response than estradiol) Among the resveratrol derivatives, 10 compounds showed significant estrogenic activity.
In our previous data, 17b-estradiol (E2) significantly inhibited TCDD-induced CYP1A1 gene expression so we examined whether resveratrol and its derivatives inhibit TCDD-induced CYP1A1 gene expression like E2. pCYP1A1-luc reporter gene was transfected into MCF-7 cells. After transfected cells were treated with chemicals, luciferase activity was determined by luciferin. Resveratrol inhibits TCDD-mediated transactivation in a dose-dependent manner.and some derivatives also inhibited TCDD-stimulated promoter activity.

[PA4-3] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

CYP1A1 gene expression is down regulated by hypoxic agents

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Since hypoxia-inducible factor-1alpha (HIF-1alpha) and the arylhydrocarbon receptor (AhR) shared the AhR nuclear translocator (Arnt) for hypoxia- and AhR-mediated signaling, respectively, it was possible to establish the hypothesis that hypoxia could regulate Cyp1a1 expression. In order to understand the mechanism of Cyp1a1 gene expression, we demonstrated here that hypoxic agents such as cobalt chloride, desferrioxamine, and picolinic acid reduced the TCDD induced Cyp1a1 promoter activity based on the determination of luciferase activity in Hepa I cells transfected with pmCyp1a1-Luc. Also cobalt chloride inhibited the TCDD stimulated Cyp1a1 mRNA level as well as EROD activities in both Hepa I and MCF-7 cells. Hypoxic agents such as cobalt chloride, picolinic acid, and desferrioxamine showed inhibition of luciferase activity that was induced by 1nM TCDD treatment with dose dependent manner. Concomitant treatment of 150μM ferrous sulfate with 1~100μM desferrioxamine or 1~100μM picolinic acid recovered from the hypoxic agents-inhibited luciferase activity that was stimulated by TCDD. Reciprocally, the hypoxic agents down regulated TCDD induced Cyp1a1 mRNA level and CYP1A1 enzyme activity in Hepa I cells.

[PA4-4] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Aryl hydrocarbon- and estrogen-mediated signals possibly cross talk to regulate CYP1A1 gene expression.

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is an environmental toxin that activates the aryl hydrocarbon receptor (AhR) and disrupts multiple endocrine signaling pathways by enhancing ligand metabolism, altering hormone synthesis, down regulating receptor levels, and interfering with gene transcription. And TCDD-mediated gene transactivation via the AhR has been shown to be dependent upon estrogen receptor (ER) expression in human breast cancer cells. In the present study, we have examined the effect of natural estrogen, phytoestrognes and environmental estrogens on the regulation of CYP1A1 gene expression in MCF-7 human breast cancer cell line, that ER and AhR are co-expressed. pCYP1A1-luc reporter gene was transiently transfected into MCF-7 cells. These cells were treated with various chemicals and then luciferase assay was carried out. 17beta-estradiol significantly inhibited TCDD stimulated luciferase activity dose dependently and this inhibition was partially recovered by concomitant treatment of tamoxifen. 17beta-estradiol metabolites, 2-hydroxyestradiol and 16alpha-estriol resulted in less potent inhibitory effect than estradiol and synthetic estrogen, diethylstilbestrol (DES) showed no effect on CYP1A1 gene expression. This study demonstrated that estrogen down-regulated TCDD stimulated CYP1A1 expression via ER mediation. And we have found out that several