levels are substantially higher than the levels intended to be reached in ongoing clinical studies. PTZ was invariably associated with EEG paroxysmal activity at an average dose of 48 mg/kg and EEG seizure activity at an average dose of 54 mg/kg. Conclusion: There was no evidence of drug-related EEG changes following administration of Noribogaine at doses up to 320 mg/kg. However, there were concurrent clinical signs that appeared to be related to central nervous system effects, which correlated with plasma exposures and resolved by the end of the monitoring period.

1209 Redox Control of Neuroinflammation by Post-Translational Activation of Glutamate Cysteine Ligase

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Neuroinflammation and oxidative stress are hallmarks of neurological diseases linked to toxicant exposure. However, whether and how the redox processes control neuroinflammation is relatively unknown. We hypothesized that elevating cellular glutathione (GSH) levels would inhibit neuroinflammation. Cellular GSH levels were elevated by a novel approach i.e. post-translational activation of glutamate cysteine ligase (GCL), the rate-limiting enzyme in GSH biosynthesis. A series of thiol-containing compounds were examined for their ability to increase intracellular GSH levels in a murine microglial cell line (BV2), of which 2,3-dimercapto-1-propanol (DMP) was found to be the most potent compound. DMP increased GCL activity and decreased LPS-induced production of an array of pro-inflammatory cytokines and iNOS induction in BV2 cells in a concentration-dependent manner. Additionally, DMP's ability to elevate GSH levels and attenuate LPS induced pro-inflammatory cytokine production was inhibited by buthionine sulfoximide, an inhibitor of GCL activity and GSH biosynthesis. DMP also increased the expression of GCL holoenzyme without affecting the expression of the subunits GCLC and GCLM or that of other Nrf2 target proteins (NQO1 and HO-1), suggesting a post-translational mechanism. Moreover, DMP attenuated LPS-induced MAP kinase activation in BV2 cells. Finally, we determined if DMP increased GSH levels and attenuated neuronal damage in a rat dopaminergic N27 cell line. DMP treatment in N27 cells increased GCL activity and GSH levels similar to the magnitude observed in BV2 cells. Furthermore, DMP inhibited cell death induced in N27 cells by paraquat, a model environmental toxicant. Together, the data demonstrate that elevation of intracellular GSH levels by post-translational activation of GCL inhibits production of pro-inflammatory cytokines and exerts neuroprotection. It also suggests that post-translational activation of GCL is a novel approach to target inflammation and cell death in neuronal disorders where adaptive responses may be impaired.
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1210 Ameliorative Effect of Propolis and Ginger versus Neurotoxicity and Oxidative Stress Evoked by Monosodium Glutamate in Male Albino Rats

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Monosodium glutamate (MSG) is a popular flavour used in food industries; excess MSG is neurotoxic. Oxidative stress is well documented in MSG induced neurotoxicity. This present study has been designed to evaluate the neuroprotective effects of both Proplis and Ginger compounds on MSG-induced neurotoxicity in rats. Fourty adult male albino rats were divided into 4 groups (each containing 10 rats). Group I (control); were orally administrated with normal saline. Group II (MSG), were orally administrated with MSG (830 mg/ Kg. B. wt). Group III (MSG + Proplis); were orally administrated with MSG and subsequently by Proplis (500 mg/kg B. wt). Group IV (MSG+ Ginger); were orally administrated with MSG and subsequently by Ginger (600 mg/kg). At the end of the treatment period (60 days in all groups), blood samples and brain tissue were collected for estimation of LPO and measurement of antioxidant status of glutathione, catalase and superoxide dismutase. Estimation of calcium, sodium and potassium ions in brain tissue and gamma aminobutyric acid level in serum was carried out. The histopathological study of brain tissue was also carried out. MSG caused a significant alteration in oxidative defense; raised levels of LPO and depletion of antioxidant levels. There were neurogenerative changes in the form of vacuolization, pyknosis and congestion in the cerebral cortex. Moreover MSG treatment induced up regulation of Bax protein in brain tissue indicating that MSG induced apoptosis. Treatment with both Propolis and Ginger significantly attenuated oxidative stress, and cerebral damage in MSG-treated animals, also significantly reduced the monosodium glutamate-induced excitotoxicity by decreasing the level of Ca (+2) and Na(+) with concomitant increase in the level of K(+). Serum gamma aminobutyric acid level was also increased in Proplis and Ginger treated animals. The histopathological evidence supports the neuroprotective activity of both. Hence, this study demonstrates that propolis and ginger possess beneficial effects against various neurotoxic insults induced by MSG in rats, returned to their antioxidant and anti-inflammatory properties.

1211 Microglia Are Biosensors of Neuroinflammogens and Neurotoxicity, Whereas Astrocytes Are Linked Only to Neurotoxicity

J. P. O'Callaghan, K. A. Kelly, A. R. Locker, L. T. Michalovicz and D. B. Miller. *CDC/NIOSH, Morgantown, WV.*

A characteristic feature of neurotoxicity is the selective and unpredictable damage to specific neural cells. This lack of target identity constitutes a major barrier to neurotoxicity detection. Evaluating astrogliosis and microglial activation overcomes this problem as these glial cell types react to neurotoxicant exposures to reveal sites of CNS damage. Thus, astroglial and microglial biomarkers often are used as indices of neurotoxicity. Previously we showed that damage from diverse neurotoxicants initiates microglial associated neuroinflammation, the subsequent activation of STAT3 and the induction of GFAP. These findings are indicative of a link between microglial-related neuroinflammation and astrogliosis. Nevertheless, anti-inflammatory treatment with minocycline can suppress neuroinflammation instigated by neurotoxicity without suppressing astrogliosis. Given these observations, it seemed possible that indices of neuroinflammation could be dissociated from neural damage and astrogliosis, despite the fact that multiple neurotoxicity models result in STAT3 activation temporally linked to induction of GFAP. To test this possibility, we employed an acute exposure to the known inflammogen, LPS, to induce neuroinflammation. Our prior data revealed that systemic administration of LPS (2mg/kg, s.c.) did not cause neurotoxicity or astrogliosis in any brain region but did result in brain-wide expression of microglia-associated proinflammatory cytokines/chemokines, Tnf-α, Osm, Ccl2, and Lif, as well as TSPO, a known micoroglial marker of neurotoxicity. LPS also activated STAT3 over a 12-hr post exposure period, when proinflammatory cytokine levels resolved to near baseline. Activation of STAT3 by LPS, unlike the activation associated with multiple models of neurotoxicity, was suppressible by acute pretreatment with the anti-inflammatory glucocorticoid, corticosterone. Neuroinflammation, expression of TSPO, and activation of STAT3 resulting from LPS did not affect the expression of GFAP in any brain region over a 72-hour time period. Together, these data serve to indicate that "acute phase" neuroinflammation caused by LPS can induce TSPO and activate STAT3 without resulting in neural damage or astrogliosis. The STAT3 pathway appears to serve as a dual "switch" for mediating acute neuroinflammatory responses separate from its role in mediating damage-induced astrogliosis.

1212 Corticosterone Priming of the Neuroinflammatory Response to AChE Inhibitors Results in Overexpression of Tlr2 and Downstream Targets, but Not Activation of the Nlrp3 Inflammasome

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Previously, we have shown that exposure to acetylcholinesterase inhibitors (AChEIs) produces inflammation in the mouse brain. Furthermore, this inflammation is greatly exacerbated, or "primed", by prior, chronic exposure to corticosterone (CORT). Inflammatory priming is a phenomenon commonly associated with the inflammasome, a component of the innate immune system comprised of a multitude of proteins including pattern recognition receptors, cytokines, caspases and other adaptor proteins. Prior work evaluating the response to chronic CORT exposure in rats found evidence for activation of the NLRP3 inflammasome. In this experiment, we investigated the involvement of the NLRP3 inflammasome in the neuroinflammatory response to the irreversible AChEIs, diisopropyl fluorophosphate (DFP) and chlorpyrifos (CPF), and the reversible AChEI, pyridostigmine bromide (PB), in male C57BL/6 mice with and without chronic (4 days) exposure to CORT (200 mg/L) in the drinking water prior to AChEI treatment. Here, we found the gene expression of toll-like receptor 2 (TLR2) and its downstream transcriptional targets, S100A8 and S100A9, to be increased in response to CORT DFP and CORT CPO 6 hrs after exposure, while TLR4 and NLRP3 expression were unaf-

fected. However, NLRP3 expression was increased when CORT exposure was extended to 7 days of treatment. Past studies in our lab revealed that PB alone or with CORT pretreatment do not produce neuroinflammation, thus it is not surprising that we found no effect on any of these genes of interest following exposure to PB. Interestingly, expression of serum amyloid a (SAA1), an endogenous ligand of TLR2, was not increased by DFP or CPF, with or without prior CORT exposure. Our data indicate potential involvement of TLR2 signaling in the CORT-priming of the neuroinflammatory response to the AChEIs, DFP and CPF. However, the enhanced expression of inflammatory cytokines in the brain following exposure to CORT and these AChEIs is independent of NLRP3 expression, which appears to be a primary effect of prolonged CORT exposure. By further examining the role of TLR2 in an augmented neuroinflammatory response following the combined CORT and AChEI exposure, we can identify potential targets for the treatment of illness associated with these exposures, such as Gulf War Illness.

1213 Revealing Behavioral Learning Deficit Phenotypes Subsequent to *In Utero* Exposure to Benzo(a)pyrene

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To characterize behavioral deficits in pre-adolescent offspring exposed *in utero* to B(a)P, timed-pregnant Long Evans Hooded rats were treated daily with B(a)P (150, 300, 600 and 1200µg/kg BW) or peanut oil (vehicle) on E14,15,16, and 17. Following birth, but during the pre-weaning period, B(a)P metabolites were examined in plasma and whole brain or cerebral cortex from exposed and control offspring. Tissue concentrations of B(a)P metabolites were 1) dose-dependent and 2) followed a time-dependence for elimination with an approximate 60% reduction by PND5 in the 1200µg/kg BW experimental group. Spatial discrimination-reversal learning was utilized to evaluate potential behavioral neurotoxicity in P40-P60 offspring. Late-adolescent offspring exposed *in utero* to 600 and 1200 µg/kg BW were indistinguishable from their control counterparts in the ability to acquire an original discrimination and reach criterion. However, a dose-dependent effect of *in utero* B(a)P-exposure was evident upon a discrimination reversal as exposed offspring perseverated on the previously correct response. This newly characterized behavioral deficit phenotype for the 1st reversal was not apparent in either the 1) original discrimination or 2) subsequent reversal sessions relative to the respective control offspring. This is the first such documented report of a spatial discrimination reversal deficit after *in utero* exposure to B(a)P. Furthermore, the expression of activity related-cytoskeletal associated protein (Arc), an experience-dependent cortical protein marker known to be up-regulated in response to acquisition of a novel behavior, was greater in B(a)P exposed offspring included in the spatial discrimination cohort versus home cage controls. Collectively, these findings support the hypothesis that *in utero* exposure to B(a)P during critical windows of development representing peak periods of neurogenesis results in behavioral deficits in later life.

1214 Exploration of the Gulf War Illness Phenotype in a Mouse Model Challenged with LPS at Long Term Time Points

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Chronic exposure to the glucocorticoid, corticosterone (CORT), at high physiological stress levels, can prime the CNS to release proinflammatory cytokines following exposure to neurotoxic exposures and systemic inflammation. Such neuroinflammatory events are associated with sickness behavior. Gulf War Illness (GWI) is a multi-symptom disorder characterized by persistent headaches, chronic fatigue, muscle pain, memory loss, confusion, gastrointestinal problems, and rashes, features also characteristic of persistent sickness behavior. Recently we found that, of the multiple exposures soldiers faced in the 1991 Gulf War theatre, two produced exacerbated neuroinflammation in mice. By mimicking the stresses of war with high physiologic exposure to CORT (200 mg/L 0.6% EtOH drinking water) over 7 days followed by sarin gas exposure with surrogate acetylcholinesterase inhibitor, diisopropyl fluorophosphate (DFP; 4 mg/kg, i.p.), we found heightened neuroinflammatory responses without evidence of astrogliosis or neurodegeneration 6 to 72 hours after DFP exposure. While these observations recapitulated the early symptoms of GWI, the essential pathobiology of GWI is the persistence of heightened responses to external stimuli for the past 20+ years. Here we employed episodic exposure of CORT in the drinking water of C57Bl6/J male mice for up to 180 days (CORT drinking water for 4 or 7 days every other week) to emulate episodic stress incurred by ill veterans following their exposures to multiple agents in theater, including sarin, 2 decades ago. Systemic exposure to LPS, at sub- and neuroinflammatory doses, were used to challenge the GWI phenotype (0.5 or 2 mg/kg, s.c., respectively). Our results show that successive waves of CORT provide a priming of the neuroinflammatory response to LPS, and that DFP (single exposure on the last day of the first CORT treatment) can exacerbate this effect. Thus, confirming this mouse model to produce a similar phenotype as that seen in soldiers diagnosed with GWI. Interestingly, we found that while 4 days of CORT in the drinking water is sufficient to produce an exacerbated neuroinflammatory response to LPS, that successive waves of CORT in 7 day, but not 4 day, exposures, every other week for 90 days produces a synergistic priming of the CNS to greatly augment the neuroinflammatory response to LPS. Together, these data suggest that GWI is a chronic, stressor primed, neuroinflammatory condition.

1215 Comparison of Nerve Excitability, Nerve Conduction Velocity, and Behavioral Tests for Acrylamide-Induced Peripheral Neuropathy

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Nerve excitability (NE) testing is a sensitive method to test for peripheral neurotoxicity in humans, and may be more sensitive than compound nerve action potential (CNAP) or nerve conduction velocity (NCV). We used acrylamide to compare the NE and CNAP/NCV methods. Behavioral tests known to be sensitive to acrylamide-induced neurotoxicity were included. Male Long-Evans rats aged 10-11 weeks were given acrylamide in their drinking water at 0, 1.5, 2.5 or 3.0 mM for 6 weeks. These concentrations resulted in an average exposure of 0, 10.3, 14.7, and 14.4 mg/kg/day of acrylamide. NE testing occurred during the 5th week, and CNAP/NCV testing was during the 6th week of treatment. Only 5 animals in the 3.0 mM group were tested due to pronounced neuromuscular and respiratory toxicity, and were not included in statistical analysis. Behavioral testing occurred weekly during treatment, prior to electrophysiology testing, and included open-field evaluations and measures of forelimb/hindlimb grip strength and landing foot splay. Both 1.5 and 2.5 mM treatments altered measures of neuromuscular and sensory function, including increased splay, lower hindlimb grip strength and rearing, and impaired gait and righting reflex. These changes worsened over the 6 weeks of exposure. NE tests indicated decreased nerve excitability, possibly coupled with altered K+ channel activation in sciatic motor nerves and tail mixed nerves. The NE changes were observed at the 2.5 mM treatment concentration. Changes in tail motor nerve NE and CNAPs/NCV in tail mixed nerves were not significant. Results indicate that for acrylamide-induced peripheral neurotoxicity, NE testing detected changes in physiological function, which differed between types of nerves, and was more sensitive than traditional CNAP/NCV methods. Behavioral changes were consistent with previous studies. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

1216 Exposure to Fine Particulate Matter Increases Glutamate Uptake in Bergmann Glia Cells

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Exposure to urban airborne particulate matter (PM) is associated with adverse health effects, and outcomes in the central nervous system have become a relevant public health issue. Recent studies have linked exposure to fine particulate matter to dysfunction of the glutamatergic neurotransmission, given the fact that its components can reach the brain and instigate damage locally or systemically. Glutamate, the main excitatory amino acid transmitter triggers a wide variety of signal transduction cascades that regulate protein synthesis at the transcriptional and translational levels. Activity dependent differential gene expression has been attributed to the activation of both membrane glutamate receptors and transporters. The bulk of glutamate uptake takes place in glia cells. Within the cerebellum, Bergmann glia cells (BGC) are responsible for most of the glutamate uptake activity through the Na+ dependent glutamate/aspartate transporter (GLAST/EAAT-1). Taking into consideration the functional role of Bergmann glia, in terms of the recycling of glutamate, the supply to neurons of lactate, and the prevention of neurotoxic insults, we decided to investigate if air pollution fine particulate matter (PM2.5) exposure affects glia cells that surround glutamater-

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

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The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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- CE Continuing Education Courses
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