3061 Neurotoxicity of Diethylene Glycol in a Rat Model

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Diethylene glycol (DEG) can be found in consumer products, but can also be an adulterant in medicines by acting as counterfeit glycerin. DEG poisonings have been characterized predominately by acute kidney injury (AKI), but have also been known to affect the nervous system via delayed neurological sequelae such as decreased reflexes, face and limb weakness, or quadreparesis, as observed in a patients 2-7 days after DEG ingestion. Characterizing these poorly understood neurological symptoms of DEG poisonings in an animal model can clarify the overall toxicity and make mechanistic connections between the kidney injury and neuropathy. Male Wistar-Han rats were administered by oral gavage a water control or doses of 4 - 6 g/kg DEG every 12 or 24 h and monitored in metabolic housing for up to 7 days. Urine was collected every 12 h and endpoint blood and cerebrospinal fluid (CSF) were collected for renal plasma biomarkers and total protein estimation, respectively. Motor function tests were conducted before and after treatment. Kidney, brain, and spinal cord tissue were harvested after euthanasia for later pathology analysis. Of the 29 rats that were treated with DEG, 8 developed AKI with confirmation by renal plasma biomarkers. AKI primarily occurred after doses that were administered every 12 h. There was a marked increase in renal DGA accumulation in rats that developed AKI, compared to rats without AKI, confirming the role of DGA in the nephrotoxicity. The level of DEG in all treated animals stayed in the same range (15-25 mg/mL), with no obvious differences between rats with and without AKI. The total protein content of CSF in rats with AKI was significantly higher than controls and rats without AKI, indicating the first evidence of nervous system damage from DEG treatment in an animal model. Significant decreases in grip strength as well as in locomotor and rearing activity were observed in rats with AKI compared to controls and to rats without AKI. Initial pilot studies did not show dramatic changes in myelination (Luxol fast blue) in animals with elevated CSF protein, compared to controls or to unaffected but treated animals. The observation of increased CSF protein and motor function deficits, only in rats with AKI, indicate the development of neurotoxicity in this subacute animal model and strongly suggest that kidney injury needs to occur before neurological symptoms are observed. *Funding Source: American Chemistry Council and NIH (R15 ES029704).*

3062 Environmental Polychlorinated Biphenyls Mixtures Inhibit the Dopamine Transporter

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Dopamine is a monoamine transmitter that contributes to the motor and reward system in in the body. When neurons experience a change in dopamine availability it can cause symptoms of addiction, attention deficit hyperactivity disorder (ADHD), and Parkinson's disease. Polychlorinated biphenyls (PCBs) congeners are man-made environmental pollutants that disrupt the dopamine transporter (DAT) that is responsible for dopamine uptake from the synaptic cleft. When DAT is altered it may lead to altered cognitive proficiency. To date 46 non-dioxin like (NDL) PCB congeners have been found to alter DAT activity and include those highly chlorinated in the ortho position. NDL PCBs are present in the environment as mixtures; however, currently how these mixtures contribute to altered activity is currently unknown. The focus of this study is to examine the activity of PCBs in binary and complex mixtures towards DAT. I will use radioligand binding assay in female rat synaptosomes, with [3H] WIN- 35, 428 in the presence or absence of single PCBs or the mixture there of. Preliminary data confirms the inhibitory activity of NDL PCB congener PCB 95. The binding assay inhibitory concentrations (IC50) from this work and that of others will then be used to develop and apply a neurotoxic equivalency scheme (NEQ) to published PCB mixtures concentration to predict DAT activity. Preliminary applications of a DAT NEQ based on the highly potent PCB 110, found that the serum of children serum in East Chicago had a NEQ of 10.73 nanograms per gram. This NEQ represents a measurement of neurotoxicity relative to PCB 110. The ability of NDL PCBs to induce DAT inhibition and alter dopamine concentrations can aid in addressing its harmful persistent neural activity during neurodevelopment and its effect on initiating neurological disorders especially Parkinson's disease. *Supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R25GM071638.*

3063 A Chemically Defined Hydrogel Substrate Promotes Accelerated Maturation and Neurite Extension of Cortical Glutamatergic and Motor Neurons for High-Throughput Screening

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Human neural cells manufactured from patient-derived induced pluripotent stem cells (iPSCs) hold great promise for modeling neurodevelopmental disorders, discovering precision therapies, and screening for potential risks from environmental toxins. However, many neurological phenotypes arise in mature neurons, and human iPSC-derived neurons can require extensive time in culture (1-3 months) to reach full maturity. These lengthy cultures slow the discovery process and are costly due to labor and reagent requirements. We hypothesized that optimizing culture substrate properties through the use of tunable synthetic matrices would improve maturation. Currently, neurons are cultured on a variety of substrates including charged polymers (poly-lysines or poly-ornithines) or animal-derived matrices. Using JMP™ software, we employed Design of Experiment (DOE) methodology utilizing Box-Behnken response surface modeling to screen for synthetic polyethylene glycol-based (PEG) hydrogel formulations that promoted viability, cell adhesion, desired morphology, and accelerated maturation of cortical glutamatergic neurons. In the experimental design, we varied PEG concentrations, crosslinkers and cell adhesion peptide composition and concentrations. To facilitate the quantitative DOE analysis, we utilized neurons derived from a human iPSC reporter line with a fusion protein comprising nanoluciferase (Nluc, Promega) and synaptophysin (SYP), a synaptic vesicle glycoprotein that is expressed in virtually all mature neurons and acts as a marker for quantification of synapses. We identified hydrogel formulations that 1) support cortical glutamatergic neuron adhesion as scored morphologically and assessed quantitatively via cellular ATP (Cell Titer Glo 2.0, Promega) and 2) accelerate maturation, as demonstrated through a time-course of synaptophysin expression. Finally, these hydrogel formulations supported over two-fold increases in neurite length over a poly-D-lysine substrate. When incorporated into neuronal high-throughput screening efforts, the identified hydrogel substrates will improve overall outcomes and decrease the culture time required to reach the necessary maturation state.

3064 Chronic Glucocorticoid Exposure Primes the Neuroinflammatory Response to Nerve Agent Sarin

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Chronic exposure to the glucocorticoid corticosterone (CORT), at levels associated with high physiological stress, can exacerbate CNS proinflammatory responses to neurotoxic insults in animal models. Persistent sickness behavior, a prominent component of Gulf War Illness (GWI), is associated with neuroinflammation. Veterans of the 1991 GW were exposed to the stresses of war, being prophylactically treated with the reversible acetylcholinesterase (AChE) inhibitor pyridostigmine (PB), organophosphate pesticides chlorpyrifos (CPO) and dichlorvos (DDVP) and potentially the nerve agent sarin. We have previously shown CORT exacerbation of the neuroinflammatory response to CPO, DDVP, and the sarin surrogate diisopropyl fluorophosphate (DFP). Here, we confirm that sarin exposure also causes a neuroinflammatory response that is exacerbated by chronic CORT pretreatment. CORT (200 ug/mL in 0.6% EtOH) was given in the drinking water for 1 week prior to sarin administration at an LD20 dose (0.1 mg/kg, s.c.) on day 8. Animals were euthanized at 6 hours and brains were dissected and then frozen for RNA and protein analysis. RNAseq analysis of cortex revealed 1535 genes that were significantly up-regulated in the CORT+sarin group. Of these, 211 were significantly greater than sarin alone. These 211 genes were interrogated with DAVID to find GO terms which included cytokine production, MAP kinase phosphatase activity, and cytokine binding. Kegg pathways include: cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, MAPK signaling pathway, and hematopoietic cell lineage. The neuroinflammatory response was further confirmed with elevated pSTAT3 protein by ELISA and elevated neuroinflammatory cytokines and chemokines mRNA (TNFα, IL6, CCL2, IL1β, LIF, and OSM) by qPCR. Together these findings confirm those we have previously shown with sarin surrogate, DFP and provide additional support for the hypothesis that GWI is a chronic, stressor-primed, neuroinflammatory condition potentially instigated by the combined exposures to stressors and irreversible AChE inhibitors.

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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 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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