of Mn exposure (1.66-2.5 mg Mn/kg per injection, 2x per week). Eleven different WM tracts in the brain were evaluated for mean diffusivity (MD) and fractional anisotropy (FA). We found a significant increase in MD at 18 months in the external capsule of Mn animals (p=0.04), with no change of MD in any other WM tract or in controls. We also observed significant increases in FA in the genu (p=0.01) and splenium (p=0.04) of the corpus collosum in Mn monkeys at 18 months. A significant increase in FA observed in the posterior thalamic radiation of control monkeys at 8 (p=0.02) and 18 months (p=0.01) was not seen in the Mn animals. While these results are not consistent with a previous study in welders (Kim et al., 2011), increased FA has been noted in mental diseases such as schizophrenia and autism. FA is usually interpreted as a marker of white matter integrity and may be influenced by a multitude of factors including myelination, gliosis, edema, and inflammation. Since DTI is a fairly new technique and many factors may influence the interpretation of results, further studies are needed to understand the biological relevance of the changes observed in this study. [Supported by NIEHS Grant # ES010975]

PS 1365 Comparison of *In Vivo* Manganese Accumulation in Nonhuman Primate and Human Brains

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Recent studies have shown that while the primary target of manganese (Mn) deposition in the brain is the basal ganglia, cortical regions are also involved in Mn neurotoxicity. Here, we aimed to compare the in vivo accumulation of Mn in the cerebral cortex of non-human primates and occupationally exposed humans.
In a non-human primate study, 4 Mn-exposed and 3 control adult male cynomolgus monkeys underwent magnetic resonance imaging (MRI). A series of inversion recovery images were acquired at baseline and after 8 months of Mn/saline exposure (3.2-5 mg Mn/kg wk). In the human study, 3D T1 relaxation images were acquired from 8 career welders (avg airborne Mn 0.10 mg/m3) and 6 controls from a manufacturer in the U.S. T1 parametric maps were calculated after coregistration and normalization of the images to their respective brain atlas. The exposed groups were compared to the control groups pixel by pixel using a nonparametric Kruskal-Wallis test.
In both humans and monkeys, the T1 parametric maps show significantly higher Mn deposition in the basal ganglia, red nucleus and substantia nigra. Increased Mn was also found in the frontal, temporal and parietal lobe, especially in the insula, primary and supplementary motor cortex. However, significant Mn changes in the visuospatial pathway were only found in monkeys most likely due to the higher levels of Mn exposure than in the human subjects.
Our automatic pixel by pixel analysis on brain Mn concentration maps reveals significant Mn deposition in the cerebral cortex, including the motor regulating network which contributes to neural impulse generation, movement planning and execution, and may underlie the mechanism of Mn-induced neurological dysfunction. The comparison between human and monkeys provides in vivo evidence for similarities in Mn distribution across different species. (NIEHS ES010975, ES020529)

PS 1366 Manganese Neurotoxicity: *In Vivo* GABA Levels Correlate with Motor Deficits in US Welders

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High manganese (Mn) exposure, as encountered in some occupational settings, has been associated with motor deficits. The primary sites for Mn deposition are the basal ganglia, which play an important role in movement via the interaction of glutamate (Glu) and γ-aminobutyric acid (GABA). We therefore measured in vivo GABA and Glu levels in Mn-exposed workers using magnetic resonance spectroscopy (MRS) and studied the relationship with fine motor skills.
Welders (n=13) and controls (n=11) were recruited from a US truck trailer manufacturer. Short-echo-time spectra were acquired from the frontal cortex and motor cortex to measure the sum of Glu and glutamine (Glx), and J-edited GABA spectra were acquired from thalamus and striatum. All subjects also underwent a neurological motor exam (UPDRS-III) and several fine motor tests.
Welders had significantly increased UPDRS-III scores and higher levels of thalamic GABA compared to controls. For all subjects increasing thalamic GABA levels correlated with increasing normalized scores of the parallel line test reflecting tremor level (r=0.437, p<0.05), and striatal GABA correlated with Finger Tapping, used to assess motor speed (r=-0.551, p<0.01). In the welders, significant inverse correlations were seen between frontal Glx levels and the grooved pegboard score (r=-0.803, p<0.01), and between motor cortex Glx levels and parallel line test scores (r=-0.651, p<0.05).
The significant correlations of thalamic GABA and frontal Glx levels with tremor level, as well as striatal GABA levels with motor skills, confirm the use of MRS to study neurotoxic effects of Mn on the direct and indirect pathways of the basal ganglia that lead to motor disturbances. (Supported by NIEHS R01 ES020529)

PS 1367 Increased Thalamic GABA in Chronic Manganese-Exposed Metal Workers and Manganism Patients

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Overexposure to manganese (Mn) has been reported to lead to parkinsonism symptoms. We hypothesize that hypokinetic symptoms associated with Mn overexposure correspond to elevated thalamic GABA levels leading to reduced glutamatergic projections to the cortex. Therefore we aimed to test whether Mn-exposed workers and manganism patients may have elevated thalamic GABA levels, as well as reduced cortical glutamate (Glu) levels.
A group of 20 Mn-exposed welders, 19 Mn-exposed smelters, 7 manganism patients and 37 controls were recruited from Guangxi Province, China. Each subject underwent magnetic resonance imaging and spectroscopy exams. Short-echo-time 1H spectra were acquired from the frontal cortex and thalamus to assess levels of Glu, the sum of Glu and its precursor glutamine (together denoted as Glx), and myo-inositol (mI, a glial marker). GABA-edited spectra were also acquired in the thalamus. Metabolites are expressed as ratios over creatine (Cr).
Over three years we consistently found significantly increased thalamic GABA/Cr in welders, smelters, and manganism patients compared to controls (p<0.01 for all comparisons). Smelters showed significantly decreased frontal Glu/Cr, thalamic Glu/Cr and thalamic Glx/Cr (p<0.05 for all comparisons). Moreover, welders had significantly increased frontal mI/Cr and both groups of workers had significantly decreased thalamic mI/Cr (p<0.05 for all comparison).
Overall our results suggest increased thalamic GABAergic inhibition in Mn-exposed workers and manganism patients, as well as decreased glutamatergic excitation and Glu-Gln cycling in the frontal cortex of smelters. These metabolic changes may aid in understanding the mechanism of Mn-caused motor and cognitive deficits. (Supported by NIH/NIEHS R21 ES017498, R01 ES020529 and NSF of China #81072320)

PS 1368 GABA Levels Correlate with Exposure Levels and Brain Deposition of Manganese in US Welders

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Excessive manganese (Mn) exposure has been associated with decline in cognitive and motor function. Our previous study in a cohort of highly Mn-exposed Chinese workers found significantly elevated thalamic γ-aminobutyric acid (GABA) levels. The current study explored the relationships among brain GABA levels measured in vivo by magnetic resonance spectroscopy (MRS), brain Mn deposition measured by MRI and individual Mn exposure levels in a typical US occupational setting.
Thirteen welders and eleven controls were recruited from a US truck trailer manufacturer. Subjects underwent personal air sampling and filled out a questionnaire of detailed work history for the estimation of individual exposure to respirable Mn. For each subject a series of 3D images were acquired on a 3T GE Signa MRI scanner and used to create high-resolution T1 relaxation maps, an inverse indicator of Mn deposition. GABA spectra were acquired from the thalamus with a TE68 MEGA-PRESS sequence and quantified using LCModel, a spectral fitting tool.
GABA levels were significantly higher in welders vs. controls [2.45±0.68 mM vs. 1.40±0.45 mM, p<0.001]. Increased thalamic GABA levels significantly correlated with (a) average exposure estimated for the previous three months before the MRI exam [R=0.649, p<0.05] and with (b) decreased T1 relaxation time in the substantia nigra, denoting increased Mn deposition [R=-0.589, p<0.05].

These results confirm the elevation of thalamic GABA levels in a typical US occupational setting. The significant correlations between increased GABA levels and recent exposure levels, as well as with brain Mn accumulation in the substantia nigra, suggest that GABA-edited MRS in conjunction with quantitative T1 relaxation MRI may serve as a biomarker of Mn exposure. (Supported by NIEHS R01 ES020529 and CDC/NIOSH T03 OH008615)

PS 1368a Potential Prevention Strategies to Reduce the Risk of Neurotoxicity Associated with Manganese-Containing Welding Fumes

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Welding generates complex metal aerosols, inhalation of which is thought to cause Parkinson's disease (PD)-like neurotoxicity, due to the presence of manganese (Mn) in the welding electrodes. As neurological disorders are generally progressive in nature, with latency between insult and appearance of clinical symptoms, a logical approach for workplace safety and health is to prevent adverse exposures. For welding, this can be achieved by minimizing welding fume (WF) generation rate and/or suitably modifying existing welding practices to reduce toxic exposures. Here, we show that by specifically modulating welding voltage, keeping current and shielding gas constant, the fume composition and neurotoxicological properties of WF can be significantly altered. Rats were exposed by whole-body inhalation to filtered air or WF particulates generated by gas-metal arc-stainless steel welding (GMA-SS; 40 mg/m3; 3h/d x 10d) either at 25V (standard/low; LVSS) or at 30V (high; HVSS) voltage. Both conditions produced good weld quality and similar particulate morphology, although aerosols from HVSS welding comprised of a larger fraction of ultrafine particulates that are characteristically considered to be more toxic than their fine counterparts. Exposure to particulates from LVSS welding caused neuroinflammation (increased Ccl2, Tnfa, Nos2; 1.5 - 3.9 fold; $P<0.05$) and decreased PD-related proteins (Th, Park5, Park7; 18 - 47%; $P<0.05$) in the dopaminergic brain areas, striatum and midbrain. Paradoxically, exposure to particulates from HVSS welding did not elicit any dopaminergic neurotoxicity. We determined that the lack of neurotoxicity may be a consequence of the reduced solubility of manganese in HVSS fumes. Our findings show promise for modified welding practices as a potential prevention strategy for Mn-related neurotoxicity during welding; however, it warrants additional investigations to determine if such modifications can be suitably adapted at the workplace to avert or reduce neurological risks.

PS 1368b The Role of the Transient Receptor Potential Ankyrin 1 (TRPA1) Channel in Methylmercury (MeHg)-Induced Ca^{2+} Dysregulation

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MeHg biphasically elevates $[Ca^{2+}]_i$, with the first (P1) and second (P2) phases attributed to Ca^{2+} release from, in part, IP_3-sensitive intracellular stores and extracellular Ca^{2+} influx through Ca^{2+}-permeable ion channels, respectively. MeHg-induced $[Ca^{2+}]_i$ dysregulations have been correlated with reduced viability of susceptible neuronal populations *in vitro*. Because paresthesia is the preeminent sign of MeHg intoxication, and the size and number of neurons of the dorsal root ganglia (DRG) are reduced in poisoned individuals, molecular entities unique to DRG may heighten sensitivity to MeHg. Heterologous expression was used in this study to investigate the contribution of TRPA1, a Ca^{2+}-permeable ion channel highly expressed in DRG, in mediating Ca^{2+} dysregulation throughout acute MeHg exposure. HEK 293 cells were transfected with human TRPA1 72 hrs prior to single-cell microfluorimetry studies. Fura-2 AM, a ratiometric Ca^{2+} fluorophore, was used to measure relative changes in $[Ca^{2+}]_i$ in transfected cells throughout exposure to MeHg (1, 2 μM). Time-to-onset of P1 was hastened in TRPA1-HEK exposed to 1 μM MeHg, as compared to untransfected HEK (UT) (5.9±0.8 min and 11.1±0.5 min, respectively; mean ± SEM). This suggests that TRPA1 provides a more kinetically favorable route of entry for low [MeHg]. Expression of TRPA1 did not alter the time-to-onset of P2 between TRPA1-HEK (39.7±2.2 min) and UT (37.4±1.5 min) exposed to 1 μM MeHg. Similarly, TRPA1 expression had no effect on the times-to-onset of neither P1 nor P2 in TRPA1-HEK (4.4±0.7 and 26.1±2.7 min, respectively) and UT (5.1±0.2 and 24.3±0.9 min, respectively) exposed to 2 μM MeHg. These results suggest Ca^{2+} entry through TRPA1 does not significantly contribute to overall $[Ca^{2+}]_i$ dysregulation following MeHg exposure. This, combined with the fact that P1 is unaffected by TRPA1 expression at higher [MeHg], suggests that TRPA1 may be a sensitive target for time- and concentration-dependent block by MeHg. Supported by NIH grant R01ES03299.

PS 1369 Methylmercury Induces Apoptosis in Neuronal Cells through ROS-Mediated Endoplasmic Reticulum Stress-Regulated Signaling Pathway

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Objectives: Methylmercury (MeHg) is a well-known environmental pollution. The human beings expose to methylmercury through ingestion, which can cause irreversible nervous system dysfunction and injuries. However, effects and possible mechanisms of MeHg-induced neurotoxicity remained unclear. In this study, we attempted to investigate the important roles of endoplasmic reticulum (ER) stress-regulated pathway in MeHg-induced neurotoxicity.
Results: MeHg significantly decreased cell viability in a dose-dependent manner (1-5 μM) and induced the increase in caspase-3 activity, annexin V-FITC binding, and the protein expressions of caspase cascades in Neuro-2a cells, indicating that MeHg could induce neuronal cell apoptosis. Moreover, exposure of Neuro-2a cells to MeHg could trigger ER-stress as indicated by several key markers (GRP-78, GRP-94, CHOP, and XBP-1) and upstream molecules (the phosphorylation of PERK, eIF2-α, and IRE-1), and caspase-12 cleavage. Pretreatment with antioxidant NAC and transfection with specific si-RNA (GRP-78, GRP-94, CHOP, and XBP-1, respectively) could effectively attenuate MeHg-induced cytotoxicity, apoptotic events and ER stress-related signals.
Conclusions: These results indicate that the ROS production triggered ER-stress signaling pathway involves in MeHg-induced neuronal cell apoptosis.

PS 1370 Effect of Methylmercury (MeHg) on RNA Expression of Voltage-Gated Calcium Channels (VGCCs) in Naïve and Differentiated F11 Cells

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MeHg is an environmental contaminant that elevates $[Ca^{2+}]_i$ in two kinetically-distinct phases. Phase one (P1) consists of Ca^{2+} release from intracellular storage organelles, whereas phase two (P2) results from an influx of Ca^{2+} through Ca^{2+}-permeable ion channels. MeHg-induced elevations in $[Ca^{2+}]_i$ have been correlated with increased cell death. This study surveyed VGCC RNA expression in MeHg-exposed F11 cells, an immortalized cell line derived from dorsal root ganglia. Changes in RNA expression of the pore-forming subunit of the L-, N-, P/Q-, R- and T-type VGCC isoforms (*cacna1c*, *1b*, *1a*, *1e*, and *1h*, respectively) following MeHg exposure was examined by polymerase chain reaction (PCR). F11 cells were cultured and differentiated (2 μM retinoic acid) for 24-72 hrs prior to 1 hr MeHg exposure (1, 2 and 5 μM). 24 hrs after MeHg exposure, RNA was isolated and converted to cDNA. PCR was performed on cDNAs and relative changes in RNA were determined by $2^{-\Delta\Delta Ct}$. Differentiation alone increases the RNA expression of *cacna1c* and *cacna1a* in F11 cells at 72 hours (2.55±0.05 and 2.51±0.05, respectively; mean fold-change ± SEM). Differentiated F11 cells also express low levels of RNA for *cacna1b* (1.01±0.04), *cacna1e* (0.45±0.04), and *cacna1h* (1.12±0.03); exposure to MeHg reduces RNA expression of these genes in a concentration-dependent manner, with 5 μM MeHg reducing *cacna1a*, *cacna1c*, and *cacna1h* RNA most markedly (0.45±0.06, 1.06±0.09, and 0.63±0.04, respectively). Downregulation of RNA expression was also dependent upon the differentiation time point; cells differentiated for longer periods displayed a greater reduction of *cacna1* expression universally. Changes in RNA expression may reflect a concomitant alteration in protein expression, thus these data may indicate distinct VGCC isoforms as critical contributors to Ca^{2+} influx in P2. Because RNA expression of *cacna1c* and *cacna1a* is most abundant following acute MeHg exposure, the L- and P/Q-type VGCCs may be significantly involved in cytotoxic mechanisms. Supported by NIH grant R01ES03299 and R25NS54467.

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