PS 2121 An Experimental Study on the Effects of Low-Level Fluoride Exposure on Memory and Learning Ability of Rats

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Neurotxic effects of fluoride on the ability of learning and memory evaluated by Morris water maze test have been reported for mice in previous studies lately. For rats, there was a study that the effects of fluoride on the ability of learning and memory of the rats were evaluated for high doses of 100 and 200 ppm in the drinking water. In this study, we evaluated the neurotoxic effects of fluoride on the learning ability of rats at low and high doses in the drinking water. Fluoride in the drinking water at 0, 25 or 125 ppm were administered to adult Wistar rats for 2 months. The body weights of the rats were recorded daily. The neurotoxic effects were evaluated by Morris water maze test for 5 days at the end of the exposure of 2 months. The indexes for the evaluation were the search time to find the target on day 1 to day 5 of the session, and the swimming distance before escaping onto the visible platform after the test for the search time on day 5. The mean body weights of the 125 ppm group were significantly lower than those of the control and the 25 ppm-group from 11 days after the beginning of the exposure. The mean search time on day 2 in the 25 ppm or 125 ppm was significantly higher than that in the control. There were no significantly differences among the groups for the swimming distance. Fluoride at 125 ppm in the drinking water decreases the body weight of adult rats. Fluoride at 25 ppm and more in the drinking water may impair the learning ability in the very early days. Further study are required for confirming the effects of fluoride on the ability of learning and memory and evaluating the neurotoxicity of fluoride.

PS 2122 Exposure to Fine Particulate Matter Reduces Glutamate Uptake in Cerebellar Bergmann Glia Cells through a src/MAPK Pathway

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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. Recent studies have linked exposure to fine particulate matter with toxicity at a neurological level, given that some of its components can reach the brain and instigate damage locally or systemically. Within the cerebellum, Bergmann glia cells are responsible for most of 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 here to investigate if air pollution particulate matter (PM) target glia cells that surround glutamatergic synapses and by these means alter the major excitatory transmitter system in the brain. To this end, we exposed cultured chick cerebellar Bergmann glia cells to fine PM isolated and concentrated from Mexico City and measured the [3H]- D-Aspartate uptake activity. A time and dose dependent decrease in uptake activity was observed. Furthermore, PM treatment resulted in the activation of a signaling cascade that included Ca2+ influx through the Na+/Ca2+ exchangers, activation of p60src, phosphatidylinositol 3-kinase, protein kinase B and p42/p44 MAPK. These results add a novel mediator of the air pollutants deleterious effects in the CNS: glia cells, strengthening the notion of the critical involvement of these cells in synaptic neurotransmission. (Financement: CONACYT #167778 and Fundación Pandea).

PS 2123 *In Vitro* and *Ex Vivo* Neurotoxicity Assessment of Brominated- and Halogen-Free Flame Retardants

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Many brominated flame retardants (BFRs) are abundant persistent organic pollutants with well-known neurotoxic properties that argue for replacement by halogen-free flame retardants (HFFRs). Since the neurotoxic potential of HFFRs is largely unknown we investigated the *in vitro* neurotoxicity of 13 HFFRs and 3 BFRs. Using PC12 cells we demonstrate that the majority of FRs induced negligible cytotoxicity, except zinc hydroxystannate (ZHS) and zinc stannate (ZS). Single-cell fluorescent Ca^{2+}-imaging revealed that aluminium trihydroxide (ATH), ZHS and ZS increased the basal intracellular calcium concentration ($[Ca^{2+}]_i$). In the low µM range, many FRs, including tetrabromobisphenol A (TBBPA), triphenylphosphate (TPP), ZHS and ZS reduced depolarization-evoked increases in $[Ca^{2+}]_i$ due to inhibition of voltage-gated calcium channels. Next, using Xenopus oocytes expressing nicotinic acetylcholine receptors (nACh-R) we demonstrate that some FRs, including TBBPA, TPP and aluminium diethylphosphinate (Alpi), act as nACh-R antagonists. Based on the *in vitro* derived neurotoxic potential we could identify suitable (e.g. Alpi) and less suitable (e.g. ZS) candidates for replacement. To substantiate this notion, we studied effects of neonatal exposure to TBBPA, Alpi or ZS on synaptic plasticity in mouse hippocampus *ex vivo*. These FRs did not significantly affect long-term potentiation and the expression of postsynaptic proteins. The FRs were absent from the brains, suggesting low bioavailability and/or rapid elimination/metabolism. Our findings demonstrate that several HFFRs could be suitable alternatives for BFRs. However, data on (*in vivo*) toxicity following prolonged (developmental) exposure is yet lacking.

PS 2124 Chronic Glucocorticoid and Nerve Agent DFP Exposures Produce a Neuroinflammatory Model of Gulf War Illness without Neurodegeneration

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Gulf War Illness (GWI) is a persistent, multi-symptom disorder with features characteristic of sickness behavior. Several exposures have been hypothesized as triggers of the recurring/chronic symptoms associated with GWI, including exposure to the nerve agent sarin that resulted from munition detonations at multiple sites. Here, we investigated the effects of exposure to the sarin surrogate, diisopropyl fluorophosphate (DFP), on peripheral and CNS inflammation. Male C57BL/6J mice were pretreated with corticosterone (CORT) in the drinking water for 7 days to mimic high physiological stress, followed 1 day later by DFP (4 mg/kg, i.p.) exposure to model GWI. DFP exposure alone did not change inflammatory markers in serum and liver, however, increases in expression of inflammatory cytokines/chemokines were found in the brain. Further, CORT exposure for 7 days prior to exposure to DFP greatly augmented inflammatory responses in the brain. Pretreatment with anti-inflammatory antibiotic, minocycline, attenuated this neuroinflammatory effect. Subsequent investigation of neurodegeneration as indexed by GFAP protein content revealed no treatment-related increases following exposure to DFP or CORT+DFP. Immunohistochemical data revealed small, region-specific (e.g. hippocampus CA-1) changes in microglia and astrocyte morphology (Iba-1 and GFAP, respectively); and no neurodegeneration was seen with silver or Fluoro-Jade B assessments of damage. These results suggest increases in neuroinflammation, findings consistent with sickness behavior, may be characteristic of GWI, potentially induced by exposure to nerve agents, and can be exacerbated by exposure to chronic stress conditions (e.g., extreme temperatures, daily threat to safety/survival). While exposure to both stress hormones and nerve agents may be enough to produce increases in neuroinflammation, which likely contribute to sickness behavior seen in GWI, these conditions do not produce neural damage. Supported by USAMRMC W81XWH-09-2-0098

PS 2125 Pyridostigmine Bromide Suppresses Neuroinflammation Induced by DFP

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Use of our Gulf War Illness (GWI) mouse model has shown that administration of diisopropyl fluorophosphate (DFP) results in neuroinflammatory responses involving multiple cytokines/chemokines. Paradoxically, pretreatment with the anti-inflammatory stress hormone corticosterone (CORT) exaggerates this response. Neuroinflammation in the CNS results in sickness behavior, a persistent element of GWI. Soldiers in the 1991 Gulf War were instructed to consume the reversible cholinesterase inhibitor pyridostigmine bromide (PB) when under threat of nerve agent exposure. Here, we investigated how exposure to PB alone and combined with our GWI model affected neuroinflammatory responses. Male C57BL6J mice acutely exposed to PB (3.0 mg/kg) or PB following 4 days of CORT (400 mg/L in the drinking water) showed no significant neuroinflammatory changes in most markers (TNF-alpha, OSM, IL-1beta, LIF, IL-6) and no signs of astrogliosis (no increases in GFAP) in the hippocampus and cortex, findings suggestive of a lack of underlying neural damage. Investigation of the effects of chronic PB treatment prior to DFP exposure revealed a general reduction of DFP-induced neuroinflam-

The Toxicologist

Supplement to *Toxicological Sciences*

54th Annual Meeting and ToxExpo™

March 22–26, 2015 • San Diego, California

The Official Journal of the Society of Toxicology

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 144, Issue 1
March 2015

www.toxsci.oxfordjournals.org

SOT | Society of Toxicology

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