thus is an ongoing health concern. Thus far, MeHg has been suggested to exert its toxicity through its high reactivity to thiols of bioactive proteins, elevation in intracellular Ca2+ concentration, and generation of reactive oxygen species, but its mechanism remains poorly understood. The present study was designed to investigate a relationship between various cytotoxic mediators such as PLA2, PC-PLC, SMase and Ca2+ and the cytotoxicity of MeHg in MDCK cells.
Here we show that MeHg induced AA release by activating cPLA2 through multiple mechanisms including calcium, phosphorylation and oxidative stress. AACOCF3, a specific inhibitor of cPLA2 , blocked MeHg-induced AA release and intracellular ROS generation, but not LDH release. N-acetyl cysteine, an antioxidant, could not protect against the cytotoxicity of MeHg despite a significant inhibition of the AA release.
MeHg induced a slight increase in DAG production, and ceramide generation with concomitant hydrolysis of SM. The activity of A-SMase, not N-SMase is markedly activated by MeHg. Monensin and NH4Cl, indirect inhibitors of A-SMase inhibited ceramide generation but not LDH release. Inhibition of PC-PLC, a well-known upstream activatior of A-SMase, inhibited the MeHg-induced DAG generation, A-SMase activation, ceramide generation, and LDH release.
MeHg increased intracellular calcium in a bimodal pattern with a sharp peak at 1 min and sustained increase up to 10 min. Chelation of extracellular calcium partially attenuated a short-term cytotoxicity of MeHg with the abolishment of the sharp peak at 1 min and significant reduction in the sustained Ca2+ increase. Interestingly, D609, PC-PLC inhibitor, completely decrease not only MeHg-induced calcium increase but also LDH release. This suggests that MeHg-induced response is composed of PC-PLC mediated Ca2+ mobilization component and a Ca2+ influx component, with the influx component being dependent on mobilization component and therefore relating with cell death.
Taken together, the present study indicates that MeHg activates cPLA2 through Ca2+-dependent and oxidative pathways. However, the resulting AA and ROS may not be implicated in its cytotoxicity, rather PC-PLC pathway is likely to play an important role in the cytotoxicity by MeHg through [Ca2+]i increase by the Ca2+ mobilization and influx.

[PA4-26] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Metallothionein gene expression in different tissues of Crucian carp (Carassius auratus) exposed to cadmium chloride

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Metallothioneins (MTs) are a goup of heavy metal-binding proteins characterized by cystein-rich low molecular weight(6000 - 10,000 Da). They plays a major role in the detoxification of heavy metals and also in scavenging of superoxide radicals. They are known to be induced by heavy metals in various organs of different species and represent a potential biomarker of aquatic heavy metal contamination. In this study, effect of cadmium accumulation on the metallothionein gene expression in the different tissues of crucian carp was investigated using reverse transcription (RT)-PCR method. Crucian carp were exposed to cadmium chloride with the concentrations of 0.01, 0.1, 0.5㎎/L, respectively. Gills, livers, and kidnies were quickly removed for RNA extraction and PCR was done using primers based on the known gold fish cDNA sequence. As results, mRNAs of MT were induced in all the tested organs with dose-dependant manner and gills were the most sensitive organ of fish, Carassius auratus, in the metallothionein induction by cadmium exposure.

[PA4-27] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Sexual Dimorphic Effects of Terbufos on Acetylcholinesterase and Lethality

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An organophosphate pesticide terbufos (S-t-butylthiomethyl-O,O-diethyl phosphorodithioate; TBF) has been extensively used as an insecticide. A sexual dimorphism in TBF toxicity was not reported and remains unclear. Objective of the work is to investigate the influence of TBF on sexual dimorphism in rats by using acetylcholinesterase (AchE). *Method*: TBF treatments were conducted as followings: In *experiment I*, 72-days-old

female (po; control, 0.1, 0.4, and 0.8 ㎎/㎏ TBF for 2 days) and male (po; control, 0.1, 0.5, and 1.0 ㎎/㎏ TBF for 3 days) rats were sacrificed 24 hr after administration. In *experiment II*, 48-days-old female and male rats (po; 0.5 ㎎/㎏ TBF for 2 days) were sacrificed 0, 6, 12, 24 and 72 hr after the last dose. In *experiment III*, 48-days-old female and male rats (po; control or 0.5 ㎎/㎏ TBF for 2 days) were sacrificed 12 hr after last dose. *Result*: In *experiment I*, mortality was 25% in 1.0 ㎎/㎏ TBF group of male and 50% in 0.4 and 0.8 ㎎/㎏ TBF groups of female rats. AchE was significantly decreased only in the frontal and entorhinal cortexes of female rats receiving 0.4 or 0.8 ㎎/㎏ TBF. In *experiment II*, no death was observed in female or male rats. The maximal inhibition in the brain regions or plasma was 2 or 3-fold higher in female, which occurred 6 or 12 hr after last dose. In *experiment III*, mortality was 20% and 0% in female and male rats, respectively. AchE activity in the frontal cortex was significantly inhibited by 60-65% in female and 10-15% in male rats treated with TBF. These results show that female is more sensitive to the inhibition of AchE or mortality than male rats, indicating that TBF causes sexual dimorphic effects on AchE inhibition or mortality in age-matched rats.

[PA4-28] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Changes of serum immunoglobulin in the subacute oral administration of bisphenol A

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Bisphenol A(BPA), a monomer used in the manufacturing epoxy resins and polycarbonates, has been reported to induce estrogenic activity, it has been considered as an environmental endocrine disruptor. But the immunomodulatory effects of BPA exposure have not been systemically evaluated. We investigated whether BPA effects on the ability of immunoglobulin(Ig) production of mice. To initiate investigation of BPA-induced alterations of the immune system, BPA at dose of 100, 500, 1000 mg/kg b.w./day with or without OVA-antigen for 30 days were orally administered to female ICR mice. Mice were sacrificed and serum was collected on day 2 following administration of BPA for 30days. Total IgG1, total IgG2a, total IgE, OVA-specific IgG1, OVA-specific IgG2a, and OVA-specific IgE in serum were determined and compared with those of non-treated mice.
In the groups of BPA with OVA antigen, total IgG1, total IgG2a, total IgE,
OVA-specific IgG1 and OVA-specific IgG2a were significantly decreased at dose of 500mg/kg/day and 1000mg/kg/day. However, in mice treated with BPA alone, total IgG1,and IgG2a were not much altered and total IgE was significantly increased at dose of 1000mg/kg/day. These results demonstrated the BPA modulates the production of immunoglobulin.

[PA4-29] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

In utero exposure to 2, 3', 4, 4', 5- Pentachlorobiphenyl (PCB 118) alters postnatal reproductive development in female rat

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Our previous study demonstrated that 2, 3', 4, 4', 5- Pentachlorobiphenyl (PCB 118) showed an antiestrogenic activity in vitro and in vivo. In the present study, we examined the effect of PCB 118 on postnatal reproductive development in female rats. PCB 118 (0.001, 0.01 or 0.1 ㎎/㎏/day) was administered to pregnant female SD rats from gestation day (GD) 6 to 18 via subcutaneous injection, and developmental parameters such as vaginal opening were determined. PCB 118 significantly delayed vaginal opening of female offsprings at dose of 0.1 ㎍/㎏/day, whereas had no effects on body weights. In addition, in utero treatment of PCB 118 caused significant decreases in serum levels of E2, T3 and T4 in female offsprings at certain doses on postnatal day (PND) 22. Our data of results indicate that in utero exposure to PCB 118 may alter postnatal reproductive development in female rat through its antiestrogenic activity.

[PA4-30] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]