Differential Effects of Methylmercury and Mercury Chloride on Cytokine-Evoked Stat3 Phosphorylation and Reactive Oxygen Species Formation

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Funded By NIH/NIEMS R01ES015550 awarded to M.D.R.

Both reactive oxygen species (ROS) formation and the disruption of signaling networks are involved in the toxicity of organic and inorganic forms of mercury; however, the time and dose-dependency of these effects is poorly appreciated. Using the SH-SY5Y human neuroblastoma cell line, we compared the toxicity of methylmercury (MeHg) and mercury chloride ($HgCl_2$) and their effects on CNTF-evoked Jak/Stat signaling. The involvement of ROS in mercury induced changes in Stat Y705-phosphorylation these was assessed in parallel with the fluorescent dye, 5-(and-6)-carboxy-2',7'-dichlorodihydro-fluorescein diacetate.

In agreement with previous reports, MeHg was 20-45 times more cytotoxic than $HgCl_2$ with acute exposures of 5h. Western Blot analysis of SH-SY5Y cells pretreated with $HgCl_2$ and H_2O_2 showed inhibition of CNTF-evoked phosphorylation of Stat3 that occurred alongside increases in ROS. Unlike $HgCl_2$, subcytotoxic amounts of MeHg caused an initial ~44% increase in Stat3 phosphorylation and a subsequent sharp inhibition of Stat3 phosphrylation at cytotoxic doses. Increases in ROS were not observed at these doses in MeHg-treated cells. Together, these data suggest that 1. MeHg does not catalyze ROS formation at the same cytotoxic doses as $HgCl_2$ 2. MeHg may enhance the Jak/Stat-response, and 3. Enhancement and inhibition of Stat3 phosphorylation by MeHg are ROS independent mechanisms.