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Review Paper

# Potential Molecular Mechanisms of Bisphenol A in Obesity Development

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## ABSTRACT

Bisphenol A (BPA), an endocrine disruptor, is associated with metabolic disorders. However, several studies have suggested that exposure to BPA can cause obesity. It has recently got more attention from scientists as a risk factor for obesity due to its ability to mimic natural estrogens and bind to their receptors. Nonetheless, the molecular mechanism underpinning the environmental etiology of metabolic disorders has not been not fully clarified. In this regard, BPA exposure directly disrupts endocrine regulation, neuroimmune and signaling pathways, and gut microbes, resulting in obesity. In addition, epidemiological studies have revealed a significant relationship between BPA exposure and the development of obesity, although conflicting results have been reported. Therefore, this review summarized the possible role and molecular mechanisms associated with BPA exposure that may lead to obesity based on in vivo and in vivo studies.

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## 1. Introduction

Obesity is an established triggering factor to develop insulin resistance, which enhances the risk of diabetes mellitus and is a main component of metabolic syndrome. Recently, the prevalence of obesity has increased remarkably worldwide along with the risk of many obesity-related diseases, such as type 2 diabetes and cardiovascular disease [1]. According to the World Health Organization (WHO), obesity is one of the most important global public health problems. The prevalence of obesity among children is rapidly increasing. Additionally, obese children are also more likely to be obese as adults, and they are more prone to develop metabolic syndrome, liver disease, and cardiovascular disease at an early age [2]. The fast increase in obesity prevalence cannot be only due to genetic or previously identified environmental factors, including energy-dense diets and lifestyles. Recent evidence has shown that epigenetic alterations related to anthropogenic chemicals may contribute to the obesity epidemic [3]. Exposure to endocrine disruptor chemicals (EDCs), such as bisphenol A (BPA) during the early stages of development can to obesity. BPA is widely used worldwide in the production of plastic polymers, which are found in many consumer products [4]. Several studies have shown that BPA increases adipocyte differentiation, resulting in excessive fat accumulation. Meanwhile, studies have shown that BPA increases adipose tissue mass and promotes weight gain [5]. EDCs interfere with endocrine signaling pathways and affect adipocytes and endocrine function, which eventually lead to the disruption of metabolic processes. It is known that disruption of hormone-related signaling by EDCs may occur by binding to hormone receptors and altering the production, metabolism, or transport of hormones [6]. In this review, we summarized the possible role and molecular mechanisms associated with BPA exposure that may lead to obesity.

## 2. Materials and Methods

A systematic search of PubMed, Web of Science, and Scopus using the keywords “BMI” OR “overweight” OR “obesity” OR “metabolic syndrome” AND “bisphenol A” or “BPA”, was done. After primary screening using MeSH terms in the titles and abstracts, the relevant articles were selected. Given the large volume of articles, we focused on the most impactful articles published in recent years. Original articles were selected using the following criteria: 1) English language and 2) Representing the molecular relationship between BPA and obesity. The following articles were excluded: 1) Lack of sufficient information on molecular mechanisms of BPA in obesity and 2) Using other isoforms of BPA on obesity.

## 3. Results and Discussion

### BPA

#### Properties and applications

BPA is an organic compound with a molecular weight of 228.29 g/moL (Figure 1). BPA has two hydroxyl para-positioned groups, which is similar to estrogens in this respect. In addition to BPA, several of its analogs can be synthesized by condensation of a ketone or an aldehyde with phenols with either variation in the carbonyl derivative or the substituents on the aromatic ring. BPA is predominantly used as an intermediate in plastics, paints/lacquers, binding materials, and filling-in materials [7]. BPA due to its chemical structure and cross-linking properties, is used to produce polycarbonate plastics, epoxy resins, and thermal papers. Approximately 90% of produced BPA is used as a component for making epoxy resins and polycarbonate plastics [8]. Epoxy resins are utilized as food-contact surface coatings for cans, metal jar lids, automobile parts, adhesives, aerospace applications, and a coating for polyvinyl chloride (PVC) water pipe walls. Polycarbonate plastics are used to make various products, such as eyeglass lenses, water bottles, and consumer electronics. In addition, some dental sealants contain BPA. It also is applicable as an antioxidant and stabilizer in the production of PVC and other plastics [9].

#### Basic levels of BPA exposure in humans

As described, there are many ways for humans to be exposed to BPA and several sources of this chemical. Since BPA has intrinsic heat resistance and elasticity, its use has ongoingly increased. Due to its high production and wide applications, the BPA usually ubiquitous in the environment. The main sources of BPA in the environment are due to its release and migration during the production, processing, and use of BPA-containing materials. BPA-containing products fall into several categories, including food/beverages, electronic equipment, and medical devices [10]. Carwile et al. reported that the concentration of BPA in the urine of subjects who consumed one serving of canned soup over five days was 1200% higher than the concentration in urine after consuming fresh food over five days [11]. The high levels of BPA in water bottles exposed to sunlight prove BPA migration from plastic surfaces into water [12]. Another

**Table 1.** Summary of in vitro studies associated with BPA and obesity

| Study | Study Model | BPA Dosage | Physiological Outcomes |
|---|---|---|---|
| Kwintkiewicz et al. (2010) [38] | Human granulosa cells | 40, 60, 80, 100 µM | ↓ E2 secretion, ↑ PPARγ activation |
| Ariemma et al. (2016) [33] | 3T3-L1 pre-adipocytes | 1 nM | ↑ Pre-adipocyte proliferation<br>↑ PPARγ, FABP4/AP2, and C/EBPα expression<br>↑ Lipid accumulation in adipocytes<br>↑ mRNA levels of Leptin, IL6, and IFNγ in adipocytes |
| Longo et al. (2020) [35] | 3T3L1 and uncommitted NIH3T3 preadipocytes | 1 nM for 8 days | ↑ mRNA levels of IL6, INFγ, TNFα, MCP1, and IL1β, reversibly |
| Pereira-Fernandes et al. (2013) [39] | 3T3-L1 pre-adipocytes | 12.5 µM | ↑ PPARγ activation |
| Ahmed et al. (2016) [40] | Murine 3T3-L1 preadipocyte | 0.01–50 µM/6 days | ↑ PPARγ activation |
| Drobna et al. (2019) [41] | Murine 3T3-L1 preadipocyte | 10 nM/12 days | ↑ Lipid levels in adipocytes<br>↑ Levels of adipogenic markers, like PPARγ and AP2 |
| Junge et al. (2018) [42] | Human adipose-derived mesenchymal stem cells | 10 µM, 50 µM during the entire differentiation period | ↑ PPARγ, SREBF1, and ESR1 activation |
| Kidani et al. (2010) [43] | 3T3-L1 pre-adipocytes | 20 µM, 40 µM, 80 µM | ↓ Adiponectin levels |
| Héliès-Toussaint et al. (2014) [44] | 3T3-L1 pre-adipocytes | A range between 0.1 mM and 1 fM | ↑ Triglyceride and neutral lipid content in adipocytes<br>↑ PPARγ and AP2 expression |

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Abbreviations: E2: Estradiol; MCP1: Monocyte chemoattractant protein 1; TNFα: Tumor necrosis factor α; INFγ: Interferon gamma; IL6: Interleukin 6; IL1β: Interleukin1β; SREBF1: Sterol regulatory element binding transcription factor 1; ESR1: Estrogen Receptor 1

main source of BPA is thermal papers, and BPA is transferred from these papers to the skin within 5 s [13]. Air is also one of the environmental means of exposure to BPA and investigation of air samples collected from plastic burning areas showed enhanced levels of BPA compared with residential and commercial regions [14].

## Obesity

Obesity is a preventable multifactorial disease that affects over a third of the world's people and it is predicted that by 2030, this number will be 50% [15]. New data indicate the increasing prevalence of obesity in less developed countries as well. Obesity is the main factor for elevated risk of diseases, such as cardiovascular disease, diabetes, and liver disease. The main leading causes of increased obesity are lifestyle changes, including unhealthy diet, physical inactivity, and cultural and economic variations [16]. Central obesity is a primary reason for the increased rate of type 2 diabetes and cardiovascular disease [17]. In addition, children with severe obesity have a high prevalence of early kidney disorders, such as albuminuria and reduced kidney function [18].

Obesity depends both on the genetic base of individuals and environmental factors during their development and adult life. Several studies have indicated that many EDCs, known for their obesogenic effect in animals, are associated with increased obesity prevalence. BPA is a commonly identified obesogen EDC that can directly increase the number of adipocytes, or generate dysfunctional adipocytes. Also, obesogen can indirectly increase adiposity by dysregulation of metabolism [19], alteration of metabolic regulators, and induction of inapt alterations in microbiome composition. The obesogenic influences of early-life exposure to EDCs are confirmed by multiple animals and epidemiological investigations. Additionally, human studies have also reported the relationship between perinatal exposure to EDCs and elevated obesity risk in the later years of life [20].

## BPA and obesity

### Epidemiological studies

Despite being used for decades, recent clinical data and in vivo trials have shown that BPA could contribute to lipid accumulations, resulting in obesity as a commonly

**Table 2.** Summary of in vivo studies associated with BPA and obesity

| Study | Study Model | BPA Dosage | Physiological Outcomes |
|---|---|---|---|
| Angle et al. (2013) [45] | Pregnant mice | 5, 50, 500, 5000, 50 000 µg/kg/d | ↑ Body and liver weight, ↑ abdominal adipocyte mass, ↑ overall abdominal fat, ↑ serum leptin, ↓ serum adiponectin in adult offspring |
| Wei et al. (2011) [46] | Pregnant wistar rats | 50, 250, or 1250 µg/kg bw/d | ↑ Body fat<br>↑ Size of adipocytes |
| Alonso-Magdalena et al. (2010) [47] | Pregnant mice | 10 and 100 µg/kg/d | ↑ Body weight, ↑ triglyceride levels, ↑ leptin levels in mothers 4 months after delivery |
| Boudalia et al. (2014) [48] | Wistar han rats | 5 µg/kg BW | ↑ Body weight |
| Ryan et al. (2010) [49] | Pregnant mice | 1 µg/kg/d (during gestation and lactation) | ↑ Body weight in weanling mice |
| Van Esterik et al. (2014) [50] | Pregnant mice | 0-3000 µg/kg bw/day | ↑ Body and liver weight in adult male offspring |
| Gao et al. (2016) [51] | Pregnant rats | 1 µg/mL, 10 µg/mL | ↑ Body weight, visceral adipose tissue, abnormal serum lipids, and ↓ adiponectin levels in offspring |
| Rubin et al. (2017) [52] | CD-1 mice | 0.25, 2.5, 25, or 250 BPA/kg bw/d perinatally or perinatally and peripubertally | ↑ Body weight in offspring |
| Meng et al. (2018) [53] | Female mice | 100 ng/g bw/day on gestational day 7 | ↑ Hepatic lipid synthesis and fatty acid accumulation genes |
| Shih et al. (2021) [54] | Sprague–Dawley rats | 50 µg/kg/d ($6^{th}$ day after pregnancy up to 36 days) | ↑Abdominal lipid weight in female offspring<br>↓ HDL levels<br>↑ TG, TC, LDL, and leptin levels |
| Taylor et al. (2018) [55] | CD-1 mice | 5 or 500 mg/kg/bw/day | ↑ Body weight and gonadal fat of prenatal mice |
| Lin et al. (2019) [56] | Wistar rats | 1 µg/mL/d (8 weeks) | ↑Deposition of fat in the visceral and liver<br>↑ Total cholesterol, TG, LDL-C, IL-17, and TNF-α levels<br>↓ HDL levels<br>↑ TLR4 and NF-κB levels in the liver |
| Neier et al. (2019) [57] | C57BL/6J mice | 50 µg/kg/d (12 days) | ↑ Body weight in offspring |

Bw: Body weight; D: Day.

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observed symptom. Numerous studies have been published to investigate the association between exposure to BPA and obesity from an epidemiological perspective and the majority of these studies are cross-sectional. In some studies, early life exposure to BPA was associated with childhood obesity, but there is controversy in results as some studies have indicated no link between exposure to BPA and obesity in children [21]. Liu et al. performed a cross-sectional study on 745 adolescents and children. They reported that BPA was associated with an increased prevalence of general and abdominal obesity [22]. A few adult population-based studies have reported the link between BPA exposure to obesity. For instance, a cross-sectional study was conducted on 1521 adults aged 20 and older from the NHANES from 2013-2014 [23]. In addition, Zhang et al. found that BPA is one of the chemicals that significantly was associated with adult obesity [24]. There is not much evidence to support the idea of sex differences in the association between BPA and obesity in humans and the conclusions are not consistent. According to the studies on Chinese students, high urine BPA levels were associated with obesity, but only among female students [25]. In a study among Chinese adults, a positive association was reported between urinary BPA concentration and the prevalence of generalized and abdominal obesity [26]. Similar results were also found in a cross-sectional study conducted on Korean adults [27].

## BPA and adipocytes

Several studies have indicated that BPA affects adipose tissue and increases fat cell numbers or sizes by alteration of endocrine-metabolic pathways and dysregulation of gene expression. BPA is a substance that has a tendency to accumulate in adipose tissues due to its lipophilic nature, which can lead to cell growth and the expression of adipogenesis markers [28]. Also, the adipocytes contribute to whole-body metabolic homeostasis under the influence of glucocorticoid receptors (GR).

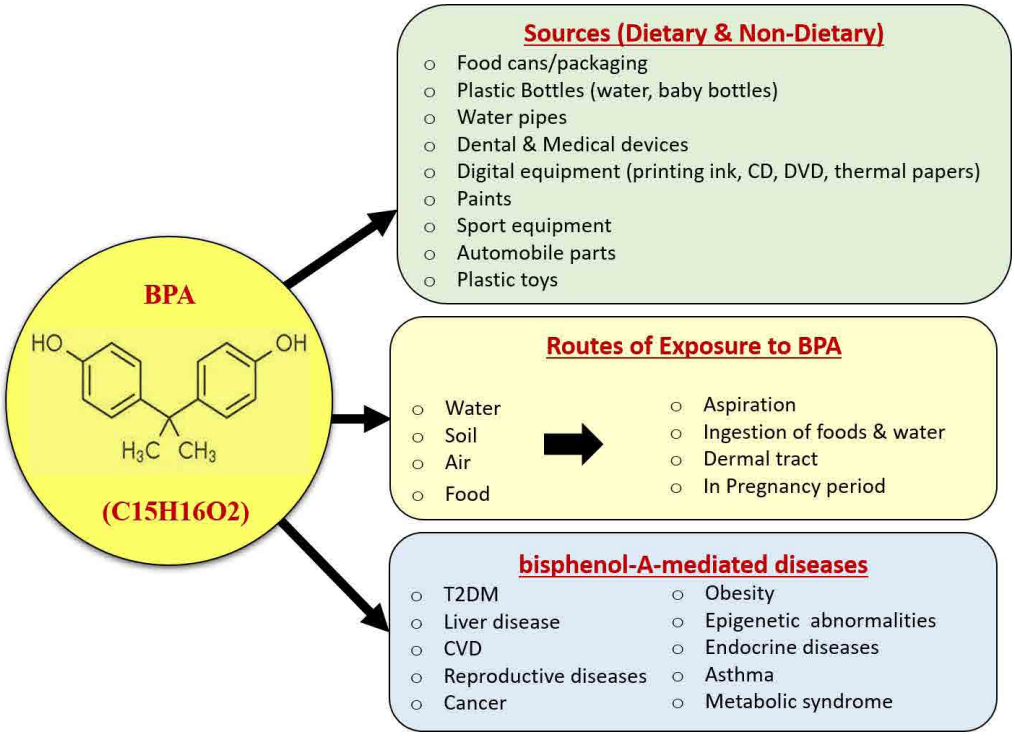


**Figure 1.** Bisphenol A sources, exposure routes, and related pathological conditions.



Depending on various physiological or pathophysiological conditions and distinct fat depots, glucocorticoids are involved in increasing or decreasing lipid storage in adipose tissues. Masuno et al. reported that BPA contributes to adipogenesis by stimulating GR in the 3T3-L1 cell line. They found that when BPA is combined with insulin, speeds up the process of converting fibroblasts to adipocytes [29]. Sargis et al. investigated the ability of several EDCs to stimulate the GR and found that BPA stimulated the activation of GR at a concentration of 1 µmol/L. They also observed that BPA increased lipid accumulation in differentiating adipocytes as well as the expression of adipogenic proteins [30]. It is demonstrated that adiponectin level reduces before the onset of type 2 diabetes, and also in obese populations. It is concluded that factors suppressing adiponectin release could promote obesity. According to the literature, BPA suppresses adiponectin release via binding to estrogen receptors (ERs), specifically ERα and ERβ [31]. Other mechanisms, by which BPA suppresses adiponectin are

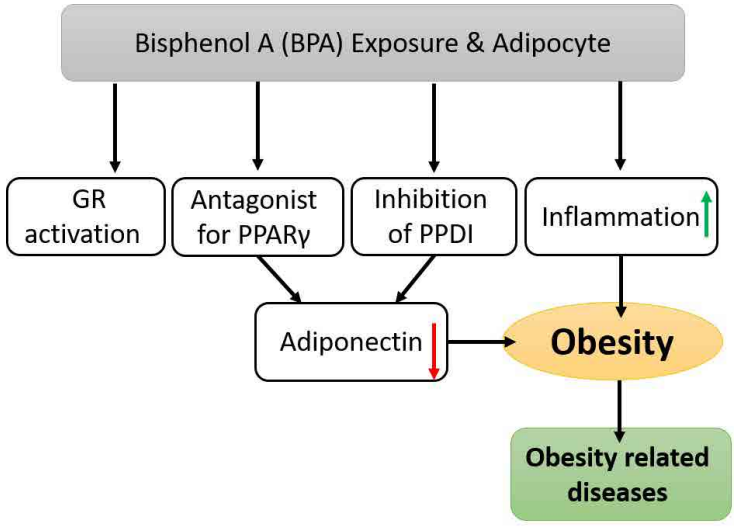




**Figure 2.** Model depicting various mechanisms in adipose tissues contributing to obesity and its related diseases.

an antagonist function of BPA against PPARγ action and inhibition of protein disulfide isomerase (PDI) [32]. Additionally, BPA alters master regulatory genes of adiposis, such as fatty acid-binding protein 4, cluster of differentiation 36, proprotein convertase subtilisin/kexin type 1, and PPARγ. This leads to the up-regulation of FABP4 produced by mature adipocytes and prevents the breakdown of free fatty acids resulting in an accumulation in the adipose tissue and over-spilling to the liver [33]. Several studies have shown an elevation of leptin, IL6, and IFNγ in adipocytes exposed to BPA compared to the controls [34]. The presence of these cytokines in the adipose tissue causes inflammation in the tissue and hinders lipolysis, leading to lipid overflows toward the oxidative tissues, like skeletal muscles. It causes ectopic fat distribution in the liver and skeletal muscles, resulting in abdominal obesity. Exposure of 3T3-L1 cells to BPA enhanced the transcription of IL6, INFγ, TNFα, and IL1β. Interestingly, the pro-inflammatory effect of BPA was reversible, and as soon as BPA was removed from the environment, the mRNA level of these cytokines decreased, similar to the control group [35]. More recently, Hong et al. demonstrated that BPA induces obesity through up-regulating IL-17A in adipocytes [36]. Accordingly, BPA is classified among obesogenic and diabetogenic agents through an increase in proinflammation, up-regulated cytokines expression, and suppression of adiponectin release (Figure 2).

### BPA exposure and obesity: In vivo & in vitro studies

The potential effect of BPA in increasing adiposity was also first identified by Rubin et al. They observed that mice treated with high or low doses of BPA had heavier offspring compared to controls, and this phenotype persisted into adulthood [37]. They found that the offspring from the lower dose were slightly heavier than the offspring of the high dose [37]. However, most studies have been conducted in animal models (Table 1) and the effects of BPA on human adipocytes have been studied quantitatively (Table 2).

## 4. Conclusion

This review summarized the potential underlying molecular mechanisms of BPA in obesity development. Exposure to BPA increases adipogenesis, lipid dysregulation, and inflammation in adipose tissue, thereby enhancing obesity risk. Our study suggests the increasing body of evidence that BPA is positively associated with obesity.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors' contributions

Conceptualization and study design: Mehdi Koushki and Nasrin Amiri-Dashatan; Data interpretation and writing: All authors.

### Conflict of interest

The authors declared no conflict of interest.

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