Review paper

The role of bisphenol A in the carcinogenesis process

Rola bisfenolu A w procesie kancerogenezy

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Abstract

Bisphenol A (BPA), one of the most common endocrine disrupting chemicals, is a carbon-based synthetic compound used in the production of water bottles, cans, food packaging, dental materials, medical equipment, thermal paper, toys and articles for children. Bisphenol A has been associated with serious health effects in humans. It elicits several disorders and plays a role in the pathogenesis of several tumors such as breast, ovarian, prostate and colorectal cancer. The aim of the research is to review the latest literature assessing participation of BPA in the process of neoplasia. There is not much research on this subject and the role of BPA in the carcinogenesis is still not understood. The present review summarizes the current knowledge of the role of BPA in carcinogenesis.

Streszczenie

Bisfenol A (BPA) jest jednym z najczęściej występujących organicznych związków chemicznych, które zaburzają gospodarkę hormonalną. Stosowany jest w produkcji tworzyw sztucznych, plastikowych butelek, puszek, opakowań do żywności, materiałów dentystycznych, sprzętu medycznego, papieru termicznego, zabawek i artykułów dla dzieci. Bisfenol A powoduje poważne skutki dla zdrowia ludzi. Wywołuje zaburzenia zdrowotne i odgrywa ważną rolę w patogenezie wielu nowotworów, takich jak rak sutka, jajnika, gruczołu krokowego, jelita grubego. Celem badań jest przegląd najnowszego piśmiennictwa dotyczącego udziału bisfenolu A w procesie nowotworzenia. Do tej pory nie przeprowadzono wystarczającej liczby takich badań, a rola bisfenolu A w procesie kancerogenezy wciąż nie została zrozumiana. W niniejszym przeglądzie podsumowano aktualną wiedzę na temat roli bisfenolu A w kancerogenezie.

Introduction

Bisphenol A (BPA, dian, 2,2-bis (*p*-hydroxyphenyl-propane)) is an organic chemical compound from the group of phenols. It constitutes a very popular raw material for the production of polycarbonate, transparent and rigid plastic and epoxy resins. Due to its high durability in a wide range of temperatures (–40°C – +145°C), hardness, resistance to acids and transparency, the polycarbonates are widely used in industry. Hence, BPA is a commonly used compound in everyday life. The main sources of exposure to BPA are food packaging, dust, dental materials, medical equipment, thermal paper, toys and articles for children and babies. Small amounts of BPA can be released from artificial materials, polycarbonate or coatings made of resin that form part of food packaging (plastic bottles, reusable food containers, baby bottles, water pipes) and get into food and drink [1–3]. This may occur as a result of damage to the plastic or coating made of resin, as well as during the decomposition of the product containing BPA under the influence of high temperature. Acidic, basic or heated plastics (changes of temperature and pH) accelerate the hydrolysis of ester bonds connecting BPA monomers, which favors the release of BPA and increases the speed of its migration. As a result, the washed out BPA is found in streams, rivers and drinking water, so the main source of its exposure is food and drink. One of the most important sources of dietary exposure to BPA is food in cans, but it can also be present in

fresh food, such as meat, milk or eggs, when animals are bred in contaminated areas, and plants watered with contaminated water [1–3]. Biomonitoring studies have shown that the urine of most people living in industrialized countries contains measurable BPA and its metabolites: glucuronide and BPA sulfate [1]. The estimated daily consumption of BPA is between < 1 and 5 μg/kg body weight/day [2].

Bisphenol A arouses special interest today, as it belongs to the group of so-called xenoestrogens, i.e. compounds with weak estrogens. Therefore, it may combine with estrogen receptors responsible for binding the natural hormone and lead to disturbance of body metabolism [1, 4].

On the basis of studies on laboratory animals it has been shown that BPA can cause formation of such changes as earlier sexual maturation, decreased sperm production, ovarian cysts, body weight gain, hyperplasia of the prostate and breast gland or tumors. At the cellular level, BPA may induce teratogenic, carcinogenic and mutagenic effects, as well as interfere with the process of chromosome separation during meiosis. More and more evidence indicates that substances disrupting endocrine function, including BPA, can act as carcinogens and increase susceptibility to neoplasms. So far, however, the role of BPA has not been established, and its influence on the occurrence and development of tumors remains unknown [1–4].

The aim of the research is to review the latest literature from the last six years assessing participation of BPA in the process of neoplasia. There is not much research on this subject and the role of BPA in the carcinogenesis is still not understood. The present review summarizes the current knowledge of the role of BPA in carcinogenesis.

In order to collect the material, a database in PubMed was searched using the keywords: BPA, carcinogenesis, breast cancer, ovarian cancer, prostate cancer, endometrial cancer, colorectal cancer, brain cancer. The search was limited to works published in English in 2012–2018. A systematic review of the literature was conducted. Papers matching the conditions for inclusion in this study were selected.

Bisphenol A and carcinogenesis

Due to the negative influence of BPA on human health, its use in production is now limited worldwide. Therefore, other bisphenols were synthesized – bisphenol B (BPB), bisphenol S (BPS) and bisphenol AF (BPAF) – with structure and functions similar to BPA. Many studies, however, also found their potential negative effects on human health. They have been detected in human biological samples and it has been demonstrated that Bisphenols (BPA, BPB, BPS and BPAF) have exerted a positive effect on estrogen receptor α-mediated transcriptional activation *in vitro* studies [3]. Using the MCF-7 breast cancer cell line, the influence of four bisphenols on estrogen signaling was studied. The results suggest that among the four bisphenols only BPAF specifically inhibited estrogen signaling and acted as an anti-estrogen against estrogen receptors α [2, 3].

A review of the meta-analysis by Murata *et al.* [4] shows that BPA is involved in the regulation of growth, survival, proliferation, migration, invasion and apoptosis of tumor cells and resistance to anticancer drugs through several signaling pathways. These regulations are activated by binding BPA to nuclear and membrane receptors or by stimulating BPA via these receptors. These receptors include the estrogen receptor α and β, the androgen receptor, the estrogen receptor coupled to the G protein (GPER, also known as the G30-protein coupled receptor, GPR30), insulin-like growth factor (IGF-1R) and estrogen receptor γ [4].

Bisphenol A can stimulate the growth and proliferation of tumor cells of ovarian cancer and breast cancer by inducing activation of the following kinases: MAPK (mitogen-activated protein kinase), ERK 1/2 (extracellular signal-regulated kinase 1/2) [5] and PI3K (phosphatidylinositol 3-kinase), and mTOR (the mammalian target of rapamycin), which play a key role in the development and proliferation of cells [4, 6].

Migration induced by BPA and invasion of tumor cells were identified based on several types of tumor cells, including ovarian (BG-1 and OVCAR-3), colorectal (SW480), lung (A549), breast (SkBr3, MDA-MB-231) and endometrial cancer cells (RL95-2) [4].

Breast cancer

Breast cancer is the most commonly diagnosed malignancy in women. Lifestyle factors, and genetic and environmental factors influence the risk of its occurrence, and exposure to endocrine disrupting compounds is suspected of contributing to an increase in the incidence of this cancer. Studies have reported that exposure to a low dose of endocrine disrupting substances (including BPA) increases the susceptibility to breast cancer occurrence, especially during puberty and breast growth when the tissue is less diverse [7, 8]. Results from previous studies on molecular mechanisms of BPA activity revealed different pathways, thanks to which BPA can stimulate cellular responses at very low concentrations. The study by Ćwiek-Ludwicka and Ludwicki [9] showed that BPA shows estrogenic activity and thus disturbs the proper functioning of the endocrine system. Studies by Nakao *et al.* [10] suggest that the action of BPA as a xenoestrogen may alter morphogenesis of the fetal mammary gland with the possibility of breast tumor creation in women and gynecomastia in men by epi-

genetic modification of gene expression. In studies of Mandrup *et al.* [11], BPA was detected in mother's breast milk and it was demonstrated that prenatal exposure to BPA may increase the tendency to breast neoplasm development in adulthood.

A risk factor for breast tumor is the inheritance of mutations in one of the breast malignancy susceptibility genes: BRCA1 or BRCA2. Studies show that people who have mutations in these two genes may be particularly susceptible to the negative impact of BPA exposure. Research by Fernandez *et al.* [12] showed that BPA induced gene expression related to DNA repair in normal human breast epithelium cells, and in BRCA1 carriers, exposure to BPA could lead to increased frequency of DNA mutation [10].

Morphogenetic factors of bone (BMP2 – bone morphogenetic protein 2 and BMP4 – bone morphogenetic protein 4) are key regulators of human breast epithelial cell differentiation and are involved in the development of breast tumor [12, 13]. In the studies of Clement *et al.* [13] the participation of BPA in the BMP pathway was studied. It was shown that BPA influences the human properties of immature breast cells and clearly changes the fate and potential of mammary epithelial differentiation by modulating BMP signaling. It may contribute to development of very early stages of breast tumor [7, 14].

Bisphenol A works through different signaling pathways in various cell types. Pupo *et al.* [15] showed that BPA induced cell proliferation and migration through the GPER receptor, EGFR signaling pathway and ERK kinase. Generally, BPA demonstrates estrogenic activity by binding with various estrogen receptors, which proves the involvement of BPA in the development of breast malignancy [15].

A study carried out by LaPensee *et al.* [16] revealed that BPA may antagonize the cytotoxic effects of several chemotherapeutic agents in both the human breast cancer cell line and the estrogen receptors, which may reduce the effectiveness of treatment with some anticancer drugs [17].

Endometrial cancer

The endometrial tumor is one of the most common malignant tumors of the female sexual organs. The best-known risk factors for endometrial malignancy include: obesity, diabetes and hypertension, late menopause and childlessness. The review of the literature showed that the influence of BPA on the risk of endometrial neoplasm development was studied. The results of the study by Chou *et al.* [18] revealed that miRNA may play an important role in tumor genesis underlying the exposure to BPA. Studies suggest that BPA decreases miR-149 expression in the ARF6-TP53-CCNE2 pathway to stop cell cycle retention and initiate migration and invasion of metastatic tumor cells. Discoveries by Chou *et al.* [18] showed the usefulness of miRNA expression profiles in response to BPA exposure and insight into the potential epigenetic mechanism of BPA exposure to the risk of endometrial tumor development.

In the study of Wang *et al.* [19] they tested biological effects and gene expression induced by BPA in human endometrial cancer cell line (RL95-2). The results showed that BPA increased the growth rate and efficiency of RL95-2 cell colony creation in a dose-dependent manner and induced epithelial-mesenchymal transition (EMT) based on morphological changes and gene expression changes associated with EMT. In addition, it was discovered that BPA at the appropriate biological dose induces COX-2 gene expression and promotes the ability of migration and invasion of RL95-2 cells. There were also carried out experiments to explain the mechanisms underlying the observed biological effects of BPA, i.e. migratory and invasive abilities. The results showed that COX-2 expression was important for induced by BPA migration and invasion of the cells. These studies provide new information into the mechanism of growth and invasion of endometrial cancer cells and potential therapeutic strategies [19].

Ovarian cancer

In many *in vitro* studies, it has also been reported that BPA may increase proliferation and inhibit apoptosis in ovarian cancer cells by regulating both estrogen-dependent and independent pathways, which may lead to the development of this tumor. BPA can also work with other hormones, causing the formation of cancerous tumors. The studies of Ptak *et al.* [20] evaluated the effect of BPA on the expression of leptin and leptin receptors in epithelial ovarian cancer cells (OVCAR-3). They analyzed the effect of leptin and BPA on cell proliferation by assessing the activation pathways: JAK (Janus-activated kinase)/STAT (signal transducers and activators of transcription), MAPK (mitogen-activated protein kinase)/ERK1/2 and PI3K/AKT. Data presented in this study clearly showed that BPA increases expression of the leptin receptor and induced proliferation by activating the signaling pathways STAT3, ERK1/2 and AKT, which may lead to the development of ovarian neoplasm [20].

Shi *et al.* [21] investigated a mechanism in which low concentrations of BPA favored proliferation and energy metabolism in the OVCAR-3 human ovarian cancer cell line. It was found that BPA increases the proliferation of OVCAR-3 cells and favors glycolysis-based metabolism, as evidenced by increased cell viability, accelerated cell proliferation, increased level of intracellular ATP, lactate and pyruvic acid. Importantly, all these effects depended on the receptor-dependent estrogen α, indicating the key role of estro-

gen receptor α-conducted signaling in BPA-induced biological effects [21].

Prostate cancer

In studies, exposure to BPA was also associated with the development of prostate tumor. An epigenetic mechanism for BPA-induced prostate neoplasm has been proposed, which includes increased stem cell renewal as well as increased expression of genes related to stem cells. In other words, human prostate stem cells seem to be directly exposed to BPA. Research confirms that there is no doubt that the epigenetic influence of BPA on the binding, synthesis and metabolism of natural estrogens plays a large role. These studies illustrate the strong action of endocrine disruptor compounds (EDC), with particular emphasis on BPA during the perinatal period, and provide evidence that BPA can be classified as a carcinogenic agent based on its role in prostate carcinogenesis [7, 12, 22]. The studies have shown that men affected by prostate neoplasm show higher levels of BPA in the urine than those without disease, suggesting that the level of BPA in the urine may have prognostic value for prostate tumor [7, 22]. Together, these data indicate that early life BPA exposure induces prostate lesions in prostate cancer models. Moreover, elevated urinary BPA levels are associated with prostate malignancy in humans [23].

Colorectal cancer

Colorectal cancer is the second in terms of mortality tumor in Poland in both women and men. Past studies have indicated that over 80% of colorectal cancer cases and deaths are caused by risk factors such as diet and environmental factors. In recent years, clinical and experimental evidence has shown that estrogens, xenoestrogens and their receptors are involved in the development and regulation of colorectal cancer. Classical estrogen receptor α, GPER and the estrogen receptor were detected in various colorectal cancer cell lines. Considering that all these receptors may mediate in estrogen signaling of endocrine disrupting substances, there is justified further evaluation of the participation of xenoestrogens, among others, BPA in the formation of tumors and progression of colorectal cancer [24]. In the studies of Chen *et al.* [24] they showed that BPA significantly alters the expression of proteins related to neoplasia and metastases in colorectal cancer cells. The results of the proteomic analysis of these studies have shown that BPA significantly modulates the expression of proteins involved in various functional activities, such as cytoskeleton dynamic flexibility, cell cycle and proliferation, ATP production, antioxidant mechanisms and protein metabolism. Considering the functions of these proteins in colon cancer and the directions in which their expression has been modulated by BPA, it has been confirmed that BPA can promote metastasis of colorectal cancer cells. In the study, both the oral equivalent and the higher BPA concentration significantly increased protein expression, suggesting that BPA may promote neoplasia of the colorectal tumor [24].

In the Chen *et al.* study [24] colorectal cancer cells treated with nanoparticles or higher concentrations of BPA were compared to the responses of the control group. The research revealed that BPA increased migration and invasion and caused epithelial to mesenchymal transitions. In addition, in BPA-induced EMT of the colorectal cancer cells stimulation of SNAIL1 protein via AKT/GSK-3β kinase is involved, and the studies show that BPA increases SNAIL1 protein expression. The studies have shown that BPA in concentrations of nanomolar and larger modulates protein profiles and promotes metastasis of the colorectal cancer cells by induction of EMT. The authors of the studies emphasize that the influence of BPA on proliferation of colorectal cancer cells and its progression should be further investigated [24].

The results of the studies by Shi *et al.* [25] indicate that the exposure for environmental concentration to BPA promotes cell migration by activating the β1/MMP-9 (matrix metallopeptidase 9) integrin pathway mediated by the estrogen receptor β, suggesting that exposure to BPA in the large intestine may be a potential tumor risk.

Brain tumors

Bisphenol A also affects other organs and physiological systems, including the central nervous system. In the studies BPA concentrations were detected in brain tissues of the hypothalamus and white matter (ranges of BPA concentrations in the hypothalamus and white matter respectively from 0.32 to 26.62 ng/g and from 0.30 to 3.32 ng/g). Determining which of the various molecular mechanisms mediates the influence of BPA on various aspects of human health is not explained and is the goal of further studies [26]. Studies on the relationship between the effects of BPA and the development of brain tumors such as gliomas and meningiomas are still limited. Thus far, a clear relationship has been found between the BPA concentration in the urine and the diagnosis of meningiomas. A study was conducted among patients diagnosed with meningioma in China, where a positive association was observed between increasing BPA levels and the occurrence of meningiomas. In case of gliomas occurring, no case-control studies have been conducted on the relationship of exposure to BPA and the occurrence of glioma [26–28].

The effects of BPA have been extensively studied in recent years. The studies show that exposure to BPA induces organ pathology occurrence that may ultimately be associated with an increased risk of neoplasm. Based on the current studies, BPA is known to disrupt the endocrine system and it is a human carcinogenic agent regardless of its way of exposure. However, the influence of BPA on the process of carcinogenesis is still unclear and requires better understanding in specific types of the neoplasm [7, 16].

Conflict of interest

The authors declare no conflict of interest.

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