Single and 28-day repeated dose toxicity studies of botulinum toxin type A(BTA) were carried out in ICR mice and SD rats, respectively. In the single dose toxicity study, BTA was injected intraperitoneally to male and female mice at a single dose of 40, 59, 89, 133 and 200 ng/kg. All animals died from 59 ng/kg. Some clinical signs were observed in most of both sexes from 59 ng/kg, but no signs were seen in all animals at 40 ng/kg. The results showed that the LD_{50} of BTA might be in the range of 40-59 ng/kg in both sexes. In the repeated dose toxicity study, the test material was administered intradermally for 28 days at doses of 0(control), 1.25, 2.5, 5.0 and 10.0 ng/head/50 $\mu\ell$ saline in male and female rats. BTA treatment significantly decreased the body weight gain rate in male of 5.0 ng/head and over and in female of 10.0 ng/head compared to control. One or more relative organ weights were increased significantly from 5.0 ng/head compared to control in both sexes. Serum biochemistry revealed increases in AST, ALT, CPK, total protein and albumin in male, and increases in AST and ALT and decreases in K^+ and Cl^- in female without dose-dependent manners. In the histopathological study, BTA treatment induced atrophy of skeletal muscle in both sexes from 2.5 ng/head. When the antibodies to toxin were determined in all animals, a significant increase in serum antibodies was observed from 5.0 ng/head. The results showed that the NOAEL of BTA might be 1.25 ng/head for 28-day repeated dose toxicity in rats. (Supported by a sub-grant from Ministry of Commerce, Industry and Energy for Medy-Tox Inc.).

[PA4-30] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Cadmium induces neurotoxicity via activation of JNK and c-JUN in human neuroblastoma cell

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Occupational exposure to cadmium (Cd) can result in brain disorders and olfactory dysfunction is the most well-known symptom. Recently Cd has been shown to induce apoptosis by activating MAPKs in various cell types. However, intracellular signaling pathways of Cd-induced cytotoxicity in neuronal cells is not known well. Thus, in the present study, we studied role of JNK and its well-known downstream transcription factor, c-JUN, in Cd-induced neuronal cell death. Treatment of SH-SY5Y cell, a human neuroblastoma cell line, with Cd caused cytotoxicity in a concentration- and time-dependent manner as measured by the MTT assay; LD50 was approximately 25 uM after 24h incubation with Cd. Cd-induced cytotoxicity involved apoptosis as determined by TUNEL staining. Western blot analysis showed that JNK was phosphorylated by Cd (1- 250 uM); its activation was seen as early as 1h after Cd exposure and thereafter sustained until 12h. In contrast, p38 was phosphorylated only at the high dose (100 uM) of Cd while Erk was not activated at all. In addition, c-JUN was also phosphorylated by Cd. Stable expression of dominant negative mutant construct of MKK4 reduced the Cd-induced cytotoxicity as well as c-JUN phosphorylation, suggesting that phosphorylation of JNK/c-JUN is responsible for cytotoxic effects mediated by Cd. Moreover, treatment of cells with N-acetyl-L-cysteine (1 mM), a free radical scavenger, increased cell viability significantly. Taken together, oxidative stress induced in cells by Cd may cause cytotoxicity, and phosphorylation of JNK and c-JUN is involved in cadmium-induced cytotoxicity in neuronal cells.
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[PA4-31] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

PAH regualtion of CYP1 gene in MCF-7 & ZR-75-1 human breast cancer cells

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Recent industrial society has human widely exposed to PAHs that are comming from the incomplete combustion of organic material as widerspread environmetal contaminants. Biological activities of PAHs are not known although PAHs are considered as carcinogens. The mechanism of action of PAHs has been studied extensively, however it is not clear how PAHs turn on CYP1A1 in human breast cancer. Our labolatory have been studied the effect of PAHs in the human breast cancer cell MCF-7. In this study, we examined the ZR-75-1 human breast cancer cells as a new system to evaluate bioactivity of PAHs and to compare the PAH action with that of MCF-7 cells. ZR-75-1 human breast cancer cell line is response to estrogen and progesteron. We have been able to estabilish long term culture system of this cells then used for the study to the effect of 13 different PAHs and environmental samples. We demonstrate that PAHs induced the CYP1A1 promoter and 7-ethoxyresolufin O-deethylase(EROD) activity in a concentration-dependant manner. RT-PCR analysis indicated that PAHs significantly up-regulate the level of CYP1A1 mRNA. Some of PAHs showed stronger stimulatory effect on CYP1 gene expression than TCDD. Apparently, ZR-75-1 cells have Aryl hydrocarbon receptors, therefore it would be good experimental tool to study the cross-talk between PAHs and steroid actions.

[PA4-32] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Environmental endocrine disruptors and endometriosis

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Endometriosis is classically defined as the growth of endometrial glands and stroma at extra-uterine sites. Although it is a common gynecological problem accompanied by chronic pelvic pain, infertility, and adhesion formation, the etiology of this disease is unknown. Endometriosis pathogenesis may involve endocrine and immune dysregulation since uterine endometrial growth is regulated by sex hormone in concert with bioactive mediators produced by uterine immune and endocrine cells. thus, exposure to environmental toxicants disrupting endocrine and immune responses potentially affect the development and progression of endometriosis.
In this study, we attempted to identify the possible association between dioxin like compounds (such as TCDD, PCDDs, PCDFs, and PCBs) and the occurrence and severity of endometriosis using CALUX (Chemically Activated LUciferase eXpression) bioassay method. We analyzed the serum levels of dioxin like compounds in the endometriosis patients (n=46) and control patients with similar symptoms (n=14). Among them, adipose tissues of 10 cases were analyzed by high resolution GC/MS for validation of CALUX bioassay. The CALUX TEQs significantly correlated with the total TEQs determine by GC/MS (r2 = 0.96). So we demonstrated that CALUX bioassay is a rapid, sensitive and quantitative assay for biomonitoring of dioxin like compounds from small volume of blood. This study showed statistically significant association between exposure to dioxin like compounds and the occurrence of endometriosis ($p < 0.003$). The mean TEQ of control patient was 0.144 ㎍ TEQ/L and the mean TEQ of endometriosis patient was 0.321 ㎍ TEQ/L. After adjusting confounding factor, we found that the higher stage of the endometriosis, the higher level of CALUX TEQ. The TEQs of endometriosis I, II, III, and IV was 0.213 ㎍ TEQ/L, 0.284 ㎍ TEQ/L, 0.352 ㎍ TEQ/L, and 0.450 ㎍ TEQ/L, respectively.

[PA4-33] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

The Inhibitory Effect of Zinc on the Cadmium-Induced Apoptosis in Human Breast