differentiation-inducing culture medium containing the metal salt. Lead caused a 50% decrease in levels of the galactolipid biosynthetic transferases, UDP-galactose:ceramide galactosyltransferase and 3Ó-phosphoadenosine-5Ó-phosphosulfate:galactocerebroside sulfotransferase at day 2 as compared to lead-free controls. These enzymes were reduced to a degree greater than expected for a delay in OL differentiation as monitored by the early OL marker, 2Ó,3Ó-cyclic nucleotide 3Ó-phosphohydrolase. The activities of the galactolipid catabolic hydrolases, galactocerebroside-beta-galactosidase and arylsulfatase A, were reduced by 20%. Unlike other enzymes, however, the activity of arylsulfatase A in lead-exposed day 6 OLs was significantly less than that found in control cultures. Our earlier studies demonstrated that lead caused human fibroblasts to mis-sort newly synthesized arylsulfatase A, thereby accounting for the lead-induced reduction of enzyme levels. The observed effect of lead on the cultured OL lineage cells is consistent with such a mechanism. The results of these experiments suggest that lead may perturb galactolipid metabolism during developmental maturation of OLs. This, in turn, may represent a contributing mechanism for lead-induced neurotoxcity. (Supported in part by grants from NIEHS, R01-ES08373, and the March of Dimes Foundation.)

893 DOPAMINE AND GLUTAMATE CHANGES IN CORE BUT NOT SHELL OF NUCLEUS ACCUMBENS (NAC) MIMIC LEAD (Pb)-INDUCED CHANGES IN FIXED INTERVAL (FI) SCHEDULE-CONTROLLED BEHAVIOR.

M. R. Bauter and D. A. Cory-Slechta. *University of Rochester Medical School, Environmental Medicine, Rochester, NY.*

Previous studies suggest that increases in NAC dopamine (DA) levels and inhibition of glutamatergic NMDA receptors may be key neurochemical mechanisms underlying increases in response rates on FI schedules of reinforcement that have been associated with chronic low-level Pb exposure. NAC, however, is composed of two main subregions, core and shell, whose respective behavioral functions are not well delineated. To determine the relative roles of core *vs.* shell subregions of NAC in the effects of Pb on FI performance, saline, DA (20-40 ug) and the NMDA receptor antagonist MK-801 (0.5-2.5 ug) were microinjected into these subregions of NAC in normal rats exhibiting stable FI performance. This was done to examine the ability of each compound to mimic Pb-induced increases in FI response rates. Intra-core administration of DA or MK-801 increased FI response rates and did so by decreasing the postreinforcement pause time (PRP), a pattern characteristic of Pb exposure. Although decreasing PRP times, intra-shell DA administration decreased rather than increased FI overall and run rates. MK-801 effects in shell paralleled those observed in core, but only in response to the higher doses of MK-801. Collectively, these findings suggest that changes in DA and/or NMDA mediated function in NAC core may be the critical site for Pb-associated behavioral toxicity on the FI schedule. These findings also support our previous suggestions of a critical role of NAC core in Pb-associated learning impairments using a similar approach (Cory-Slechta *et al.*, 1999) ES01247, ES05017, ES05903.

894 EXPRESSION OF HUMAN PRESENILIN-1 GENE MUTATIONS IN MICE LEADS TO INCREASED TOXICANT-INDUCED NEURODEGENERATION THROUGH THE INHIBITION OF NUCLEAR FACTOR-KAPPA B.

C. A. Kassed and K. R. Pennypacker. *Universtiy of South Florida, Department of Pharmacology and Therapeutics, Tampa, FL.*

Exposure to trimethyltin (TMT) leads to memory deficits, seizures and other neurological manifestations in humans. TMT intoxication results in regionally specific responses by neurons and astrocytes in the rodent hippocampus and other limbic structures, providing a useful paradigm in which to study cellular processes associated with neuronal degeneration. The Nuclear Factor-KappaB (NF-κB) transcription factor regulates gene expression after inflammatory and stress-inducing stimuli. Signal transduction pathways converging on NF-κB are involved in the brain injury response of neurons surviving a neurotoxic injury. We have shown that NF-κB activation is elevated for several days in hippocampal neurons following excitotoxic, ischemic and neurotoxic insult and coincides with the period of regeneration and repair, suggesting a role for this transcription factor in neuronal survival in the post-injury environment. The human mutant presenilin-1 (mPS-1) gene is linked to 50% of all cases of early onset familial Alzheimer's disease, however the mechanism by which proteins encoded by mPS-1 genes promote this disease is not known. Expression of the human mPS-1 gene in cultured cells increases susceptibility to apoptosis, and activation of NF-κB blocks mPS-1-supported apoptosis. We have discovered increased neurodegeneration in the hippocampi and cortices of mice expressing the mPS-1 gene relative to wildtype mice seven days after TMT treatment. This suggests that a paucity of NF-κB activation may be responsible for increased neurotoxicant-induced neurodegeneration.

895 *IN VITRO* AND IN VIVO EFFECTS OF TRIBUTYLTIN ON THE N-METHYL-D-ASPARTATE (NMDA) RECEPTORS IN THE BRAIN OF MICE.

N. Konno, M. Tsunoda, K. Nakano, K. Nakano, Y. Liu and Y. Suzuki. *Fukushima Medical University School of Medicine, Public Health, Fukushima, Japan.*

Tributyltin compounds have been widely used as antifouling paints for marine vessels. The behavioral effects of acute exposure to tributyltin chloride (TBTCl) have been suggested in rats. NMDA receptor, a subclass of glutamate receptor, plays an important role in a variety of neural processes. The purpose of this study was to clarify the effects of TBTCl on the NMDA receptors in the mice brain. *in vitro*, the binding of [3H] MK-801, which is the NMDA receptor non-competitive antagonist, was investigated in membrane preparations from the cerebral cortex of intact mice. Saturation experiments revealed a single binding site with a Kd value of 10.27}1.97 nM and an apparent Bmax value of 1.75}0.21 pmol/mg of protein. In order to investigate the toxicological profile of [3H]MK-801 binding to these membrane preparations, displacement studies were carried out with a concentration range of 0.1ÊM to 2mM of TBTCl. Ki value of 639.3}128.7ÊM was obtained. In vivo, groups of 6 male mice (BALB/c, 5-6 weeks, 20-22g) received TBTCl in the diet *ad libitum* for 30 days. TBTCl concentrations in feed were 0 (control), 1, 5, 25 or 125 ppm. The weights were similar for all dose groups, including control, at the day of sacrifice. [3H]MK-801 binding to cortical membrane preparations from each mouse was measured at a final concentration of 2 nM, using 10ÊM MK-801 to define nonspecific binding. [3H]MK-801 binding to membranes from control, 1, 5, 25 and 125ppm exposed group were 0.323}0.038, 0.345}0.069, 0.251}0.050, 0.338}0.046 and 0.244}0.066 pmol/mg protein, respectively. [3H]MK-801 binding was significantly lowered (p 0.05) in 5 and 125ppm exposed animals compared to the controls. These results suggest that the NMDA receptors in the mouse brain are sensitive to the TBTCl exposures, at a level similar to that of environmental contamination.

896 NEUROTOXICITY OF TRIMETHYL TIN (TMT) ASSESSED USING AUTOANTIBODIES TO NEUROTYPIC AND GLIOTYPIC PROTEINS.

H. A. El-Fawal[1] and J. P. O'Callaghan[2]. *[1]Mercy College, Pharmacology & Toxicology, Dobbs Ferry, NY and [2]CDC-NIOSH, Molecular Neurotoxicology Laboratory, Morgantown, WV.*

Previous studies in both humans 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 or organophosphorus compounds. These studies suggest a correlation with exposure and clinical deficits. The neurotoxic organometal, TMT, has been used as a denervation tool to validate the enhanced expression of GFAP as a biomarker astrogliosis resulting from neuronal damage and cell death. In the present study TMT was used to assess the detection of serum autoantibodies as peripheral marker of neurotoxicity. 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). Five weeks post administration, serum was collected and rats were sacrificed for collection of brains. Serum autoantobodies (both IgM and IgG isotypes) to NF68, NF160, NF200, MBP and GFAP were assayed using an ELISA. Saline rats did not have detectable levels of autoantibodies. Only sera from TMT-exposed rats had detectable titers of autoantibodies to NFs with IgG, the isotype associated with secondary challenge and pathology, predominating. Anti-NF68 titers were highest (600 + 75 ng/ml) compared to NF160 (85 + 15 ng/ml) or NF200 (160 + 45 ng/ml). Autoantibodies to MBP and GFAP were also detected, however, they were predominantly IgM, the isotype associated with primary challenge or recent injury. Hippocampal GFAP, detected at this time, was significantly ($p<0.05$) higher (300%) than in control brains indicating astrogliosis. The detection of anti-NF, as indicative of neuronal insult, was consistent with loss of hippocampal neurons in CA3c and CA4. This study suggests that detection of autoantibodies to neurotypic and gliotypic proteins may be used to indicate chemical neurotoxicity. (Supported by NIH HD35965).

Society of Toxicology

40th Annual Meeting

An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES
Formerly Fundamental and Applied Toxicology

The Toxicologist

Abstracts of the 40th Annual Meeting

Oxford University Press

Volume 60, Number 1, March 2001

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 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332

http://www.toxicology.org