repolarization - were assessed over a 4 hr period. At that time bronchoalveolar lavage was performed on the cardiac lobe and portions of the lung and heart were removed for immunohistochemical analysis. ROFA-exposed pigs had a 8.3 fold increase in BAL PMNs and a 2.4 fold increase in BAL protein compared with pigs exposed to saline. There was a 4.8 mm Hg increase in pulmonary artery systolic pressure following ROFA exposure compared with a 2.3 mm Hg decrease after saline exposure. In ROFA-exposed pigs, heart rate increased by 19 bpm and ARIs decreased, compared to saline-exposed animals. In this pig model, ROFA increases lung injury and inflammation, pulmonary hypertension, and affects cardiac impulse formation and repolarization. This abstract does not necessarily reflect EPA policy.

1320 BIOAVAILABLE CONSTITUENTS MEDIATE CARDIAC MOLECULAR EFFECTS OF PULMONARY DEPOSITED FUEL OIL COMBUSTION PARTICLES.

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Environmental health effects studies have shown the ability of particulate air pollution to affect cardiac autonomic control. The mechanism(s) by which particulate air pollution alters cardiac physiology are unknown. It is also not known what cardiac molecular effects, if any, may relate to specific combustion particles present within the fine fraction of particulate air pollution. This study examines the ability of fuel oil combustion particles, residual oil fly ash (ROFA), deposited in the lung to induce cardiac molecular effects and determines the mechanism(s) by which these effects arise. Gene expression profiling detected an increase in mRNA levels for several cytokines and matrix metalloproteinases within hearts recovered from ROFA-instilled rats at 1 - 6h and 24h post-exposure. Protein profiling detected an increase in the total phosphotyrosine protein content and the activation of several protein kinases in hearts recovered from ROFA exposed rats as early as 0.25 - 1h post-exposure, indicating a rapid alteration in cardiac intracellular signaling homeostasis. Pulmonary exposure to ROFA did not increase plasma levels of IL-1beta, TNFalpha, IL-10 or endothelin-1. Elevated plasma vanadium (V) content was observed in ROFA-exposed rats as early as 15 min post-exposure which remained elevated up to 6h post-exposure before decreasing towards control saline levels by 24h post-exposure. Exposure of cardiac fibroblast/myocyte co-cultures to a particle free ROFA leachate produced similar molecular responses as observed *in vivo*. These results demonstrated the ability of ROFA to produce cardiac molecular effects that were temporally correlated with plasma V content. These effects occurred rapidly and prior to the development of pulmonary inflammation, and could be replicated *in vitro*. These findings suggest that bioavailable metal constituents are responsible for the cardiac molecular effects following *in vivo* or *in vitro* exposure to fuel oil combustion particles.

1321 TRANSCRIPTIONAL INVOLVEMENT IN NEUROTOXICITY.

N. H. Zawia. *Biomedical Sciences, University of Rhode Island, Kingston, RI.*

It has become more apparent that exposure to various chemicals and environmental hazards elicits changes in the expression of a variety of genes. The study of gene expression and transcriptional regulation is an important aspect of understanding the mechanisms associated with neurotoxicity. The availability of whole genome sequences and the development of new tools to identify and monitor transcriptional activity have accelerated the rate of discovery. This has led to the identification of new genes and the ability to monitor the activity of multiple genes that act in concert in response to a stimulus. This symposium will deal with recent advances related to the elucidation of genes expression associated with the neurotoxic response as well as deciphering of signal transduction/transcription coupling that is altered following exposure to neurotoxic agents.

1322 THE SP FAMILY OF TRANSCRIPTION FACTORS MEDIATE METAL-INDUCED CHANGES OF GENE EXPRESSION.

N. H. Zawia. *Biomedical Sciences, URI, Kingston, RI.*

Sp1 is a transcription factor which contains a zinc finger motif and whose activity is modulated both *in vivo* and *in vitro* by heavy metals such as Pb, Hg, and Cd. Some of the genes under Sp1 control include ornithine decarboxylase, myelin basic protein, proteolipid protein, NMDAR1 subunit, and metallothionein. It has now become apparent that Sp1 belongs to a family of proteins whose members include Sp2, Sp3, Sp4. All the Sp factors recognize the same DNA element. While the role of Sp2 is unknown, Sp3 is suspected of being a negative modulator of transcription and Sp4 exhibits tissue specificity for the brain. The interactions of Sp1 with cell cycle regulatory proteins, including p53, retinoblastoma protein, and cyclins is consistent with its developmental role. Furthermore, Sp1 has been shown to play a critical role during the differentiation of oligodendrocytes in the human brain. This presentation will discuss metal-induced changes in the activity and structure of this transcription factor family. Specific focus will be placed on the different roles of the various members of the Sp family in the regulation of gene expression.

1323 GENE EXPRESSION AND CELL-SIGNALING EVENTS ASSOCIATED WITH TOXICANT-INDUCED GLIOSIS.

J. P. O'Callaghan[1], K. Sriram[1], M. I. Luster[1] and D. M. Felschow[2]. [1]*Molecular Neurotoxicology, CDC-NIOSH, Mogantown, WV and* [2]*Ciphergen Biosystems, Fremont, CA.*

Astrogliosis represents a sensitive and early response of the nervous system to all types of neurotoxic injuries. The generality of the glial reaction, despite the target selectivity of specific neurotoxic insults, implies that there are common "signals" underlying this cellular response. The discovery and characterization of such signals would, therefore, broaden our understanding of molecular mechanisms underlying diverse neurotoxic responses and lead to early "predictors" of neurotoxic outcomes. We present evidence for candidate genes and signaling pathways underlying the glial response to neuronal damage resulting from exposure to the dopaminergic neurotoxicant, MPTP. In our model, a single 12.5 mg/kg dose of MPTP to the C57 Bl6/J mouse results in a 50% decline in dopamine and TH protein. The accompanying astrogliosis, as assessed by immunoassay of GFAP, begins at 12 hrs and peaks at 48 hrs post dosing. Striatal homogenates prepared from mice sacrificed by focused microwave irradiation to preserve steady-state phosphorylation revealed activation of the JAK-STAT pathway in the earliest phase of MPTP-induced gliosis. This effect was not observed in non-target regions and was completely reversed by neuroprotection with nomifensine. These results were indicative of effects specific to the neurotoxic condition and implicated potential upstream effectors in the JAK/MAP kinase modules, such as cytokines and trophic factors acting through the gp130/Ras pathways. Gene array analysis revealed enhanced expression of TNF-α mRNA and the Ciphergen Protein Chips®platform of SELDI-TOF/MS analysis revealed a striatal-specific induction of 18 kD proteins consistent with induction of TNF-α. TNF-α receptor deficient mice showed complete neuroprotection against the neurotoxic effects of MPTP. Together these data show that a gene- protein- and phospho-specific antibody "arrays" can reveal novel mechanisms potentially underlying the glial response to neurotoxic insult.

1324 GENE EXPRESSION PATTERNS IN LEAD NEUROTOXICITY.

T. R. Guilarte. *Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Human studies and animal models have clearly demonstrated the impact of developmental lead (Pb) exposure on behavior and cognitive function. Experimental animals exposed to environmentally relevant levels of Pb express deficits in tests of spatial learning and in synaptic plasticity such as long-term potentiation (LTP). The hippocampus is a brain structure essential for both of these processes and its known to be affected by Pb exposure. We have been interested in understanding the molecular basis associated with these deficits and have identified changes in the expression of specific subunits of the NMDA receptor in the hippocampus of Pb exposed rats. This presentation will discuss Pb-induced changes in the expression of selective genes associated with NMDA receptor-dependent signal transduction and calcium homeostasis. [Supported by NIEHS grant ES06189]

1325 INDUCTION OF TRANSCRIPTION FACTORS IN NEURONS THAT SURVIVE NEUROTOXICITY.

K. R. Pennypacker. *Pharmacology, USF, Tampa, FL.*

We report that levels of Fos-related antigen-2 (FRA-2) are elevated long-term in several models of chemical-induced brain injury as well as after ischemia suggesting that this protein is involved in enhancing the transcription of genes related to the process of regeneration and repair. Trimethyltin, which causes degeneration of neurons primarily in the hippocampus and other limbic regions, results in a 5-fold induction of FRA-2 immunoreactivity in neurons in the pyramidal and dentate layers of the hippocampus starting at seven days post treatment and persisting for 60 days. Ischemic insult caused by middle cerebral artery occlusion results in an increase in FRA-2 expression the hippocampus ipsilateral to the ischemic lesion at 6 hours

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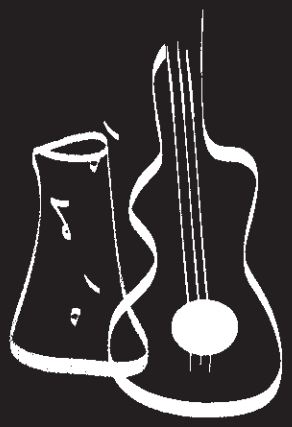

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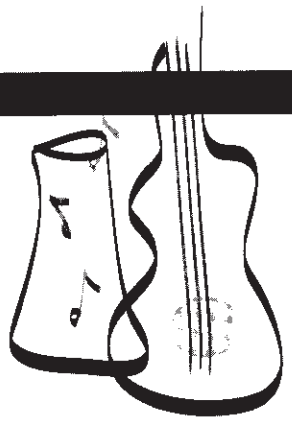

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