MINI REVIEW

Exposure to bisphenol: A and its analogues in neurodevelopmental disorders among girls

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BPA is estimated to be produced in excess of 6 billion pounds per year.These chemicals in the environment that disrupt the endocrine system have been linked to negative health effects. Bisphenol-A (also known as 2,2-bis-(4-hydroxyphenyl)propane) is a hormone disruptor. Ingestion of BPA-containing food and drink is the most common way for humans to be exposed to the chemical. Prenatal BPA exposure was linked to anxiety and hyperactivity in a study of mothers and their children. BPA at low doses, can affect estrogen, androgen, and thyroid signaling by binding into respective receptors.

Key Words: *Bisphenol A; ADHD; Infertility; Neurodevelopmental disorder; Nutrition; Oxidative stress*

INTRODUCTION

BPA exposure during pregnancy has an effect on fetal neocortical development by hastening neuronal differentiation and migration during the early embryonic stage. The mechanism by which BPA affects the nervous system is a complex matter that has yet to be fully understood. Given the restrictions on its use, finding suitable and safer alternatives is critical. Bisphenol F (BPF) and halogenated bisphenol A (BPA), for example, are suspected of impairing biological processes. The biological toxicological effects of BPA analogues on the nervous system are poorly understood. Some BPA substitutes are more resistant to environmental deterioration than BPA. There should be regulation to limit the use of BPA and its analogue by using BPA-free products available on the market.

BISPHENOL-A

Bisphenol-A is estimated to be produced in excess of 6 billion pounds per year, with approximately 100 tons released into the atmosphere. Environmental chemicals that interfere with the endocrine system have been linked to negative health effects in humans, domestic animals, and wildlife species, according to mounting evidence [1]. An exogenous agent that interferes with the synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process, according to the US Environmental Protection Agency (EPA) [1]. Bisphenol-A A (2,2-bis-(4-hydroxyphenyl)propane) is one of the most common endocrine disrupting chemicals. BPA can be found in digital media (such as CDs and DVDs), computer appliances, vehicles, construction glazing, sports protection equipment, medical devices (such as dental sealants), tableware, reusable bottles (such as baby bottles), and food storage containers [2]. BPA intake from canned foods accounts for 10%–40% of daily BPA intake.

EFFECTIVEMEASUREMENT OF BISPHENOL-A

Ingestion of BPA-containing foods and beverages is the main source of human exposure [3].BPA concentrations of up to 1.49 ng/ml (6.5 nM) were found in human serum samples in a study published over ten years ago [4]. Adult serum, amniotic and placental fluids, and infant urine have all been found to contain BPA. Recent studies have shown the presence of BPA in human amniotic fluidto be as high as 8.3 ng/ml (36 nM). BPA-glucuronide is a stable biomarker of BPA exposure and is a major BPA metabolite in urine. After 42 hours, BPA doses are fully recovered in urine as BPA-glucuronide. As a result, the most appropriate and preferred method is to measure BPA glucuronide in urine [5].

ASSOCIATION OF BISPHENOL-A WITH NEURODEVELOPMENTAL DISORDERS

The term neurodevelopmental refers to disorders that include some type of disturbance in brain development.This term encompasses a broad variety of neurological and psychological disorders, such as schizophrenia, autism, ADHD, and epilepsy [6].In the past few years, it is seen that there is an increasing number of human studies which have evaluated the relationship between exposure to BPA and neurodevelopment [7].From thisvarious studies, it was found that BPA had an effect on various neurodevelopmental disorders like ADHD,depression, anxiety, and spatial learning and memory functions on young children [8].Braun and colleagues conducted an ongoing prospective birth cohort in Cincinnati, Ohio (USA) of mothers and their children who were participants in the Health Outcomes and Measures of the Environment Study. Three spot urine samples were taken from women between 16 and 26 weeks of pregnancy, as well as at birth, for this study. Urine samples were collected at sixteen weeks during prenatal care visits, and at 26 weeks when women received their glucose tolerance test for gestational diabetes screening. High-performance liquid chromatography (HPLC)-isotope dilution tandem mass spectrometry was used to determine BPA concentrations. The above study findings, have linked prenatal BPA concentrations and externalizing behaviors in 2-year-old girls was discovered in maternal urine BPA concentrations measured at 16 weeks of pregnancy. Childhood externalizing behavior(aggression, delinquency, and hyperactivity), a behavioral problem that is a major risk factor for later juvenile delinquency, adult crime, and violence.Childhood externalizing behavior and juvenile delinquency are being increasingly viewed as a public health problem [9].Furthermore, it was suggested that BPA exposure during pregnancy was linked to anxiety and hyperactivity. It was also notable that this association was more prevalent among girls than among boys. [10] Prenatal BPA exposure was found to impair endocrine or other neurotransmitter pathways, as well as disrupt brain sexual differentiation, resulting in gender-dependent behavior changes in some animal studies [11]. However, the exposures and behavioral end points used in some animal studies may not be applicable or equivalent to humans [11]. When compared, all of these studies show inconsistency due to variations in

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urinary BPA concentration. Another major source of inconsistency could be the duration of exposure and the gender or sex of the individual.

Mechanism of action of BPA

The exact mechanism of BPA affecting the nervous system is a complex matter and still not made clear. Concerns have also been raised about potential sex specific effects on neurobehavior and development due to agonist effects on estrogen receptors by BPA. In a laboratory study done, it was seen that prenatal exposure to BPA interfered with estrogen signaling pathways [7].Studies have also shown the modification in the dopaminergic process due to exposure of BPA. Other studies have shown BPA interaction with estrogen receptors is believed to beto cause ADHD disorder and anti-social behavior. Some studies have shown that affecting thyroid hormone, which is essential in fetal brain development to be responsible. Recent study using cell culture showed that BPA decreased potassium chloride cotransporter 2 (Kcc-2) mRNA expression in developing cortical neurons [12]. It is also reported that BPA delays the perinatal chloride shift, which might be relevant to BPA mechanism of action affecting neurodevelopment. Prenatal exposure of BPA affects fetal neocortical development by accelerating neuronal differentiation and migration during the early embryonic stage [13]. The biochemical assays have shown that BPA binds to the estrogen receptor and can affect estrogen, androgen and thyroid signaling at low dose levels. It also can bind a variety of other receptors, including aryl hydrocarbon receptors and peroxisome proliferator activated receptor, many of which are associated with hormones of the endocrine systems [14].

Usage of BPA analogues as a substitut

Given BPA's toxicity and usage restrictions, efforts to find suitable and safer alternatives are critical. In everyday supplies, BPS, BPF, and BPB are gradually replacing BPA [15]. Surprisingly, these BPA substitutes have been shown to be harmful to human health as well. Bisphenol F (BPF) and halogenated BPA, for example, are used in everyday items and are suspected of harming biological processes [16]. The estrogenic activity of BPA and related compounds was investigated using an estrogen response factor reporter gene assay in MCF-7 human breast cancer cells. Several chemicals were discovered to have higher estrogenic activity than BPA, including tetrachlorobisphenol A (TCBPA), bisphenol AF (BPAF), bisphenol B (BPB), 2-(4-hydroxyphenyl)-2-phenylpropane (HPP), 1,1-bis(4-hydroxyphenyl) cyclohexane) (BPCH), 4-hydroxydiphenyl-methane (HDM), and 3,3-dimethyl- As a result, estrogenic BPs can cause neurodevelopmental disorders by disrupting ER-dependent pathways [17]. In “BPA-free” thermal printing paper, BPS is frequently used as a BPA substitute. BPS has a minor estrogenic effect, according to an estrogenic activity test [18]. At low doses that are likely to be present in food, BPS tended to interfere with the cell-membrane ER and influence non-genomic signaling, potentially affecting cell function [19].

BPA and nutraceuticals

Several nutraceuticals have been studied for their potential role in preventing the endocrine disrupting effects of BPA. Several *in vivo* studies have confirmed that the anti-oxidant properties of nutraceuticals, as well as their therapeutic actions, may reverse the negative health effects of BPA, [20] Several *in vivo* studies have shown that Bifidobacteria can combat BPA. This probiotic, in fact, has the ability to reduce BPA entry into the bloodstream and facilitate its excretion (Oishi et al.). Because gametogenesis is extremely sensitive to environmental insults, BPA exposure can have an impact on fertility [21]. Resveratrol (RES), a phytoestrogen found in grapes, mulberries, red wine, and other fruits, can counteract its effects [22]. ATRA (All trans retinoic acid), a natural vitamin A metabolite capable of inhibiting BPA's estrogenic activity. Melatonin activity against BPA-induced oxidative toxicity in male and female reproductive tissues was discovered in *in vivo* and *in vitro* studies, preserving gamete quality and fertility [23].

DISCUSSION

Future understanding of BPA and nutrition

The epigenome is vulnerable to environmental exposures, especially during embryogenesis, according to new research. Estrogen-like properties and functions, such as BPA, have the potential to influence and modify epigenome determination [24]CpG islands demethylation and ectopic expression of the agouti gene were observed in the offspring of pregnant females who were dietary exposed to BPA. As a result, offspring's coats changed from brown to yellow (pseudoagouti), and obesity and cancer susceptibility increased. Genistein co-administration during pregnancy can counteract this effect. As a result, nutraceuticals may help to preserve epigenetic signatures [25].

A better understanding of the relationship between nutritional intake, central nervous system function, and immune function, all of which influence an individual's psychological health status. These findings may lead to a greater acceptance of the therapeutic value of dietary intervention in the treatment of psychological disorders among health practitioners and health care providers [25].

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CONCLUSION

However, there are still a lot of unknowns, and there are still a lot of heated debates going on. Despite the high levels of BPA exposure in developing countries, epidemiological research on the link between BPA and neurodevelopmental disorders is limited. As a result, studies on childhood BPA exposure and those aimed at reducing the risk of neurodevelopmental disorders are in high demand. Why BPA has such broad effects on neurobiological processes at such low concentrations is still unknown. As a result, we must reduce or limit the use of BPA by using BPA-free products available on the market, reducing canned foods, and, more importantly, replacing plastic containers with stainless steel, porcelain, and glassware.

LIMITATIONS

The biological toxicological effects of BPA analogues on the nervous system are currently unknown. Furthermore, little is known about the biological mechanisms of BPA analogues or the bioactivity of their metabolites, and there have been no in vivo studies. Some BPA substitutes are more resistant to environmental deterioration than BPA. This should alert us to the fact that not only BPA, but also its analogues, should be used with caution or in moderation

REFERENCES

1. Kavlock RJ, Daston GP, DeRosa C, et al. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: A report of the US EPA-sponsored workshop. Environ Health Perspect. 1996;104:715-740.
2. Huang YQ, Wong CKC, Zheng JS, et al. Bisphenol A (BPA) in China: a review of sources, environmental levels, and potential human health impacts. Environ Int. 2012;42:91-99.
3. Tewar S, Auinger P, Braun JM, et al. Association of Bisphenol A exposure and Attention-Deficit/Hyperactivity Disorder in a national sample of U.S. children. Environ Res. 2016;150:112-118.
4. Takeuchi T, Tsutsumi O. Serum bisphenol a concentrations showed gender differences, possibly linked to androgen levels. Biochem. Biophys Res Commun. 2002;291:76-78.
5. Markham DA, Waechter JM, Wimber M, et al. Development of a Method for the Determination of Bisphenol A at Trace Concentrations in Human Blood and Urine and Elucidation of Factors Influencing Method Accuracy and Sensitivity. J Anal Toxicol. 2010;34:293-303.
6. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. Lancet Psychiatry. 2016;4:339-346.

7. Jiang Y, Li J, Xu S, et al. Prenatal exposure to bisphenol A and its alternatives and child neurodevelopment at 2 years. J Hazard Mater. 2019;388:121774.
8. Pan R, Wang C, Shi R, et al. Prenatal Bisphenol A exposure and early childhood neurodevelopment in Shandong, China. Int J Hyg Envir Heal. 2019;222:896-902.
9. Liu J. Childhood Externalizing Behavior: Theory and Implications. J Child AdolescPsychiatrNurs. 2004;17:93-103.
10. Braun JM, Yolton K, Dietrich KN, et al. Prenatal Bisphenol A Exposure and Early Childhood Behavior. Environ Health Perspect. 2009;117:1945-1952.
11. Braun JM, Kalkbrenner AE, Calafat AM, et al. Impact of Early-Life Bisphenol A Exposure on Behavior and Executive Function in Children. AAP. 2011;128:873-882.
12. Yeo M, Berglund K, Hanna M, et al. Bisphenol A delays the perinatal chloride shift in cortical neurons by epigenetic effects on the Kcc2 promoter. PNAS USA. 2013;110:4315-4320.
13. Wolstenholme JT, Rissman EF, Connelly JJ. The role of Bisphenol A in shaping the brain, epigenome and behavior. Horm Behav. 2011;59:296-305.
14. Michalowicz J. Bisphenol A – Sources, toxicity and biotransformation. Environ Toxicol Pharmacol. 2014;37:738-758.
15. Zhang X, Li C, Pan J, et al. Searching for a bisphenol A substitute: Effects of bisphenols on catalase molecules and human red blood cells. Sci Total Environ. 2019;669:112-119.
16. Inadera H. Neurological Effects of Bisphenol A and its Analogues. Int J Med Sci. 2015;12:926-936.
17. Kitamura S, Suzuki T, Sanoh S, et al. Comparative Study of the Endocrine-Disrupting Activity of Bisphenol A and 19 Related Compounds. Toxicol Sci. 2005;84:249-259.
18. Molina-Molina J-M, Amaya E, Grimaldi M, et al. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol Appl Pharmacol. 2013;272:127-136.
19. Vinas R, Watson CS. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. Environ Health Perspect. 2013;121:352-358.
20. Stefani A, Pierantozzi M, Olivola E, et al. Homovanillic acid in CSF of mild stage Parkinson's disease patients correlates with motor impairment. Neurochem Int. 2017;105:58-63.
21. Caserta D, Segni N, Mallozzi M, et al. Bisphenol a and the female reproductive tract: an overview of recent laboratory evidence and epidemiological studies. ReprodBiolEndocrinol. 2014;12:37.
22. Turedi S, Yulug E, Alver A, et al. Effects of resveratrol on doxorubicin induced testicular damage in rats. ExpToxicolPathol Off J GesToxikolPathol. 2014;67:229-235.
23. Zhang T, Zhou Y, Li L, et al. Melatonin protects prepuberal testis from deleterious effects of bisphenol A or diethylhexyl phthalate by preserving H3K9 methylation.J Pineal Res. 2018;65:2.
24. Chianese R, Troisi J, Richards S, et al. Bisphenol A in Reproduction: Epigenetic Effects. Curr Med Chem. 2018;25:748-770.
25. Rosenfeld CS, Sieli PT, Warzak DA, et al. Maternal exposure to bisphenol A and genistein has minimal effect on Avy/a offspring coat color but favors birth of agouti over nonagouti mice. Proc Natl AcadSci U S A. 2013;110:537-542.