to undergo apoptosis with morphological changes such as condensed and fragmented nuclei (TUNEL assay), increased caspase-3 activation, and poly ADP-ribose polymerase cleavage. In cytotoxicity assays and TUNEL assays, tBHQ pretreatment (10 μM) attenuated hydrogen peroxide-induced cell death and the number of TUNEL-positive cells, respectively. We hypothesize that tBHQ-mediated activation of the antioxidant response element (ARE) is critical for generating the protective response. Our laboratory has recently shown that a selective inhibitor of phosphatidylinositol 3-kinase (PI3-kinase), LY294002, blocks ARE activation by tBHQ. Addition of LY294002 30 min prior to tBHQ treatment completely reversed the protective effect of tBHQ. Oligonucleotide microarrays were used to analyze the gene expression profile associated with tBHQ treatment in the absence and presence of LY294002. 63 genes showed transcriptional upregulation by tBHQ. RT-PCR for selected genes also confirmed the gene expression pattern. Many of these genes function to combat oxidative stress and increase the cells detoxification potential through increased production of NADPH, glutathione (reduced form), and ATP. Some examples are NAD(P)H:quinone oxidoreductase, gamma-glutamylcysteine ligase regulatory subunit, thioredoxin reductase, glutathione reductase, and cytosolic malic enzymes. Inhibition of PI3- kinase significantly blocked the enhanced expression of 49 of the 63 genes induced by tBHQ. These are the first data to show the gene set involved in conferring protection from an oxidative stress-induced apoptosis and imply that the PI3-kinase-Nrf2-ARE pathway is critical in mediating protection from oxidative stress in human neuroblastoma cells.

1372 IS THERE A RELATIONSHIP BETWEEN URINARY AND LEUKOCYTE 8-HYDROXYDEOXYGUANOSINE IN HUMANS?

M. Toraason, P. Mathias, A. Ruder, M. A. Butler, L. Taylor, C. Forrester, E. Krieg and D. G. DeBord. *NIOSH, Cincinnati OH, OH.*

8-Hydoxydeoxyguanosine (8-OHdG) is typically measured in DNA of white blood cells (WBCs) or in urine. Urine measurement is believed to provide an index of oxidative DNA damage repair. WBCs are considered a surrogate for target tissues. These markers are used almost interchangeably to assess the adverse effects of a variety of environmental factors. Only a few of the hundreds of studies assessing 8-OHdG as a biomarker of oxidative DNA damage in humans, have measured 8-OHdG in both urine and WBC DNA. Two recent studies reported non-significant inverse associations between urinary excretion of 8-OHdG and WBC DNA 8-OHdG. We examined this relationship in male roofers with (n=26) or without (n=12) exposure to polycyclic aromatic compounds and female dry cleaners and launderers with (N=18) or without (N=20) exposure to perchloroethylene. For males, urine and blood were obtained pre-shift at the start and post-shift at the end of a work week. For females, urine was obtained pre- and post-shift mid-work week, and blood was obtained once pre-shift mid-work week. 8-OHdG was measured by HPLC-ECD. Linear models were used to look for relationships between leukocyte DNA and urine levels of 8-OHdG. Terms for gender, exposure, smoking, and race were included. Interaction terms were also included to see if the relationship between blood and urine levels varied by these terms. The models were also used to estimate and test individual slopes. For the model comparing pre-shift urine with pre-shift blood, no main effects or interactions were statistically significant, but a significant inverse association (b = -0.1231, p = 0.0336) was noted for the individual sub-group of female controls. For the model comparing pre-shift blood with post shift urine no main effects or interactions or individual slopes were statistically significant. For the model comparing post-shift blood to post shift urine, the smoking interaction was significant (p = 0.0314). Results demonstrate a limited association between leukocyte DNA 8-OHdG and urinary excretion of 8-OHdG

1373 EFFECTIVE FACTORS ON URINARY 1-HYROXYPYRENE IN A KOREAN POPULATION.

M. Yang[1], S. Lee S[1], D. Kang[1], H. Shin[3], S. Kim[2] and J. Jang[2]. [1]*Preventive Medicine, Seoul National University, Seoul, South Korea and* [2]*Preventive Medicine, Ajou University, Suwon, South Korea.*

Urinary 1-hyroxypyrene (1-OHP) has been used as a biomarker for exposure to environmental carcinogenic polycyclic aromatic hydrocarbons (PAHs). For proper biological monitoring of the PAH exposure, associated factors with 1-OHP bioproduction should be clarified. In this study, we investigated effects of lifestyle, environmental factors, and genetic polymorphisms of metabolic enzymes, i.g., GSTM1, GSTT1, CYP1A1, and CYP1B1 on urinary 1-OHP levels in 700 Korean population (male, 65 % ; female, 35 % ; mean-age, 36 yrs, std. 10.79 yrs) who were not occupationally exposed to PAHs. Using questionnaire, we obtained information of cigarette smoking, indoor heating-system, housing-environment, consumption of well-done meat, vegetables, yogurts, coffee, alcohol, etc. We analyzed urinary 1-OHP and cotinine, a biomarker of smoking, by HPLC. To determine genotypes of the enzymes, we used PCR-RFLP and single base extension methods. As results, urinary 1-OHP was detected in 76 % of the subjects (range, 0.1-3.8 ug/L). In the Korean population, CYP1B1 codon 48 and 119 polymorphism were completely linked and CYP1B1 codon 48 polymorphism was associated with codon 432 polymorphism ($p < 0.05$). Urinary 1-OHP was correlated with urinary cotinine level, number of cigarette smoked before sampling, yogurts consumption, and GSTT1 polymorphism (Spearman Rank correlation, $p < 0.05$). However, polymorphisms of GSTM1, CYP1A1, and CYP1B1 were not associated with urinary 1-OHP levels. After multiple regression analysis, urinary 1-OHP was associated with only number of cigarette smoked before sampling ($p < 0.05$). In conclusion, recent cigarette smoking affects urinary 1-OHP compared to any other environmental, food- or genetic factors.

1374 NEUROPATHY TARGET ESTERASE (NTE) IN WHOLE BLOOD: BIOMARKER FOR EXPOSURE TO NEUROPATHIC ORGANOPHOSPHORUS COMPOUNDS (OPS).

G. F. Makhaeva[1], L. V. Sigolaeva[2], L. V. Zhuravleva[1], A. V. Eremenko[2], I. N. Kurochkin[2], R. J. Richardson[3] and V. V. Malygin[1]. [1]*Institute of Physiologically Active Compounds Russian Academy of Science, Chernogolovka, Russian Federation,* [2]*Center of Molecular Diagnostics and Therapy, Moscow, Russian Federation and* [3]*Toxicology Program, Michigan University, IL.*

NTE is the target protein for neuropathic OPs that cause OP-induced delayed neurotoxicity (OPIDN). The inhibition/aging of brain NTE within hours of exposure predicts the potential for the development of OPIDN in susceptible animal models. Lymphocyte NTE has also found limited use as a biomarker of human exposure to neuropathic OPs. Recently, we developed a highly sensitive biosensor for NTE assay using a tyrosinase carbon-paste electrode to detect phenol produced by the hydrolysis of the substrate, phenyl valerate. The biosensor enabled NTE to be assayed in whole human and hen blood, whereas the usual colorimetric assay is impossible. NTE activity in hen and human blood was found to be 0.10 ± 0.03 and 0.19 ± 0.02 nmol/min x mg of protein, respectively. Mipafox I_{50} values for hen and human blood NTE were found to be 4.22 ± 0.12 and 6.27 ± 0.43 μM, respectively. To study the possibility of using blood NTE inhibition as a biochemical marker of neuropathic OPs exposure, NTE inhibition in brain and lymphocytes as well in brain and blood was studied 24 hr after dosing hens with the neuropathic OP, O, O-dipropyldichlorvinyl phosphate. Brain, lymphocyte and blood NTE were inhibited in a dose-responsive manner. There were strong correlations of NTE inhibition between brain and lymphocyte, brain and blood, and lymphocyte and blood. Taking into account the small sample volume required, simplicity of sample preparation, rapid analysis time, stability of samples after freezing, and strong correlation of NTE inhibition between blood and brain, our biosensor NTE assay for whole blood shows promise, not only as a biomarker of human exposure to neuropathic OP compounds, but as a predictor of OPIDN and an adjunct to its early diagnosis. Supported by ISTC, Project 1055.2.

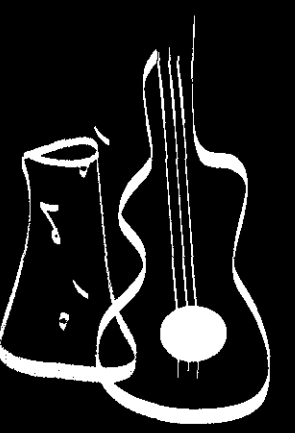
1375 CHOLINESTERASE ACTIVITY IN MICE CHRONICALLY EXPOSED TO PYRIDOSTIGMINE BROMIDE.

R. D. Grubbs, W. A. Price, B. S. Mauck, I. Bernatova, S. J. Paton, D. R. Cool, J. B. Lucot and M. Morris. *Pharmacology & Toxicology, Wright State University, Dayton, OH.*

Pyridostigmine bromide (PB), given to soldiers during the Persian Gulf War as a prophylactic against potential nerve gas attack, is now thought to be a possible causative agent of the symptoms of Gulf War Syndrome. We have developed a murine model to test the effect of chronic exposure to PB on cholinesterase (ChE) activity in the blood and the brain. C57B/J mice were surgically implanted with osmotic mini-pumps to deliver a steady dose of PB over 7 days. ChE activity was determined by a modified version of the colorimetric assay of Ellman, et al. Total ChE activity was measured in diluted whole blood and brain homogenate samples. Blood acetylcholinesterase (AChE) activity was determined by inhibiting butyrylcholinesterase (BChE) with iso-OMPA (tetraisopropylpyrophosphoramide). BChE activity was then calculated by subtracting AChE activity from total ChE activity. Following 7 days of exposure to PB, reductions of blood ChE activity of 27%, 42%, and 55% were seen in the 3, 6 and 10 mg/kg/D dosage groups, respectively, when compared to pretreatment levels. The decrease in blood ChE activity, due primarily to a drop in AChE activity, indicated that the osmotic mini-pump delivery system was functioning properly. We found no change in CHE activity in sham-implanted control animals. Interestingly, while analysis of prefrontal cortex showed no significant change in AChE activity after exposure to PB, we observed a dose-dependent decrease in AChE activity (48% at 3 mg/kg) in the hypothalami of PB treated mice (see Ropp, et al. abstract, this meeting). We are currently evaluating ChE activity in other brain regions of these animals and other mice exposed to both chronic stress and PB. Our findings indicate that chronic exposure to PB pro-

Society of Toxicology

41st Annual Meeting & ToxExpo™

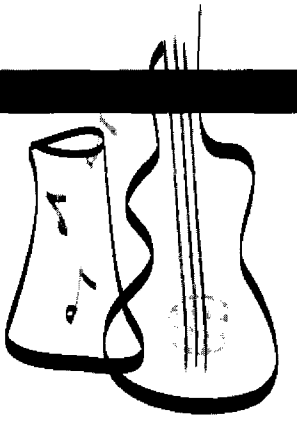


An Official Journal of the Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES

Society of Toxicology

41st Annual Meeting & ToxExpo™



An Official Journal of the Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES
Formerly Fundamental and Applied Toxicology

Abstracts of the 41st Annual Meeting

The Toxicologist

Oxford University Press

Volume 66, Number 1-S, March 2002

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.

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