Down-regulation of Inducible Nitric Oxide Synthase Gene Expression by 4-Nonylphenol in Macrophages

Kim JiYoung°, Jeong HyeGwang

Department of Pharmacy, College of Pharmacy, Chosun University, Kwangju, South Korea

4-Nonylphenol (NP) is a degradation product of a widely used non-ionic surfactant group, alkylphenol polyethoxylates that are mainly found as an intermediate in the chemical manufacturing industry. In this study, we investigated the effect of NP on the regulation of inducible nitric oxide synthase (iNOS) in murine macrophages. NP alone did not affect the expression of iNOS, in contrast, suppressed the LPS-induced gene expression of iNOS, in a dose-dependent manner as determined by RT-PCR analysis. NO production was assessed by measurement of nitrites in the medium. The level of NO was found to correlate well with a decrease in transcripts of iNOS. Since the promoter in iNOS gene contains binding motifs for NF-kB, the effect of NP on the inactivation of this transcripts factor was determined by transient transfection assay. Employing a transfection and reporter gene expression system with p(NF-kB)3-Luciferase, the treatment of NP produced a dose-dependent inhibition of luciferase activity in RAW 264.7 murine macrophages cell line. These results suggest that suppression of iNOS gene expression by NP might be mediated by the inhibition of NF-kB activation.

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

Differential Effects of Glutamine Synthase in Cell-free Brain Homogenate, Cultured Mixed Gilal Cells and Brain Regions of Rats Exposed to Methylmercury

Park YoungJin°, Ryu JaeChun, Kwon OhSeung

Toxicology Lab., Korea Institute of Science and Technology, Seoul 136-791

Glutamine synthase (GS), known as a glial-specific enzyme catalyzes the synthesis of glutamine from glutamate and ammonia and has been reported to be associated with ischemic injury and several neurological diseases. Central nervous system is a known target for methylmercury (MeHg). In this study, we investigated whether MeHg exposure in the cell-free brain homogenate, cultured mixed glial cells and rat models has adverse effects on GS. Cell-free brain homogenates were prepared from dissected brain regions of untreated rats. Primary cultures of mixed glial cells were obtained from postnatal day (PND) 1 cerebral cortex of rats, and MeHg (0-10 μM) was exposed to subcultured glial cells for 6 days from 5 days in vitro. To Sprague-Dawley rats (PND 36), multiple dosage of MeHg (0, 1, 4, and 10 mg/kg) was intraperitoneally administered for 3 days. Body weight was measured for administration period. In each experimental model, GS activity was measured spectrophotometrically based on the γ-glutamyl transfer reaction. MeHg exposure (0.1 to 100 μM) to cell-free brain homogenate produced dose-dependent decreases of GS activity in cerebellum, hippocampus and frontal cortex. In cultured mixed glial cells, MeHg exposure (0-10 μM, for 6 days) resulted in dose-dependent increases of GS activity. Cell viability, total cell number, and protein content were significantly decreased in primary culture of mixed glial cells. Western blot with GS antibody showed a qualitative increase of GS protein. In the glial cells exposed to 5 μM MeHg for 6 days, GS activity was significantly increased (2-fold), but MeHg exposure from 6 to 48 hr was not affected on GS activity. GS activity was significantly increased in frontal cortex and caudate nucleus of 4 or 10 mg/kg MeHg-treated rats, but not the entorhinal cortex, hippocampus and cerebellum. GS activity, however, was significantly decreased in liver tissue at 4 and 10 mg/kg MeHg doses. These results showed that MeHg exhibited differential effects on GS at the relatively low concentrations of MeHg, indicating that MeHg may potentiate GS activity in living organisms against MeHg-induced stresses.

[PA4-19] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

In utero sumithrin exposure affects postnatal reproductive development in rat offspring