New evidence for a role of Bisphenol A in cell integrity. Implications in the human population

RAFAEL MORENO-GÓMEZ-TOLEDANO1,*; MARÍA I. ARENAS2; ESPERANZA VÉLEZ-VÉLEZ3; RICARDO J. BOSCH1

1 Universidad de Alcalá, Laboratory of Renal Physiology and Experimental Nephrology, Department of Biological Systems/Physiology, 28871, Alcalá de Henares, Spain
2 Universidad de Alcalá, Cell Biology Unit, Department of Biomedicine and Biotechnology, 28871, Alcalá de Henares, Spain
3 Jiménez Díaz Foundation, Fundación Jiménez Díaz School of Nursing, Madrid, 28040, Spain

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Abstract: Bisphenol A (BPA) is a xenoestrogen known for its implications for the endocrine systems and several other organs, including the kidneys. Recent renal studies have shown that BPA can induce alterations of the cytoskeleton and cell adhesion mechanisms such as a podocytopathy with proteinuria and hypertension, alterations involved in the progression of renal diseases. These data and the fact that BPA is known to be present in the urine of almost the entire population strongly suggest the critical need to reevaluate BPA exposures considered safe.

Introduction

Bisphenol A (BPA) is a xenobiotic molecule classified within the category of endocrine disruptors, and thanks to its properties as an estrogen modulator, it is also called xenoestrogen (Taylor et al., 2011). BPA is found in countless everyday utensils, such as food containers, bottles, cans, toys, and is even found in clothing (Vandenberg et al., 2007; Dursun et al., 2016; EFSA, 2016; Li and Kannan, 2018; Freire et al., 2019). Its use is not restricted to the domestic sphere, as its ability to improve the qualities of plastics has made it an essential element in other industries, as it is used in the manufacture of cars, LED lights, and even medical-surgical material (Duty et al., 2013; Olabisi and Adewale, 2016; Testai et al., 2016).

Presentation of the Viewpoint

BPA is a molecule whose properties as an estrogen modulator were discovered in the 1930s by Dodds and Lawson (Dodds and Lawson, 1936). For this reason, numerous works study its possible relationship with reproductive or genitourinary disorders (Rochester, 2013; Ziv-Gal and Flaws, 2016; Pergialiotis et al., 2018; Tomza-Marciniak et al., 2018). However, in the last two decades, it has been shown that BPA can exert other types of actions on other organs or systems, favoring the accumulation of fatty tissue, the appearance of diabetes, cancer, and even cognitive and behavioral disorders (Provvisiero et al., 2016; Akash et al., 2020; Wu et al., 2020; Nesan et al., 2021). In recent years, our team has made interesting advances on the possible implications of BPA on the renal and vascular system.

Using experimental animals models we observed that BPA is capable to promote hypertension and renal damage (podocytopathy) as well as to participate in the mechanism of progression of chronic kidney disease (CKD) (Olea-Herrero et al., 2014; Saura et al., 2014; Moreno-Gómez-Toledano et al., 2020; Reventun et al., 2020), reviewed by Bosch et al. (2016).

Our first work with podocytes (cells that are part of the glomerular filtration barrier) were carried out with immortalized mouse cultures. Podocytes cell lines (mice and human) have a particular condition: at 33°C, they remain undifferentiated, allowing their replication, and at 37°C, they become quiescent, lose their mitotic capacity, and begin to differentiate for 11–15 days. After that time, the podocyte in culture is considered a differentiated, mature, and fully functional podocyte.

The administration of BPA to this cell line demonstrated that low exposure to this molecule (10 and 100 nM) could induce death mechanisms in cultured mouse podocytes (Olea-Herrero et al., 2014) (Fig. 1). Similarly, the intraperitoneal administration of BPA in mice demonstrated that BPA could induce cellular sampling mechanisms in the podocytes of the glomerulus of the animal (Olea-Herrero et al., 2014). These animals developed podocytopenia with...
proteinuria, similar to those seen in diabetic nephropathy. Although there are limitations when using mouse models for assessing renal failure or long-term histomorphological changes (Breyer et al., 2005), our findings may have pathophysiological implications since the amount of proteinuria and podocytes number are reliable predictors of the progression of renal disease (Meyer et al., 1999; D’Amico and Bazzi, 2003).

Subsequently, we observed that in human podocytes in culture (generously provided by Dr. M Saleem, University of Bristol), 100 nM BPA promotes a novel type of podocytopathy characterized by an impairment of cell adhesion. Transcriptomic and proteomic studies demonstrated that BPA promotes alterations in the expression of structural and adhesion proteins (and messengers). Subsequent western blot and immunofluorescence assays demonstrated alterations in the relative expression of structural proteins such as actin, tubulin, vimentin, and podocin, as well as alterations in proteins related to adhesion mechanisms, such as coflin-1, vinculin, E-cadherin, nephrin, VCAM-1, tenascin-C, and β-catenin (Moreno-Gómez-Toledano et al., 2020) (Fig. 1). In this way, it was possible to observe solid evidence that the cellular microenvironment and the elements that make it up, including xenobiotic compounds, can substantially affect the cellular structure.

Adamakis et al. (2018) observed that BPA in the aquatic environment, at environmentally relevant BPA concentration, was capable of promoting alterations in the cytoskeleton of the seagrass Cymodocea nodosa, even stating that the integrity of the actin filament is the most sensitive biomarker to exposure to BPA. Stavropoulou et al. (2018) also observed BPA-mediated alterations in the actin filaments of the Zea mays (corn) plant. In cell cultures, Yin et al. (2020) described BPA-mediated cytoskeletal alterations in a mouse neuroblastoma cell line (neuro-2a cells). When using BPA doses in the micromolar range, they observed a reduction in the number of dendrites and a lower signal intensity when performing phalloidin (F-actin) immunofluorescence. Similarly, Rameshrad et al. (2018) observed that BPA is capable of inducing alterations in the expression of VCAM (adhesion protein) in human umbilical vein endothelial cells, also in the micromolar range.

Analysis of the Impact of the Viewpoint

It is evident that BPA can affect cell structure, not only in human cell cultures but also in murine cell cultures and even aquatic and terrestrial plants. This effect in the podocyte is especially interesting since its inability to regenerate makes it a cell of particular relevance in CKD (Glassock and Rule, 2016). Technically, BPA-induced podocyte loss could be as damaging to kidney function as cell death. The loss of podocytes induces an increase in the compensatory mesangial matrix, progressively reducing the renal filtration capacity. However, new studies have observed that although the podocyte does not have replicative capacity per se, the surrounding glomerular parietal epithelial cells could play a decisive role in podocyte regeneration, differentiating towards this cell type (Shankland et al., 2017). In any case, when the regenerative capacity cannot compensate for the loss, the kidney will progress to CKD. Since BPA is a possible environmental factor involved in this type of pathology, the degree of exposure to which the susceptible population is exposed,
such as patients in intensive care or patients undergoing dialysis techniques, is of particular importance.

As we previously described, mean urinary BPA values have been observed in patients undergoing conventional dialysis between 52.73-155.84 ng/ml (1.11-3.28 µg/kg BW/day, 230.98-682.64 nM) (Moreno-Gómez-Toledano et al., 2021). These values are lower than those considered safe by the European Food Safety Authority, 4 µg/kg BW/day (TDI, Tolerable Daily Intake) (EFSA, 2016). However, this dose has been calculated using animal models as reference (Tyl et al., 2008), to which several correction factors were applied. As shown in Fig. 1, our cellular models show considerable evidence of the effects produced by BPA at the same doses, which should be a critical element to take into account when extrapolating animal studies to humans. Furthermore, the doses observed in CKD patients in dialysis treatment are lower than the proposed TDI but between 2 and 6 times higher than the concentrations used in the cell models.

However, it must be mentioned that BPA is among other chemicals that can be found circulating in the body. In recent years, various compounds have been identified, such as phthalates (Wang et al., 2019), as well as other phenolic derivatives, such as bisphenol S, F, or AF (BPS, BPF, or BPAF, respectively) (Chen et al., 2016). It has been observed that the combination of these elements could enhance the damage that they can already exert individually. Thus, it has been observed that the combination of BPA and dibutyl phthalate (DBP) increases cytotoxicity, oxidative stress, and genotoxicity in liver cell cultures (Li et al., 2017). In animal models, it has been determined that co-exposure of BPA with Di-(2-Ethylhexyl) -phthalate (DEHP) appears to increase susceptibility to tumor development (Zhang et al., 2021).

Furthermore, computer models that have recently been published showed synergy or antagonism as a function of the combination of phenolic derivatives (Jatkowska et al., 2021). According to Kataria et al. (2015), oxidative stress might represent a common pathway that mediates renal injury associated with exposure to environmental chemicals such as BPA, phthalates, polycyclic aromatic hydrocarbon, polychlorinated biphenyl, perfluoroalkyl acid as well as dioxins. This mechanism has biological plausibility and justifies further investigation when examining the adverse effects of these chemicals. Interestingly, these authors also suggest that other functional disturbances contribute to the adverse cardiorenal effects elicited by the described compounds, including effects on modifiable patient-associated factors, such as obesity.

Conclusion

The latest advances in BPA study have determined that it is a molecule with the potential to induce alterations in the cytoskeleton and the capacity for cell adhesion. The concentrations to which the susceptible population is exposed could worsen their pathologies, particularly in patients with CKD. The widespread usage of BPA, especially in the composition of the surgical medical material, should be evaluated and act accordingly, as it could be a crucial factor in the evolution of specific pathologies. Future translational studies need to evaluate the impact of BPA in the human population and reevaluate BPA exposures considered safe.

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