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Running Title: Chemoresistance by Bisphenol A

Key Words: bisphenol A, breast cancer cells, chemotherapeutic agents, cytotoxicity, estrogen receptors

Abbreviations:
BPA- bisphenol A
CSS - charcoal-stripped serum
DES- diethylstilbestrol
E2- estradiol
ERα/β- estrogen receptor α or β
ERR- estrogen-related receptor
GPR30 - G protein-coupled receptor 30
MTT- 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a]pyrimidin-3-yl]phenol
PHTPP - 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a] pyrimidin-3-yl]phenol

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    BPA, at low nM concentrations, protects cells from doxorubicin-induced cytotoxicity
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Abstract

Background. Resistance to chemotherapy is a major problem facing breast cancer patients, and identifying potential contributors to chemoresistance is a critical area of research. Bisphenol A (BPA) has long been suspected to promote carcinogenesis, but the high doses of BPA used in many studies generated conflicting results. In addition, the mechanism by which BPA exerts its biological actions is unclear. While estrogen has been shown to antagonize anti-cancer drugs, the role of BPA in chemoresistance has not been examined.

Objective. The objective was to determine whether BPA at low nanomolar concentrations opposes the action of doxorubicin, cisplatin and vinblastine in the ERα positive T47D and the ERα negative MDA-MB-468 breast cancer cells.

Methods. The responsiveness of cells to anti-cancer drugs and BPA was determined by the MTT cytotoxicity assay. Specific ERα and ERβ inhibitors and real-time PCR were used to identify potential receptor(s) that mediate the actions of BPA. Expression of anti-apoptotic proteins was assessed by Western blotting.

Results. BPA antagonizes the cytotoxicity of multiple chemotherapeutic agents in both ERα positive and negative breast cancer cells independent of the classical ERs. Both cell types express alternative ER receptors, including GRP30 and members of the estrogen related receptor (ERR) family. Increased expression of anti-apoptotic proteins is a potential mechanism by which BPA exerts its anti-cytotoxic effects.

Conclusions. BPA at environmentally relevant doses reduces the efficacy of chemotherapeutic agents. These data provide considerable support to the accumulating evidence that BPA is hazardous to human health.