DEHP Decreases Estradiol Synthesis through cAMP in FSH-stimulated Human Granulosa Cells

Kristina Pogrmic-Majkic[1], Biljana Tesic[1], Dragana Samardzija Nenadov[1], Stevan Milatovic[2,3], Nebojsa Andric[1]

[1] University of Novi Sad, Faculty of Sciences, Department of Biology and Ecology, Laboratory for Endocrine Disrupters and Signaling (ENDOS), Serbia
[2] University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[3] Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina, Novi Sad, Serbia

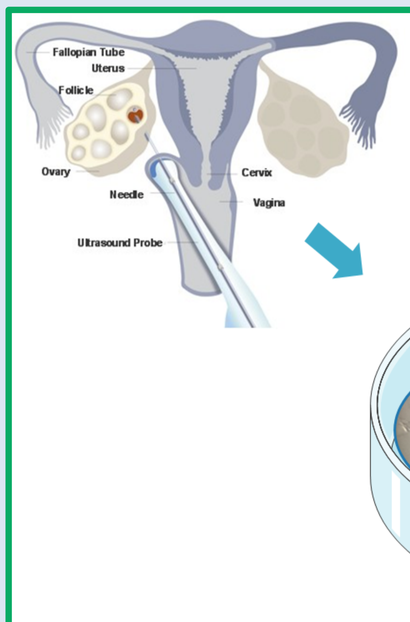
e-mail: nebojsa.andric@dbe.uns.ac.rs

INTRODUCTION & OBJECTIVES

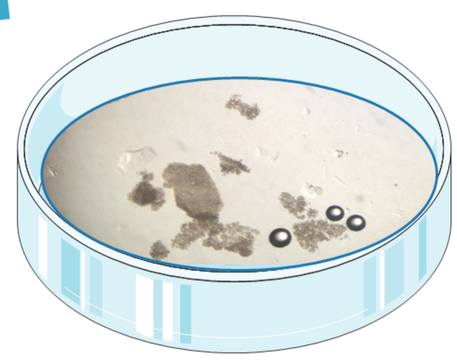
The growing body of evidence suggesting that commonly used chemical substances including endocrine-disrupting chemicals (EDCs) and pharmaceuticals are contributing to the declining fertility observed in humans. The potential causes of EDC-induced infertility are poorly known and the mechanisms have not been fully elucidated.

Di-(2-ethylhexyl) phthalate (DEHP) is a potent endocrine disruptor that belongs to the group of phthalates. In women, occupational exposure to phthalates is associated with an increased risk of miscarriage, decreased pregnancy rates, and endometriosis. DEHP is found in human serum and urine, whereas its metabolites are detected in women's follicular fluid in nM range. It has been shown that DEHP can affect human ovarian function by disrupting the follicle-stimulating hormone (FSH)-stimulated estradiol production in human granulosa cells. However, the potential mechanism by which DEHP affects FSH-induced estradiol production remains unknown. This study aimed to investigate the possible molecular pathway of DEHP action on the FSH-stimulated estradiol production in human granulosa cells.

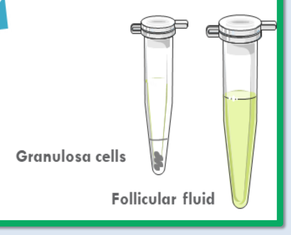
MATERIAL & METHODS



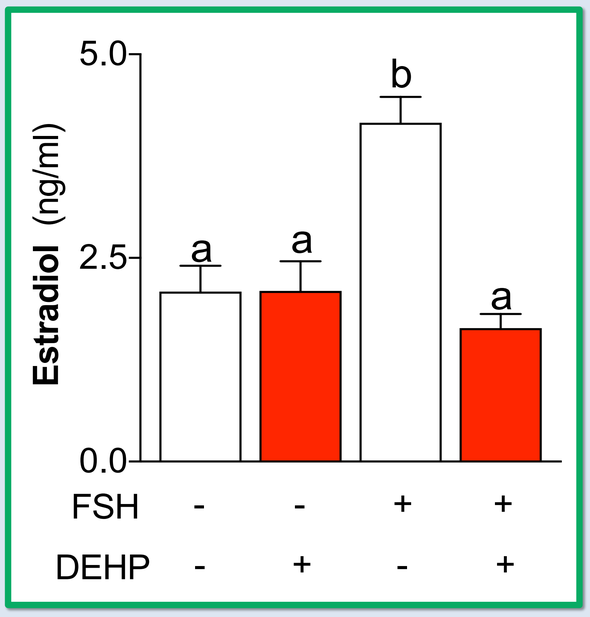
Human cumulus granulosa cells → obtained from patients undergoing *in vitro* fertilization (IVF), treated with 25 uM DEHP and FSH or forskolin or 8-Br-cAMP for 48 h.

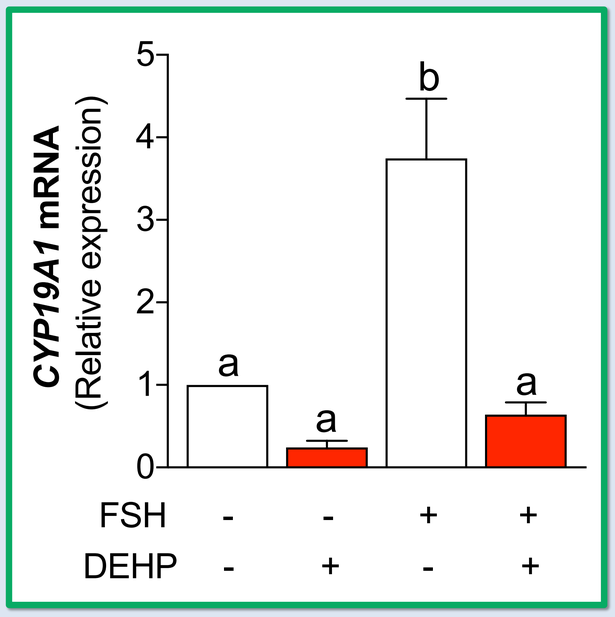


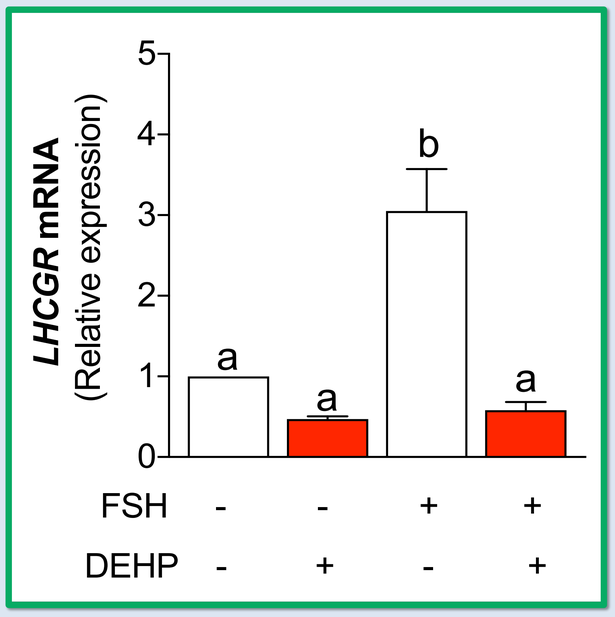
ELISA → levels of estradiol and cAMP
Quantitative RT-PCR → mRNA levels of *CYP19A1 and LHCGR*

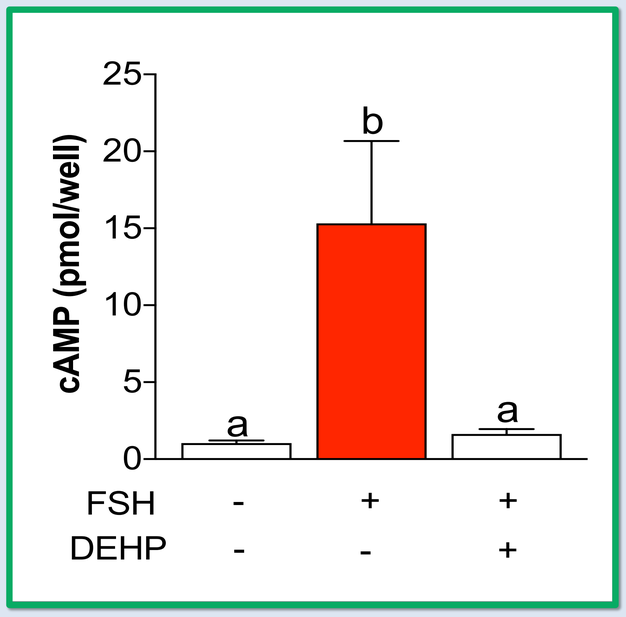


RESULTS



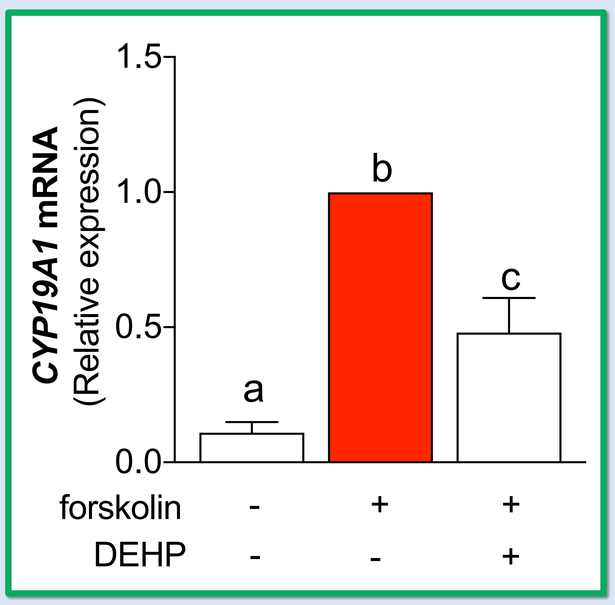


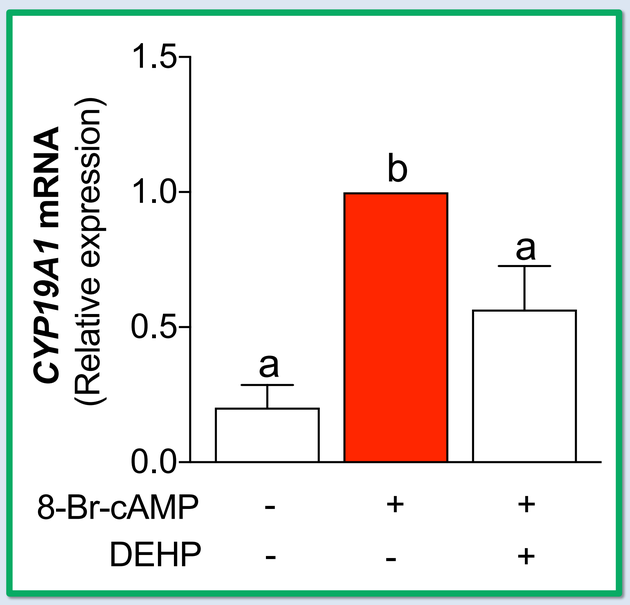




CONCLUSIONS

DEHP decreased the FSH-stimulated estradiol production and reduced the aromatase (*CYP19A1*) and luteinizing hormone receptor (*LHCGR*) gene expression. The mechanistic investigation showed that DEHP decreased cAMP accumulation in the FSH-stimulated human granulosa cells and abolished *CYP19A1* mRNA expression in the forskolin- and 8-Br-cAMP-stimulated human granulosa cells. This study showed that the molecular pathway of DEHP action might involve disruption of the cAMP production, which can further cause changes in the estradiol production, *CYP19A1* and *LHCGR* expression in the FSH-stimulated human granulosa cells.





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