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

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

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-

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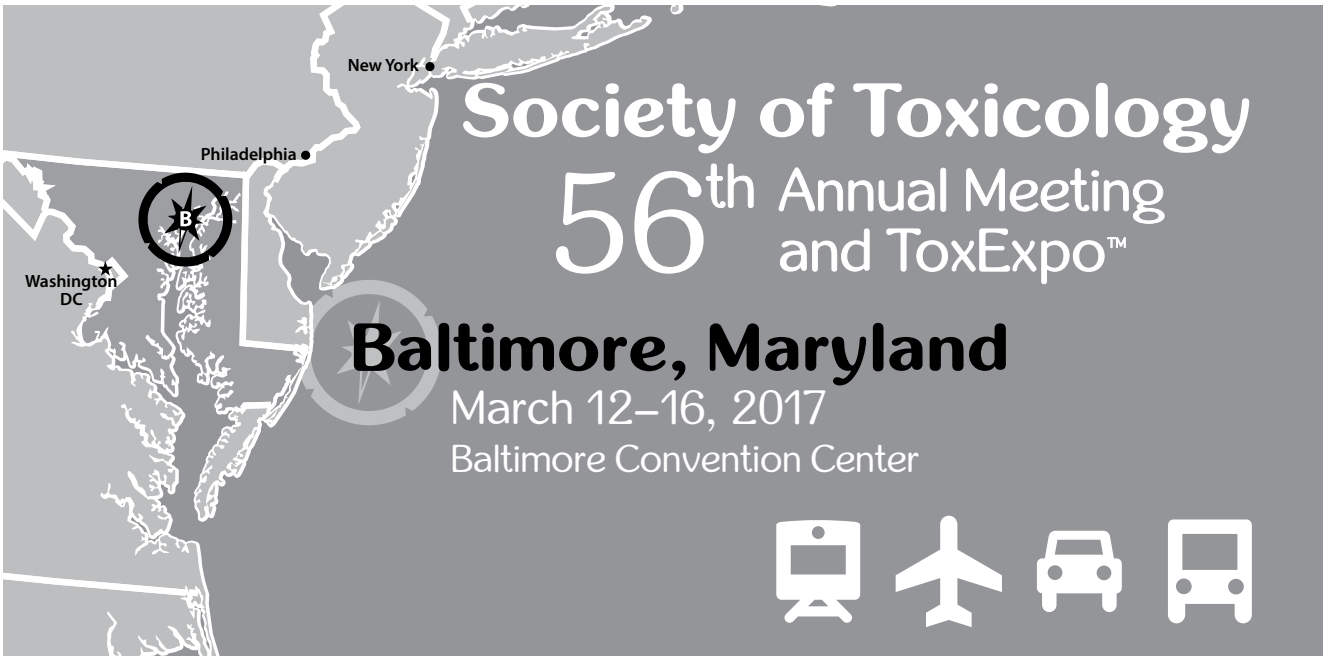

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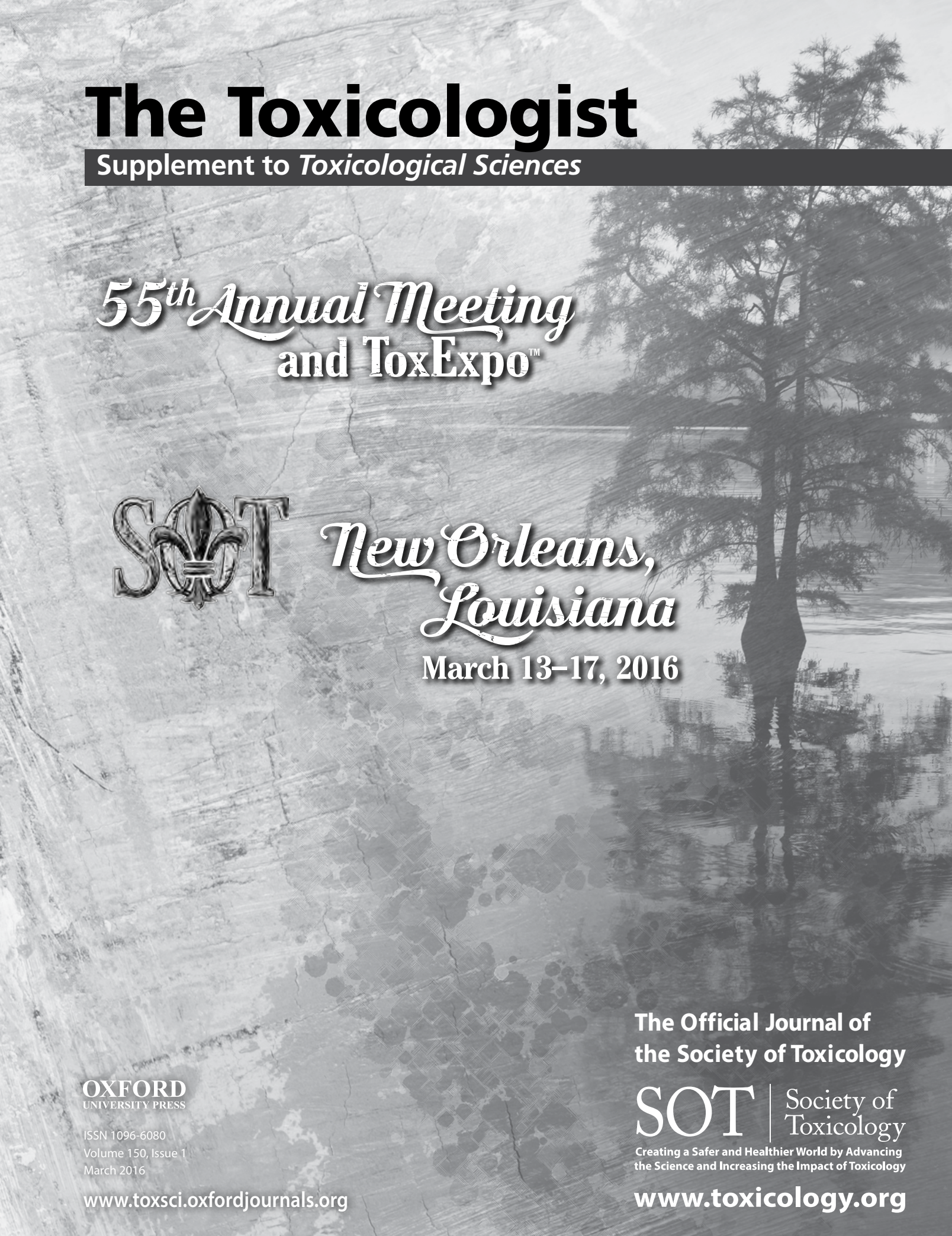

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Preface

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.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

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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- IS Informational Sessions
- PL Platform Sessions
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