



Timing of Exposure and Bisphenol-A: Implications for Diabetes Development

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Bisphenol-A (BPA) is one of the most widespread endocrine disrupting chemicals (EDCs). It is used as the base compound in the production of polycarbonate and other plastics present in many consumer products. It is also used as a building block in epoxy can coating and the thermal paper of cash register receipts. Humans are consistently exposed to BPA and, in consequence, this compound has been detected in the majority of individuals examined. Over the last decade, an enlarging body of evidence has provided a strong support for the role of BPA in the etiology of diabetes and other metabolic disorders. Timing of exposure to EDCs results crucial since it has important implications on the resulting adverse effects. It is now well established that the developing organisms are particularly sensitive to environmental influences. Exposure to EDCs during early life may result in permanent adverse consequences, which increases the risk of developing chronic diseases like diabetes in adult life. In addition to that, developmental abnormalities can be transmitted from one generation to the next, thus affecting future generations. More recently, it has been proposed that gestational environment may also program long-term susceptibility to metabolic disorders in the mother. In the present review, we will comment and discuss the contributing role of BPA in the etiology of diabetes. We will address the metabolic consequences of BPA exposure at different stages of life and comment on the final phenotype observed in different whole-animal models of study.

Keywords: Bisphenol-A, diabetes, pancreatic β -cell, timing of exposure, metabolic programming

Diabetes mellitus is among the most prevalent metabolic disorders and the current number of cases is approaching epidemic proportions. According to the latest Global Burden Disease report (2015), the prevalence of diabetes has risen from 333 million people in 2005 to approximately 435 million in 2015 (1). The predictions suggest that it will be the seventh leading cause of death in 2030 (2). As proposed by the American Diabetes Association (ADA), the classification of this pathology includes type 1 (T1DM), type 2 (T2DM) and gestational diabetes mellitus (GDM), as well as other forms of diabetes (3). Despite differences on the underlying causing factors, all of them lead to hyperglycemia, which results from defects on insulin secretion, insulin resistance or a combination of both (4).

More than 90% of patients with diabetes have T2DM (5). The etiology of T2DM is multifactorial with a clear genetic background but also with an important environmental compound (6). Poor nutrition, lack of exercise and overweight are commonly seen as contributing factors to cause T2DM but other environmental factors like endocrine disrupting chemicals (EDCs) are also key. EDCs are defined as any chemical or mixture of chemicals able to disrupt any aspect of endocrine function (7). They constitute a heterogeneous range of compounds widely used in consumer products including food packaging, personal care products, pesticides or building materials, among others. General population is exposed to EDCs through different routes, mainly the oral, dermal or inhalation ones (8). From a mechanistic point of view, it is well described that they can interfere with hormonal signaling pathways principally by binding to hormone receptors and/or altering hormone production, metabolism and transport (8, 9). Over the last decade, burgeoning scientific evidence have disclosed that a subset of EDCs are able to modify sensitive metabolic processes leading to altered energy homeostasis and/or glucose and lipid metabolism (10–12). One of the best documented example is the case of bisphenol-A (BPA), firstly synthesized by Dianin in 1891 and reported to show estrogenic properties in 1930s (13). BPA is a monomer that is used as the base compound in the manufacture of polycarbonate and other plastics, and it is also employed as a building block in epoxy can coating and the thermal paper of cash register receipts. It became one of the most pervasive chemical in modern life from the moment it was introduced in the plastic industry in the 50s. Today, it constitutes one of the highest volume chemical produced widespread, with over 6 billion pounds manufactured every year. BPA has been found to migrate from polycarbonate containers and leach into food or water because of overheating, the presence of acidic or basic conditions and/or a repetitive use. Thermal paper has also been shown to constitute an important source of exposure to this EDC (14). The ubiquitous nature of BPA makes human exposure to occur on a virtually constant basis. In consequence, it has been detected in the majority of individuals examined (15, 16).

As regards the regulatory aspects, back in the 80s the Environmental Protection Agency (EPA) established the lowest adverse effect level (LOAEL) for BPA at 50 mg/kg/day and, based on that, the safety level was set on 50 µg/kg/day (17). Although many studies have shown deleterious effects of BPA at doses below the calculated safe dose (8, 18), the reference value of 50 µg/kg/day is still in force. For the European Food Safety Authority the tolerable daily intake has been recently established in 4 µg/kg/day (19). Remarkably, both the reference dose and the tolerable daily intake are higher than the 95th percentile BPA intake level for adults (1.5 µg/kg/day) estimated by the World Health Organization (WHO). This estimation has been done based on published exposure estimation in several countries and regions, as well as taking into account the information available regarding information on food consumption patterns, and BPA presence in foods relevant to the population groups (20).

OVERVIEW OF THE MOLECULAR MECHANISMS LINKING BPA EXPOSURE AND DIABETES

Current molecular and cellular evidence support that BPA may augment diabetes risk by affecting pancreatic β -cell function and/or insulin action in different metabolically active tissues (8, 10, 21). Before commenting on that, we will briefly describe some general aspects of BPA mode of action.

BPA is mainly considered a xenoestrogen due to its capacity to promote estrogen-like activities. Structurally, BPA has two phenolic and two (4, 4')-OH substituents that confer the ability to join into the ER-binding structure. Thus, BPA can bind to both estrogen receptor α (ER α) and β (ER β) although with 1,000 to 2,000-fold less affinity than the natural hormone 17- β -estradiol (E2) (22, 23). Based on that, BPA was considered a weak estrogen for many years. Nevertheless, today we know that, when acting through non-classical ER pathways, BPA can elicit responses with the same potency than E2. Non-classical ER pathways mainly include nuclear mechanisms of estrogen responses elicited by recruiting different transcriptional co-activators or co-repressors, as well as extranuclear-initiated signaling pathways which regulate different cellular pathways such as, gene transcription as well as ion channel and kinase activity. We here summarize some of the principal mechanisms behind BPA action triggered via non-classical estrogen pathways. For more information readers are referred to the following reviews (24–28).

Scientific evidence support that BPA-dependent estrogenic activity flows, at least in part, through rapid, non-genomic alterations of Ca^{2+} handling. Both BPA and E2, in the pico and nanomolar range, have shown to rapidly increase [Ca^{2+}] in GH3/B6 pituitary tumor cells resulting in prolactin secretion (29). In a similar manner, BPA, at exactly the same doses than E2 (100 pM–1nM), potentiated Ca^{2+} signaling and insulin release in pancreatic β -cells (30, 31), while in pancreatic α -cells BPA mimicked E2 action by inhibiting low-glucose induced [Ca^{2+}] oscillations (32). Importantly, *in vivo* studies also reported rapid insulin release in response to low doses of BPA (33). Rapid effects of BPA have also been observed in cardio myocytes. Low dose concentrations of BPA and E2 induced arrhythmic actions in isolated ventricular myocytes from female rats by altering Ca^{2+} handling (34); an effect that depends on the balance between ER α and ER β (35). These BPA actions on cardio myocytes were characterized by non-monotonic dose responses (36).

Another major mechanism of BPA-induced extranuclear signaling pathways involves the activation of ERK/MAPK kinases. A wide range of BPA concentrations have been shown to rapidly increase the phosphorylation state of ERK1/2 in developing cerebellar neurons (37). In pancreatic islets of Langerhans BPA increased insulin content with the same potency than E2 acting through ER α . This was not an acute but a long-term effect which required the activation of ERK (38).

Furthermore, BPA showed binding affinities for GPR30, a relatively novel 7-transmembrane estrogen receptor (39). Several data support BPA action within nanomolar range via GPR30 in

several systems. For example, BPA led to testicular seminoma cell proliferation through GPR30 (40). In pancreatic cells, BPA promoted insulin secretion dysfunction which was connected with inhibition of Pdx-1 and decreased expression of miR-338 (41).

Overall, it has been proposed that these plethora of mechanisms could account for the low dose effects of BPA that have been defined as “any biological change occurring in the range of typical human exposures or at doses lower than tested in traditional toxicological assessments” (42). Hundreds of studies have been published over the years providing strong evidence for low dose BPA effects having the potential to pose health hazards. These low dose effects have been observed for a variety of endpoints including metabolic parameters but also prostate weight, spermatogenesis, brain and mammary gland development as well as hormone levels, among others (18, 43). In addition, it is important to highlight that BPA, like hormones, do not obey the Paracelsus principle of “the dose makes the poison.” On the contrary, a typical feature of BPA actions includes non-monotonic dose response curves (NMDRCs) often manifested as U- or inverted U-shaped curves. The mechanisms behind these NMDRCs are typically related to cytotoxicity, receptor selectivity, receptor down regulation or competition with endogenous hormones (44). In addition to its estrogenic activity, BPA may act as an antagonist of androgenic (at doses in the range of 100 nM–10 μ M) (45) and thyroid (1–100 μ M) (46) activity, and may also activate the human estrogen-related receptor (26 nM) (47), pregnane receptor (2 μ M) (48) and the glucocorticoid receptor (1 μ M) (49).

A large number of cellular studies have demonstrated that BPA targets pancreatic β -cells. Environmental relevant doses of BPA have been shown to modulate K_{ATP} channel activity, which is key in the stimulus-secretion coupling process that culminates with insulin secretion. In both mouse and human islets, BPA provoked a rapid closure of the K_{ATP} channel and subsequently, increased insulin release. This effect was mediated by the extranuclear activation of the estrogen receptor beta (ER β) (30, 50). Additionally, BPA may enhance glucose-induced insulin biosynthesis and content via binding to extranuclear ER α (38). In several models of β -cell lines, BPA has also been reported to affect insulin release. In the nanomolar range, it enhances basal (51, 52) and glucose-stimulated insulin secretion (GSIS), leading to ER stress. Conversely, at higher doses in the micromolar range, it displays the opposite effect (53). Furthermore, BPA treatment has been shown to increase reactive oxygen species production and DNA damage (54) as well as to augment apoptosis (53).

BPA may also alter glucose regulation by disrupting insulin action in different peripheral metabolic tissues. In the murine adipose cell line 3T3-L1 and in human adipocytes, BPA impaired insulin-stimulated receptor phosphorylation and signaling, which led to decreased insulin sensitivity and glucose disposal (55, 56). BPA treatment also provoked an up-regulation of inflammatory signaling pathways (56) and induced adipogenesis (57–59).

BPA has also been reported to exert direct effects on hepatocyte physiology. In different hepatic cell lines, BPA

has been shown to induce lipid accumulation, favoring the development of hepatic steatosis (58, 60).

RELEVANCE OF EXPOSURE TIMING: THE CONCEPT OF METABOLIC PROGRAMMING

David Barker and colleagues suggested for the first time that early-life nutrition is associated with a number of offspring health outcomes including coronary heart disease, hypertension and T2DM (61–63). These first observations established the bases of the fetal origins of adult disease hypothesis, which states that events occurring during early development may increase the risk of specific diseases later in life. This concept was later expanded to other aspects of developmental plasticity such as early postnatal period and intergenerational influences, and set the framework of the Developmental Origins of Health and Disease (DOHaD) theory (64).

Overall, this paradigm relies on the fact that there exist specific developmental periods whereby an organism is more sensitive to environmental insults. While those insults were initially referred to nutritional imbalance, today it is well demonstrated that the exposure to some environmental chemicals during development may also lead to increased incidence to non-communicable diseases like T2DM (65). The understanding of the molecular mechanisms behind this phenomenon is far to be complete. Nevertheless, it has been proposed that environmental agents acting during specific windows of sensitivity may promote changes in gene expression, cell metabolism, hormone regulation or cellular plasticity, among others. Such functional changes might permanently modify the organism's physiologic and metabolic homeostatic set points, programming the individual to later risk for metabolic diseases (11).

So far, epigenetics processes have been proposed to be the major driving mechanism in the altered programming during development. These epigenetic changes entail chemical modifications of DNA which are heritable and reversible but with no changes in the underlying DNA sequence. Rather, epigenetic marks are capable to alter DNA accessibility and chromatin structure and, therefore, regulate gene expression patterns. They comprise DNA methylation, histone modification, states of chromatin condensation or non-coding RNA-associated gene silencing (66–69). As it will be described later, early life exposure to BPA has been shown to induce epigenetic alterations associated with diabetogenic outcomes.

METABOLIC CONSEQUENCES OF DEVELOPMENTAL EXPOSURE TO BPA

A review of the currently available literature reveals increasing number of animal studies exploring BPA effects on metabolic developmental programming. Although most of the studies differ in the route and timing of BPA exposure (gestation or gestation and lactation), dose, and animal strain used, they generally strengthen the evidence of the diabetogenic action of BPA. Here we review studies reported in the literature addressing the

contributing role of BPA in the etiology of diabetes. Detailed information on dosage, age, gender and timing of exposure can be found in **Supplemental Table 1**.

Initial observations came in 2010 when it was shown that the treatment of pregnant dams on days 9–16 of gestation with two different doses of BPA (10 or 100 $\mu\text{g}/\text{kg}/\text{day}$) resulted in impaired glucose homeostasis in male adult offspring. Of note, the metabolic phenotype observed was different depending on the BPA dose administered. Thus, animals intrauterine exposed to the lowest dose showed marked insulin resistance, hyperinsulinemia, altered glucose tolerance and increased triglyceride levels. Pancreatic β -cell function was also found to be affected as reflected by enhanced GSIS, both *in vivo* and *in vitro*, probably as a compensatory mechanism for the insulin resistance developed. On the contrary, animals exposed to the highest dose showed mild glucose intolerance with no changes on insulin sensitivity (70).

Later on, a wider BPA dose range study came out with doses tested from 10-fold below EPA reference dose (50 $\mu\text{g}/\text{kg}/\text{day}$) to 10-fold above the no-observed-adverse-effect level (NOAEL, 5,000 $\mu\text{g}/\text{kg}/\text{day}$). Offspring's metabolic changes following oral exposure of pregnant dams to BPA (5, 50, 500, 5,000, and 50,000 $\mu\text{g}/\text{kg}/\text{day}$, days 9–18 of gestation) were evaluated in CD1 mice. The authors found a non-monotonic dose response for body weight changes and increased adipocyte number and volume in the offspring. In addition, offspring from all BPA groups, except for the highest dose one, developed glucose intolerance. Intrauterine BPA-exposed animals to 5 $\mu\text{g}/\text{kg}/\text{day}$ displayed higher plasma insulin levels, and those treated with the doses of 5 and 5,000 $\mu\text{g}/\text{kg}/\text{day}$ showed insulin resistance (71).

A similar study by Liu and collaborators focused on a range of timing of exposure instead of on a range of doses. Preimplantation (days 1–6 of pregnancy), fetal (P6-PND0), neonatal (PND0-PND21) or fetal and neonatal (P6-PND21) periods were explored with the same dose of BPA (100 $\mu\text{g}/\text{kg}/\text{day}$ by subcutaneous injection). The authors reported changes on body weight that were dependent on the animal gender and the exposure timing to BPA. Regarding glucose metabolism, female mice exposed to BPA during fetal and preimplantation periods manifested glucose intolerance at the age of 3 and 6 months. In the case of male offspring, glucose intolerance was observed in fetal, neonatal, and fetal and neonatal exposed-groups at 3 months of age and persisted at 6 and 8 months of age in the first group. Insulin sensitivity was also altered. Reduced insulinogenic index was observed in the 3 month-old female fetally BPA-exposed as well as in males receiving BPA in the fetal, neonatal and fetal and neonatal periods. Together with changes in the insulinogenic index, these animals showed attenuated response to insulin that only persisted in the male fetally exposed-group up to 8 months of age. A transient impairment of pancreatic β -cell function was observed in *in vitro* assays, which was thought to be a functional issue rather than morphological abnormalities, since pancreatic β -cell mass remained invariable or even increased. Isolated islets released less insulin in response to glucose in the fetal female as well as in the fetal, neonatal, and fetal and neonatal male exposed groups. Nevertheless, no changes on insulin secretion were observed when animals reached 8 months

of age (72). Of note, in a similar experimental animal model, BPA promoted impaired insulin signaling and glucose transport expression in the prefrontal cortex at 8 months of age (73). Furthermore, glucose intolerance in adult BPA offspring has also been connected with alterations in the structure of hypothalamic energy balance circuitry (74, 75).

In another study, pregnant rats were exposed to 1 and 10 $\mu\text{g}/\text{mL}$ BPA (drinking water) from gestation day 6 through lactation, and then male offspring was studied at postnatal days 50 (PND50) and 100 (PND100). Increased body weight was manifested on PND7 and persisted at PND100 together with hyperglycemia, insulin resistance, decreased adiponectin levels and increased oxidative stress (76).

Not only murine but also large-animal model-based studies have found postnatal metabolic outcomes related to fetal exposure to BPA at a level relevant to human exposure. In line with this, Veiga-Lopez and collaborators explored pregnancy as a critical period for BPA exposure by treating female sheep with 50, 500, or 5,000 $\mu\text{g}/\text{kg}/\text{day}$ (subcutaneous injection) from days 30–90 of gestation. Increased fasting blood glucose in the lowest BPA dose group and a marked tendency to decreased insulin sensitivity in all BPA groups were found in the female offspring at 6 weeks of age. In the postpubertal period (13 months of age), insulin resistance was observed in the 500 $\mu\text{g}/\text{kg}/\text{day}$ BPA-exposed group. Moreover, enhanced mean adipocyte area and diameter in the visceral adipose tissue, as well as increased inflammation in the subcutaneous adipose tissue depot were reported (77).

It should be mentioned that some reports did not find developmental BPA effects on glucose regulation. This is the case of Ryan and collaborators' article, in which perinatal pregnant CD-1 mice were exposed to BPA (1 ppb via the diet) from embryonic day 0 until weaning. The authors observed that BPA mice were heavier and longer at the moment of weaning but the body weight returned to normal levels in adulthood compared to controls. They did not find any effects on glucose tolerance neither at 8 nor 15 weeks of age. No other metabolic parameters such as insulin sensitivity or GSIS were analyzed. It is remarkable that the authors did not explore more advanced ages in which metabolic abnormalities were revealed in other animal studies (78). In a similar manner, no impairment on glucose tolerance was observed in male 20 week-old offspring after BPA perinatal exposure, although dose-dependent increases of body weight were reported with no changes on global hepatic DNA methylation (79, 80).

Intrauterine exposure to low BPA doses has been shown to affect not only pancreatic β -cell function in the adult offspring but also pancreas development. Increased pancreatic β -cell mass has been found in BPA-exposed animals at the moment of birth, which was also observed at the moment of weaning and PND30. This early life alteration was mainly related to overexpression of cell cycle genes, culminating with a rise in β -cell division as well as decreased apoptosis. All together, these abnormalities led to marked hyperinsulinemia. It is noteworthy to mention that this excessive insulin signaling has been proposed to be crucial for the metabolic phenotype observed in BPA animals later in life (81). Furthermore, BPA

has been shown to have an impact on pancreas morphology with a greater number of islet-cell clusters at embryonic day 18.5 (82).

In order to reveal and/or exacerbate any underlying metabolic disorder that accounts for BPA action, the so-called high fat diets (HFD) have been used in several laboratory studies. This approach has helped to shed some light into the metabolic derangements following prenatal BPA exposure. In one study, pregnant rats were exposed to BPA at doses of 50, 250, or 1,250 $\mu\text{g}/\text{kg}/\text{day}$ by oral gavage through gestation and lactation, and later, offspring was fed with either standard diet (STD) or HFD from the moment of weaning. While some detrimental effects were observed at 26 weeks of age on the BPA animals fed with STD, those effects were accelerated and exacerbated by HFD and became apparent at the age of 15 weeks. Increments in body weight, insulin plasma levels, GSIS and pancreatic β -cell mass were observed in the BPA lowest dose fed with STD group. The same group of animals challenged with HFD exhibited glucose intolerance, hyperglycemia, dyslipidemia and hyperleptinemia. Remarkably, no adverse effects were observed at the highest doses (83). In a different report, pregnant dams were subcutaneously treated with BPA (10 $\mu\text{g}/\text{kg}/\text{day}$) from day 9 to 16 of gestation and then 1-month-old male offspring were maintained during 13 or 24 weeks on STD or HFD. In BPA-treated mice, body weight at birth was decreased followed by catch-up growth with similar weight than HFD mice at 22 weeks of age. At the 17th week, BPA animals showed fasting hyperglycemia, increased NEFA and insulin levels, and a tendency to be glucose intolerant, which was severely impaired at the 28th week in STD. In addition, intrauterine exposure to BPA led to changes in the expression of genes involved in glucose and lipid metabolism in liver and adipose tissue as well as in pancreatic β -cell function that were similar to those observed with HFD treatment (84). Similar metabolic outcomes have also been observed in sheep, including insulin resistance, increased adipocyte size and deposition, and inflammation in BPA-exposed and postnatal overfeeding groups (77). Furthermore, metabolomic analysis revealed changes in metabolic profiling related to prenatal BPA exposure, such as variations in glucose, pyruvate, some amino acids and neurotransmitters, which were evident soon after birth (85, 86).

As stated before, epigenetics has been outlined as one of the major links between genes, environment, and developmental outcomes. Several articles have shown that gestational exposure to environmentally relevant BPA doses are able to promote epigenetic changes in the progeny that correlate to adverse multigenerational health effects. Thus, at the age of 3 weeks, male offspring perinatally exposed to BPA (50 $\mu\text{g}/\text{kg}/\text{day}$) exhibited overexpression of the methyltransferase 3B mRNA. This phenomenon was related to decreased hepatic global DNA methylation and resulted in reduced hepatic glucokinase gene expression. No changes in insulin sensitivity were found at this age. However, at 21 weeks of age, impaired glucose tolerance and insulin resistance showed up, suggesting that the global methylation changes contributed to the metabolic disarrangement observed in adulthood (87). Epigenetic changes

have been connected not only with F1 generation but with subsequent generational effects. In line with this, decreased insulin sensitivity and glucose intolerance were found in F2 generation. These effects were proposed to be transmitted through the male germ line and to be associated with changes in glucokinase DNA methylation (88). Later on, more evidence came out confirming multigenerational phenotypic inheritance upon perinatal BPA exposure. Pregnant mice were treated with two different doses of BPA (10 $\mu\text{g}/\text{kg}/\text{d}$ and 10 $\text{mg}/\text{kg}/\text{day}$) and the effects on the offspring were studied. Overall, increased body weight, glucose intolerance and reduced GSIS were observed in both F1 and F2 male offspring. Importantly, it was demonstrated for the first time that maternal glucose homeostasis was affected in F0 but not in F1 pregnant mice, suggesting that the alterations observed were not caused by an abnormal maternal metabolic milieu but were rather related to epigenetic changes. In particular, the authors reported fetal increased expression of the imprinted *Igf2* gene and enhanced DNA methylation at the *Igf2* differentially methylated region 1 both in F1 and F2 embryos (89). In the same year, another report confirmed the presence of glucose intolerance and pancreatic β -cell dysfunction in male BPA F2 generation; abnormalities that were associated with the dysregulation of *Igf2/H19* in the islets of Langerhans (90). More recently, relying on the same epigenetic bases, metabolic effects found in F1 and F2 generation have been extended to impaired mitochondrial function and insulin secretion, reduced β -cell mass and islet inflammation (91).

These above-mentioned multigenerational effects differ from the transgenerational ones. While the former has been defined as “an exposure that directly influences multiple generations”, the latter implies transmission across generations but with no direct exposure or involvement, and are manifested from F3 generation. Up to date, much of the work has focused on outcomes in the BPA-exposed F1 generation or the intergenerational F2, but little is known about the transgenerational (F3 and beyond) outcomes, with just some evidence of embryonic exposure to BPA and obesogenic effects in F3 (92, 93).

Contrary to the case of T2DM, the experimental data supporting the contributing role of BPA in the developmental programming of T1DM is still very scarce. One study published in 2014 addressed this issue by using non-obese diabetic (NOD) mice, an animal model of T1DM. The study described how transmaternal orally-exposed female offspring (10 mg/L drinking water) showed aggravated severity of insulinitis together with increased apoptosis and decreased number of resident macrophages at 11 weeks of age. This determined increased prevalence of diabetes later at 20 weeks of age (94).

Regarding the possible interactions with the immune system, perinatal exposure to BPA (50 $\mu\text{g}/\text{kg}/\text{day}$) has also been shown to promote systemic immune imbalances in male adult mice offspring. Remarkably, these alterations occurred in parallel to microbial disturbances and impaired glucose tolerance. The authors proposed that these disturbances precede the development of obese phenotype as the animals get old (95).

METABOLIC CONSEQUENCES OF ADULT EXPOSURE TO BPA

Multiple studies conducted in adult animal models have observed alterations in glucose and lipid metabolism following BPA treatment. Firstly, one of the most described outcomes is the insulinotropic action of BPA, i.e. its ability to stimulate insulin release from pancreatic β -cells. A single injection of BPA at a low dose of 10 $\mu\text{g}/\text{kg}$ of body weight potentiated plasma insulin levels in mice within just 30 min (33). Likewise, BPA treatments with different durations and a wide range of doses, from 5 $\mu\text{g}/\text{kg}/\text{day}$ to 20 $\text{mg}/\text{kg}/\text{day}$, also increased plasma insulin levels (33, 41, 96–99). Accordingly, further studies in islets from BPA-treated mice showed an increase in several parameters including GSIS (96), enhanced insulin content (33, 41), improved β -cell area and mass (41), and augmented islet Pdx1 transcript and protein levels, and NeuroD mRNA levels (41). It is important to note that hyperinsulinemia may eventually lead to insulin resistance and, therefore, may contribute to obesity and T2DM development (33, 100). In contrast, other reports described decreased plasma insulin levels after exposing mice to 100 $\mu\text{g}/\text{kg}/\text{day}$ BPA for 20 days (101) or 28 days (102), or even unchanged plasma insulin levels after 8 months of BPA administration (5–5,000 $\mu\text{g}/\text{kg}/\text{day}$) (103). These discrepancies in the observed outcomes might be due to the use of different mouse strains and/or variations in the administration protocol. Secondly, BPA-treated adult mice displayed impaired glucose tolerance after 4 days receiving BPA at 100 $\mu\text{g}/\text{kg}/\text{day}$ (33) and after 2 months of BPA treatment with 500 $\mu\text{g}/\text{kg}/\text{day}$ (41) and 5,000 $\mu\text{g}/\text{kg}/\text{day}$ (103). One study reported no changes in the glucose excursions in response to a glucose load after 8 days of treatment with BPA 100 $\mu\text{g}/\text{kg}/\text{day}$ (96). Furthermore, some reports also described insulin resistance following BPA exposure (33, 41, 96). Overall, these effects on glucose homeostasis suggested that, besides the endocrine pancreas, other tissues involved in the regulation of glucose metabolism also displayed alterations. In fact, the insulin signaling pathway was altered in skeletal muscle and liver from BPA-treated mice, which showed diminished insulin-stimulated phosphorylation of the insulin receptor β subunit and Akt phosphorylation (96, 97, 104). Such failure in hepatic insulin signaling seems to be responsible for the impaired hepatic glucose oxidation and glycogen content found in rats treated with high doses of BPA (20 and 200 $\text{mg}/\text{kg}/\text{day}$) for 30 days (97). Furthermore, hepatic glucokinase activity was acutely (2 h) suppressed in response to an oral BPA bolus of 50 $\mu\text{g}/\text{kg}$ (105). Additional analysis with liver samples showed that long-term exposure to BPA (20–200 $\text{mg}/\text{kg}/\text{day}$) potentiated the mRNA and protein levels of GLUT2 (97), as well as important factors involved in lipogenesis and biosynthesis of cholesterol when employing doses in the range of 5–5,000 $\mu\text{g}/\text{kg}/\text{day}$ BPA (99, 103). Accordingly, augmented plasma triglycerides and cholesterol have been detected following BPA administration (0.5 and 2 $\text{mg}/\text{kg}/\text{day}$) during 4 weeks (103, 106), and hypercholesterolemia remained after 8 months of BPA exposure (5–5,000 $\mu\text{g}/\text{kg}/\text{day}$) (103). Finally, experimental studies employing T1DM animal models reported increased diabetes incidence following BPA treatment (107–109). In NOD

mice, 1 mg/L BPA in drinking water accelerated spontaneous diabetes development, insulinitis and islet apoptosis, and decreased numbers of tissue resident macrophages prior to insulinitis (107, 108). Similarly to what has been previously described in other studies regarding the BPA non-monotonic dose response, the authors reported that the highest BPA dose (100 mg/L) did produce less severe insulinitis than the lowest one (1 mg/L) (107). In parallel, in streptozotocin (STZ)-treated mice, drinking water containing BPA at 1 and 10 mg/L promoted diabetes incidence and affected T-cell immunity (109). Oral gavage administration of BPA 5 mg/kg for 5 days also increased the insulin positive area and transcript expression of estrogen receptors in pancreas, and the hepatic expression of inflammation-related genes in STZ-induced diabetic mice (98).

A NEW PERSPECTIVE FOR THE CONCEPT OF METABOLIC PROGRAMMING

Over the years steroid hormone research has set the framework for addressing how EDCs may cause endocrine actions. Many biological principles that operate for natural hormones are also central for the mode of action of EDCs. This applies for the activational and organizational concepts. As originally described, organizational effects refer to permanent changes occurring during critical periods of development. They are precisely time-dependent, and affect morphogenesis and differentiation processes of organ systems. It is important to note that some of the organizational effects are not manifested up to later in life, which is in line with the concept of developmental programming. For example, intrauterine exposure to estrogenic compounds is well known to promote abnormalities in the reproductive tract as well as functional changes at puberty and throughout adulthood. This is well exemplified by the case of diethylstilbestrol (DES). Animal studies have shown that perinatal exposure to DES promote a wide range of gene expression changes that have been associated with the increased incidence of neoplasm and vaginal clear cell carcinoma observed in the DES-daughters (110–112). Although initial studies were focused on the reproductive tract, metabolic disturbances may also encompass organizational effects. By contrast, activational effects typically occur in adulthood, are transient in nature, and commonly persist as long as the stimulus is present. An example of this is the effect of abnormal estrogenic activity on adult female fertility (113).

Under this paradigm, we would expect that pregnancy exposure to BPA affect maternal metabolism in a temporary manner whenever the metabolic disruptor were present but this was not the case. We will describe how BPA exposure during pregnancy promotes long-lasting effects in the mothers that were visible months after delivery.

BPA exposed dams (10 or 100 $\mu\text{g}/\text{kg}/\text{day}$) from day 9 to 16 of gestation developed glucose intolerance that was more evident in the lowest exposed dose group (70). Moreover, they showed increased insulin resistance, which underlied defects

on the insulin signaling cascade. In particular, decreased Akt phosphorylation in response to insulin was found both in liver and skeletal muscle of BPA mums (70, 114). Interestingly, gestational glucose intolerance related to BPA exposure was found to be associated with abnormalities in the tryptophan catabolism. Diet supplementation with vitamin B6 rescued the disrupted metabolic phenotype in the dams (115). It is important to highlight that any degree of glucose intolerance first recognized during pregnancy is diagnosed as GDM. Thus, we can conclude that exposure to low doses of BPA during pregnancy may compromise maternal metabolic status similarly to GDM.

It has also been reported that metabolic disturbances were resolved after parturition but appeared again months later. At 3 months postpartum no differences on glucose tolerance or insulin sensitivity were found between BPA and control dams. However, at 4 months postpartum early symptoms of altered glucose homeostasis showed up. The metabolic status of BPA mice got worse over time and 7 months postpartum animals exhibited enhanced glucose intolerance, severe insulin resistance together with decreased pancreatic β -cell function and mass (114). These findings demonstrate for the first time that a brief exposure to an EDC during pregnancy could have long-term effects on the mother's metabolism and defined a new window of susceptibility for increased incidence of diabetes.

In view of this data, we should keep in mind that metabolic programming induced by EDC exposure could be extended to other critical periods of life as it is the case of pregnancy for the mother. Hence, we should be cautious when considering the importance of the disruption of normal signaling pathways for metabolic memory beyond early development.

CONCLUSIONS

BPA is one of the most pervasive and ubiquitous EDCs. Laboratory animal and human epidemiological studies have revealed the importance of BPA as a contributing factor in the etiology of T2DM. We know that timing of exposure is critical for determining the consequences of exposure to

BPA. Developmental period has been outlined as an extremely sensitive window of vulnerability since early-life exposure to this EDC can program the risk for metabolic disorders in adult life. An additional aspect of concern is that the incidence of metabolic abnormalities may increase not only in the exposed individuals but also in the subsequent generations. Some of these multigenerational and transgenerational effects may have an epigenetic origin. Evidence described here also underscore the importance of examining pregnancy, an often understudied critical exposure window for long-term metabolic effects in the mother. Gestational exposure to BPA has been linked to metabolic programming of maternal T2DM, yet more research is needed to understand the molecular mechanisms underlying this phenomenon.

AUTHOR CONTRIBUTIONS

ET and PA-M wrote the manuscript. RDS, LM, IQ, and EF contributed to the discussion and reviewed and edited the manuscript. All of the authors reviewed and edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2018.00648/full#supplementary-material>

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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