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Maternal bisphenol A alters fetal endocrine system: Thyroid adipokine dysfunction

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ABSTRACT

Because bisphenol A (BPA) has been detected in animals, the aim of this study was to investigate the possible effects of maternal BPA exposure on the fetal endocrine system (thyroid-adipokine axis). BPA (20 or 40 μg/kg body weight) was orally administered to pregnant rats from gestation day (GD) 1–20. In both treated groups, the dams and their fetuses had lower serum thyroxine (T4) and triiodothyronine (T3) levels, and higher thyrotropin (TSH) level than control dams and fetuses at GD 20. Some histopathological changes in fetal thyroid glands were observed in both maternal BPA groups at embryonic day (ED) 20, including fibroblast proliferation, hyperplasia, luminal obliteration, oedema, and degeneration. These disorders resulted in the suppression of fetal serum growth hormone (GH), insulin growth factor-1 (IGF1) and adiponectin (ADP) levels, and the elevation of fetal serum leptin, insulin and tumor necrosis factor-alpha (TNFα) levels in both treated groups with respect to control. The depraved effects of both treated groups were associated with reduced maternal and fetal body weight compared to the control group. These alterations were dose dependent. Thus, BPA might penetrate the placental barrier and perturb the fetal thyroid adipokine axis to influence fat metabolism and the endocrine system.

1. Introduction

Endocrine-disrupting compounds (EDCs), including many agents of chemical or natural origin, are able to imbalance hormone-driven processes in animals and humans (Gore et al., 2015; Ahmed, 2016a; Ejaredar et al., 2016). Among these products, bisphenol A (BPA, 2,2-bis (4-hydroxyphenyl) propane) is a high-volume production chemical compound routinely detectable in humans (Leung et al., 2016; Muhamad et al., 2016). The US Environmental Protection Agency (EPA) and US National Toxicology Program (NTP) assigned BPA as the third highest Toxicological Priority Index (ToxPi) score of the 309 chemicals examined based on its ability to interact with a number of signaling pathways (Vandenberg et al., 2013). It is a ubiquitous industrial chemical used mainly in the manufacture of food packaging, including polycarbonate plastics and epoxy resins lining metal cans, as well as in thermal papers or flame retardants (Johnson et al., 2015; Ahmed, 2016a; Sharma et al., 2016). The vital route of BPA exposure appears to be oral from food contact materials (Thayer et al., 2015), and daily intake for adults is estimated at 0.4–1.4 μg/kg/day (Food and Agriculture Organization of the United Nations, World Health Organization, 2010). Notably, bio-accumulation of BPA has been revealed to be higher in fetal tissues compared to maternal tissues (Poimenova et al., 2010). Furthermore, in humans, BPA is mainly stored in the adipose tissue, with an elimination half-life of approximately 6 h (Rochester, 2013).

Previous evidence has demonstrated that human and wildlife populations are exposed to levels of BPA (xenobiotics/xenoestrogen) which cause developmental defects in a number of different wildlife species and laboratory animal models (Popa et al., 2014). Also, rodent studies suggest that early-life BPA exposure may result in an anxious, hyperactive state (Rebuli et al., 2015; Ling et al., 2016) and impact numerous physiological functions (Li et al., 2016), including the developmental pituitary-thyroid axis (Franssen et al., 2016; Soriano et al., 2016) and immune system (Fischer et al., 2016). On the other hand, in animal and human examinations, EDCs have been shown to disturb adipocytokine, body weight, energy expenditure and fat depots (Ahmed, 2013; Ariemma et al., 2016). However, studies on potential connections between BPA and adipokine concentration changes associated with thyroid dysfunction during the gestation period are limited.

As BPA can be distinguished in human umbilical cord blood, amniotic fluid, urine samples (National Health and Nutrition

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Examination Survey) and maternal milk (Wei et al., 2011; Behnia et al., 2016), special consideration has been paid to exposure during the gestation period. During this period, most functions of the organism are immature and considered particularly vulnerable to adverse environmental factors, including EDCs. Thus, the objective of this study was to evaluate the effect of maternal BPA exposures on aspects of the development of the fetal thyroid axis and adipokine markers in albino rats during the gestation, specifically at GD 20.

2. Materials and methods

2.1. Experimental animals

Mature white albino rats (*Rattus norvegicus*, Wistar strain) were obtained from the National Institute of Ophthalmology, Giza, Egypt. 24 mature virgin females weighing about 160–180 gm and 12 mature males for mating only were used in this study. They were kept under observation in the department animal house for 2 weeks to eliminate any intercurrent infection and adapt to the new conditions. The animals were kept in stainless steel separate bottom well aerated cages at the normal atmospheric temperature (23 ± 2 °C), constant daily 12 h light/12 h darkness each (lights on at 6 h) and 50 ± 5% relative humidity in the animal house of my department. They were received a free access to tap water (drink *ad libitum*) and standard rodent pellet diet manufactured by an Egyptian company during the experimental period (Ahmed et al., 2015; Ahmed, 2016b). All animal procedures were in agreement with the general guidelines of animal care and the recommendations of the Canadian Council on Animal Care (Olfert et al., 1993). All efforts were made to diminish the animal suffering and to reduce the number of animals used.

Daily examination of the vaginal smears of each female was carried out to determine the estrous cycle. Estrous females displayed the presence of cornified cells in vaginal smears by the microscopic examination (Goldman et al., 2007). Mating was induced by housing proestrous females with the males in a separate cage at a ratio of two females and one male overnight for 1 or 2 consecutive days. The presence of sperm in vaginal smear determined the 1st day of gestation (Marcondes et al., 2002). Then, the pregnant females were moved into separate cages without males to start the experiment.

2.2. Experimental strategy

Non-anesthetized pregnant rats received two doses of BPA (20 & 40 μg/kg bw/day) orally by gastric intubation and daily from gestation day (GD) 1 to GD 20. BPA was dissolved in corn oil vehicle. The vehicle control group received the same amount of corn oil during the same period. These doses were previously reported by Nakamura et al. (2012) and Aloisi et al. (2002), respectively. In the United States (the US Environmental Protection Agency, USEPA), Europe (the European Food Safety Authority, EFSA), and Canada (the Health Canada), regulating bodies have determined that 25–50 μg/kg bw/day of BPA exposure is the recent tolerable daily intake (TDI) for humans, based largely on rodent multigenerational, sub-chronic, oral toxicity studies, measuring endpoints such as body weight and developmental deformations (Rochester, 2013; Kinch et al., 2015). Also, pharmacokinetic experiments, taking into account the alterations in BPA metabolism between rodents and humans have assessed that exposures to 400 μg/kg bw/day produce bioactive BPA concentrations in their blood, within the range of recorded human blood concentrations (Vandenberg et al., 2012).

The maternal body weight gain and fetal body weight were determined before decapitation. Dams and their fetuses were decapitated under mild diethyl ether anesthesia in the early morning and sampled at GD 20 (before the delivery). The maternal blood samples (6 per group) were taken from a jugular vein. Fetal blood samples (6 per group) were collected directly from the umbilical cord at ED 20. Serum was separated by centrifugation at 3000 rpm (1006.2 g) and 15–24 °C for 30 min. The clear supernatant sera were rapidly removed, divided into three portions for each individual animal, and kept at −70 °C until use for different hormonal assays. In addition, the thyroid glands of fetuses were fixed in 10% neutral buffered formalin (Bancroft and Stevens, 1982). All reagents were of the purest grades commercially available.

2.3. RIA examination

Maternofetal serum T4 (Thakur et al., 1997), T3 (Maes et al., 1997) and TSH (Mandel et al., 1993) levels and fetal GH (Reutens, 1995) and IGF1 (Dauncey et al., 1993) levels were detected quantitatively by RIA at the Diabetic Endocrine Metabolic Pediatric Unit, Center for Social and Preventive Medicine, New Children's Hospital, Faculty of Medicine, Cairo University, Egypt. The kits were obtained from Calbiotech INC (Spring Valley, CA, USA).

2.4. Histological examination of fetal thyroid glands

Thyroid tissue samples, intended for histological investigation by light microscopy, were immediately fixed in 10% neutral buffered formalin and processed through a series of graded ethanol solutions. Then, they were embedded in paraffin, serially sectioned at 6 μm, and stained with hematoxylin–eosin at the National Cancer Institute, Cairo University, Egypt. The sections were cut parallel to the longitudinal axis of the trachea. The slides were examined under a light microscope for the presence of any histological changes.

2.5. ELISA examination

Serum fetal leptin, ADP, insulin, and TNFα levels were detected by ELISA and measured with a microplate reader (Spectra Max 190-Molecular Devices, Sunnyvale, CA, USA) in biochemistry department, faculty of medicine, Cairo University, Egypt. Commercial kits were utilized for the measurement of leptin, ADP, and insulin (ELISA kit-Millipore, St. Charles, MO, USA). TNFα kit was purchased from Invitrogen Corporation 542 Flynn Road, Camarillo, CA 93012 (USA).

2.6. Calculations and statistics

The experimental data were retrieved and processed with the software PC-STAT (University of Georgia, 1985). The data were evaluated by one-way analysis of variance (ANOVA) followed by LSD analysis to discern the main effects and compare various groups with each other. F-probability for each variable expresses the general effect between groups. The data were presented as mean values and standard error (SE) and the statistical differences at $P < 0.01$ and $P < 0.001$ were considered statistically highly significant and very highly significant, respectively.

3. Results

3.1. Maternal BPA-induced a maternofetal hypothyroidism

Both dosage administrations of BPA (20 and 40 μg/kg) to pregnant rats from GD 1 to GD 20 resulted in a profound decrease (LSD; $P < 0.01$) in serum T4 and T3 levels and a significant increase (LSD; $P < 0.01$) in serum TSH level at GD 20 with respect to control (hypothyroid state) (Table 1). Also, the levels of T4 and T3 were

Table 1
Effect of BPA in thyroid functions [thyroxine (T4, ng/100 ml), triiodothyronine (T3, ng/100 ml), T4/T3 ratio and thyrotropin (TSH, ng/100 ml)], and body weight gain (g) of pregnant rats during the gestational period.

Day	BPA (μg/kg)	Serum T4	Serum T3	T4/T3 ratio	Serum TSH	Body weight gain
GD 20	0	20.96 ± 0.13^{a}	6.78 ± 0.15^{b}	3.09	12.69 ± 0.24^{c}	70.79 ± 0.63^{a}
	20	13.45 ± 0.33^{b}	3.11 ± 0.16^{a}	4.32	17.51 ± 0.33^{b}	63.61 ± 0.93^{b}
		−35.83%	−54.12%		+37.98%	−10.14%
	40	8.11 ± 0.13^{c}	1.92 ± 0.17^{c}	4.22	18.78 ± 0.25^{a}	54.84 ± 0.88^{c}
		−61.30%	−71.68%		+47.99%	−22.53%
ANOVA	P < 0.001					
LSD 5%		0.2730	0.2016		0.3470	1.7793
LSD 1%		0.3775	0.2788		0.4799	2.4607

Data are expressed as mean ± SE. Number of animals in each group is six. Values which share the same superscript symbols are not significantly different. ANOVA (F-probability) expresses the effect between groups, where P < 0.001 is very highly significant. Where, GD is gestational day.

found to be decreased about 7.51 and 3.67-fold in the 1st treated group (20 μg/kg BPA) and about 12.85 and 4.86-fold in the 2nd treated group (40 μg/kg BPA), respectively, whereas the level of TSH exhibited about 4.82 and 6.09-fold increase in the 1st treated group and 2nd treated group, respectively when compared to respective control values. The increase of maternal T4/T3 ratio was greater in both treated groups as compared to the control group during the considered day. Also, in these dams, the mean body weight gain was significantly (LSD; P < 0.01) lower in the 2nd treated group than that in the 1st treated group or control group at examined day (54.84 vs. 63.61 or 70.79, respectively) (Table 1).

In fetuses of both treated groups, the increase in serum TSH level was associated with a marked reduction (LSD; P < 0.01) in serum T4, T3, GH and IGF1 levels at ED 20 with respect to the control group (Table 2). The value of fetal TSH in the high dose group (14.18 ng/100 ml) was very high if compared to the levels in the age-matched normal control (6.97 ng/100 ml) or in the low dose group (10.65 ng/100 ml). Fetal T4/T3 ratio was higher in the high dose group than the control or the low dose group (7.00 vs. 4.04 or 4.20, respectively), while GH and IGF1 levels were lower in the high dose group (−64.77% & −71.90%) or in the low dose group (−47.72% & −34.71%) than the control group (Table 2). A one-way analysis of variance (ANOVA) showed that the effect between the groups on all previous parameters was very highly significant (P < 0.001; F-prob.) at examined day (Tables 1 and 2).

3.2. Maternal BPA-induced a fetal thyroid dysgenesis

Fetuses of both treated groups did show some differences in the thyroidal histology when compared with the control group (Fig. 1). The fetal thyroid glands of the control exhibited a normal distribution, morphology, and architecture of follicles and parafollicular cells at ED 20 (Fig. 1A). The lumina of these follicles varied from irregular rounded to a tubular shape and had a single layer of cuboidal cells lining the epithelium. Both maternal dosage administrations of BPA led to the histopathological alteration of the fetal thyroid characterized by follicular hyperplasia in the low dose group (Fig. 1B) or in the high dose group (Fig. 1C). These follicles were damaged, and their lumina exhibited a degree of degeneration in the high dose group (Fig. 1C). There was also fibroblast proliferation between the follicles, oedema, and luminal obliteration at ED 20 (Fig. 1B and C). Importantly, the follicles became very irregular and abnormal, also, both maternal BPA administrations led to thyroid dysgenesis.

3.3. Maternofetal hypothyroidism-induced by maternal BPA altered the fetal adipocytokines levels and body weight

Both maternal dosage administrations of BPA affected the fetal serum adipocytokine levels and body weight at ED 20 (Table 3). These administrations had a severe effect on the ADP level and body weight, where their percentage index was −31.81% & −28.87%, respectively in the low dose group, and −72.72% & −49.15%, respectively in the high dose group. However, the leptin, TNFα, and insulin levels were detectably increased in both treated groups in comparison with the corresponding control. Their elevations in the low dose group were +117.07% for leptin, +168.96% for TNFα, and +80.15% for insulin. These variabilities became more significant in the high dose group. Based on one-way ANOVA of these parameters, it was found that the general effect between the groups was very highly significant (P < 0.001; F-prob.) at ED 20 (Table 3).

4. Discussion

In the present study, the levels of maternofetal serum T4, T3, and TSH have supported the pregnancy and fetal development. This state may be required to prevent the appearance of any thyroid disorders during the embryonic or fetal periods (Ahmed, 2013; Bourgeois et al., 2016; Nieto et al., 2016; Sanjay et al., 2016). Also, the associations between the levels of fetal serum GH, IGF1, ADP,

Table 2
Effect of maternal BPA in fetal thyroid functions [thyroxine (T4, ng/100 ml), triiodothyronine (T3, ng/100 ml), T4/T3 ratio, thyrotropin (TSH, ng/100 ml)], growth hormone (GH, ng/100 ml), and insulin-growth factor-1 (IGF1, ng/100 ml) during the gestational period.

Day	BPA (μg/kg)	Serum T4	Serum T3	T4/T3 ratio	Serum TSH	GH	IGF1
ED 20	0	10.96 ± 0.33^{b}	2.71 ± 0.23^{a}	4.04	6.97 ± 0.57^{c}	0.88 ± 0.04^{a}	1.21 ± 0.14^{b}
	20	6.18 ± 0.28^{c}	1.47 ± 0.49^{b}	4.20	10.65 ± 0.61^{b}	0.46 ± 0.03^{b}	0.79 ± 0.27^{a}
		−43.61%	−45.75%		+52.79%	−47.72%	−34.71%
	40	4.27 ± 0.39^{a}	0.61 ± 0.29^{c}	7.00	14.18 ± 0.80^{a}	0.31 ± 0.01^{c}	0.34 ± 0.16^{c}
		−61.04%	−77.49%		+103.44%	−64.77%	−71.90%
ANOVA	P < 0.001						
LSD 5%		0.4203	0.4412		1.0396	0.0474	0.1036
LSD 1%		0.5813	0.6102		1.4377	0.0656	0.1433

Data are expressed as mean ± SE. Number of animals in each group is six. Values which share the same superscript symbols are not significantly different. ANOVA (F-probability) expresses the effect between groups, where P < 0.001 is very highly significant. Where, ED is gestational day.

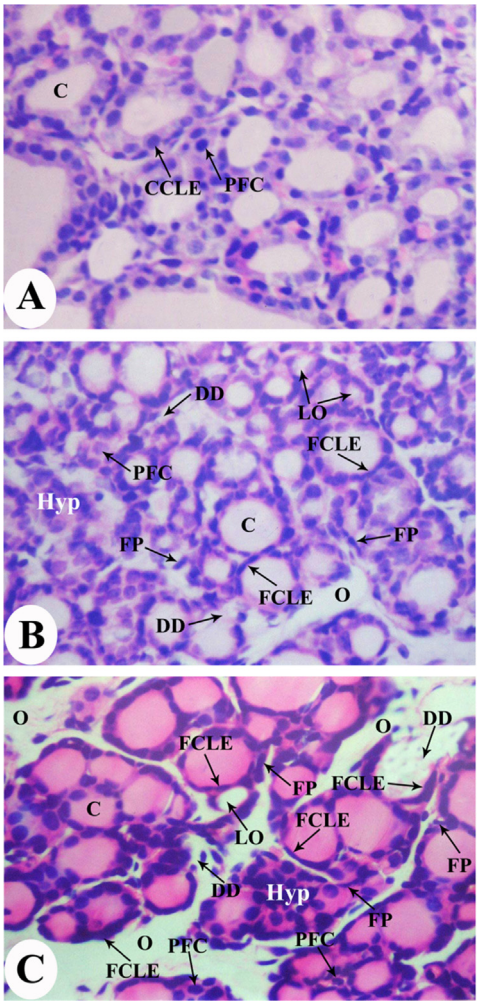

Fig. 1. Sagittal sections in the thyroid gland of fetal rats at ED 20 in control (A), 20 μg BPA (B) and 40 μg BPA (C). (H. & E. stain, 400 ×). Where, C: colloid; CCLE: cuboidal cell lining epithelium; DD: destructive degeneration; FCLE: flattened cell lining epithelium; FP: fibroblast proliferation; Hyp: hyperplasia; LO: luminal obliteration; O: oedema and PFC: parafollicular cell.

leptin, TNFα and insulin at ED 20 could mediate the actions of developing thyroid hormones (THs), and in general the prenatal development (Ahmed et al., 2015; Candelotti et al., 2015; Cremaschi et al., 2016). This might support the normal appearance of thyroid tissue and intact follicular structure as noted in the current study. This was accompanied by normal values in the maternal body weight gain and fetal body weight. In addition, the aforementioned markers were significant hormones regulating the fat mass storage, appetite, and energy homeostasis, and could, therefore, be fundamental components of the perinatal adaptation (Hytinantti et al., 2008; Palcevska-Kocevska et al., 2012; Lee et al., 2016). This synergistic action may be simplified by the maternofetal hypothalamic pituitary thyroid axis (HPTA) and required for the development of fat metabolism, regulation of energy balance, and glucose homeostasis.

In the current study, both maternal dosage administrations of BPA affected thyroid structure and function during gestation. These administrations caused a thyroid dysgenesis and exhibited some histopathological changes, such as fibroblast proliferation, hyperplasia, luminal obliteration, oedema and destructive degeneration at ED 20. These histopathological alterations were associated with a remarkable decline in the levels of maternofetal serum T4 and T3, and a clear increase in the level of maternofetal serum TSH at GD 20 as compared to a control group. These alterations were dose dependent.

The previous results of many authors suggested the following mechanisms in the impairment of thyroid histo-functional features by BPA: (1) BPA (50, 100 & 200 mg/kg bw/day) altered the size of the thyroid follicles (flattened thyrocytes) with vacuolated colloid and thickening of para follicular cells (Hernandez-Rodriguez et al., 2007); (2) A tall cuboidal cell lining with rounded nuclei and depletion of thyroid colloid were noticed in BPA-treated rats (5, 10 and 100 mg/kg bw) (Kaur et al., 2008); (3) BPA significantly impaired the thyrocytes transcriptome in a time-dependent manner (Porreca et al., 2016) and caused a subclinical hypothyroidism (Wang et al., 2015). Similarly, 2,3,6-2′,5'-pentachlorinated biphenyl (PCB 95) administration induced a hypothyroidism via thyroid dysgenesis (hyperplasia of the epithelia in follicles, colloid content reduction, vascularization, and lymphocytic infiltration in the perifollicular areas) and dyshormonogenesis (Ahmed, 2013; 2016a). (4) BPA disrupted the thyroid hormone receptors (TRs), androgen receptor (AR), estrogen receptors (ERs), peroxisome proliferator-activated receptor-γ (PPARγ), and other endocrine-relevant signaling pathways (Wetherill et al., 2007); (5) BPA interfered with the TH functions and homeostasis by inhibiting hormone synthesis (suppressed the transcriptional activity by inhibiting T3 binding to the TR and by recruiting N-CoR on the promoter), reducing the ability of THs to bind the transport proteins (transthyretin) in the bloodstream (Wetherill et al., 2007), or increasing catabolism of THs (Evans et al., 2014); (6) BPA-induced uridine diphosphate glucuronyl transferase (UDP-GT) activity in European polecats (Nieminen et al., 2002); (7) BPA potentially altered the thyrotropin-releasing hormone (TRH) that induced TSH secretion and inhibited sodium iodide symporter (NIS)-mediated iodide uptake in a concentration-dependent manner (Wu et al., 2016); (8) BPA changed the DNA structure by adding methyl groups to DNA (vom Saal et al., 2007), and impaired the non-genomic pathways of THs (Wetherill et al., 2007); and (9) BPA disordered the normal pituitary development (Brannick et al., 2012). These disturbances may be a substantial risk factor for

Table 3
Effect of maternal BPA in serum concentrations of fetal leptin (ng/dl), adiponectin (ng/dl), insulin (ng/dl), TNFα (ng/dl), and body weight (g) during the gestational period.

Day	BPA (μg/kg)	Leptin	Adiponectin	Insulin	TNFα	Fetal body weight
ED 20	0	0.41 ± 0.03^{c}	1.10 ± 0.01^{a}	1.26 ± 0.27^{b}	0.29 ± 0.05^{c}	7.10 ± 0.12^{a}
	20	0.89 ± 0.07^{b}	0.75 ± 0.06^{b}	2.27 ± 0.04^{c}	0.78 ± 0.03^{b}	5.05 ± 0.17^{c}
		+117.07%	−31.81%	+80.15%	+168.96%	−28.87%
	40	1.56 ± 0.29^{a}	0.30 ± 0.13^{c}	3.41 ± 0.55^{a}	1.84 ± 0.01^{a}	3.61 ± 0.43^{b}
		+280.48%	−72.72%	+170.63%	+534.48%	−49.15%
ANOVA	P < 0.001					
LSD 5%		0.2178	0.1046	0.4413	0.1398	0.3459
LSD 1%		0.3012	0.1447	0.6102	0.1933	0.4784

Data are expressed as mean ± SE. Number of animals in each group is six. Values which share the same superscript symbols are not significantly different. ANOVA (F-probability) expresses the effect between groups, where P < 0.001 is very highly significant. Where, ED is gestational day.

thyroid diseases (Tang et al., 2013). Although it is not clear which among these probable mechanisms are most significant for facilitating the effects of BPA on circulating levels of THs, it is possible that all are important to some extent in experimental models. Based on these results, it can be suggested that the administration of BPA might act antagonistically with developmental HPTA and this may lead to adverse developmental defects.

In view of the present study, a potential decrease in the levels of fetal serum GH and IGF1 in maternal BPA-hypothyroid groups was noticed at ED 20 in comparison with control. Previously, BPA has been shown to suppress GH release and GH-mRNA expression (Ramakrishnan and Wayne, 2008), and cause a growth retardation (Golub et al., 2010). This suppression was attributed to the elevation in protein disulfide isomerase (PDI) (Okada et al., 2007) and alteration in ER-receptors (α and β) pathways (Wetherill et al., 2007) or in ion transport (Richter et al., 2007; Wetherill et al., 2007). Also, this deterioration can be potentially linked to the disturbances in the actions of THs, in the synthesis and release of growth hormone-releasing hormone (GH-RH), IGF1 and in their receptors (Ahmed, 2013; Osfor et al., 2013). It is also relevant to mention that the diminution in the level of IGF1, in the current study, might be correlated to the variations in the actions of THs and insulin that may delay the growth. It is proposed that the BPA might disrupt the GH/IGF1 axis during the gestation period via HPTA.

Although the levels of fetal serum leptin, insulin and TNFα were highly significantly increased, the level of serum ADP was highly significantly decreased in maternal BPA-hypothyroid groups at ED 20 in comparison with their corresponding control. It was also depicted in the current study that the high dose of maternal BPA administration exerted its most potent effect on these markers as compared to the low dose. This is possibly due to the disruption in the hormonal homeostatic mechanisms at this embryonic day.

In accordance with the current study, the level of plasma leptin in mice was elevated during gestation after subcutaneous BPA treatment (Alonso-Magdalena et al., 2010). This elevation may partially result from the hyperinsulinemia, insulin resistance or adipocyte synthesis (Wei et al., 2011). Also, this hyperleptinemia might be elucidated by the reduction in the leptin turnover and degradation (Ahmed, 2013, 2016a), or stimulation the HPTA in response to low TH levels in rats, canine and human (Mazaki-Tovi et al., 2010). In agreement with the present study, a negative correlation was found between the level of ADP and BPA (Kidani et al., 2010). In parallel, Ben-Jonathan et al. (2009) reported that BPA has the capacity to inhibit ADP by (1) Binding differently to the ligand binding domain of ERs and recruiting a different set of co-regulators; and (2) Inhibiting the PDI. Also, the reduction in ADP (Bastard et al., 2006; Ahmed, 2016a), and disruption in its receptors (AdipoR1 and AdipoR2) (Tsuchida et al., 2005) with hypothyroidism (Schultz et al., 2011) are related to several diseases such as hypertriglyceridemia, hypertension, and metabolic syndrome (Cinar and Gurlek, 2013). In other studies, the gestational BPA is associated with a diversity of metabolic dysfunctions in adulthood, including hyperinsulinemia, glucose intolerance and insulin resistance (Whitehead et al., 2016) by induction of oxidative stress (Moghaddam et al., 2015) and alterations in DNA methylation (Ma et al., 2013). Also, this seems to be ERα-dependent and includes signaling through a non-genomic pathway via extracellular regulated kinase1/2 (Alonso-Magdalena et al., 2008). The controversy in these markers might reflect the maternofetal thyroid dysfunction due to BPA. Thus, any factor that suppresses the release of ADP could lead to insulin resistance and metabolic diseases (Hugo et al., 2008).

The present results are also in accordance with the previous publications which supported the positive association between the level of fetal serum TNFα and maternal exposure to BPA. Previously, the exposure to BPA promoted the production of proinflammatory adipokine, such as TNFα and interleukins (IL-6 or IL-12) by infiltrating macrophages (Ben-Jonathan et al., 2009), stimulating both T and B cells (Yoshino et al., 2004) and transactivating the nuclear factor (NF)-kappaB transactivation (Wetherill et al., 2007). Also, BPA caused a rapid response via non-genomic mechanisms by activating membrane-anchored ERs (Watson et al., 2007), estrogen related receptors-γ (ERRγ), unidentified non-classical membrane ERs (Alonso-Magdalena et al., 2005), calcium uptake (Wozniak et al., 2005), G-protein-coupled receptor (Filardo and Thomas, 2005) or cAMP-responsive element-binding protein (CREB) (Quesada et al., 2002). In similar, TNFα is amplified in patients with thyroid dysfunction (Cinar and Gurlek, 2013). Interestingly, the parallel disruption in TNFα and insulin actions, in the current study, might be responsible for the HPTA dysfunction. Thus, BPA might change the development through its effect on the expression of some cytokines and the immune function.

According to the study herein, the maternal administrations of BPA produced a considerable decrease in the maternal weight gain and fetal body weight at examined day as compared with that of the control group. Formerly, a high dose of BPA-induced a substantial decline in the body weight, fat depots, energy metabolism, and feeding efficiency of rats (Nunez et al., 2001), mice (Li et al., 2016), children with exposed mothers (Miao et al., 2011) and ewes and fish (Ramakrishnan and Wayne, 2008). BPA might harm the fetal growth by disrupting the TH pathway (Ramakrishnan and Wayne, 2008), placental connection (Troisi et al., 2014), steroid hormone synthesis and metabolism (Padmanabhan et al., 2010), intracellular signal transduction pathways (changes the transactivational activity of nuclear hormone receptors) (Wetherill et al., 2007), cytokine networks (Benachour and Aris, 2009), genotoxicity (Tayama et al., 2008), cell death (Cantonwine et al., 2010) and oxidative stress (Cho et al., 2009). However, some animal studies have revealed that BPA exposure may have a role in weight gain and obesity development through several mechanisms, including its action on preadipocytes, ERRγ, TH and PPARγ (antagonistic behavior), and pancreatic endocrine functions (agonistic behavior) (Shankar and Teppala, 2011). On the other hand, earlier studies did not find a relationship between birth weight and maternal BPA exposure *in utero* (Wolff et al., 2008). These studies had deviating results, including negative, positive or no associations. This inconsistency could be dependent on differences in the design, experimental models, developmental period and animal species. To sum, the evidence of BPA affecting birth weight is ambiguous. Thus, a loss of body weight due to BPA might cause a developmental defect,

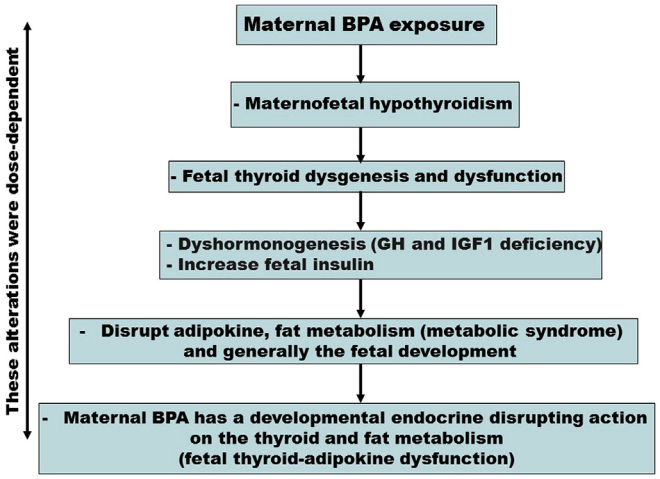

Fig. 2. Effect of maternal BPA on the developmental thyroid-adipokine axis.

metabolic disease, and other health disorders during the perinatal, childhood, and adult (Rochester, 2013), which can be vital in the interpretation of thyroid effects in energy homeostasis.

In conclusion, this study provides *in vivo* evidence that both dosage administrations appear to induce maternofetal hypothyroidism via thyroid dysgenesis and dyshormonogenesis. This state seems to alter the fetal adipokine axis, fat metabolism and, in general, prenatal development. Also, the maternal administrations of BPA seem to cause fetal thyroid-adipokine dysfunction (Fig. 2). These changes may be either directly or indirectly related to maternofetal TH action. It should be noted that the toxicity of BPA can be attributed to the period of exposure, developmental period and the species involved. Thus, further studies are necessary to explicate the prospective associations with human health.

Declaration of interest

The author declares that there is no conflict of interest that could be supposed as prejudicing the impartiality of the study reported.

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References

Ahmed, R.G., 2016b. Maternal iodine deficiency and brain disorders. Endocrinol. Metab. Syndr. 5, 223. http://dx.doi.org/10.4172/2161-1017.1000223.
Ahmed, R.G., Abdel-Latif, M., Mahdi, E., El-Nesr, K., 2015. Immune stimulation improves endocrine and neural fetal outcomes in a model of maternofetal thyrotoxicosis. Int. Immunopharmacol. 29, 714–721.
Ahmed, R.G., 2016a. Neonatal polychlorinated biphenyls-induced endocrine dysfunction. Ann. Thyroid. Res. 2 (1), 34–35.
Ahmed, R.G., 2013. Early weaning PCB 95 exposure alters the neonatal endocrine system: thyroid adipokine dysfunction. J. Endocrinol. 219 (3), 205–215.
Aloisi, A.M., Della Seta, D., Rendo, C., Ceccarelli, I., Scaramuzzino, A., Farabollini, F., 2002. Exposure to the estrogenic pollutant bisphenol A affects pain behavior induced by subcutaneous formalin injection in male and female rats. Brain Res. 937, 1–7.
Alonso-Magdalena, P., Laribi, O., Ropero, A.B., Fuentes, E., Ripoll, C., Soria, B., Nadal, A., 2005. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ 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., Ropero, A.B., Carrera, M.P., Cederroth, C.R., Baquie, M., Gauthier, B.R., Nef, S., Stefani, E., Nadal, A., 2008. Pancreatic insulin content regulation by the estrogen receptor ER alpha. PLoS ONE 3, e2069.
Alonso-Magdalena, P., Vieira, E., Soriano, S., Menes, L., Burks, D., Quesada, I., Nadal, A., 2010. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ. Health Perspect. 118, 1243–1250.
Ariemma, F., D'Esposito, V., Liguoro, D., Oriente, F., Cabaro, S., Liotti, A., Cimmino, I., Longo, M., Beguinot, F., Formisano, P., Valentino, R., 2016. Low-dose bisphenol-A impairs adipogenesis and generates dysfunctional 3T3-L1 adipocytes. PLoS One 11 (3), e0150762.
Bancroft, J.D., Stevens, A., 1982. In Theory and Practice of Histological Techniques, second ed. Churchill-Livingstone, Edinburgh, UK, p. 121.
Bastard, J.P., Maachi, M., Lagathu, C., Kim, M.J., Caron, M., Vidal, H., Capeau, J., Feve, B., 2006. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur. Cytokine Netw. 174–182.
Behnia, F., Peltier, M., Getahun, D., Watson, C., Saade, G., Menon, R., 2016. High bisphenol A (BPA) concentration in the maternal, but not fetal, compartment increases the risk of spontaneous preterm delivery. J. Matern. Fetal Neonatal Med. 1–7.
Benachour, N., Aris, A., 2009. Toxic effects of low doses of bisphenol-A on human placental cells. Toxicol. Appl. Pharmacol. 241, 322–328.
Ben-Jonathan, N., Hugo, E.R., Brandebourg, T.D., 2009. Effects of bisphenol A on adipokine release from human adipose tissue: implications for the metabolic syndrome. Mol. Cell. Endocrinol. 304 (1–2), 49–54.
Bourgeois, M.A.N., Van Herck, S., Vancamp, P., Visser, T.J., 2016. Characterization of chicken thyroid hormone transporters. J. Endocrinol. 157 (6), 2560–2574.
Brannick, K.E., Craig, Z.R., Himes, A.D., Peretz, J.R., Wang, W., Flaws, J.A., Raetzman, L.T., 2012. Prenatal exposure to low doses of bisphenol A increases pituitary proliferation and gonadotroph number in female mice offspring at birth. Biol. Reprod. 87, 82.
Candelotti, E., De Vito, P., Ahmed, R.G., Luly, P., Davis, P.J., Pedersen, J.Z., Lin, H.-Y., Incerpi, S., 2015. Thyroid hormones crosstalk with growth factors: old facts and new hypotheses. Immun. Endoc. Metab. Agents Med. Chem. 15, 71–85.
Cantonwine, D., Meeker, J.D., Hu, H., Sánchez, B.N., Lamadrid-Figueroa, H., Mercado-García, A., Fortenberry, G.Z., Calafat, A.M., Téllez-Rojo, M.M., 2010. Bisphenol A exposure in Mexico City and risk of prematurity: a pilot nested case control study. Environ. Health 9, 62.
Cho, S.H., Choi, M.H., Kwon, O.S., Lee, W.Y., Chung, B.C., 2009. Metabolic significance of bisphenol A-induced oxidative stress in rat urine measured by liquid chromatography-mass spectrometry. J. Appl. Toxicol. 29, 110–117.
Cinar, N., Gurlek, A., 2013. Association between novel adipocytokines adiponectin, vaspin, visfatin, and thyroid: an experimental and clinical update. Endocr. Connect. 2, R30–R38.
Cremaschi, G.A., Cayrol, F., Sterle, H.A., Díaz Flaqué, M.C., Barreiro Arcos, M.L., 2016. Thyroid hormones and their membrane receptors as therapeutic targets for T cell lymphomas. Pharmacol. Res. pii: S1043-6618(16)00040-2.
Dauncey, M.J., Rudd, B.T., White, D.A., Shakespear, R.A., 1993. Regulation of insulin-like growth factor binding proteins in young growing animals by alteration of energy status. Growth Regul. 3, 198–207.
Ejaredar, M., Lee, Y., Roberts, D.J., Sauve, R., Dewey, D., 2016. Bisphenol A exposure and children's behavior: a systematic review. J. Expo. Sci. Environ. Epidemiol. http://dx.doi.org/10.1038/jes.2016.8.
Evans, S.F., Kobrosly, R.W., Barrett, E.S., Thurston, S.W., Calafat, A.M., Weiss, B., Stahlhut, R., Yolton, K., Swan, S.H., 2014. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. Neurotoxicol 45, 91–99.
Filardo, E.J., Thomas, P., 2005. GPR30: a seven-transmembrane-spanning estrogen receptor that triggers EGF release. Trends Endocrinol. Metab. 16, 362–367.
Fischer, C., Mamillapalli, R., Goetz, L.G., Jorgenson, E., Ilagan, Y., Taylor, H.S., 2016. Bisphenol A (BPA) exposure in utero leads to immunoregulatory cytokine dysregulation in the mouse mammary gland: a potential mechanism programming breast cancer risk. Horm. Cancer (in press).
Food and Agriculture Organization of the United Nations, World Health Organization, 2010. Joint FAO/WHO Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A Ottawa, Canada. Available at: http://www.who.int/foodsafety/chem/chemicals/BPA_Summary2010.pdf. [Accessed 22.06.11.].
Franssen, D., Gérard, A., Hennuy, B., Donneau, A.F., Bourguignon, J.P., Parent, A.S., 2016. Delayed neuroendocrine sexual maturation in female rats after a very low dose of Bisphenol A through altered GABAergic neurotransmission and opposing effects of a high dose. J. Endocrinol. 157 (5), 1740–1750.
Goldman, J.M., Murr, A.S., Cooper, R.L., 2007. The rodent estrous cycle: characterization of vaginal cytology and its utility in toxicological studies. Birth Defects Res. Part B Dev. Reproductive Toxicol. 80, 84–97.
Golub, M.S., Wu, K.L., Kaufman, F.L., Li, L.-H., Moran-Messen, F., Zeise, L., George V Alexeeff, G.V., Donald, J.M., 2010. Bisphenol A: developmental toxicity from early prenatal exposure. Birth Defects Res. Part B 89, 441–466.
Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36, E1–E150.
Hernandez-Rodriguez, G., Zumbado, M., Luzardo, O.P., Monterde, J.G., Blanco, A., Boada, L.D., 2007. Multigenerational study of the hepatic effects exerted by the consumption of Haniokanonylphenol and 4-octylphenolntaminated drinking water in Sprague-Dawley rats. Environ. Toxicol. Pharmacol. 23, 73–81.
Hugo, E.R., Brandebourg, T.D., Woo, J.G., Loftus, J., Alexander, J.W., 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.
Hytinantti, T., Kajantie, E., Karonen, S.L., Andersson, S., 2008. Postnatal changes in ghrelin, adiponectin, insulin and leptin concentrations in term newborns. Int. J. Endocrinol. Metab. 3, 127–134.
Johnson, S.A., Javurek, A.B., Painter, M.S., Ellersieck, M.R., Welsh Jr., T.H., Camacho, L., Lewis, S.M., Vanlandingham, M.M., Ferguson, S.A., Rosenfeld, C.S., 2015. Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A clarity-BPA study. Horm. Behav. S0018–506X(15)30082-9.
Kaur, G., Kassim, N.M., Ismail, R., Mohdc, M.A., 2008. Hormonal changes and altered thyroid histology caused by bisphenol A and nonylphenol. In: Presented in 22nd MSPP Scientific Meeting.
Kidani, T., Kamei, S., Miyawaki, J., Aizawa, J., Sakayama, K., Masuno, H., 2010. Bisphenol A downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-L1 adipocytes. J. Atheroscler. Thromb. 17, 834–843.
Kinch, C.D., Ibhazehiebo, K., Jeong, J.-H., Habibi, H.R., Kurrasch, D.M., 2015. Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. PNAS 112 (5), 1475–1480.
Lee, Y.-S., Chin, Y.-T., Yang, Y.S., Wei, P.-L., Wu, H.-C., Shih, A., Lu, Y.-T., Pedersen, J.Z., Incerpi, S., Liu, L.F., Lin, H.-Y., Davis, P.J., 2016. The combination of tetraiodothyroacetic acid and cetuximab inhibits cell proliferation in colorectal cancers with different K-ras status. Steroids 111, 63–70.
Leung, A.M., Korevaar, T.I.M., Peeters, R.P., Zoeller, R.T., Köhrle, J., Duntas, L.H., Brent, G.A., Demeneix, B.A., 2016. Exposure to thyroid-disrupting chemicals: a

transatlantic call for action. Thyroid 26 (4), 1–2.
Li, J., Wang, Y., Fang, F., Chen, D., Gao, Y., Liu, J., Gao, R., Wang, J., Xiao, H., 2016. Bisphenol A disrupts glucose transport and neurophysiological role of IR/IRS/AKT/GSK3β axis in the brain of male mice. Environ. Toxicol. Pharmacol. 43, 7–12.
Ling, W., Endo, T., Kubo, K., Nakajima, K., Kakeyama, M., Tohyama, C., 2016. In utero bisphenol A exposure induces abnormal neuronal migration in the cerebral cortex of mice. Front. Endocrinol. Lausanne 7, 7.
Ma, Y., Xia, W., Wang, D.Q., Wan, Y.J., Xu, B., Chen, X., Li, Y.Y., Xu, S.Q., 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.
Maes, M., Mommen, K., Hendrickx, D., Peeters, D., D'Hondt, P., Ranjan, R., De Meyer, F., Scharpe, S., 1997. Components of biological variation including seasonality in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. Clin. Endocrinol. 46, 587–598.
Mandel, S.J., Brent, G.A., Larsen, P.R., 1993. Levothyroxine therapy in patients with thyroid disease. Ann. Intern. Med. 119, 492–502.
Marcondes, F.K., Bianchi, F.J., Tanno, A.P., 2002. Determination of the estrous cycle phases of rats: some helpful considerations. Braz. J. Biol. 62 (4A), 609–614.
Mazaki-Tovi, M., Feuermann, Y., Segev, G., Klement, E., Yas-Natan, E., Farkas, A., Kol, A., Shamay, A., 2010. Increased serum leptin and insulin concentrations in canine hypothyroidism. Vet. J. 183, 109–114.
Miao, M., Yuan, W., Zhu, G., He, X., Li, D.K., 2011. In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod. Toxicol. 32, 64–68.
Moghaddam, H.S., Samarghandian, S., Farkhondeh, T., 2015. Effect of bisphenol A on blood glucose, lipid profile and oxidative stress indices in adult male mice. Toxicol. Mech. Methods 25 (7), 507–513.
Muhamad, M.S., Salim, M.R., Lau, W.J., Yusop, Z., 2016. A review on bisphenol A occurrences, health effects and treatment process via membrane technology for drinking water. Environ. Sci. Pollut. Res. Int. 23 (12), 11549–11567.
Nakamura, K., Itoh, K., Dai, H., Han, L., Wang, X., Kato, S., Sugimoto, T., Fushiki, S., 2012. Prenatal and lactational exposure to low-doses of bisphenol A alters adult mice behavior. Brain & Dev. 34, 57–63.
Nieminen, P., Lindstrom-Seppa, P., Juntunen, M., Asikainen, J., Mustonen, A.M., Karonen, S.L., 2002. In vivo effects of bisphenol A on the polecat (mustela putorius). J. Toxicol. Environ. Health A 65 (13), 933–945.
Nieto, P.A., Peñaloza, H.F., Salazar-Echegarai, F.J., Castellanos, R.M., Opazo, M.C., Venegas, L., Padilla, O., Kalergic, A.M., Riedel, C.A., Bueno, S.M., 2016. Gestational hypothyroidism improves the ability of the female offspring to clear Streptococcus pneumoniae infection and to recover from pneumococcal pneumonia. J. Endocrinol. 157 (6), 2217–2228.
Nunez, A.A., Kannan, K., Giesy, J.P., Fang, J., Clemens, L.G., 2001. Effects of bisphenol A on energy balance and accumulation in brown adipose tissue in rats. Chemosphere 42, 917–922.
Okada, K., Imaoka, S., Hashimoto, S., Hiroi, T., Funae, Y., 2007. Over-expression of protein disulfide isomerase reduces the release of growth hormone induced by bisphenol A and/or T3. Mol. Cell. Endocrinol. 278 (1–2), 44–51.
Olfert, E.D., Cross, B.M., McWilliam, A.A. (Eds.), 1993. Guide to the Care and Use of Experimental Animals., 1. CCAC, Ottawa, Ontario, Canada.
Osfor, M.M.H., Elmadbouly, M.A., Elsoadaa, S.S., Metair, A.H., Hussain, A.A.A., 2013. Relation between hypercholesterolemia and insulin like growth factor-1 in elderly women suffer from hypothyroidism. J. Nat. Sci. Res. 3 (5), 160–164.
Padmanabhan, V., Sarma, H.N., Savabieasfahani, M., Steckler, T.L., Veiga-Lopez, A., 2010. Developmental reprogramming of reproductive and metabolic dysfunction in sheep: native steroids vs. environmental steroid receptor modulators. Int. J. Androl. 33, 394–404.
Palcevska-Kocevska, S., Aluloska, N., Krstevska, M., Shukarova-Angelovska, E., Kojik, L., Zisovska, E., Kocevski, D., Kocova, M., 2012. Correlation of serum adiponectin and leptin concentrations with anthropometric parameters in newborns. Srp. Arh. Celok. Lek. 140 (9–10), 595–599.
Poimenova, A., Markaki, E., Rahiotis, C., Kitraki, E., 2010. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. J. Neurosci. 167 (3), 741–749.
Popa, D.-S., Bolfa, P., Kiss, B., Vlase, L., Păltinean, R., Pop, A., Cătoi, C., Crişan, G., Loghin, F., 2014. Influence of genista tinctoria L or methylparaben on subchronic toxicity of bisphenol A in rats. Biomed. Environ. Sci. 27 (2), 85–96.
Porreca, I., Ulloa Severino, L., D'Angelo, F., Cuomo, D., Ceccarelli, M., Altucci, L., et al., 2016. "Stockpile" of slight transcriptomic changes determines the indirect genotoxicity of low-dose BPA in thyroid cells. PLoS ONE 11 (3), e0151618.
Quesada, I., Fuentes, E., Viso-Leon, M.C., Soria, B., Ripoll, C., Nadal, A., 2002. Low doses of the endocrine disruptor bisphenol-A and the native hormone 17β-estradiol rapidly activate transcription factor CREB. FASEB J. 16, 1671–1673.
Ramakrishnan, S., Wayne, N.L., 2008. Impact of bisphenol-A on early embryonic development and reproductive maturation. Reprod. Toxicol. 25, 177–183.
Rebuli, M.E., Camacho, L., Adonay, M.E., Reif, D.M., Aylor, D.L., Patisaul, H.B., 2015. Impact of low-dose oral exposure to bisphenol A (BPA) on Juvenile and adult rat exploratory and anxiety behavior: a clarity-BPA consortium study. Toxicol. Sci. 148 (2), 341–354.
Reutens, A.T., 1995. Evaluation and application of a highly sensitive assay for serum growth hormone (GH) in the study of adult GH deficiency. J. Clin. Endocrinol. Metab. 80, 480–485.
Richter, C.A., Birnbaum, L.S., Farabollini, F., Newbold, R.R., Rubin, B.S., Talsness, C.E., Vandenbergh, J.G., Walser-Kuntz, D.R., Vom Saal, F.S., 2007. In vivo effects of bisphenol A in laboratory rodent studies. Reprod. Toxicol. 24, 199–224.
Rochester, J.R., 2013. Bisphenol A and human health: a review of the literature. Reprod. Toxicol. 42, 132–155.
Sanjay, G., Carlos, M., Katrin, H., Thomas, B., Werner, K., Gabor, S., 2016. Cell growth dynamics in embryonic and adult mouse thyroid revealed by a novel approach to detect thyroid gland subpopulations. Thyroid 26 (4), 591–599.
Schultz, M., Kistorp, C., Raymond, I., Dimsits, J., Tuxen, C., Hildebrandt, P., Faber, J., 2011. Cardiovascular events in thyroid disease: a population based, prospective study. Horm. Metab. Res. 43, 653–659.
Shankar, A., Teppala, S., 2011. Relationship between urinary bisphenol A levels and diabetes mellitus. J. Clin. Endocrinol. Metab. 96 (12), 3822–3826.
Sharma, R., Kotyk, M.W., Wiltshire, W.A., 2016. An investigation into bisphenol A leaching from materials used intraorally. J. Am. Dent. Assoc. pii: S0002-8177(16)00068-4.
Soriano, S., Ripoll, C., Alonso-Magdalena, P., Fuentes, E., Quesada, I., Nadal, A., Martinez-Pinna, J., 2016. Effects of bisphenol A on ion channels: experimental evidence and molecular mechanisms. Steroids 111, 12–20.
Tang, J.-M., Li, W., Xie, Y.-C., Guo, H.-W., Cheng, P., Chen, H.-H., Zheng, X.-Q., Jiang, L., Cui, D., Liu, Y., Ding, G.-X., Duana, Y., 2013. Morphological and functional deterioration of the rat thyroid following chronic exposure to low-dose PCB118. Exp. Toxicol. Pathol. 2993 (13), 00028–00036 pii: S0940.
Tayama, S., Nakagawa, Y., Tayama, K., 2008. Genotoxic effects of environmental estrogen-like compounds in CHO-K1 cells. Mutat. Res. 649, 114–125.
Thakur, C., Saikia, T.C., Yadav, R.N., 1997. Total serum levels of triiodothyronine (T3), thyroxine (T4) and thyrotropin (TSH) in school going children of Dibrugarh district: an endemic goiter region of Assam. Ind. J. Physiol. Pharmacol 41, 167–170.
Thayer, K.A., Doerge, D.R., Hunt, D., Schurman, S.H., Twaddle, N.C., Churchwell, M.I., Garantziotis, S., Kissling, G.E., Easterling, M.R., Bucher, J.R., Birnbaum, L.S., 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environ. Int. 83, 107–115.
Troisi, J., Mikelson, C., Richards, S., Symes, S., Adair, D., Zullo, F., Guida, M., 2014. Placental concentrations of bisphenol A and birth weight from births in the Southeastern U.S. Placenta 35 (11), 947–952.
Tsuchida, A., Yamauchi, T., Takekawa, S., Hada, Y., Ito, Y., Maki, T., Kadowaki, T., 2005. Peroxisome proliferator-activated receptor (PPAR)α activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARα, PPARγ, and their combination. Diabetes 54, 3358–3370.
Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, J.R., Lee, D.H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., 2012. Hormones and endocrine-disrupting chemicals: low dose effects and nonmonotonic dose responses. Endocr. Rev. 33, 378–455.
Vandenberg, L.N., Ehrlich, S., Belcher, S.M., Ben-Jonathan, N., Dolinoy, D.C., Hugo, E.R., Hunt, P.A., Newbold, R.R., Rubin, B.S., Saili, K.S., Soto, A.M., Wang, H.-S., vom Saal, F.S., 2013. Low dose effects of bisphenol A. Endocr. Disrupt. 1 (1), e26490. http://dx.doi.org/10.4161/endo.26490.
vom Saal, F.S., Akingbemi, B.T., Belcher, S.M., Birnbaum, L.S., Crain, D.A., Eriksen, M., 2007. Chapel hill bisphenol A expert panel consensus statement. Reprod. Tox 24 (2), 131–138.
Wang, N., Zhou, Y., Fu, C., Wang, H., Huang, P., Wang, B., Su, M., Jiang, F., Fang, H., Zhao, Q., Chen, Y., Jiang, Q., 2015. Influence of bisphenol A on thyroid volume and structure independent of iodine in school children. PLoS ONE 10 (10), e0141248.
Watson, C.S., Bulayeva, N.N., Wozniak, A.L., Alyea, R.A., 2007. Xenoestrogens are potent activators of nongenomic estrogenic responses. Steroids 72, 124–134.
Wei, J., Lin, Y., Li, Y., Ying, C., Chen, J., Song, L., Zhou, Z., Lv, Z., Xia, W., Chen, X., Xu, S., 2011. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. J. Endocrinol. 152, 3049–3061.
Wetherill, Y.B., Akingbemi, B.T., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenschein, C., Watson, C.S., Zoeller, R.T., Belcher, S.M., 2007. In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol. 24, 178–198.
Whitehead, R., Guan, H., Arany, E., Cernea, M., Yang, K., 2016. Prenatal exposure to bisphenol A alters mouse fetal pancreatic morphology and islet composition. Horm. Mol. Biol. Clin. Investig. 25 (3), 171–179.
Wolff, M.S., Engel, S.M., Berkowitz, G.S., Ye, X., Silva, M.J., Zhu, C., et al., 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environ. Health Perspect. 116, 1092–1097.
Wozniak, A.L., Bulayeva, N.N., Watson, C.S., 2005. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-α- mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ. Health Perspect. 113, 431–439.
Wu, Y., Beland, F.A., Fang, J.L., 2016. Effect of triclosan, triclocarban, 2,2',4,4'-tetrabromodiphenyl ether, and bisphenol A on the iodide uptake, thyroid peroxidase activity, and expression of genes involved in thyroid hormone synthesis. Toxicol. Vitro 32, 310–319.
Yoshino, S., Yamaki, K., Li, X., Sai, T., Yanagisawa, R., Takano, H., Taneda, S., Hayashi, H., Mori, Y., 2004. Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. Immunol 112, 489–495.