BIOCELL
2022 46(2): 305-308

Tech Science Press

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

Rafael MORENO-GÓMEZ-TOLEDANO[1,*]; María I. ARENAS[2]; Esperanza VÉLEZ-VÉLEZ[3]; Ricardo J. BOSCH[1]

[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

Key words: Bisphenol A, Podocyte, Cytoskeleton, Cell Adhesion, Chronic Renal Diseases, Dialysis

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 podocitopathy with

*Address correspondence to: Rafael Moreno-Gómez-Toledano, rafael.moreno@uah.es
Received: 15 June 2021; Accepted: 08 July 2021

Doi: 10.32604/biocell.2022.017894

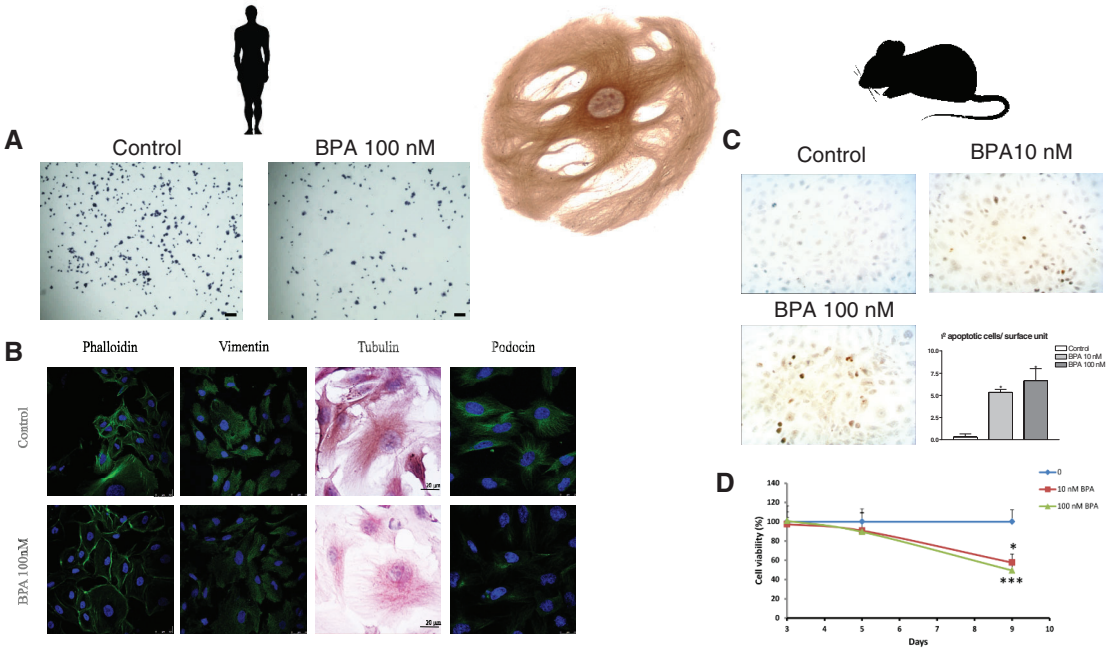

FIGURE 1. Interspecies differences in the effects promoted by BPA in the podocyte. A) Exposure to BPA induces a reduction in the adhesion capacity of the human podocyte (x40) (scale bar: 60 μm). B) Reduction in the relative expression of structural proteins after treatment with BPA, analyzed by immunofluorescence (scale bar: 50 μm) and immunohistochemistry (scale bar: 20 μm). C) In the mouse podocyte, the administration of BPA induces an increase in the mechanisms of cell death (x300). D) Treatment with BPA significantly reduces cell viability (MTT). Figure made with our own results published in the Journal of Cellular Physiology (Olea-Herrero *et al.*, 2014), and Scientific Reports (Moreno-Gómez-Toledano *et al.*, 2020).

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 cofilin-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.

Copyright of Figures: We want to thank the Journal of Cellular Physiology (Olea-Herrero *et al.*, 2014), and Scientific Reports (Moreno-Gómez-Toledano *et al.*, 2020) for publishing our research results, part of which has been used in Fig. 1.

Author Contribution: The authors confirm contribution to the paper as follows: study conception and design: R. Moreno-Gómez-Toledano; M. I. Arenas; E. Vélez-Vélez; R. J. Bosch; draft manuscript preparation: R. Moreno-Gómez-Toledano; M. I. Arenas; E. Vélez-Vélez; R. J. Bosch. All authors reviewed the results and approved the final version of the manuscript.

Funding Statement: This work was supported in part by grants from Instituto de Salud Carlos III (PI15/02139) -Fondo Europeo de Desarrollo Regional (FEDER)-. R. Moreno-Gómez-Toledano is recipient of a research contract from CAM (B2017-BMD-3686).

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

Adamakis IDS, Malea P, Panteris E (2018). The effects of Bisphenol A on the seagrass Cymodocea nodosa: Leaf elongation impairment and cytoskeleton disturbance. *Ecotoxicology and Environmental Safety* **157**: 431–440.

Akash M, Sabir S, Rehman K (2020). Bisphenol A-induced metabolic disorders: From exposure to mechanism of action. *Environmental Toxicology and Pharmacology* **77**: 103373. DOI 10.1016/j.etap.2020.103373.

Bosch RJ, Quiroga B, Munoz-Moreno C, Olea-Herrero N, Arenas MI et al. (2016). Bisphenol A: An environmental factor implicated in renal vascular damage. *Nefrología (English Edition)* **36**: 5–9.

Breyer MD, Böttinger E, Brosius FC, Coffman TM, Harris RC et al. (2005). Mouse Models of Diabetic Nephropathy. *Journal of the American Society of Nephrology* **16**: 27–45.

Chen D, Kannan K, Tan H, Zheng Z, Feng YLL, Wu Y, Widelka M (2016). Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity–A Review. *Environmental Science & Technology* **50**: 5438–5453.

D'Amico G, Bazzi C (2003). Pathophysiology of proteinuria. *Kidney International* **63**: 809–825.

Dodds EC, Lawson W (1936). Synthetic Estrogenic agents without phenanthrene nucleus. *Nature* **137**: 996.

Dursun E, Fron-Chabouis HH, Attal JP, Raskin A (2016). Bisphenol a release: Survey of the composition of dental composite resins. *Open Dentistry Journal* **10**: 446–453.

Duty SM, Mendonca K, Hauser R, Calafat AM, Ye X et al. (2013). Potential sources of bisphenol A in the neonatal intensive care unit. *Pediatrics* **131**: 483–489.

EFSA (2016). Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA Journal* **13**: 3978.

Freire C, Molina-Molina JM, Iribarne-Durán LM, Jiménez-Díaz I, Vela-Soria F et al. (2019). Concentrations of bisphenol A and parabens in socks for infants and young children in

Spain and their hormone-like activities. *Environment International* **127**: 592–600.

Glassock RJ, Rule AD (2016). Aging and the kidneys: Anatomy, physiology and consequences for defining chronic kidney disease. *Nephron* **134**: 25–29.

Jatkowska N, Kudłak B, Lewandowska P, Liu W, Williams MJ, Schiöth HB (2021). Identification of synergistic and antagonistic actions of environmental pollutants: Bisphenols A, S and F in the presence of DEP, DBP, BADGE and BADGE·2HCl in three component mixtures. *Science of the Total Environment* **767**: 144286.

Kataria A, Trasande L, Trachtman H (2015). The effects of environmental chemicals on renal function. *Nature Reviews Nephrology* **11**: 610–625.

Li AJ, Kannan K (2018). Elevated concentrations of bisphenols, benzophenones, and antimicrobials in pantyhose collected from six countries. *Environmental Science & Technology* **52**: 10812–10819.

Li X, Yin P, Zhao L (2017). Effects of individual and combined toxicity of bisphenol A, dibutyl phthalate and cadmium on oxidative stress and genotoxicity in HepG 2 cells. *Food and Chemical Toxicology* **105**: 73–81.

Meyer TW, Bennett PH, Nelson RG (1999). Podocyte number predicts long-term urinary albumin excretion in Pima Indians with Type II diabetes and microalbuminuria. *Diabetologia* **42**: 1341–1344.

Moreno-Gómez-Toledano R, Arenas MI, González-Martínez C, Olea-Herrero N, Reventún P et al. (2020). Bisphenol A impaired cell adhesion by altering the expression of adhesion and cytoskeleton proteins on human podocytes. *Scientific Reports* **10**: 16638.

Moreno-Gómez-Toledano R, Arenas MI, Sánchez-Esteban S, Cook A, Saura M et al. (2021). Critical analysis of human exposure to bisphenol a and its novel implications on renal, cardiovascular and hypertensive diseases. *Hot Topics in Endocrinology and Metabolism [Working Title]*, pp. 1–20. IntechOpen.

Nesan D, Feighan KM, Antle MC, Kurrasch DM (2021). Gestational low-dose BPA exposure impacts suprachiasmatic nucleus neurogenesis and circadian activity with transgenerational effects. *Science Advances* **7**: eabd1159.

Olabisi O, Adewale K (2016). Handbook of thermoplastics, second edition. *Plastics Engineering* **41**: 1003.

Olea-Herrero N, Arenas MI, Muñóz-Moreno C, Moreno-Gómez-Toledano R, González-Santander M et al. (2014). Bisphenol-A induces podocytopathy with proteinuria in mice. *Journal of Cellular Physiology* **229**: 2057–2066.

Pergialiotis V, Kotrogianni P, Christopoulos-Timogiannakis E, Koutaki D, Daskalakis G et al. (2018). Bisphenol A and adverse pregnancy outcomes: A systematic review of the literature. *Journal of Maternal-Fetal & Neonatal Medicine* **31**: 3320–3327.

Provvisiero DP, Pivonello C, Muscogiuri G, Negri M, de Angelis C, Simeoli C, Pivonello R, Colao A (2016). Influence of bisphenol A on type 2 diabetes mellitus. *International Journal of Environmental Research and Public Health* **13**: 989. DOI 10.3390/ijerph13100989.

Rameshrad M, Imenshahidi M, Razavi BM, Iranshahi M, Hosseinzadeh H (2018). Bisphenol A vascular toxicity: Protective effect of Vitis vinifera (grape) seed extract and resveratrol. *Phytotherapy Research* **32**: 2396–2407.

Reventun P, Sanchez-Esteban S, Cook A, Cuadrado I, Roza C, Moreno-Gomez-Toledano R, Muñoz C, Zaragoza C, Bosch RJ, Saura M (2020). Bisphenol A induces coronary endothelial cell necroptosis by activating RIP3/CamKII dependent pathway. *Scientific Reports* **10**: 4190. DOI 10.1038/s41598-020-61014-1.

Rochester JR (2013). Bisphenol A and human health: A review of the literature. *Reproductive Toxicology* **42**: 132–155.

Saura M, Marquez S, Reventun P, Olea-Herrero N, Arenas MI et al. (2014). Oral administration of bisphenol A induces high blood pressure through angiotensin II/CaMKII-dependent uncoupling of eNOS. *FASEB Journal* **28**: 4719–4728.

Shankland SJ, Freedman BS, Pippin JW (2017). Can podocytes be regenerated in adults? *Current Opinion in Nephrology and Hypertension* **26**: 154–164.

Stavropoulou K, Adamakis IDS, Panteris E, Arseni EM, Eleftheriou EP (2018). Disruption of actin filaments in Zea mays by bisphenol A depends on their crosstalk with microtubules. *Chemosphere* **195**: 653–665.

Taylor JA, Richter CA, Ruhlen RL, vom Saal FS, Saal FS vom (2011). Estrogenic environmental chemicals and drugs: Mechanisms for effects on the developing male urogenital system. *Journal of Steroid Biochemistry and Molecular Biology* **127**: 83–95.

Testai E, Hartemann P, Rodriguez-Farre E, Rastogi SC, Bustos J et al. (2016). The safety of the use of bisphenol A in medical devices. *Regulatory Toxicology and Pharmacology* **79**: 106–107.

Tomza-Marciniak A, Stępkowska P, Kuba J, Pilarczyk B (2018). Effect of bisphenol A on reproductive processes: A review of *in vitro*, *in vivo* and epidemiological studies. *Journal of Applied Toxicology* **38**: 51–80.

Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP et al. (2008). Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice. *Toxicological Sciences: An Official Journal of the Society of Toxicology* **104**: 362–384.

Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV (2007). Human exposure to bisphenol A (BPA). *Reproductive Toxicology* **24**: 139–177.

Wang Y, Zhu H, Kannan K (2019). A review of biomonitoring of phthalate exposures. *Toxics* **7**: 21.

Wu W, Li M, Liu A, Wu C, Li D, Deng Q, Zhang B, Du J, Gao X, Hong Y (2020). Bisphenol A and the risk of obesity a systematic review with meta-analysis of the epidemiological evidence. *Dose-Response* **18**: 1559325820916949. DOI 10.1177/1559325820916949.

Yin Z, Hua L, Chen L, Hu D, Li J, An Z, Tian T, Ning H, Ge Y (2020). Bisphenol-A exposure induced neurotoxicity and associated with synapse and cytoskeleton in Neuro-2a cells. *Toxicology in Vitro* **67**: 104911. DOI 10.1016/j.tiv.2020.104911.

Zhang X, Cheng C, Zhang G, Xiao M, Li L, Wu S, Lu X (2021). Co-exposure to BPA and DEHP enhances susceptibility of mammary tumors via up-regulating Esr1/HDAC6 pathway in female rats. *Ecotoxicology and Environmental Safety* **221**: 112453.

Ziv-Gal A, Flaws JA (2016). Evidence for bisphenol A-induced female infertility: A review (2007–2016). *Fertility and Sterility* **106**: 827–856.