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

flavonoids such as genistein, kaempferol, daidzein, naringenin, and alkylphenols such as nonylphenol, 4-octylphenol and resveratrol also inhibited TCDD induced CYP1A1 expression like estrogen.
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[PA4-5] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Toxicity test of new solubilizer for paclitaxel in Beagle dog

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Paclitaxel is currently administered i.v. as a slow infusion of a solution of the drug in an ethanol: cremophor EL: saline admixture. However, poor solubilization and toxicity are associated with this drug therapy. We have tried to develop a new surfactant for paclitaxel to improve efficacy and reduce toxicity of solubilizer. We performed the hemolysis test for chemicals which passed the paclitaxel-stabilizing test and 5 chemicals showing relatively low hemolytic effects were tested for a single dosing toxicity test. And then aceporol 330, which showed the most favorable result, was introduced to the repeated dosing toxicity tests in mouse and beagle dog. According to data based on body weight, mortality, dissection, homological test and biochemical test, Aceporol 330 exhibited much more reduced toxicity than cremophor EL.

[PA4-6] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Gender-Related Difference in Organophosphate Pesticide Terbufos Neurotoxicity in Rats: More Vulnerability in Female than Male Rats

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An organophosphate pesticide terbufos (S-t-butyl thiomethyl O,O-diethyl phosphorodithioate, TBF) has extensively used as an insecticide. A sexual dimorphism in the cholinergic innervation between both sexes was reported in certain species. However, a sexual dimorphism on TBF neurotoxicity was not reported and remains unclear. Objective of the work is to investigate whether TBF exerts a sexual dimorphism on TBF neurotoxicity. TBF was orally administered to male and female rats, where female rats were received 0, 0.1, 0.4 and 0.8 mg/kg TBF for 2 consecutive days and male rats 0, 0.1, 0.5 and 1 mg/kg TBF for 3 consecutive days. Body weights and mortality were measured. Brain (frontal cortex, cerebellum and entorhinal cortex) and liver tissues were dissected and blood was collected 24 hr after the last dose for measurement of neuropathy target esterase (NTE) and acetylcholinesterase (AChE) activity. Body weight was significantly changed at only 0.8 mg/kg TBF-treated group in female, but not male rats. Mortality was higher in female than male rats. NTE activity was significantly decreased in frontal cortex of female, but not male rats. In other brain regions, NTE activity was not changed in female or male rats. AChE activity was significantly decreased in frontal cortex, entorhinal cortex and liver of female rats given 0.4 and 0.8 mg/kg TBF. For male rats, AChE activity was significantly different from controls in frontal cortex and entorhinal cortex at only high dose (1 mg/kg TBF) group and in cerebellum of 0.5 and 1 mg/kg TBF-treated group. In conclusion, female rats were more vulnerable than male in alteration of body weight, mortality, NTE and AChE activity, suggesting that TBF neurotoxicity is highly related to gender-specific alteration of AChE and NTE activity.

[PA4-7] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]