Toxicogenomic Solution (III) on Neurotoxicity of Methylmercury : Gene Expression Profiling of Methylmercury to Reveal Potential New Mechanistic Markers of Neurotoxicity in Nerve Differentiation Phase

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Methylmercury (MeHg) has been an environmental concern to public health and regulatory agencies for over 50 years because of its toxicity to the human nervous system. Observations of greater neurotoxicity with fetal compared with adult exposure suggest a unique susceptibility of the developing nervous system to MeHg. To determine definitive molecular mechanisms underlying the neurotoxic effects of MeHg in developing nervous system, differentiating (fetal model) and differentiated (adult model) SH-SY5Y neuronal cell models were applied in this study. First, the effects of MeHg on neurite outgrowth and cell viability were quantified at each cell models. In differentiating and differentiated cells, following 48-h exposure, 1.8 uM MeHg significantly decreased retinoic acid (RA)-stimulated neurite outgrowth. Cell viability was assessed in the same cultures by MTT assay. In undifferentiated cells, the IC_{20} of MeHg was I.8 uM. In differentiating and primed cells, the cytotoxicity of MeHg were at least 5-fold higher than undifferentiated cells. To better understand the molecular mechanisms, we monitored global gene expression changes by DNA microarray analysis of 8000 genes to study MeHg-regulated gene expression in the undifferentiated (no RA+MeHg), differentiating (RA+MeHg) and differentiated (MeHg after RA treatment) cells. Differentially expressed genes (10 up and 16 down-regulated genes compared of differentiated cell) were identified in differentiating cells. Clustering analysis revealed some novel changes in the expression of genes that appeared to be associated with differentiation of neuron, cytoskeleton, cell cycle, ion transport and cell signalling, etc. We conclude that gene expression profiling coupled with exposure of MeHg during differentiation affords promising opportunities to reveal potential new mechanistic markers of toxicity in developing neuron system.