The role of bisphenol A and its analogues as endocrine disruptors influencing the thyroid gland: a short review

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ABSTRACT

Bisphenols (BPs) are common plastic additives widely used in industry, hence, human exposure to BPs is inevitable. The best known BP is bisphenol A (BPA), the production of which and its analogues has been increasing worldwide. This chemical is classified as an endocrine-disrupting chemical, inferring with hormonal homeostasis. Indeed, BPA is associated with the development of oestrogen-dependent neoplasms, infertility, metabolic disorders and neurobehavioral disturbances. However, there is a lack of evidence regarding the impact of BPA and its analogues on the thyroid, with most studies mainly performed on animals or in vitro. This review aims to summarise the knowledge regarding the relationship between BPA and its analogues on the thyroid gland.

Introduction

Bisphenols (BPs) are common plastic additives widely used in industry. They are products in the manufacture of polycarbonate plastics, such as water bottles, toys, food boxes, teethers, baby pacifiers, thermal paper, inner linings of beverage and food containers, dental sealants, epoxy resins [1-6]. People are exposed to BPs mainly due to contaminated food, especially in high temperatures or acidic conditions [6, 7]. Nonetheless, the other possibilities of exposure to BPs include transdermal or inhalation routes [8].

The most common BP is bisphenol A (BPA; 4,4′-isopropylidenediphenol), which is composed of two benzene rings and two 4,4′-OH substituents (**Figure 1**). Since its industrial application, many studies have revealed the harmful effects of this chemical on human health, especially on hormonal homeostasis. Subsequently, BPA has been classified as an endocrine-disrupting chemical (EDC) [5, 9-11]. BPs act as xenoestrogens, impacting the development of oestrogen-dependent neoplasms (e.g., breast or endometrial cancers) [12-14], as well as being associated with infertility [15] and polycystic ovary syndrome [16]. More-
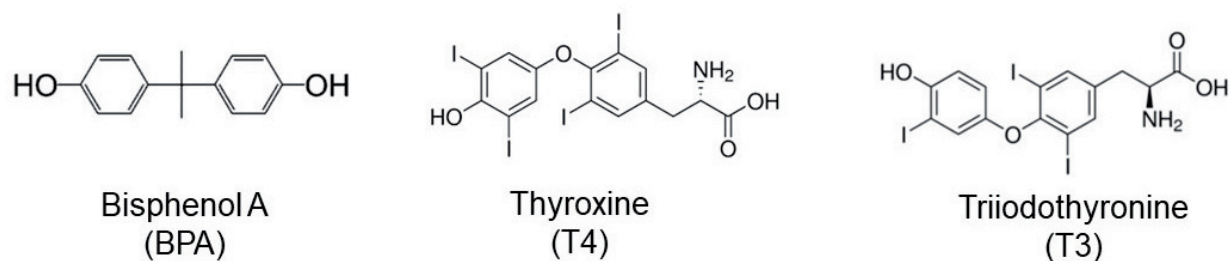
Figure 1. Chemical structures of bisphenol A, thyroxine and triiodothyronine

over, BPA may contribute to the development of metabolic disorders (e.g., insulin resistance, diabetes, obesity) [17] and neurobehavioral disturbances [18]. Furthermore, the specific molecular structure that mimics thyroid hormones allows BPA to influence thyroid hormone homeostasis [19-21] but most of these studies were conducted in vitro [19, 22, 23] or on animals [24, 25].

Types of BPA analogues

Since the use of BPA in products for children has been prohibited, the large-scale production of BPA analogues has escalated. Ideally, substitutes intended to replace a specific chemical should be less toxic than the original substance. Unfortunately, many chemical replacements introduced into the industry have never been studied and are often more harmful than the original chemical.

BPA analogues are compounds with a chemical structure similar to BPA, which means they include at least two phenyl rings, but their substituents differ depending on the type of the analogue (i.e., methyl, bromine or chlorine substituents in 3,3' or 3,5-positions of the phenyl rings). BPA analogues include bisphenol F (BPF), bisphenol B (BPB), bisphenol Z (BPZ), bisphenol C (BPC), bisphenol P (BPP), bisphenol M (BPM), bisphenol AP (BPAP), bisphenol AF (BPAF), bisphenol AD (BPAD), tetrabromobisphenol A (TBBPA), tetrachlorobisphenol A (TCBPA), tetramethylbisphenol A (TMBPA), and dimethylbisphenol A (DMBPA) [19, 22, 23, 26].

Metabolism of BPA

After oral consumption, BPA undergoes first-pass metabolism in the intestine and liver, then it is metabolised by UDP-glucuronosyltransferase in the liver. After glucuronidation, BPA is eliminated via renal clearance within 24 hours [27]. Nonetheless, there is a concern about the other **routes** of human exposure to BPA, mainly via inhalation or transdermally, which bypass the first pass in the gastrointestinal tract, hence there is a longer exposure to unconjugated BPA. It is well documented in the literature that BPA is ubiquitous and has been measured in a variety of human body fluids [28] including placenta, maternal milk and amniotic fluid [29, 30]. The detection rates of BPs differ according to the detection method used (LC-MS, GC-MS, HPLC, HPLS-MS/MS) and the form of BPs (conjugated, unconjugated or total). Importantly, there is a lack of information regarding the metabolism of BPA analogues in humans.

Mechanisms of action of BPs on the thyroid

BPs can interact with the thyroid gland via a variety of routes, therefore, the potential crosstalk needs to be considered at multiple levels. BPA is the first environmental chemical known to bind to the thyroid receptor (TR) and affect thyroid hormone homeostasis in vitro [25]. Lee et al. [22], as well as Moriyama et al. [21], suggested that BPA can influence thyroid hormones at the transcriptional level. Moreover, Schmutzler et al. [31] reported that BPA interferes with thyroid function by inhibiting recombinant thyroid peroxidase (TPO) activity. Furthermore, an in vitro study of Kudo et al. [32] found the antagonistic ability of BPA derivatives to triiodothyronine (T3) in binding to transthyretin (TTR), which is the transport protein for thyroid hormones.

Influence of BPs on thyroid function

The results regarding the influence of BPs on thyroid function are conflicting and depend on the study design (in vivo or in vitro) and the examined group (human, animals, cell lines). According to in vitro studies of rat pituitary (GH3) cells, BPs (BPA, BPAF, BPAP, BPB, BPC, BPF, BPM, BPP, BPZ) have an agonistic effect on thyroid hormones, which is dose- and time-dependent [23]. Co-exposure of GH3 cells to 17β-oestradiol enhanced this effect. Similarly, in another study [22] on rat pituitary (GH3) and thyroid follicular (FRTL-5) cells, the authors suggested that the results were different according to cell type, with BPA and its analogues (BPAF, BPAP, BPB, BPF, BPM, BPP, BPS, BPZ, BPC) significantly downregulating *tshβ, tra, trβ, dio1* or *dio2* genes in GH3 cells, whereas in FRTL-5 cells, the genes responsible for hormone synthesis were upregulated. Furthermore, in the first in vitro study on the influence of BPA on thyroid [21], BPA antagonised T3 action at the transcriptional level in a dose-dependent manner. Kitamura et al. [19] reported that in the rat pituitary cell line GH3, selected BPs exhibited thyroid hormonal activity (TBBPA, TCBPA, TMBPA), while others (BPA, BPF, BPS, BPAF, BPAD, BPB, DMBPA) did not show such effect. The authors suggested that the chemical structure (the type of substituents of the phenyl rings of BPs) is crucial for the thyroid hormonal activity, particularly, hydroxyl groups in 4,4'-positions and methyl, bromine or chlorine in 3, 3', 5 and 5'-positions of the phenyl rings.

The results of the animal studies are inconsistent. Perinatal exposure to BPA in pups [33] or adult polecats [34] did not show any statistically significant influence on thyroid hormones, whereas there was a positive relationship between concentrations of BPA and thyroxine (T4) levels in rats [25]. Also, Lee et al. [26] demonstrated that selected BPs disrupted thyroid hormone levels by increasing T3 and T4 in embryo-larval zebrafish, suggesting that the potency of BPA analogues could be even stronger than that of BPA. It is of note that BPA derivatives could be more harmful than BPA as they act in much lower concentrations than BPA itself.

Regarding human studies, the data considering the relationship between BPs and thyrotropin (TSH) and T4 are conflicting. According to correlations between TSH and BPs in humans, there is an inverse relationship in both sexes [35] and only in women [36], suggesting that exposure to BPs may lead to the development of hyperthyroidism. Also, Meeker et al. [37] measured BPA concentrations in the urine of 1346 adults and 329 adolescents (aged 1–19 years) from the National Health and Nutrition Examination Survey (NHANES) in the period 2007–2008, observing a suggestive inverse association (but without statistical significance) between urinary BPA and TSH. In contrast, Andrianou et al. [28] suggested a positive correlation between BPA with its derivatives and TSH, which could lead to the development of hypothyroidism. Furthermore, there was a positive association between urinary BPA and serum TSH in lean individuals [38]. Taking into the consideration that BPs influence thyroid hormones in humans, the authors of several studies in pregnant women reported that BPA levels were positively [35] or inversely [20] correlated with maternal T4 levels, with two other studies found no association [36, 39].

BPs influence on the formation of thyroid nodules

Nodular goitre and thyroid cancer are related to endogenous oestrogen activity [40-42], hence, as a xenoestrogen, BPA could impact the formation of thyroid nodules. Zhou et al. [43] showed that higher BPA concentrations in urine are potentially linked to the genesis of nodular goitre and papillary thyroid carcinoma (PTC), with women with nodular goitre and PTC having higher concentrations of BPA than men. Moreover, females from the PTC group presented lower urinary BPA levels than those of the nodular goitre group. Furthermore, Marotta et al. [44] described a dose-independent correlation between BPAF and the risk of development of differentiated thyroid cancer in subjects with thyroid nodules. Li et al. [45] also showed a significant association between BPA and a higher risk of thyroid nodules in Chinese women, but only in subjects with positive TgAb and TPOAb, whereas Wang et al. [46] observed a negative correlation between urinary BPA and the risk of forming multinodular goitre, but not of solitary thyroid nodules in schoolchildren. In another study, Andrianou et al. [28] reported no association between BPs and higher risk of thyroid nodules in adult females.

BPs influence on autoimmune thyroid disease

Several studies have assessed the relationship between BPA and the development of autoimmune diseases, including autoimmune thyroid disease [47-49]. BPA can affect the immune system directly and indirectly [50]. Özaydın et al. [48] proved the influence of BPA on the alteration of immune parameters, such as cytokine profile and the distribution of CD8$^+$ and CD4$^+$ T lymphocytes in rats which can result in the development of immunodeficiencies and autoimmune diseases. Also, two case reports described the possible relationships between BPA exposure and immune system-related diseases [51, 52]. Chailurkit et al. [47] also documented the independent, statistically significant association between BPA and thyroid peroxidase antibodies (TPOAb).

Conclusions

In conclusion, the results of the studies concerning the impact of BPs on the thyroid are conflicting and are dependent on the study design and the detection methods used. It seems that BPA derivatives could be even more harmful to humans than BPA as they could act in much lower concentrations than BPA itself. As the exposure to these endocrine disruptors is inevitable, there is a strong need for large randomised human trials to establish the potentially detrimental effects of BPA and its analogues before their industrial application.

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