BPA CONTENTIN HEMODIALYSIS MEMBRANES IMPACT ON REDOX STATUS AND INFLAMMATION

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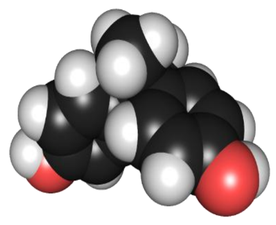
INTRODUCTION AND AIMS

Exposure to bisphenol A (BPA) from plastics and resins is associated with kidney and cardiovascular injury in human and animals studies suggesting a causative link. Health authorities allow BPA use because its rapid renal excretion in healthy humans, but dialysis patients have negligible renal excretion and therefore may accumulate BPA. In a cross-over clinical trial using dialysis membranes containing BPA (polysulfone) or not (polynephron) ,we have recently shown that BPA-containing membranes are associated with higher BPA plasma concentrations and inflammatory biomarkers (JASN 2016). The present work further extends the relationship between BPA and inflammation as well as the potential molecular targets and mechanisms of BPA-associated toxicity in the hemodialysis patient.

METHODS

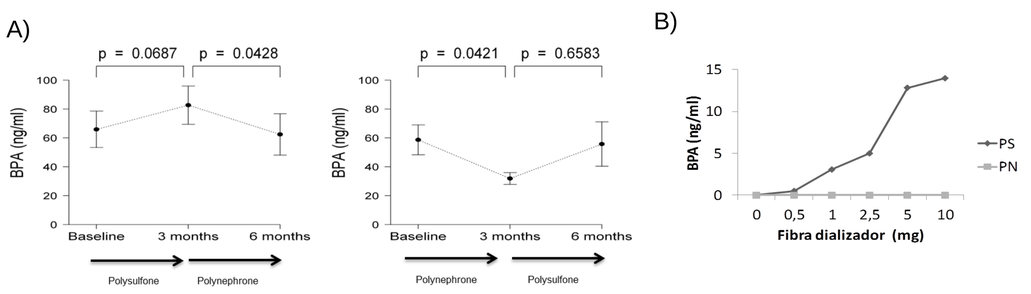
Plasma measurement of inflammation and redox state-related biomarkers by immunoassays. Additionally gene expression by qPCR. were evaluated in peripheral blood mononuclear cells (PBMCs) In vitro analysis : PBMCs obtained from healthy donors stimulated with BPA or dialyzer membranes fibers.Parameters associated with inflammation, oxidative stress and mitochondrial function were examined.Apoptosis and mitochondrial function was also assessed in proximal tubular epithelial call (PTEC) in response to BPA.



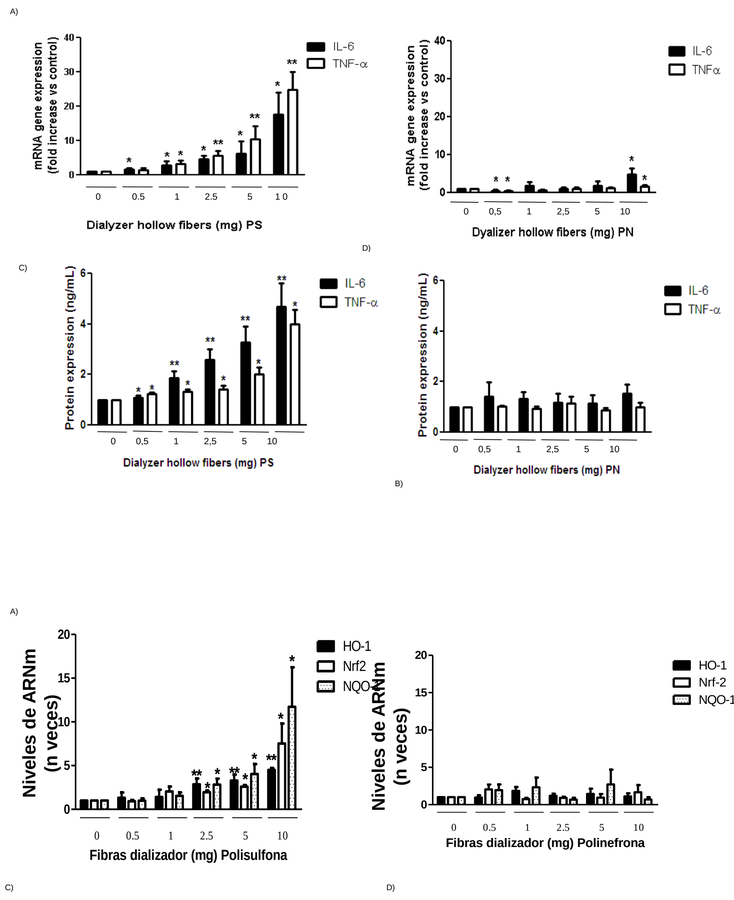
RESULTS

Peripheral Blood mononuclear cell

BPA cuantitation in plasma patients and cultura medium with fibers

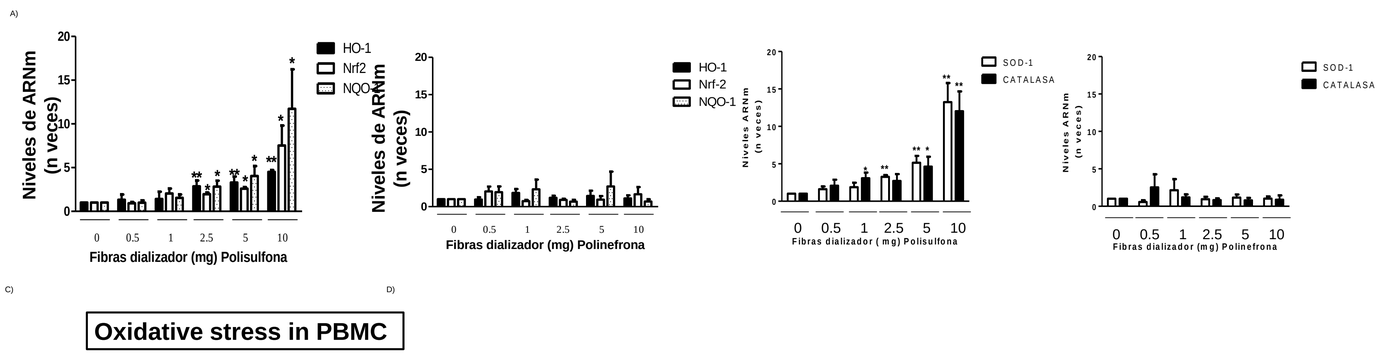


Serum BPA in hemodialysis patients dialyzed with polysulphone or polynephron dialyzers. A) Mean predialysis serum BPA over time for 6 months. B) BPA is released to the supernatants from dialyzer fibers (polysulfone or polynephron) in culture for 24 hours (mean of 2 experiments).



Expression IL-6 and TNF-α in PBMC

mRNA expression for those cytokines is increased up to 22-fold for TNF-α and 16-fold for IL-6 with 10 mg of polysulfone. The aforementioned results can be replicated by addition of BPA to the culture media, a similar induction of 20-fol for TNF-α mRNA is reached at 137 ng/ml of BPA at 24 h. The range of induction is similar to those observed in hemodialysis patients. The cytokine induction with BPA is also dose-dependent and a plateau is reached before apoptotic induction is observed

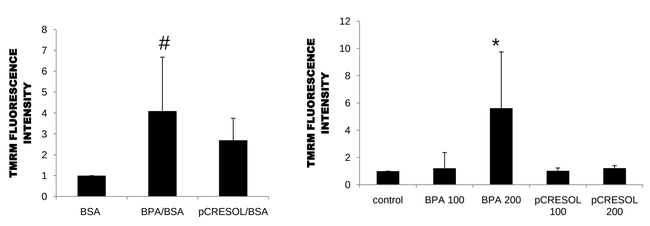


Oxidative stress in PBMC

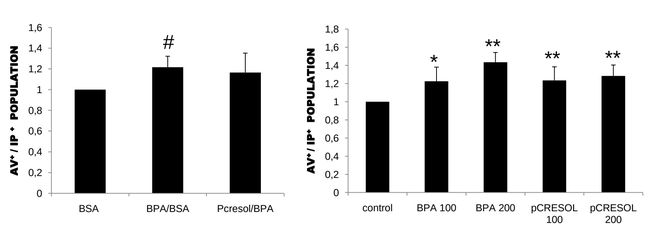
As it is difficult to accurately measure oxidative stress in plasma, we measure the antioxidant response in PBMCs of patient undergoing dialysis. In which, we observe an increase on Nrf2 (key factor on antioxidant response) on patient with higher BPA levels.We perform in vitro experiments on isolated PBMCs from donors stimulated with polysulfone fiber or BPA. In this case, we have studied the expression of various genes involved in oxidative stress response, as Nrf2, HO-1, NQO-1, SOD-1 and catalase. Observing a consistent induction of all these factor in response to an increase of fiber amount or BPA concentration.

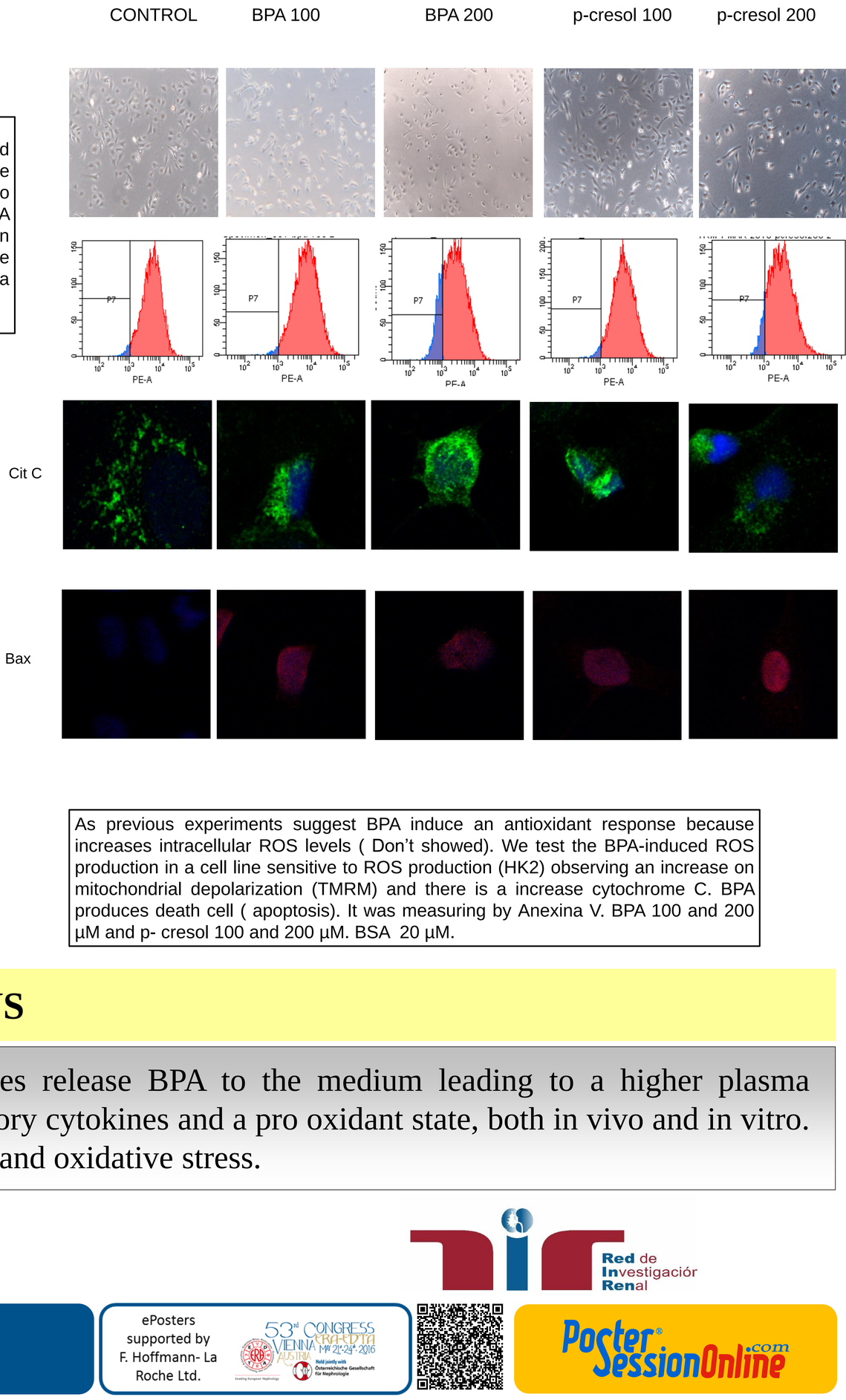
Tubullar cells human HK2

BPA and p-Cresol produces Mitochondrial despolarization



BPA and p-cresol produces apoptosis





As previous experiments suggest BPA induce an antioxidant response because increases intracellular ROS levels (Don't showed). We test the BPA-induced ROS production in a cell line sensitive to ROS production (HK2) observing an increase on mitochondrial depolarization (TMRM) and there is a increase cytochrome C. BPA produces death cell (apoptosis). It was measuring by Anexina V. BPA 100 and 200 µM and p- cresol 100 and 200 µM. BSA 20 µM.

CONCLUSIONS

Our results indicate that in patients on hemodialysis, polysulfone membranes release BPA to the medium leading to a higher plasma concentration. This augmentation was associated to the release of proinflammatory cytokines and a pro oxidant state, both in vivo and in vitro. The mechanisms involved seem to be related with mitochondrial depolarization and oxidative stress.

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Chronic Kidney Disease. Lab methods, GFR measurement, urine proteomics.

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