[PA4-41] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Acute effects of 2-bromopropane and 1,2-dibromopropane on hepatotoxic and immunotoxic parameters

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2-Bromopropane (2-BP) is a major component of the mixture of SPG-6AR and Solvent 5200 that is a substitute of chlorofluorocarbon. Many female workers exposed to 2-bromopropane in a Korean electronic company were found to have amenorrhea and male workers were diagnosed with oligospermia. In the present studies, immunotoxic effects of 2-BP and an analog, 1,2-dibromopropane (1,2-DBP), were investigated in female BALB/c mice. The mice were treated po with either 2-BP at 2000 and 4000 mg/kg or 1,2-DBP at 300 and 600 mg/kg once. The mice were immunized ip with sheep red blood cells (SRBCs). The spleen and thymus weights were reduced by 1,2-DBP. The number of splenic cells was decreased by 1,2-DBP. In addition, the antibody response to SRBCs was suppressed by the treatment with either 2-BP or 1,2-DBP. Meanwhile, these parameters were not significantly changed by the treatment with much lower doses of 2-BP. In a subsequent study, the time course effects of 2-BP and 1,2-DBP on the hepatotoxic and immunotoxic parameters were compared in mice. When mice were treated po with either one of these chemicals once for 6, 12, 24 and 48 hr, the activities of serum alanine aminotransferase and aspartate aminotransferase were significantly elevated only by 1,2-DBP 24 hr after the treatment. The hepatic content of glutathione was reduced by 1,2-DBP. The present results suggest that 1,2-DBP cotained in the Solvent 5200 may contribute to the immunotoxicity, although 2-BP is a major component. (Supported by grant from Korea Science and Engineering Foundation (grant No. RO1-2000-00182)).

[PA4-42] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Cytochrome P450 발현 및 기능 조절제의 탐색 및 응용에 관한 연구

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To develop cytochrome P450 (P450) modulators with low toxicity from natural products, we have evaluated more than 20 compounds in mouse and rat models. Among those, the effects of 1,8-cineole and diallyl sulfide (DAS) were most profound in modulating P450 expression. In this presentation, the effects of 1,8-cineole and diallyl sulfide (DAS) on P450 expression were introduced. In addition, these two compounds were applied to investigate the role of metabolic activation in thioacetamide-induced hepatotoxicity and/or immunotoxicity in animal models. When rats were treated orally with 200, 400 and 800 mg/kg of 1,8-cineole for 3 consecutive days, the liver microsomal activities of pentoxyresorufin- and benzyloxyresorufin-O-dealkylases and erythromycin N-demethylase were dose-dependently induced. The Western immunoblotting analyses clearly indicated the induction of P450 2B1/2 and P450 3A1/2 proteins by 1,8-cineole. When rats were pre-treated orally with 800 mg/kg of 1,8-cineole for 3 days, thioacetamide-induced hepatotoxicity and immunotoxicity were significantly potentiated. When rats were treated orally with 100, 200 and 400 mg/kg of DAS in corn oil for three consecutive days, the liver

microsomal activity of p-nitrophenol hydroxylase was dose-dependently suppressed. In addition, the activities of benzyloxyresorufin- and pentoxyresorufin-O-dealkylases were dose-dependently induced by the treatment with DAS. The Western immunoblotting also showed the suppression of P450 2E1 and the induction of P450 2B1/2 and P450 3A1/2 proteins. To investigate a possible role of metabolic activation by P450 enzymes in thioacetamide-induced hepatotoxicity, rats were pre-treated with 400 mg/kg of DAS for 3 days, followed by a single intraperitoneal treatment with 100 and 200 mg/kg of thioacetamide in saline for 24 hr. The activities of serum alanine aminotransferase and aspartate aminotransferase greatly increased by thioacetamide were recovered in DAS-pretreated animals. Taken together, our present results indicated that 1,8-cineole and DAS might be useful P450 modulators in investigating the possible role of metabolic activation in chemical-induced hepatotoxicity and immunotoxicity. (This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ2-PG3-21605-0002).

[PA4-43] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Development and Validation of the Custom Human cDNA Microarray (KISTCHIP-400) for Monitoring Expression of Genes involved in Hormone Disruption

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Transcript profiling is a particularly valuable tool in the field of steroid receptor biology, as these receptors are ligand-activated transcription factors and therefore exert their initial effects through altering gene expression in responsive cells. Also, an increased awareness of endocrine disrupting chemicals (EDCs) and their potential to affect wildlife and humans has produced a demand for practical screening methods to identify endocrine activity. Here we developed an in-house cDNA microarray, named KISTCHIP-400, with 401 clones, hormone related genes, factors, and ESTs, based on public database and research papers. Theses clones contained estrogen, androgen, thyroid hormone & receptors, sex hormone signal transduction & regulation, c-fos, c-myc, ps2 gene, metabolism related genes etc. And to validate the KISTCHIP-400, we investigated gene expression profiles with reference hormones, 10^{-8} M 17beta-estradiol, 10^{-7} M testosterone, 10^{-7} M progesterone, and thyroxin in MCF-7 cell line. Although it is in first step of validation, low doses and combinations of EDCs need to be tested. Our preliminary results that indicate the developed microarray may be a useful laboratory tool for screening EDCs and elucidating endocrine disrupting mechanism.

[PA4-44] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Identification of Differentially Expressed Genes by Methylmercury in Neuroblastoma cell line using suppression subtractive hybridization (SSH) and cDNA Microarray

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Methylmercury (MeHg), one of the heavy metal compounds, can cause severe damage to the central nervous system in humans. Many reports have shown that MeHg is poisonous to human body through contaminated foods and has released into the environment. Despite many studies