $\mu\text{g/L}$ and in water bottles at concentrations from 0.07 to 4.21 $\mu\text{g/L}$ [26,27]. Furthermore, human exposure to BPA can occur from non-dietary sources such as air (indoor and outdoor), cosmetics, thermal paper, dust, toys, cars and more [15,28].

Because BPA production is currently very prominent it is inevitably found in the environment. The degradation half-life of BPA in soils ranges from 1 to 10 days depending on soil composition and temperature [29–31]. Thus, BPA is not considered a persistent organic pollutant (POP) but its presence in sediments and urban ecosystems underlines the necessity to decrease both plastic pollution and BPA production, and to increase plastic recycling.

BPA is found in human serum throughout the general population in levels ranging from 0.0002 to 66 ng/mL [32–35]. Moreover, it is also found in umbilical blood at levels of 0.5 to 52.26 $\mu\text{g/L}$ reflecting both a maternal and a fetal exposure [36–38]. Administered orally, BPA is rapidly absorbed reaching a maximum blood concentration within 2 hours and has a

half-life time of approximately 6 hours [39,40]. Over 90 % of BPA is metabolized into BPA glucuronide (BPA-G) and it has been suggested that BPA phase II metabolism occurs in the small intestine [41–43]. The kinetic behavior of BPA-G appears more complex than BPA because of a prolonged terminal phase due to renal reabsorption [44]. BPA elimination occurs in a two-compartment model manner and the kidneys are the main way of elimination with a total elimination after 24 hours.

BPA is now well characterized as an ED but its glucuronide conjugate does not show estrogenic activity [45,46]. However, BPA-G has been shown to induce adipogenesis through an ER-independent pathway, confirming the complexity of the effects of BPA exposure [47].

3 - Impact of BPA in obesity

Epidemiological studies

Several recent reviews have been published concerning epidemiological data and the link between BPA exposure and obesity [39,48–51].

Rochester JR et al. (2013) reviewed the literature up to 2013 of BPA and its effects on human health and described that obesity and body weight were two of the most studied endpoints [8]. Nine of the ninety one articles analyzed reported that higher urinary or blood BPA concentration was significantly correlated with higher BMI or body weight [8]. However, because of the cross-sectional nature of these studies and controversial data, Rochester JR concluded that causal links may be complex and consequently difficult to interpret [8]. Lakind JS *et al.* (2014) reviewed the literature concerning the association of BPA exposure and diseases like obesity, diabetes and cardiovascular events. In this review, nine articles were selected that did not give evidence of a positive association between BPA exposure and obesity, BMI, waist circumference and body weight. Moreover, this review included studies carried out at single time point in adults, children and pregnant women and made interpretations for this population. This review also highlighted some controversial data [48]. Mirmira P and Evans-Molina C (2014) summarized human epidemiologic studies that have investigated links between BPA levels and obesity. Ten articles were selected that primarily showed associations between urinary BPA levels and obesity. However, no information about the criteria of selection of the articles was given and this work also highlights a number of caveats and controversies that should be considered in the article's interpretation [49]. Oppeneer S and Robien K (2015) supplied a detailed analysis and review of literature concerning the obesogenic activity of BPA

in humans. Eighteen studies were selected but evidence was unclear regarding the association between BPA exposure and increased BMI [50]. Most recently, Stojanoska MM *et al.* (2016) analyzed selected epidemiological studies of the effects of BPA on obesity and concluded that BPA has an indisputable role in the development of obesity in humans of BPA [39]. Collectively, all these reviews conclude: first, that BPA exposure may be involved in the development of obesity, however, that epidemiological data currently available are not sufficient to determine a positive correlation between high BPA exposure and obesity, second, that some results are divergent even when discussing controversies in the association of BPA and obesity and third, that significant limitations in methods do not currently permit a true meta-analysis.

However, as described above, obesity is a pathological condition with excessive fat mass. Adipose tissue is now considered an endocrine organ that actively secretes a number of adipokines. Zhao H.Y. *et al.* (2012) highlighted that high BPA exposure was associated with higher urinary levels of leptin, an adipokine that acts to induce satiety and regulates long term energy balance [52]. Elevated leptin levels contribute over time to the development of leptin resistance, a contributing factor to increase in fat mass [53,54]. More recently, Rönn M. *et al.* (2014) showed that increased adiponectin, an adipokine secreted in order to counteract insulin resistance, and leptin circulating levels were associated with an increased BPA level even without an increase in fat mass. In this study, which was performed with 870 subjects >70 years of age, elevated BPA levels were also associated with a decrease in ghrelin level [55]. Ghrelin is a hormone released from organs of the digestive system and from the hypothalamus and possesses orexigenic activity. Ghrelin is also known as a short and long term regulator of body weight and low ghrelin levels are associated with obesity in human patients [56,57]. Thus, these studies suggest that elevated BPA exposure is associated with changes in adipokine levels that are involved in regulation of appetite and satiety and generally associated with the pathophysiology of obesity. From these data it seems that adipose tissue is a target of BPA and produces adipocyte dysfunction.

Limitations for epidemiological studies

In epidemiological cross-sectional studies, BPA exposure is assessed by urine collection or serum dosages. The pharmacokinetic elimination of BPA is a two compartment model with a half-life of approximately 6 hours and a total elimination after 24 hours [40]. In addition, BPA is ubiquitously present in the atmosphere but its concentration considerably changes following

the seasons [58]. Thus, huge variations of BPA levels in the environment is a limitation for studying BPA exposure. Indeed, the general population is exposed to very low BPA doses through several routes of exposure and levels of BPA fluctuate throughout the life time. Given the pharmacokinetic properties of BPA, and that urinary dosage is generally measured by morning urine collection, measurements mainly display BPA exposure of the day before and only this day. Ye X *et al.* (2011) performed urinary BPA measurements on eight subjects continuously for one week. They observed a high within-person variability for urinary BPA concentrations accompanied with an important inter-variability [59]. In addition, dietary factors must be considered for epidemiological studies interpretations. Indeed, higher food intake is associated with a higher risk for BPA as well as obesity [50,51].

Thus, only longitudinal and prospective studies would supply sufficient information to draw conclusions regarding the obesogenic activity of BPA in adulthood.

Infant / in utero exposure

Because BPA is classified as an ED, the developmental periods that include prenatal, infancy and childhood are critical windows with increased sensitivity to BPA effects and exposure can lead to endocrine perturbations and metabolic disorders [51]. Several epidemiological studies regarding early-life exposure to BPA are available (Table I).

Table I: Summary of epidemiological studies regarding prenatal and early-life exposure to BPA

Country and cohort	Age or status of subjects (n)	BPA dosages (technique)	↗ BPA level was associated with: (main results)	Ref.
USA (NHANES 2003 - 2008) Cross sectional	6 – 19 y.o. (2838)	1 spot urine sample (HPLC-MS/MS)	Obesity for all ages and sex but only for non-Hispanic white children	Trasande L. <i>et al.</i> (2011) [60]
China (2011) Cross sectional	8 – 15 y.o. (259)	1 spot urine sample (HPLC-MS/MS)	↗ BMI after adjustment for age and sex	Wang H. <i>et al.</i> (2012) [61]
USA (CHAMACOS 2000 - 2010) Longitudinal	Pregnant women (402) 5 y.o. (319) 9 y.o. (311)	1 spot urine sample (HPLC-MS/MS) Prenatal (1 st and 3 rd trimester) Children 5 y.o. Children 9 y.o.	9 y.o., BPA prenatal exposure: ↘ BMI z-score and %BF only for girls 9 y.o.: ↗ BMI z-score, WC and %BF for both sex	Harley KG. <i>et al.</i> (2013) [62]
USA (NHANES 2003 - 2008) Cross sectional	6 – 18 y.o. (2200)	1 spot urine sample (HPLC-MS/MS)	↗ BMI for both sex and predominantly in non-Hispanic white boys	Bhandari R. <i>et al.</i> (2013) [63]
China (2011)	9 – 18 y.o. (1326)	1 spot urine sample (HPLC-FD)	↗ BW, HC, WC, waist-to-height ratio, ST and BMI only for girls aged from 9 to 12	Li DK. <i>et al.</i> (2013) [64]
USA (NHANES 2003 - 2010) Cross sectional	6 – 18 y.o. (3370)	1 spot urine sample (HPLC-MS/MS)	↗ BMI and waist-to-height ratio	Eng DS. <i>et al.</i> (2013) [65]
USA (NHANES 2003 - 2010) Cross sectional	6 – 18 y.o. (2836)	1 spot urine sample (HPLC-MS/MS)	↗ waist-to-height ratio only for boys and non-Hispanic children	Wells EM. <i>et al.</i> (2010) [66]
South Korea (2011)	6 – 14 y.o. (127, girls)	1 spot urine and 1 spot serum samples (GC-MS)	No differences for anthropometric measurements	Choi J. <i>et al.</i> (2014) [67]

France (EDEN 2002 – 2006)	520 mother-child pairs (boys only)	1 spot urine sample (HPLC-MS/MS) 3 rd trimester of pregnancy Children 3 y.o.	No differences for anthropometric measurements	Philippat C. <i>et al.</i> (2012) [68]
USA (HOME 2003 - 2006)	297 mother-child pairs	1 spot urine sample (HPLC-MS/MS) 2 nd and 3 rd trimester of pregnancy Children 2 – 5 y.o.	No differences for anthropometric measurements	Braun JM. <i>et al.</i> (2014) [69]
India (2012 – 2013)	2 – 14 y.o. (76)	1 spot urine sample (HPLC-MS/MS)	Obese and overweight children have lower BPA urinary levels	Xue J. <i>et al.</i> (2015) [70]
Spanish (INMA 2004 – 2006)	Pregnant women (470) 7 y.o. (470)	1 spot urine sample (HPLC-MS) 3 rd trimester of pregnancy	No differences for anthropometric measurements	Agay-Shay K. <i>et al.</i> (2015) [71]
Greece (Crete) (Rhea 2007 – 2008)	Pregnant women (235) 2.5 y.o.(235) 4 y.o. (500)	1 spot urine sample (HPLC-MS) 1 st trimester of pregnancy Children 2.5 y.o. Children 4 y.o.	4 y.o.: ↗ BMI z-score, WC and ST for boys but ↘ for girls 4 y.o.: ↗ BMI z-score, WC, ST.	Vafeiadi M. <i>et al.</i> (2016) [72]
USA (CCCEH 1999 – 2013) Longitudinal	Pregnant women (369) 3 y.o. (408) 5 y.o. (518) 7 y.o. (325)	1 spot urine sample (HPLC-MS/MS) 3 rd trimester of pregnancy Every 3 months until 3 y.o. then every 6 months	7 y.o.: ↗ FMI, %BF, WC with a sex-specificity for girls for FMI. No change in BMI z-score	Hoepner LA. <i>et al.</i> (2016) [73]

%BF: % of Body Fat, BMI: Body Mass Index, BW: Body Weight, FMI: Fat Mass Index, HC: Having Weight, ST: Skinfold Thickness, WC: Waist Circumference

Collectively, most data from epidemiological studies performed in adulthood (11/16) indicates that BPA exposure during developmental periods is associated with an increased risk of programmed obesity. However, the presence of studies showing no association or an opposite correlation does not allow this to be a definitive conclusion. In agreement with Braun JM (2016), we observed that available epidemiological data concerning the obesogenic activity of BPA is ambiguous [51]. Indeed, there are multiple sources of BPA exposure and obesity is a complex pathology for which the definition is still debated [74–76]. Moreover, evaluation of obesity in infants and children appears to be imprecise, notably by the disregard of additional parameters such as height. Thus, epidemiological studies should be more focused on other metabolic disorders such as glucose tolerance, insulin resistance, triglycerides and cholesterol levels, adipokines secretion and inflammatory markers such as circulating cytokines [39,77,78].

Such markers of metabolic disorders play an important role in adipose tissue development and energy homeostasis and may be more accurate for the characterization of the link between BPA exposure and the pathophysiology of obesity.

In vivo studies

Numerous studies have been published concerning the pathophysiology of obesity after BPA exposure in animals. In most of these reports, mice or rats were used and treated daily with 5 to 5000 µg/kg BPA by gavage or in drinking water for 4 weeks to 8 months. Conversely to the epidemiological trend, no increase in body weight was observed at the end of these experiments with BPA supplementation [79–82]. Nevertheless, animals treated with low doses of BPA presented metabolic dysfunctions associated with obesity including increased expression of genes involved in fatty acid metabolism, cholesterol and triglyceride biosynthesis [79]. These metabolic disorders are also found in animals fed with high fat diet (HFD) compared to animals fed with standard diet [82].

It has also been reported that BPA exposure induces disorders of the gut microbiota. In mice, BPA induces gut dysbiosis and the BPA-associated alterations of the microbiota were similar to those altered by HFD or high sucrose diet (HSD) [83,84]. Furthermore, because BPA is an environmental compound and a component of plastic cans, the BPA-dietary exposure has been evaluated in dogs fed with canned dog food. In this study, the authors reported a correlation between a higher BPA serum concentration and gut microbiome changes [85]. The gut microbiota has been identified as a sensor and a regulator of energy homeostasis that can communicate with peripheral organs such as brain, liver and adipose tissue and can eventually lead to the development of obesity [86,87]. Thus, even if the association between an increased body weight and an increased BPA exposure is not clear from animal studies, it is perfectly demonstrated that BPA can lead to metabolic and gut microbiota disorders that are directly linked with obesity.

Moreover, epidemiological studies show that the impact of BPA exposure in the pathophysiology of obesity is mostly explained by prenatal exposure (Table II).

Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Mice (CF-1)	2 et 20 µg/kg/d, gavage	Standard + 6,5% soja	GD11-17	↑ PND185	= PND23-310		Ashby J. <i>et al.</i> (1999) [88]
Mice (CF-1)	0.2-2-20-200 µg/kg/d, gavage	Standard	GD11-17	↑ PND36-90			Cagen SZ. <i>et al.</i> (1999) [89]
Rat (Wistar)	0.01-0.1-1.0-10 ppm, drinking water	Standard	WPM2-PND22	=PND90			Cagen SZ. <i>et al.</i> (1999) [90]
Mice (CF-1)	2,4 µg/kg/d, gavage		GD11-17	↑ PND22	↑ PND22		Howdeshell KL. <i>et al.</i> (1999 and 2000) [91,92]
Rat (SD)	0.1-1.2 mg/kg, drinking water	Standard	GD6-PND21	↑ PND4-110	↑ PND4-110		Rubin BS. <i>et al.</i> (2011) [93]
Mice (ICR/Jcl)	2-20 µg/kg/d, SC	Standard	GD11-17	↓ PND0-60	↓ PND0-60		Honna S. <i>et al.</i> (2002) [94]
Mice (C57Bl6/N)	2-20-200 µg/kg/d, gavage	Standard	GD11-17	= PNW12			Nagao T. <i>et al.</i> (2002) [95]
Rat (LE)	2.4 µg/kg/d, gavage	Standard	GD12-PND21	↑ PND90			Akingbemi BT. <i>et al.</i> (2004) [96]
Mice (CD-1)	0.5-10 mg/kg/d, SC	Standard	GD15-18		↑ PNW16		Nikaido Y. <i>et al.</i> (2004) [97]
Mice (ICR)	1-10 µg/kg/d, drinking water	High fat	GD10-PND31	↑ PND30	↑ PND30	M: ↑ adipose tissue weight, ↑ TG F: ↑ adipose tissue weight, ↑ total cholesterol	Miyawaki J. <i>et al.</i> (2007) [98]
Rat (LE)	2-20-200 µg/kg/d, gavage	Standard	GD7-PND18	= PND150			Howdeshell KL. <i>et al.</i> (2008) [99]
Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Rat (SD)	1 mg/l, drinking water	Standard during gestation, standard or high fat after birth	GD6-PND21	↑PNW9-14 For the high fat diet group	↑PND1-PNW14 For both groups	F: ↑ white and brown adipose tissue weight, adipocyte hypertrophy, overexpression of lipogenic genes	Somm E. <i>et al.</i> (2009) [100]

Mice (OF-1)	10-100 µg/kg/d, SC	Standard	GD9-16	= PND22- 180	↓PND22- 180	M: ↑ insulin resistance, ↓ glucose tolerance, ↑ plasma insulin, ↑ TG, ↑ plasma leptin	Alonso- Magdalena P. <i>et al.</i> (2010) [101]
Mice (CD-1)	1 µg/kg/d, food	Standard, high fat from SPN9	GD0- PND21	= PNW14	= PNW14		Ryan KK. <i>et al.</i> (2010) [102]
Rat (Wistar)	50-250-1250 µg/kg/d, gavage	Standard or high fat	GD0- PND21	↑PNW3- 26	↑PNW3- 26	M + F: ↑ serum insulin, ↓ glucose tolerance, ↑ adipocyte hypertrophy	Wei J. <i>et al.</i> (2011) ^o [103]
Mice (Agouti a/a)	0.05-50- 50 000 µg/kg/d, food	Standard	2 w. before coupling- PND22	=PNM3- 9	↓PNM3- 9	M + F: ↑ energy expenditure F: ↓ Fat mass	Anderson OS. <i>et al.</i> (2013) [104]
Mice (CD-1)	5-50-500- 5 000-50 000 µg/kg/d, gavage	Standard	GD9-16	↑ PND0- PNW19		M: ↑ abdominal fat weight, adipocyte hyperplasy and hypertrophy, ↑ serum insulin and leptin, ↓ serum adiponectin, ↓ glucose tolerance	Angle BM. <i>et al.</i> (2013) [105]
Mice (C57Bl6)	100 µg/kg/d, SC	Standard	GD6- PND0 PND0-21 GD6- PND21	↓ PNM3-8 ↑ PNM3-8 = PNM3-8		↓ glucose tolerance ↓ glucose tolerance ↓ glucose tolerance	Liu J. <i>et al.</i> (2013) [106]
Mice (C57Bl6/JxFVB)	3-10-30-100- 300-1 000- 3 000 µg/kg/d, food	Standard High fat for F PNW17-21	2 w. before coupling- PND21	↑ PNW6- 21	↓ PNW8- 21	M: ↓ serum glucagon, ↓ physical activity, adipocyte hypertrophy F: ↓ adipose tissue weight, ↓ TG, ↓ serum leptin and adiponectin	Van Esterik JCI. <i>et al.</i> (2014) [107]
Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Mice (California)	50 mg/kg of food	Low phytoestrogen AIN93G	2 w. before coupling- PND30	= PND90	= PND90	F + M: ↓ voluntary physical activity, = serum glucose, insulin, leptin and adiponectin	Johnson SA. <i>et al.</i> (2015) [108]
Mice (CD-1)	0.25, 2.5, 25, or 250 µg/kg/d, osmotic pump (dams), drinking water (peripubertal)	Standard	GD8- PND16 PND21-35	↑ PNW43	↑ PNW43	M: ↑ adiposity F: ↑ serum glucose and insulin, insulin resistance, ↑ serum leptin, ↑ TG,	Rubin BS. <i>et al.</i> (2016) [109]
Mice (OF-1)	10-100 µg/kg, SC	Standard	GD9-16	↑ PND120		↑ serum insulin, ↑ serum leptin,	García- Arévalo M <i>et al.</i>

							(2016) [110]
Rat (SD)	1-10 µg/mL, drinking water	Standard	GD6- PND21	↑ PND50	↑ PND50	M: ↑ perirenal adipose tissue F: ↑ perigonadal adipose tissue M + F: ↑ TG, ↑ total cholesterol	Gao L. <i>et al.</i> (2016) [111]
M, male; F, female; GD, gestation day; PND, post-natal day; PNW, post-natal week; PNM, post-natal month; SC, subcutaneous; TG, triglycerides; WPM: week prior mating.							

Table II depicts that a majority of studies, although notably not all (13/24 for males and 8/15 for females), reported an association between prenatal exposure of BPA and an increased body weight of animal pups. Some studies also reported no association (8/24 for males and 3/15 for females) and others reported an inverse correlation (2/24 for males and 4/15 for females). These divergent results, as in the epidemiological studies, raise concerns about the data and do not allow definitive conclusions. The central difficulty is the variability of methods that differ in terms of doses, window of exposure and age of animal pups at the end of the experiments. Despite a large library of available literature, one cannot identify a precise window and dose of exposure to BPA that is responsible for an increased risk to develop obesity. Liu J. *et al.* (2013) well demonstrated the differences in body weight variations of mice between different windows of exposure (prenatal, lactation or both) for the same dose of BPA [106].

BPA is classified as an ED and consequently obeys the new paradigms of toxicology. Parameters like the latency of effects, timing and sensitivity as well as the sex should be considered during experiments. Additionally, because very low doses of BPA are potentially sufficient to produce an effect and because BPA is readily found in the environment, the relevance of the control group in these studies may be questioned. Indeed, how can it be attested that the control group is a non-exposed group while BPA is detected in animal cages and drinking water [27,112–114] ? Thus, the blood concentration of BPA has to be checked for all groups for each experiment to improve stringency in these studies. In light of these observations, meta-analyses, by examination of heterogeneity and identification of sources of variations, now appears to be a relevant way to supply the strength of evidence characterizing the association between BPA exposure and the development of obesity.

Despite the outlying reports, a majority of these studies indicates a positive association between prenatal BPA exposure and metabolic disorders, notably concerning adiposity and glucose and lipid homeostasis. A dysregulation of adipokine secretion can lead to adipocyte dysfunction and be involved in obesity-induced inflammation and insulin resistance [115]. Leptin is a hormone targeting the hypothalamus in order to inhibit orexigenic neurons and ultimately inducing satiety [116]. Obesity is associated with leptin resistance and high serum leptin levels [117,118]. Adiponectin is an adipocyte-derived hormone capable of targeting several tissues in order to increase insulin sensitivity [115]. In table II and in line with epidemiological data, prenatal exposure of BPA in animals enhances serum leptin levels and decreases serum adiponectin level in association with the pathophysiology of obesity.

In addition, type 2 diabetes is a major comorbidity of obesity and includes, at least, in part, a decrease in glucose tolerance, insulin resistance and elevated plasma insulin levels. As indicated in table II, prenatal exposure to BPA induces glucose homeostasis disorders, a predisposition to diabetes and a sustained obesogenic activity.

In vitro studies

Epidemiological and animal studies reveal that BPA exposure leads to perturbations in adipokine secretion and to adipocyte dysfunction suggesting that the adipose tissue is a central target of BPA activity. *In vitro* studies have identified molecular targets and signaling pathways that may be involved in the pathogenesis of obesity after BPA exposure. The effect of BPA in metabolic and endocrine disorders has already been reviewed on endoderm-derived organs (thyroid, pancreas, liver, gut, prostate and lung) [119]. However, the following are delineated *in vitro* results from studies examining BPA effects in adipocyte function.

Masuno H. *et al.* demonstrated that BPA treatment (8.8 μ M, 2 mg/L) in murine 3T3-L1 fibroblasts before and after the adipocyte differentiation stimulus increases triacylglycerol (TG) content, LPL activity and GPDH activity, two enzymes involved in lipid metabolism [120]. Thus, BPA exposure induces adipocyte differentiation and increases intra-cytosolic lipid accumulation. Similarly, Ohlstein J.F. *et al.* demonstrated that 1 μ M for 21 days was able to enhance adipogenesis of human adipose stromal/stem cells (ASCs) [121]. These results indicate that BPA, in a μ M concentration range, induces adipocyte differentiation. In another study, Valentino R. *et al.* exposed differentiated 3T3-L1 to 1 nM of BPA for 48 hours. They noted that BPA exposure under this treatment condition decreased adipocyte insulin sensitivity [122]. These results were associated with a decrease of Glucose Transporter 1 (GLUT1) expression, insulin receptor phosphorylation and overall insulin sensitivity, suggesting that BPA also induces disorders in glucose metabolism and may increase the risk of type 2 diabetes, a devastating complication in many obese patients [122,123]. In addition, BPA increases IL-6 and IFN- γ expression and activates the pro-inflammatory JNK/STAT3/NF κ B pathway [122,124]. All together, these results suggest that BPA, in a μ M concentration range, induces adipocyte differentiation, and in a nM concentration range, induces an adipocyte dysfunction reflected by a decrease in insulin sensitivity and a stimulation of pro-inflammatory responses.

Several molecular targets have been identified to explain the obesogenic effect of BPA [39,51,125]. Indeed, it has been reported that BPA, in concentration ranges of μ M, interacts with Nuclear Receptors (NR), Estrogen Receptors (ER), Glucocorticoid Receptors (GR),

peroxisome proliferator-activated receptor γ (PPAR γ), the Retinoid X Receptor (RXR) and Thyroid Receptors (TR) [126–129]. All these receptors are involved in adipogenesis [130–134]. By activating these receptors, BPA may promote adipocyte differentiation and increases in lipid storage.

Furthermore, activation of C/EBP- α , LPL and mammalian Target Of Rapamycin (mTOR), which are involved in lipogenesis and adipokine secretion, has also been described after adipocyte exposure to BPA, concurrent with a decrease of adiponectin secretion [121,126,128,135]. Thus, BPA induces inflammatory activation, adipogenesis and lipogenesis pathways and modulates adipokine secretion contributing to adipocyte dysfunction, which may explain lipid accumulation and the increase of fat mass observed (Figure 2). These results are in agreement with those from human and animal studies and confirm the impact of BPA exposure on adipocyte dysfunction found in obesity.

Interestingly, most BPA is metabolized to BPA-G initially. Boucher J.G. *et al.* evaluated the effect of 10 μ M of BPA-G on the differentiation of human and 3T3L1 murine preadipocytes. They demonstrated that BPA-G was able to promote adipocyte differentiation and that this effect was associated with an increase of mRNA of sterol regulatory element binding factor 1 (SREBF1), LPL, protein levels of LPL, aP2, and adipsin, all adipogenic markers [47]. These results indicate that not only BPA but also its predominant metabolite are able to induce adipocyte differentiation.

Figure 2: Signaling pathways activated by low and high doses of BPA during adipocyte differentiation.

Epigenetics:

Several data have demonstrated the ability of BPA to induce genetic modifications with dramatic consequences on reproductive functions and cancer development [136,137]. However, available data regarding the impact of BPA exposure on genetic aspects of obesity remains sparse so far. Among genome-wide association studies (GWAS) findings, the locus *fat mass and obesity associated (FTO)* was described as the most associated gene with an increased BMI, each risk allele of this locus increasing risk of obesity from 20 % to 30 % in humans [138–141]. Other genes regulating expression of signaling molecules involved in glucose and lipid homeostasis and in feeding behavior were also identified such as those encoding *melanocortin receptors (MCRs)*, *proopiomelanocortin (POMC)*, *Agouti* or *brain-derived neurotrophic factor (BDNF)* [140]. The regulation of gene expression is predominantly mediated by DNA methylation, RNA silencing, histone acetylation and nucleosome remodeling, four epigenetic mechanistic processes [142–144]. In the viable yellow Agouti (A

^{yy}) mouse model, fetal exposure of BPA decreases methylation of the *Agouti* promoter, leading to a statistically significant shift in offspring coat color phenotype toward yellow [145]. In addition, in an embryonic mouse hypothalamus cell line, BPA alters gene expression levels that can be linked to the observed BDNF modification of expression [146]. These results suggest that BPA fetal exposure induces epigenomic alterations in genes involved in the pathophysiology of obesity, thus confirming the *in utero* programming of obesity after BPA exposure, as described in animal and epidemiological studies [147].

CONCLUSION and PERSPECTIVES

Despite its rapid elimination time, the ubiquitous presence of BPA in our environment ensures that humans are continuously exposed. This review of the available literature favors the conclusion that BPA should be considered an obesogenic environmental compound. Metabolic disorders or adipocyte dysfunctions are described in epidemiological, animal and *in vitro* studies following BPA exposure. In addition, the effects of BPA on obesity development should thus be measured not only by BMI but also by contribution to adipogenesis, lipid and glucose dysregulation and adipose tissue inflammation. Although some data in the literature remains controversial regarding the link between BPA and obesity, evidence continues to grow that EDs like BPA are involved in the huge rise of the obesity epidemic. Meta-analyses conducted on data obtained from the current literature are now needed to definitively answer on the effects of BPA on obesity.

Due to increased evidence regarding the deleterious effects of BPA, numerous alternatives to BPA for use in manufacturing have arisen such as bisphenol AF (BPAF), bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS) and 4-cumylphenol (HPP). These compounds are gradually replacing BPA in plastics and thermal paper. However, it has been confirmed these compounds have an estrogenic and androgenic activity *in vitro*, indicating they have similar endocrine disrupting capability than BPA and distribute to the body and are also a concern for fetal exposure during pregnancy [148–151]. However, data remains sparse as to whether or not these alternative compounds contribute to adipocyte dysregulation, and subsequently, obesity. BPS, BPA analog used for thermal paper, is the only compound among these BPA alternatives that has been shown to exert obesogenic activity in mice and *in vitro* as evidenced by an association with increased body weight, perturbations in adipokine secretion and in dysregulation of glucose homeostasis [152–154]. These data clearly support the urgent need to both decrease human bisphenol exposure and to find new alternative compounds for the plastic manufacturing.

Importantly, the role of EDs in the growth of the obesity epidemic worldwide is now well established [155,156]. However, the contribution of each suspected obesogen in this epidemic remains unclear, likely because of synergistic effects between all of these chemicals. Additional studies evaluating the effects of environmental obesogens are now needed and would offer new tools for the prevention of obesity.

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