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BISPHENOL A AND HUMAN DISEASES. MECHANISMS OF ACTION

© N.I. Dergacheva, E.L. Patkin, I.O. Suchkova, H.A. Sofronov

Institute of Experimental Medicine, Saint Petersburg, Russia

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❀ The review describes the molecular mechanisms and biological effects of bisphenol A exposure, which is a chemical (ecotoxicant) that destroys the endocrine system and has epigenetic toxicity.

❀ **Keywords:** xenoestrogens; epigenetic modifications; epimutation; gene expression; congenital abnormalities; chronic diseases; cancer; ontogenesis.

БИСФЕНОЛ А И БОЛЕЗНИ ЧЕЛОВЕКА. МЕХАНИЗМЫ ДЕЙСТВИЯ

© Н.И. Дергачева, Е.Л. Паткин, И.О. Сучкова, Г.А. Софронов

ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург

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❀ В обзоре рассматриваются молекулярные механизмы и биологические эффекты воздействия экотоксиканта бисфенола А, который относится к химическим веществам, разрушающим эндокринную систему, и обладает эпигенетической токсичностью.

❀ **Ключевые слова:** ксеноэстрогены; эпигенетические модификации; эпимутации; экспрессия генов; врожденные патологии; хронические болезни; рак; онтогенез.

BACKGROUND

Many chemical and physical environmental factors, depending on the dose and duration of exposure, can result in anomalies in development in embryonal and postnatal periods and become the reason for a number of diseases of adults. Currently, special attention of researchers is focused on endocrine-disrupting chemicals (EDCs). They are rather widely spread in the environment and are natural or synthetic compounds, which, after entering the organism even in small doses, can prevent the biosynthesis, storage, release, transfer, and/or receptor interaction of endogenous hormones, changing their functions and destroying the system of internal regulation of the organism. This, in turn, results in increased number of pathologies connected to hormonal disorders. In particular, obesity, diabetes mellitus, and various oncological diseases (breast, ovarian, prostate, and testicular cancers) can occur along with changes in the reproductive system (cryptorchidism, hypospadias, low quality of seminal fluid, and female sterility), cognitive disorders, and deviations in behavior and neuromental development. According to the latest data, only a small part of the available 800 commercial EDCs has been checked for potential effects causing disorders in the functioning of the endocrine system [1, 2].

EDCs primarily affect people and animals via oral, dermal, and inhalation ways. Their bioavailability depends on the mode of penetration. As not all absorbed EDCs can be metabolized, the original compounds become bioavailable. For the major part of EDCs, the most biologically active form is nonmetabolized compound also known as the final toxicant reacting with organic molecules. After entering the blood flow, the final toxicant is able to reach the target cell(s) and affect it [3, 4]; the phenotypical consequences caused by EDC depend a lot on the gap of effect. The EDC effect is mostly crucial for the organism during pregnancy, babyhood, early childhood, and teenage stage. As the mechanism of detoxication in the developing fetus and the newborn is not finally formed, the organism is especially sensitive to EDC in these periods. In the prenatal and neonatal periods, the targets for the EDC effect are the primary germ cells. This, in turn, can result in not only to a disruption of gametogenesis in children whose mothers have been directly affected by EDC, but also to the transmission of different phenotypic anomalies

(including predisposition to socially significant diseases) in a row of generations.

Currently, the molecular mechanisms of the EDC effect are unknown. Available data indicate that the mechanisms of the EDC effect are complicated; studies in this area are decisive for understanding the occurrence of unfavorable phenotypes as well as for the development of strategies of interference and/or preventive actions [5].

It is noteworthy that some chemicals due to their nature can have negative "biological effects," although according to up-to-date regulations they are attributed to nontoxic ones after appropriate tests, and the possible remote consequences of such chemicals effect are not considered [6]. In this regard, it is necessary to consider the new concept of toxicity, namely the "epigenetic toxicity" [7]. Epigenetic toxicity is a phenomenon in which exogenous chemicals affect the epigenome and unfavorably affect living organisms, which can explain the long-term effects and remote consequences of the chemical impact as well as the predisposition to diseases caused by harmful environmental factors. Due to the development of new and improvement of existing analytical technologies, the number of chemicals that have epigenetic toxicity is constantly growing [8], and the understanding of the molecular mechanisms of epigenetic toxicity is enhanced.

This review describes the molecular mechanisms and biological effects of ecotoxicant bisphenol A (BPA) exposure that is attributed to EDC and, as it becomes clear, has epigenetic toxicity.

CHEMICAL PROPERTIES AND OCCURRENCE OF BPA

BPA (4,4'-dihydroxy-2,2-diphenylpropane) is one of the widespread organic synthetic compounds. BPA is used in the industry for the production of various plastic items and is available in the content of epoxy resins used as coating of water supply pipes and the inner surface of cans and packages for food and drinks [9–11]. BPA can be released from containers and enter food and drinks and then can be accumulated in humans and animals [12, 13]. BPA can enter humans via the – gastrointestinal tract as well as through the skin, for example, in contact with thermal paper [14]. As the modern life is "surrounded" by plastic items, BPA exposure on living organisms occurs permanently and in different doses.

PATHOLOGIES CONNECTED TO BPA CHRONIC EXPOSURE

For several decades, studies on the different doses of BPA exposure on health have been conducted around the world using laboratory animals and in clinical practice. Currently, it has been shown that BPA has hepatotoxicity, and its exposure can result in oncological diseases (breast cancer, prostate cancer, and cancer of thyroid glands) and pathologies of the nervous system (disturbance of neurogenesis, stroke, and Parkinson's disease), cardiovascular system (ischemic heart disease, hypertensive disease, and clotting defect), endocrine system (diabetes and obesity), and reproductive system (disturbance of sexual cycle, endometriosis, and changes in breast and prostate gland and testis). BPA exposure can be one of the reasons for chronic respiratory diseases (asthma) as well as arrested development and mental disorders (anxiety, depression, hyperactivity, and aggression) [15–18].

Currently, approximately 347 million people in the world have diabetes. Together with genetic factors, the possible reasons promoting the development of this disease include ways of life and intake of incorrect food as well as the inevitable chronic effect of xenobiotics. Experimental studies demonstrated that BPA affects the metabolism of glucose with the participation of different mechanisms, including resistance to insulin, dysfunction of beta-cells of the pancreatic gland, adipogenesis, inflammation, and oxidation stress, which prove the availability of the connection between BPA exposure and diabetes development [19, 20]. It has been shown that BPA can stipulate the dysfunction of mitochondria due to oxidation stress (for example, in GC-2 cells) and lipid metabolism (for example, in HepG2 and INS-1 cells) [21]. It is supposed that BPA exposure can promote the effect of other risk factors of diabetes, which result in obesity, regulate eating behaviors, or change the differentiation of adipocytes.

BPA exposure is associated with chronic respiratory diseases such as asthma. For example, children with asthma demonstrated increased concentrations of BPA in urine [22]. Besides, it has been shown that BPA exposure in the prenatal period increases the risk of dyspnea development in children in the neonatal period, although a further negative effect of BPA is reduced in the first 3 years after birth [23].

At the present time, it has been shown that men and women exposed to BPA have a higher risk of developing of the coronary artery atherosclerosis. Thus, patients with severe stenosis of coronary arteries demonstrated increased BPA concentration in urine compared with people without atherosclerosis [24, 25]. It also has been shown that carriers of some genetic polymorphisms are more sensitive to cardiovascular and respiratory diseases associated with reduced cell response to oxidation stress [26]. It should be noted that one of the possible molecular mechanisms of BPA exposure can be its impact on oxidation stress [27].

BPA can result in changes in the brain structure and mental and neurological disorders. For example, mice and rats exposed to BPA were more aggressive compared with controls. This was observed only in certain age periods and was not connected to the increase in testosterone concentration [28, 29]. In studies of laboratory animals it was found that BPA exposure in the prenatal period affects brain development. Thus, large doses of BPA reduce the proliferation activity of multipotent neuronal stem cells; low doses, on the contrary, accelerate the differentiation

and migration of neurons. This further results in abnormal neocortical architecture and corticothalamic projection and disturbed neurotransmitter system and behavior in postnatal period and adult age [30, 31]. In addition, it was observed that BPA exposure in the early postnatal period leads to vacuolization, pycnosis, edema, degenerative changes, reduction of sizes and number of cells in the cerebral hemispheres and cerebellum, as well as results in the disturbance of hypothalamus sexual differentiation. In cultivated cells of the hypothalamus of rat embryos, BPA exposure caused the development of dendrites and synapses by increasing the level of presynaptic protein of synapsin I and microtubulin-associated protein 2 [27, 32]. It has been shown that BPA can cause cognitive disorders, autism, schizophrenia, Parkinson's disease, and Alzheimer's disease [18, 33, 34].

Epidemiological studies demonstrated that BPA can cause disorders of the reproductive system and sexual behavior of men and women, although no deviations have been observed in the genitals and hormonal status [35–37]. However, according to the latest data, it cannot be considered that BPA exposure in small doses on adults actually affects reproductive health [38]. Probably, this is connected to the fact that different populations (and groups) have been studied in published works, different doses of BPA have been examined, and different schemes and methods of BPA measurement in biological fluids have been used.

Many works showed the connection between BPA exposure during pregnancy and pathologies in fetal development. Available data state that if the mother took food containing BPA, then this toxicant was detected in the blood serum, follicular fluid, and amniotic fluid as well as in embryonal serum. This indicates that BPA can penetrate the placenta (even in small doses) and has a negative effect during the entire prenatal period [39, 40]. The analysis of BPA content in the organism demonstrated reduced ability to metabolize the chemical in mothers, often coinciding with fetal development defects [41]. For example, it was shown that BPA intrauterine exposure resulted in anomalies in the development of genitals of boys in approximately 37% of cases [42], and it was the reason for prematurity and the birth of children with small weight (especially male babies) [43]. Therefore, Welshos et al. [44] called the inborn defects and disturbances in development caused by BPA as "the large effects of small exposures."

Moreover, presented data indicate that exposure on fetus of small doses of BPA changes cell proliferation and affects apoptosis and the time of breast development, which can further stipulate the predisposition to breast cancer in adult age [45, 46]. BPA exposure during pregnancy, in combination with diet enriched with fats, significantly increases the risk of breast cancer development in offspring [47, 48]. It is supposed that BPA can enhance the oncogenesis of the breast by the direct stimulation of estrogen-dependent growth of tumor cells and/or by molecular changes in fetal glands without associated morphological changes [47]. It should be noted that BPA can also affect the proliferation and apoptosis of ovary cells and terminate steroidogenesis in ovaries by changing steroidogenic enzymes, which in turn can promote the progression of ovarian tumor [48, 49].

The latest data indicate that exposure of small, ecologically valuable doses of BPA in the embryonal period affects the cells of the prostate gland, enhancing the predisposition to premalignant lesions of this organ and hormonal disorders in adults. There is an opinion that cells of the prostate gland are more sensitive to BPA exposure in the embryonal period than in adult age. A number of researchers demonstrated that BPA could enhance the proliferation and migration of prostate cancer cells and induce DNA adducts in case of pathology [50, 51].

Currently, the molecular mechanisms in which BPA affects the fetus and causes the development of ovarian, breast, and prostate cancers in adults are unclear, requiring further studies. Propositions have been made about the possible direct interaction of BPA with receptors of steroid hormones [estrogenic (ER) and androgenic (AR)], which play a decisive role in the origin and progression of these pathologies. In particular, ERα and ERβ start expression on the 12th day of embryonal development in mesenchymes surrounding the embryonal anlage and regulate the growth of breast canals both before and after the birth. That is why BPA exposure in these periods can be crucial for the development of breast cancer in adult age [52]. The mechanisms of BPA exposure in prostate cancer are more complicated compared with that in breast and ovarian cancers, as the studies shown.

In general, considering the connection of BPA with different pathologies, two main conclusions can be made: (1) BPA is a typical xenoestrogen, and its estrogenic, estrogen-independent "steroid" activity is probably involved in the carcinogenesis of different organs and development of endocrine and/or hormone-dependent diseases, and (2) BPA exposure (even in small doses) in critical periods of ontogenesis (prenatal, neonatal, and teenage) can result in long-term negative effects in adults.

MOLECULAR MECHANISMS OF BPA EXPOSURE ON LIVING ORGANISMS: CONNECTION TO CHRONIC DISEASES

The issue of the mechanisms in which BPA can negatively affect humans and animals is still open. Currently, it is accepted that BPA acts as mutagen as well as the endocrine-active compound that affects DNA methylation and histone modifications. These mechanisms do not conflict, although studies on the epigenetic mechanisms of BPA exposure are still insufficient; most likely, they depend on its endocrine activity [15, 53–55].

The main mechanisms of BPA exposure on vertebrates are presented in Fig. 1.

Genetic damages caused by BPA

Different cell lines of humans and animals have been used to demonstrate that BPA is genotoxic and cytotoxic. It causes disorders of the cell cycle (in both mitosis and meiosis) and results in the gene, chromosomal, and genome mutations [51, 56, 57]. The cases of aneuploidy due to the disorders of the segregation of chromosomes during cell division are described for Chinese hamster V79 (lung fibroblasts) and golden hamster SHE (embryonal cells) cell lines [58]. BPA is frequently a reason for DNA damage, formation of DNA adducts, and apoptosis. For example, cell cultivation in the presence of BPA caused apoptosis in ER-positive of breast adenocarcinoma MCF-7 cell line and ER-negative of the human embryonal kidney HEK293 cell line as well as in the line of male germ cells of mice GC-2 [59–61]. It has been reported that the speed of formation of DNA adducts depends on the dose of BPA exposure; in particular, the larger the dose is, the quicker is the formation of such compounds. In the cell line of human prostate gland after exposure to large doses of BPA, DNA adducts formed within 24 h, whereas under the effect of low doses of this ecotoxicant their formation took 2 months [51, 62]. It is supposed that the mutagenic effect of BPA, as of any other xenobiotics, can be due to the formation of free radicals, electrophiles, nucleophiles, and redox reagents that are accumulated and damage the plasma membrane and cell components [63]. Genetic damages caused by BPA exposure can result in changes in proteome in the breast and can be the reason of inborn defects, miscarriage, female and male sterility, and the development of many other pathologies mentioned above.

Mechanisms of BPA effect as a substance destroying the endocrine system

BPA is a xenoestrogen rather than an estrogen imitator. Its effect on the organism as a synthetic hormone is explained by the fact that, like steroid hormones, it has phenol groups; therefore, the nuclear receptors of estrogen (ERα and ERβ as well as recently detected in bone ERγ) perceive BPA as the signal for the initiation of the estrogenic pathway of the activation of transcription of estrogen-sensitive genes. In vertebrates, this toxicant can change hormonal balance by directly interacting with receptors ERα, ERβ, and ERγ or affecting enzymes by ensuring the metabolism of these hormones. For example, BPA can affect the ERβ-mediated transcription of the target genes by inhibiting ERβ degradation and ubiquitination [64].

It should be noted that nuclear receptors ERα and ERβ are functionally and genetically different; they differ in their affinity and specificity and have different spatial time types of expression. In this regard, cells of different types can respond in a different way to the same estrogenic in-

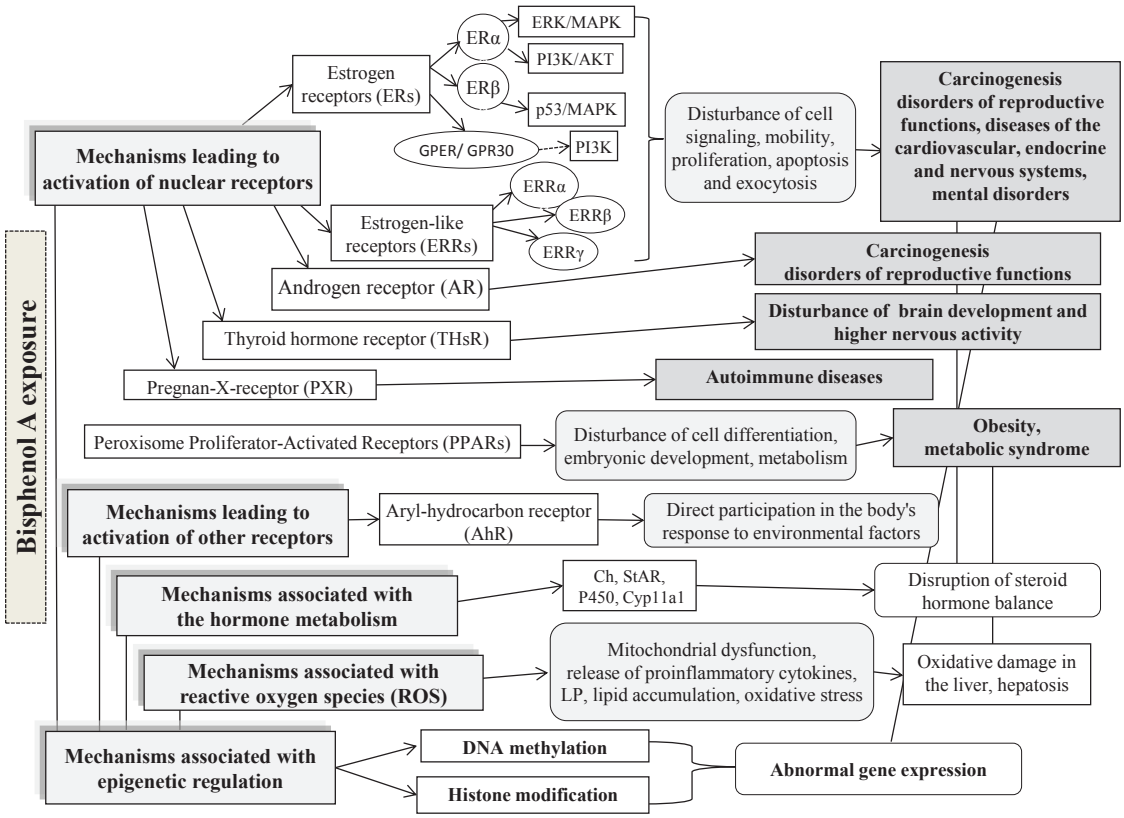

Fig. 1. Scheme of the main mechanisms of BPA effect on the organs of vertebrate animals (based on data in Refs. [51, 71, 79])

centives depending on the ratio and expression of the two subtypes of receptors in the cell; therefore, the "pathogenic" effect of BPA can be different in different types of tissue. Masking for natural germ hormones, BPA can disturb endocrine regulation and result in different changes in the target organs of estrogens, including the brain, ovaries, thyroid gland, breasts, and prostate gland. Thus, the interaction of BPA with receptors of steroid hormones can be the reason for hormone-associated oncological diseases of the ovaries, breasts, and prostate gland [52].

Currently, the existence of additional membrane receptors to estrogens in the brain is supposed (similar to catecholaminergic receptors detected in the pancreas), which can explain the mechanism of estrogen effect on cognitive functions, pain development, delicate motor functions, emotional behavior, neuroprotection action in Parkinson's and Alzheimer's diseases, multiple sclerosis, depression, schizophrenia, and cerebral thrombosis [16]. In this connection, the presence of BPA in the organism can have a negative effect on these processes.

Moreover, there are data about BPA effects directly on the expression of the genes-receptors of hormones, in particular estrogens. For example, this has been demonstrated in the culture of cells of the rat cerebellum and human neuroblastoma as well as on human cell lines H295R (suprarenal cortex, angiotensin II sensitive, and steroid-producing line), HEK293 (embryonic kidney cells), and HepG2 (hepatic carcinoma) [65–67].

BPA is related to endocrine destructors, as it can interact with classical and nonclassical membrane receptors of estrogens. BPA exposure on metabotropic receptors transfers chemical signals to receptors jointed with G-proteins (for example, GPR30) and receptors jointed with the fragments, thus resulting in the disturbance of the regulatory ways of androgens, glucocorticoids, thyroid hormone, prolactin, insulin, and the dopaminergic system [68–70]. Besides, BPA negatively affects the organism through "nonsteroid pathways" affecting the activity of the genes participating in cell and tissue differentiation [60, 71].

BPA can cause functional effects not only through the activation of receptors of steroid hormones but also through signal pathways, such as nuclear factor-κB, STAT3, phosphatidylinositol-3-kinase/AKT (PI3K/AKT), and mitogen-activated protein kinase (MAPK) [72]. This xenobiotic can also affect sodium, calcium, and chlorine ion canals, ionotropic glutamate receptors, and nicotinic and GABA receptors, changing the excitability and signal transmission in the neurons [73, 74]. In addition, BPA exposure can increase the activity of the markers of oxidizing stress and reduce the activity of antioxidant markers. In this connection, it was supposed that the hypothyroid condition induced by BPA in the neonatal period can affect the thyroid gland–brain axis by the formation of free radicals, which in turn can disturb plasma membrane and cell components resulting in the delay of brain development [27].

As there are data indicating that estrogenic proteins affect the epigenetic status of the target genes (both at the level of DNA methylation and chromatin proteins) changing the level of their transcriptional activity [75, 76], it can be supposed that BPA exposure has similar epigenetic mechanisms. A limited number of works have been published regarding research of epigenetic consequences of BPA exposure on the developing organism [77–79]. The obtained data confirmed that this xenobiotic can actually cause changes in the status of the expressed gene DNA methylation.

Epigenetic effects of BPA and gene expression

At the present time, studies have been conducted regarding the links between xenobiotic effect and changes in epigenome [80]. Three main epigenetic regulations of gene activity are known, which can be involved in the occurrence of pathologies connected to the EDC effect. These are DNA methylation, hydroxymethylation, different posttranslational modifications of histones (methylation, acetylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation of histones) and noncoding RNA. It should be underlined that these epigenetic mechanisms do not work in isolation from each other, but together in a complicated regulatory network. Different combinations of these modifications can significantly affect the chromatic status and result in transcriptional silencing and, on the contrary, increase the activity of transcription [81–83]. These covalent modifications do not cause classic genetic mutations, are rather liable, and are the most sensitive targets for the direct and indirect (metabolism products) effect of ecotoxicants on the epigenome of living organisms even in low doses. Disorders in any of the mentioned epigenetic regulatory mechanisms are connected to the elevated risk of disease [84]. The incorrect epigenetic regulation that occurs in primary germ cells ensures the mechanism of epigenetic inheritance of abnormal phenotypes in the number of generations, including the inheritance of predisposition to the number of the socially significant diseases [80].

The first studies of epigenetic changes caused by xenobiotics were conducted using the model of changing the color of the mouth fur *Agouti viable yellow* (Avy). It was demonstrated that the mother's diet with different content of sources of methyl groups (for example, folic acid) affects the degree of methylation of retrotransposon IAP located upstream of the *Agouti* gene, affects the level of gene transcription, and results in changes in the descendants' fur color [85, 86]. Such effect was found in BPA exposure on pregnant females. It turned out that this ecotoxicant reduces IAP methylation of *Avy* and *CapblAP* genes [87]. Besides, the hypomethylation of imprinted *Igf2r*, *Peg3*, and *H19* genes was observed in mice with increased concentration of BPA, resulting in increased mRNA level of these proteins, which in turn suppressed the maturation of oocytes due to the abnormal structure of the spindle during meiosis [88]. The authors

came to the conclusion that BPA exposure in the embryonal period can change the cell processes and pathways of development through epigenetic mechanisms by changing the phenotype of the descendants. Exposure to low doses of BPA in the preimplantation period in laboratory mice can disturb DNA methylation during cleavege and at later stages of embryonal development. BPA caused the dose-dependent reduction of DNA methylation level in the 1-cell and 2-cell embryos and in blastocysts, which was accompanied by inhibition of cleavage. In germ cells on the 9th day of development, i. e., during early organogenesis, a small increase in the level of genome-wide DNA methylation was observed. At the same time, on the 12th day of embryonal development, both DNA hypomethylation and hypermethylation were detected depending on the body part (tissue type) and the germ weight [77–79]. The obtained data confirmed that preimplantation development is a highly sensitive period to BPA exposure. This was due to active reprogramming processes connected to the different pattern of changes in DNA methylation in the whole genome. Probably, this process involves different repeated DNA sequences that are also important for the regulation of gene activity, chromosome arrangement, and nuclear architecture.

It appeared that BPA can reduce the genome-wide DNA methylation in combination with the reduction of expression of DNA methyltransferase Dnmt1, which is stipulated by the disturbance of estrogenic mechanisms [89]. The reduction of the level of the genome-wide methylation of sequences LINE1 of DNA in sperm of males after BPA exposure was reverse proportional to the BPA level in urine, but it was not observed for methylation LINE1 in blood cells [90]. This indicated that epigenetic changes explained by DNA methylation are one of the possible mechanisms of the unfavorable effect of BPA on hematogenesis and fertility.

Futhermore, BPA exposure in the prenatal period caused disturbance in gene expression crucial for brain development, including the main (spiral-turn-spiral) transcriptional factors, which could be connected to epigenetic changes in CpG islands associated with the promoters of these genes [30]. For example, BPA exposure on developing neurons in the brain cortex of mice, rats, and humans reduced the level of mRNA of chlorine potassium transporter 2 gene (*Kcc2*). Probably, this was connected to the increased activity of bonding of methyl-CpG-bonding protein 2 (MECP2, MBD2) with "cytosine-phosphate-guanine coasts" of promoter of gene *Kcc2* and due to the reduction of interaction with acetylated histone H3K9 surrounding the site of transcription initiation. Wherein it were observed sex differences: the BPA effect was stronger in females than in males [91]. The reduction of expression of DNA methyltransferases and hypomethylation of genes connected to lipid synthesis was also detected after BPA exposure in Hepa1-6 (mouth hepatoma) and BeWo (human trophoblasts, chorion carcinoma) cell lines [60, 92, 93].

BPA can result in DNA hypomethylation as well can cause the increase in the level of DNA methylation. Hypermethylated DNA was found in tissues of tail of the mouth successors, which was exposed to low BPA doses in the perinatal period, i. e., in successors of the second generation [94]. Experiments with laboratory animals demonstrated that this toxicant results in the stable expression of certain genes, including lactoferrin, epidermal growth factor, and proto-oncogenes (c-fos and c-jun), inhibiting the methylation process [53]. It was shown that BPA exposure in the neonatal period causes hypermethylation of the promoter of the receptor gene of estrogen in rat testicles [95]. Exposure to low doses of BPA on the cells of the primary culture of epithelium of the human breast results in the increase in methylation of CpG islands of DNA of the lysosomal-bound membrane protein 3 gene (*LAMP3*) and the suppression of transcription of this gene, which indicates the role of BPA in the enhancement of breast cancer development risk [96]. The epigenetic mechanism of regulation of BPA effects in breast carcinogenesis is also indicated by the elevated expression of trimethylated histone H3 as per lysine EZH2 after exposure to this xenoestrogen [97]. BPA can also increase the level of transcription of the cytokine gene of the family of tumor necrosis factor (*TNFSF11* and *RANKL*) and the family of genes coding secreted signal proteins (*WNT-4*) required in embryogenesis regulate proliferation, participate in carcinogenesis of stem cells of breast, and play an important role in the metabolism of the bone tissue [98]. It was reported that BPA can increase the expression level of microPHK-146a, which is important in immune response [94]; therefore, the regulation of the epigenetic program and microRNA can become one of the areas of study and probably cancer therapy associated with BPA exposure.

It was demonstrated that BPA exposure during pregnancy (in mice and rats) can induce in the brain the successors of the first generation in puberty the sex-dependent, dose-dependent, and area-specific (in brain areas) changes in expression of genes coding receptors of estrogen (ERα, ERβ, and ERRγ). Together with the changes in estrogen-associated receptors, the dose-dependent changes of the mRNA level of DNA methyltransferases *DNMT1* and *DNMT3A* genes were observed in juvenile cortex (male) and hypothalamus (female) as well as the level of methylation of *ER*α gene [16–99]. Besides, such successors (male) demonstrated changes in the regulation of glucocorticoid, namely increased DNA methylation in *Fkbp5* gene and reduction of the level of this protein in the hippocampus, which resulted in anomalies in behavior and response to stress of these animals [100]. BPA exposure in the prenatal and neonatal periods also disturbs the expression of methyl-CpG binding protein 2 in hypothalamic cells, which can be the reason for the disorders of the normal development of hypothalamus and its functions [99].

Thus, all these data indicate the interaction of two regulation systems, epigenetic and receptor (hormonal), and

underline the importance of the study of BPA exposure effects on the health of humans and animals. Obviously, the methodological differences in research of BPA exposure on living organisms (studies *in vivo* and *in vitro*, different objects of study, different ways of exposure and experimental doses of BPA, and exposure of individual compounds and mixtures) explain an alternative hypothesis about the molecular mechanisms of this xenoestrogen effect. For example, mice and rats are different models for understanding the mechanisms of the human disease occurrence. Moreover, it should be noted that the same dose of BPA can result in DNA hypomethylation and hypermethylation or does not change it depending on the gender differences in response of the organism to the exposure, stage of development, cell differentiation, and tissue type.

CONCLUSION

Data on epidemiological studies indicate potentially harmful chronic exposure of BPA on human and animal ontogenesis; therefore, BPA penetration into the organism (even in small doses) should be limited as much as possible, especially during pregnancy, taking into account its possible remote negative effects on health. It should be noted that some individuals have a low risk of pathology development under the effect of harmful environmental factors, whereas others are more sensitive to such effects. This is explained by genetic features, although individual epigenome differences should not be excluded at the current stage. Results of many studies indicate that the molecular mechanisms of xenobiotic effect go far beyond the limits of interaction with the DNA sequence. Apparently, additional research and development of new test systems are required for the assessment of the actual ratios of the dose and the effect and the mechanisms of ecotoxicant action in pathology development, as stated in the review. The development of preventive measures for the negative effect of xenobiotics requires research of the features of epigenomic/epigenetic modifications and DNA methylation first of all. Such studies shall be preferably conducted at different levels of arrangement – from molecular (DNA and chromatin), cell, and tissue to the entire organism – in experimental models *in vivo* and *in vitro*, taking into account different sensitivities to unfavorable BPA consequences.

One more very important aspect that should be given attention is the fact that epimutations caused by BPA in early embryogenesis result in changes in gene normal expression that can be kept in adults and transferred to the next generations through germ cells resulting in the intergeneration inheritance of abnormal phenotypes. Besides, it should be kept in mind that we actually are exposed to a mixture of pollutants; as a result, adaptive and synergetic effects take place, including BPA with other widespread compounds. Finally, it should be underlined that the approaches used in ecotoxicology based only on the analysis of nucleotide DNA sequence are currently insufficient for the complete explanation of the risks of diseases that can be modulated by nongenetic or extragenetic mechanisms.

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❀ Authors and affiliations

Natalia I. Dergacheva – Master of Biology, PhD student, Researcher, Laboratory of Molecular Cytogenetics of Mammalian Development, Department of Molecular Genetics. Institute of Experimental Medicine, St. Petersburg, Russia. SPIN: 3343-2970. E-mail: natalia-9999@mail.ru.

❀ Информация об авторах

Наталья Игоревна Дергачева — магистр биологии, аспирант, научный сотрудник, лаборатория молекулярной цитогенетики развития млекопитающих, отдел молекулярной генетики. ФГБНУ ИЭМ, Санкт-Петербург. SPIN: 3343-2970. E-mail: natalia-9999@mail.ru.

❀ Authors and affiliations

Eugene L. Patkin – DSc, PhD (Biology), Professor, Head of Laboratory of Molecular Cytogenetics of Mammalian Development, Department of Molecular Genetics. Institute of Experimental Medicine, St. Petersburg, Russia. SPIN: 4929-4630. E-mail: elp44@mail.ru.

Irina O. Suchkova – PhD (Biology), Senior Researcher, Laboratory of Molecular Cytogenetics of Mammalian Development, Department of Molecular Genetics. Institute of Experimental Medicine, St. Petersburg, Russia. SPIN: 4155-7314. E-mail: irsuchkova@mail.ru.

Henrikh A. Sofronov – DSc, PhD (Medicine), Professor, Academician of RAS Scientific Director. Institute of Experimental Medicine, St. Petersburg, Russia. SPIN: 7334-4881. E-mail: gasofronov@mail.ru.

❀ Информация об авторах

Евгений Львович Паткин — д-р биол. наук, профессор, заведующий лабораторией молекулярной цитогенетики развития млекопитающих, отдел молекулярной генетики. ФГБНУ ИЭМ, Санкт-Петербург. SPIN: 4929-4630. E-mail: elp44@mail.ru.

Ирина Олеговна Сучкова — канд. биол. наук, старший научный сотрудник, лаборатория молекулярной цитогенетики развития млекопитающих, отдел молекулярной генетики. ФГБНУ ИЭМ, Санкт-Петербург. SPIN: 4155-7314. E-mail: irsuchkova@mail.ru.

Генрих Александрович Софронов — д-р мед. наук, профессор, академик РАН, научный руководитель. ФГБНУ ИЭМ, Санкт-Петербург. SPIN: 7334-4881. E-mail: gasofronov@mail.ru.