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THE REGULATION OF CYP1A1 GENE EXPRESSION BY ESTRADIOL AND ITS METABOLITES

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the most potent halogenated aromatic hydrocarbon congener that induces expression of several genes including CYP1A. Exposure to TCDD results in many toxic actions such as carcinogenesis, hepatotoxicity, immune suppression, reproductive toxicity and developmental toxicity. Dramatic differences in dioxin toxicity have been observed between the sexes of some animal species, suggesting hormonal modulation of dioxin action. Many studies have been reported and proposed several mechanisms of anti-estrogenic effects of TCDD. In contrast, the effect of estrogen on the regulation of CYP1A1 are not clear at present. There are several reports showing conflicting results. The purpose of this study is to investigate the regulation of TCDD-induced CYP1A1 gene expression by 17β estradiol (E2) and its metabolites, 2-hydroxyestradiol (2OH E2) and 16α estriol (E3). In the liver cell lines, E2 and E3 significantly inhibited TCDD-induced EROD activity in a dose dependent manner. EROD activity in the presence of 10-5 M E2 and 10-9 M TCDD was reduced by 65% compared to that of in the cells exposed to 10-9 M TCDD alone. And co-treatment of cells with 10-9 M TCDD plus 10-5 M E3 resulted in a 73% decrease compared to 10-9 M TCDD alone. In comparison to E2 and E3, 2OH E2 had no effect on the TCDD-induced EROD activity. Further, we measured CYP1A1 mRNA level in Hepa 1c1c7 cells exposed to estrogen and TCDD to determine whether the reduced monooxygenase activity reflected altered CYP1A1 mRNA expression. In contrast to EROD activity, E2 and E3 slightly decreased TCDD- stimulated CYP1A1 mRNA (It is not significant). Therefore, to investigate if the suppressive effects of E2 and E3 reflected not transcriptional inhibition but their perturbation of CYP1A1 monooxygenase function, we measured EROD activity by the co-treatment of estrogen and ethoxyresorufin to the TCDD treated cells. 10-5 M E2 plus ethoxyresorufin and 10-5 M E3 plus ethoxyresorufin significantly decreased TCDD-induced EROD activity comparing to TCDD alone (by 70% and 24%, respectively). These data suggest that the suppressive effects of E2 on the

TCDD-induced EROD activity are mediated by the interaction of E2 and CYP1A1 enzyme. And the suppressive effects of E3 on the TCDD-induced EROD activity are partially mediated by the interaction of E3 and CYP1A1 enzyme.

In the breast cell lines, E2 and its metabolites did not alter TCDD-induced EROD activity and CYP1A1 mRNA level by the co-treatment of estrogen and TCDD. However, in MCF-7 cells, E2 significantly increased TCDD-induced EROD activity by the pre-treatment of E2 and in ZR-75-1 cells, E2, E3 and 2OH E2 increased TCDD-induced EROD activity by the pre-treatment. And we also performed transient transfection with an AhR responsive reporter plasmid containing 5' flanking region of the human CYP1A1 gene to examine whether E2 and its metabolites had effects on TCDD-induced CYP1A1 gene expression at the transcription level. In consistent to EROD activity results, E2 had no effects on the TCDD-induced luciferase activity by co-treatment but significantly increased TCDD-induced luciferase activity by pre-treatment.

Keyword : CYP1A1, Estradiol, TCDD