Short Communication

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New molecular mechanism of PAH mixture action in ovarian Granulosa cells

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Abstract

Methods

STUDY QUESTION: Does, dependent on structural characteristics, PAH mixture acts as endocrine disruptors in human granulosa cell.

WHAT IS KNOWN ALREADY: Effects of PAHs in reproductive tissues could reflect their multiple modes of action, like activation of aryl hydrocarbon receptor (AhR)-dependent metabolism, as well as, activation of estradiol receptor (ER) in ER-sensitive cells. Antiestrogenic activity of PAHs was observed in a yeast assay system, while estrogenic activity was found in hormone dependent, breast cancer MCF-7 cells.

STUDY DESIGN, SIZE, DURATION: The analysis of the concentrations of 16 PAHs identified as priority pollutants by both the US Environmental Protection Agency and the European Commission, in maternal and cord blood showed similar content of these compounds in both. It points to cross through placenta and indicate that exposure to PAHs during fetal life may contribute to abnormal ovarian function in adult.

To explore the mechanism of PAHs action we used HGrC1 (human no luteinized granulosa cell line) originally derived from mural granulosa cells, possess the characteristics of granulosa cells in early stage follicles. The cells were exposed for 24 and 48h on 2 mixture: M1 composed of all 16 PAH and M2 composed of five not classified as human carcinogens (naphthalene, phenantrene, anthracene, fluoranthene and pyrene) observed at the highest levels in maternal and cord blood. At the end of the culture, we examined estradiol level in medium by ELISA. FSH, AhR, AR, ER, CYP19 protein expression was measured by Western blot and cell proliferation by AlamarBlue assay. Additionally, estradiol level and cell proliferation were evaluated after AhR, AR and ER gene silencing.

MAIN RESUTS: Both PAH mixtures had no effect on FSH protein expression. However, differences in the action on AhR, ER and AR was pronounced. Mix 1 increased AhR and ER expression and was without effect on AR expression, while M2 increased both AR and ER expression and had no effect on AhR expression. Both mixture had inhibitory effect on basal and FSH-stimulated estradiol secretion however without effect on aromatase activity. In basal condition AhR gene silencing had no effect on estradiol secretion while ER and AR gene silencing caused increase estradiol secretion. In cells exposed for mixture siAhR reversed inhibitory action of both mixture on basal and FSH stimulated estradiol secretion. After ER and AR gene silencing still inhibitory effect on estradiol secretion was noted.

CONCLUSION: Independent on mixture composition both cross talk between AhR/ER and AhR/AR exist. We suggest that, in real life mixture, not only compounds regarded as carcinogenic, but also till now not classified as cancerogenic, are responsible for the antiestrogenic action of the mixture.

Biograph :

MSc Karolina Zajda is a PhD student in Department of Physiology and Toxicology of Reproduction , Jagiellonian University in Krakow. She is specialized in cancerogenic action of endocrine disruptor in ovarian cancer. She has graduated from Jagiellonian University in Krakow, Poland. She has authored 3 peer-reviewed articles in leading journals such as Toxicology, Cancer Genomics and Proteomics and Reproductive Toxicology. Member of The Polish Society for Reproductive Biology. Research topics focusing on the effects of different single and mixture of endocrine compounds in hormone dependent cancer