Genotoxicity and Clastogenicity of Bisphenol A

Adelina Ismaili[1], Flaka Pasha[2]

[1]Researcher, Department of Nursing, University of Prishtina "Hasan Prishtina", Kosovo, [2]Researcher, Department of Pharmacology and Toxicology and Clinical Pharmacology, University of Prishtina "Hasan Prishtina", Kosovo

Abstract

Objectives: This review represents a critical and constructive analysis of literature in the content of genotoxicity and clastogenicity of Bisphenol A. The review is generated through summary, classification, analysis and comparison of already existing material and researches on field.

Methods: Databases as Scopus, PubMed, Medline and Web of Science were used to extract data for the review. Search terms like "Bisphenol A", "endocrine disruptors","clastogenicity" and "genotoxicity" were inquired. Out of 350 research articles screened, 60 most relevant studies are included in this review.

Conclusion : This review highlights the endocrine disrupting potential of Bisphenol A, thus leading to genotoxic and clastogenic events, especially impacting fragile categories like pregnant women, infants and children. BPA induces oxidative stress, inflammatory response, DNA strand break, chromosome aberrations and epigenetic changes, affecting neuroendocrine and reproductive system, metabolism, immunity, liver function, and increases the incidence of thyroid, liver, breast, uterine and ovary cancer.

We can conclude that human exposure to BPA, as one of the leading environmental contaminants, represents a major global issue. BPA by its genotoxic and clastogenic potential can be debilitating for human health. Further research on field considering BPA distribution, varying exposure rates, racial disparities and inter-species differences, should be conducted. Avoiding exposure to BPA and finding safer alternatives to refine, reduce or replace BPA in market should remain a priority.

Keywords: *BPA; endocrine disruptors; clastogenicity; genotoxicity;*

Introduction

Bisphenol A (BPA), 2,2-bis(4-hydroxyphenyl) propane (CAS No. 80-05-7), is a synthetic chemical excessively produced worldwide.[1] BPA commercial production began in the United States in 1957, followed by Europe one year later. Its global production grows consistently, varying between 0% and 5% annually, with the strongest growth occurring in China.[2] A yearly increase of 4.6% in production of BPA is envisioned to happen from 2013 to 2019.[3]

Bisphenol A is synthetized by the condensation of phenol with acetone in the presence of a catalyst, a strongly acidic ion-exchange resin. BPA consists of a central tetrahedral carbon atom with two methyl and two phenol groups. BPA is relatively water-soluble (120-300 mg/L) [4], dissociates in alkaline environment, has a moderate bioaccumulation rate, low vapor pressure, high melting point, and low half-life in air (0.2 days).[5,6]

Bisphenol A is used to manufacture polycarbonate plastics and epoxy resins.[7]Out of the total production of BPA, 65% is dedicated to polycarbonate synthesis, 25% for epoxy resins and the rest 10% for our daily use products such as food storage containers, food antioxidants, metal food cans, baby bottles, thermal papers, dental seals, medical devices, personal care products, safety helmets, sunglasses, lenses, cosmetics, infant incubators, CD/DVDs, hair dryers, fridges, computers and smartphones.[8]

The United States Environmental Protection Agency (EPA) reported that more than 400,000 kilograms of

Corresponding author:
Dr. Flaka Pasha,
Str: Fehmi Agani 141, Prishtine, 10000, Kosovo
Email: flaka.pasha@uni-pr.edu; +383 44584005

BPA leach into environment every year.[9] BPA leaches into environment and can impact human health during its production, processing or waste disposal.[10] BPA leaches also when polycarbonate and epoxy resin-containing products are exposed to heat, are re-used or their pH changes.[11] BPA products in contact with heat, acidic or basic conditions, accelerate the hydrolysis of the ester bonds between BPA molecules, thus exposing humans to its harmful metabolites. This happens when people heat cans to sterilize food, place acidic or basic food in cans or polycarbonate plastic, and keep heating or washing these products regularly.[12,13] Even though ingestion of contaminated food is the most common way how human get exposed to BPA, inhalation and skin absorption are considered to be of great importance too.[14,15] In addition, moderate levels of active unconjugated BPA have been detected in human serum, adipose tissue, breast milk, placenta, maternal and fetal plasma, indicating that BPA can accumulate in human body.[16,17,18]

Bisphenol A mechanisms of action and its endocrine disrupting potential

BPA is qualified as a xeno-estrogen that disturbs synthesis, transport, activity and metabolism of endogenous estrogens, consequently affecting the development, growth and reproduction of organisms.[19,20]

BPA can mimic or antagonize endogenous hormones, subsequently perturbing endocrine function, by binding weakly to several steroid receptors including the estrogen receptors (ER α and β) and thyroid hormone receptor.[21,22,23] As well, BPA strongly binds to transmembrane endoplasmic reticulum, G protein-coupled receptor 30 (GPR30) and estrogen-related receptor gamma (ERRγ).[24,25] BPA can activate peroxisome X receptor (PXR) and the aryl hydrocarbon receptor (AhR), often involved in cross-talk with steroid receptors.[26,27] Many of these receptors play an important role in gene regulation, suggesting that BPA may influence normal differentiation and maturation processes especially during embryonic and fetal development.

The United States Environmental Protection Agency established a reference dose (RfD) for humans of 50 µg BPA/kg body weight (BW) day^{-1}, based on a thousand□ fold reduction of the lowest observed adverse effect level (LOAEL) of 50 mg kg^{-1}BW day^{-1}.[28,29] Studies indicate that daily human intake of BPA is less than 1 µg kg^{-1} BW day^{-1}, rendering the reference dose to be considered safe to humans.[30]

However, studies have shown that administration of low-dose BPA as 0.2 µg kg^{-1} BW day^{-1} can reduce fertility and sperm production in male animals,[31,32] or at doses of 0.23–23 ng kg^{-1} BPA the calcium ion signaling in pancreatic cells can be suppressed leading to diabetes mellitus.[33,34,35]

Genotoxic and clastogenic potential of Bisphenol A

Several studies have revealed that the main course of DNA damage caused by BPA is in single strand-breaks (SSBs), especially recognized in peripheral blood mononuclear cells (PBMCs). BPA also induces DNA damage in human epithelial type 2 cells (HEp-2) and human lung fibroblasts (MRC-5), that can be evaluated by comet assay and micronuclei induction. Though, BPA in submicromolar levels can prompt DNA synthesis and elevate cell cycle protein expression in human hepatocyte line.[36]

In addition, BPA can impair chromosome synapses and disrupt meiotic double strand break repair (DSBR) through DNA dependent protein kinase (DNA-PK) activity. BPA can disturb normal spindle assembly, chromosome alignment and kinetochore microtubule attachment, affecting first polar body extrusion and can cause DNA damage through inhibiting telomerase activity in a non-monotonic manner mediated by activation of ER/GPR 30-ERK transduction pathway. BPA can also induce cell apoptosis through mitochondrial damage, energy depletion and increased levels of oxidative stress.[36]

In recent studies, even submicromolar doses of BPA are thought to elicit aneugenic effects by interfering with microtubule assembly, spindle apparatus function, chromosome segregation during mitosis [37,38], and disturbing DNA damage signaling pathways [39], thus affecting DNA stability and potentially leading to carcinogenesis.

Epigenetic modifications such as DNA methylation, histone modification and non-coding RNA regulation were reported to influence BPA genotoxicity potential as well. BPA can induce DNA hypermethylation through up-regulation of Dnmt1, decreasing MMPs and WNT2/b-catenin, glutamate transporter Slc1a1 or downregulation of TET enzymes, thus resulting on preeclampsia, changes on placenta formation or impaired neurobehavioral development.

In addition, BPA can lower histone H3 and H3K14 acetylation levels, thus inhibiting testosterone synthesis and testicular development. Or BPA decreases histone3 lysine 4 trimethylation abundance in Gnhr promoter, thus altering neuroendocrine control.

Furthermore, BPA can increase the oncogenic miR-19a and miR-19b expressions and modifies expression of phosphatase, PTEN, p-AKT, p-MDM2, p53 and PCNA.[36]

A comparison of various studies assessing genotoxic and clastogenic potential of BPA

Numerous studies investigating BPA's genotoxic and clastogenic potential, present controversial results.

A genotoxic study revealed that BPA induces an increase of DNA damage in the Hep-2 cell line and an oxidative damage in the MRC-5 cell line, while cytotoxicity analysis showed that BPA did not affect cellular viability.[40] In contrast, another study potentiates BPA cytotoxic effect on RAW264.7 macrophages, by observing parallel trends on cytotoxicity, apoptosis, genotoxicity, p53 phosphorylation, BCL2 family expression exchange, caspase-dependent/independent apoptotic pathways and ROS generation.[41] Further, assessing BPA's activity in CHO cells revealed significant increases in cytotoxicity and DNA damage, significant increases in micronucleus frequency and conventional chromosome aberrations as breaks, gaps and fragments.[42]

Micronucleus, chromosome aberration and single cell gel electrophoresis (SCGE) assays revealed that BPA exposure causes significant increase in the frequency of micronucleus (MN) in polychromatic erythrocytes (PCEs), structural chromosome aberrations in bone marrow cells and DNA damage in blood lymphocytes and as well decreased glutathione activity in liver of rats.[43]

Moreover, increased reactive oxygen species (ROS), lipid peroxidation (LPO), depletion of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione-s-transferase (GST) antioxidant activities were observed in Drosophila melanogaster BPA treated group in comparison to the control. Suggesting that BPA exposure induces oxidative stress, which could be the possible mechanism for induction of genotoxicity.[44] In addition, assessing the potential adverse effects of BPA on dam rats and their first generation females in a comparative toxicological study revealed that long term exposure to BPA depicted total genomic damage, significant alterations in liver enzymes, lipid profile, antioxidant enzymes and reproductive hormones with up-regulation in the expression of ERβ.[45]

Studies assessing the effect of BPA, bisphenol S, bisphenol F and bisphenol AF on DNA bases oxidation, found an oxidative damage to DNA pyrimidines and even more strongly to purines in human peripheral blood mononuclear cells.[46] In contrast, in another study none of the eight BPA structural analogues (BPF, BPAF, BPZ, BPS, DMBPA, DMBPS, BP-1, and BP-2) showed a mutagenic effect in Salmonella typhimurium, whereas potential genotoxicity was determined in the human hepatoma cell line (HepG2) at non-cytotoxic concentrations after 24-hour exposure.[47]

BPA's ability to alter multiple molecular pathways in cells, namely G protein-coupled receptor (GPER), estrogen-related receptor gamma (ERRγ), HOXB9 (homeobox-containing gene), bone morphogenetic protein 2 (BMP2) and 4 (BMP4), immune-regulatory cytokine disturbance in the mammary gland, EGFR-STAT3 pathway, FOXA1, enhance zeste homolog 2 (EZH2) and epigenetic changes [48], may increase the incidence of multiple cancers like breast [49,50,51], ovarian [52,53] and uterine cancer [54].

Furthermore, a study assessing the sensitivity threshold of DNA adduct detection by 32P-postlabelling in both liver and mammary cells of female CD-1 mice receiving BPA, resulted in a dose-dependent formation of multiple DNA adducts in liver (3.4-fold higher levels than in controls) and in target mammary cells (4.7-fold higher than in controls). Although DNA adducts do not necessarily evolve into tumors, the formation of these molecular lesions in target mammary and liver cells may suggest for BPA's potential involvement in breast and liver carcinogenesis [55].

Additionally, a ten year study comparing BPA levels in amniotic fluid between pregnant mothers with normal and abnormal karyotype fetuses highlighted that mothers with abnormal karyotype fetuses had higher levels of BPA concentrations in amniotic fluid, in comparison to pregnant women with normal karyotype fetuses. Therefore, these findings highlight the distorting potential BPA has in DNA stability and carcinogenesis induction [56].

Nonetheless, another study suggests that BPA can be included in the group of substances with dual effects, involving genotoxic and DNA-protective activity. While rising concentrations of BPA increase the risk of DNA double-strand breaks and modified purines in human lymphocytes through ROS, in contrast BPA can manifest a protective ability toward plasmid DNA from the damage of iron ions in cell-free system [57].

Conclusions and Perspectives

As stated previously, Bisphenol A can induce oxidative stress, inflammatory response, DNA strand break, oxidative DNA damage, chromosome mutations and epigenetic changes, thus affecting neuroendocrine and reproductive system, distorting metabolism, immunity, liver function, and potentially increasing the incidence of thyroid, liver, breast, uterine and ovary cancer.

To date, studies investigating BPA's genotoxicity and clastogenicity potential had different population sample size, sample sources, sample storage and detection, which resulted in inconsistent conclusions in population-based studies. Thus, to further understand BPA toxicity we should consider studying exosomes, ncRNA (circRNA and long non coding RNA), gene chips and monitor BPA metabolites.

Additionally, more complex, systematic and diverse studies analyzing BPA's impact on endoderm derived organ's transcriptomes, by using in-vitro toxicogenomics, would serve as an ideal tool for identification of new BPA toxicity mechanisms and would help us on having a clearer picture of its long-term adverse health outcomes [58].

Replacing Bisphenol A with its analogues and derivatives, proved to be not a good choice, as some of these compounds revealed even higher levels of toxicity in comparison to BPA [59,60].

Therefore, exposure to endocrine disrupting chemicals as BPA must be carefully regulated by authorities, especially for vulnerable population categories, in order to avoid BPA's potential at impairment of growth and neurological development, disturbance of metabolism or increased risk of cancer [61]. Standardized procedures and statistical tests should be used as the base for developing a protocol to assess human exposure rates to EDCs, to build strategies and health policies which would help on reducing human exposure to EDCs, thus mitigating and avoiding EDCs debilitating life-time consequences [62].

To conclude, implementing prevention and control measurements is highly important on reducing long life term genotoxic potential of Bisphenol A. These measurements must include: elimination and substitution of BPA, meeting legal requirements and policies regarding BPA's management, offering engineering control of local BPA exhaust through regular ventilation of working spaces, implementing safe working procedures by using personal protective equipment, maintaining high personal hygiene and potentially eliminating or reducing time to BPA exposure through alternating work tasks. The last, but the most important is to train employers on how to deal with emergency cases of excessive BPA exposure and continuously raise their awareness in BPA's genotoxic potential that can accur only after long time of exposure [63].

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