Role of polycarbonate monomer bisphenol-A in insulin resistance

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Bisphenol-A (BPA) is a synthetic unit of polycarbonate polymer plastics that could be hydrolyzed spontaneously or in a photo- or temperature- catalyzed process, providing widespread environmental distribution and chronic BPA exposure to contemporary human populations. Bisphenol-A is also a xenoestrogen, an endocrine disruptor chemical (EDC), that interferes with the endocrine system mimicking the effects of an estrogen and could potentially keep our endocrine system in a constant perturbation that parallels endocrine disruption arising during pregnancy, such as insulin resistance (IR). While it hasn't been explicitly scientifically proven, the hypothesis states that unnoticed, constant and chronic exposure to this environmental chemical might potentially lead to the formation of constant low-level endocrine disruptive state that resembles gestational insulin resistance, which might contribute to the development of diabetes. In this review, I present the recent findings and provide an overview of arguments and mechanisms for the proposed role of bisphenol-A in insulin resistance and diabetes.

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Abstract

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Bisphenol-A is also a xenoestrogen, an endocrine disruptor chemical (EDC), that interferes with the endocrine system mimicking the effects of an estrogen and could potentially keep our endocrine system in a constant perturbation that parallels endocrine disruption arising during pregnancy, such as insulin resistance (IR). While it hasn't been explicitly scientifically proven, the hypothesis states that unnoticed, constant and chronic exposure to this environmental chemical might potentially lead to the formation of constant low-level endocrine disruptive state that resembles gestational insulin resistance, which might contribute to the development of diabetes.

In this review, I present the recent findings and provide an overview of arguments and mechanisms for the proposed role of bisphenol-A in insulin resistance and diabetes.

Introduction

Bisphenol-A (BPA) is one of the most extensively used synthetic monomers that in a polymerized state constitutes polycarbonate plastics and epoxy resins and makes up the majority of the plastic environment that surrounds modern human species. On no account humans can escape the exposure to BPA and it could well be considered a common environmental factor present since 1957, when the first production of BPA started. With over 6 billion pounds of BPA produced per year and incorporated in polycarbonate polymers, BPA represents one of the most abundant chemicals surrounding human populations world-wide (1). BPA is found in plastic bottles, plastic food containers, baby and water bottles, can and glass linings, various medical and dental devices, sealants for dental fillings, compact disks and electronics, eyeglass lenses, and even in the lining of water pipes and tanks (2). Bisphenol-A is a main monomer of epoxy resin which is being used as a coating agent on the interior of many water storage tanks. Hence, BPA leaching from such widely used polymers may influence human health inadvertently through consuming water or food. Whether the extent of such exposure is significant has been debated, and various evidence have been presented supporting that the tight regulation of BPA is necessary.

Here, I review the chemical properties of BPA polymers, their hydrolysis reaction and leaching concentrations present in the environment and human tissues. Next, I present an overview of the gestational insulin resistance (GIR) and gestational diabetes that may be provoked with the exposure to the endocrine disruptor chemicals such as BPA. I elaborate on the proposed mechanism of BPA endocrine disruption, its transgenerational effects on male offspring and on somewhat ambiguous role of estrogen in insulin resistance (IR). Finally, I review the literature on biological effects of BPA in mice and humans including insulin resistance and diabetes, as well as in cardiovascular (3) and other disorders that BPA might contribute to.

Survey Methodology

In order to survey the effects of BPA on insulin resistance I searched for studies analyzing BPA and insulin resistance on Pubmed or Pubmed Central (PMC) from their inception through May 2, 2017 using the following search algorithm: (*bpa[Title/Abstract] OR bisphenol-A[Title/Abstract]) AND ("insulin resistance"[MeSH Terms] OR ("insulin"[Title/Abstract] AND "resistance"[Title/Abstract]) OR "insulin resistance"[Title/Abstract]).* This search yielded the list of 19 publications on Pubmed Central and 86 publications on Pubmed. Survey of influence of BPA on cardiovascular diseases was performed by applying search algorithm: (*bpa[Title/Abstract] OR bisphenol-A[Title/Abstract]) AND "cardiovascular disease*"[Title/Abstract],* which yielded 33 publications on Pubmed and no publications on PMC. The search with algorithm: *(bpa[Title/Abstract] OR bisphenol-A[Title/Abstract]) AND "cardiovascular"[Title/Abstract]* yielded 97 publications on Pubmed and 5 publications on PMC. Survey of papers describing chemical properties of BPA molecule was performed with algorithm: *(bpa[Title/Abstract] OR bisphenol-A[Title/Abstract]) AND "chemical properties"[Title/Abstract]*, which yielded 27 publications on Pubmed and no items on

PMC. Survey for BPA concentration levels in environment and human tissues was performed with algorithm: *(bpa[Title/Abstract] OR bisphenol-A[Title/Abstract]) AND "concentration*"[Title]*, yielding 89 publications on Pubmed and 12 on PMC. Papers with subject relevant to the search term and not present in the initial search were obtained through Similar Article Pubmed function. Initial papers that describe BPA structural and functional properties as estrogen-like molecules from 1936 and 1938 were not present in the Pubmed or PMC databases and were found on Wikipedia and obtained from JStore database. In addition, in cases where applicable search was performed using '*' symbol that denotes truncated search terms to increase the number of publications obtained. After reviewing, articles were excluded from the study in case they were published in languages other than English or if they described subjects that were not related to the main search topic. Papers that did not contributed to the scientific understanding of the search topic were excluded, as well as papers that were addressing the same or similar subjects in order to eliminate redundant studies. After filtering for each search term the number of papers retained were: BPA chemical properties - 6, BPA and insulin resistance relationship - 11, and BPA and cardiovascular and other diseases - 4, BPA and environmental and human tissue concentrations - 18.

BPA chemical properties, polymerization and hydrolysis.

Bisphenol A (BPA), is an organic synthetic molecule composed of the two hydroxy-phenyl groups connected through a carbon atom, thus belonging to the group of diphenylmethane derivatives, with the formula $(CH_3)_2C(C_6H_4OH)_2$. BPA holds certain sterical resemblance to the estrogen molecule especially in the span of outer hydroxyl groups, and although it does not have a complete steroid ring structure, it's behavior as a synthetic estrogen is based on their similar chemical properties, mimicking of estrogen and on a weak interaction with the estrogen receptor. BPA has an average mass of mass 228.3 D, while estrogen (i.e. 17-beta-estradiol) has an average mass 272.4 Da (4). BPA possesses experimental melting point of 153-158 °C (Alfa Aesar), while estrogen has a similar, but higher value 175-178 °C (Alfa Aesar). Acidic dissociation constant, K_a, for BPA is 10.29 and for estrogen is 10.27 (5). Its cross-linking properties have propelled its utilization in the manufacturing of polycarbonate plastics and epoxy resins. The polymer structural properties and efficiency of polymerization and degradation when exposed to higher than normal temperatures are essential for the degree of contamination of the environment. The glass-liquid transition temperature (Tg, in amorphous materials represents transition from a compact glassy state into a viscous state) of BPA polycarbonate polymers is 147 °C, while heat deflection temperature is 128 °C under 1.8 MPa. Direct photochemical effect on BPA involves irreversible photo-scission leading to bisphenol-like products (6,7) and only secondary photo-reactions are influenced by oxygen and may involve Photo-Fries rearrangement of the benzyl groups. On the other side, photo aging of the BPA polycarbonate has been shown also to occur through ring oxidation, e.g. resin was photo-oxidized under both sunlight (A > 300 nm) and Hg arc light (A > 280 nm) which indicated the loss of aromatic groups (8). Capillary gas chromatogram showed BPA to be highly prevalent in the photo-aged polycarbonate product mixture (9). BPA, therefore has the potential of leaching out from the food and

liquid storage units, as well as from the medical and dental materials especially if exposed to higher temperatures or through a photo-oxidation mechanism.

BPA exposure levels in human tissues

In the late 90s Japan can industry has changed it formula for plastic can linings, which has been associated to over 50% decrease in human BPA levels and to the loss of correlation between usage of canned drinks and urine BPA levels in Japan (10). A wider range of BPA concentrations were detected in adult and fetal serum in humans. Only two studies did not detect any BPA in humans, while in all other studies serum BPA was detected with the concentrations ranging from 0.32 to 4.4 ng ml^{-1} (11). Several studies testing various human tissues detected even higher BPA concentrations than those present in the serum, with the highest in placenta 11.2 ng ml^{-1} (12), umbilical cord 4.4 ng ml^{-1} (13), and amniotic fluid 8.3 ng ml^{-1} (14), as well as in colostrum (late pregnancy milk) 3.4 ng ml^{-1} (15) and breast milk 7.3 ng ml^{-1} (16). These independent findings are indication of potentially elevated BPA exposure traversing from mothers to the progeny, either through placenta or breast feeding. The highest concentrations of BPA were found in human saliva immediately after the sealant application, 42.8 ng ml^{-1}, with the levels dropping to 7.9 ng ml^{-1} 1h after the application (11,17). Recent study found significant difference of BPA concentrations in saliva between a group of patients with tooth surfaces filled with polymer-based dental materials and a control group without any polymer-based materials (pval=0.044, Mann-Whitney U test) (18). These findings imply potential long term exposure of BPA after dental surgeries.

In the human urine, BPA was found with detection rates from 52-100% (11). Focusing on the most recent studies from 2005, BPA was found in human urine with detection rates of 96% (19), 89% (20), 97% (21), 97.5% (22) and 94% (23). These results indicate that in the recent years BPA in human urine has been almost completely detectable in all tested individuals and confirms broad human exposure to BPA. Another source of newborn and infant exposure to BPA might be the persistent leaching from the baby bottles. While a study from 1997 failed to detect any traces of BPA in baby bottles (24), study from 2001 found 2.1 ng ml^{-1} in distilled water that came in contact with the baby bottles for 30 s at 100 °C (25). Similarly, a study from 2003 found BPA in concentration of 0.23 ng ml^{-1} in distilled water after 1h at 100 °C, as well as increased BPA levels of 6.7-8.4 ng ml^{-1} after repeated cycles of washing and brushing of baby bottles (26).

A study from 2004, found BPA leaching levels from a polycarbonate tubing to be as high as 3 ng ml^{-1} per day released into the passing water (27). More recent study found that BPA was detected in 46.9% of cardboard samples for the take-out food that could potentially be leaching the chemical to the packaged food (28). These results indicate that water and food may also be sources of BPA contamination depending on composition of the material used for their packaging or transport.

BPA-induced endocrine disruption and insulin resistance

Gestational diabetes mellitus (GDM) is a form of insulin resistance and glucose intolerance that could appear during pregnancy (29). GDM is one of the most dominant pregnancy complications as it affects from 2% to 10% of all pregnancies (30). During pregnancy peripheral insulin resistance appears as a physiological response to changes in steroid balance in the organism (31). In fact, similar effect could be observed with the application of hormonal contraceptives, primarily those containing estrogen, that have been associated with changes in carbohydrate metabolism and increased insulin resistance (32). For example, one study showed 43-61% increase in plasma glucose levels on the oral glucose-tolerance test (OGTT) in women taking oral contraceptives (33), while other studies, in addition to increased OGTT plasma glucose, have found elevated fasting and post-glucose insulin levels and recommended that estrogen content of oral contraceptives should be reduced to minimize the diabetogenic effects (34).

In 2014 study, it has been shown in mice that offspring from BPA-exposed mothers showed adverse symptoms of diabetes (35). The BPA treated group of mice, similar to the groups of mice fed with high fat diet (HFD) and with high fat diet plus BPA, showed fasting hyperglycemia, glucose intolerance and higher levels of insulin and free fatty acids. In 17-week old male offspring, in the fasted state, the BPA group of mice was hyperglycemic compared to the control, however this effect of BPA was masked when treated with high fat diet. At 17-week, the BPA, HFD and HFD-BPA groups showed higher insulin levels than the control group. Intraperitoneal glucose tolerance test (ipGTT) showed higher glucose intolerance in the HFD and HFD-BPA groups compared to the control, while BPA group showed a similar but not significant tendency. In 28-week old male offspring, BPA group had the highest fasting plasma glucose levels and highest insulin levels, even compared to HFD and HFD-BPA groups. At 28 weeks, ipGTT showed that all three test groups (BPA, HFD and HFD-BPA) presented higher glucose intolerance compared to the control. In addition, at 28 weeks, insulin sensitivity, measured by intraperitoneal insulin tolerance test (iiGTT), showed high tendency of impairment in BPA, HFD and HFD-BPA groups compared to the control group. Remarkably, the BPA group gained more weight starting from the 18th week compared to the control, and kept increasing the weight until it reached the levels of the HFD and HFD-BPA groups. Model animals, therefore, present a valuable source of information on the effect of BPA on insulin resistance, type 2 diabetes and obesity and unveil the connection of environmental estrogens to these diseases.

Molecular mechanisms of BPA in promoting endocrine disruption, gestational insulin resistance and diabetes mellitus

BPA has been first reported to act as a synthetic estrogen in 1936 (36), well before the scientists discovered that it could be polymerized into polycarbonate plastic in the 1950s. As a xenoestrogen and an endocrine disruptor chemical, BPA has a potential to intervene with any aspect of the hormone function, to change the hormonal equilibrium and subsequently affect many different tissues and physiological processes. The

mechanism of BPA as a xenoestrogen is thought to be through binding and competing for estrogen receptors, ER-alpha and ER-beta (Figure 1) (37). However, the interactions of BPA with ER receptors are relatively weak, almost 2-3 orders of magnitude lower than those of estrogen, and therefore whether chronic and low-dose BPA exposures function through the ER pathways is still debatable, as risk assessment of xenoestrogens based solely on reporter gene assays may be inadequate (38). Recent findings indicate that BPA may act also through an estrogen-related receptor gamma (ERR-γ) (39,40). ERR-gamma is a member of estrogen-related receptor class of genes, a subfamily of orphan nuclear receptors, closely related to the ERs. BPA was found to bind ERR-gamma in both a direct receptor binding assays (FRET), as potent as a tracer for ERR-gamma, and in a cell-based reporter assay where it rescues high constitutive ERR-gamma activity in HeLa cells (39). Whether BPA exerts its effect on insulin resistance through one of these mechanisms by mimicking estrogen action remains to be shown.

Role of estrogens in gestational insulin resistance

Insulin resistance and hyperinsulinemia are a common among women consuming oral contraceptives and during pregnancy, and diminished peripheral glucose uptake was observed among normal subjects treated with ethinyl estradiol (41). Studies suggest that in humans the lipolytic effect of placental lactogen directs maternal metabolism toward lipids, rather than glucose utilization, in the same time adding to the preservation of glucose for the fetus (42). However, the role of estrogens in developing insulin resistance during pregnancy, a feature that chronic bisphenol-A exposure is supposed to be mimicking, is somewhat dichotomous, where some studies seem to show protective effect of estrogen on insulin resistance. In a 2012 study, male and ovariectomized female C57BL/6J mice had higher propensity to developing insulin resistance, while the administration of 17β-estradiol (E2) to ovariectomized females reduced insulin resistance in both high and low fat diet groups, as measured by AUC in the glucose tolerance test (43). However, the study did not show the effect of 17β-estradiol on non-ovariectomized females, therefore drawing conclusions only on the stabilizing effect of estrogen on hormone-deficient mice. Similarly, ArKO mice (transgenic mice with inactivated aromatase enzyme, essential for 17β-estradiol synthesis) developed glucose intolerance and insulin resistance reversible by E2 (44) and ER alpha -/- mice are glucose intolerant and insulin resistant (45). A study in rats found that treatment of male rats with 17β-estradiol protected against accumulation of fatty acids in pancreatic islets and against pancreatic beta cell failure (46), therefore preparing the islets for increased insulin production during the pregnancy and gestational insulin resistance. Study, nevertheless, proposes ER alpha or beta receptors as a promising therapeutics to prevent β cell failure in T2D. Estrogens, though with a protective role on beta-pancreatic cells through ER receptors signaling, in peripheral tissues are shown to promote insulin resistance. In non-diabetic women, employing the intravenous glucose tolerance test in 296 oral contraceptive users and 95 nonusers, estrogen based contraceptives reduced the glucose elimination constant and reduced insulin sensitivity by 30-40% (47). Other studies showed that users of oral

contraceptives with synthetic estrogen had up to 61% higher plasma glucose levels, up to 40% higher insulin response and up to 40% higher C peptide response (33). More recent meta-analysis showed less disturbance in carbohydrate metabolism (48), potentially due to the change in composition of contraceptives that contain fewer estrogen content.

BPA effects transmitted to offspring

While mice treated with environmental doses of BPA during gestation develop severe glucose intolerance, decreased insulin secretion and reduced pancreatic beta-cell mass (49), no effects were observed on non-pregnant females. On the other hand, BPA-treated pregnant females (10 μg/kg on days 9–16 of gestation) produced male progeny that showed altered glucose metabolism at 17 and 28 weeks of age (35), therefore indicating that treatment with endocrine disruptor chemicals leads to the perturbation of glucose metabolism of pregnant females that is being transmitted to the offspring. Recently, it has been shown that BPA treatment of pregnant female mice (10 and 100 μg/kg per day) promotes increased expression of cell division genes in the beta cells of pancreas followed with increased pancreatic beta-cell growth and increased insulin levels at postnatal days 0, 21 and 30 in male mice offspring (50). Conversely, at postnatal day 120 beta cell mass diminished and mice showed increased fasting glucose levels and tendency towards glucose intolerance. Therefore, parental BPA exposure leads to the surplus of insulin signaling during early life in male mice offspring that could advance into the impaired glucose tolerance of adulthood. Damaging long-term consequences in glucose metabolism induced by EDC could therefore be actively transmitted to the developing mouse embryo (Figure 2). A 2016 study in humans showed association of prenatal creatinine-adjusted urinary BPA concentrations with BMI levels and waist circumference in male children of 1-4 years of age (51). For female offspring, prenatal urinary BPA was inversely associated with BMI and adiposity measures, confirming similar gender-related trends seen in animal studies.

BPA in cardiovascular diseases

The previous studies on BPA treatment in animal-models found evidence of interference on the mechanisms underlying insulin signaling and diabetes, however the underlying mechanisms of association on prevalence of cardiovascular diseases are not evident. In a 2008 study (52), 1455 adults (694 men and 761 women) aged 18-74 years had measured urinary BPA and creatinine levels. Regression association was adjusted for the creatinine concentration in urine, as well for a set of standard factors, such as age, sex, ethnicity, education, body mass index, etc. Tested sample provided 80% power and detected that higher BPA concentrations in urine were associated with cardiovascular diagnoses in models adjusted for age and sex and in a fully adjusted model (OR=1.39 per 1-SD increase in BPA, 95% confidence interval 1.18-1.63, full adjustment pval=0.001). Whether BPA exerts it effect on cardiovascular diseases through its loose binding to the estrogen receptor or via binding to the estrogen related receptors, and whether this is a shared downstream mechanism with the effect on

insulin resistance remains to determined, especially considering that estrogen receptor signaling exhibits pleiotropic effects on the cardiovascular system.

Proposed BPA involvement in other diseases

In epidemiological studies, bisphenol-A exposure has been linked to various disorders in humans, such as insulin resistance and diabetes (53), cardiovascular diseases (52), and obesity (54). In 2008 study (52), higher BPA concentrations were associated with diabetes mellitus (OR=1.39 per 1-SD increase in BPA, 95% confidence interval 1.21-1.60, full adjustment pval < 0.001). In addition, out of 8 blood serum analytes, urinary BPA was associated with clinically abnormal concentrations of the liver enzymes γ-glutamyltransferase (OR=1.29 per 1-SD increase in BPA, 95% CI 1.14-1.46, full adjustment pval < 0.001), alkaline phosphatase (OR=1.48, 95% CI 1.18-1.85, pval = 0.002) and lactate dehydrogenase (pval = 0.04). As no significant associations with the other common disorders were found, the specificity of the associations to insulin resistance, diabetes and cardiovascular disease implicated BPA in modulation of common mechanisms perturbed in these diseases. On the other side, an association of BPA and the enzymes present in liver, γ-glutamyltransferase and lactate dehydrogenase, was preserved in a cohort without cardiovascular diseases or diabetes (glutamyltransferase OR=1.22, 95% CI 1.02-1.45, pval= 0.03; lactate dehydrogenase OR=1.31, 95% CI 1.06-1.62, pval= 0.01), suggesting that mechanisms underlying the BPA effect on liver are distinct from the cardiovascular and insulin resistance/diabetes effects and therefore exclude reverse causation of these diseases. In addition, in patients with BMI less than 25, BPA preserved significant association with γ-glutamyltransferase (pval= 0.03).

Discussion

In the last two decades, bisphenol-A has been a target of strong public and scientific scrutiny. The number of papers on BPA available on Pubmed reaches 10,668, with several hundred papers published each year. An overwhelming body of knowledge has accumulated since, both mechanistic, in animal models or epidemiological, that has contributed to our better understanding what are the implications of the widespread and chronic exposure of human population to BPA. Even though BPA properties as estrogen mimicking molecule have been discovered in 1936 (36) and 1938 (37), its widespread use as a synthetic polymer unit starting in the late 1950s hasn't been influenced by the fact that it may behave as endocrine disruptor chemical. Driven by the industrial tendencies and novel emerging markets, BPA based polycarbonate polymers have infiltrated almost every aspect of the human life, including food containers, baby and water bottles, can and glass linings, various medical and dental devices, eyeglass lenses, and finally the epoxy lining of water pipes and tanks, making the large majority of human population chronically exposed to the low levels of this chemical.

Whether the widespread use of bisphenol-A in the modern plastic-filled environment surrounding humans is related to the expansion of insulin resistance, diabetes and obesity-related diseases is unclear. One can contemplate that this is most probably not a direct or unique cause of insulin resistance and diabetes, but peculiarly enough the time frames of the expansion of elevated fasting plasma glucose levels and diabetes prevalence in humans and the use of plastic bottles coincide, hence the question becomes more quantitative than qualitative. The prevalence of glycaemia and diabetes are rising globally since 1980 with a mean fasting plasma glucose level increasing 0.09 mmol/L per decade, while the number of people with diabetes increased from 153 million in 1980 to 347 million in 2008, more than doubling in size during 3 decades (55). How much is human population exposed to bisphenol-A depends primarily on the how chemically effective the hydrolysis or photo-degradation of polycarbonate polymers is in their natural environment and that depends on the content, stability and storage conditions of plastic polymers or coating materials. On higher temperatures, increased hydrolysis leads to the excess of leached BPA in the neighboring environment. Certain polycarbonate plastics and coatings may represent greater sources of leaching BPA levels, e.g. food containers that will be exposed to higher temperatures in microwave ovens. Therefore, unknowingly humans may further increase the hydrolysis of polycarbonates and subsequently their exposure to BPA by, e.g. microwaving food in plastic containers, refilling plastic water bottles or leaving plastic water bottles in the sun exposed to light, with BPA polymers undergoing photo-oxidative degradation.

BPA traces have been detected leaching from the polycarbonate plastic products, as well as present in various human tissues. BPA environmental levels correspond to the tissues level, appearing in the concentrations of the same order of magnitude (ng ml^{-1}), indicating effective transfer from the environment to the human internal organs and tissues. BPA has been detected in human serum with concentrations up to 4.4 ng ml^{-1} (11) and urine with detection rates up to 97.5% (22). As several tissues that exhibited the highest BPA concentrations up to the levels of 11.2 ng ml^{-1} were related to the embryo development, like placenta, umbilical cord, and amniotic fluid, as well as tissues related to maternal influence to postnatal development of infants, like breast milk and colostrum - late pregnancy milk, it may not be surprising that experimental studies in mice, as well as epistemological studies in humans, showed pronounced effects of BPA in offspring. The question of mechanism for gender-related differences still remains open, as to why only male offspring exhibits increased insulin resistance, while female offspring shows negative BMI correlation. The explanation may come from a gender-related differences in BPA-processing liver enzyme levels and subsequent BPA clearance from the organism. For instance, it has been shown that female rats harbor higher UDP-glucuronosyltransferase liver levels, as well more effective BPA glucuronidation reaction that eliminates BPA from the organism (56). Skepticism could emerge due to the fact that BPA has much lower affinity for estrogen receptors, therefore questioning whether its effects are indeed minimal. However, it may be possible that effects of prolonged exposure to low affinity binders mimic the short term effect of high affinity binders, providing mechanistic explanation for direct BPA action. Similarly, low affinity binders may have profound effects on the pathogenesis of obesity

and insulin resistance, as shown in the case of insulin-like growth factor (IGF) binding proteins (IGFBPs) containing both IGF high- and low-affinity binders (57,58).

Even though at present day BPA-free plastic products are getting more available, e.g. BPA-free water bottles, the use of BPA-free polymers has not reached widespread levels. In addition, the level of public education on this subject remains relatively poor and the amount of BPA present in the environment still remains at the levels of a substantial health threat. Consistently, it will take years of regulation of environmental and industrial BPA levels to achieve reduced BPA concentrations or its complete elimination to the pre-industrial levels.

BPA may have an effect that humans need to decipher from the existing data to prevent its long-term negative impact. As once, unaware of the health risks, Roman populations were gradually poisoned by increased lead content in the water through utilization of leaded pipes in their water distribution network (59), which subsequently contributed to the decline of the Roman empire, the environmental and health toll of BPA plastics in the human environment needs to be addressed seriously in the modern world. Further experimental and epidemiological efforts are necessary to fully establish a magnitude of potentially hazardous effect of BPA on humans, and its association to insulin resistance and diabetes, as well as other human diseases.

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Figure legends

Figure 1. Model of BPA effect on insulin resistance and diabetes

Global model of BPA endocrine disruptor contribution to promotion of insulin resistance and diabetes in humans. Light and temperature induced hydrolysis of polycarbonate plastics release BPA into water and food sources. Once in human tissues BPA exerts its effects through ER receptors alpha, beta and gamma and estrogen mediated gene expression. BPA induced disruption may contribute to the development of insulin resistance induced through other means such as diet. ER - estrogen receptor. ERR - estrogen-related receptor.

Figure 2. Transmission of BPA effects to male offspring in mice

Acute BPA treatment during gestation leads to severe glucose intolerance, decreased insulin production, and altered glucose metabolism is being transferred to male offspring. During the early life in male offspring there is a surplus in insulin signaling and insulin production that ultimately leads to decreased pancreatic beta mass and glucose intolerance in adulthood. Female offspring is protected from the BPA effects due to higher enzyme levels that are involved in the BPA glucuronidation process and elimination of BPA from the organism.

Figure 1(on next page)

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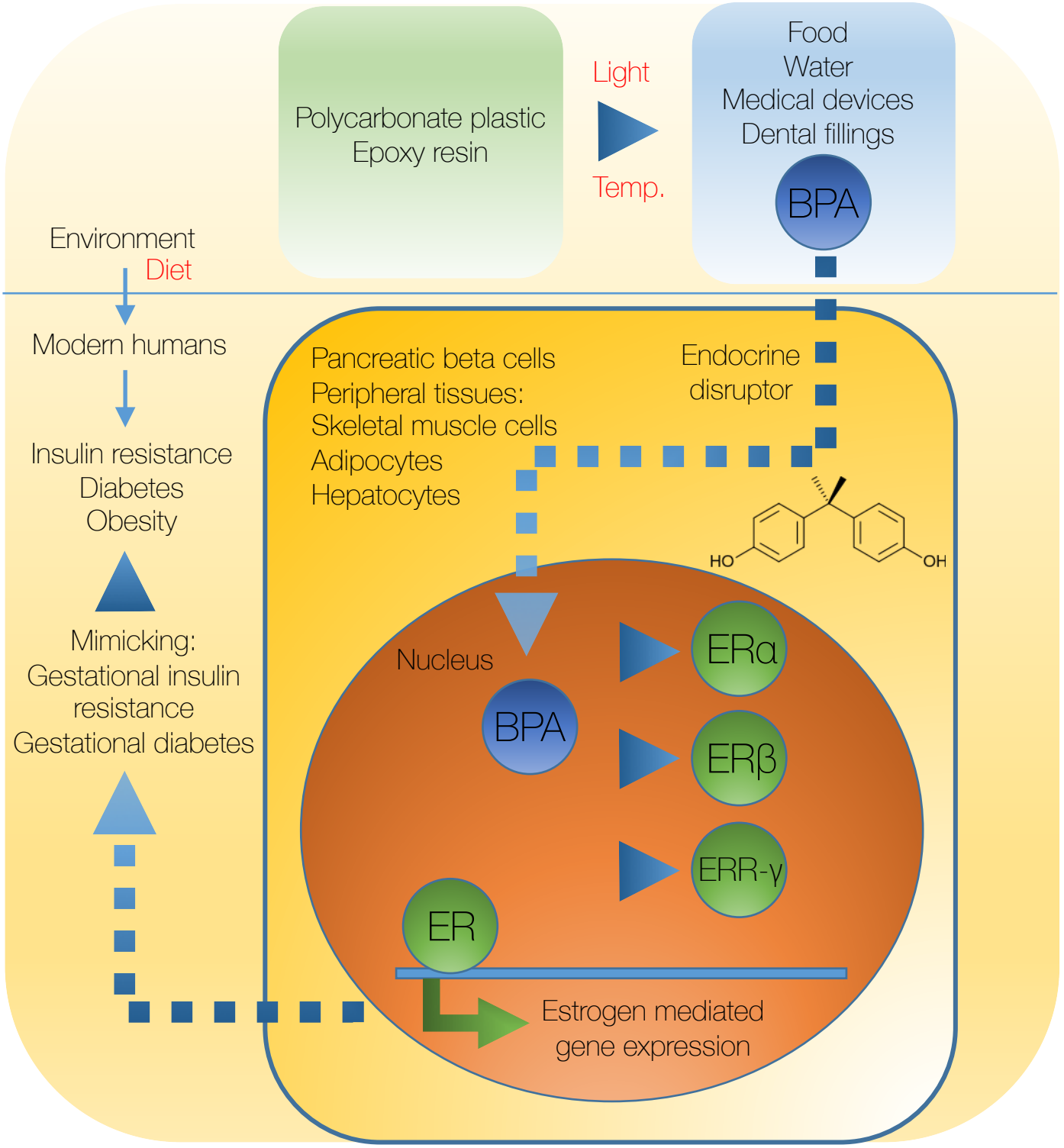
Polycarbonate plastic
Epoxy resin
Light
Temp.
Food
Water
Medical devices
Dental fillings
BPA
Environment
Diet
Modern humans
Insulin resistance
Diabetes
Obesity
Mimicking:
Gestational insulin resistance
Gestational diabetes
Pancreatic beta cells
Peripheral tissues:
Skeletal muscle cells
Adipocytes
Hepatocytes
Endocrine disruptor
HO
OH
Nucleus
BPA
ERα
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ERR-γ
ER
Estrogen mediated gene expression

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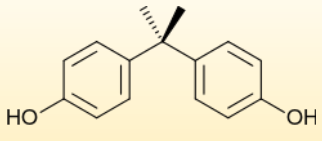

BPA

Treatment with BPA on pregnant females

Acute treatment
10 µg/kg on days 9–16 of gestation

Parental generation

Severe glucose intolerance
Decreased insulin secretion
Reduced pancreatic beta-cell mass

Transmission of altered glucose metabolism to offspring

Female offspring

Male offspring

No observed effect

Higher UDP-glucuronosyl-transferase liver levels

BPA glucuronidation

Elimination of BPA from the organism

Early life – D0, D21, D30

Surplus of insulin signaling

Increased pancreatic beta-cell mass
Increased insulin levels

Adulthood – D100

Decreased pancreatic beta-cell mass
Increased fasting glucose
Glucose intolerance
Diabetes
Obesity