vitro GW chemical exposure on electrophysiological parameters of hippocampal neurons. PAFR activation can be amplified by increased production of PAF and PAF-like compounds contained within microvesicle particles (MVP). Imipramine, a tricyclic antidepressant, has been demonstrated to also inhibit the generation of MVP and thus can block the amplification of PAF signaling. Here, we will present data characterizing the effects of GW chemicals on behavior and hippocampus and evaluate the effectiveness of imipramine as a potential countermeasure. **Methods:** The GWI was modeled by exposing male Sprague Dawley rats for 28 consecutive days to DEET and PER via dermal absorption and PB via gavage, at concentrations of 40, 0.13, and 1.3 mg per kg body weight, respectively. As part of the GWI model, rats were additionally subjected to a mild stress exposure consisting of a 5-min placement in a tube in which movement is restricted. Control rats were given ethanol dermally and water via gavage for 28 consecutive days. Physiological endpoints were measured 4-5 months following completion of the 28-day exposure. Imipramine was given to a subset of GWI rats via gavage for 5 days per week for 1 or 4 weeks prior to euthanasia. A subset of control and GWI rats were subjected to an inflammatory challenge via intraperitoneal injection of 0.03 mg lipopolysaccharide (LPS) per kg body weight prior to euthanasia. **Results:** Elevated zero maze test revealed that GWI rats significantly traveled a greater distance in the open arms (401±51 cm) compared to control rats (187±41 cm), which may suggest increased impulsivity or hyperactivity. Motor activity tests revealed that GWI rats spent significantly less time in the center of the open field chamber (11.4±0.9%) versus the periphery compared to control rats (14±0.8%) as measured using unpaired, two-tailed t-test, which may suggest increased anxiety tendencies. GWI rats treated with imipramine for 1 or 4 weeks no longer showed significant increases in the distance traveled in the open arms of the elevated zero maze test (343±61 cm, 297±57 cm) compared to control rats. Additionally, GWI rats treated with imipramine for 4 weeks, but not 1 week, did not show significant decreases in the % time spent in the center of the motor activity open field chamber (13±0.9%) compared to control rats. Electrophysiological measurements showed a slight but significant reduction in long term potentiation (LTP) of hippocampal neurons from GWI rats (16±3.5%) that were challenged with low dose LPS compared to control rats (30±6.8%) that were also challenged with low dose LPS. GWI rats treated with imipramine (1 or 4 weeks) prior to LPS challenge did not show a statistically significant reduction in LTP (28±6.7%, 17.0±2.7%). Altogether, these data indicate that imipramine can partially reverse the changes in hippocampal LTP as well as the increased impulsivity/hyperactivity and anxiety tendencies detected in GWI rats. We also found a significant reduction in glutamate levels in homogenized brains from GWI rats (412.8±13 µg/ml) that were challenged with LPS compared to control rats (462.3±18 µg/ml) also challenged with LPS. However, treatment with imipramine (1 or 4 weeks) failed to reverse the reduced glutamate levels (401.1±13, 385.9±9 µg/ml). Analysis of immunohistochemistry and confocal imaging revealed significantly reduced hippocampal neurons in GWI rats compared to control rats, with or without the LPS challenge (~8-11% reduction). Preliminary analysis revealed that imipramine treatment did not reverse the neurodegeneration detected in the hippocampus of GWI rats (~8-13% reduction). Furthermore, there was a 22% and 25% increase in IL-6 and IL-13 plasma levels, respectively, from GWI rats compared to control rats that was not mitigated by imipramine. **Conclusions:** Although there were beneficial effects observed, imipramine treatment did not reverse all the effects detected in GWI rats. Based on these data, we hypothesize that the delayed hippocampal neurodegeneration (reported as decreased neuronal number and glutamate levels) and systemic inflammation (reported as increased plasma cytokine levels) detected in GWI rats are mediated by pathways independent of PAF and/or MVP. We further hypothesize that the systemic inflammation can subsequently trigger PAFR activation and MVP generation causing the observed changes in long term synaptic plasticity as well as hyperactivity and anxiety tendencies. These hypotheses provide a plausible explanation as to why treatment with imipramine that blocks amplification of PAF signaling can reverse the effects detected in the hippocampal plasticity recordings and behavioral tests but not in glutamate or cytokine levels.

PS 3765 Chronic high physiological stressor mimic, corticosterone, primes the neuroinflammatory response in cortex to dermal sulfur mustard exposure: a potential contribution to initiation of Gulf War Illness

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Background and Purpose: Nearly a third of veterans from the 1991 Gulf War returned with a multi-symptom disorder characterized by debilitating fatigue, cognitive dysfunction, chronic widespread pain, gastrointestinal distress, respiratory problems, skin abnormalities, and other symptoms. Taken together with deployment at that time, this disorder is now known as Gulf War Illness (GWI). The symptoms of GWI also are consistent with features of chronic sickness behavior, the underlying basis of which is neuroinflammation. Many wartime exposures have been proposed to serve as the instigating event for GWI including pesticides, nerve agent prophylactic, oil well fires, vaccinations, sand and dust particles, and chemical and biological weapons. While the potential for organophosphate nerve agent exposures has received the most attention with respect to GWI, due to their known neurological effects, it also is believed that Iraq was in possession of additional chemical weapons, including mustard agents. In our initial studies, we focused on exposure to organophosphate compounds such as the nerve agent sarin, as well as chlorpyrifos and dichlorvos pesticides. We found that combing these agents with the rodent stress hormone, corticosterone (CORT), as a stressor surrogate, results in marked and persistent neuroinflammation in mice and rats. We not that there is evidence of similar symptomology after sulfur mustard exposures. Mustard agents can cause acute toxicity to the nervous, respiratory, cardiac, dermal, and digestive systems with chronic conditions lasting many years after exposure. **Methods:** Here, we have used our established chronic CORT priming regimen (7 days of 200 mg/L 0.6% EtOH in the drinking water) prior to an acute (4-8 min) dermal sulfur mustard exposure in adult male C57BL/6J mice. Tissues were collected at 6- and 24-hours post-mustard exposure with hippocampus and cortex brain areas evaluated for inflammatory cytokine mRNA expression. **Results:** Results revealed significant (% or fold range) increases in TNFα, C-C motif chemokine ligand 2 (CCL2), and IL-1β in the cortex of CORT + sulfur mustard mice at 6 hours post-exposure, as well as a significant increase in the astrocyte marker, glial fibrillary acidic protein (GFAP), mRNA 6 hours after CORT + sulfur mustard exposure in the cortex; these changes resolved by 24 hours. Additionally, no significant changes in mRNA expression were measured in the hippocampus at either 6 or 24 hours after sulfur mustard exposure. **Conclusions:** These initial results suggest that dermal sulfur mustard exposure is capable of producing CORT-primed neuroinflammatory responses similar to what has been previously observed in our organophosphate-based GWI model. Thus, exposure to non-organophosphate nerve agents like sulfur mustard, particularly in combination with stress, may have the potential to develop the underlying neuroimmune dysfunction that has been associated with GWI pathology and warrants further study.

PS 3766 Comparison of two polyphenols on neural functions in a model of Gulf War Illness

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Background and Purpose: Roughly 30% of the 1991 Gulf War veterans experienced Gulf War Illness (GWI), neurologically marked by cognitive and mood deficits. Chronic exposure to various GWI-related chemicals (GWIR-Cs), such as drugs to prevent nerve gas, repellants and pesticides, with physical stress underlies the development of GWI. The hippocampal dentate gyrus (DG) is a unique brain structure that conducts adult neurogenesis, where neuronal circuits are regulated by environmental and intrinsic factors. We previously revealed that continuous exposure to natural polyphenol antioxidant products, amorphous formula of curcumin (CUR) and α-glycosyl isoquercitrin (AGIQ), from developmental stages promotes fear memory extinction by strengthening synaptic plasticity. Here, we first investigated the alterations in cellular signaling strengthening DG structural plasticity by continuous AGIQ exposure from developmental stage. We then compared the chemopreventive effects of the two polyphenols, CUR and AGIQ, against cognitive and mood deficits in a rat GWI model. **Methods:** Experiment 1: AGIQ at 0.5% in the diet was maternally exposed from gestational day 6 to postnatal day 77, and offspring brains were immunohistochemically analyzed in terms of the changes in the signaling of the glutamatergic and GABAergic neural circuits in the DG. Experiment 2: Ten-week-old rats received GWIR-Cs (pyridostigmine bromide, permethrin, and N, N-diethyl-*meta*-toluamide) and 5-min restraint stress for 28 days, and then fed a diet containing 0.1% CUR or 0.5% AGIQ for 126 days. Animals were subjected to behavioral tests after 90 days of the polyphenol treatments. Immunohistochemical and gene expression analyses in the hippocampal DG were performed in terms of oxidative stress, neuroinflammation, adult neurogenesis, and synaptic plasticity. **Results:** Experiment 1: In the DG, AGIQ exposure from developmental stage increased VGLUT2 immunoreactivity in the granule cell layer (GCL) and PSD95 immunoreactivity in the whole structure. AGIQ also increased VGAT immunoreactivity in all DG laminae as well as the number of hilar GABAergic interneurons (INs) expressing NMDAR2D in subpopulations expressing CB1R, PVALB or SST. Experiment 2: GWI rats affected behavioral endpoints in terms of novel object recognition, sucrose preference, novelty suppressed feeding, and contextual fear conditioning tests, and CUR ameliorated them. AGIQ exerted anxiety-like behavior and improved fear memory extinction. GWI rats downregulated NRF2-Keap1 pathway-related genes in the DG, while CUR exposure upregulated *Keap1*, *Gpx4*, and *Mt2a*, and AGIQ exposure also upregulated *Nfe212*, *Keap1*, *Hmox1*, *Gpx4*, *Mt1*, and *Mt2a* in this model, suggesting that CUR and AGIQ exert antioxidative effects through NRF2-Keap1 pathway. GWI rats increased the numbers of $CD68^+$ and $CD163^+$ microglia/macrophages in the DG hilus and downregulated *Il6*, suggesting induction of both proinflammatory and anti-inflammatory responses. In contrast, both polyphenols decreased the number of $CD68^+$ cells and upregulated *Il1a*, suggesting an attenuation of neuroinflammation. GWI rats decreased $GFAP^+$ cells but increased DCX^+ and $PCNA^+$ cells in the DG subgranular zone (SGZ) and/or GCL, decreased hilar SST^+ and $GAD67^+$ INs and downregulated *Pvalb*, suggesting suppressed neurogenesis targeting type-1 neural stem cells (NSCs) through suppression of INs supports and compensatory proliferation of neural progenitor cells (NPCs) to increase in type-3 NPCs. CUR reversed the numbers of $GFAP^+$ NSCs and SST^+ INs, suggesting amelioration of suppressed neurogenesis. Both polyphenols increased VGLUT1 immunoreactivity

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