neural outgrowth, a developmental process, in hippocampal pyramidal cells in primary culture. Hippocampal neurons go through a highly stereotyped developmental sequence leading to outgrowth of axons. Stage 1 involves generalized motility, Stage 2 involves the outgrowth of short minor processes and Stage 3 involves the outgrowth of a long axon. Hippocampal cells isolated from 18 day old rat embryos were exposed *in vitro* for 24 hrs to 0.125μM, 0.25μM, 0.5μM, 1μM, or 2μM TMT, or TMT-free solutions as a control. TMT was subsequently removed, and photos of developing cells were taken at 24, 48 and 72 hrs after completing treatment. The number of cells in each stage was counted. TMT-free solutions did not compromise the outgrowth of hippocampal neurons at 24, 48 or 72 hours. By 72 hours, ~ 65% of the cells had progressed to Stage 3, and less than 20% remained in Stage 1. In contrast, TMT had a concentration-dependent action to suppress neuronal process outgrowth of hippocampal neurons. At low concentrations (0.125-0.5 μM) TMT moderately slowed the progression of neurons from stage 1 to subsequent stages. By 72 hrs, ~ 25-35% of the cells had progressed to Stage 3. However, at 1 and 2μM TMT, the slowing of growth progression was more prominent, and more long-lasting. Less than 25% of the cells progressed to Stage 3 under these conditions, and 40-50% of the cells remained in Stage 1. Thus acute exposure to TMT can affect the processes of neuronal growth and differentiation in hippocampal neurons in culture. Supported by NIH grant R03-ES10176.

1028 AUTOANTIBODIES TO NERVOUS SYSTEM PROTEINS FOLLOWING TRIMETHYL TIN (TMT) EXPOSURE: A COMPARISON OF ELISA AND WESTERN-BLOT ANALYSIS.

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Previous studies in both human and animals have demonstrated the presence of serum autoantibodies to neurotypic [e.g., neurofilament triplet (NF)] and gliotypic proteins [myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP)] following exposure to some heavy metals, solvents, or pesticides. TMT has been used as a denervation tool to validate the enhanced expression of GFAP as a biomarker of astrogliosis resulting from neuronal damage and cell death. In particular, TMT targets hippocampal pyramidal neurons in CA3 and CA1. In the present study TMT was used to assess the detection of the serum polyclonal IgG responses against NFs, measured by ELISA, as a peripheral marker of neurotoxicity. Western-blots, using purified NF proteins, or hippocampal homogenates, were used to confirm ELISA. Male Long-Evans rats (45 days of age) were administered either TMT (8mg/kg; sc; n=16) or an equal volume of sterile 0.9% saline (n=16). At 3 weeks post-administration, serum was collected, and rats were sacrificed for the collection of brains. The polyclonal IgG response to NF68, NF160, and NF200, using ELISA, showed detectable titers of IgG autoantibodies to NFs in sera from TMT-exposed rats, only. Anti-NF68 titers were highest compared to NF160, or NF200. Immunostaining of Western-blots using HRP-conjugated anti-rat IgG confirmed the presence of antibodies, against purified proteins or hippocampal homogenates, in sera of rats exposed to TMT. This corresponded to the molecular weights of NF 68, NF160, and NF200. Immunoblot confirmed the use of the ELISA as a means of detecting the autoantibody response. This study suggests that the detection of autoantibodies to neurotypic proteins, using ELISA, may be used to indicate chemical neurotoxicity. (Supported by NIH HD36965 and USDE P217A990192).

1029 ZINC-INDUCED MODULATION OF CHOLINE TRANSPORT IN CULTURED CHOROID PLEXUS.

K. M. Kransler and A. R. Villalobos. *Environmental Medicine, University of Rochester, Rochester, NY.* Sponsor: M. McCabe, Jr..

Removal of choline from cerebrospinal fluid (CSF) by choroid plexus is a potentially critical regulatory point in central cholinergic homeostasis. Modulation of the transport pathway by chemical stress may alter choline availability in the CNS. We examined the potential effects of zinc on choline removal from CSF in primary cultures of neonatal rat choroid plexus epithelium. Cultures were exposed to 10 μM $ZnCl_2$ in serum-free medium for 1.5 h (37°C). After 0-12 h recovery in Zn-free medium/5% NuSerum ± severe heat shock (SHS, 45°C, 1 h) ventricular uptake of 10 μM 3H-choline ± 750 μM hemicholinium-3 was assayed in artificial CSF (30 min, 37°C). LDH release was assayed to evaluate cytotoxicity. HSP70 accumulation was analyzed by immunoblot and normalized to actin band intensity. To assess cytoskeleton integrity and general cell morphology, actin was probed with TRITC-labeled phalloidin and viewed by fluorescence microscopy. After Zn exposure choline uptake was comparable to that by untreated controls with LDH release increasing 12%. However, uptake was stimulated 15% after 1-h recovery. Stimulation persisted through 12-h recovery, at which time uptake was enhanced 50%. Thermotolerance of transport was also enhanced with recovery. Without Zn/recovery preconditioning, SHS increased LDH release <5% but reduced choline uptake 50%. However, after Zn exposure, SHS reduced uptake by only 25%. In cultures subjected to SHS after 1-6 h recovery, uptake was comparable to that by non-SHS controls. After 12-h recovery, SHS reduced uptake by 20%. Thus complete thermoprotection was transient. Zn exposure also induced HSP70 accumulation, with levels peaking 3-6 h post Zn exposure and declining thereafter. While overall cell morphology was maintained, Zn-exposure induced migration and localization of actin filaments to the cell periphery. These data suggest that zinc may induce latent stimulation and thermoprotection of choroid plexus removal of choline from CSF, possibly correlated with induction of HSP70 and the actin cytoskeletal reorganization. ES10439; NS39452

1030 TRANSPORT OF ZINC IN THE OLFACTORY PATHWAYS OF RATS.

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The olfactory route provides a pathway for metals to the brain, thus allowing them to circumvent the blood-brain barrier. In the present study zinc-65 was instilled intranasally in rats and the disposition of the metal in the olfactory system was examined. Autoradiography with tape-sections showed a transport of the metal to the terminals of the primary olfactory neurons in the glomeruli of the olfactory bulbs, followed by a passage across the synapses to the interior of the bulbs. Cell fractionations showed that the zinc in the olfactory epithelium and the olfactory bulbs was present both in the cytosol and in association with various particulate cell constituents. Gel filtrations of the cytosolic fractions on a Superdex 30 column showed that the zinc was eluted in the void volume (MW >10, 000 Da). Intranasal pretreatment of rats with cadmium, to induce metallothionein, did not affect the subcellular distribution of zinc. Our results show that zinc is transported along the olfactory pathway. The data indicate that during this process the metal is bound to both particulate cellular constituents and cytosolic components, the latter having a high molecular weight.

1031 ENVIRONMENTAL RISK FACTORS FOR ALZHEIMER'S DISEASE.

K. J. Ghosal, O. K. Siddiqi and N. H. Zawia. *Biomedical Sciences, URI, Kingston, RI.*

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder, characterized, in part, by the extra-neuronal accumulation of beta-amyloid peptide. This peptide is a cleavage product of the amyloid precursor protein (APP). Aggregation of this peptide is suspected to lead to neuronal damage and cell loss. The factors that result in the aggregation of this peptide are not known, however, it is possible that exposure to environmental agents could promote such aggregation. Previous studies have alluded to the presence of Zn and potentially other metals in the amyloid plaques (Bush et al., JBC, 2000). In an attempt to identify environmental contributors to such a process, we screened a variety of metals and tested their ability to enhance beta-amyloid aggregation. Synthetic Abeta (1-40) peptide was obtained and used in an assay to determine its aggregation in the presence of a series of metals. The assay involved measuring Abeta aggregation by examining the fluorescence spectra that are produced at 482nm only when the aggregated peptide binds to the Thioflavin T probe. Initially the aggregation of the peptide was studied by varying the pH (pH 5-8) of the buffer. Subsequently, various metals were tested for their ability to enhance aggregation beyond that produced by pH alone. The metals studied were Zn, Pb, Mn, Ba. Pb and Mn promoted aggregation at pH 5-6, at a concentration of 10μM, while both Zn and Ba had minimal effects at this concentration. These preliminary results suggest that environmental metals may contribute to amyloidogenesis, however, further *in vivo* and *in vitro* studies are needed to confirm such an outcome.

1032 INHIBITION OF HUMAN SQUALENE MONOOXYGENASE BY SELENIUM COMPOUNDS.

N. Gupta and T. D. Porter. *Graduate Center for Toxicology, University of Kentucky, Lexington, KY.* Sponsor: M. Vore.

Excessive selenium exposure leads to a variety of toxicities in animals and in man. However, the chemical species of selenium and the molecular targets that mediate its toxicity are not well characterized. Methylated metabolites of tellurium, which is located directly below selenium on the Periodic Table, are potent inhibitors of squalene monooxygenase, the second enzyme in the committed pathway for cholesterol biosynthesis, and lead to a peripheral demyelinating neuropathy similar to that seen in selenosis. To evaluate the toxicity of selenium and its methylated metabolites, we

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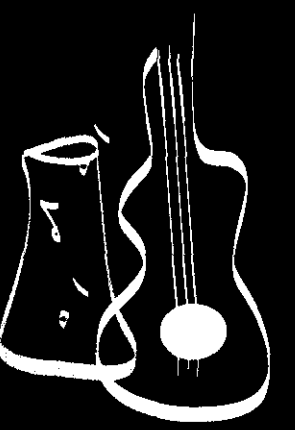

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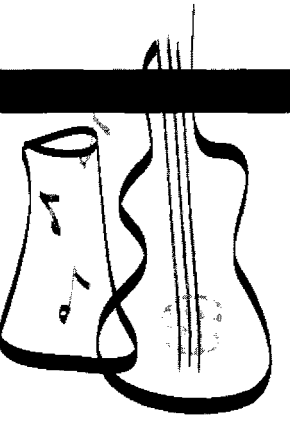

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Additional Late-Breaking Abstracts are issued in a supplement to this publication and are available at the 41st Annual Meeting and through the Society of Toxicology Headquarters office.

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